Exploring the Intersection of Tropical Medicine and Migrant Health

(Image: NASA)

Migrant Clinicians Network Webinar
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Wednesday, April 18th 2012

Objectives

- Introduce the evolution of Tropical Medicine as a discipline with infectious disease and public health priorities
- Review the impact of the human history of trade, migration, and displacement on health and development
- Discuss the emergence of the Neglected Tropical Diseases as WHO priority
- Review the known NTDs that impact the US Migrant Stream and the paucity of existing epidemiologic and surveillance data
- Discuss the pathophysiology, presentation, and recommended therapy and prevention for Dengue, Leishmaniasis, and Chagas Disease.

(Image: CDC)

IMPERIAL FEDERATION. MAP OF THE WORLD SHOWING THE EXTENT OF THE BRITISH EMPIRE IN 1886.


LONDON SCHOOL OF HYGIENE
AND TROPICAL MEDICINE


1
ERADICATE EXTREME POVERTY AND HUNGER
2
ACHIEVE UNIVERSAL PRIMARY EDUCATION
3
PROMOTE GENDER EQUALITY AND EMPOWER WOMEN
4
REDUCE CHILD MORTALITY
5
IMPROVE MATERNAL HEALTH
6
COMBAT HIV / AIDS, MALARIA AND OTHER DISEASES
7
ENSURE ENVIRONMENTAL SUSTAINABILITY
8
GLOBAL PARTNERSHIP FOR DEVELOPMENT

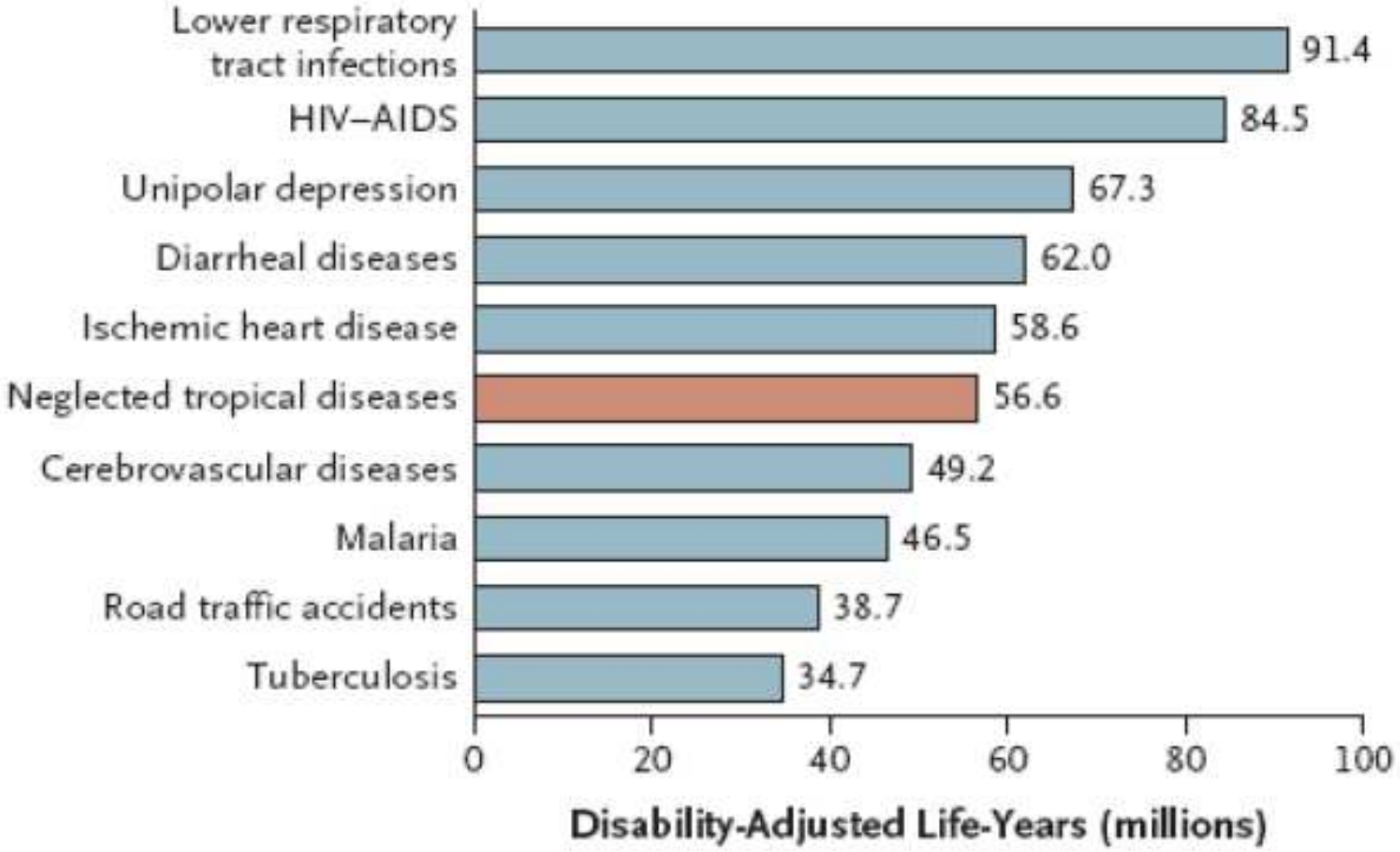

Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.

N Engl J Med 2007;357:1018-27.

DALYs

- DALYs = Disability Adjusted Life Years

= YLL + YLD

  - Sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability

  – YLL = Years Lost due to Disease
  – YLD = Years Lived with Disability

WHO NTD

- Buruli Ulcer
- Chagas Disease
- Dengue
- Drancunculiasis
- Fascioliasis
- Echinococcosis
- Human African trypanosomiasis
- Leishmaniasis
- Rabies
- Cysticercosis
- Hansen's Disease (Leprosy)
- Lymphatic filariasis
- Onchocerciasis
- Schistosomiasis
- Soil transmitted helminthiasis
- Trachoma
- Yaws

<u>Neglected conditions</u>

- Snakebite
- Podoconiosis
- Strongyloidiasis

DNDi

- Buruli Ulcer
- **Chagas Disease**
- Dengue
- Drancunculiasis
- Fascioliasis
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<u>Neglected conditions</u>

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DNDi

- MSF (1999): Nobel Peace Prize
  - Committed its funds to R&D for new rx for NTD
- Geneva, Switzerland
- Essential Rx to treat the world's poor
    - Too expensive
    - No longer produced
    - Highly toxic
    - Ineffective
- Goal:
  - 6-8 new treatments by 2014
  - Develop a strong R&D portfolio

(www.dndi.org)

DNDi

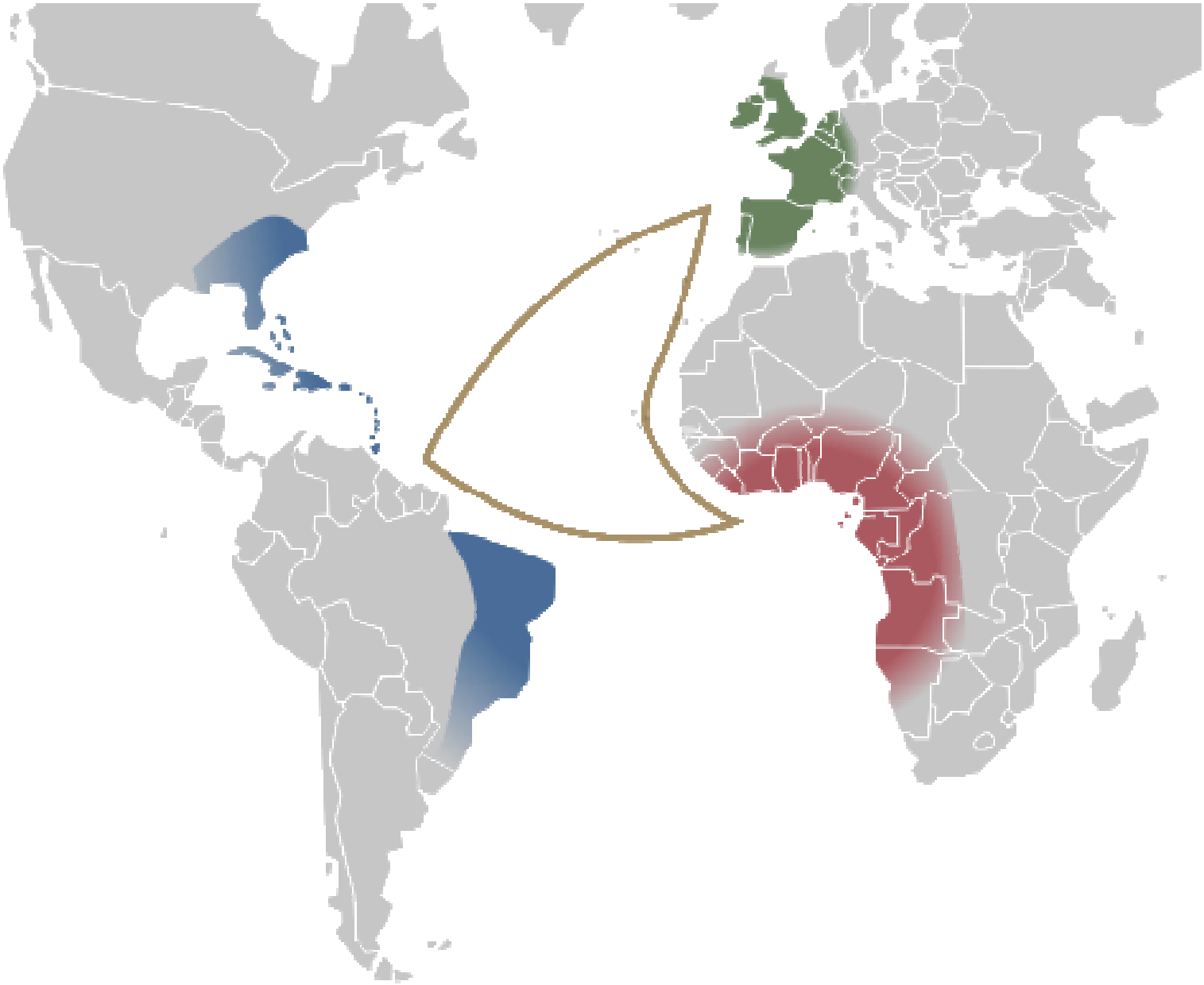
- From 1975-2004:
  - 1,556 new drugs approved
  - Only ***21*** (1.3%) specifically developed for tropical disease and tuberculosis
  - Though these diseases account for 11.4% of the global disease burden

(www.dndi.org)

Features of NTDs

- Proxy for poverty and disadvantage
- Affect populations with low visibility and little political voice
- Do not travel widely
- Cause stigma and discrimination
  - Especially of girls and women
- Have an important impact on morbidity and mortality
- Are relatively neglected by research
- Can be controlled, prevented, and possible eliminated
  - Using effective, feasible, and ***low cost*** solutions

(Hotez, PJ "Control of Neglected Tropical Diseases", *NEJM*, 2007; 1018-27.)



NTDs in the US

- Prevalence in regions of poverty in selected areas of the US, especially along the Migrant Stream, South, and inner-cities
- High rates of chronic parasitic and bacterial co-infections among the poor in these regions
- Disproportionate impact on underrepresented minority populations
- Poverty promoting

(Hotez, P, "Neglected Diseases Amid Wealth in the US and Europe" *Health Affairs; Nov/Dec 2009; 28, 6.)*

NTDs in the US

- Lack of awareness about these conditions and the vulnerable populations they affect
- Ignorance by public health and professional health care communities as well as local, state, and national government officials
- Dearth of active surveillance data
- Absence of epidemiologic investigative efforts to determine actual transmission in affected communities
- Lack of a concerted research and development effort to improve diagnostic testing methods, drugs, or vaccines

(Hotez, P, "Neglected Diseases Amid Wealth in the US and Europe" *Health Affairs; Nov/Dec 2009; 28, 6.)*

NTDs in the Migrant Stream

- Many currently endemic on both sides of the border
- Most common infections of the poorest 120 million people in the Americas who live on <$2/day
- Together producing a burden of disease that exceeds HIV/AIDS in certain regions of W. Hemisphere
- Traps Latin America's "bottom 100 million" in poverty
  - Stunting effects on physical/intellectual development
  - Deleterious pregnancy outcomes
  - Decreased worker productivity

(Hotez, et al. "Texas and Mexico: Sharing a Legacy of Poverty and Neglected Tropical Diseases, PLoSNTDs March 27, 2012)

NTDs in the Migrant Stream

- Dengue
- Leishmaniasis
- Chagas Disease
- Soil Transmitted Helminths
- Amoebiasis
- Schistosomiasis
- Vivax malaria
- Blinding Trachoma
- Hansen's Disease (Leprosy)
- Cysticercosis
- Lymphatic filariasis
- Brucellosis
- Leptospirosis
- Onchocerciasis

(Hotez, et al. "Texas and Mexico: Sharing a Legacy of Poverty and Neglected Tropical Diseases, PLoSNTDs March 27, 2012)

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Disease	Estimated Number of Cases in Latin America and the Caribbean [1,5]	Estimated Number of Cases in Mexico [3,5,17,18]	Disease Endemic to Texas?
Trichuriasis	100 million	18 million	Unknown
Ascariasis	84 million	9 million	Unknown
Hookworm	50 million	1 million	Previously endemic
Amoebiasis	Not determined	8–9 million	Unknown
Chagas disease	8–9 million	2–6 million	Yes – up to 267,000 cases
Schistosomiasis	2–7 million	None	None
Blinding trachoma	1.1 million	<1,000	None
Vivax malaria	<0.9 million reported cases in 2004	<3,000 cases reported in 2005 and 2009; <1,000 cases up to week 44 in 2011[a]	None
Lymphatic filariasis	0.7 million	None	None
Dengue	0.5 million	27.2 cases per 100,000	Yes
Cysticercosis	0.4 million	<10,000 reported; incidence of 0.4 per 100,000	Yes
Leishmaniasis	67,000	<10,000 reported	Yes
Leprosy	33,953 registered cases	478 registered cases at the end of the first quarter of 2011	Unknown
Brucellosis	Not determined	24,000 reported; incidence of 2–3 per 100,000	Unknown
Leptospirosis	Not determined	Not determined	Unknown
Onchocerciasis	Near elimination	Near elimination	None

[a]The number of cases of malaria in 2005 is published in [5]. These numbers were updated in 2009 in an unpublished report (Secretaria de Salud, Anuario de Morbilidad 2009, Mexico D.F., 2010) and up to week 44 in 2011 (Secretaria de Salud, Boletin Epidemiologia, Semana 44, Mexico D.F., 2011).

doi:10.1371/journal.pntd.0001497.t001

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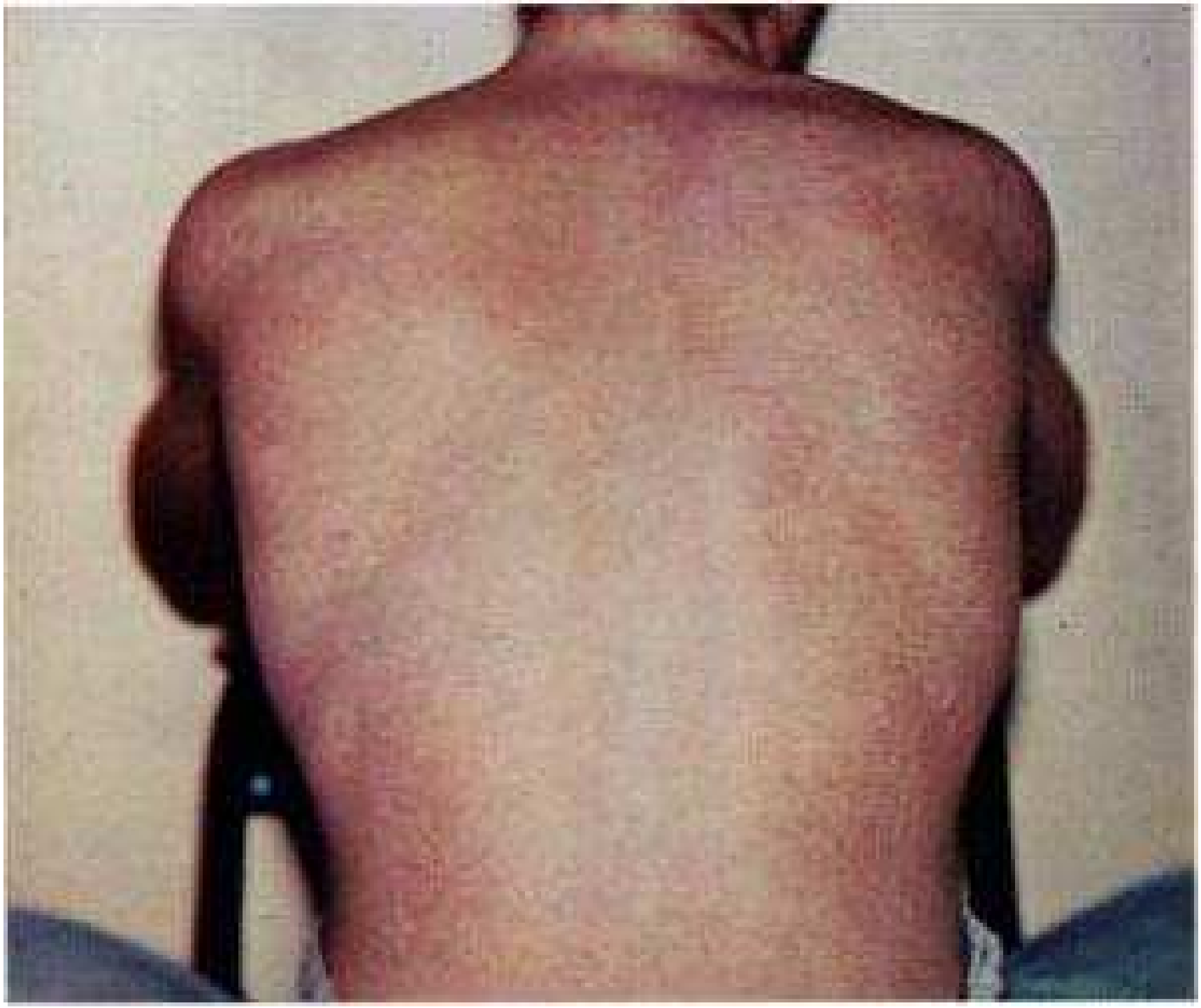
(www.ncfh.org)

Case

- 36 year-old Sonoran male
  - CC: fever, h/a, myalgia, arthralgia, retro-orbital pain, and nausea x 2 days. Returned to WA 1 week ago from his family home in Hermosillo, MX.
  - PMHx: HIV +
- Exam: Febrile (39 C), flushed, puritic maculopapular rash of the trunk, and petechiae of the lower limbs
- CXR: bilateral pleural effusions

Case

- Labs:
  - decreased leukocytes, lymphocytes, and platelets
  - Hct 52% Plt 90
  - Decreased serum albumin
    - Indicating ***vascular leak syndrome***
  - CD4 count 266, improving on HAART
  - ELISA: IgM specific Abs for etiology found 7 days following onset of symptoms



Dengue

- Causative Agent
  - Single, +-strand RNA virus
  - Genus *Flavivirus,* family *Flaviviridae*
  - Four related viruses DENV-1,2,3, and 4
    - Infection with one serotype provides lifelong immunity to that one only
      - Short-term (< 2-9 mos) cross-protection for the rest

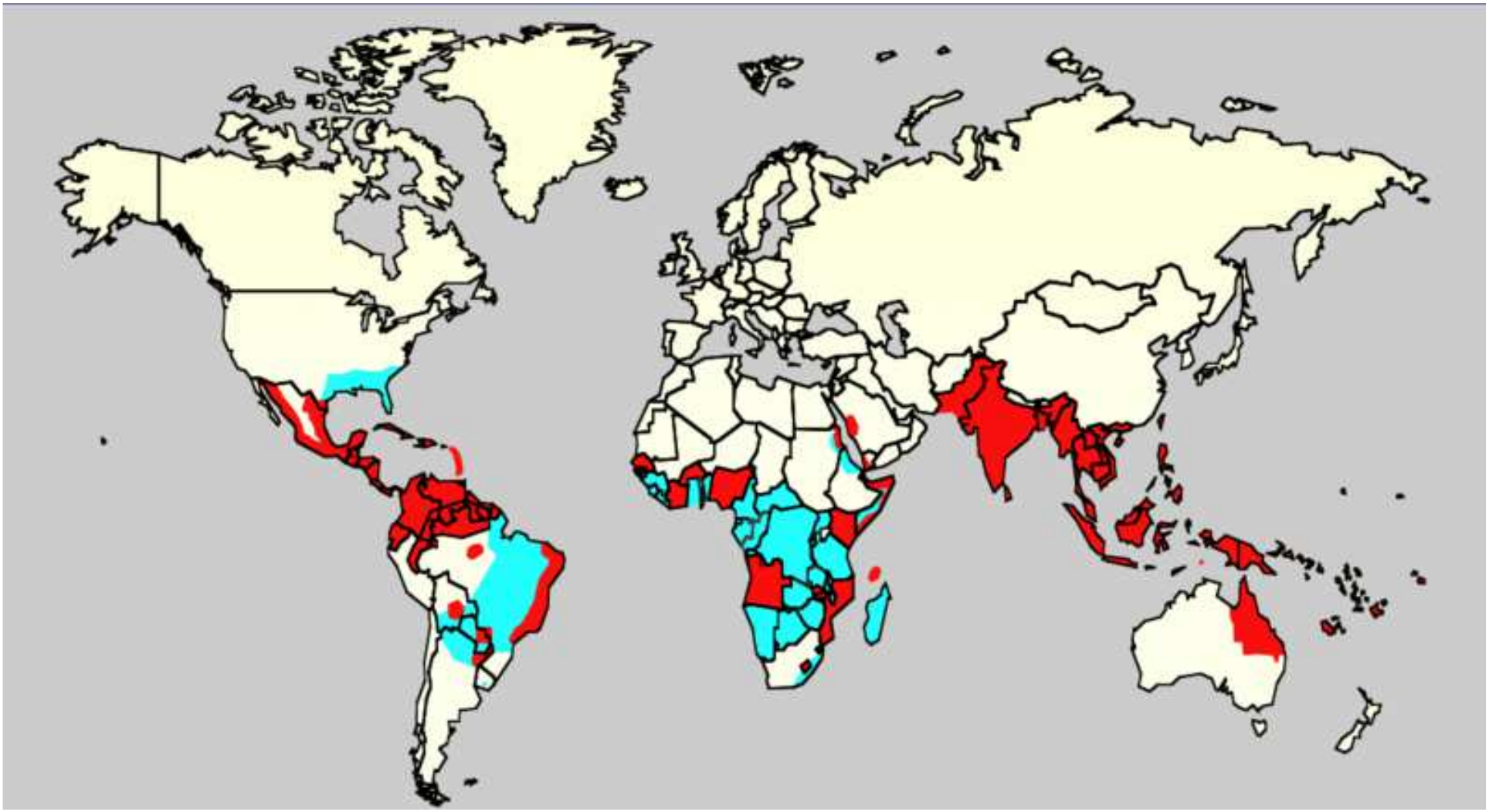
Dengue

- **Epidemiology**
  - "Breakbone Fever"
    - Described for several hundred years
    - Dengue Hemorrhagic Fever
      - First described in 20th century in SE Asia
  - Widespread (reported in over 100 countries)
    - Urban and residential areas
    - Similar geographic reach to malaria
      - Universally between Tropic of Cancer and Capricorn
    - Vector also present in subtropical regions (incl. Southern US)
    - Global Pandemic
      - 100 million cases/year
        - » 2.5 billion persons at risk
  - US Outbreaks
    - 7 along the Texas-Mexico border
    - 2 Florida (2009/2010)
    - 1 Hawaii (2001)

CDC Yellow Book, (2010) Map 5-1, Distribution of Dengue in the W. Hemisphere

Dengue

- Epidemiology
  - Transmission is *vector dependent*
    - *Aedes aegypti (*at times, *Aedes albopictus* or *A. polynesiensis)*
      - Peri-domestic, i.e. breed best in collections of freshwater around homes (e.g. old car tires, 50 gallon drums, standing water)
      - Female mosquito feeds on humans (*anthropophilic)*, **day-time feeders**
      - Requires blood from infected individual to become infected
        - » Viral replication (8-12 days), then *aedes* can transmit again
        - » I.e. *vector dependent* (no human-to-human cases recorded)
  - Less common modes
    - Blood transfusion, solid organ/bone marrow transplant, noscomial injury
    - Vertical transmission



(Clark, G., “Dengue: An emerging arboviral disease”

Dengue

- Surveillance
  - (2009) DENV infections nationally reportable to State Public Health Depts/CDC
  - Infection rates from GeoSentinel network
    - Leading cause of systemic febrile illness for travelers returning Caribbean, S. America, SE/SC Asia
    - 2nd most common cause of hospitalization among travelers returning from the tropics
  - Limited literature regarding vertical transmission
    - 24 cases described
    - Avg time of onset of neonatal symptoms 7 days
    - All cases with fever and thrombocytopenia
      - Many with hepatomegaly and hemorrhage

Dengue

- Clinical Presentation
  - Non-specific febrile illness to asymptomatic infection
    - Two main clinical syndromes:
      - Dengue Fever (DF)
      - Dengue Hemorrhagic Fever (DHF)

Dengue Fever (DF)

- Classic syndrome (50% of cases)
  - Defined by acute febrile illness with > 2 of the following symptoms:
    - Headache, **retro-orbital pain**, muscle/joint pain, rash (macular or maculopapular-generalized), hemorrhagic manifestations, leucopenia, flushed facies, nausea/vomiting.
    - Other symptoms
      - High Fever
      - Photophobia
      - Lymphadenopathy
      - Flushed skin, nausea, and vomiting
      - 1% of DF develop DHF as fever subsides
      - Subsequent infection with different DENV is associated with more severe disease
    - May have petechia, bleeding diathesis/spontaneous hemorrhage
      - not apart of DHF diagnosis
    - 1/3 have + tourniquet test of the forearm
      - following +BP cuff on for 5 min = > 20 petechiae on the forearm

Dengue Hemorrhagic Fever (DHF) or "Severe Dengue"

- Clinical presentation
  - Initially non-specific febrile illness
    - May have a petechial rash
    - Any hemorrhage
    - Systemic vascular leak
  - Hallmark: evidence of vascular permeability and plasma leakage (days 3-7)
    - (incl. increased Hct by >20% above avg for age)
      - Or decrease by > 20% after fluid replacement
    - May have edema and effusions (pleural, cardiac, etc…)
    - Also restless, lethargic, abdominal pain/tender hepatomegaly
    - Labs: *pancytopenia* (low platelets, leukopenia, anemia)
      - Virus can be isolated by PCR
      - IgM/IgG can be detected by ELISA
    - Low platelets (< 100, 000) **not indicative of DHF itself
    - Ascites, or hypoproteinemia

Dengue Shock Syndrome (DSS)

- Hypotension
- Narrow pulse pressure (<20 mmHg)
- Frank shock

Differential Diagnosis

- Fevers with arthralgia or rash
  - *Arborviruses (*chikyngunya, West Nile, Ross River, Colorado Tick Fever)
  - *Other viruses* (rubella, measles, herpes, enteroviruses)
  - *Bacteria* (meningococcus, typhoid)
  - *Spirochetes* (leptospirosis, Lyme disease, relapsing fever)
  - *Rickettsiae* (typhus, Rocky Mtn Spotted Fever)
  - *Parasites* (malaria)
- Fevers with hemorrhage
  - *Arboviruses* (yellow fever, Rift Valley, etc…)
  - *Other viruses* (hanta, hepatitis, Lassa, S. Amer hemorrhagic fevers, Ebola, Marburg)
  - *DIC*
  - *Drug reaction*

Dengue-Diagnosis

- With compatible travel history/recent stay in endemic area + symptom profile:
  - DENV sequences/antigens
    - Nonstructural protein 1; NS 1 antigen
      - (acute febrile stage)
    - IgM anti-DENV
      - (+ > 5 days after sx onset)
  - Anti-dengue IgG ~ indeterminate past infection
    * Cross--reactivity with other flaviviruses
      - West Nile, Yellow, Fever, Japanese Enchephalitis
      - Prev flavivirus vaccination : false + anti-dengue IgG

Dengue-Management

- Dengue Fever
  - Most cases are self-limiting
  - Symptomatic care
    - Hydration and anti-pyretics (acetaminophen)
      - Treatment of headache, back pain, and myalgias
      - Avoid NSAIDs/ASA ~ bleeding risk!
    - Rash and lethargy may remain during recovery.
  - Recommend immediate evaluation if
    - Fever > hypothermia
    - Severe abdominal pain
    - Persistent vomiting
    - Bleeding
    - Dyspnea
    - Altered mental status

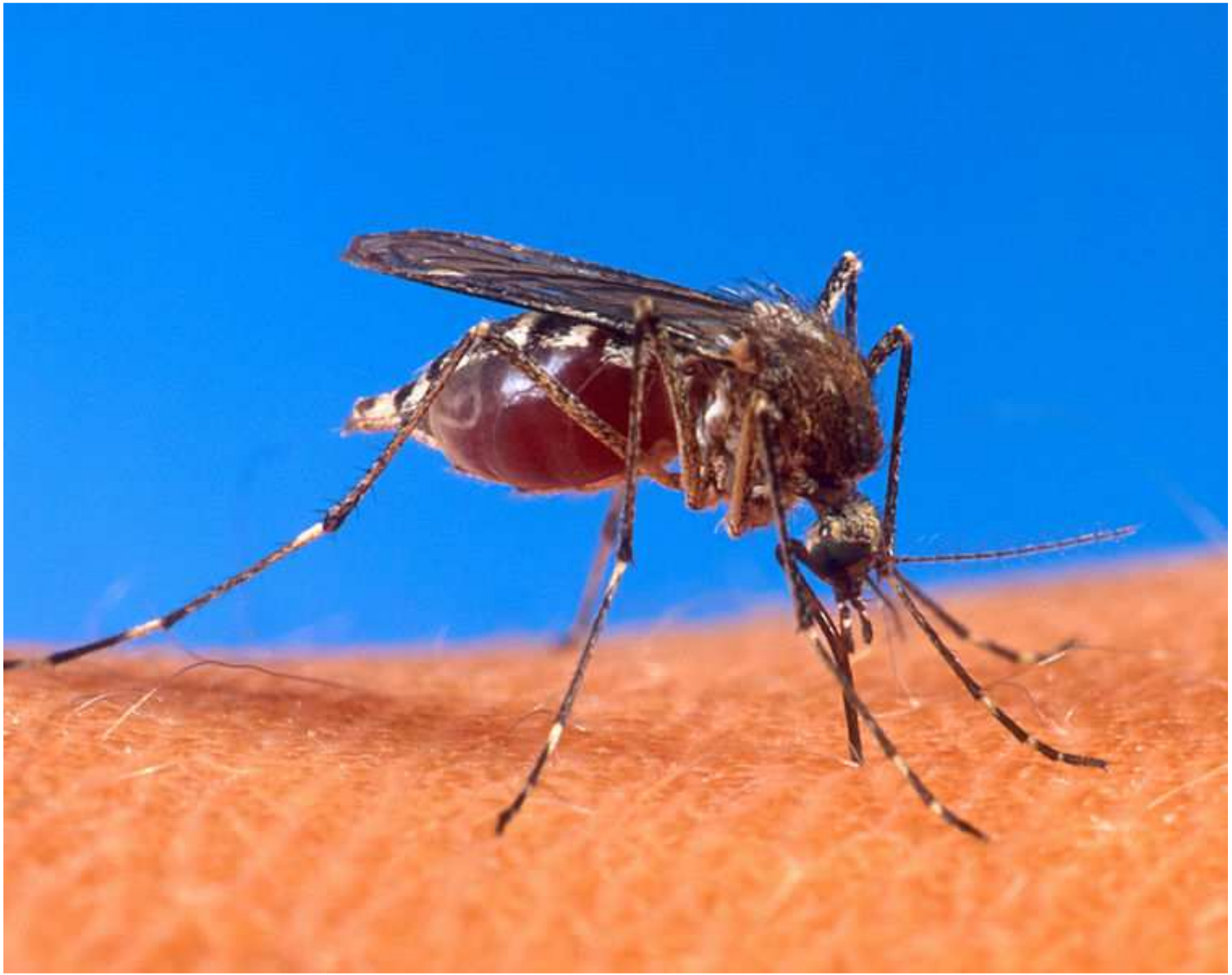
Dengue-Management

- **Dengue Fever (DF)**
    - Bed rest and oral fluids
        - Instruction on warning signs for DHF/DSS
            - » Change from fever to hypothermia
            - » Severe abdominal pain
            - » Persistent vomiting
            - » Bleeding
            - » Difficulty breathing
            - » Altered mental status
- **Dengue Hemorrhagic Fever (DHF)/Dengue Shock Syndrome (DSS**
    - Hospitalization with close monitoring of vital signs
    - Lab monitoring (Hct/Plts)
    - Montoring central venous pressure (CVP)
    - Prompt and judicious IV crystalloids or IV colloids if shock persists

      *Be wary of fluid overload and stop infusions if occurs

Dengue-Prevention

- Control of the *Aedes* mosquitoes
  - Public education to remove collections of standing water and use of insecticides during epidemics
  - Cover or clean out water storage barrels
  - Treating stored water with larvicides
- Avoid bites!
  - Highest risk of *Aedes* bites (early morning, several hours after dawn, late afternoon-prior to sunset)
  - Good screening of lodging facilities
    - *Aedes* live indoors: found in dark, cool places
  - Adequate coverage by clothing (early am/late pm)
  - Insect repellant to skin and clothing (e.g. permethrin)
    - Use of DEET!
- Vaccine in development
  - Tetravalent vaccines in development
    - Live attenuated
    - Recombinant DNA



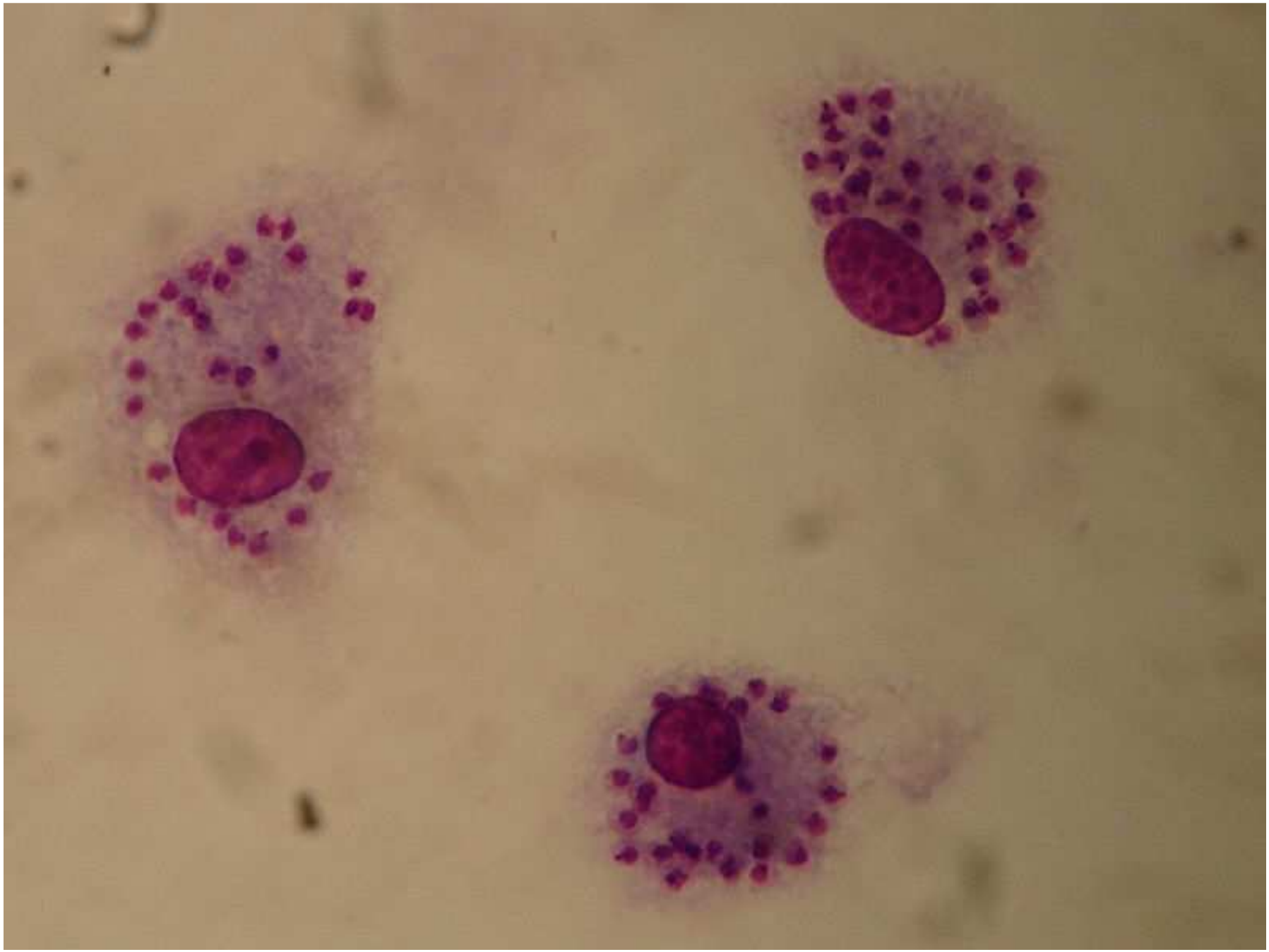
Case

- 16 year-old Guatemalan girl
  - 1 year of skin lesions on arm and abdomen
  - Initially began as a painless papule
    - Enlarged slowly over the past 10 months
  - Now
    - Crusted with scale and central ulceration
- ROS: LAD (axillary and inguinal)

(Photo: CDC, B. Arana, MERTU, Guatemala)

Case

- Data:
  - Punch biopsy
    - Intracellular Leishman-Donovan bodies



(CDC, DPDx)

Case

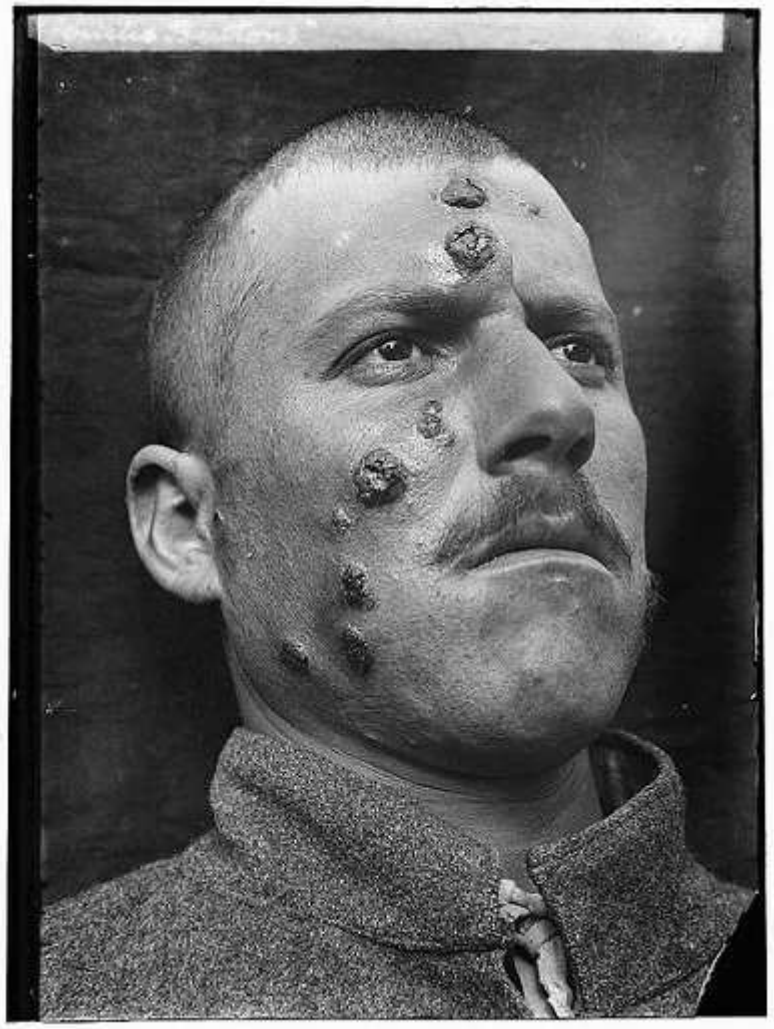
- Data:
  - Tissue culture and PCR assay confirmed diagnosis
    - *Leishmania brazilensis peruviana*

Causative Agent

- 1903: Protozoan first described by Leishman and Donovan
  - Complex grouping of species
  - ~21 species known, 17 cause human disease
    - Visceral
      - Systemic (fever, weight loss, hepatosplenomegaly)
      - Fatal without treatment
    - Cutaneous
    - Mucocutaneous

Causative Agent

- **<u>Cutaneous</u>** ***(most common)***
  - Aleppo/Jericho buttons
  - Baghdad boil
  - Chiclero ulcer
  - Ulcera de Bejuco
  - Pendjeh sore
- **<u>Mucocutaneous</u>**
  - Espundia
- **<u>Visceral</u>** (***most severe)***
  - Burdwan fever
  - Cachectic fever
  - Kala Azar
  - Ponos



Leishmaniaisis

- Trypomastid parasite
  - Flagellated protozoa
- Genus *Leishmania*
- Transmitted by phlebotomine sandfly
  - 500 identified species
  - 30 known to transmit *Leishmania*
  - Only female sandfly transmits parasites
    - *Lutzomyia* (New World*)*
    - *Phlebotomus* (Old World*)*
- Zoonotic (mostly CL)
  - Dogs (some VL)
  - Opossum
  - Sloth
  - Anteater
- Anthroponotic (both VL/CL)
  - Largest focus in South West Asia
  - Related to population density, poor sanitation, vector exposure, cross-border migration

Vector

Epidemiology

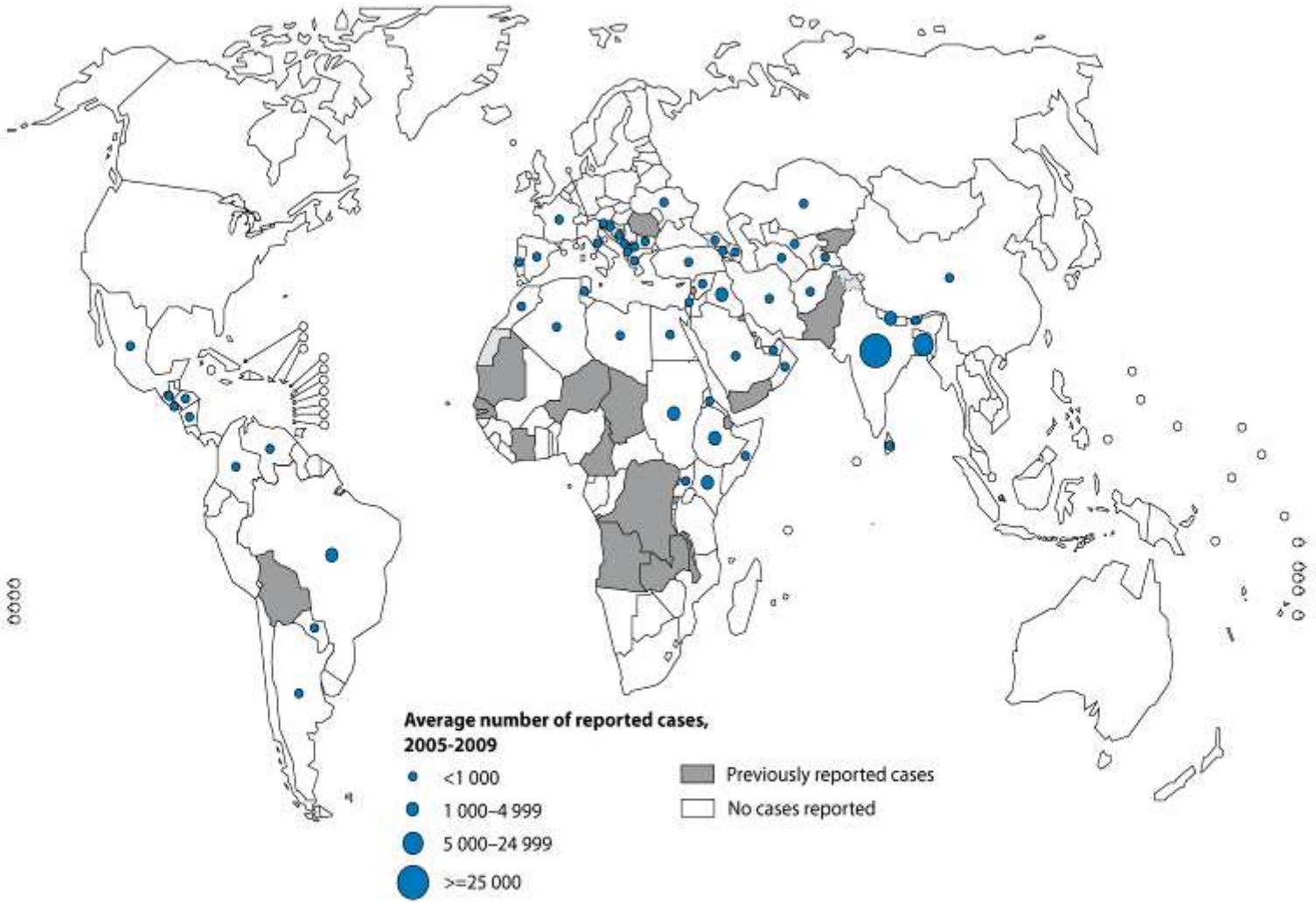
- Endemic in 88 countries (72 developing)
  - Africa, Asia, Europe, N/S America
  - 12 million cases worldwide
    - 1.5-2 million new cases/year
  - Greater incidence in Old World
    - Persian Gulf/Iraq soliders (2002-03)
      - 22 cases
      - *Leishmania major*
      - 150 cases recorded since 2003
  - New World
    - Highest incidence in Peru and Brazil

- **Risk factors**
  - Rural areas/poverty
  - Congested urban environments
  - Difficult healthcare access
  - Malnutrition: famine, complex emergencies, mass population movement
  - Malnutrition
  - Displacement
  - Poor housing
  - Illiteracy
  - Gender discrimination
  - Immunosuppression
  - Environmental disruption
    - Deforestation
    - Dam building
    - Irrigation schemes
    - Urbanization

Epidemiology

- **Economic impact**
  - 2.4 million DALYs
  - 70,000 deaths/year
- **90% cutaneous infections**
  - Afghanistan
  - Pakistan
  - Syria
  - Saudi Arabia
  - Algeria
  - Iran
  - Brazil
  - Peru
- **90% visceral infections**
  - India
  - Bangladesh
  - Nepal
  - Sudan
  - Brazil
- **90% mucocutaneous infections**
  - Bolivia
  - Peru
  - Brazil

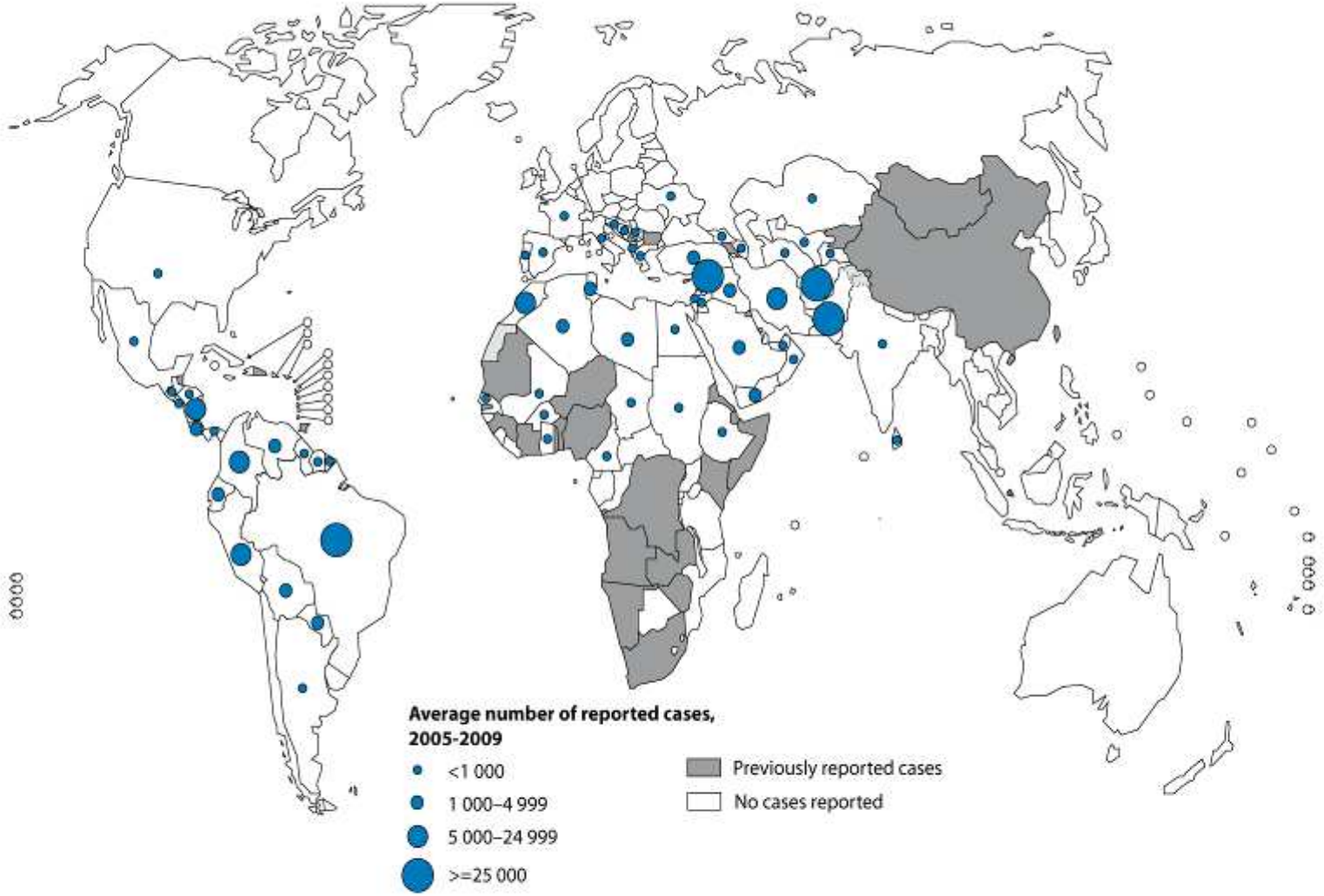
Distribution of visceral leishmaniasis, worldwide, 2009



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

World Health Organization

Distribution of cutaneous leishmaniasis, worldwide, 2009



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

World Health Organization

<u>New World Species</u>

L. mexicanna complex

- ***L. m. mexicana***
- ***L. m. amazonensis***
- ***L. m. venezuelensis***

***Viannia* subgenus**

- ***L. b. guyensis***
- ***L. b. panamensis***
- ***L. b. braziliensis***
- ***L. b. peruviana***
- ***L. donovani* species**
- ***L. d. chagasi***

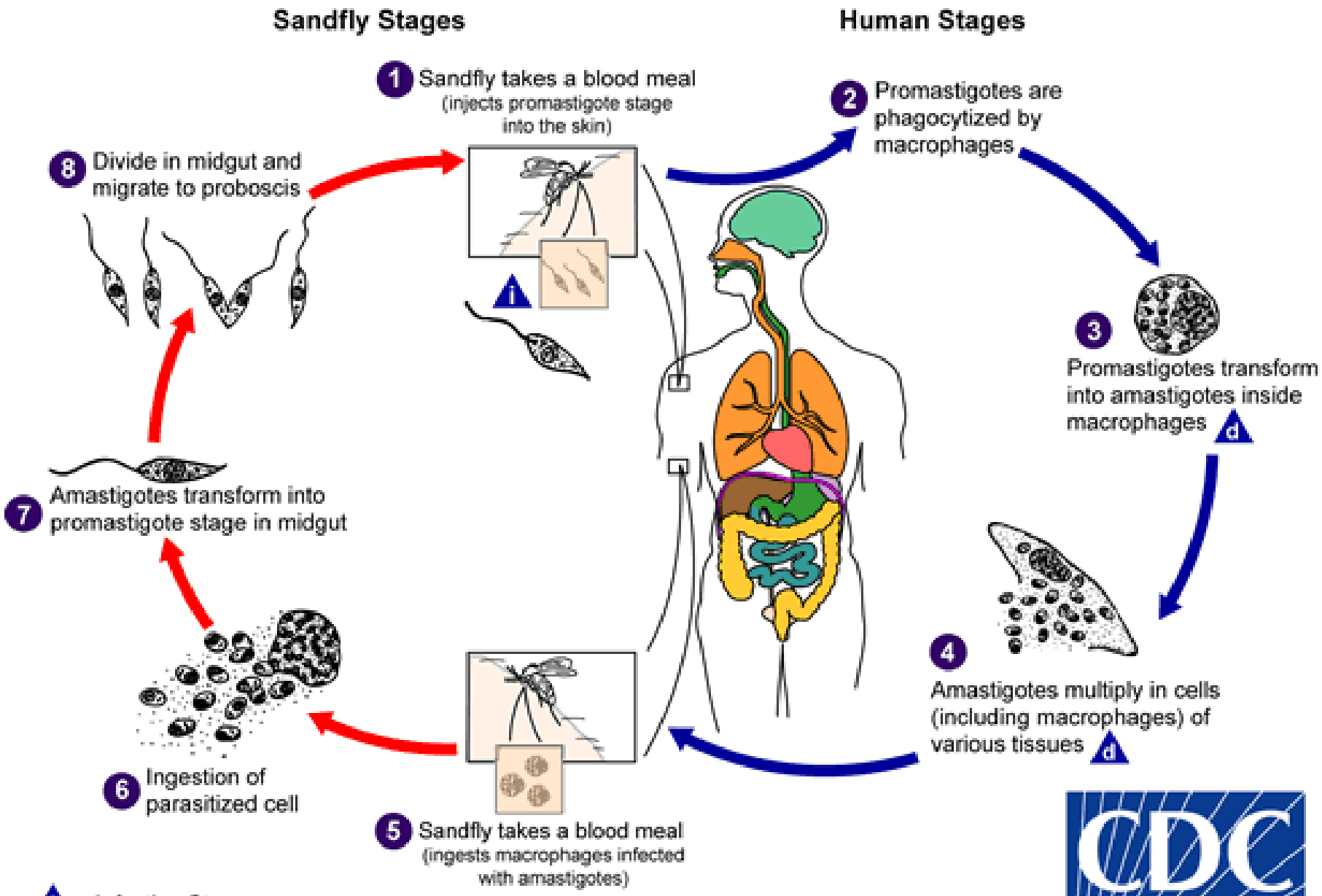
(Source: WHO/NTD/IDM HIV/AIDS, Tuberculosis and Malaria (HTM) World Health Organization, October 2010)

Causative Agents

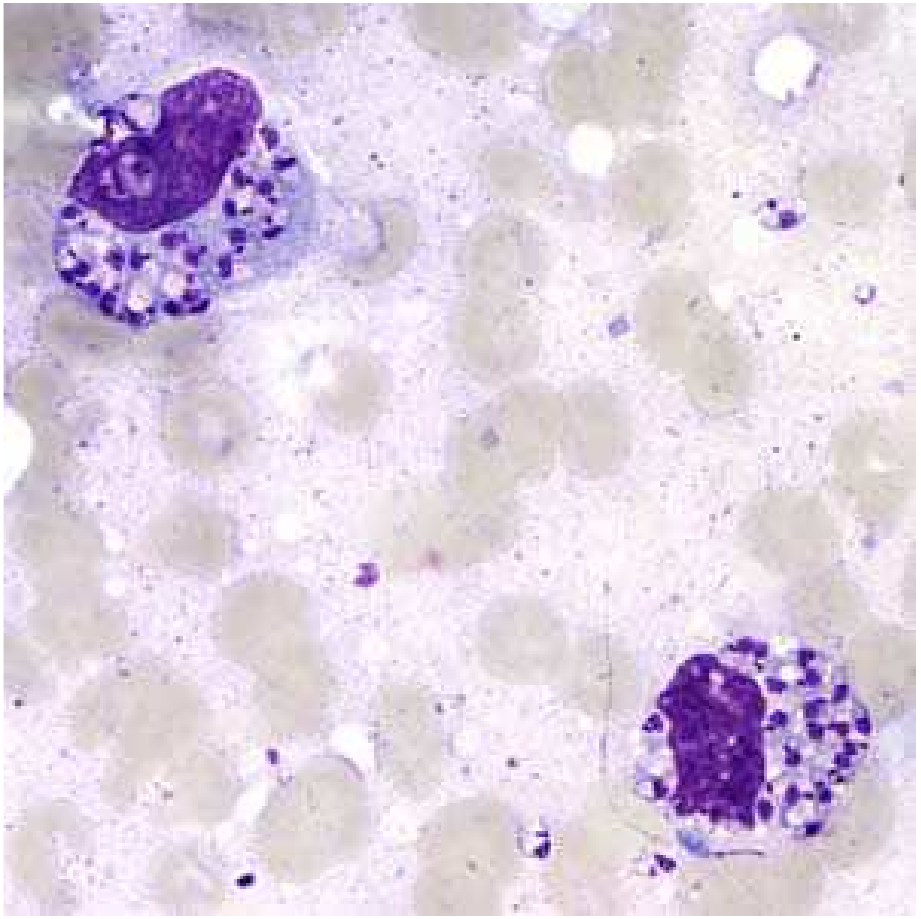
- Old World
  - *Leishmania donovani*
  - *Leishmania infantum*
  - *Leishmania major* (Dry, desert)
  - *Leishmania tropica* (Urban)
- New World
  - *Leishmania leishmania*
    - *L. mexicana*
    - *L. chagasi* (visceral)
    - *L. amazonensis*
  - *Leishmania viannia*
    - *L. braziliensis*
    - *L. guyanensis*
    - *L. panamensis*

Causative Agent

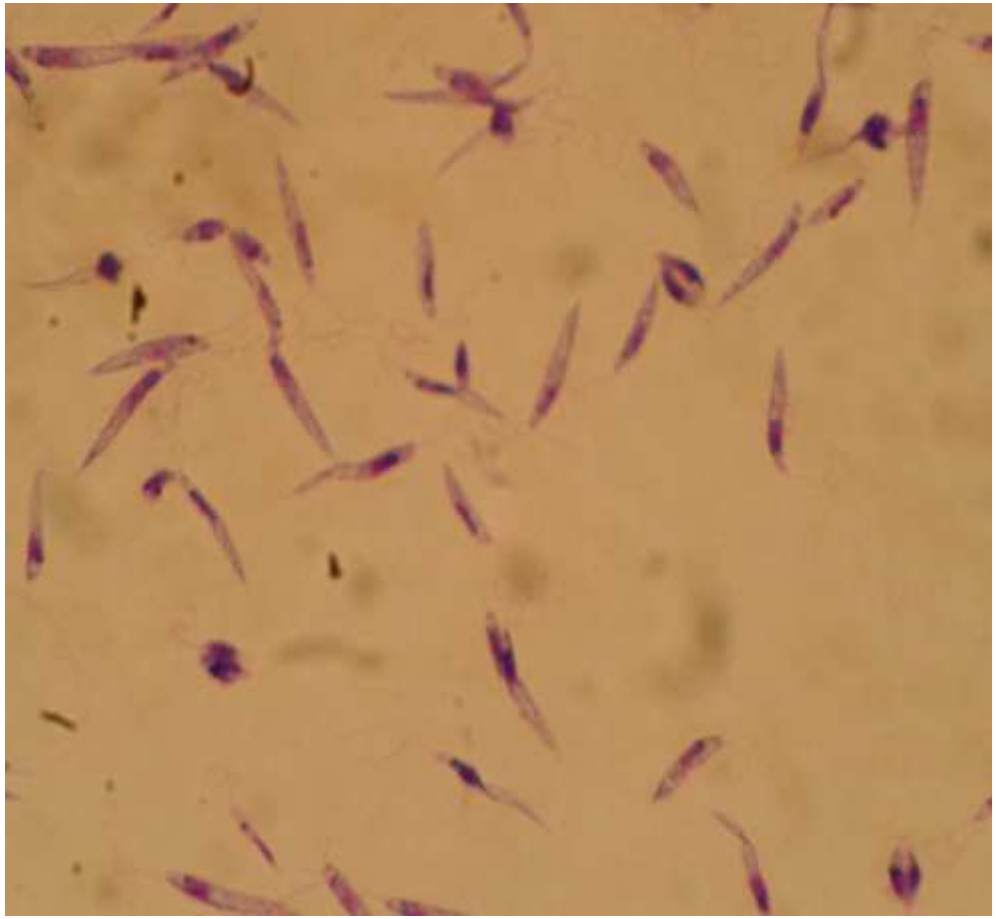
- Protozoa
  - Promastigote
    - Anterior flagellum
    - Develops in sandfly as procyclic parasites
    - *Metacyclic promastigote*: infectious form
      - Develops in foregut/hindgut (species dependent)
      - Enters human host with sandfly bite
      - Is ingested by host macrophages
      - Survives the lysosomal environment to become amastigote
  - Amastigote
    - Obligate, intracellular, non-motile
    - Cause of human disease
    - Affects cellular immunity
    - Transmissable form


Sandfly Stages
Human Stages
1 Sandfly takes a blood meal
(injects promastigote stage into the skin)
2 Promastigotes are phagocytized by macrophages
3 Promastigotes transform into amastigotes inside macrophages d
4 Amastigotes multiply in cells (including macrophages) of various tissues d
5 Sandfly takes a blood meal
(ingests macrophages infected with amastigotes)
6 Ingestion of parasitized cell
7 Amastigotes transform into promastigote stage in midgut
8 Divide in midgut and migrate to proboscis
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™
http://www.dpd.cdc.gov/dpdx

Amastigote



Promastigote



(CDC, DPDx, “Leishmaniasis” Microscopy)

Clinical Manifestations

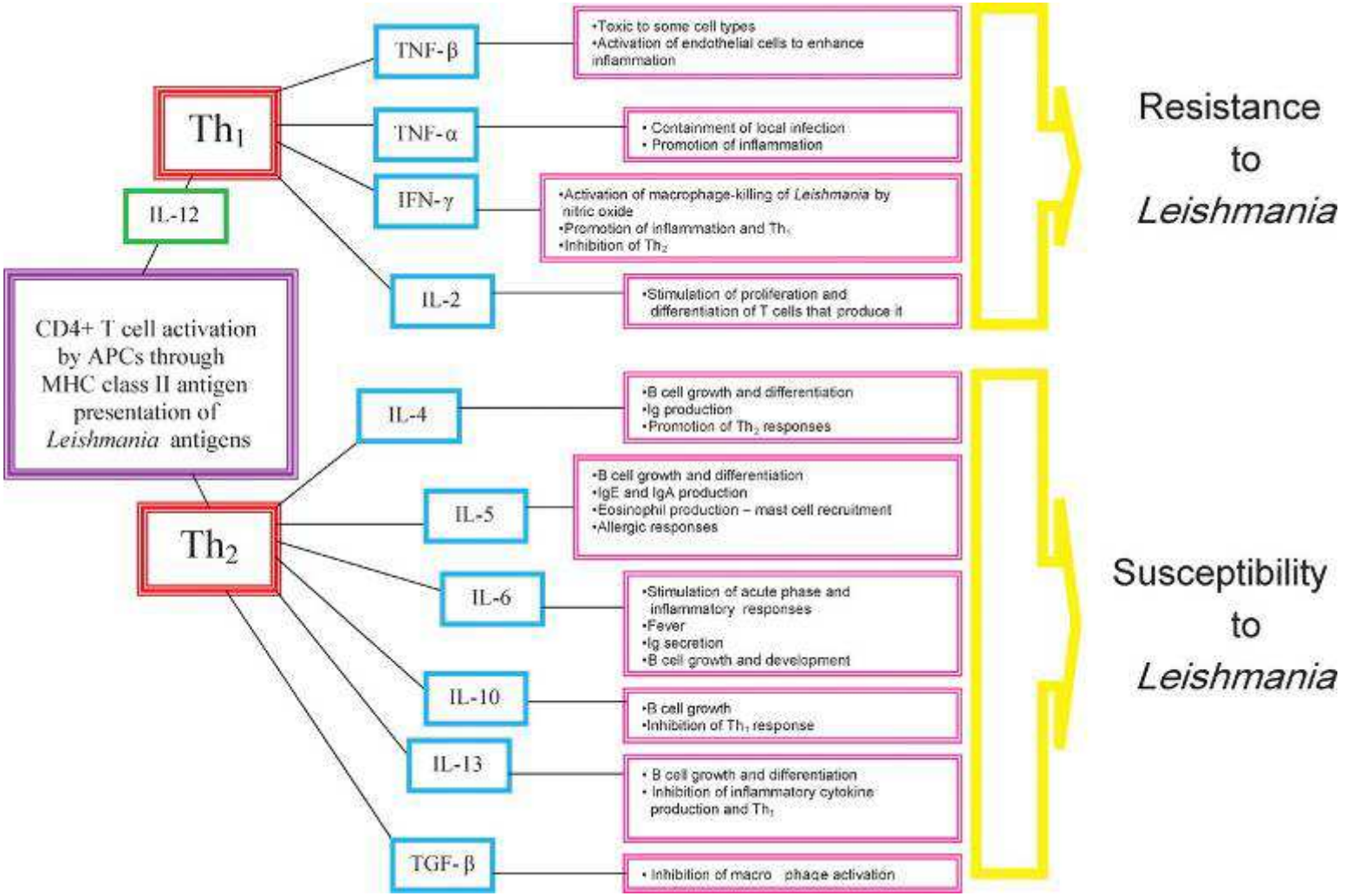
- Range dependent upon
  - Innate and timely acquired T-cell dependent immune responses (CMI)
    - Affected by immunogenetic polymorphisms
- Local versus disseminated/metastatic infection
  - Most symptomatic infections remain localized in the skin and adjacent lymph nodes
  - Some species escape to nasal and oropharyngeal mucosa, cutaneous sites
    - Liver
    - Spleen
    - Bone marrow
    - Distant lymph nodes (“kala azar”)

VL: Clinical Manifestations

- Fever
- Weight loss
- Organomegaly
- Adenopathy
- Anemia
- Darkening skin
- Leukopenia/thrombocytopenia

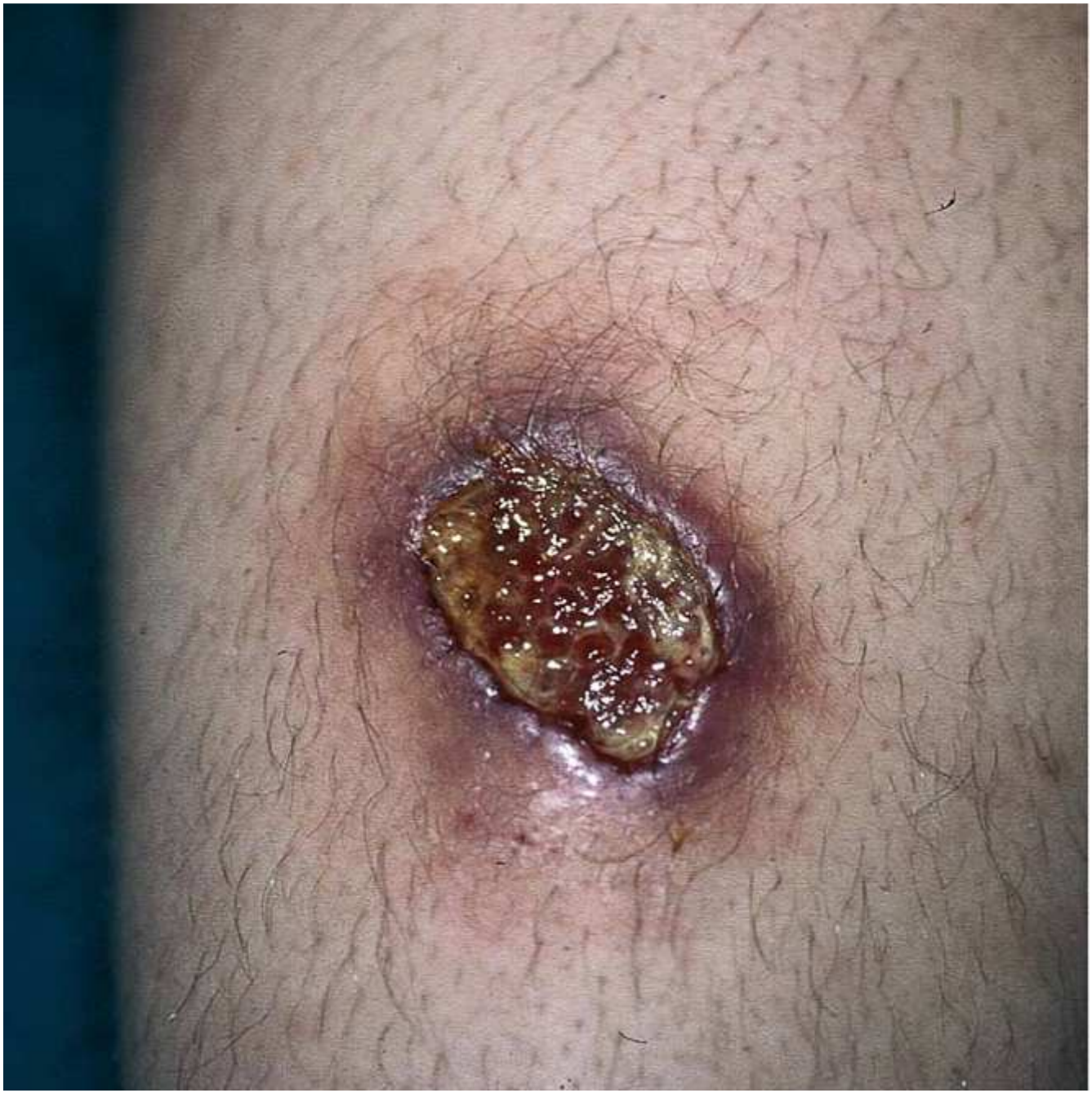
- Ulcerative skin lesions
- Destructive mucosal inflammation
- Disseminated visceral infection (‘kala azar’)
- Post Kala-azar Dermal Leishmaniasis

Antagonistic Th1 and Th2 responses that confer either resistance or susceptibility to Leishmania.

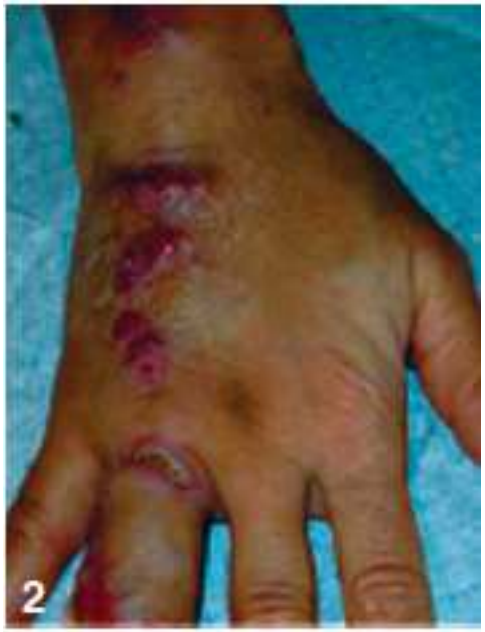


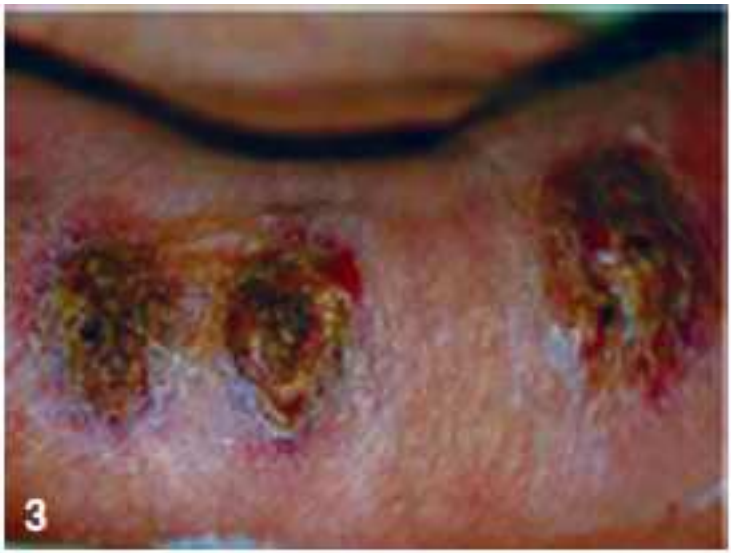
Dunning N Bioscience Horizons 2009;2:73-82

BioscienceHorizons



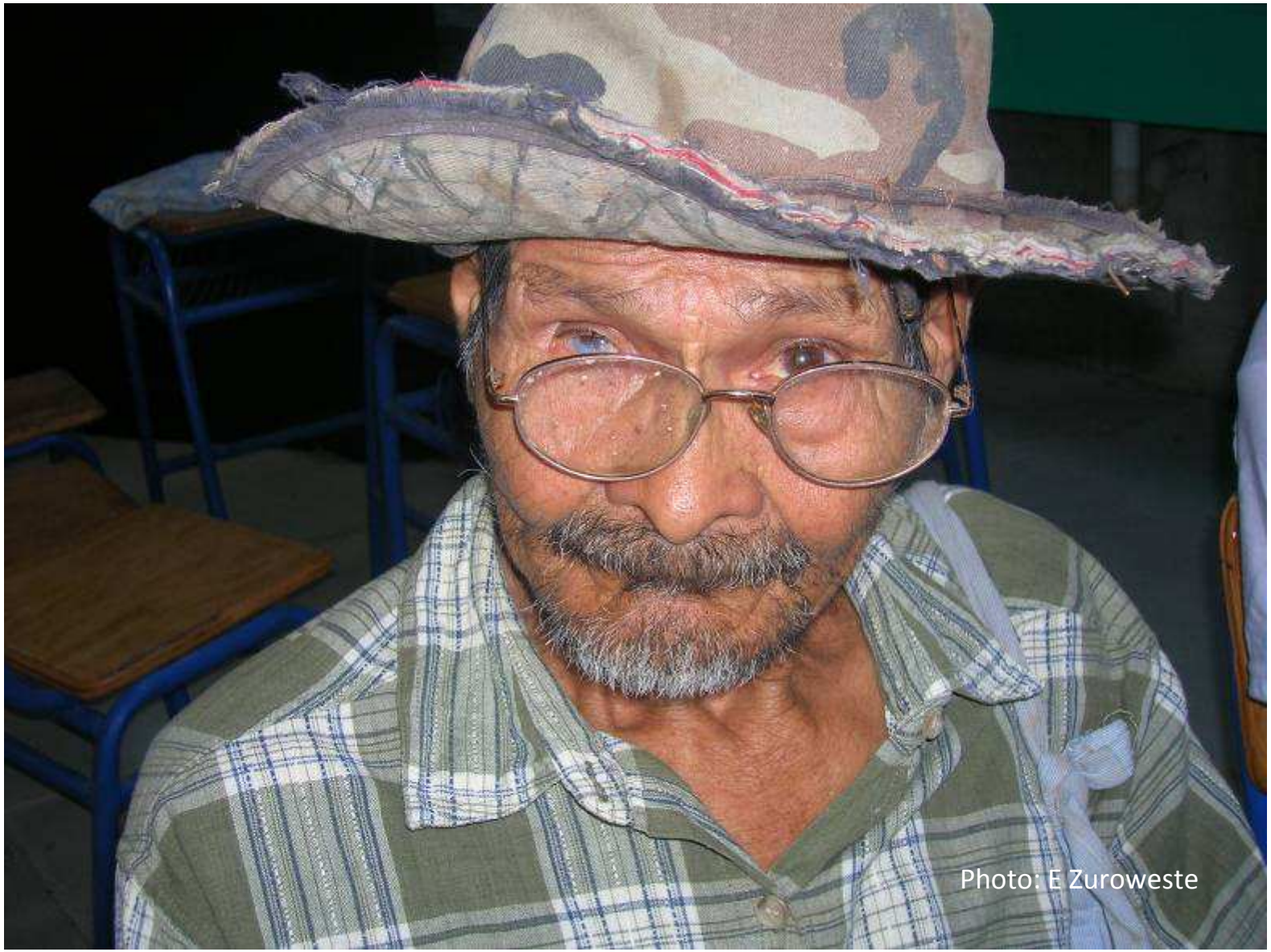
(BMJ *329 : 842 7 October 2004)*



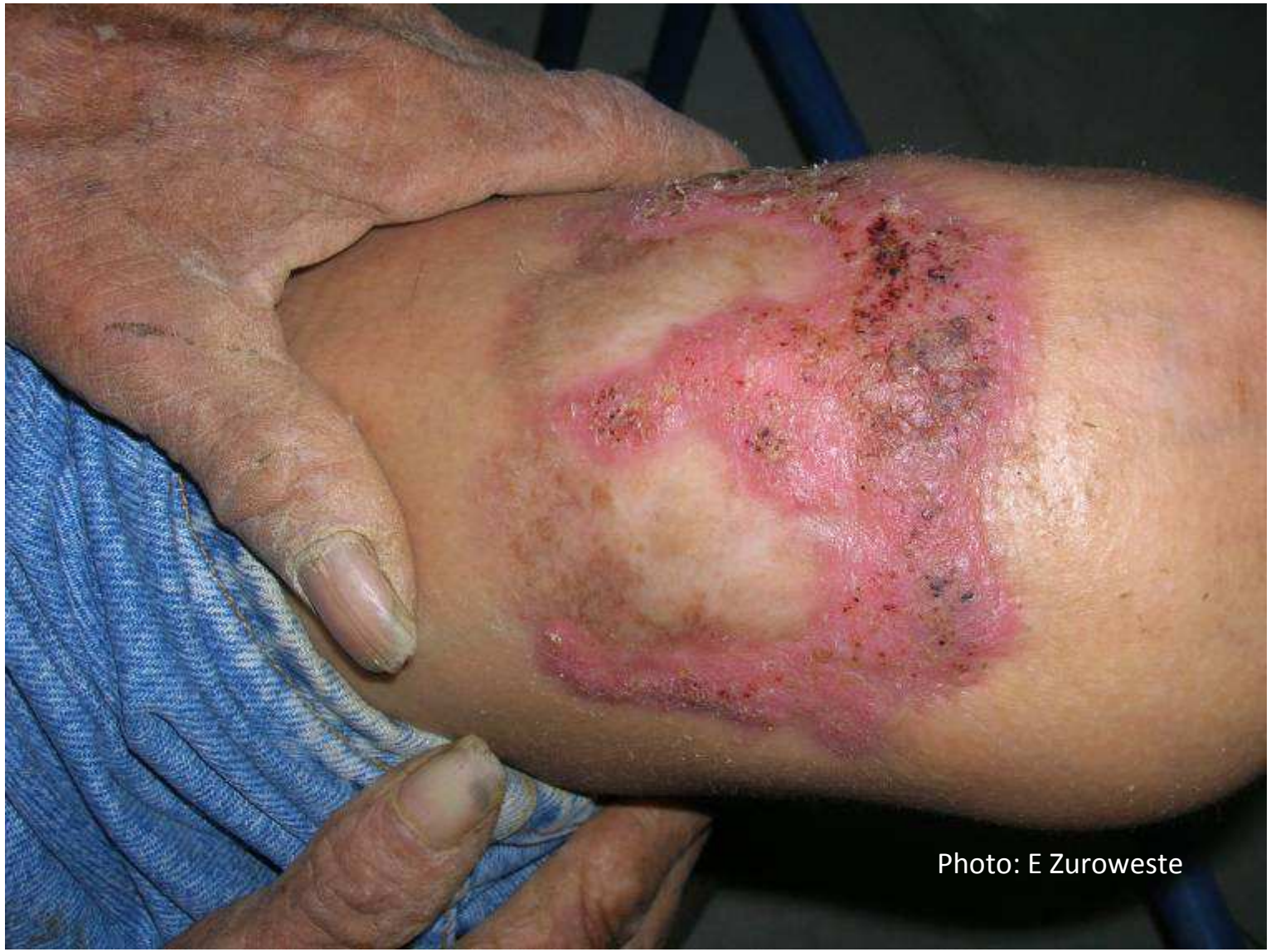


(Goldman, Cecil's Medicine 24th ed., Fig. 356-2)

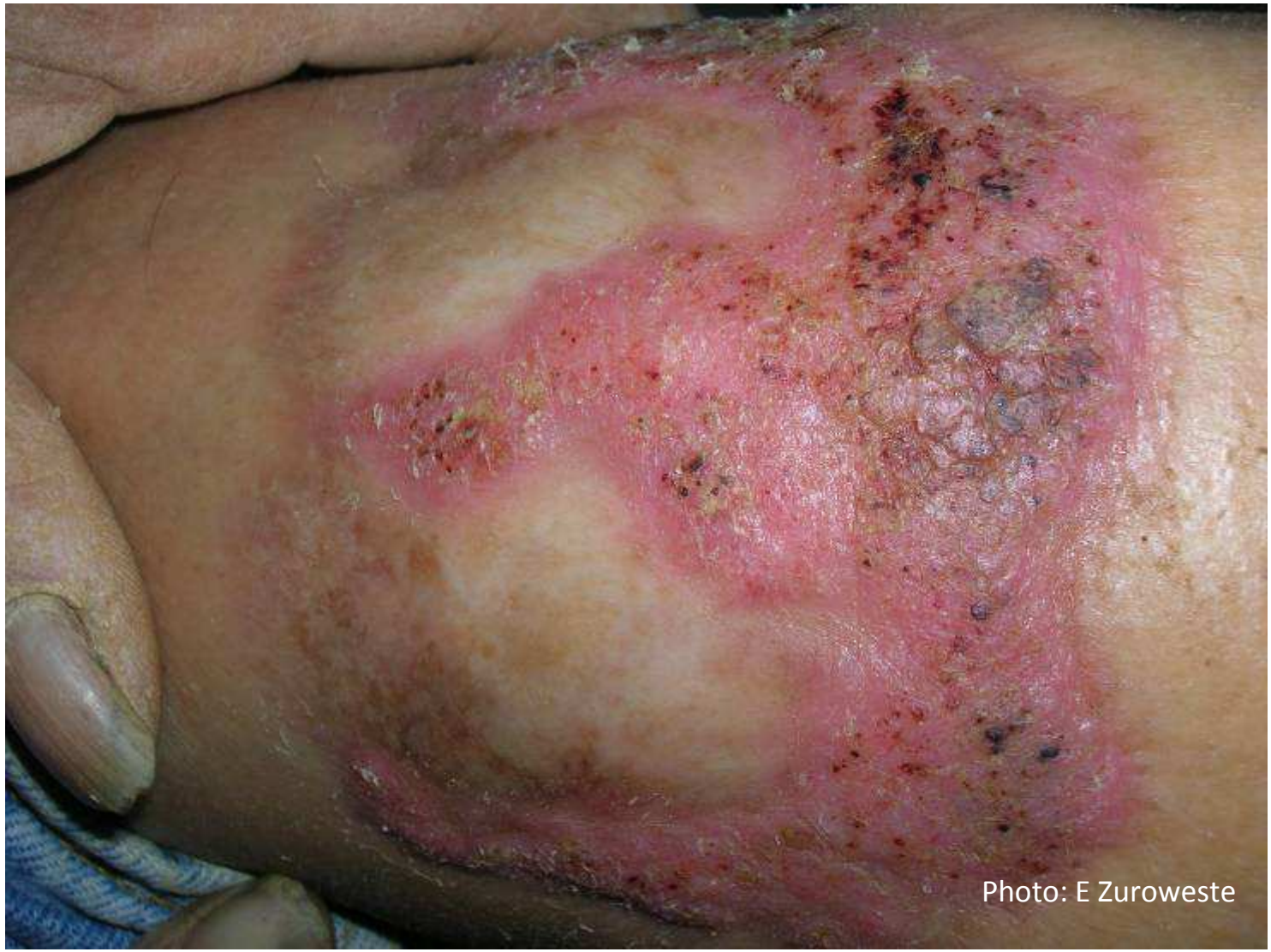
Cutaneous Leishmaniasis 2007



Cutaneous Leishmaniasis 2007

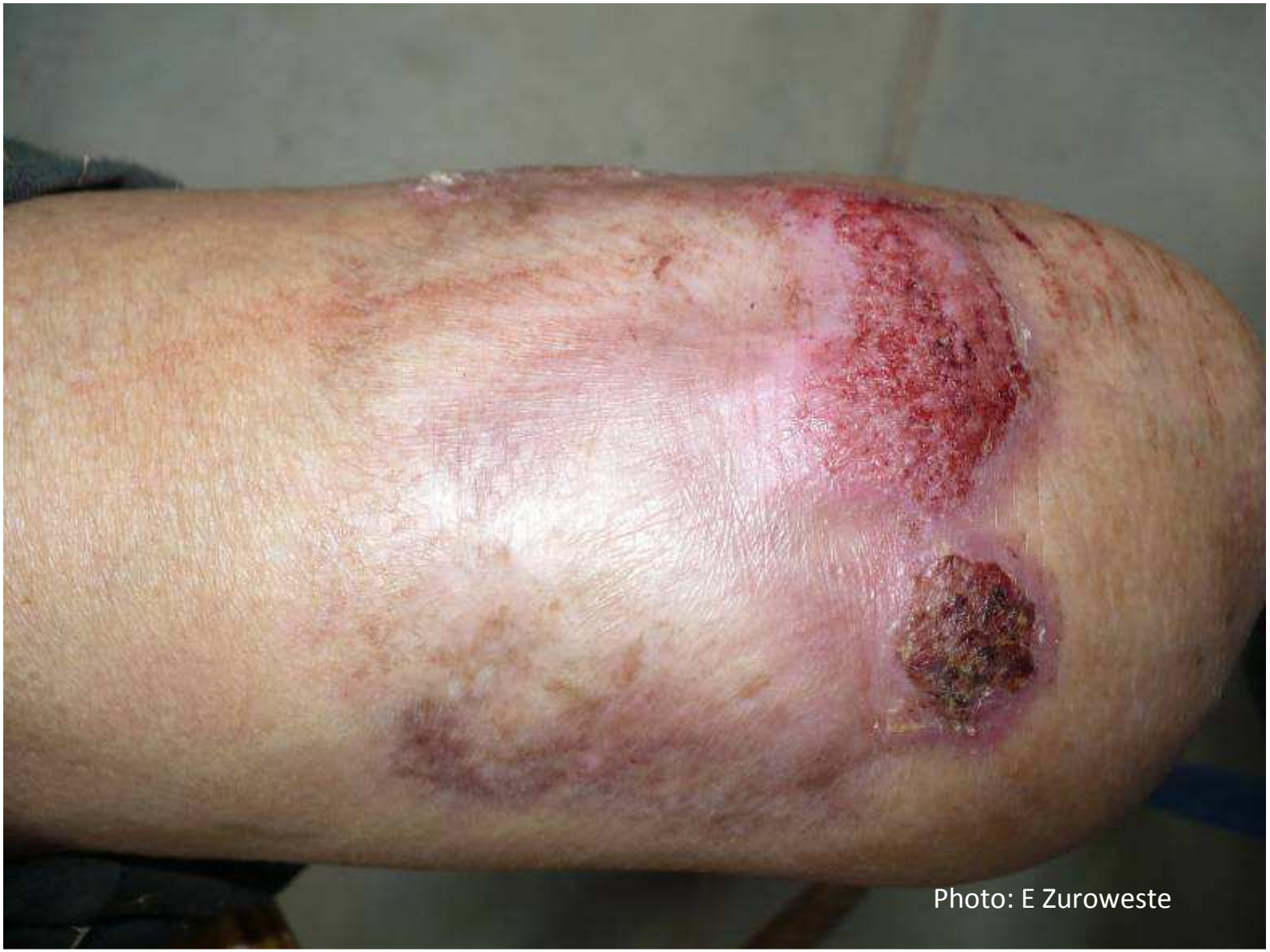


Cutaneous Leishmaniasis 2007

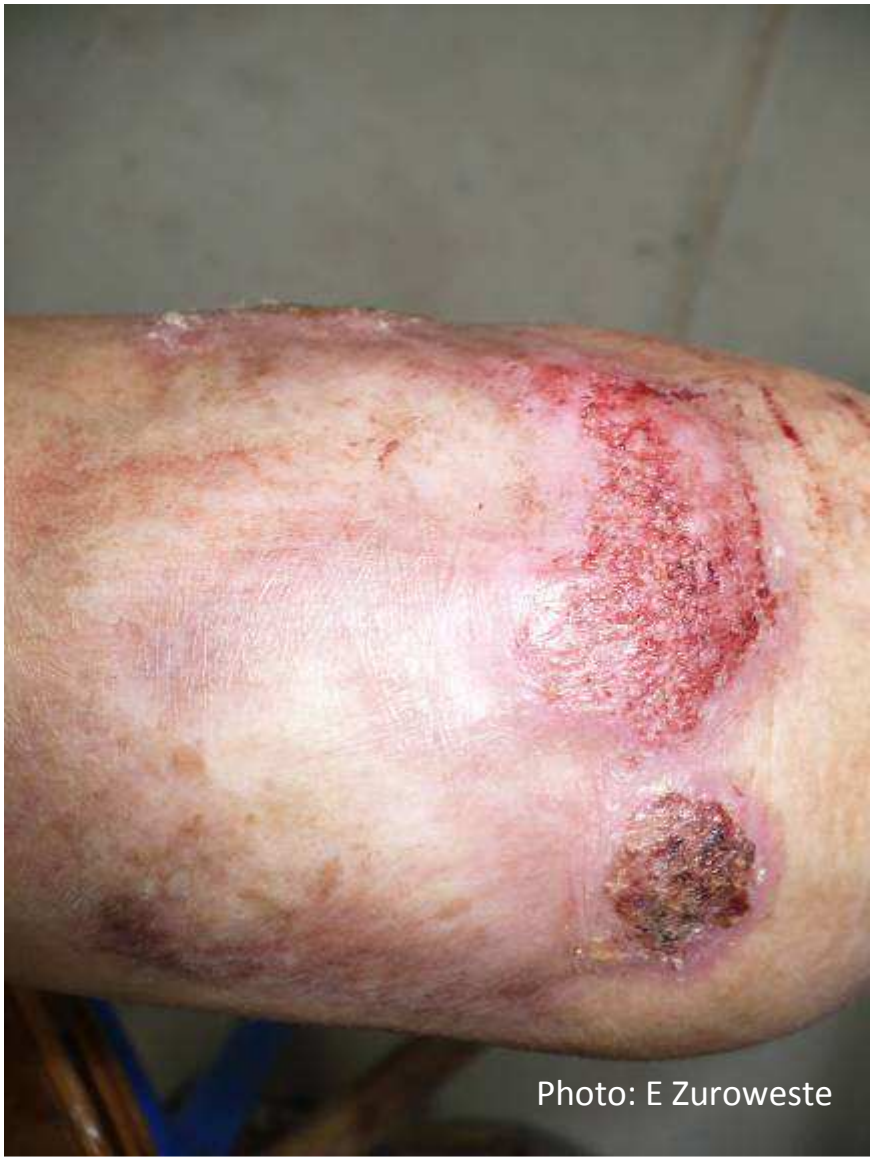


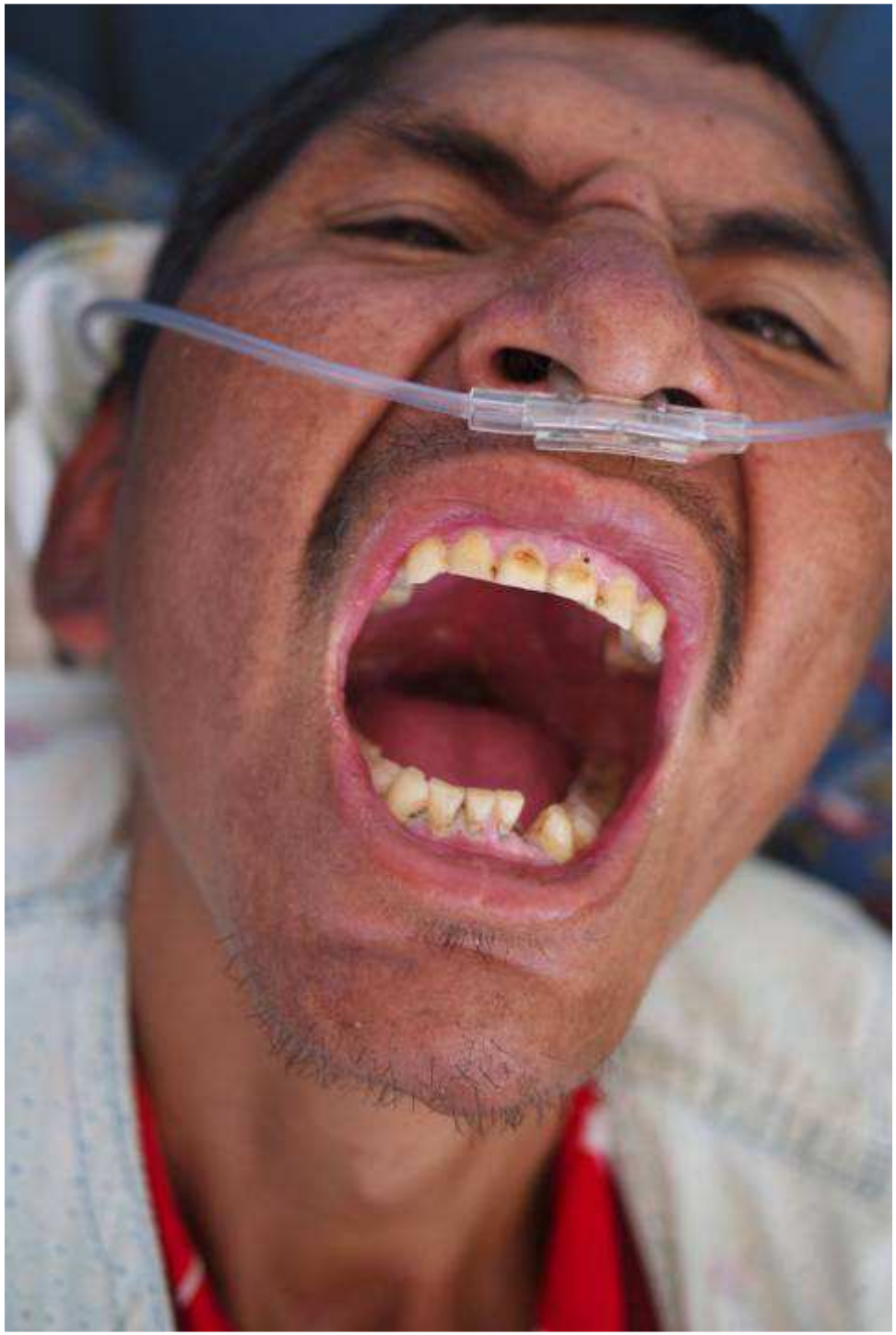
Cutaneous Leishmaniasis 2008

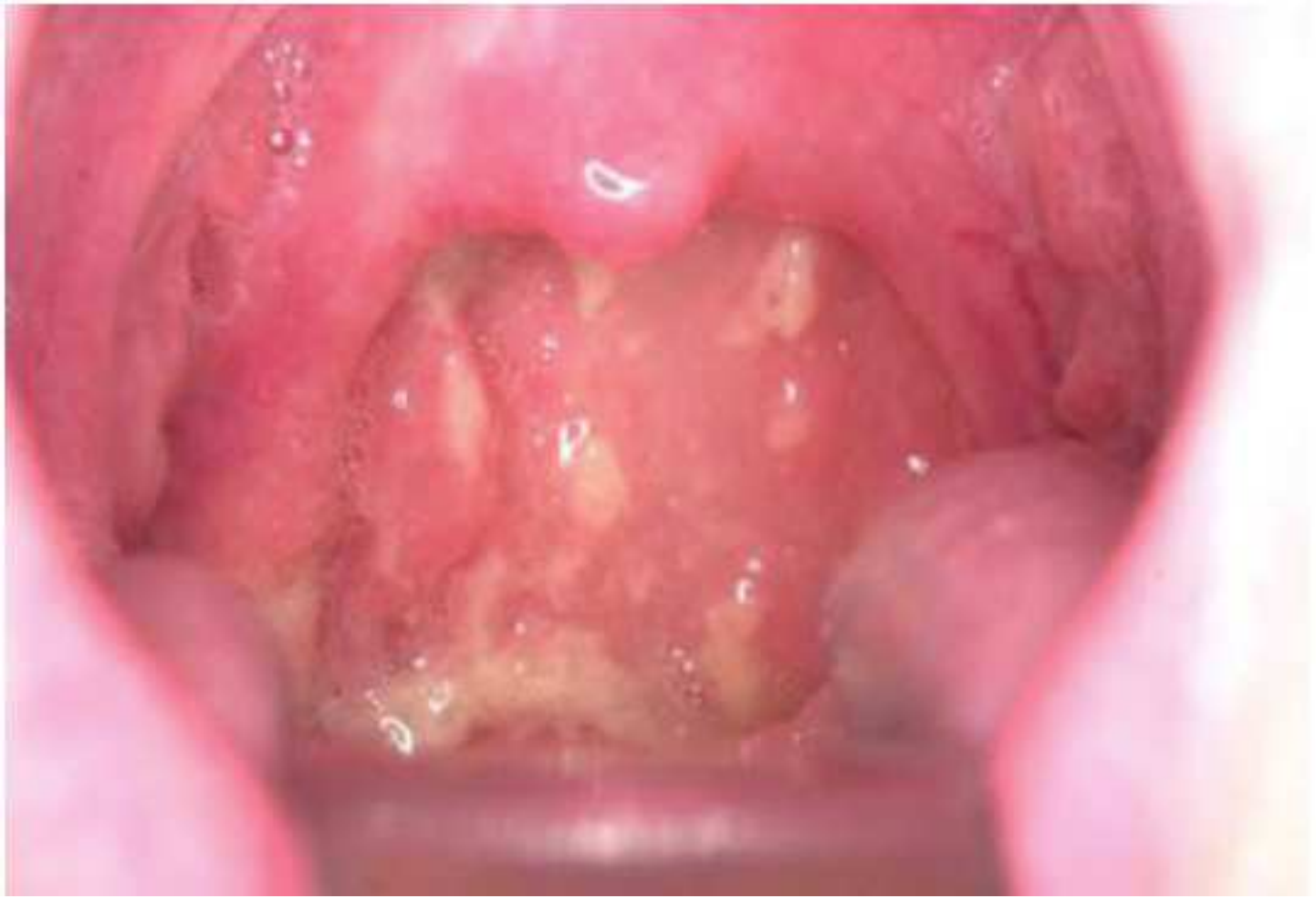
Cutaneous Leishmaniasis 2008



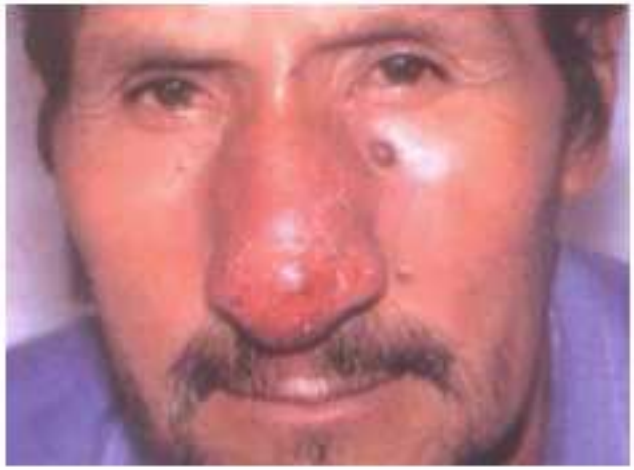
Cutaneous Leishmaniasis 2008

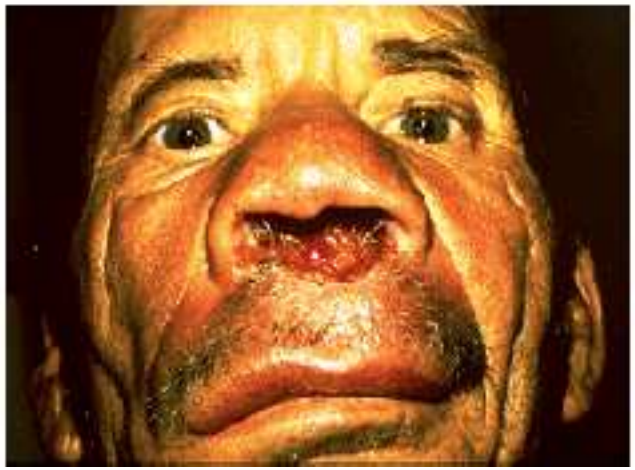


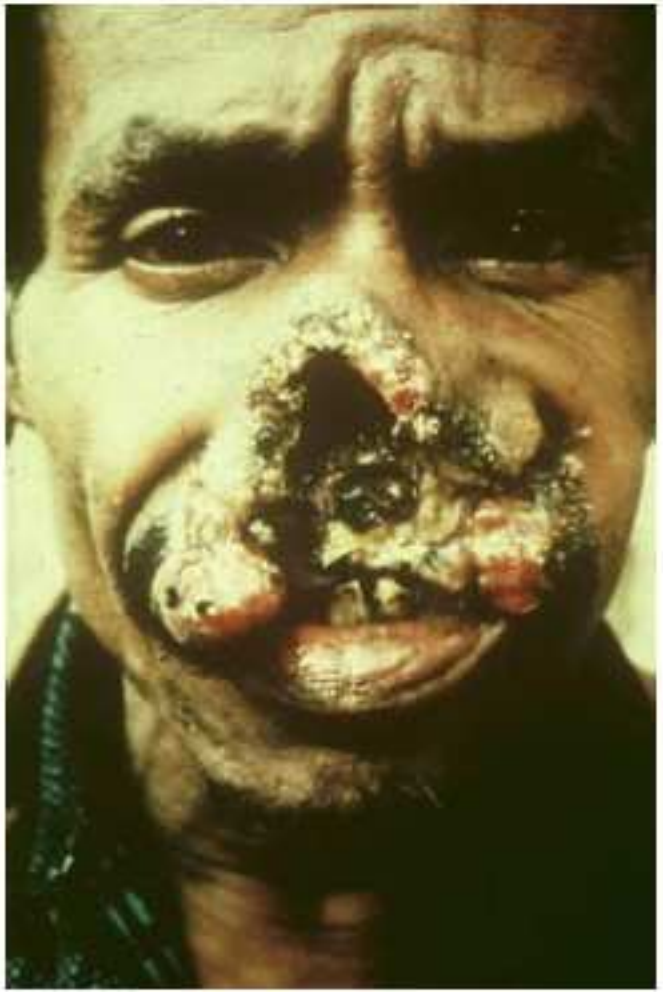




Lawn, Whetham, Chiodini et al. Q J Med 2004;97:781-8.







(Bailey, M., “Cutanous Leishmaniasis”, LSHTM, 2011)

Brief DDx

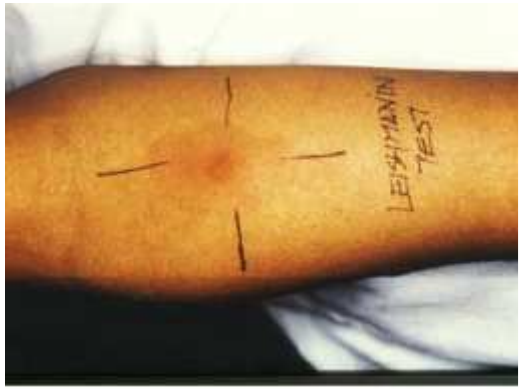
Cutaneous

- Bacterial skin infections
- Blastomycosis
- Cutaneous anthrax
- Eczema
- Fungal skin infections
- Leprosy
- *M. marinum*
- Myiasis
- Sarcoidosis
- Skin cancer
- Sporotrichosis
- Tuberculosis

Mucocutaneous

- Behcet's syndrome
- Discoid lupus
- Histoplasmosis
- Neoplasms
- Paracoccidiomycosis
- Rhinoscleroma
- Sarcoidosis
- Syphillis
- Tuberculosis
- Wegener's granulomatosis

Diagnosis



- Direct parasite visualization
  - Tissue
    - Cutaneous scraping
    - Punch biopsy
    - Needle aspirate
  - In vitro culture
  - Animal inoculation
- Detection of parasitic DNA (PCR)
  - Kinetoplastid DNA
  - 16-18S rDNA gene (species specific)
- Parasite culture
  - Novy-Nicolle-McNeal media
  - Allows identification, characterization, and storage of the isolate
- Serology
  - Monoclonal/polyclonal antibodies
  - ELISA (for IgG)
  - Direct agglutination test
    - 97-100% sens; 91-95% specific
  - Dip-stick/Immunochromotagraphic test
    - K39 antigen
      - 98-100% sensitive (VL in India)
      - Indirect
  - Leishmanin (Montenegro Test)
    - DTH reaction
    - Uses preserved promastigotes
    - Useful for epidemiologic surveys

HIV Co-infection

- Leishmaniasis
  - Important opportunistic infection
  - Both VL and HIV lower CMI
- Endemic regions
  - Many infections are asymptomatic
  - Concomitant HIV increases risk of active VL
  - HAART required for VL management and reduction of other OIs

Treatment

- Cutaneous disease: not life-threatening
  - Often self-healing
  - Degree of morbidity v. Potential tx side-effects
- Choice of treatment
  - *Leishmania* species (esp. New World spp.)
  - Lesion(s) character
    - Number
    - Size
    - Location
  - Availability of certain modalities

Treatment (CL)

- Antimonials
    - Pentavalent antimonials
    - Sodium stibogluconate
        - IND protocol from CDC
            - » (not FDA approved)
    - Meglumine antimoniate
- Oral antifungals
    - Variable results, *spp*. and location dependent
- Pentamidine isethionate
- Liposomal amphotericin B
    - Efficacy against several *spp.*
    - Optimal dose regimen not established
    - Not FDA approved for CL
- Others (efficacy data limited/not avail in US)
    - Topical paromomycin
    - Oral miltefosine
    - Thermotherapy
    - Intralesional pentavalent antimonals

(www.cdc.gov/parasites/leishmaniasis)

Treatment (VL)

- Main constraints (as for CL)
  - Drug cost and availability
  - Drug resistance
- HIV Co-infection
  - Prompt initiation of HAART
- High case fatality in absence of treatment
  - > 90%

Treatment (VL)

- Liposomal amphotericin B
  - Highest efficacy
  - Most favorable safety profile
- Conventional amphotericin B
  - High efficacy
  - Renal toxicity
- Parenteral paromycin and miltefosine
  - Each added in the past decade
  - Neither available in the US

Principles of Prevention/Control

- Passive/Active Case detection
  - Successful treatment of anthroponotic infection
    - CL (*L. tropica*)
    - VL (*L. donovani*)
- Chemotherapy
  - Response to sodium stibogluconate/amphotericin B is unsatisfactory
  - Promising responses to miltefosine (Poeppl, et al)
- Vaccine development
- Control/cull the reservoir hosts
  - CL: *L. major* (rodents)
  - VL: *L. infantfum* (dogs)
- Control the vector, or access to vector
  - Insecticides, fogging
  - Bednets
    - Impregnated: 50% disease reduction in Syria
  - Impregnated dog collars

Am J Trop Med Hyg. 2011 Apr;84(4):562-5.

Case

- 24 y/o Mexican woman
  - CC: Referred to clinic by Red Cross
  - HPI: Asymptomatic. Donated blood at work, unit found by serologic assay to be + *T. cruzi*.
  - ROS: No s/sx of CHF. + occas. consitpation (relived with OTC tx), o/w nl BM.
  - Ob Hx: G1P1
    - Not pregnant at present time
  - PMHx: Denies
  - Meds: Denies
  - All: NKDA

Case

- Soc Hx: Born in Colima, MX.
  - Lived first 4 yrs there, then moved to WA State with parents.
  - Returns to MX annually to visit family, for stays of 1-2 weeks.
  - Married. 3 year-old daughter. Non-smoker/non-drinker.

- Fam Hx: reports that all immediate family members are healthy and well.

Case

- ROS: She reports a history of valvular heart disease. Otherwise, no positive findings across 12 system review.

- Physical Exam: Afebrile, not tachycardiac, nor tachypneic. No rash. No gross, nor focal, abnormalities noted on physical exam.

Case

- Data:
  - Initial screening for *T. cruzi* (ELISA): +
  - 2nd stage test (RIPA): +
  - Confirmatory PCR: +

Case

- Management/Plan:
  - CDC contact for IND protocol
  - Tx recommended
  - CBC/CMP/EKG/UPT baseline performed
  - Nifurtimox recommended x 90 days
  - Screening of family members (Husband/daughter)
  - Avoid alcohol, ensure contraception for > 90 days

Causative Agent/ Transmission

- *Trypanosoma cruzi*
- Infective route(s)
  - Contact with stool of infected triatomine
- *Other routes:*
  - Mother-to-child (vertical/congenital)
  - Contaminated blood products (transfusions)
  - Organ transplanted from an infected donor
  - Laboratory accident
  - Contaminated food or drink (rare)

Epidemiology (Vector)

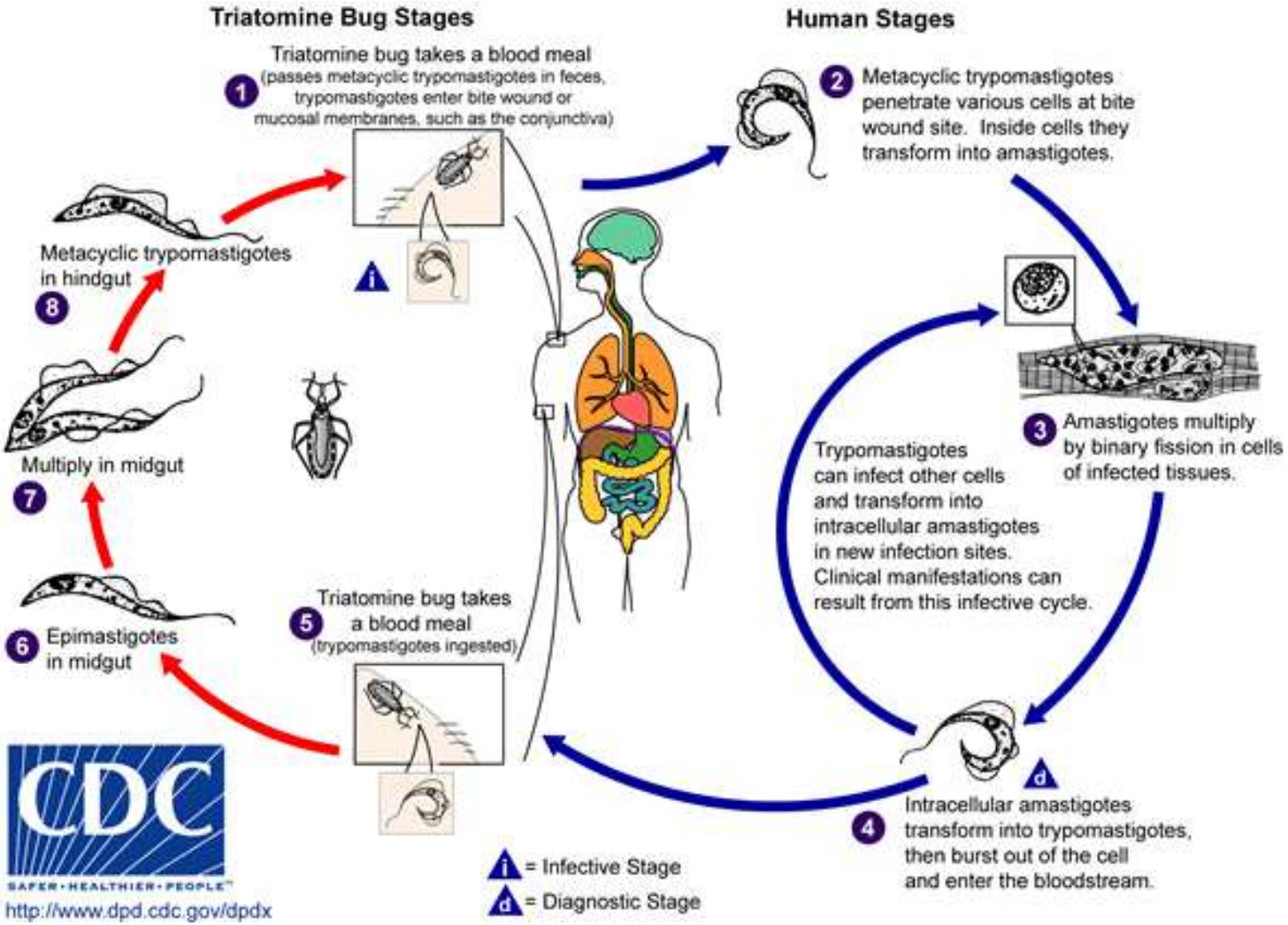
- Triatomine/Reduviid bugs
  - Assassin bugs “Benchuca”
  - Cone-nosed bugs “Chinche”
  - Blood suckers “Barbeiro”
  - *T. cruzi* carried in their gut
- Indoors
- Cracks and holes in substandard housing
- Variety of outdoor settings

Epidemiology (Vector)

- Triatomine range
  - Southern Argentina to the SE United States
  - As far north as CA, CO, IL, OH, and PA
- Nocturnal
  - Feed on blood of mammals *(**zoonosis**)*
  - Live in close proximity to a blood host
  - Next in cracks and holes of substandard housing
- If found locally
  - Do not touch or squash!
  - Slide into a container and take to health department or university laboratory for identification

    …or contact CDC DPDx (parasites@cdc.gov)

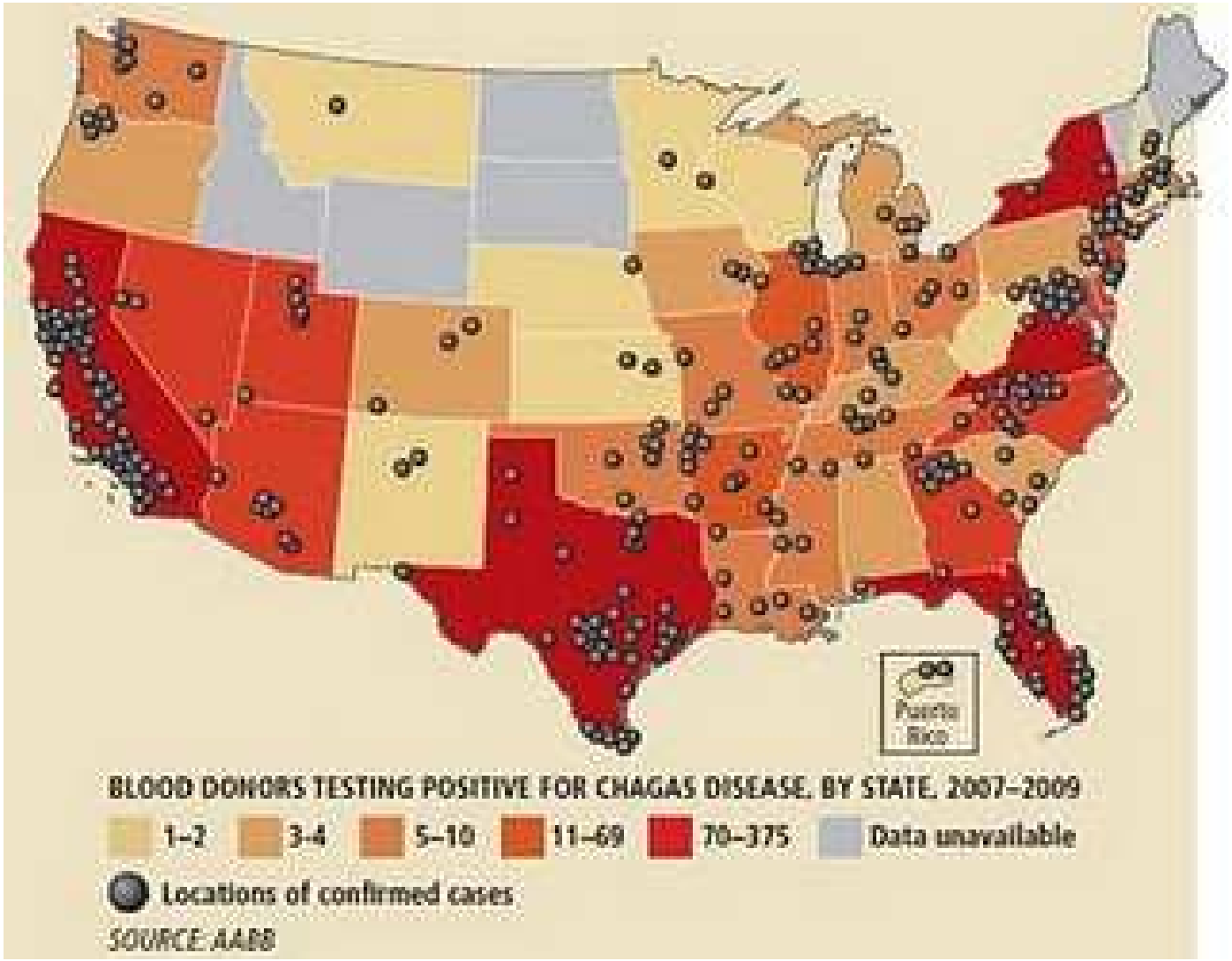
Biology (Life Cycle)



(www.dpd.cdc.org)

Epidemiology

- At risk populations
  - 8-11 million estimated infections
    - 300,000-400,00 living in non-edemic countries (Spain and US)
    - 41,200 new cases occur annually in endemic countries (Mexico, Cent Am/South Am)
    - 20,000 deaths are attributed to Chagas disease each year.
  - Individuals from endemic regions
  - US
    - 300,000 infections (CDC estimates)
      - Using seroprevalence figures
      - Most acquired while in endemic countries
      - 7 autocthonous cases reported in the
      - Since 2007: Screening US Blood Supply (AABB)
        - » http://www.aabb.org/programs/biovigilance/Pages/chagas.aspx
  - Persons in the US typically acquire infection while residents of endemic countries
  - The estimated burden of disease in terms of disability-adjusted life years (DALYs) declined from 2.7 million in 1990 to 586,000 in 2001



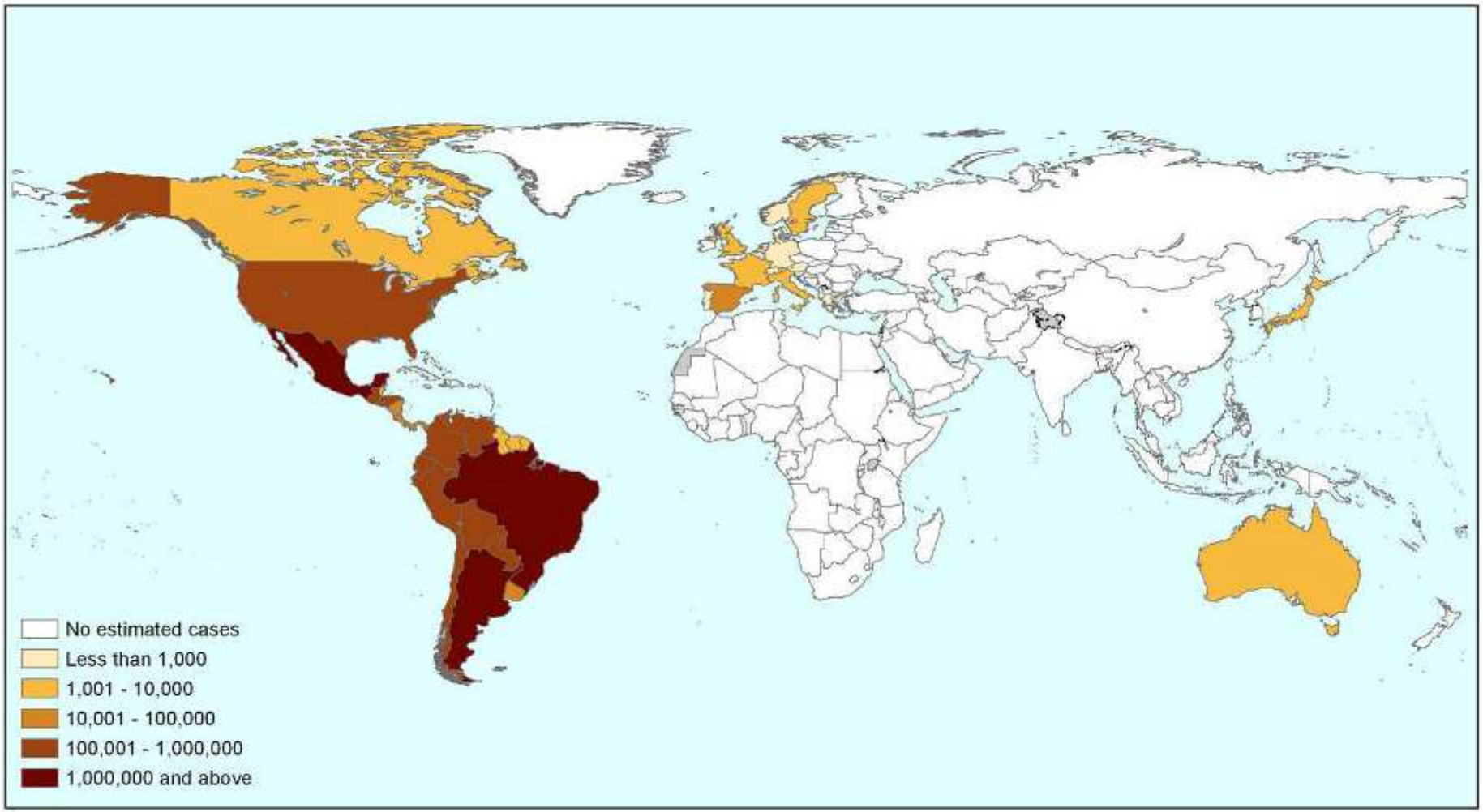
(Scientific American January 2010)

Triatomine Occurrence by State

(www.cdc.gov)

We will update this map regurlarly (version: June 2009)

Estimated global population infected by *Trypanosoma cruzi*, 2009



Sources:
1. OPS/HDM/CD/425-06 Estimación cuantitativa de la enfermedad de Chagas en las Américas.
2. Guerri-Guttenberg RA, Grana D.R., Giuseppe Ambrosio, Milei J. Chagasic cardiomyopathy: Europe is not spared! European Heart Journal (2008); 29: 2587-2591.
3. Schmunis, G. A. Epidemiology of Chagas Disease in non-endemic countries: the role of international migration. Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. 102(Suppl. I): 75-85, 2007.
4. De Ayala A.P, Pérez-Molina J.A, Norman F., and López-Vélez R.Chagasic cardiomyopathy in inmigrants from Latin America to Spain. Emerging Infectious Disease Volume 15, Number 4–April 2009.
5. According to the numbers of inmigrants registered for 2007in the website of the Japanese Ministry of Justice and estimated seroprevalence for non endemic countries according to Paricio-Talayero J.M. Vigilancia epidemiológica de la transmisión vertical de la enfermedad de Chagas en tres maternidades de la Comunidad Valenciana. Enferm Infecc Microbiol Clin 2008;26(10):609-13.

“Despite gaps in the evidence base, current knowledge is sufficient to make practical recommendations to guide appropriate evaluation, management, and etiologic treatment of Chagas disease.”

Bern, et al (2007) JAMA

Chagas Disease

- Pathogenesis
  - Acute (may last up to 90 days)
    - Mild/asymptomatic
    - Swelling around site of inoculation (*Romaña's Sign)*
      - Unilateral palpebral/periocular swelling
    - Rarely, results in severe myocarditis/encephalitis/meningitis
    - Chronic phase: prolonged/asymptomatic
      - Many infected remain asymptomatic for life
    - High parasitmeia:
      - Blood films reveal parasites circulating in blood
  - Chronic
    - Indeterminate (~70-80% of infections remain)
      - Low parasitemia
    - Symptomatic/Determinate (~20-30% progress)
      - Cardiac disease (sp. conduction abnormalities) appear first
        - » Followed by apical aneurysm/thrombus formation
      - Cardiomyopathy, Myocarditis, etc…
      - GI manifestations
        - » Megaesophagus, megacolon
    - Increased risk of CVA

Table 2. Cardiac Abnormalities Associated with Chagas' Disease.

Conduction-system dysfunction
Right bundle-branch block
Left anterior fascicular block
Atrioventricular block, including complete heart block
Sinus-node dysfunction, often presenting as sinus bradycardia
Primary T-wave changes, abnormal Q waves, or both
Dysrhythmias
Ventricular premature beats, often multiform
Nonsustained ventricular tachycardia, often polymorphic
Ventricular fibrillation
Atrial fibrillation
Myocardial abnormalities
Increased cardiac weight
Dilated left ventricle, right ventricle, or both
Segmental left ventricular dysfunction
Diffuse left ventricular dysfunction, right ventricular dysfunction, or both
Decreased left ventricular ejection fraction
Diastolic dysfunction
Ventricular aneurysms
Intracardiac thrombus
Pericardial effusion (during the acute phase)

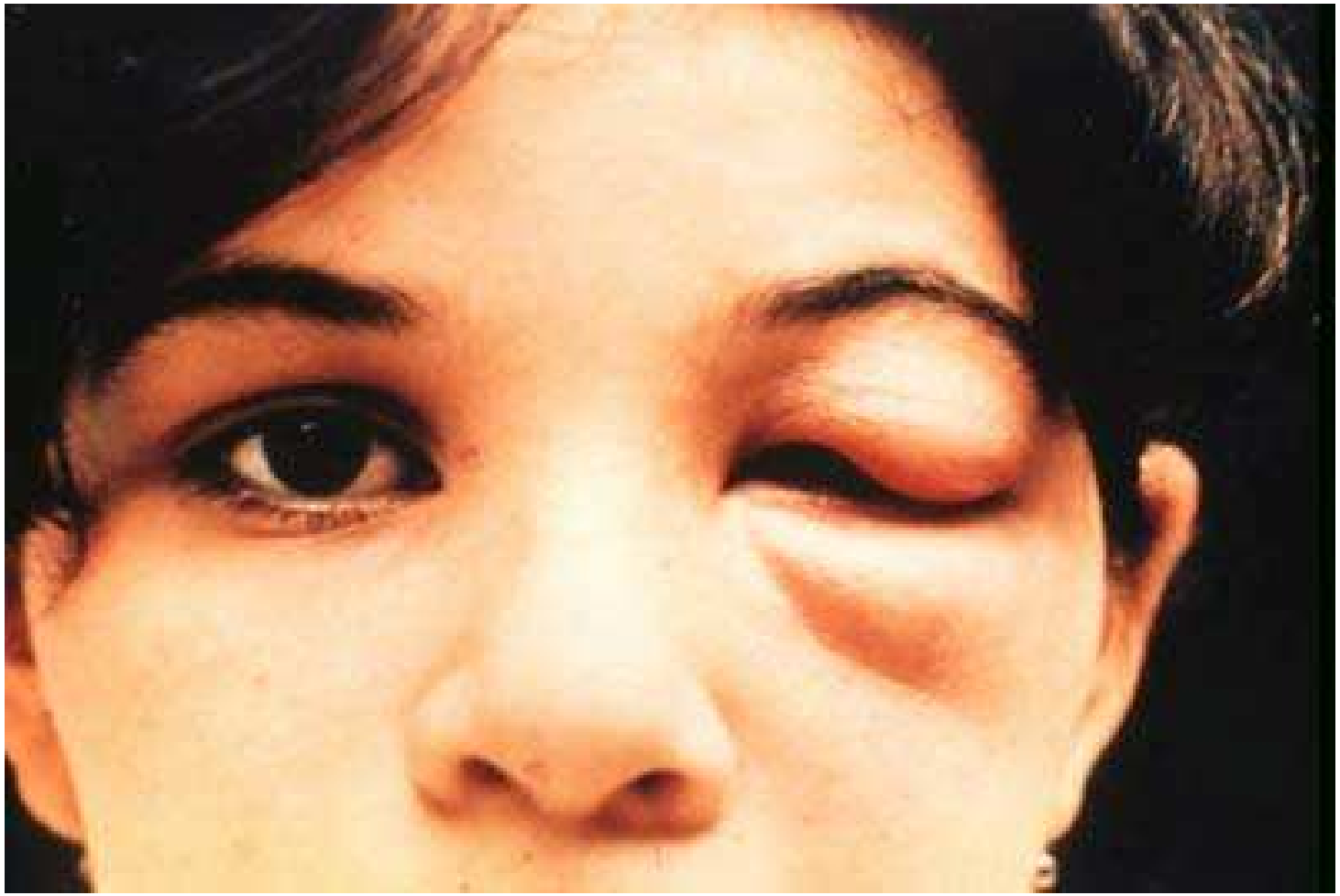
Isselbacher E et al. N Engl J Med 2010;362:254-262

GI Manifestations (Chagas' Disease)

- Disease spectrum:
  - Mild achalasia to severe megaesophagus
- Other presentations:
  - Dysphagia
  - Odynophagia
  - Esophageal reflux
  - Weight loss
  - Aspiration
  - Cough
  - Regurgitation

(de Oliveira RB, et al, "The spectrum of esophageal motor disorders in Chagas' disease. *Am J Gastroenterology*, 1995;90(7):1999)

Romaña's Sign



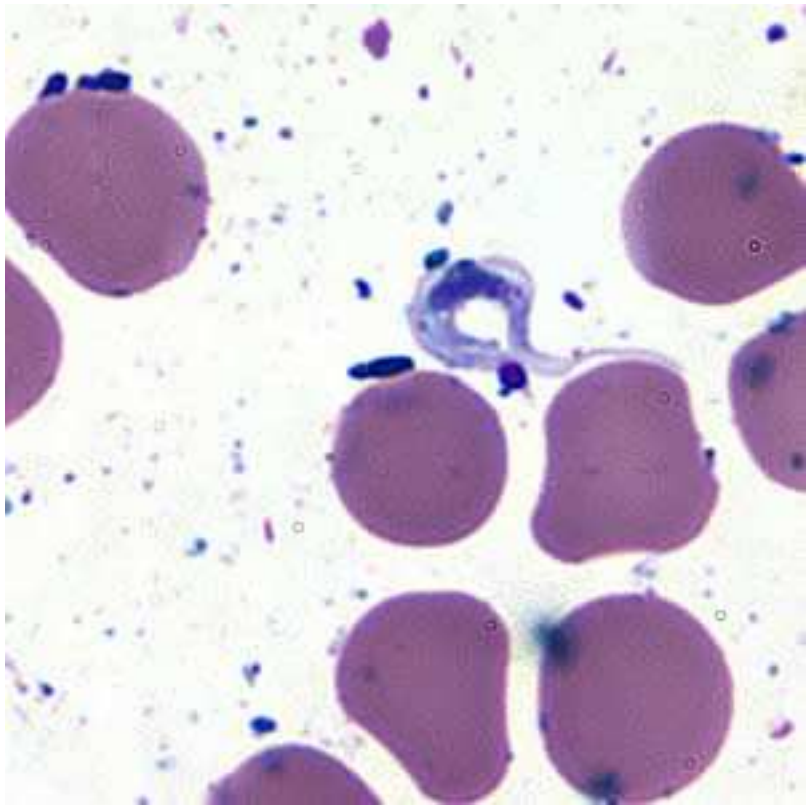
(WHO/TDR)

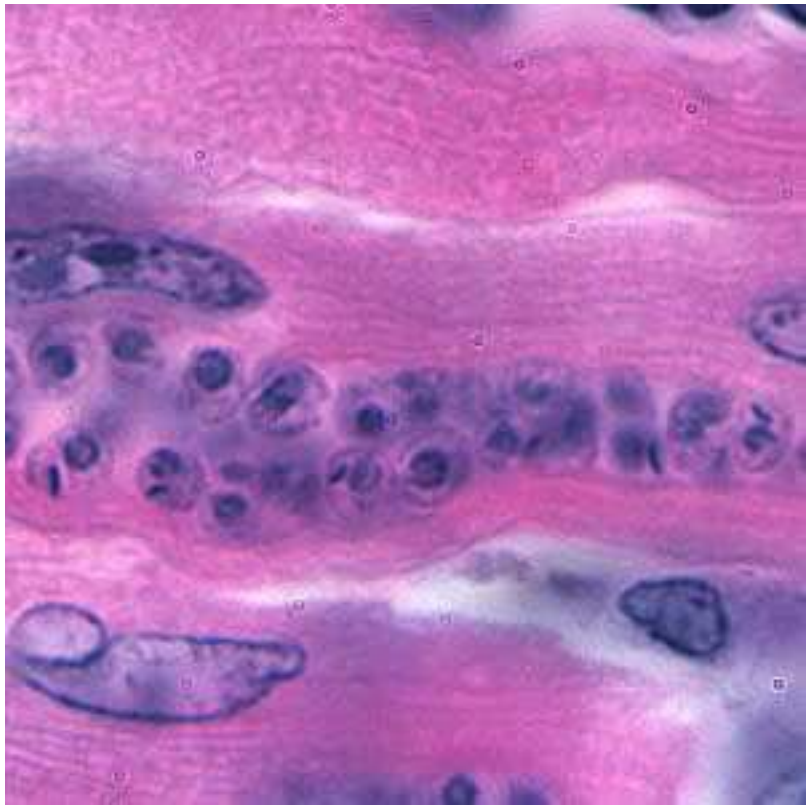
Diagnosis

- Serologies drawn may be forwarded to:
  - Local County/State Health Department
  - CDC
- AABB/Red Cross
  - Initial Ortho ELISA +
  - RIPA: repeat reactive units tested and confirmed

Chagas Disease

- Lab Diagnosis
  - Direct microscopy
    - Fresh anticoagulated blood/buffy coat for motile parasites
    - Thick/thin blood smears (Giemsa)
  - Isolation of the agent
    - Indirect flourescent antibody (IFA)
      - From suspension of epimastigotes
    - Inoculation in culture
    - Inoculation into mice
    - Xenodiagnosis
      - Examining triatomine gut contents 4 weeks following blood meal on patient's blood





(www.dpd.cdc.gov)

Chagas Disease

- Immunoassays
  - Complement fixation
  - Indirect hemagglutination
  - Indirect fluorescence assays
  - Radioimmunoassays
  - ELISA
  - RIPA

New Diagnosis

- Medical history
- Physical examination
- Resting 12-lead EKG (w/ 30s Lead II strip)
- If all of the above is normal, no further testing
  - Repeat this screening annually
- If findings suggest Chagas heart disease
  - Comprehensive cardiac evaluation
    - Incl. 24-hr ambulatory EKD monitoring
    - Echocardiography
    - GXT
- If GI symptoms present
  - Barium contrast studies

(Bern, C. et al, "Evaluation and Treatment of Chagas Disease in the United States", *JAMA*, 2007;298(18):2171-2181.)

Treatment

- Recommendations (CDC):
  - Antitrypanosomal Tx for:
    - All acute and congenital cases
    - Reactivated infection
    - Chronic *T. cruzi* (< 18 y/o)
  - Etiologic treatment
    - Cases 19-50 y/o w/out advanced heart disease
  - Optional treatment
    - Cases > 50 y/o

(Bern, C. et al, "Evaluation and Treatment of Chagas Disease in the United States", *JAMA*, 2007;298(18):2171-2181.)

Treatment

- Individualized care
  - Balance potential benefit with harm of tx
  - Prolonged course
  - Frequent adverse effects of tx
- Strong consideration
  - HIV+
  - Organ transplant recipients

(Bern, C. et al, "Evaluation and Treatment of Chagas Disease in the United States", *JAMA*, 2007;298(18):2171-2181.)

Chagas Disease

- Treatment
  - Benznidazole
  - Nifurtimox
    - Neither available commercially.
    - Only available from CDC-IND protocols
    - CDC Drug Service: 404-639-3670
      - Evenings, weekends, or holidays: 770-488-7100

Chagas Disease

- Prevention
  - Endemic regions:
    - Improved housing, use of screening/treated bed nets
    - Spraying to eliminate triatomine bugs
      - Avoiding ingestion of bugs/feces
    - Screening of blood donations
      - Avoidance of blood transfusion/organ donation, if possible
    - Early detection and treatment
      - Mother to baby (vertical)
    - Vaccine *(*in development)*
  - U.S.
    - Screening of blood donations
    - Screening of organ transplants
    - Early detection and treatment of vertical transmission

(www.bvs.hn/E/chagas.html)

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DNDi

Drugs for Neglected Diseases *initiative*
Iniciativa Medicamentos para Enfermedades Olvidadas
Iniciativa Medicamentos para Doenças Negligenciadas

Resources

Websites:

- WHO Department of NTD's: http://www.who.int/neglected_diseases/en/
- PLoS NTD: http://www.plosntds.org/home.action
- CDC NTDs: http://www.cdc.gov/globalhealth/ntd/diseases/index.html
- CDC DPDx: http://www.dpd.cdc.gov/dpdx/Default.htm
- CDC Yellow Book, Ch 9. "Migrant Health Resources": http://goo.gl/DvEAc
- Refugee Health Guidelines: http://goo.gl/Z2aWx
- Diploma of Tropical Medicine Courses (ASTMH Approved): http://www.astmh.org/Approved_Diploma_Courses/2867.htm

Books:

- Cook, G., Manson's Tropical Diseases 22nd ed., Saunders, 1898.
- Hotez PJ, Forgotten People, Forgotten Diseases, ASM Press, 2008.
- Jong, E., The Travel and Tropical Medicine Manuel 4th ed., 2008.

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