

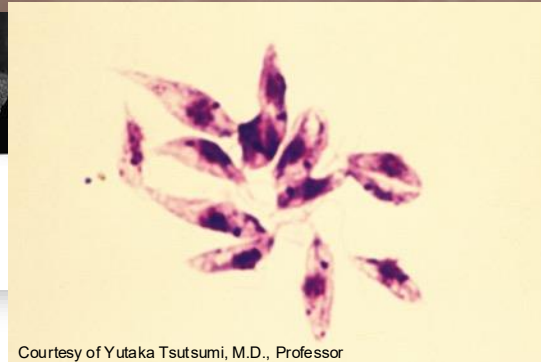
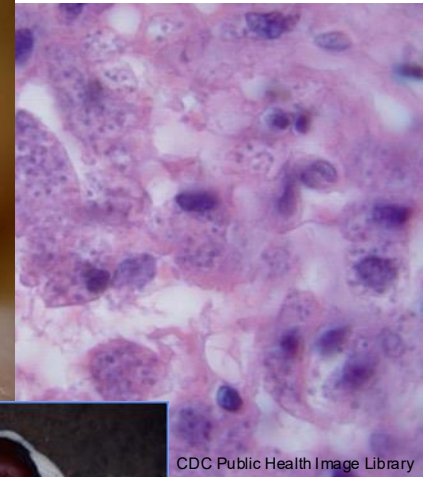
Introduction to fly-borne diseases



REDUCING DEATHS AND SUFFERING
FROM TROPICAL DISEASES



Leishmaniasis



**REDUCING DEATHS AND SUFFERING
FROM TROPICAL DISEASES**



Leishmaniasis

- Transmitted by the bite of an infected female *Phlebotomine* or *Lutzomyia* sandfly
- 500 fly species, 30 carry Leishmaniasis. Small (2-3 mm long)
- Most forms of disease transmissible only from animals (zoonosis),
- but some can be spread between humans (kala azar).

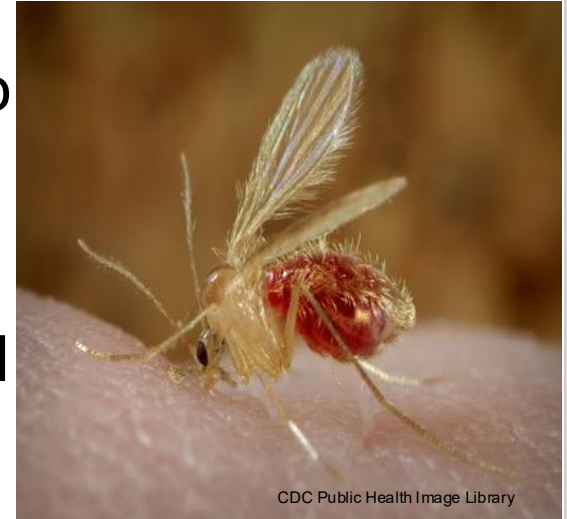


REDUCING DEATHS AND SUFFERING
FROM **TROPICAL DISEASES**



Leishmaniasis

- Transmitted by the bite of an infected female Phlebotomine sandfly, at night
- Over 90 sandfly species are known to transmit leishmania
- They live and breed in domestic waste and cracks of buildings, behind bark, and animal burrows.
- Sandflies become infected when they suck blood from an infected person or animal



Leishmaniasis – Vector

- Over a period of between 4 and 25 days, the parasites develop in the sandfly
- When the infectious female sandfly then feeds on a fresh source of blood, it inoculates the person or animal with the parasite
- 3 forms: Visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis



Leishmaniasis – Epidemiology/Endemicity

- Out of 200 countries and territories reporting to WHO, 97 countries and territories are endemic for leishmaniasis. This includes:
 - 65 countries that are endemic for both VL and CL
 - 10 countries that are endemic for VL only
 - 22 countries that are endemic for CL only
- An estimated 700,000 to 1 million new cases and 20,000 to 30,000 deaths occur annually

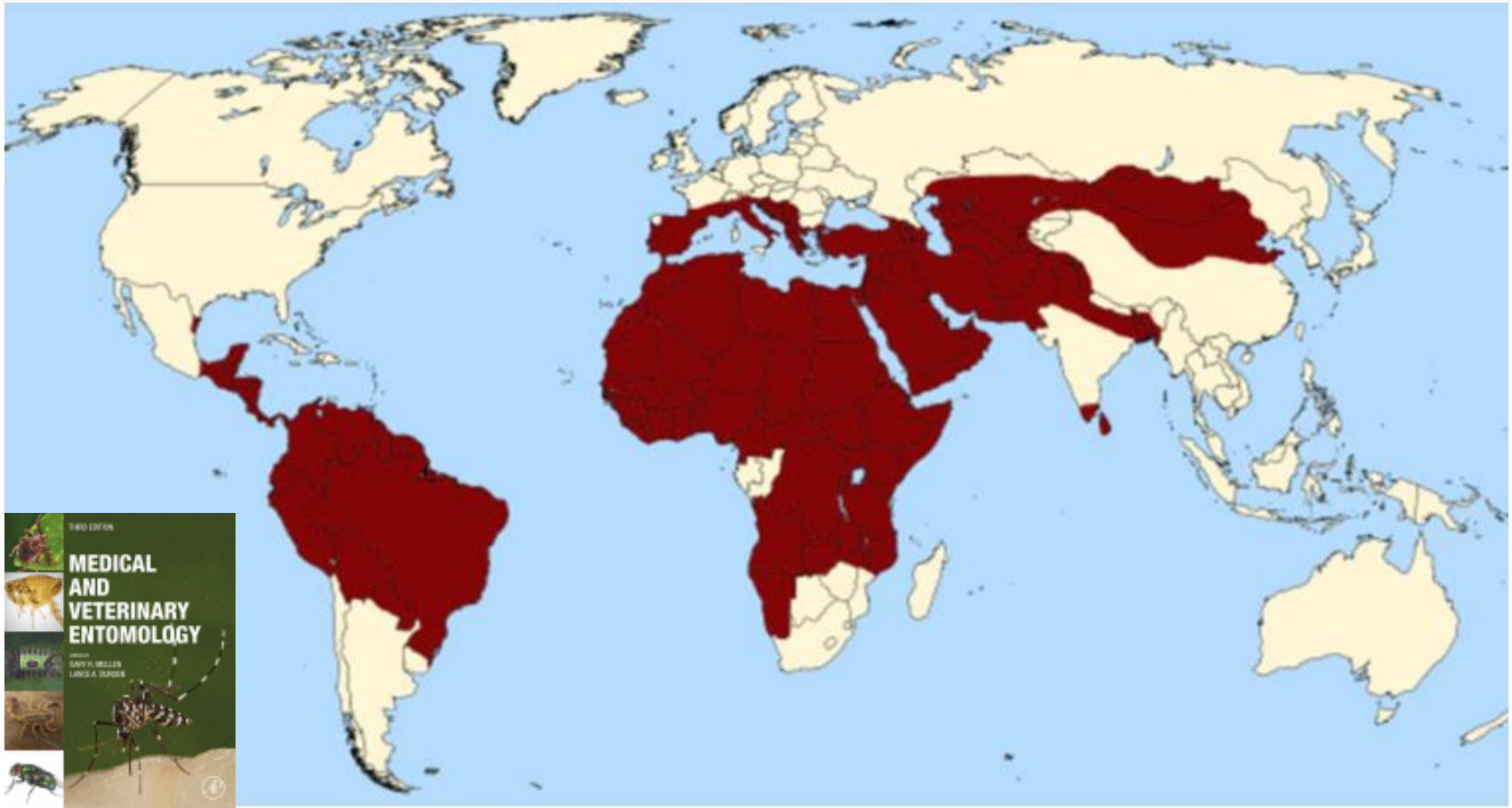
WHO (2018) Factsheet leishmaniasis



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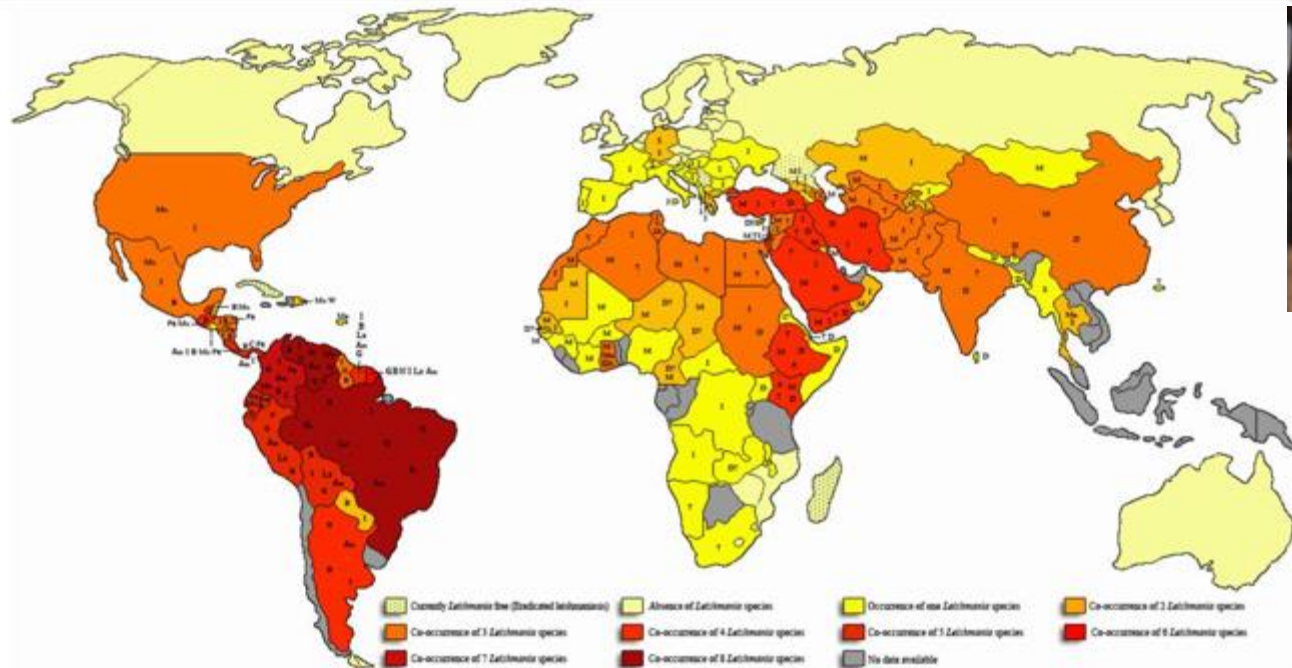
Phlebotomine Sand Flies Global Distribution



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Leishmaniasis Global Distribution



Mohammad Akhoundi et al. Leishmania infections: Molecular targets and diagnosis. Molecular Aspects of Medicine, Volume 57, 2017, 1-29. <https://doi.org/10.1016/j.mam.2016.11.012>

WHO estimates 700 000 to 1 million new cases occur annually.

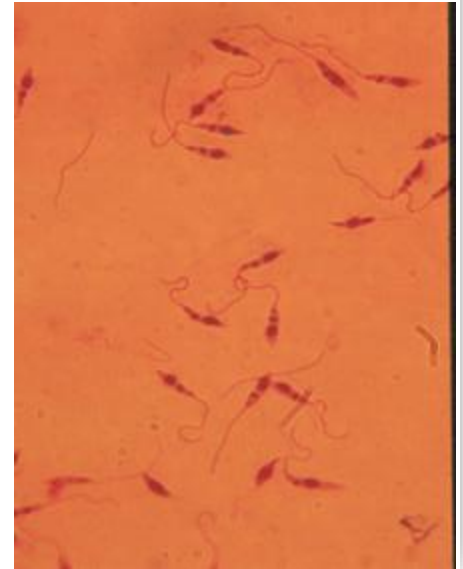


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Leishmania species

- Infection caused by about 21 of 30 species of *Leishmania* - obligate intracellular protozoan parasite that infect mammals.
 - *L. donovani* complex: *L. donovani*, *L. infantum*, and *L. chagasi*
 - *L. mexicana* complex: *L. mexicana*,
 - *L. amazonensis*, and *L. Venezuelensis*
 - *L. tropica*; *L. major*; *L. aethiopica*



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Leishmaniasis – 3 Clinical forms

- **Visceral leishmaniasis (VL)**
 - without treatment, this form of the disease is nearly always fatal
- **Cutaneous (CL)**
 - 2-3 weeks after infective bite
 - papules or nodules progress to ulcers at the site of the vector bite
 - clinically rarely causes death
- **Mucocutaneous (ML)**



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Visceral leishmaniasis

- Also known as kala-azar
- Fatal if left untreated in over 95% of cases
- Characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia

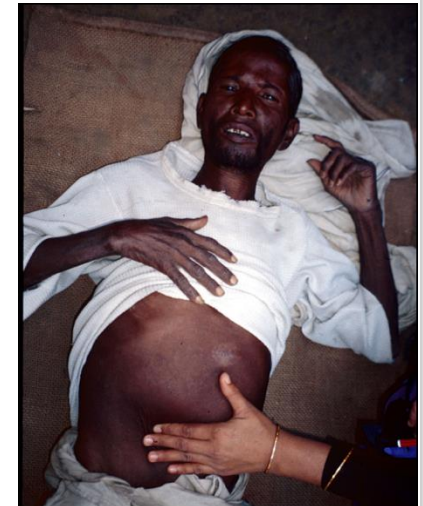


Photo by D. Scott Smith

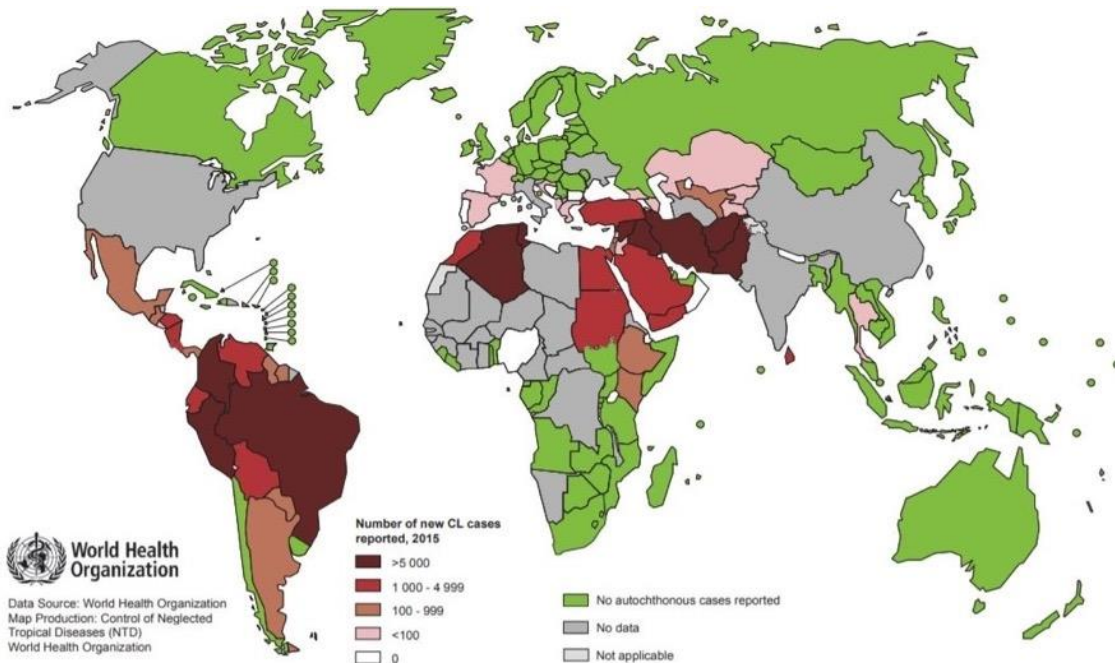
WHO (2017) Factsheet on leishmaniasis



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Visceral Leishmaniasis – Endemicity



Estimated 50,000 to 90,000 new cases of VL occur worldwide each year

>90% of new cases reported to WHO (2015) were in :
Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan



Cutaneous leishmaniasis

- Most common form of leishmaniasis
- Causes skin lesions, mainly ulcers, on exposed parts of the body, leaving life-long scars and serious disability
- About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia



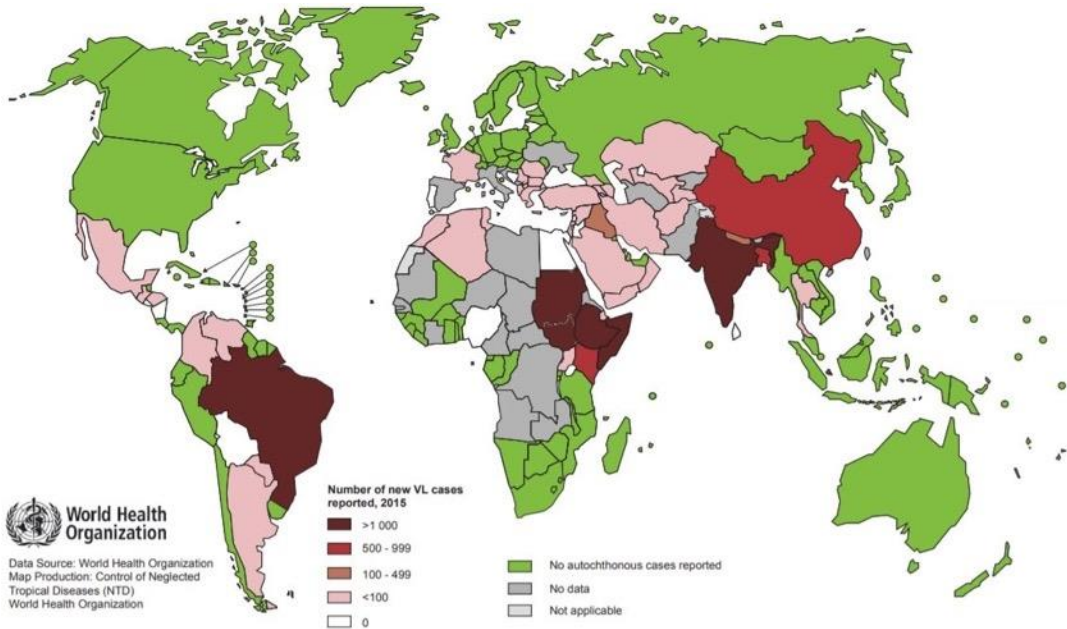
WHO (2017) Factsheet on leishmaniasis



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Cutaneous Leishmaniasis – Endemicity



- >66% of new CL cases occurred in : Syria, Iran, Brazil, Colombia, Afghanistan, and Algeria,
- Estimated 600,000 to 1 million new cases occur worldwide annually



Mucocutaneous leishmaniasis

- Appears first as cutaneous then mucosal disease: 1 month to 24 years
- Leads to partial or total destruction of mucous membranes of the nose, mouth and throat
- >90% of cases occur in Bolivia, Brazil, Ethiopia and Peru



Gomes, C.M. et al. (2014). Complementary Exams in the Diagnosis of American Tegumentary Leishmaniasis. An Bras Dermatol. 2014; 89(5):701-11.

WHO (2017) Factsheet on leishmaniasis



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Leishmaniasis – Treatment

- Leishmaniasis is treatable, but the drugs used are difficult to administer, require repeat treatments, and can have painful side effects.
- Stibogluconate sodium (Pentostam®)
- Meglutamine antimoniate (Glucantime®)
- Liposomal amphotericin B (AmBisome®)
- Miltefosine:

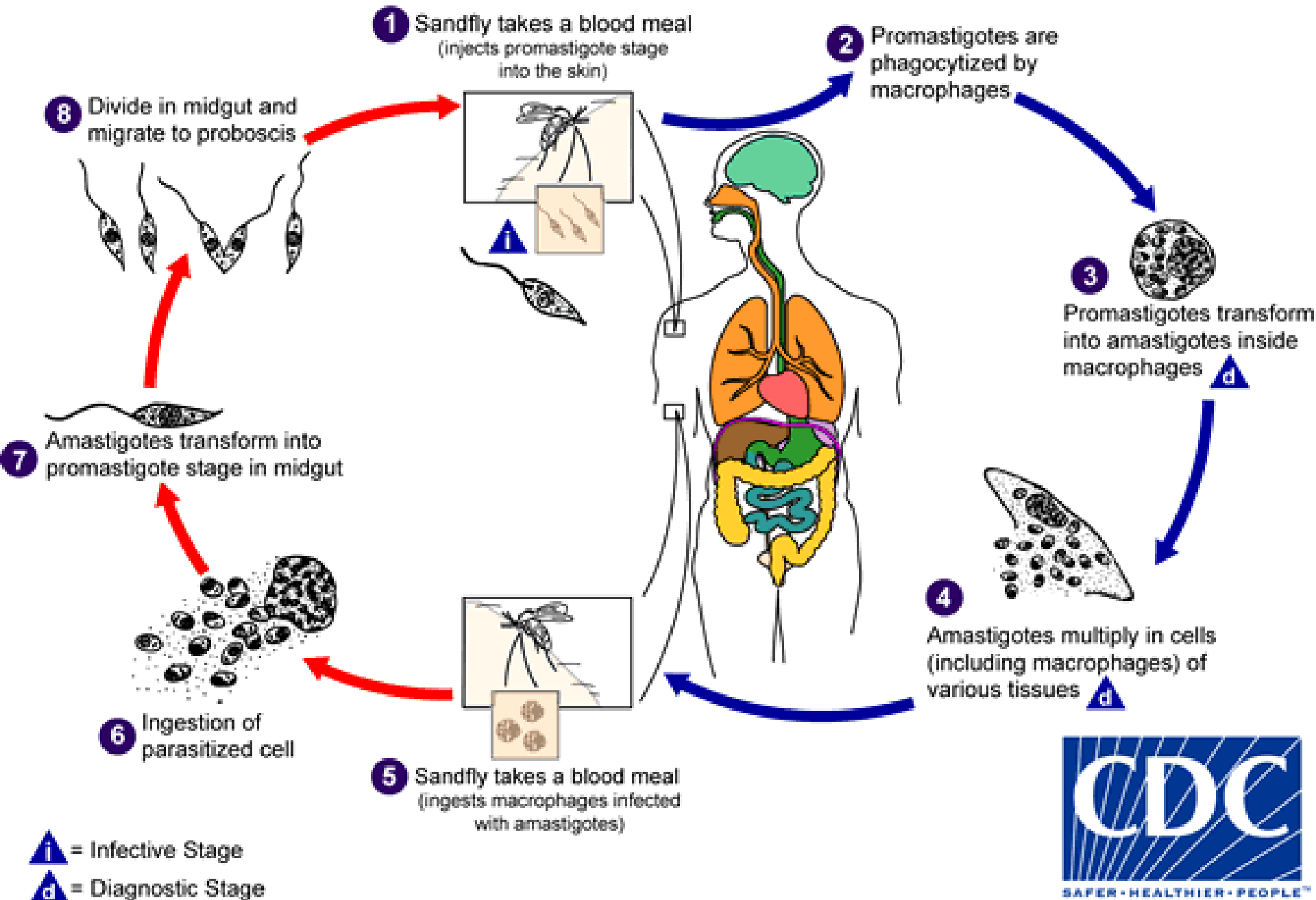


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Sandfly Stages

Human Stages



Leishmaniasis: Clinical

Three human forms of the disease:

- **Cutaneous Leishmaniasis (CL)**
700,000-1.2 million.
Clinically rarely causes death.
- **Visceral leishmaniasis (VL)**
<100,000 cases/year, without treatment, this form of the disease is nearly always fatal
- **Mucocutaneous (ML)**



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Cutaneous Leishmaniasis

- Appears 2-3 weeks after infective bite
- Begins as papules or nodules
- Progresses to ulcers at the site of a vector bite



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Visceral leishmaniasis (kala-azar)

Incubation period is 2-6 months

- Presents with fever, massively enlarged spleen and pancytopenia
- Progresses to weakness, emaciation and death



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Leishmaniasis epidemiology

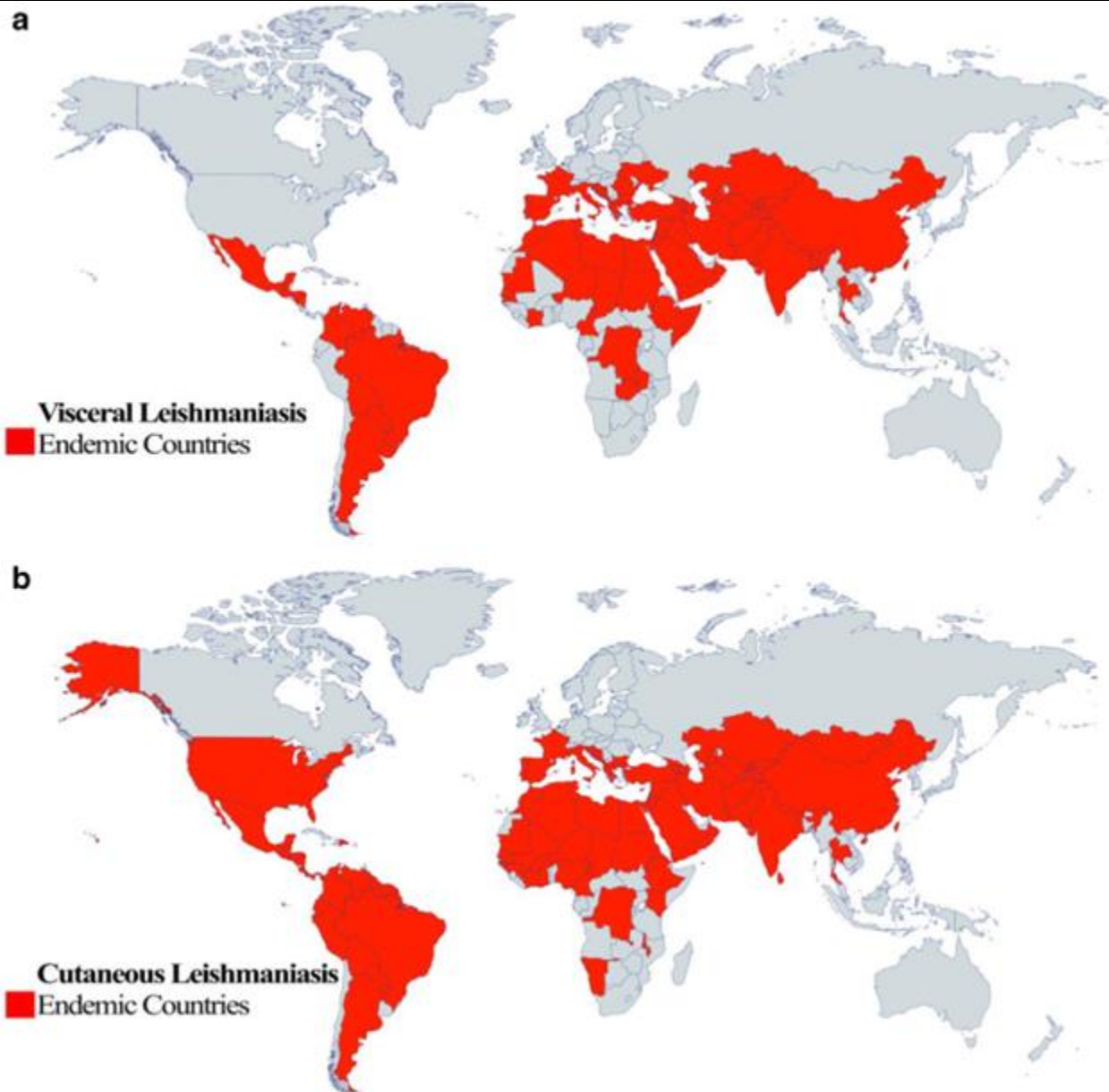
- Currently, leishmaniasis occurs in 92 countries on 5 continents
- Population at risk = 1 billion
- 90% of VL cases occur in 6 countries - Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan.
- 95% of CL cases occur in 7 countries — Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria
- >1 million cases of CL a year
- <100,000 reported cases of VL each year, ~10% death rate
- Reported case numbers have increased exponentially over the last 20 years



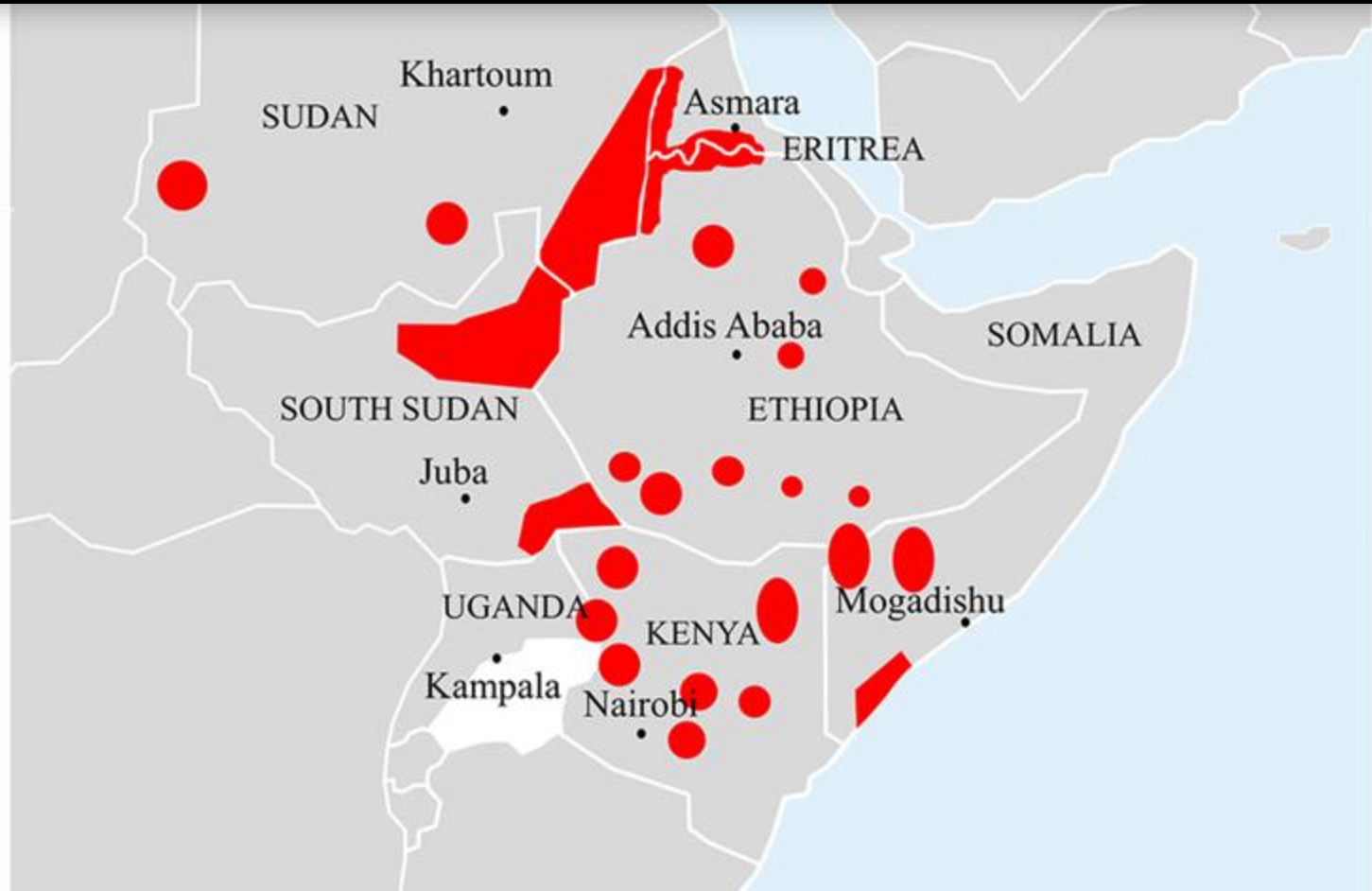
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Leishmaniasis: Endemic countries 2021



Visceral Leishmaniasis and HIV Coinfection in East Africa



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Risk Factors



- Infants and children and malnutrition predispose to disease-no immunity
- HIV infection increases risk
- Living in proximity to termite mounds & acacia trees – breeding ground of sand flies-increases risk



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Diffuse Cutaneous Leishmaniasis

- Localized papule that does not ulcerate.
- Satellite lesions develop around the initial papule
- Disseminated nodules - face and extremities.
- Protracted course



Diffuse cutaneous leishmaniasis

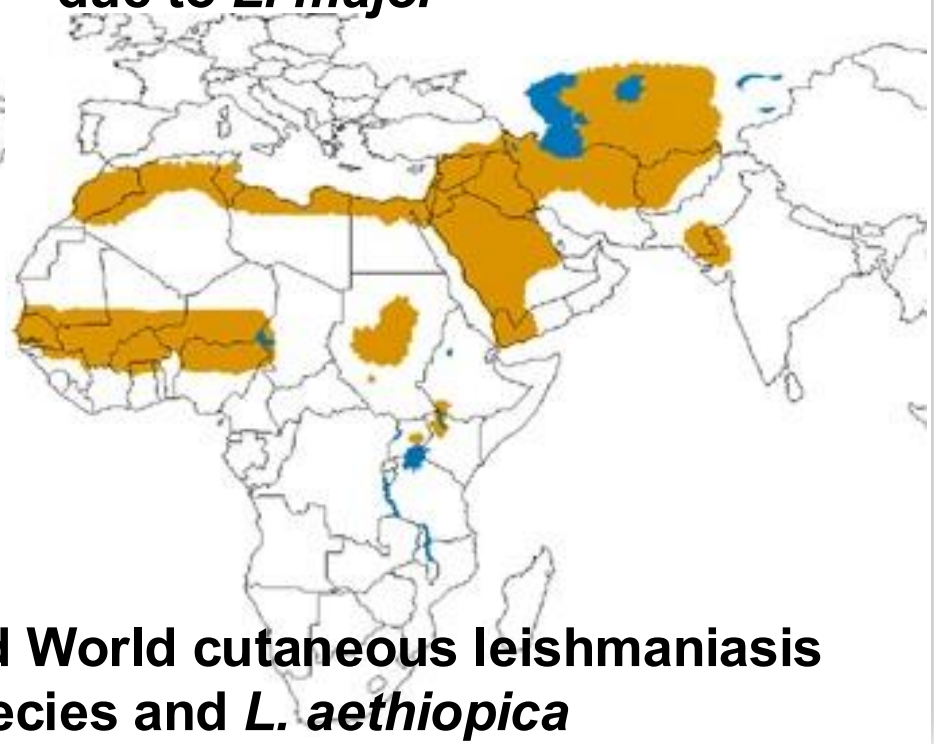


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Epidemiology- Distribution of CL in Old World

Geographical distribution of Old World cutaneous leishmaniasis due to *L. major*



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



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Leishmaniasis Recidivans

- Relapsing, tuberculoid form of cutaneous leishmaniasis caused by *L. tropica*
 - Lesions are usually on the face
 - Leishmaniasis recidivans is chronic and can last for decades.



Leishmania recidivans



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Leishmaniasis: Mucocutaneous

Mucocutaneous leishmaniasis, a rare form of the disease can occur months or years after the healing of a CL ulcer.

This form of the disease can affect the nasal septum, palate and other parts of the nasopharynx.



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Onchocerciasis

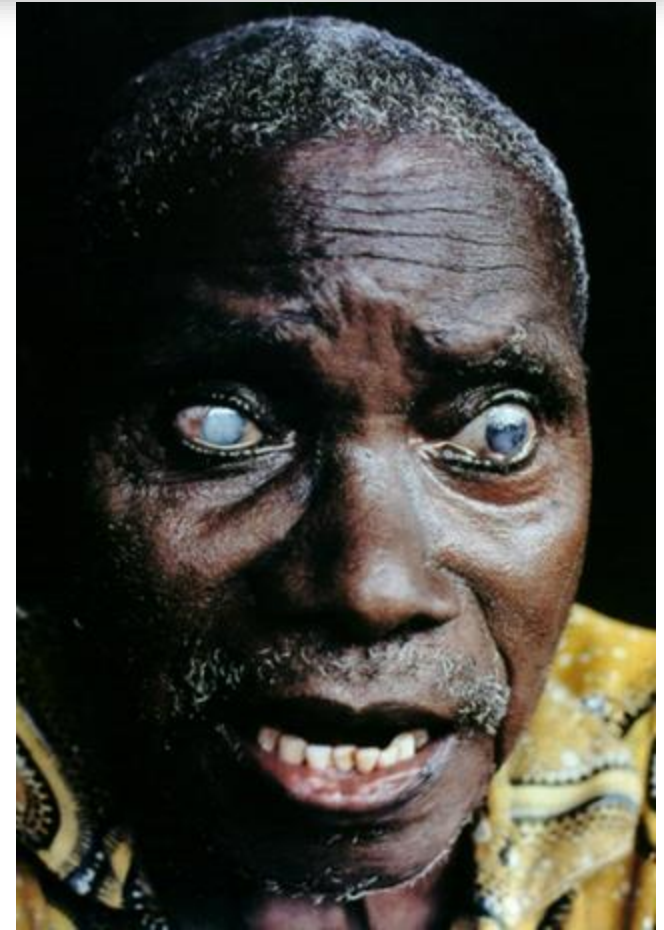


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Onchocerciasis

- Onchocerciasis (**river blindness**) is a parasitic disease caused by infection with the nematode *Onchocerca volvulus*
- Onchocerciasis is the world's second-leading infectious cause of blindness.



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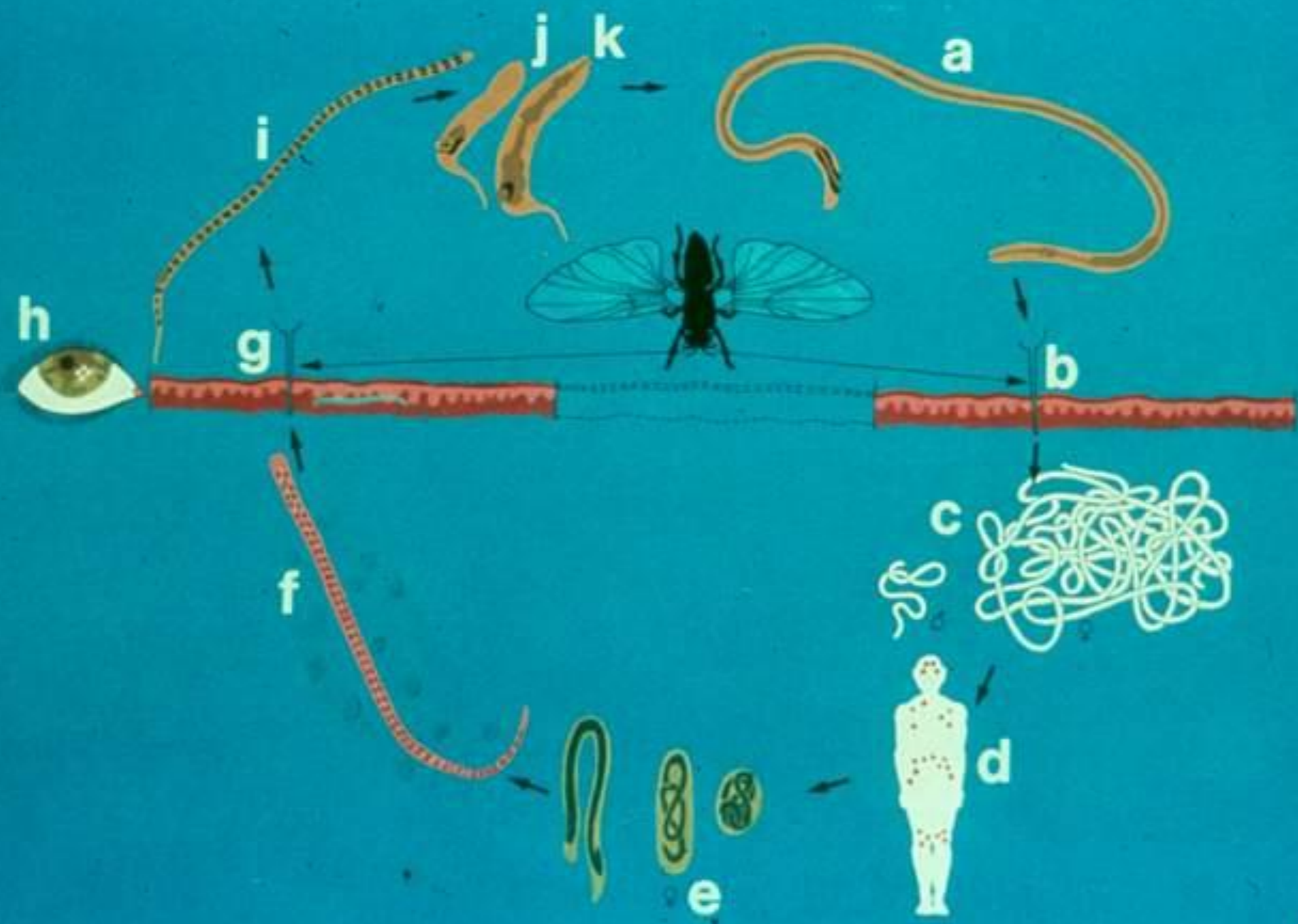
Onchocerciasis

- Transmitted to humans through the bite of a black fly of the genus *Simulium*.
- The larval nematodes spread throughout the body. When the worms die, their *Wolbachia* symbionts are released, triggering a host immune system response that can cause severe itching, and can destroy optical tissue in the eye.



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Onchocerciasis: Clinical

- Intense dermatitis, pruritis, leopard skin
- Subcutaneous nodules

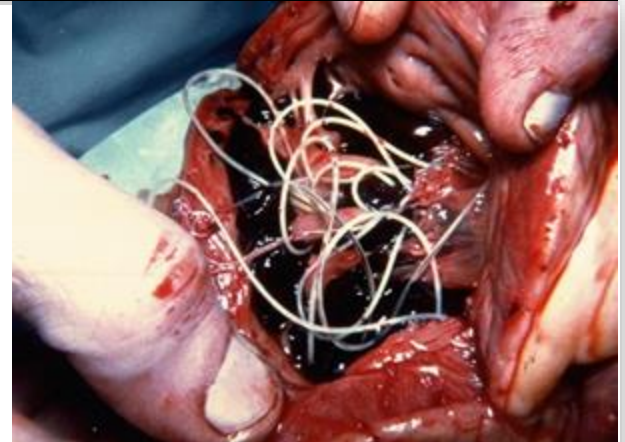


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Onchocerciasis

- Subcutaneous nodules
- *Micrifilaria onchocerciais* worms migrate uncontrolled in the human body causing a wide range of damage to tissue and especially eyes



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Fig. 8-3-43 Adults blinded by onchocerciasis in the Sudan



Onchocerciasis: Epidemiology

- Infection found in tropical climate (Sub-Saharan Africa)
- 36 countries endemic: 31 in Africa, 2 in the Americas & Yemen
- 180 million persons at risk
- 27 million persons infected with *Onchocerca volvulus* worldwide; more than 99% are in Africa
- 8.6 million with skin disease; 126,000 blind, 426,000 visual impairment
- 1,397,000 DALYs, no deaths
- No animal reservoir



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Epidemiology- Continued

- Risk is in rural agricultural areas near streams or rivers where *Simulium* blackflies rest and breed.
- Many bites are needed before being infected
 - people who travel to endemic areas have a low chance of becoming infected with *O. volvulus*
- No animal reservoir
- Focal Distribution linked to vector habitat
 - fast-flowing rivers or streams

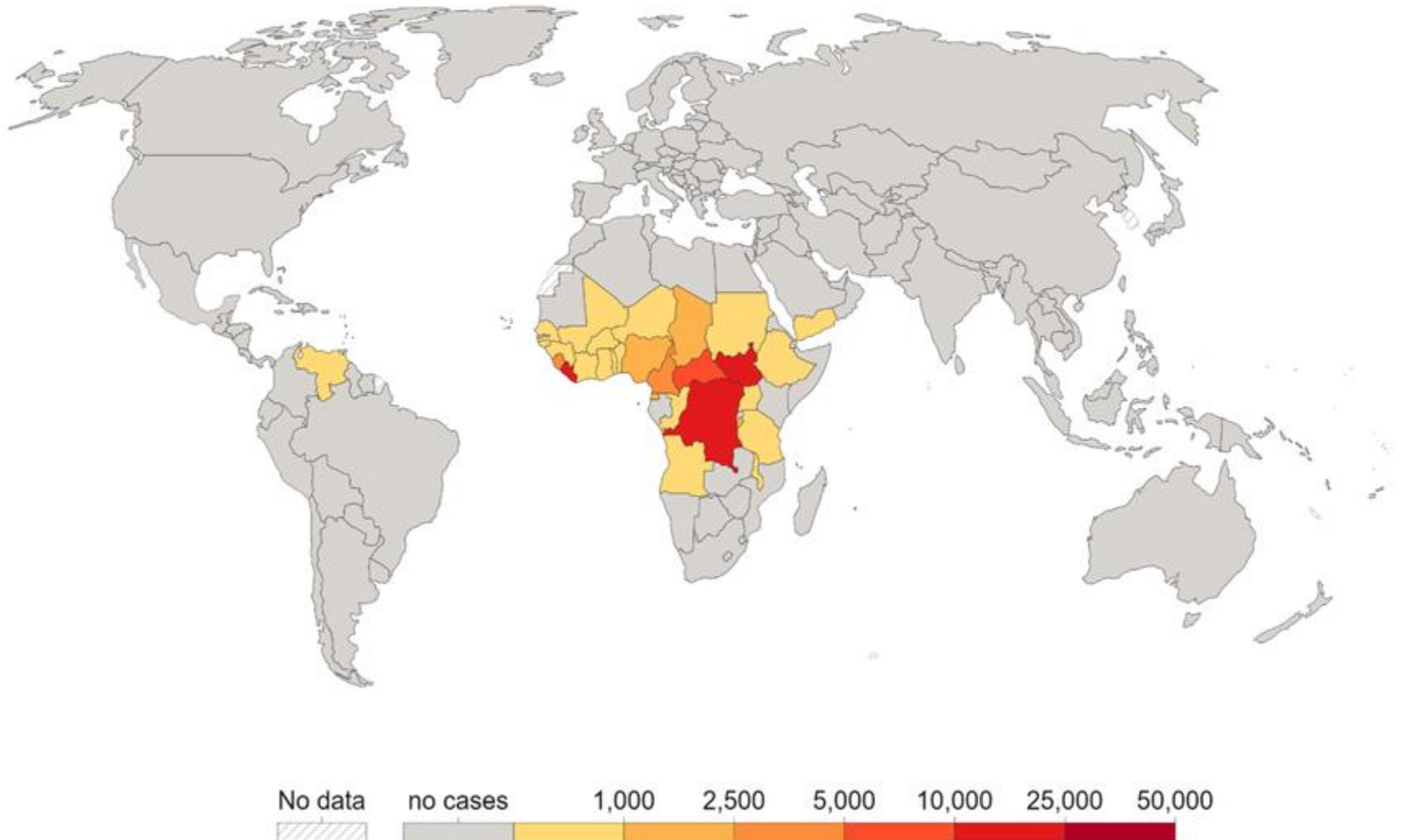


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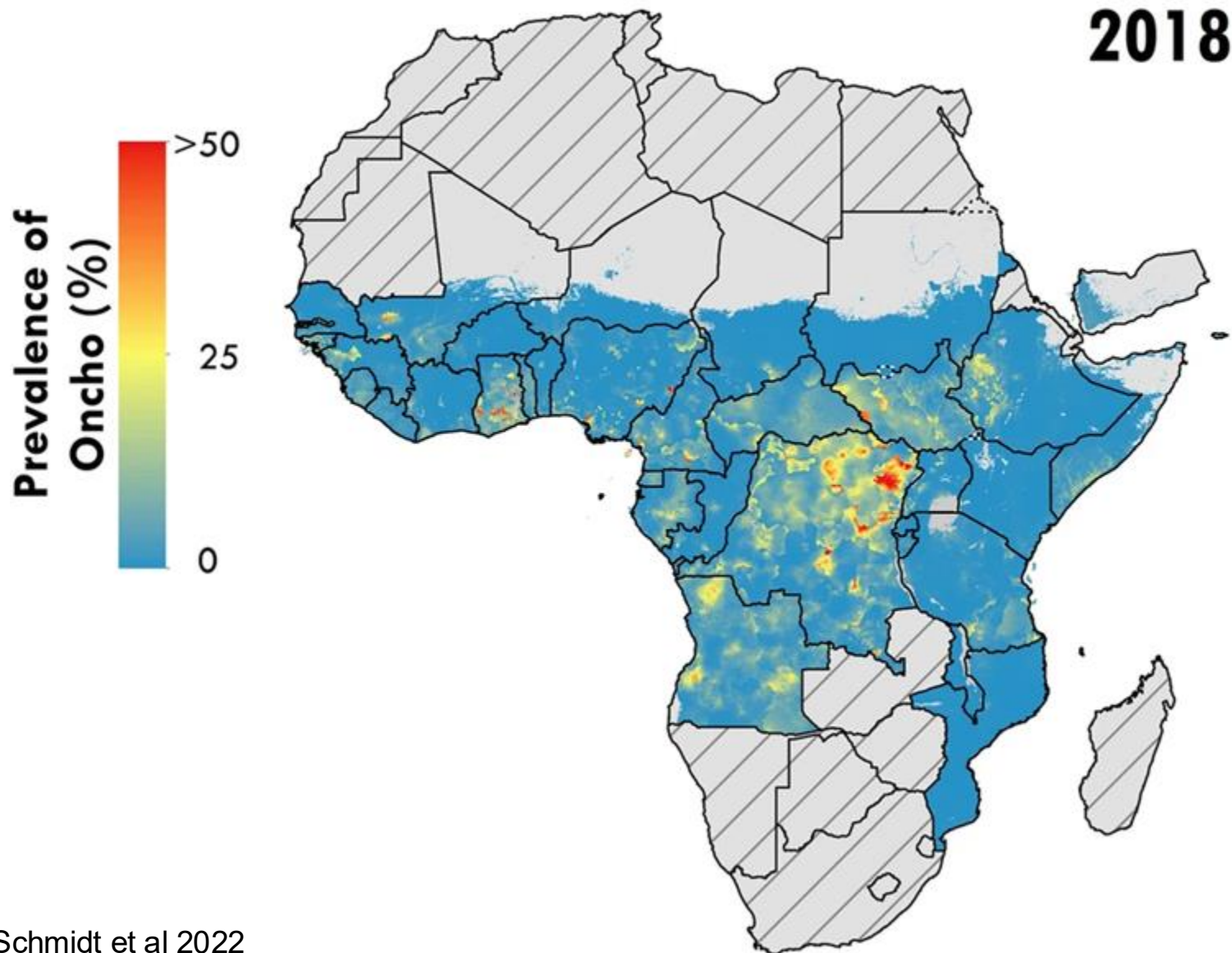


Prevalence of onchocerciasis, 2019

The prevalence of onchocerciasis in a population measured per 100,000 people. Onchocerciasis, also called river blindness, is an eye infection caused by parasitic worm, which can lead to blindness.



Distribution of Onchocerciasis in Africa and the Middle East

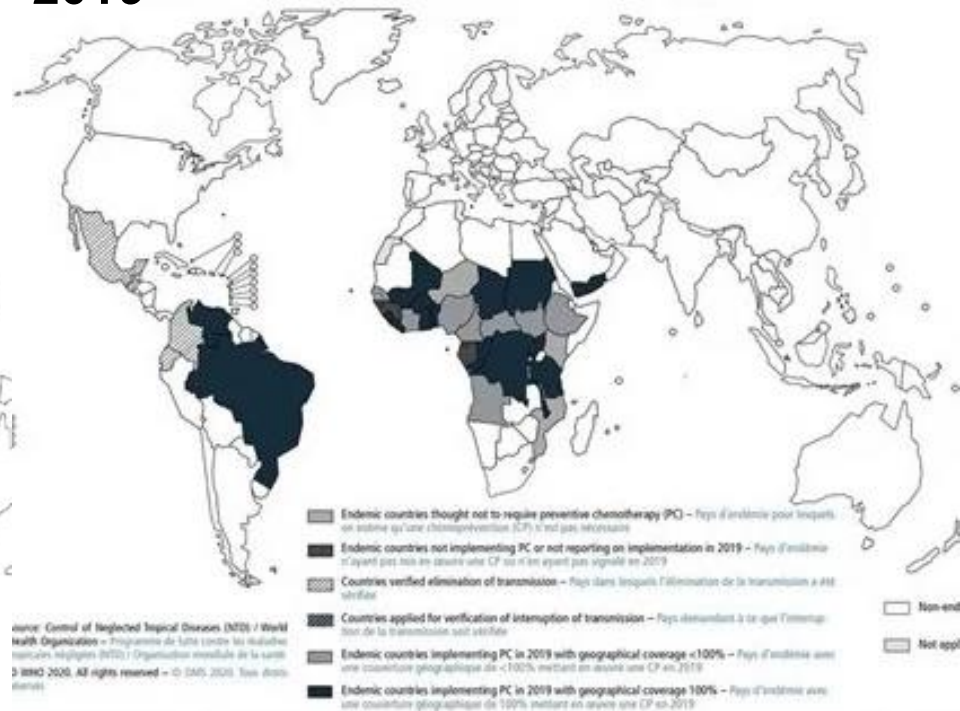


Status of MDA for Onchocerciasis in endemic countries

2015



2019

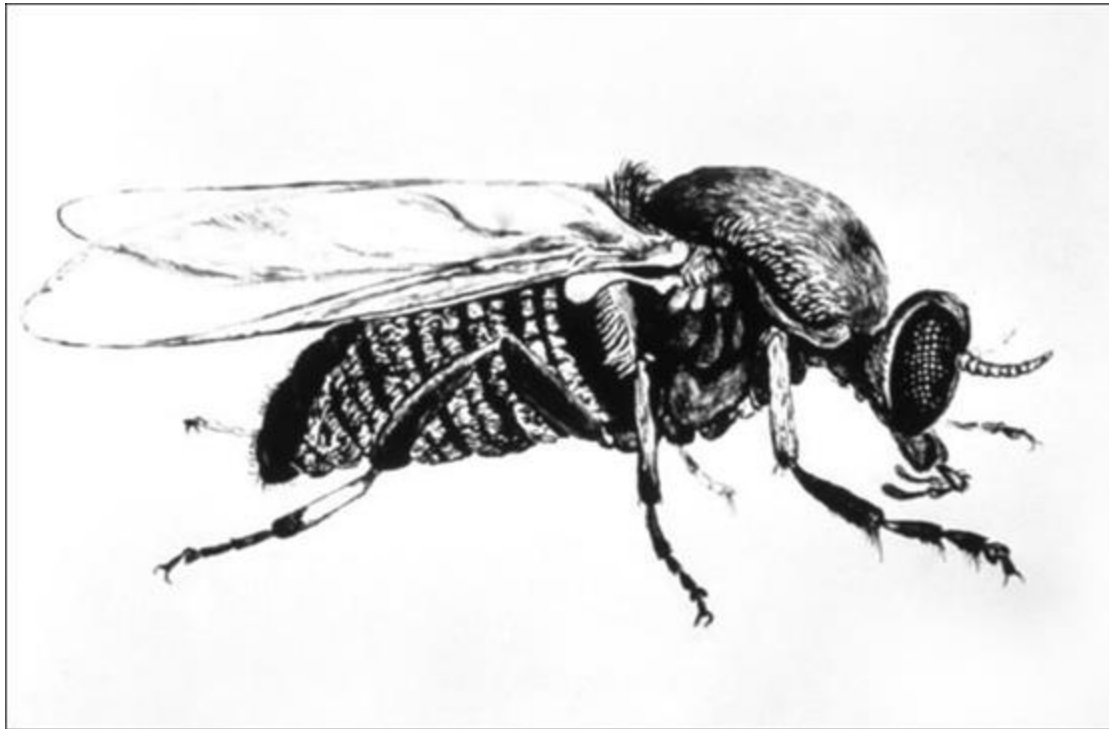


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Onchocerciasis 2018 Updated Review: Smith et. al.

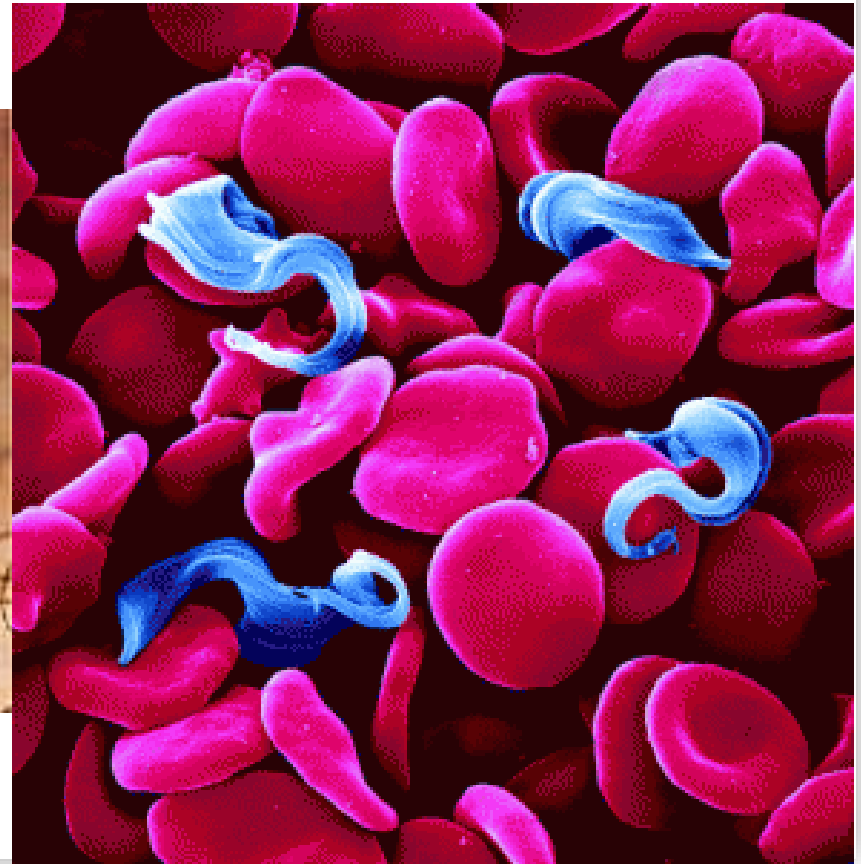
<http://emedicine.medscape.com/article/224309-overview>



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Human African Trypanosomiasis (Sleeping Sickness)

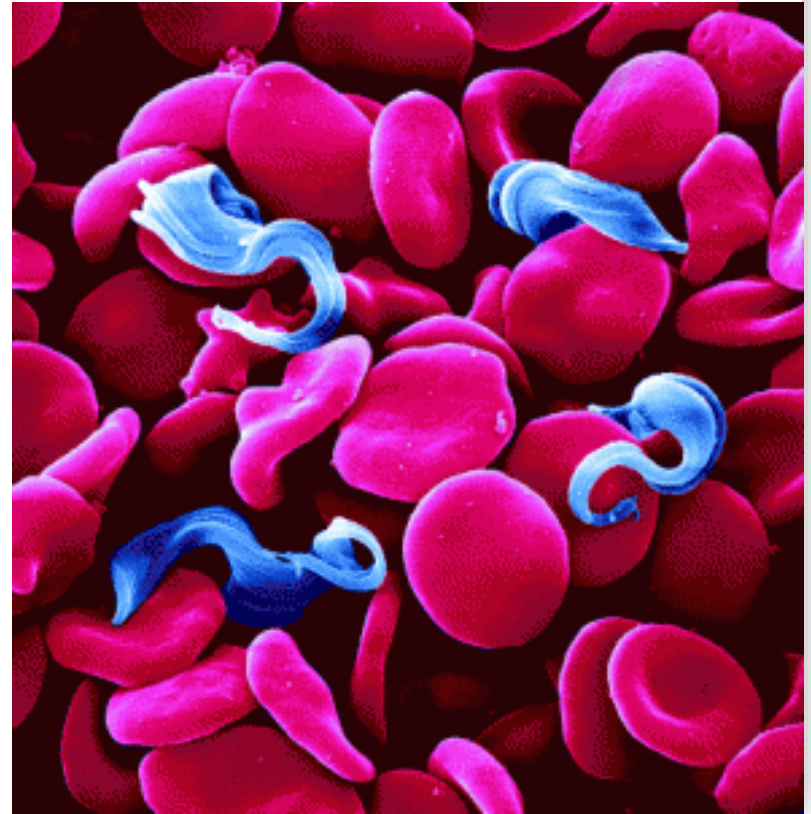


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Causal Agent: *Trypanosoma brucei*

- Protozoan blood parasite
- 3 subspecies:
 - *Trypanosoma brucei gambiense*
 - *Trypanosoma brucei rhodesiense*
 - *Trypanosoma brucei brucei* (animals only)



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African Sleeping Sickness

- Transmitted by Tsetse flies
- Affects 36 countries
- >80% of cases limited to northern Angola, DR Congo, South Sudan & neighboring countries
- Slow disease development over months and years
- Treatment is difficult
- 100% fatal if untreated

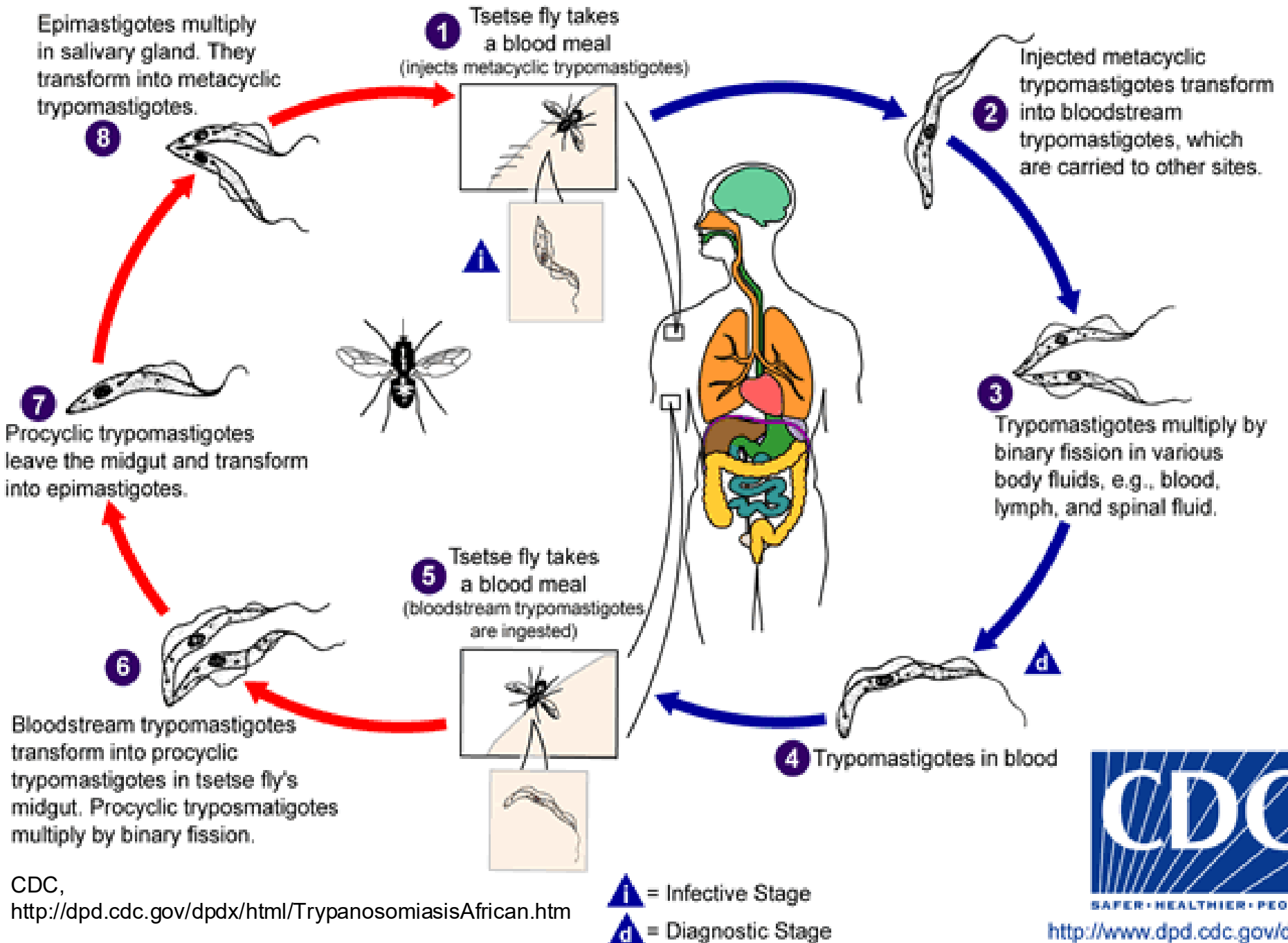


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Tsetse fly Stages

Human Stages



Transmission of Trypanosomiasis

- *T.b.gambiensis*
 - Usually rural population
 - Mostly person to person via tsetse fly vector
 - Several zymodemes: pigs, cattle, dogs, wild ungulates (kob, hartebeest)
 - Duration of illness is months to years, thus ongoing transmission
- *T.b.rhodesiensis*
 - Rural population in proximity to animal source, tourists
 - Many domesticated animals, cattle, wild ungulates, lions
 - Blood transfusion
 - Congenital
 - Short clinical course (<9 months)

D. Scott Smith, MD



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African Sleeping Sickness

- Was rampant at the turn of the 20th Century
- Reduced massively during colonial control programmes to kill tsetse
- Re-emerged after independence of central African countries
- Now at pre colonial levels again
- Part climate, part war impacts

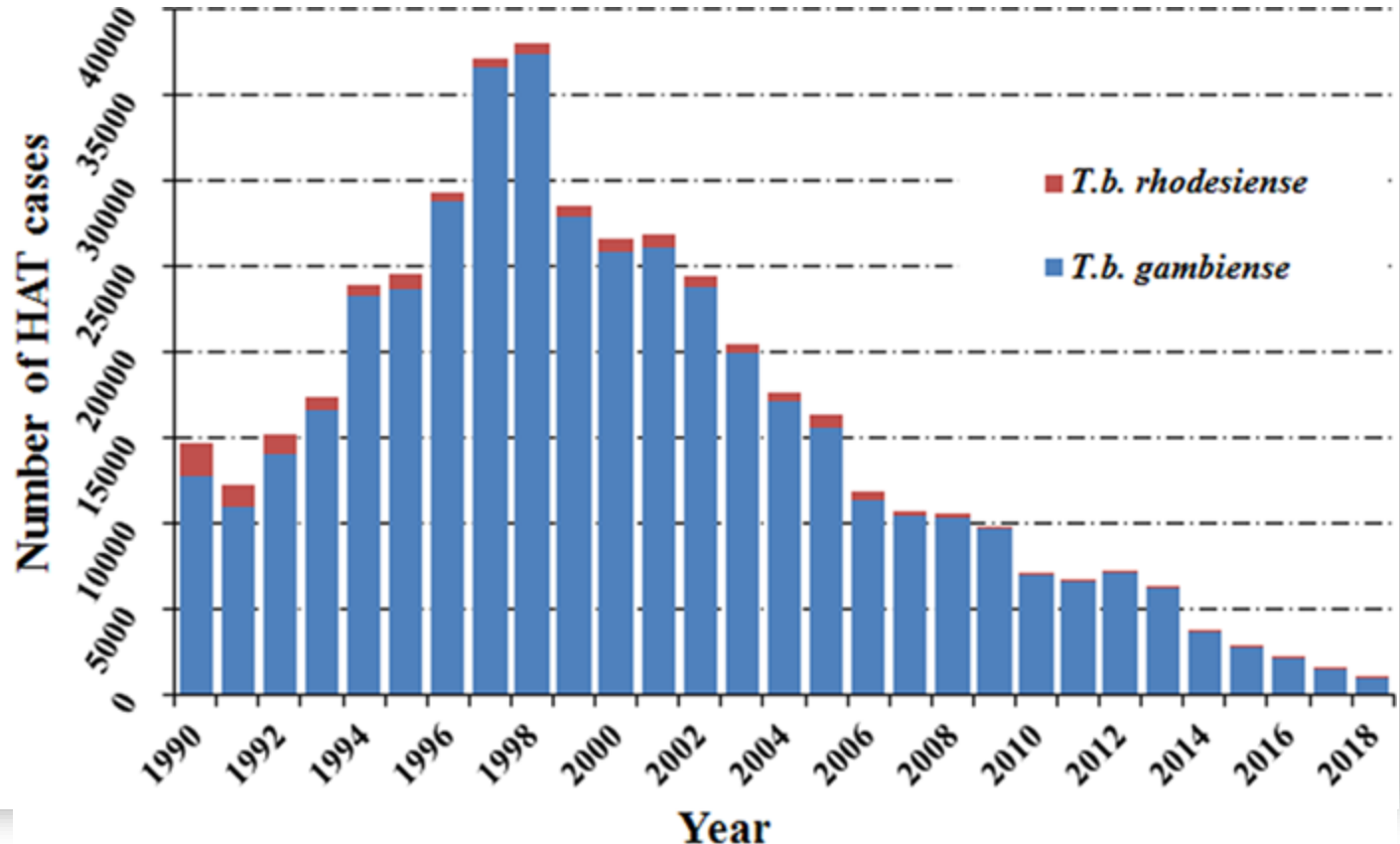


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HAT Epidemiology

- The total amount of reported HAT cases has decreased substantially over time.



Cases reported to
WHO

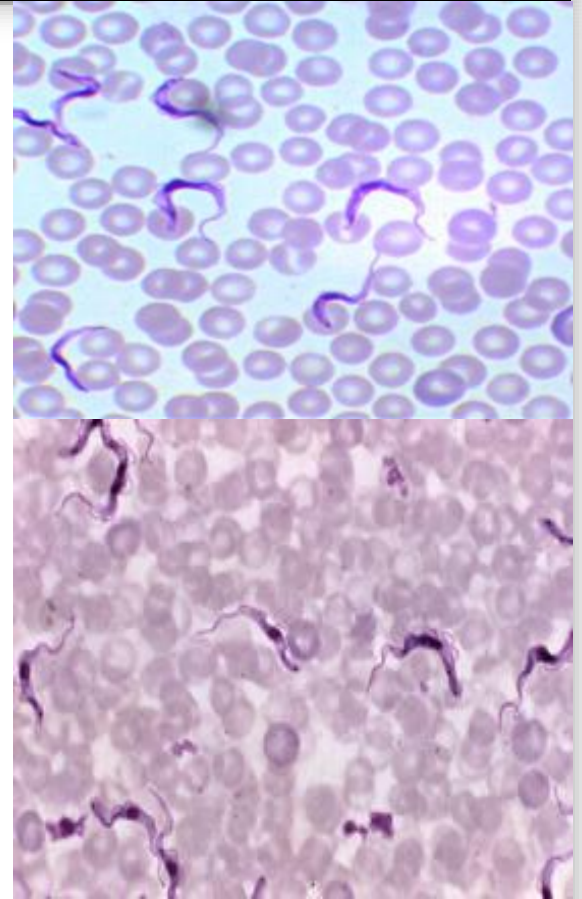


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African Sleeping Sickness

- Multiple HAT outbreaks have occurred over the last century.
- Armed conflict in Africa has escalated disease rates in recent years.
- Continued displacement of populations may cause many more outbreaks.
- Displacement widens the geographic disease spread.

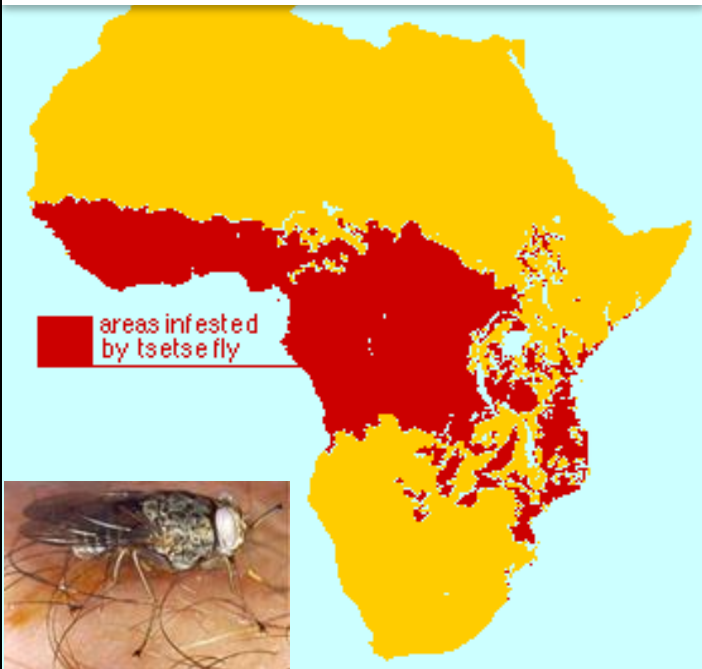


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Geographical Distribution of African Trypanosomiasis

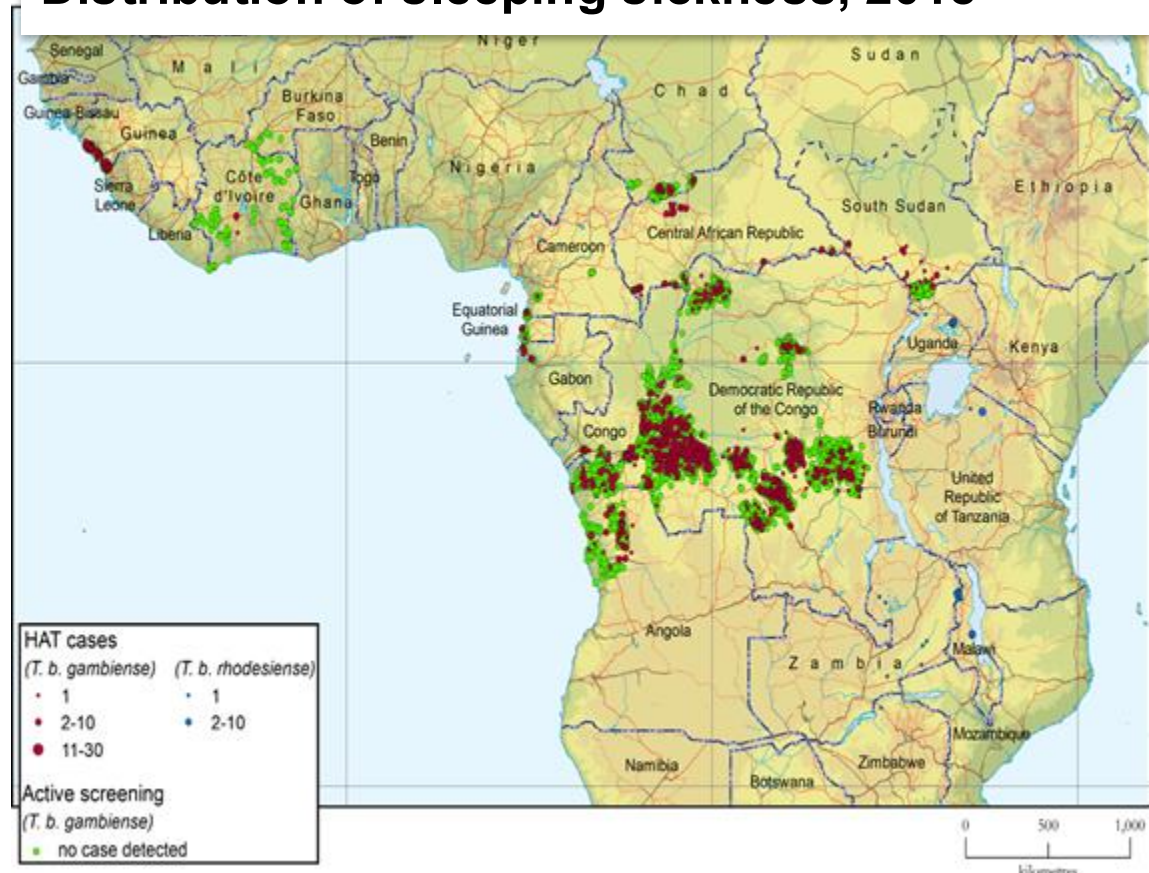
Areas infested by the Tsetse Fly



- *Tb gambiense* (97% all cases) is found mostly in Western and Central Africa
- *T.b. rhodesiense*, mostly in Eastern and Southern Africa

- 200 active foci of HAT between latitude 15 degrees North and 15 degrees South (1998 - WHO)

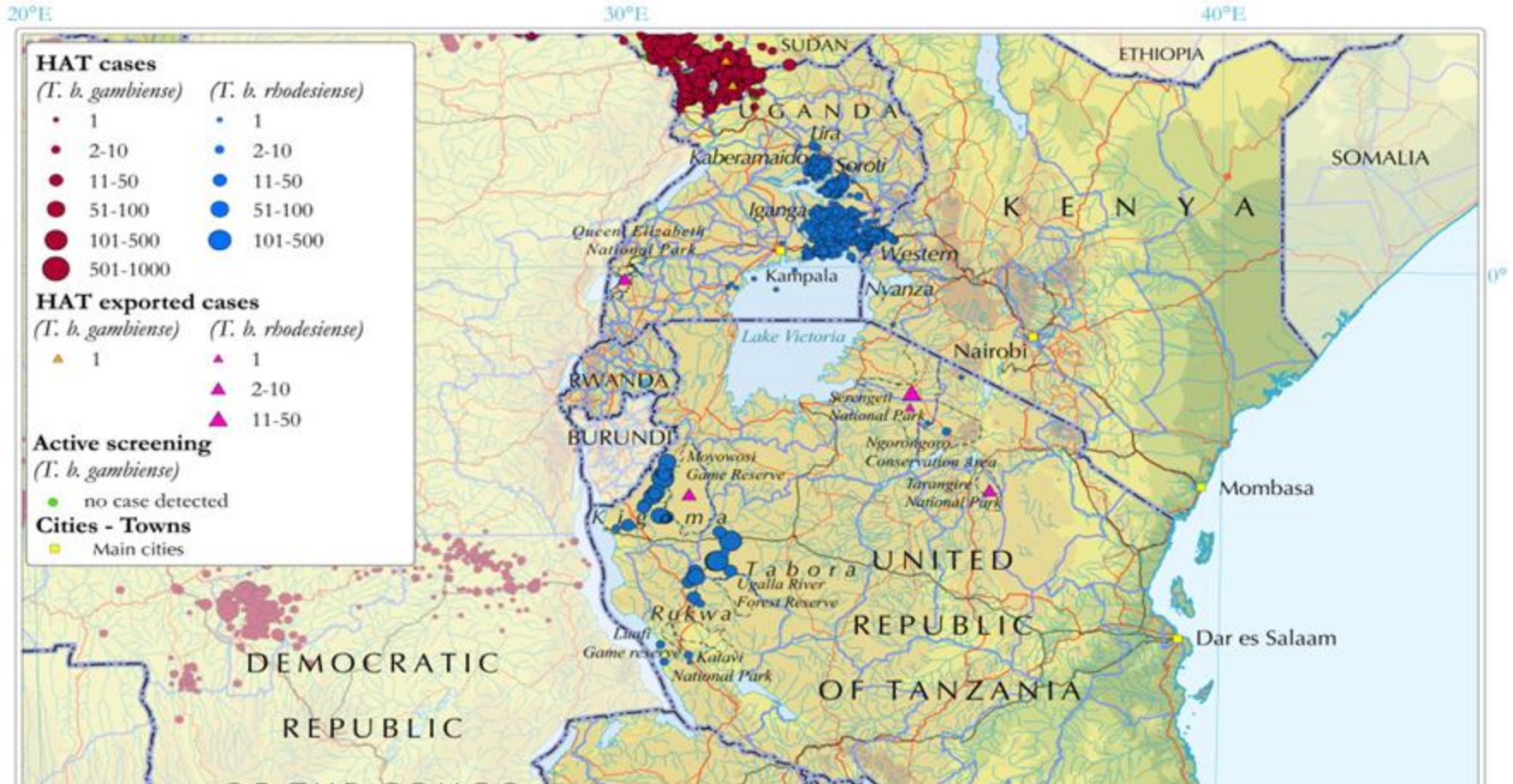
Distribution of sleeping sickness, 2018



African Trypanosomiasis in East Africa.

The Atlas of human African trypanosomiasis (2000-2009)

Eastern and South-eastern Africa



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Most tsetse fly bites occur at water points when humans are distracted

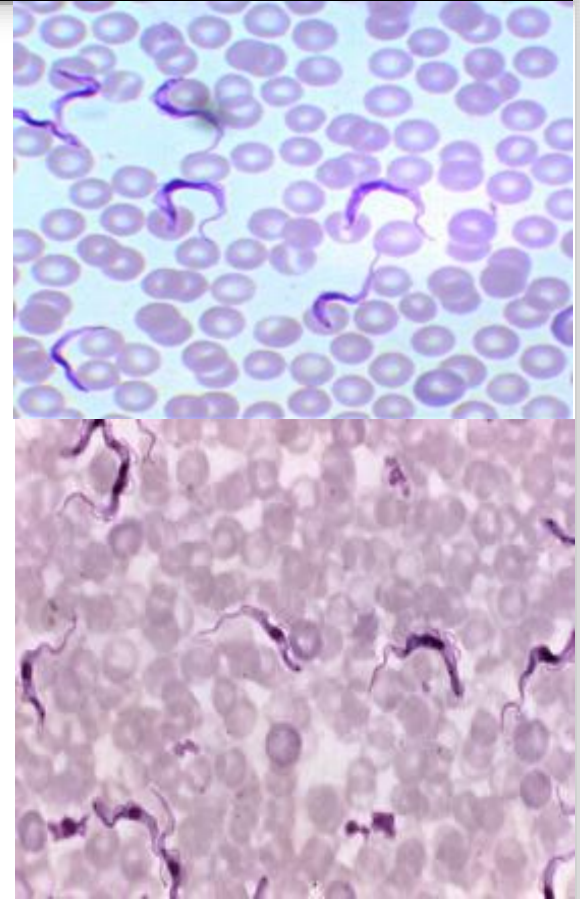


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Epidemiology of HAT

- Approx. 50 million people live in areas conducive to disease transmission
- **The number of cases reported annually is considered to be a fraction of the real burden (663 in 2020)**
- The likely number of cases is estimated to be at least 20,000 per year
- HAT affects 36 countries in sub-Saharan Africa



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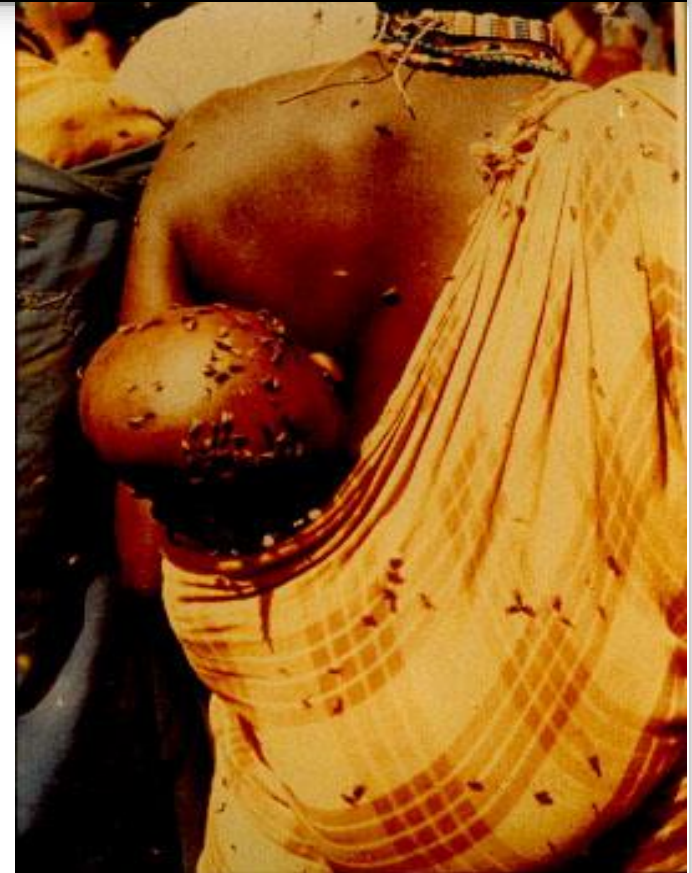
Mechanical Vectors of Immediate Disease Risks



What is *Mechanical Transmission*?

“a form of indirect transmission in which the infectious agent does not undergo physiologic changes inside the vector” (CDC definition)

21 species of filth flies transmit human gastrointestinal diseases (viral, bacterial, parasitic). So can cockroaches.



Hinshaw, J. (2000)..



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Flies breed in domestic, human & animal waste all year round



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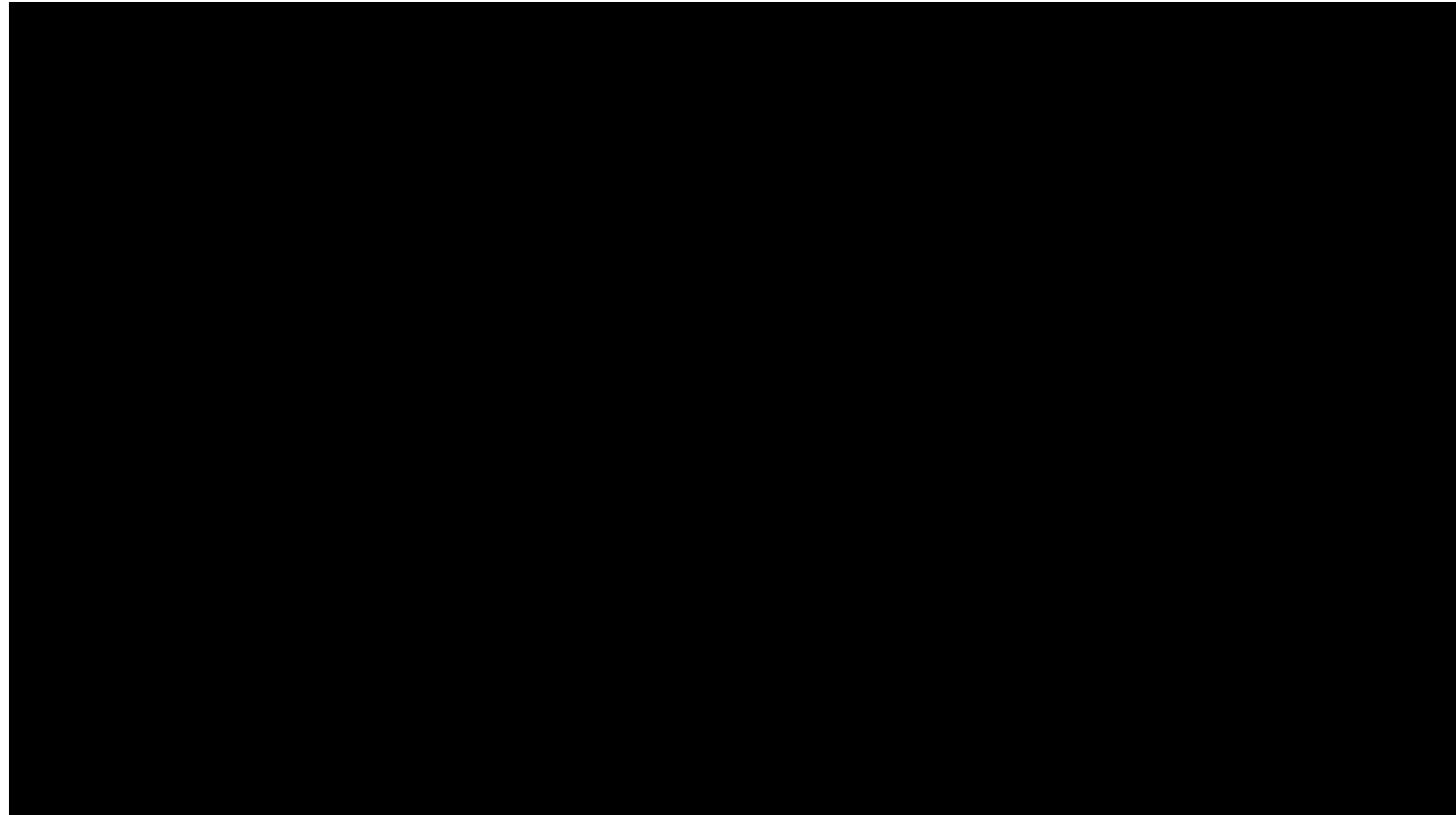
Flood Damage & Mechanical Vector Breeding Sites

- Open defecation sites are common amongst the displaced .
- Flies breed exponentially in these sites.
- Handwashing facilities?



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“Super” Transmitters

Carry Pathogens on:

- Spongy mouthparts
- Body and leg hairs (*setae*)
 - sticky substance
 - adherence during fly resting periods
- Sticky pads of the feet (*tarsi*)



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Mechanical Transmission

- Pathogens transferred from an infected host, or a contaminated substrate, to a susceptible host.
- These cause gastrointestinal diseases = “diarrheal disease”

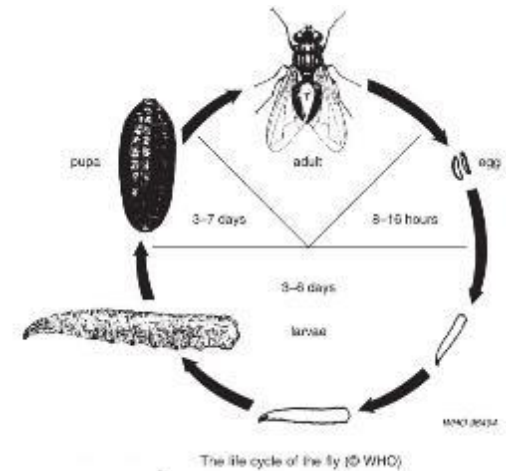


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Flies – Life Cycle

- Eggs are usually laid in masses on organic material such as manure and garbage. Hatching occurs within a few hours
- 6 - 42 days for the egg to develop into the adult fly (species, temperature, type & quantity of food available)
- The length of life is usually 2–3 weeks (longer when colder)



WHO: Biology of houseflies

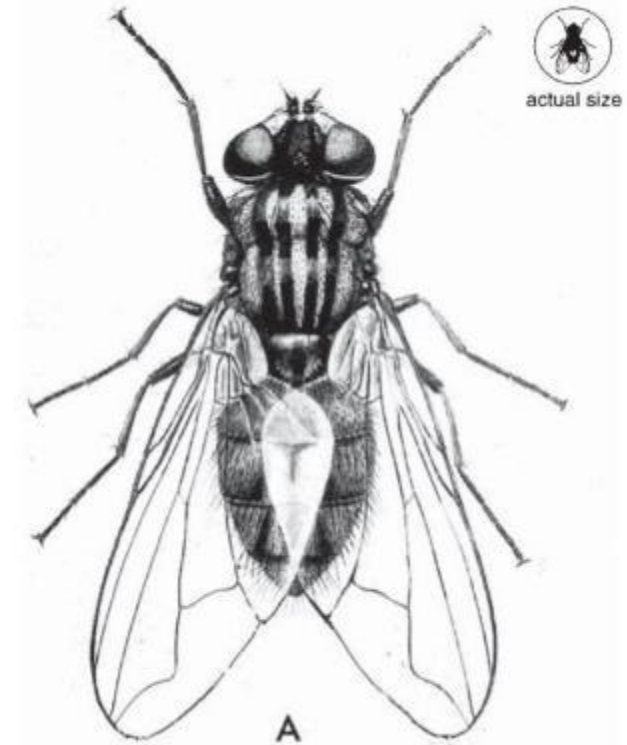


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Vectors - (*Musca domestica*)

- Lives in close association with people
- Thorax is a shade of grey, (sometimes even black), with four longitudinal bands of even width on the dorsal surface
- Serve as mechanical vectors to over 100 pathogens, such as those causing typhoid, cholera, and salmonellosis



WHO: Biology of houseflies



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Vectors - (*Musca sorbens*)

- Needs temperatures between about 16 to 40°C with 28°C being optimal
- 6 mm long, 2 dark stripes on the thorax
- Breeds in human faeces
- Feeds on the secretion produced by eyes of people
- Responsible for the transmission of *Chlamydia trachomatis*

Musca sorbens



Figure 2.3.
***M. sorbens* (WHO, 1997)**

WHO: Biology of houseflies



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Vectors - (*Chrysomya* spp.)

- Breeds in open latrines, garbage, animal excrement
- Compact body, 10-12 mm
- Metallic blue or green bodies
- Responsible for diarrhoeal diseases, dysentery, transmission of intestinal worm eggs

***Chrysomya* spp.**



Figure 2.4.
***Chrysomya* spp. (UNHCR, 1996)**

WHO: Biology of houseflies



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Cholera



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NOTICE.

PREVENTIVES OF

CHOLERA!

Published by order of the Sanatory Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!

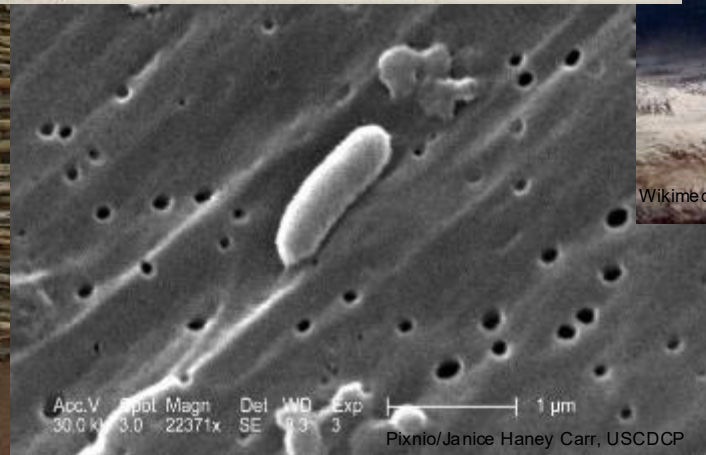
Avoid Raw Vegetables and Unripe Fruit !.

Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

New York Historical Society



Wikimedia Commons



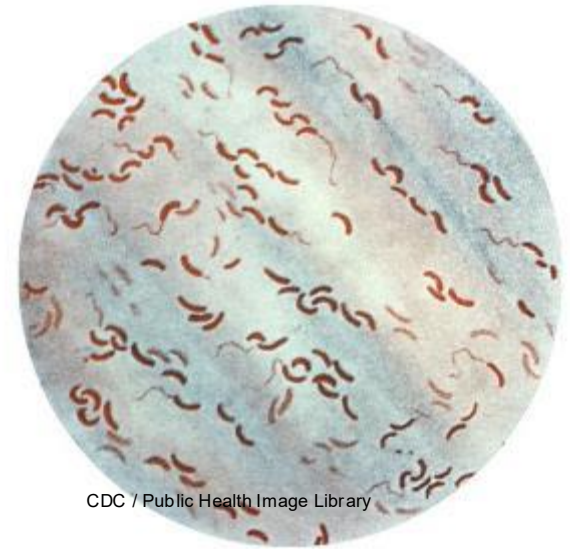
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Pixnio/Janice Haney Carr, USDCDP



Vibrio cholerae

- Family: *Vibrionaceae*
- Gram-negative, non-spore-forming curved rod, about 1.4–2.6mm long
- Motile by means of a single, sheathed, polar flagellum
- Capable of respiratory and fermentative metabolism



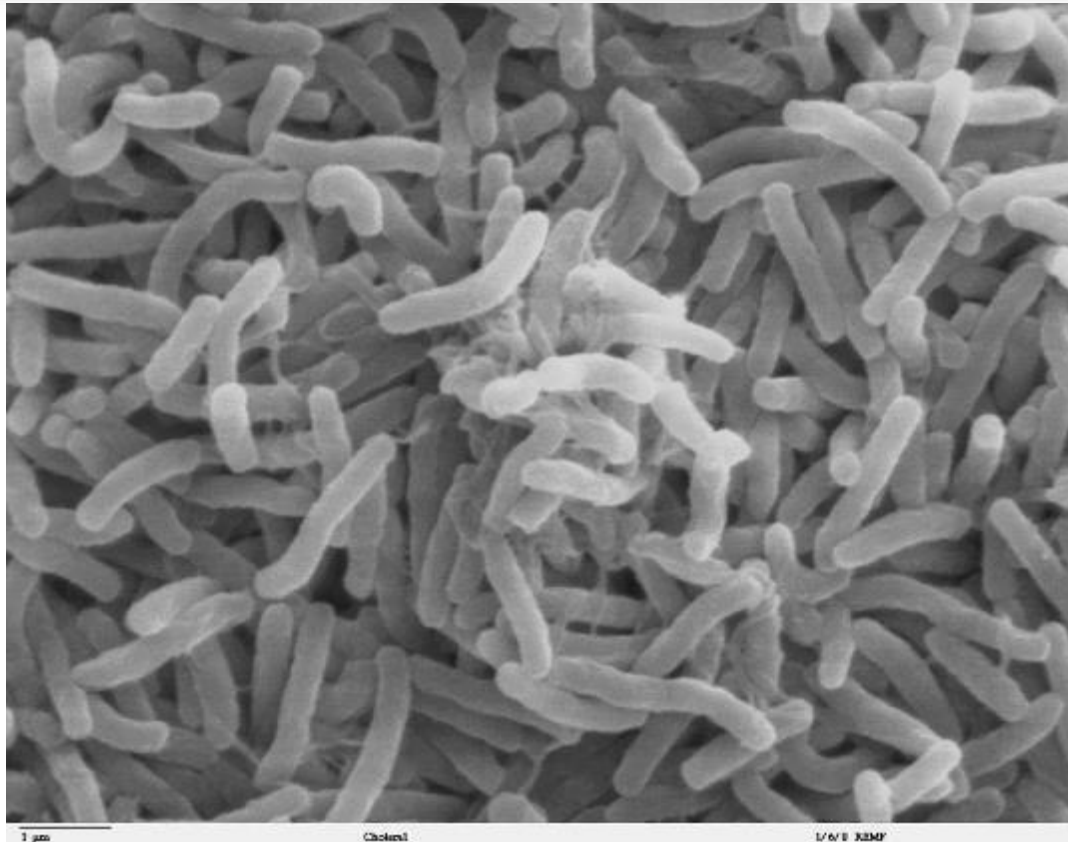
WHO: Guidelines for Drinking-Water Quality – *Vibrio Cholerae*



REDUCING DEATHS AND SUFFERING
FROM **TROPICAL DISEASES**



Vibrio cholerae



T.J. Kim, M.J. Lafferty, C.M.P Sandoe and R.K. Taylor, 2000, "Delineation of pilin domains required for bacterial association into microcolonies and intestinal colonization", Molecular Microbiology, Vol. 35(4):896-910



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Vibrio cholerae

- Many different types or serogroups
- Only two can cause epidemic cholera: Serogroup O1 and serogroup O139
- Other serogroups are known collectively as non-O1 and non-O139. These serogroups can cause a diarrheal disease but with less severity than cholera and do not have epidemic potential

WHO: Guidelines for Drinking-Water Quality – Vibrio Cholerae



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Vibrio cholerae

- After passage through the acid barrier of the stomach, the organism colonizes the small intestine
- Enterotoxin produced by vibrios is secreted across the bacterial outer membrane and disrupts the ion transport by intestinal epithelial cells
- The subsequent loss of water and electrolytes leads to the severe diarrhoea characteristic of cholera

WHO: Guidelines for Drinking-Water Quality – Vibrio Cholerae



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Cholera - Transmission

- Transmission is closely linked to inadequate access to clean water and sanitation facilities
- The source of contamination is usually the faeces of an infected person that contaminates water and/or food



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Cholera - Transmission

Mechanical vectors
such as flies and
cockroaches can
disseminate *V.
cholerae*



Wikimedia Commons/Romerito Pontes

Fotedar, R. (2001). Vector potential of houseflies (*Musca domestica*) in the transmission of *Vibrio cholerae* in India. *Acta Tropica*, 78(1).

Nazni, W.A.; Seleena, B.; Lee, H.L.; Jeffery, J.; Rogayah, T.A.R.; Sofian, M.A. (2005) Bacteria Fauna from the House Fly, *Musca domestica* (L.). *Tropical Biomedicine*, 22 (2).



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Cholera - Transmission



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Cholera - Epidemiology

- Estimated 1.3 million to 4.0 million cases of cholera, and 21,000 to 143,000 deaths worldwide
- During 2017, 1 227 391 cases were notified from 34 countries (5654 deaths) → Discrepancy due to many cases not being recorded due to limitations in surveillance systems and fear of impact on trade and tourism

WHO (2018) Factsheet on cholera

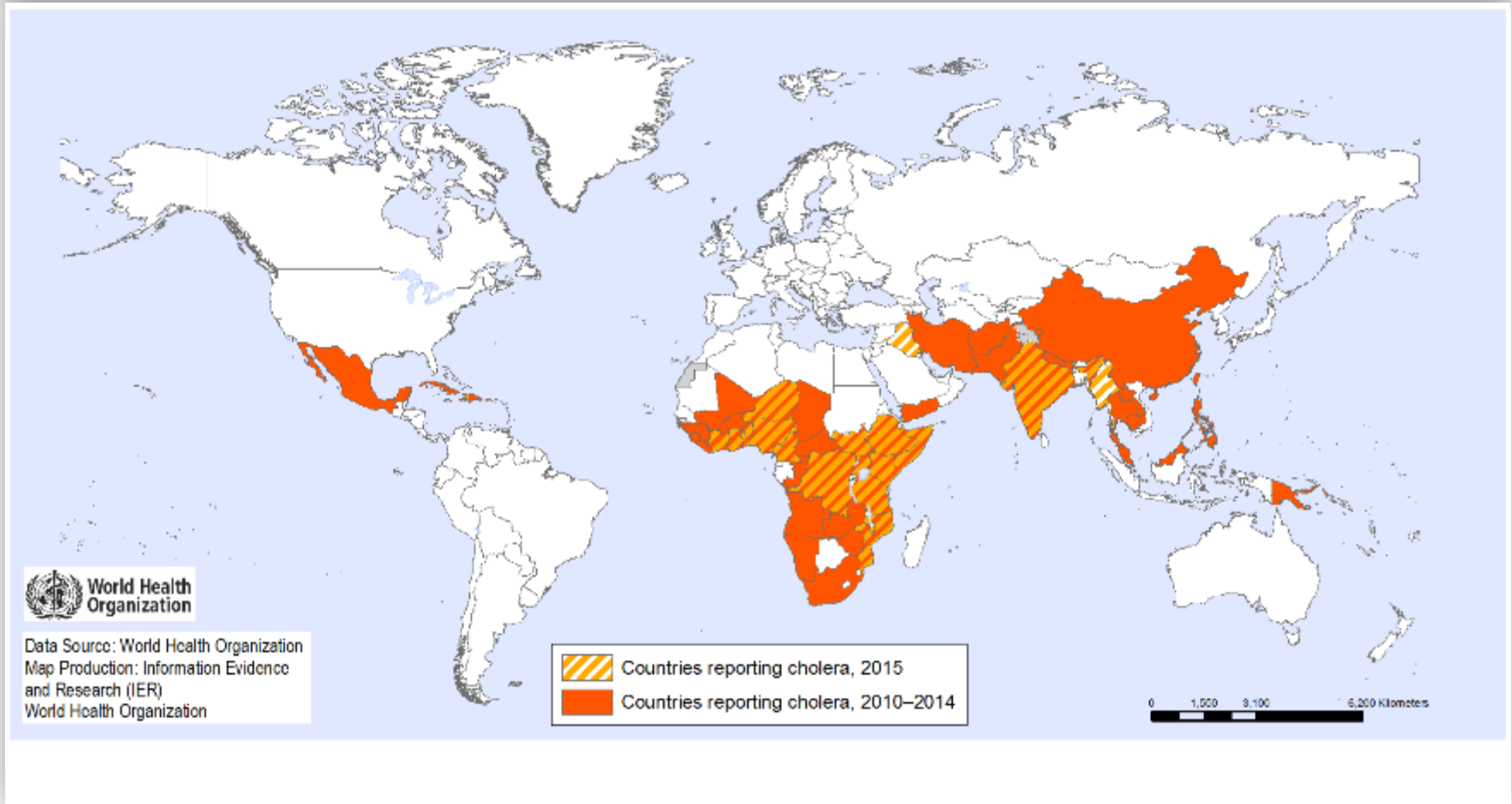
Ali, M. et al. (2015). Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis; 9:6.



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Cholera - Epidemiology



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Cholera – Clinical Symptoms



Pixnio/Kendra Helmer, USAID



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Cholera – Clinical Symptoms

- Clinical spectrum that ranges from asymptomatic colonization to cholera gravis, the most severe form of the disease
- Following ingestion, *V. cholerae* colonizes the small intestine for 12 to 72 hours before symptoms appear
- Begins with stomach cramps and vomiting followed by diarrhoea, which may progress to fluid losses of up to 1 litre per hour

WHO (2018) Factsheet on cholera



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Cholera – Clinical Symptoms

- Fluid losses result in severe fluid depletion
→ may lead to circulatory collapse and death
- Symptomatic patients may shed vibrios before the onset of illness and will continue to shed organisms for 1 to 2 weeks
- Asymptomatic patients typically shed vibrios in their stool for 1 day



Wikimedia Commons/Mark Knobil

WHO (2018) Factsheet on cholera

Nelson, E.J. et al. (2009). Cholera transmission: the host, pathogen and bacteriophage dynamic. Nat Rev Microbiol.; 7(10).



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Cholera – Diagnosis

- Gold standard: Isolation and identification of *V. cholerae* by culture of a stool specimen
- “Culture of the bacteria or its detection by PCR remains essential for the confirmation of the presence of the etiologic agent of cholera”



Pixnio/USCDCP

WHO (2017) – Global Task Force on Cholera Control Target Product Profile (TPP) for the development of improved Cholera rapid diagnostic tests



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Cholera – Diagnosis

- Crystal® VC is an RDT for the qualitative determination of antigens of both O1 and O139 serogroups from stool specimens
- Can provide an early warning to public health officials in areas with limited or no laboratory testing
- Sensitivity and specificity not optimal



Flickr / Ashley Greiner, CDC

CDC/*Vibrio cholerae* infection – Diagnosis and Detection



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Cholera – Treatment

- Most people can be treated successfully through prompt administration of oral rehydration solution
- Patients may require up to 6L of ORS to treat moderate dehydration on the first day
- Severely dehydrated patients require rapid administration of intravenous fluids
- Should also be given antibiotics to limit amount and duration of *V. cholerae* excretion in their stool

WHO (2018) Factsheet on cholera



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Cholera – Treatment: ORS



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Cholera – Vaccines

- WHO pre-qualified oral cholera vaccines (OCV):
- Dukoral® is administered with a buffer solution
- Can be given to all individuals over the age of 2 years



Wikimedia Commons / Dvermeirre

WHO (2018) Factsheet on cholera



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Cholera – Vaccines

- Shanchol™, and Euvichol® do not require a buffer solution for administration
- They are given to all individuals over the age of one year
- Vaxchora (oral) FDA US 6/2016

WHO (2018) Factsheet on cholera



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Prevalence of Parasitic Infections

Disease	At risk population	Estimated Cases	Annual Deaths
Malaria	3.3 billion	250 million	0.64 million
Schistosomiasis	251 million	>75 million	~200,000
Lymphatic Filariasis	50 million	51 million	?
African Trypanosomiasis	50 million	>3,500	~1360
Leishmaniasis	1 billion	~1.2 million	20,000 – 50,000
Onchocerciasis	180 million	7 million	?

The tip of the iceberg = The eyes of the hippopotamus

