EXOTIC TROPICAL INFECTIONS

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Introduction

An exotic infection should strictly be understood as an infection originating from another country or one that is unfamiliar to a region. It can also refer to a disease in a region under a government eradication program or one that is being monitored. From an epidemiological perspective, an exotic infection is a disease that is more likely to occur in certain parts of the target population than others.

According to the World Health Organization (WHO) "tropical diseases" web page, there are eight diseases that occur exclusively in tropical regions. These are primarily infectious diseases that thrive in hot and humid climates. These diseases include protozoan infections such as malaria, leishmaniasis, Chagas' disease, and sleeping sickness. Other diseases are caused by worms, such as schistosomiasis, onchocerciasis, and lymphatic filariasis, while one is viral, namely dengue fever. These eight tropical diseases listed by WHO are typically transmitted to humans via various vectors, generally hematophagous insects. However, schistosomiasis is an exception as it involves intermediary hosts like snails, which release infectious forms into water, subsequently infecting humans.

The term "tropical diseases" was not coined by the WHO; it has been part of medical terminology since the 19th century. This designation did not emerge at a specific point in time but gradually became established as microorganisms were identified as disease -causing agents and their transmission methods were understood. During the colonial expansion of countries like England, France, and other minor powers, including the United States, into the Caribbean, Pacific, and African regions, a new world of exploitable resources was discovered, along with unfamiliar and undesirable diseases. Because many of these new colonies were situated in tropical regions, these strange and exotic diseases were labeled as "tropical." These diseases primarily occur in countries between the Tropic of Cancer and the Tropic of Capricorn, between latitudes 27° 23' north and south. However, there are exceptions in Middle and Eastern countries,

where underdevelopment and poverty contribute to the prevalence of these diseases.

Recognizing this situation, agencies such as UNICEF, the World Bank, and the WHO launched the Special Program for Research and Training in Tropical Diseases (TDR) thirty years ago. This program focused on infectious diseases that disproportionately impact the “poor and outcast populations” globally. The TDR quickly added tuberculosis and leprosy to the WHO’s list of classical tropical diseases. Over time, additional diseases were included in the Neglected Tropical Diseases list (NTD), such as Trachoma, Buruli ulcer, Dracunculiasis, Dengue fever, and Yaws. Currently, the list comprises fourteen neglected tropical diseases. Paradoxically, this number tends to increase as health conditions in underdeveloped populations improve. This is because only one of these diseases (dracunculiasis) is near eradication, while the others have been neglected due to more pressing ailments that have gained prominence in global health initiatives. This neglect has contributed to the phenomena of emerging and reemerging diseases. These exotic tropical infections are discussed below:

African Trypanosomiasis

African trypanosomiasis, commonly known as sleeping sickness, is a quintessential tropical disease caused by two subspecies of Trypanosoma brucei, both specific to humans. The disease shows clinical polymorphism, but in its severe form, it remains asymptomatic for a prolonged period before the central nervous system becomes critically affected. This leads to paralysis, lethargy, cognitive decline, and ultimately death. Initially called "Negro lethargy," the disease was renamed "sleeping sickness" as it began to affect white settlers. While the disease is now treatable, the treatment remains costly and challenging to administer.

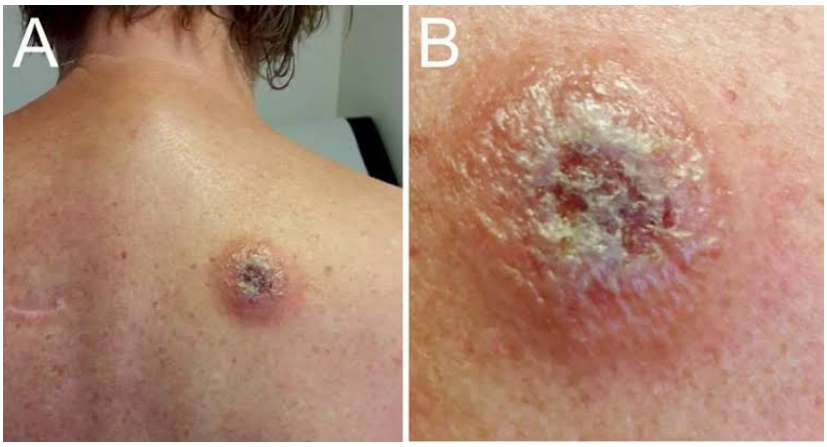

Fig 1: Trypanosomal chancre

In the 19th and 20th centuries, millions of Africans were afflicted by sleeping sickness, with an estimated 300,000 to 500,000 people infected in 1990 alone. The disease manifests in episodic epidemic outbreaks and has never been reported outside Africa, whether in the tropics or elsewhere. Trypanosomiasis is prevalent across a vast swath of African territory, home to about 70 million people, stretching from the Indian Ocean to the Atlantic, and from the Sahara Desert to the Kalahari, sparing only the northern and southern edges of the continent. The reason for this geographic limitation is the disease's transmission by the voracious hematophagous tsetse fly, which thrives only within these boundaries. This area, known as the "tsetse belt," spans roughly between latitudes 20° N and 20° S. Numerous species of tsetse flies (genus Glossina) spread different trypanosomes among wild mammals, reptiles, and birds. This has significant economic implications, as they also transmit diseases to domestic animals such as cattle, sheep, goats, and horses. Pigs, a favored host of the tsetse fly, also carry trypanosomes, including those that infect humans.

The human trypanosomes, Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense, are transmitted by tsetse flies from the Palpalis and Morsitans groups, respectively. Palpalis glossinas thrive in ancillary woods or shrublands near water bodies and typically feed on the blood of large reptiles like crocodiles. Morsitans glossinas, on the other hand, prefer savannas and primarily bite wild ruminants. Neither species of fly exists outside the tsetse belt. Despite the extensive slave trade, neither glossinas nor African trypanosomiasis established themselves in the New World. Although many other flies, such as the common housefly and the blowfly, made the

journey, the tsetse fly did not. Nor did it spread eastward, despite long-standing trade routes between Africa, India, and the Middle East. The strict geographic confinement of Glossina to Africa explains why sleeping sickness remains a tropical disease—more accurately, a strictly African disease.

Onchocerciasis

Onchocerciasis, though not as exclusively African as some other diseases, remains fundamentally tropical. It is caused by the nematode Onchocerca volvulus, which resides in the human dermis. Here, small male worms (around 4 cm) and larger female worms (up to 50 cm) coil and intertwine, forming skeins that develop into nodules or dermal swellings, which resemble tumors. These nodules, while not always suppurative, are unsightly and tend to appear on exposed areas of the skin, particularly the face and scalp. In populations that are naked or semi-nude, these nodules, or onchocercomas, can appear anywhere on the body. The worms reproduce within the dermis, where female worms release larvae called microfilariae (about 0.5 cm long). These larvae move subcutaneously and can reach the eye's humor, cornea, and retina, causing inflammatory reactions that often result in blindness.

Onchocerciasis is a significant health issue in Equatorial Africa, where nearly 18 million people are affected, including 250,000 who are already blind. The disease is transmitted by black flies of the genus *Simulium*, which breed in clear water rivers and streams. The suffering caused by the disease is so profound that the World Health Organization's gardens in Geneva feature a sculpture depicting a child leading a blind, onchocercotic old man.

Ivermectin, the drug used to treat onchocerciasis, is provided free of charge by its manufacturer to support anti-onchocerciasis programs. The disease has also spread to the New World, affecting regions in Ecuador, Colombia, Venezuela, Central America, southern Mexico, and particularly the Amazon region of Brazil. However, in the Americas, the disease affects fewer people and generally does not lead to blindness, possibly due to differences in the filariae's affinity for the retina and cornea.

Despite the widespread presence of black flies in Brazil, especially in regions where

slave traffic once thrived, onchocerciasis is surprisingly less common, and its distribution is limited primarily to the Amazon region. This limited occurrence raises questions about the disease's transmission dynamics and the environmental or biological factors that may influence its prevalence.

Could onchocerciasis be a specifically equatorial disease, that is, a subtype of tropical disease? Perhaps the interaction between the microfilariae and black flies is facilitated by the specific environmental conditions found in equatorial regions that support both the survival of black flies and the development of the parasite. Therefore, the equatorial regions of Africa and the New World are indeed conducive to the transmission of onchocerciasis due to the optimal climatic conditions necessary for the life cycle of the parasite and the breeding of black flies. This geographic restriction underscores the link between tropical diseases like onchocerciasis and the environmental conditions that support their transmission.

Lymphatic Filariasis

Lymphatic filariasis, caused by parasitic worms such as Wuchereria bancrofti and Brugia malayi, is indeed another example of a tropical disease. It is found predominantly in tropical and subtropical regions worldwide. Wuchereria bancrofti is widespread throughout the tropics, including Africa, Asia, the Western Pacific, and parts of the Americas. Brugia malayi, on the other hand, is mainly found in Southeast Asia.

Infection occurs when infected mosquitoes transmit larvae (microfilariae) to humans during a blood meal. These larvae mature into adult worms in the lymphatic vessels, where they can live for several years. Adult female worms produce microfilariae that circulate in the bloodstream, where they can be taken up by mosquitoes during subsequent blood meals, completing the cycle. The adult worms of Wuchereria bancrofti and Brugia malayi are specialized to live and reproduce exclusively in the lymphatic system of humans. They are not known to infect any other animal species.

Over time, repeated infections with these worms can lead to lymphatic dysfunction and

enlargement, a condition known as lymphedema or elephantiasis. This occurs due to the blockage and damage of lymphatic vessels by the worms, causing swelling and accumulation of lymphatic fluid.

The restricted geographic distribution of lymphatic filariasis is influenced by the specific environmental conditions required for both the mosquitoes that transmit the disease and the development of the parasitic worms in humans. This reinforces the association between tropical diseases and their dependence on particular ecological and climatic factors found in tropical regions.

Fig 2: Lymphatic Filariasis (Credit: Department of clinical microbiology and parasitology irrua specialist teaching hospital irrua edo state Nigeria)

Lymphatic filariasis, caused by filarial worms transmitted through mosquitoes, particularly species like Culex, affects over 120 million people globally, with Brazil alone reporting approximately 50,000 cases. The disease can lead to debilitating conditions

like elephantiasis in around 40 million individuals. Despite mosquitoes like Aedes and Anopheles also capable of transmitting filarial parasites, Culex species are considered the most significant vectors. Efforts to combat filariasis, including free distribution of treatment drugs by pharmaceutical companies, have been pivotal in global control programs, contributing to a decline in disease incidence worldwide. However, the disease remains confined to tropical regions, where these mosquitoes thrive and transmit the infection across all societal groups indiscriminately.

Schistosomiases

Schistosomiasis, caused by parasitic worms and transmitted by snails, affects around 200 million people worldwide. Half of these cases are in Africa, with the remainder in the Middle East and South America, notably in Brazil and Venezuela. Three less severe forms of schistosomiasis are found in Southeast Asia, including China and Japan.

Schistosoma mansoni, one of the major species, resides in the intestinal veins. Eggs that fail to reach the intestines may cause liver inflammation and fibrosis, potentially leading to cirrhosis. Schistosoma haematobium, another major species, inhabits the veins of the vesical plexus. Its eggs can cause fibrosis and minor urinary hemorrhages, which, if chronic, can result in anemia of varying severity.

The history of Mansoni schistosomiasis in Brazil is a fascinating example of how diseases can be transported and established through human movement, in this case, the transatlantic slave trade. Schistosoma mansoni, the parasite responsible for this type of schistosomiasis, found a suitable environment in Brazil due to the presence of Biomphalaria snails, which serve as intermediate hosts. This compatibility allowed the disease to proliferate, affecting millions by the mid-20th century.

On the other hand, Schistosoma haematobium, which causes haematobic schistosomiasis, did not establish itself in Brazil despite similar conditions because it relies on specific Bulinus snail species that did not adapt to the Americas. This distinction underscores the importance of intermediate hosts in the life cycle of parasitic diseases and their geographic distribution.

The persistence of haematobic schistosomiasis in Africa, particularly in regions with

suitable Bulinus species, illustrates the concept of geographic stoicism, where certain diseases remain confined to specific areas despite global human movement. This limited spread is due to the intricate ecological requirements of the parasites and their hosts, demonstrating how environmental and biological factors influence the epidemiology of diseases.

Leishmaniases

Leishmaniases are a group of diseases caused by different species of the intracellular protozoa Leishmania, affecting humans and various animals. The cutaneous form found in the Amazon region epitomizes the "tropical curse," highlighting the disease's prevalence in certain tropical areas. However, leishmaniases are not confined to tropical regions alone; they extend to parts of the Mediterranean, including the Iberian Peninsula, Italy, Greece, and Turkey. This broader geographic distribution shows that these diseases affect both developing and developed regions.

Visceral leishmaniasis, caused by Leishmania donovani, is the most severe form of the disease. Known as kala-azar or black fever, it was first documented in India and is also found in Africa and Latin America. Visceral leishmaniasis is particularly dangerous due to its systemic nature, affecting internal organs such as the liver and spleen, and can be fatal if untreated. The global distribution and impact of leishmaniases underscore their significance as a public health concern beyond the tropics.

Visceral leishmaniasis, a severe form of leishmaniasis, affects approximately 500,000 new individuals annually. The disease is characterized by chronic and debilitating progression due to the proliferation of Leishmania parasites within the macrophages of the spleen, liver, and bone marrow. Its diagnosis is challenging, and without treatment, it is fatal. The countries most affected include India, Brazil, Ethiopia, Sudan, and several North African nations. Although it was once a significant health issue in China, it is now under control there.

In Brazil, about 3,000 new cases are reported each year. While this number is substantial, it pales in comparison to the 600,000 new cases of malaria and 100,000 cases of tuberculosis annually.

Other forms of leishmaniasis, caused by different Leishmania species, result in cutaneous or mucocutaneous ulcerations. These are disfiguring and aesthetically unpleasant but are rarely fatal. The Old World leishmanias, such as Leishmania tropica, tend to be more benign, whereas the New World species, like Leishmania braziliensis, are more aggressive. Leishmania braziliensis, identified by Gaspar Viana, is particularly notorious for causing severe lesions in the buccal and pharyngeal mucosa, which can lead to the destruction of nasal cartilage and significant facial deformities.

According to WHO estimates, around 1 million new cases of leishmaniasis are reported worldwide each year, with about 30,000 of these cases occurring in Brazil. The New World leishmaniases are endemic to the Americas and were not introduced post-Columbus; evidence suggests their presence since the arrival of Homo sapiens 30,000 to 10,000 years ago. This is supported by findings of characteristic lesions in Inca mummies and ancient statuettes dating back over 4,000 years.

Leishmania parasites are transmitted to humans by tiny sand flies, belonging to the family Phlebotomidae. In the Old World, these sand flies are of the genus Phlebotomus, while in the New World, they belong to the genus Lutzomyia. These sand flies are hematophagous, feeding on a variety of vertebrates, including amphibians, reptiles, birds, and mammals, thus spreading trypanosomes and leishmanias among them.

Different species of sand flies target various hosts for the transmission of leishmanias. For instance, visceral leishmaniasis is often associated with infected humans or dogs. This complex interaction between the sand flies, their vertebrate hosts, and the Leishmania parasites underscores the challenges in controlling and managing leishmaniasis across different regions.

In most of the world, humans are the primary reservoirs for visceral leishmaniasis. However, in Brazil, dogs play a significant role as reservoirs. For Brazilian cutaneous leishmaniasis, the main reservoirs are wild rodents, particularly abundant in the Amazon Forest and recently deforested areas.

Visceral leishmaniasis often occurs in or near houses and can be controlled effectively. This is demonstrated by China’s success in the 1950s, where mass treatment, insecticide spraying, and dog elimination reduced kala-azar cases from 500,000 to just

200.

In contrast, cutaneous-mucocutaneous leishmaniasis, especially in the Amazon region, is more challenging to control. The sand flies of the genus Lutzomyia, responsible for transmitting the disease, are ubiquitous in the forest. They feed on the prevalent rodents, which are continuous reservoirs for Leishmania parasites. When humans disrupt this cycle, especially in newly settled areas where deforestation occurs, they become more likely targets for sand flies. This increased risk stems from the displacement of rodents, making humans a more accessible food source for the flies.

This situation highlights the inherent difficulty of controlling cutaneous leishmaniasis in the Amazon, where the environment and ecological dynamics create a persistent risk for human infection.

Attempting to spray the entire forest or exterminate all rodents and other reservoirs to control leishmaniasis would indeed cause more harm than the disease itself. This underscores the need for an effective vaccine, which remains elusive. The combined impact of "poverty" and "tropics" has historically exacerbated the suffering of millions, as reflected in the Disability Adjusted Life Years (DALY) index, a measure developed by the WHO. The DALY combines years of life lost due to premature mortality and years lived with disability, providing a comprehensive assessment of the disease burden.

For tropical diseases, the DALY indices from the WHO are:

- Malaria: 46.5 million years lost
- Tuberculosis: 35 million years lost
- Filariasis: 5.8 million years lost
- Leishmaniases: 2 million years lost
- Schistosomiases: 1.7 million years lost
- Sleeping sickness: 1.5 million years lost
- Chagas’ disease: 667 thousand years lost
- Dengue fever: 616 thousand years lost
- Onchocerciasis: 484 thousand years lost
- Leprosy: 199 thousand years lost

In terms of annual deaths, the situation is similarly grim:

- Tuberculosis: 1.5 million deaths
- Malaria: 1.2 million deaths
- Visceral leishmaniasis: 51 thousand deaths
- Sleeping sickness: 48 thousand deaths
- Dengue fever: 19 thousand deaths
- Schistosomiases: 15 thousand deaths
- Chagas' disease: 14 thousand deaths

Life expectancy starkly contrasts between regions, with Japan averaging around 80 years, while many countries in tropical Africa have life expectancies of only about 40 years. However, the "tropical fate" can be significantly improved through economic and sanitary development and the strategic allocation of resources. These efforts can mitigate the impact of these diseases, improving the quality of life and health outcomes in affected regions.

Chagas' Disease

Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi*, is endemic to the New World. This parasite has been evolutionarily separated from its African relatives, which cause sleeping sickness, for at least 100 million years due to the continental drift that separated Africa and South America. This ancient separation led to distinct evolutionary paths for the trypanosomes and their vectors: Africa retained the ancestors of the tsetse flies (*Glossina*), while South America became home to the ancestors of triatomine bugs.

Triatomine bugs, also known as "barbeiros" in Brazil, are hematophagous insects belonging to the Hemiptera order, with species primarily classified into three genera: Triatoma, Panstrongylus, and Rhodnius. These bugs inhabit various biomes across North, South, and Central America, thriving in both natural and human-modified environments. They can be found in burrows, caves, and treetops, particularly in palm trees. As generalist feeders, they consume the blood of a wide range of mammals, including armadillos and primates, making them effective vectors for transmitting T. cruzi to humans.

This situation illustrates a clear case of tropical "biogeographic fate," where the

distribution and evolution of vectors and pathogens are deeply influenced by historical geographic events. Europe, being fortunate to lack these specific ancestors, does not face the same endemic challenges posed by Chagas' disease. In contrast, the diverse habitats and broad host range of triatomine bugs in the Americas ensure the persistence and spread of this disease.

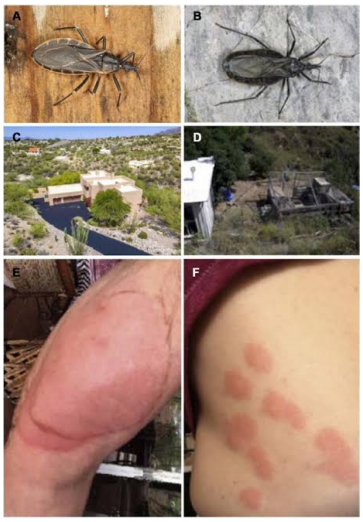

Fig 3: Chagas Disease (Photo credit: sciencedirect.com)

Marsupials and armadillos were likely the original hosts of Trypanosoma cruzi. Due to the hematophagous promiscuity of kissing bugs, T. cruzi was eventually disseminated to various mammalian orders in South and later North America. Humans likely became part of this transmission cycle when they arrived in the Americas 30,000 to 10,000 years ago, and particularly when they started domesticating animals infected with T. cruzi.

Pre-Colombian populations, such as those in the Andes who raised guinea pigs (Cavia spp.) for food, inadvertently provided additional hosts for kissing bugs (Triatoma spp.). Over time, species like Triatoma infestans adapted to living in human households, feeding on humans and their domesticated animals. They particularly favored the dark, warm crevices of wattle and daub houses common throughout Brazil. At night, these bugs would emerge to feed on humans, often biting the tender skin around the eyes or face, hence the Brazilian name "barbeiros" (barbers) or kissing bugs.

While feeding, the bugs defecate on their host's skin. The feces contain infectious trypanosomes, which enter the body through the bite wound or mucous membranes, leading to infection. Inside the host, the trypanosomes invade and multiply within cells,

eventually causing the cells to burst and releasing more parasites into the bloodstream. This bloodstream dissemination allows the trypanosomes to infect new cells and perpetuate the cycle. Kissing bugs become infected when they ingest blood containing circulating trypanosomes, thus maintaining the transmission cycle of T. cruzi.

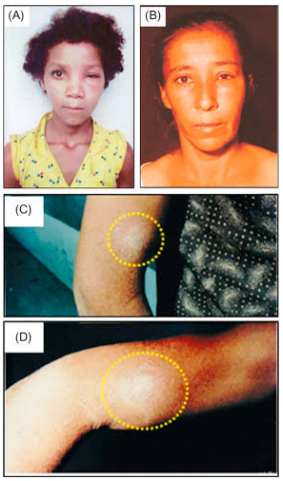

Fig 4: Manifestation of Chagas Diseases (Credit: sciencedirect.com)

In humans, Trypanosoma cruzi primarily targets the neurons of the autonomic nervous system and the muscle cells of the heart. The progressive destruction of these cells leads to the symptoms observed in the chronic stage of Chagas' disease. Key manifestations include:

- Cardiac Issues: Damage to the heart's motor systems can cause arrhythmias, blockages, and even cardiac arrest. Additionally, lesions to the heart muscle fibers reduce contractility, leading to heart failure.
- Gastrointestinal Problems: Damage to the nerve cells controlling the stomach's sphincters and the sigmoid flexure can cause progressive occlusion and enlargement of the esophagus (megaesophagus) and colon (megacolon).

Chagas' disease can be fatal during the acute phase or at any point during the chronic phase, although it typically progresses over several years.

Treatment with medication is challenging, particularly during the chronic phase. The available drugs have limited efficacy and are associated with significant risks and side effects, complicating management of the disease. This highlights the need for better therapeutic options and the importance of early detection and intervention.

Chagas' disease, along with malaria, was one of the most serious endemic diseases in Brazil. Until the 1970s, approximately 20 million Brazilians were infected with Trypanosoma cruzi, and there were at least 120,000 new cases annually until 1980. However, it was known by then that the disease could be controlled through household insecticide spraying, as demonstrated by the successful efforts in the state of São Paulo.

In the 1980s, the Southern Cone Chagas Initiative was launched by Argentina, Brazil, Chile, Paraguay, Uruguay, and the Pan-American Health Organization (PAHO). This intensive program aimed to combat the kissing bugs responsible for transmitting Chagas' disease. The initiative was highly successful. In Brazil, systematic and well-planned insecticide spraying led to a dramatic reduction in the number of new cases, which fell practically to zero within a few years. This achievement highlights the effectiveness of coordinated public health interventions in controlling and nearly eliminating the transmission of Chagas' disease.

Chagas' disease transmitted by domestic kissing bugs (Triatoma and Panstrongylus) has proven to be controllable in regions where systematic interventions have been implemented. Despite a few sporadic cases of household transmission, these are now residual foci of a disease on the verge of extinction in areas with permanent health surveillance.

However, many Latin American countries did not implement similar programs. For instance, Bolivia still reports over 80,000 new cases annually. In countries north of the Equator, the primary vectors of T. cruzi to humans and dogs are kissing bugs of the genus Rhodnius and the domestic Triatoma dimidiata. While the strategies to control transmission differ from those adopted by the Southern Cone countries, they are feasible. Central American countries have organized their regional control efforts through the Central America Chagas Initiative.

In Brazil and other regions, including the United States, T. cruzi remains present in wild mammals and kissing bugs. This reservoir of infection means that the parasite and its vectors are unlikely to be eradicated. Consequently, new foci of Chagas' disease can emerge, particularly in areas densely populated by infected mammals and kissing bugs. The Amazon region is especially prone to such outbreaks due to its favorable ecological

conditions.

This underscores the importance of ongoing vigilance and adaptable strategies to manage and control Chagas' disease, even in regions where household transmission has been largely curtailed. The persistence of T. cruzi in wild populations necessitates continuous monitoring and preventive measures to address potential outbreaks.

The prevalence of Chagas infection has been partly due to the ingestion of fruit juices (especially açaí) and sugar cane accidentally contaminated with kissing bugs infected with trypanosomes from wild animals. These outbreaks of oral infection usually affect dozens of people at a time but are always limited in scope.

While such episodes can occur at any moment, a nationwide scourge of Chagas' disease is unlikely to happen again. Despite the persistent presence of kissing bugs and trypanosomes, widespread development and improved sanitation have significantly mitigated the risk.

In Brazil, the decline in the number of mud huts, which serve as ideal habitats for kissing bugs, and regular insecticide spraying by health authorities have been crucial in controlling the disease. Financial resources and permanent health surveillance have further contributed to this success.

Development has proven to be the most effective antidote to the biogeographic fatalism associated with Chagas' disease. By improving living conditions and maintaining vigilant health measures, Brazil has substantially reduced the threat posed by this disease. However, the continued presence of the vectors and parasite necessitates ongoing efforts to ensure that Chagas' disease remains under control.

Other Tropical Diseases

Yaws, also known as frambesia, is a skin treponematosis similar to syphilis and can be easily treated with penicillin. The disease persists mainly because the affected populations lack access to health services.

Buruli ulcer, caused by Mycobacterium ulcerans, is rare or often undiagnosed in the New World. This mycobacterium leads to extensive cutaneous lesions, typically on the lower limbs, and primarily affects populations living near rivers or in marshy areas. The disease can cause significant morbidity due to its destructive nature and the difficulty in

accessing adequate treatment in affected regions.

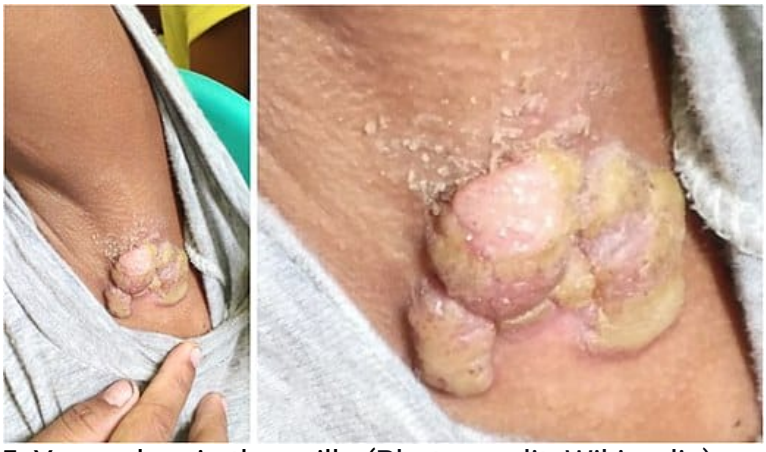

Fig 5: Yaws ulcer in the axilla (Photo credit: Wikipedia)

Trachoma, a chlamydial eye infection, occurs only sporadically in Brazil but affects 80 million people worldwide, leaving 6 million blind. Additionally, intestinal worm infections, while less alarming, remain prevalent in underdeveloped countries alongside diseases like cholera and childhood diarrheas. These diseases, often referred to as tropical diseases or diseases of underdevelopment, are grouped under the term "neglected diseases" by the WHO, highlighting the impact of poverty and lack of resources rather than geographic factors alone.

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