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REVIEW

# Imported Skin Infections from Tropical Regions by Travelers and Immigrants to the Belgian Mosan Region

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### **ABSTRACT**

Bacterial and fungal skin infections are common in tropical medicine. They represent a spectrum of diseases somewhat different from the presentations seen in temperate and cooler climates. Some are typically exotic and confined to specific geoclimatic regions. Other more common conditions have different rates of prevalence according to regional effects. Travelers coming back from tropical regions and immigrants from these geoclimatic environments possibly transfer

such dermatoses to Western residents. The global warming climate change in the world progressively alters some regional distributions of arthropod-borne-infectious diseases. The future must be framed by considering such world climatic changes responsible for progressive migration of vector-transmitted diseases inside temperate geoclimatic regions. Crowds of immigrants from warring regions eventually represent a distinct population at risk for other groups of dermatoses.

#### INTRODUCTION

Dermatoses that are easily identified in temperate regions are commonly altered in their clinical presentation and natural history following exposure to environmental warm and moist/dry status of tropical regions. The term tropical is used in a meteorological sense emphasizing a warm climate. It is commonly interchangeable with a geographic connotation. The concept further takes on different manifestations largely depending on environmental moisture, faulty sanitation, and on the nature of the local flora. Skin infections are particularly influenced by such distinct aspects. Furthermore, the combinations with malnutrition, deficient therapy, and concomitant diseases influence the patterns of skin disorders[1]. These factors vary noteworthy according to the diversity in behavioral and sociocultural habits, local living conditions, and occupational activities. Tropical dermatoses are present in affluent as well as in developing regions, including major cities and isolated dwellings. Some skin conditions correspond to cutaneous manifestations of systemic infections.

Various typical pattern distributions of skin diseases in tropical regions differ considerably from the situation in industrial countries. Bacterial and fungal skin infections, as well as parasitic disorders abound in the equatorial belt because of climatic and ecological conditions, generally combined with a low economic status of the population. Broadly speaking, non-infective inflammatory dermatoses appear to be less frequent and milder, with a few remarkable exceptions, than in developed regions. The occurrence of skin malignancies clearly depends on ethnic factors. Skin changes triggered by chronic sun exposures mainly affect fair-skinned people, and rarely trouble the darkly pigmented population. The ratio between infective-parasitic skin disorders and non-infectious

dermatoses which prevails in rural areas of developing countries is primarily an index of the socio-economic conditions. However, in some large cities under the tropics this ratio is progressively reversed, and the primarily non-infectious diseases outnumber the infective-parasitic ones. Such a trend in inverted ratio is considered as a global indicator of economic prosperity, sophistication, and development.

About 80% of the world population comprises individuals with pigmented skin. Globally darker and fair skins differ in their reactivities and various disease presentations. Indeed, physical differences among different ethnic groups commonly lead to variable prevalences and clinical presentations of skin disorders. Disease patterns in a given ethnic population are generally influenced by different ecologic and socio-economic factors. Darker skin is a blessing regarding photoprotection from sun damage and photoaging, but it represents a curse for being vulnerable for excess melanin in a wide range of dermatoses (Figure 1). Such a differential prevalence in skin disorders according to different ethnic populations points to a series of socio-cultural and geoclimatic factors in addition to genetic determinants.

# TROPICAL DERMATOLOGY IN DISTINCT GEOCLIMATIC AND BIOCLIMATIC ENVIRONMENTS

Skin represents a large part of the body directly exposed to a variety of environmental conditions. Seven distinct geographic entities (Table 1) are conveniently distinguished with their respective risks of tropical infectious dermatoses<sup>[1,2]</sup>. Clearly, the incidence and prevalence of imported cutaneous manifestations of tropical diseases in Europe vary in time and among ethnic clusters of immigrants.

#### RAINFALL AND SUNSHINE CONNECTION

Macroclimate refers to the combination of the overall environmental temperature, seasonal rainfall amount, and overall humidity in a given geographic area. The total annual precipitation distinguishes wet regions (more than 2 meters) from dry regions (less than 1 meter). By contrast, the microclimate refers to the close environment of people. It is largely related to the ethnic and socio-economic status in the community. It is influenced by the occupation, the rural or citizen housing, the proximity with animals, as well as the diet and clothing habits. The life cycle of arthropods and other vectors influence the transmission of some infections, and the type of vegetation affects the reservoirs of some transmitted agents.

Inside the large geographic territories, distinct bioclimatic conditions are commonly present. They correspond to the equatorial rain forest, to savannah and steppe in tropical semi-arid regions, as well as desert in arid conditions. Because of their cooler temperature, the Mediterranean region and mountainous areas represent distinct bioclimatic territories. In such a diversity in these environmental conditions, skin is expected to adapt itself to a wide range of conditions, to provide a barrier to various noxious microorganisms, and to withstand a variety of physical threats.

In the equatorial and subequatorial areas with abundant rainfalls and high temperature due to intense sunshine, the vegetation is luxuriant and the wildlife is diversified (Figure 2). Arthropod-borne infections are common all over the year. Leishmaniasis, filariasis, skin bacterial and fungal infections are frequent. Among the transmitted diseases, streptococcal and staphylococcal infections are common conditions, as well as loasis and Buruli ulcer in some areas.

Table 1 Regional variations in frequency of skin infections (bacterial, mycotic and parasitic disorders).	
Region	Prelevement skin infections
- Latin America	Tuberculosis, leprosy, leishmaniasis leptospirosis, plague, chagas disease, dermatomycoses, anthrax, venereal infections
- Caribbean islands	Tuberculosis, leprosy, dermatomycoses, filariasis leishmaniasis, venereal infections
- Northeen Africa, Near and Middle East	Tuberculosis, leishmaniasis, leprosy, cutaneous diphtenia, antrax, brucellosis, dermatomycoses, schistosomiasis, venereal infections
- Sub-Saharian Africa and Madagascar	Tuberculosis, leprosy, dermatomycoses, schistosomiasis, anthrax, diphtenia, brucellosis, leishmaniasis, filariasis, venereal infections
- India and Sri Lanka	Tuberculosis, leprosy, leishmaniasis, dermatomycoses, venereal infections
- South-east Asia	Tuberculosis, leprosy, filariasis, dermatomycoses, leishmaniasis, venereal infections
- Oceania	Leprosy, dermatomycoses, venereal infections

#### Table 2 Questions facing a tropical skin infection.

- When and in what countries have you traveled or lived?
- What was your occupation abroad?
- Did you visit or live in only large urban areas and visit only tourist attractions?
- · Did you wade in water or swim?
- Did you visit and eat in rural areas or stay overnight in native dwellings or tents?
- · Were you protected by screens or mosquito nets?
- Were you bitten by mosquitoes or other insects? During daytime or at night?
- Were you backpacking?
- Did you receive gamma globulin, antimalaria medication, antibiotics, or antidiarrhea medication? How much and how often?
- Were you vaccinated? Against what? When?
- Were you in contact with clean or contaminated food and water?
- When did you note the onset of the earliest symptoms?
- What were the initial body sites involved?What was the aspect of the earliest lesions?
- Did you noticed any associated systemic symptoms?
- Family history

In the tropical environment with alternate seasons, the epidemiology of transmitted infections is different during the dry and rainy seasons. During the dry season, populations are frequently clustered around water wells. Their contacts with vectors are common, leading to inoculation dermatoses. During rainy season, many skin infections are due to surface water and their many related diseases (Figure 3). In the flat lands of the savannah, deep mycoses are frequent. Onchocerciasis often abounds along the rivers.

In arid and semi-arid tropical regions, heat due to the intense sunshine contrasting with the night cool, and low humidity are typically present (Figure 4). Pyodermatoses are quite frequent.

#### SKIN TYPOLOGY AND CLIMATE

The majority of the world population consists of dark-skinned people. Fitzpatrick skin types IV, V and VI correspond to such color typology. Individuals with an olive skin hue corresponding to a beige complexion or genetically lightly tanned skin, are identified in the type IV skin group. Brown skin is characteristic for type V melanotype, and Black skin is qualified as type VI. These phototypes rarely or never burn on sun exposure and they tan readily. Those individuals belong to South, Southeast and East Asia, Hispanics,

African Blacks, Afro-Caribbean and African-American Blacks. Some groups represent a composite of different ethnic ancestries.

In countries of the tropical belt, the diagnosis of dermatoses is affected by the heterogeneity in ethnic backgrounds and skin colors in the populations. Darker and fair skins differ by their potential biologic responses and disease presentations. Ethnic differences in skin characteristics explain some disparities in epidemiology and presentation of dermatoses. Five ethnic groups have been distinguished, namely the Caucasoid, Congoid, Mongoloid,



Figure 1 Pigmented aspect of papules of lichen planus in a patient with skin type VI.



Figure 2 Edge of a rain forest in Africa.



Figure 3 Large river in a forest region of Latin America.

Australoid and Capoid. Of note, mixed type individuals are increasing in numbers, and, in most regions, they frequently outnumber those of original unmixed ancestry.

Skin color is mainly determined by melanocytes. Ethnic differences in skin color are not linked to differences in the numerical density in melanocytes. Indeed, they are linked to variations in the number, size, and aggregation pattern of the melanosomes inside melanocytes and keratinocytes. Melanosomes are more abundant and larger in darker skin melanocytes than in lighter skin. In addition to differences in melanosome clustering, an increased number of basal layer melanosomes (about 340 per basal keratinocyte) is present in darker skin compared with fair skin (about 120 melanosomes per basal keratinocyte).

Other ethnic physical differences include variability in hair structure in darker-skinned people compared with fair-skinned individuals. The skin color differences in part account for the lower skin cancer incidence, and a lower prevalence and different presentation of photoaging in darker-skinned people compared with fair-skinned subjects. By contrast, a higher incidence of pigmentary disorders and of certain types of alopecia in dark-skinared individuals compared with those of other ethnic background is explained by this way.

The stratum corneum (SC) structure is part of ethnic typology involved in both the adherence of microorganisms to the skin, and the development of some related superficial infections. The mechanical integrity of the SC is an essential part of its protective function. It is largely determined by the forces binding adjacent individual corneocytes. Such intercellular cohesive force is, however, progressively abated sheding smoothly corneocytes from the skin surface. Intracorneal cohesion is an integral part of the mechanism of desquamation<sup>[3]</sup> related to the keratinocyte cell production (Figure 5). Factors involved in these processes include cytokine and other mediator release, as well as some endocrine effects. They are active in a time frame different from other distinct factors of desquamation, such as the external mechanical stimulation of clothing, toilet, and social contacts.

The climatic conditions and a variety of other environmental factors affect several skin characteristics facilitating and/or conditioning the outbreak of a series of dermatoses. For instance, a low environmental relative humidity (RH) increases skin permeability, thickens the epidermal layers, and boosts the production of inflammatory mediators. These changes are particularly observed in patients with chronic inflammatory dermatoses such as psoriasis, atopic dermatitis, and senile xerosis. Pruritus is usually more severe in cold dry climates.

### **WORLD CLIMATE CHANGE**

The world climate change (WCC) corresponds to lasting variations in regional and global climates over relatively long periods. WCC is conditioned by several natural factors including variations in solar radiation received on earth, plate tectonics, the dynamics of ocean processes, and volcano eruptions. In addition, human activities using fossil energy lead to greenhouse gas accumulation in the atmosphere<sup>[2-5]</sup>. Global climate warming, changes in rainfalls, deforestation, land consumption, industrial processes, as well as some agriculture practices further affect the global WCC. All these factors contribute to variations in the geoclimatic distribution of vectors of some skin infections such as leishmaniasis and borreliosis. Warm and humid environment helps the skin colonization by various bacterial and fungal microorganisms. It alters some disease

expansions.

Origins magnitude, and impacts of climate changes on life represent important aspects of the global warming linked to WCC. The average earth surface temperature has increased by 0.6°C over the past century. It is expected to be limited to about 2°C by the end of this century<sup>[6]</sup>. The global rise in extreme climatic events includes major changes in both the average and peaks of temperature, environmental RH, atmospheric pressure, rainfall amounts, wind forces, glacier melting, as well as ocean pH, salinity and tide coefficient<sup>[7]</sup>. Climatic factors influence both the frequency and severity of extreme weather events. Sea levels are rising leading to aggravate floodings<sup>[8]</sup>. Clearly, climatic changes explain shifts in the distribution and behavior of several arthropod species and consequently of vector-borne-diseases<sup>[9–13]</sup>. The relationship between climatic and social factors is intricated with a variety of arthropodrelated diseases. This process is associated with many possible confounding factors such as the diagnostic procedures of diseases, vector resistance to antibiotics and insecticides, environmental RH, and demographic shifts.

Studies focusing on WCC effects on human skin are not yet numerous<sup>[4,6,13]</sup>. However, skin is the major organ of the human body being the most exposed to environmental variations. Hence, some skin conditions are inclined to present a high sensitivity to climate<sup>[14]</sup>. Climatic factors influence several functional skin features facilitating or worsening the incidence, signs and symptoms of specific skin conditions.

# TROPICAL SKIN INFECTIONS IN NATIVES OF TROPICAL COUNTRIES

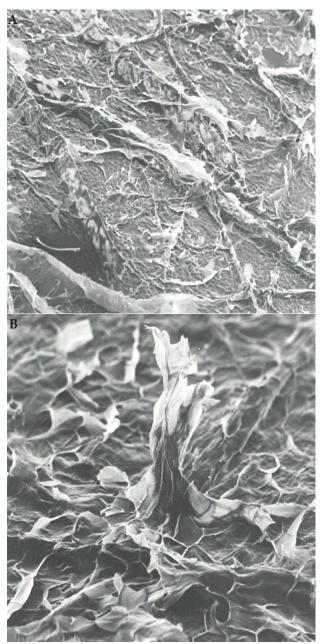
In their native environment, people of the tropical belt possibly suffer from a variety of skin infections boosted by geoclimatic and socio-economic factors. The disease history is commonly unreliable in these populations. A high prevalence of specific skin infectious disorders is however expected in some regions.

Ethnic predispositions to skin diseases are uncertain because they are closely intermingled with socio-economic factors including occupational activity. Geoclimatic factors such as heavy yearly rainfalls for 9-10 months per year probably contribute to some high infection prevalences. The close proximity to animals is a common source of infections (Figure 6). In addition a large part of the population is chronically undernourished. The basic diet is commonly deficient in animal proteins and vitamins. Disease transmission is boosted by overcrowding and deficient hygiene prevailing in most periurban and rural dwellings. A high prevalence for sexually transmitted infections is recognized including gonorrhea, syphilis and HIV infection. Local habits and traditional medicine impact the occurrence and course of a variety of infectious tropical dermatoses (Figure 7). They vary considerably among different regions and ethnic groups.

Infectious and parasitic disorders represent a large group of dermatoses in many tropical regions. Among them, superficial dermatomycoses are frequent (Figure 8). The split up of dermatomycoses in the local populations is almost similar in many tropical environments. Nevertheless, some variations are acknowledged in infection rates in some tropical areas. They evoke the putative existence of some natural anti-infective compounds in their diet, secretion of potent antiseptic / anti-infective agents at the skin surface, and/or some genetic factors contributing to establish a resistance against these infections.



Figure 4 Isolated dwelling in Sahara



**Figure 5** Cyanoacrylate skin surface stripping of xerotic skin showing an uneven intercorneocyte cohesion with partially lifted cells. a-X 50; b-X 300.

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Parasitic disorders form another group of common conditions. They are endemic and represent major public health problems in many tropical regions. Among these conditions, onchocerciasis represents a chronic, multi-systemic parasitic disease caused by the nematode Onchocerca volvulus transmitted by the black fly Simulium damnosum. The diversity in the clinical spectrum of the skin manifestations includes acute and chronic papular onchodermatitis, chronic lichenified onchodermatitis, sowda, lizard skin, leopard spotting, hanging groin and onchocercoma.



Figure 6 Herbivore close to human dwelling.



Figure 7 Village women clustered nearby a waterfall in Latin America.



Figure 8 Superficial dermatomycosis.

# TROPICAL SKIN INFECTIONS IN TRAVELERS AND IMMIGRANTS

Globally, a general lack of awareness surrounds the nature and consequences of many incoming tropical dermatoses in Western countries. Both health care and living styles in the West contrast with those of immigrants, refugees, alien students and tourists arriving on their doorsteps bringing diseases from tropical regions. Some cultural practices influence the risk of tropical diseases. The access to the full disease history helps establishing the diagnosis of most infectious dermatoses. Laboratory tests are advisable for some dermatoses, and indispensable in others. Among them, the cyanoacrylate skin surface stripping is a convenient and minimally invasive process binging sound, cheap and rapid Information in many bacterial and mycotic skin infections<sup>[15]</sup>.

In Western countries, the initial diagnostic step identifying tropical infections in travelers and immigrants derives from the disclosure of any travel and residence in tropical regions, as well as the time spent abroad<sup>[16]</sup>. The distinction between travel and residence abroad is occasionally confusing for some people. They frequently deny traveling, but commonly admit residence abroad. The specific geographic area where the patient traveled or dwelled must be identified. The knowledge of the season period of travel, the climate characteristics of the visited environment, as well as the gender and specific occupational activities of the patient are further helpful. Some basic relevant queries are listed in table II.

It is important to notify the disease duration, the initial body site involved, the aspect of the earliest lesion(s), the lesion distribution, the recurrence pattern if any, the dermatological signs, the systemic symptoms, as well as any attempt of prior therapy. High fever, shock, hemorrhagic manifestations, intense diarrhea, dyspnea, and varying degrees of central nervous system disturbances, including prostration, confusion and coma, warn that the patient possibly acquired a severe disease outside a Western environment.

The social status of a subject influences the risk of exposure to diseases, the severity of infection, the duration of illness, the access to health care services, and the impact of illness on family life. Indeed, it is obvious that a series of tropical diseases including leprosy, malaria, leishmaniasis<sup>[16]</sup>, filariasis, Chagas disease, and schistosomiasis prevail among populations deprived of basic sanitation, clean water and food.

Both genders in regions where tropical diseases are endemic commonly suffer from poverty and deprivation. Women are particularly at a disadvantage due to societal factors making them dependent on men, and allot them a lower socio-economic status. It is assumed that tropical skin infections in the local populations, and access to health care resources are globally similar irrespective of the genders. However, marked gender differences prevail in the medical coverage and social status in the field of tropical skin infections. The access to food is gender-determined in many cultures. In addition, women are commonly burdened by several traditional roles and a series of other social responsabilities.

#### PHYSICAL EXAMINATION

Tropical infections remain in some instances a matter of life and death. At the general physical examination, careful attention should search for changes in liver and spleen sizes, presence of pruritus<sup>[17]</sup>, fever<sup>[18]</sup>, lymphadenopathies, edema, and any neurologic deficit, particularly analgesia<sup>[19]</sup>. For instance, African trypanosomiasis

and cerebral malaria due to Plasmodium falciparum cause unconsciousness. They represent life-threatening conditions unless treated promptly following clinical suspicion. Skin should be thoroughly examined under adequate light because rashes, sores and ulcerations possibly represent clues to the illness nature. In some patients, diagnostic evidences are possibly disclosed on body sites remote from their main attention. Any skin change must be reported with care.

A laboratory expertise is required or desirable in a number of conditions<sup>[20]</sup>. The methods include among others routine microbiology, smears and skin snips examination, cyanoacrylate skin surface strippings and conventional dermatopathology (Figure 9). Blood eosinophilia determination is frequently of interest<sup>[21]</sup>. Molecular biology is added to the list but require adequate facilities that are not always available.

## TROPICAL SKIN INFECTIONS IN TRAVELERS

While visiting tropical regions, Western citizens are occasionally exposed to a variety of unusual infectious agents. In addition, the local hygiens standards differ from those of their environment of origin. Most lifelong Western residents traveling to tropical countries lack adequate immune protection against a series of nearly ubiquitous communicable diseases. Therefore, travelers are commonly exposed to the risk of infectious dermatoses prevailing in tropical areas<sup>[22,23]</sup>. Such diseases correspond to both ubiquitous communicable dermatoses and typical tropical disorders encountered outside Western countries<sup>[24]</sup>. The risk of acquiring any tropical disorder is in part linked to changes in the regular activities and lifestyle of the traveler. Compared to their own country, the overall risk of exposure potentially remains similar to or increases for some skin infections. Susceptibility factors including age influence the risk of acquiring tropical skin infections. Malaria transmitted by mosquito bites is particularly virulent in susceptible adults<sup>[25]</sup>. Hitchhikers, back-packers, students on tour around the world, and some other travelers are at increased risk.

Urban environments in tropical countries, particularly expose to interindividual transmission of microorganisms through aerosols, hand-to-hand contacts following fecal or pharyngeal contamination, absorption of contaminated foods and drinks, sexual contacts<sup>[26]</sup>, and purposeful or inadvertent parenteral inoculations. In addition, urban setting exposes people to a number of free-living organisms such as Mycobacteria species. The HIV infection and its consequences are currently prevailing in a number of cities<sup>[27,28]</sup>.

Rural recreational settings commonly expose to short-term sylvan environments during picnicking, hiking, hunting, camping, or exploring the surroundings. Short visits to rural settings expose travelers to the risk of bites by infectious agent-carrying arthropods<sup>[29]</sup>, or contacts with infected animals, and exposure to parasites and microorganisms in soil, water, and dust<sup>[30]</sup>. Any recreational swim in a lake or stream exposes to skin-penetrating, water-borne bacteria and parasites. In areas where schistosomiasis and leptospirosis are endemic, swimming exposes travelers to either disease.

Outside Western countries, many rural settings imply low socioeconomic conditions, crowded living areas, primitive sanitary measures, unusual dietary practices, and restricted subsistence livelihood. Such environments are commonly contaminated by human and animal wastes. Travelers in rural environments for a long time are commonly exposed to certain diseases that occur with decreasing frequency in illegal aliens, refugees, immigrants, visitors,

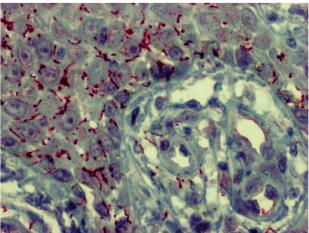


Figure 9 Immunohistochemical aspect of Treponema pallidum (red rods) inside the epidermis.

and Western citizens with unconventional overseas lifestyles and occupations. Rural and some crowded urban surroundings usually shelter disease-carrying insects such as Triatoma bugs and fleas. However, even prolonged rural exposure of Western residents to such environments is not likely to provide exposure similar to that of native children living in the same environment. People wearing foot coverings and avoiding eating rare or under-cooked meat, fresh vegetables, and unpeeled fruits commonly live with minimal risk in human settlements teeming with infective eggs and larvae. Following such proscriptions is impractical for most local children.

Encounters with marine and poisonous land organisms occasionally cause discomfort. Jellyfish man-of-war, and sea urchin stings are commonly and temporarily disabling<sup>[31]</sup>. In some instances, they cause blistering, tissue necrosis, and secondary bacterial infections. Coral cuts tend to be infected by Streptococci, and many infections are accompanied by severe secondary lymphangitis. Hazards on tropical land include snakes, scorpions, centipedes, bedbugs, leeches, ticks, bees and spiders<sup>[32]</sup>.

# TROPICAL SKIN INFECTIONS OF IMMIGRANTS

A large proportion of regular immigrants to Western countries are educated professionals or business people. They lived in large cities abroad and their lifestyles and disease exposure profiles were rather similar to those of Western citizens. Some people who enter Western countries are not immigrants, but alien visitors, and some of them are sick[33-36]. Of note, a large proportion of those visitors originate from countries with a high incidence and prevalence of communicable diseases. Tourists, alien students, and business travelers from tropical countries are not usually from the lowest socioeconomic urban or rural populations. The incidence of tropical skin infections is likely quite low, although not absent. At the exception of malaria<sup>[37]</sup>, such people are only exceptionally infected with tropical organisms. The incidence of obvious tropical skin infections is likely to be quite low in immigrants as a whole. By contrast, in unregistered alien children, the prevalence of multiple parasites [38-40] tinea capitis and impetiginized dermatoses<sup>[41]</sup>, is probably high in some instances.

Immigrants who floe from wars are quite different. They come predominantly from urban suburbs, rural low socioeconomic groups or regions under the threats of armed forces. Most of these immigrants are inadequately nourished. On arrival in Western

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countries, many of these immigrants live in crowded dwellings in conditions amplifying the incidence risk of new infections or exacerbating poorly controlled previous infections. Clearly, some of these immigrants carry communicable diseases, and their risks for some of these diseases equal or exceed those for Western citizens. Such an increased risk occurs almost exclusively in poor immigrants from rural regions, and is related to faulty hygiene, crowded living conditions, and frequent exposure to zoonotic and parasitic agents. The probability of communicable diseases in this group of patients is rather high.

Some immigrants suffer from changes in food habits<sup>[42]</sup> and they persist in using traditional and archaic medicines impeding some regular treatment procedures in Western countries. By contrast, other remedies such as banana leaves appear as valid alternative agents for wound dressing<sup>[43]</sup>.

#### CONCLUSIONS

Skin tropical infections originate from the tropical and subtropical regions of Africa, Asia, Latin America and Oceania. Seven distinct geographic regions are commonly identified, following their different geoclimatic conditions and their relative disease prevalences. The risks for travelers and immigrants from these regions to develop and transfer a tropical disease are important to be managed adequately. The clinical presentations vary according to the ethnic background and the way of life including the economic conditions. The overlap between tropical diseases of immigrants and travelers is important among some professions including archaeologists, anthropologists, back-packers, geologists, paleontologists and Peace Corps workers living for prolonged periods in rural settings, and who adopt local cultural and behavioral habits. Crowds of immigrants from warring countries represent groups distinct from regular immigrants from peaceful regions.

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#### CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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