SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 23

TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

# MEDICINA DEI VIAGGI E DELLE MIGRAZIONI

20 Marzo 2023 – Ore 16.00-19.00

Responsabile scientifico: Prof. Spinello Antinori

## Gestione ambulatoriale dopo soggiorno in area tropicale: quali indicazioni

Dr. Andrea Angheben


Viaggi e salute
gestione ambulatoriale

# DISCLOSURE
# I have no conflicts of interest

Dr Andrea Angheben

# Indicazioni a gestione ambulatoriale di patologia legata al viaggio

Tutto ciò  che sfugge a dinamiche di urgenza che in medicina dei viaggi sono:

1. Sdr febbrile acuta
2. Sdr flogistica delle vie respiratorie
3. Sdr gastro-intestinale acuta
4. Sdr neurologica acuta
5. Morso di animale, patologia dermatologica severa

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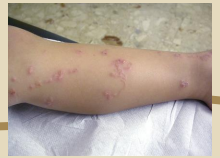
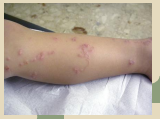
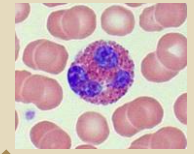
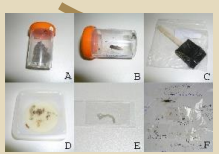
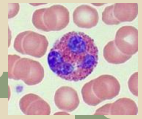
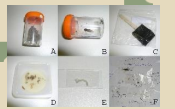









# 01

# Febbre/Febbricola prolungata o ricorrente

# Il viaggiatore al rientro con febbre

Nella valutazione del paziente sintomatico al rientro da un viaggio utile valutazione secondo due approcci:

- Approccio geografico (zona visitata, specificità del viaggio)
- Criterio temporale
- Approccio sindromico (febbre, sint. genito-urinaria, respiratoria, enterica, sindrome eosinofila)

http://www.simetweb.eu/document/2566


# Il criterio geografico

# Approccio geografico: Africa sub-sahariana

- Estremamente diffuse malattie legate a cibo ed acqua
- Shigellosi, colera
- **Amebiasi**, Echinococcosi
- **Epatite A**

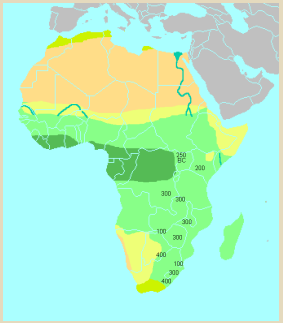
- Zoonosi (**brucellosi**, leptospirosi, peste, **rabbia**)

- Meningite

- **Schistosomiasi**

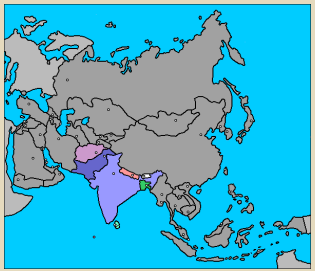
- **Epatite B, TBC, HIV**

- Polio → solo Nigeria



# Approccio geografico: Asia → Sub-continente indiano

- Diffuse malattie da artropodi: Malaria ubiquitaria <2000 m s.l.m. (Goa), dengue, chikungunya, encefalite giapponese (focolai), rara la peste
- Comuni le affezioni legate a cibo ed acqua: batteriche (compreso colera, NB tifo), parassitarie (**ameba**, giardia)
- Pakistan + Afghanistan → polio
- Elmintiasi: Fasciola, Clonorchis, Epistorchis, Paragonimiasi, Echinococcosi, Cisticercosi
- **Epatiti A, B**
- **TBC**



# Approccio geografico: Asia → Sud-Est

- Estremamente diffuse malattie da artropodi: Malaria (anche R), Encefalite giapponese, Dengue, Chikungunya
- Diffusissime le affezioni legate a cibo ed acqua: batteriche (compreso colera), **epatite A** ed E
- Elmintiasi: Distomatosi (Fasciola, Schistosomiasi da japonicum e mekongi, Opistorchis, Chlonorchis)
- **Epatiti B, HIV** altamente prevalenti
- Meloidosi

# Approccio geografico: America Meridionale

- Malattie da artropodi: comuni la Malaria (Pv, Pf clorochino-S), **Chagas**, Filariosi, **Leishmaniosi**, FG, dengue nelle aree tropicali soprattutto
- Bartonellosi (Ande)
- Zoonosi: **brucellosi**, **rabbia**, echinococcosi
- Hantavirus
- Diffuse le malattie da alimenti ed acque: batteriche (compreso colera sul Pacifico), **amebiasi**, shigellosi
- Nei centri urbani: **epatite B, HIV, TBC**

ORIGINAL INVESTIGATION

# Etiology and Outcome of Fever After a Stay in the Tropics

*Emmanuel Bottieau, MD; Jan Clerinx, MD; Ward Schrooten, MD, PhD; Erwin Van den Enden, MD; Raymond Wouters, MD; Marjan Van Esbroeck, MD; Tony Vervoort, MD; Hendrik Demey, MD; Robert Colebunders, MD, PhD; Alfons Van Gompel, MD; Jef Van den Ende, MD, PhD*

| Africa (n=1321) | Asia (n=355) | America (n=129) |
|---|---|---|
| ***Plasmodium falciparum* Malaria 395 (30%)** | Unknown Etiology 69 (19%) | Unknown Etiology 42 (33%) |
| Unknown Etiology 324 (25%) | Respiratory Tract Infection 45 (13%) | Respiratory Tract Infection 20 (16%) |
| Respiratory Tract Infection 127 (10%) | **Dengue 43 (12%)** | Bacterial Enteritis 12 (9%) |
| **Nonfalciparum Malaria 65 (5%)** | **Nonfalciparum Malaria* 33 (9%)** | **Dengue 11 (9%)** |
| Bacterial Enteritis 63 (5%) | Bacterial Enteritis 33 (9%) | Genitourinary Infection 8 (6%) |
| **Rickettsial Infection 53 (4%)** | Mononucleosis-like Syndrome 25 (7%) | Noninfectious Condition 7 (5%) |
| Skin/Soft Tissue Infection 46 (3%) | Skin/Soft Tissue Infection 14 (4%) | Mononucleosis-like Syndrome 6 (5%) |
| Genitourinary Infection 37 (3%) | **Enteric Fever 12 (3%)** | **Nonfalciparum Malaria* 5 (4%)** |
| Mononucleosis-like Syndrome 36 (3%) | Genitourinary Infection 12 (3%) | Skin/Soft Tissue Infection 5 (4%) |
| **Acute Schistosomiasis 33 (2%)** | ***Plasmodium falciparum* Malaria 8 (2%)** | **Protozoan Enteritis 2 (2%)** |

**Figure.** Ranked prevalence of imported febrile diseases (tropical cause in boldface) according to last continent of exposure: top 10 diagnoses. Thirty-seven other patients had visited more than 1 continent, including 5 diagnosed as having *Plasmodium falciparum* malaria and 1 as having rickettsial infection. *Exclusively *Plasmodium vivax* malaria.

*Arch Intern Med. 2006;166:1642-1648*

ORIGINAL RESEARCH | **Annals of Internal Medicine**

# GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011

**Karin Leder, MBBS, MPH, PhD; Joseph Torresi, MBBS, PhD; Michael D. Libman, MD; Jakob P. Cramer, MD, MSc; Francesco Castelli, MD, PhD; Patricia Schlagenhauf, PhD; Annelies Wilder-Smith, MD, PhD, MIH; Mary E. Wilson, MD; Jay S. Keystone, MD, MSc; Eli Schwartz, MD; Elizabeth D. Barnett, MD; Frank von Sonnenburg, MD, PhD; John S. Brownstein, PhD; Allen C. Cheng, MBBS, PhD, MPH; Mark J. Sotir, PhD, MPH; Douglas H. Esposito, MD, MPH; and David O. Freedman, MD, for the GeoSentinel Surveillance Network***

**Background:** International travel continues to increase, particularly to Asia and Africa. Clinicians are increasingly likely to be consulted for advice before travel or by ill returned travelers.

**Objective:** To describe typical diseases in returned travelers according to region, travel reason, and patient demographic characteristics; describe the pattern of low-frequency travel-associated diseases; and refine key messages for care before and after travel.

**Design:** Descriptive, using GeoSentinel records.

**Setting:** 53 tropical or travel disease units in 24 countries.

**Patients:** 42 173 ill returned travelers seen between 2007 and 2011.

**Measurements:** Frequencies of demographic characteristics, regions visited, and illnesses reported.

**Results:** Asia (32.6%) and sub-Saharan Africa (26.7%) were the most common regions where illnesses were acquired. Three quarters of travel-related illness was due to gastrointestinal (34.0%), febrile (23.3%), and dermatologic (19.5%) diseases. Only 40.5% of all ill travelers reported pretravel medical visits. The relative frequency of many diseases varied with both travel destination and reason for travel, with travelers visiting friends and relatives in their country of origin having both a disproportionately high burden of serious febrile illness and very low rates of advice before travel (18.3%). Life-threatening diseases, such as *Plasmodium falciparum* malaria, melioidosis, and African trypanosomiasis, were reported.

**Limitations:** Sentinel surveillance data collected by specialist clinics do not reflect healthy returning travelers or those with mild or self-limited illness. Data cannot be used to infer quantitative risk for illness.

**Conclusion:** Many illnesses may have been preventable with appropriate advice, chemoprophylaxis, or vaccination. Clinicians can use these 5-year GeoSentinel data to help tailor more efficient pretravel preparation strategies and evaluate possible differential diagnoses of ill returned travelers according to destination and reason for travel.

**Primary Funding Source:** Centers for Disease Control and Prevention.

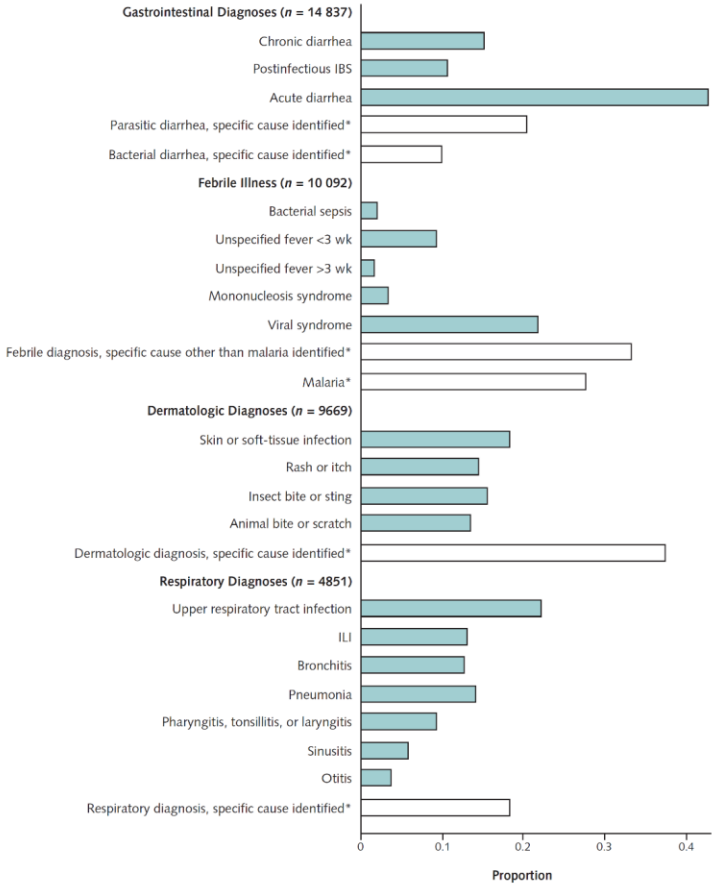
*Ann Intern Med.* 2013;158:456-468. www.annals.org

For author affiliations, see end of text.

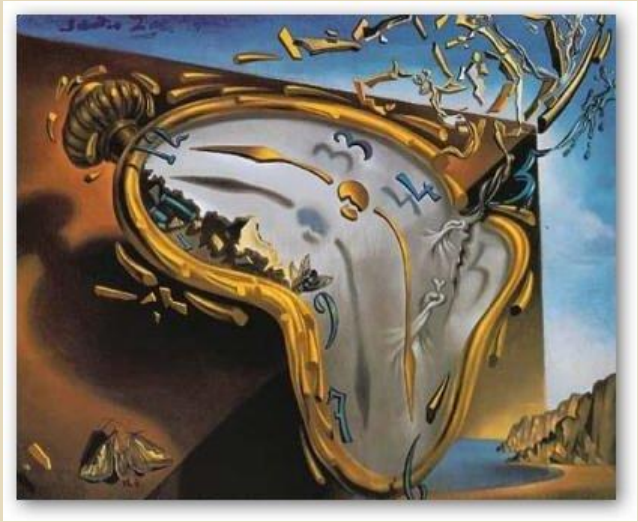
* For a list of GeoSentinel Surveillance Network members, see the **Appendix** (available at www.annals.org).

- 53 Centri Geosentinel network (24 paesi, 30% circa europei)
- 2007-2011
- 42173 pazienti
- 23,3% con febbre.

*Figure 1.* **Proportion of major syndromic groupings for gastrointestinal, febrile, dermatologic, and respiratory illnesses among ill returned travelers.**




IBS = irritable bowel syndrome; ILI = influenza-like illness.
* Each bar represents a mutually exclusive classification. Green bars depict the proportion of each diagnostic category with the given syndromic grouping. White bars depict the proportion with the given specific cause, and the top diagnoses within each of these categories are shown by region in **Figure 2**.



# Il criterio temporale

# Criterio temporale (esordio della febbre)

**Table 4. Prevalence of Tropical Diseases According to Period Between Return or Arrival From Endemic Countries and Fever Onset***

| Tropical Disease | Before and Within the First Month of Return or Arrival (n = 1434) | Within the Second Month of Return or Arrival (n = 137) | Within the Third Month of Return or Arrival (n = 66) | Within 4-12 Months of Return or Arrival (n = 205) | Total, No. (N = 1842) |
|---|---|---|---|---|---|
| *Plasmodium falciparum* malaria | 373 (26) | 20 (15) | 7 (11) | 8 (4) | **408** |
| Nonfalciparum malaria | 28 (2) | 23 (17) | 16 (24) | 36 (18) | **103** |
| Rickettsial infection | 60 (4) | 0 | 0 | 0 | **60** |
| Dengue | 56 (4) | 0 | 0 | 0 | **56** |
| Acute schistosomiasis | 24 (2) | 6 (4) | 2 (3) | 1 (0.5) | **33** |
| Enteric fever | 14 (1) | 1 (1) | 0 | 0 | **15** |
| Invasive amebiasis | 7 (0.5) | 1 (1) | 0 | 2 (1) | **10** |
| Protozoan enteritis | 9 (1) | 0 | 1 (2) | 0 | **10** |
| Other tropical diseases | 24 (2) | 2 (1) | 0 | 1 (0.5) | **27** |
| Total tropical diseases | **595** (41) | **53** (39) | **26** (39) | **48** (23) | **722** |

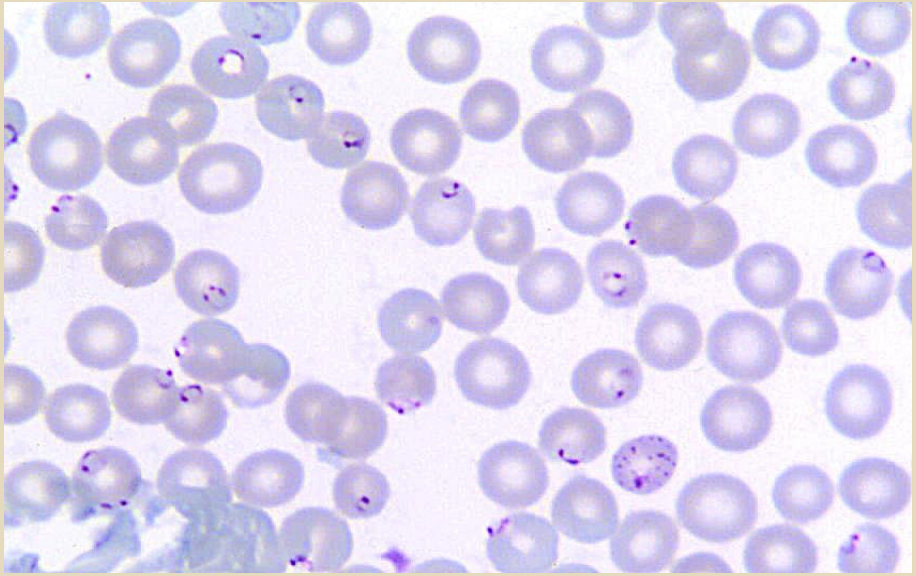
*Data are given as number (percentage) of cases unless otherwise specified. Percentages may not add to total owing to rounding.

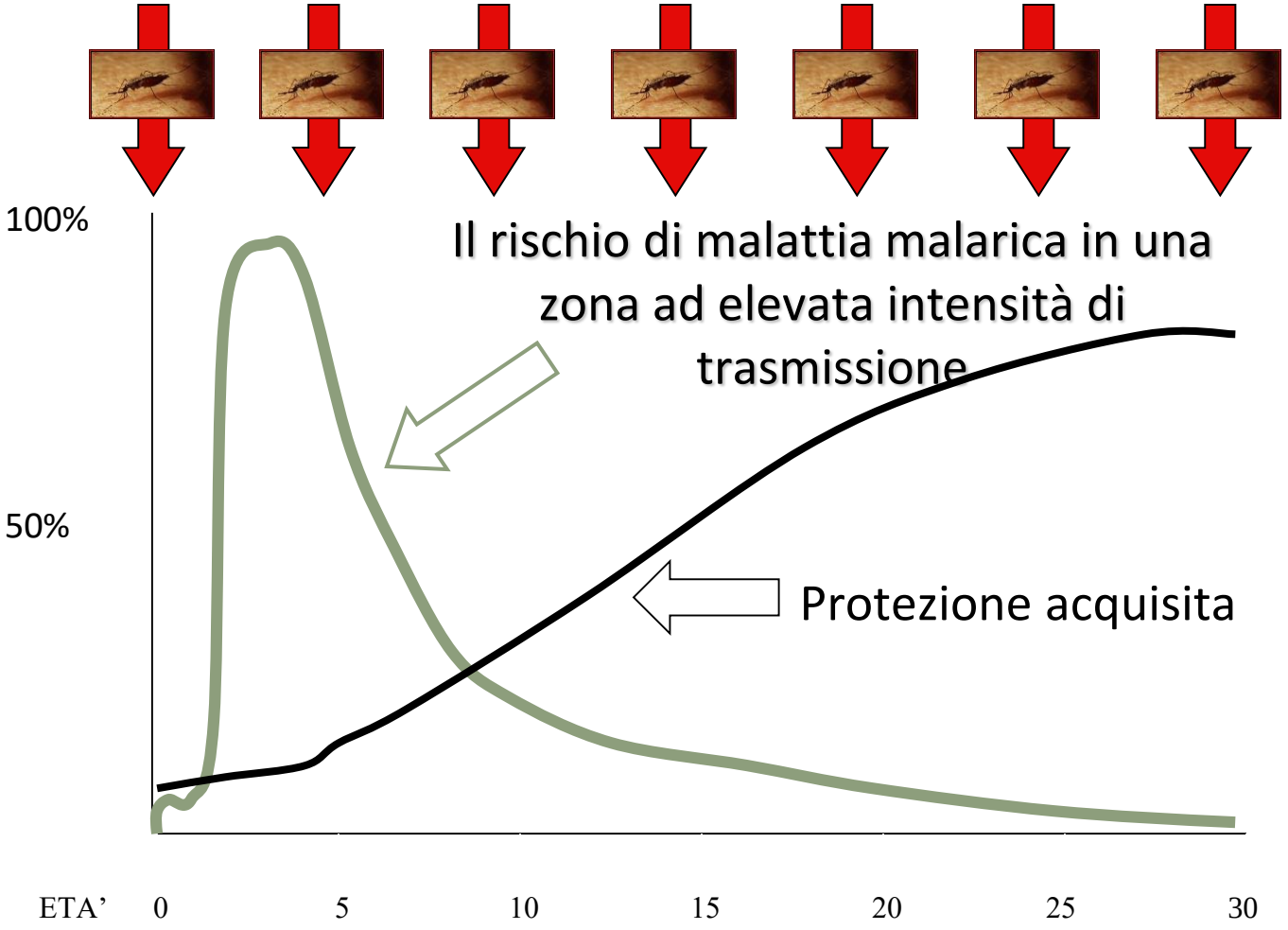
*Arch Intern Med. 2006;166:1642-1648*


Luke Fildes: The doctor; 1887

# Il criterio clinico

# Malaria




100%
50%
Il rischio di malattia malarica in una zona ad elevata intensità di trasmissione
Protezione acquisita
ETA'
0
5
10
15
20
25
30

# Malaria

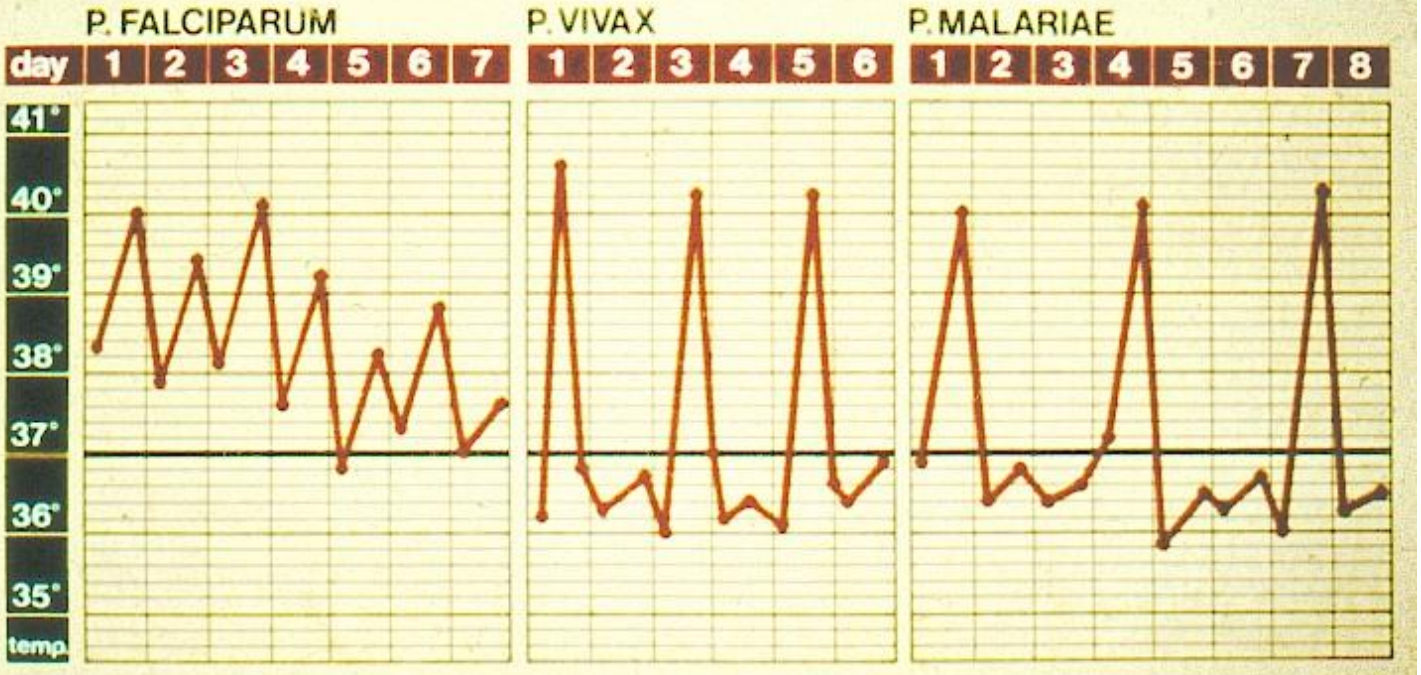
## Clinical features

# Acute Malaria attack

## SYMPTOMS

fever (>38°C)
headache
nausea, vomiting, diarrhoea
myalgias
prostration

periodic fever at relapse



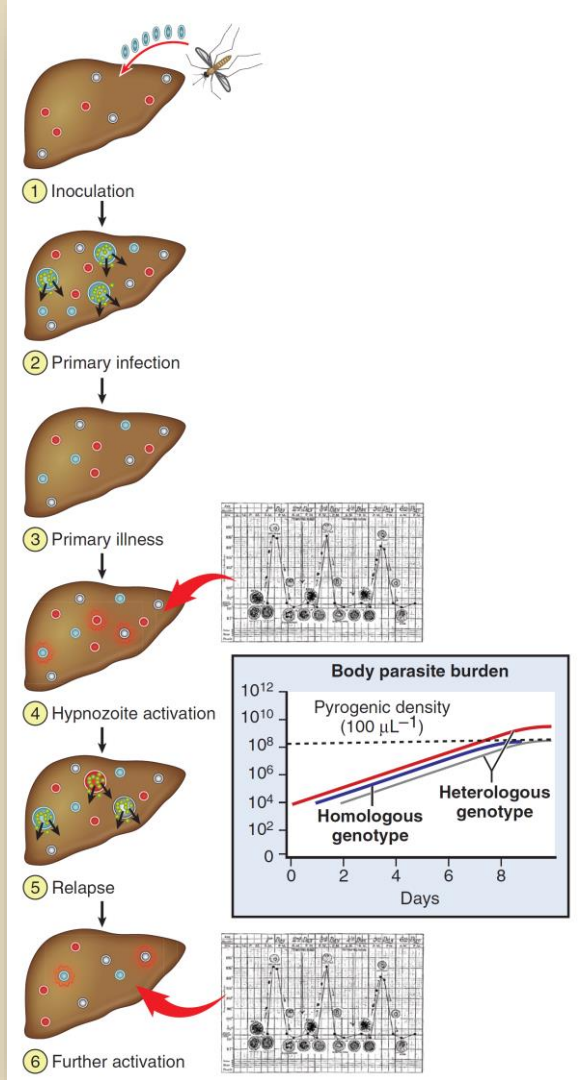

48 h

72 h

# *P. vivax* malaria relapses

*daily fever*

*periodic fever*




White *Malaria Journal* 2011, **10**:297
http://www.malariajournal.com/content/10/1/297

# P. vivax malaria

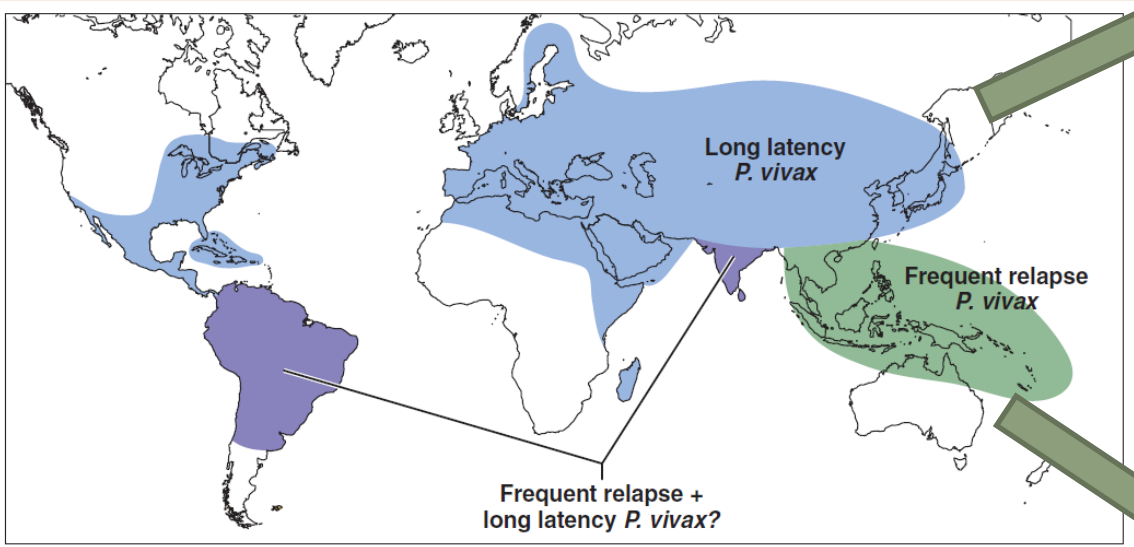
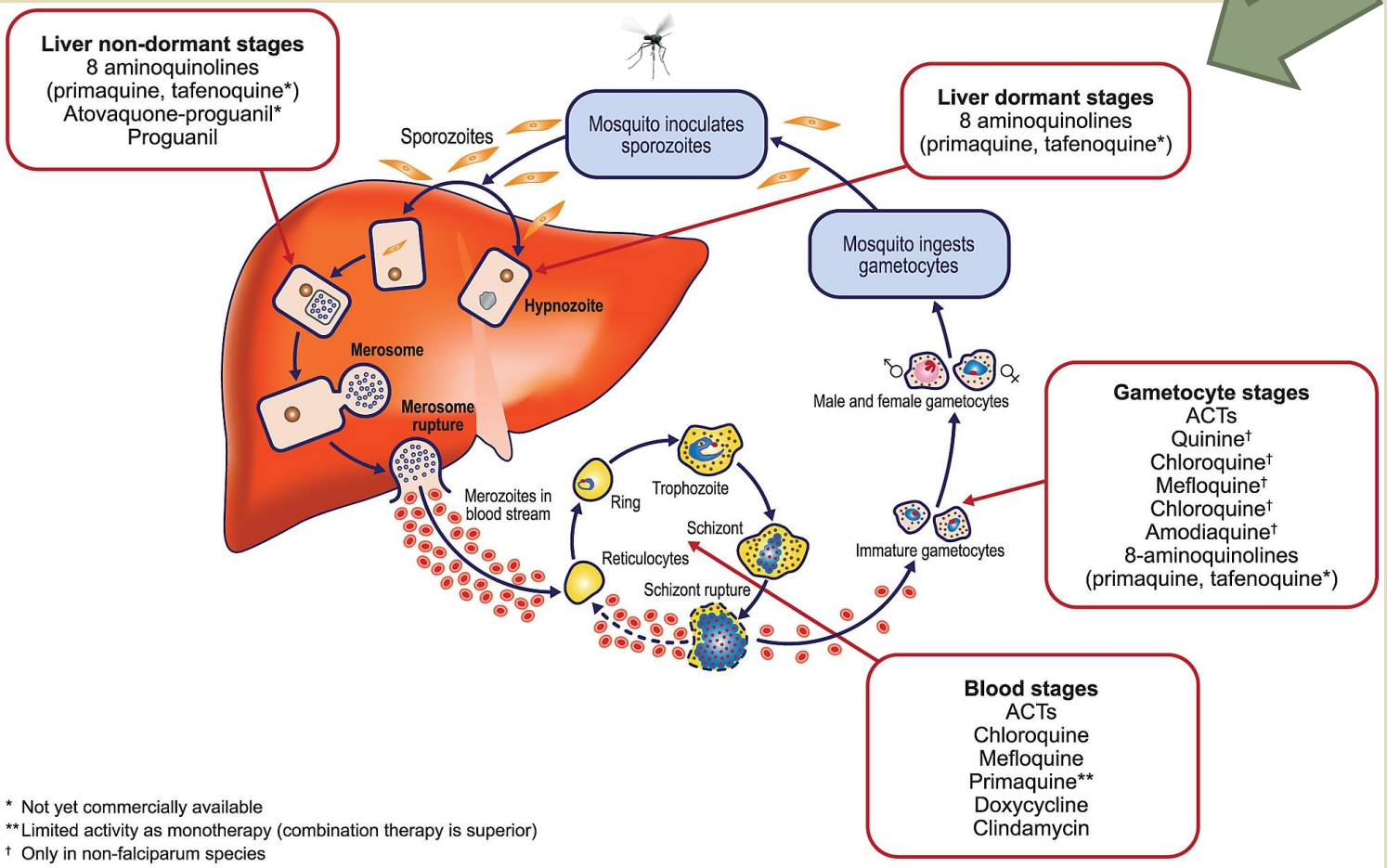



FIGURE 40-17 The areas where tropical "frequent relapse phenotypes" are prevalent are shown in *green*. The areas where both frequent relapse and long-latency phenotypes have been reported are shown in *purple*, and areas where long-latency phenotypes were prevalent are shown in *blue*. Although both South America and India are generally considered to predominantly harbor frequent relapse phenotypes, there is evidence that long-latency phenotypes are present in both areas (particularly across northern India). Without genotyping, it may be difficult or impossible to distinguish two phenotypes within an endemic area. *(From White NJ:* Determinants of relapse periodicity in Plasmodium vivax malaria. *Malar J 2011;10:297.)*

In temperate regions, *P. vivax* relapses can occur 8 to 10 months after primary infection

In tropical regions, *P. vivax* relapses can occur every 3 to 4 weeks, or every 6 to 8 weeks after treatment with a slowly eliminated drug.

White *Malaria Journal* 2011, **10**:297
http://www.malariajournal.com/content/10/1/297

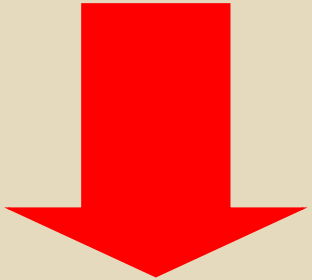



https://plos.figshare.com/articles/figure/_P_vivax_life_cycle_and_sites_of_action_for_different_antimalarials_/369042

Fever (>38°C)

+

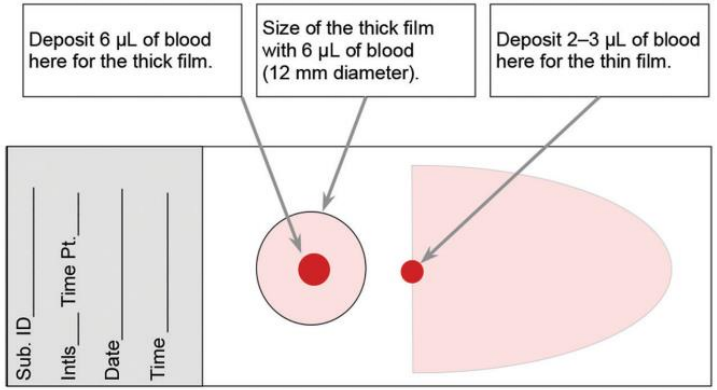
travel to malaria endemic area



Thin and thick blood film

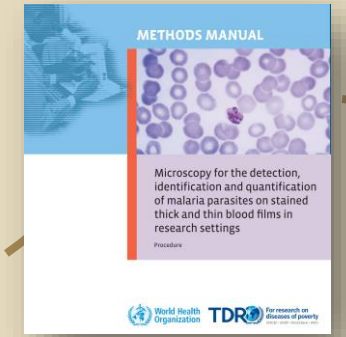
(at least)

**Figure 1. Template for preparation of slides with thick and thin blood films**



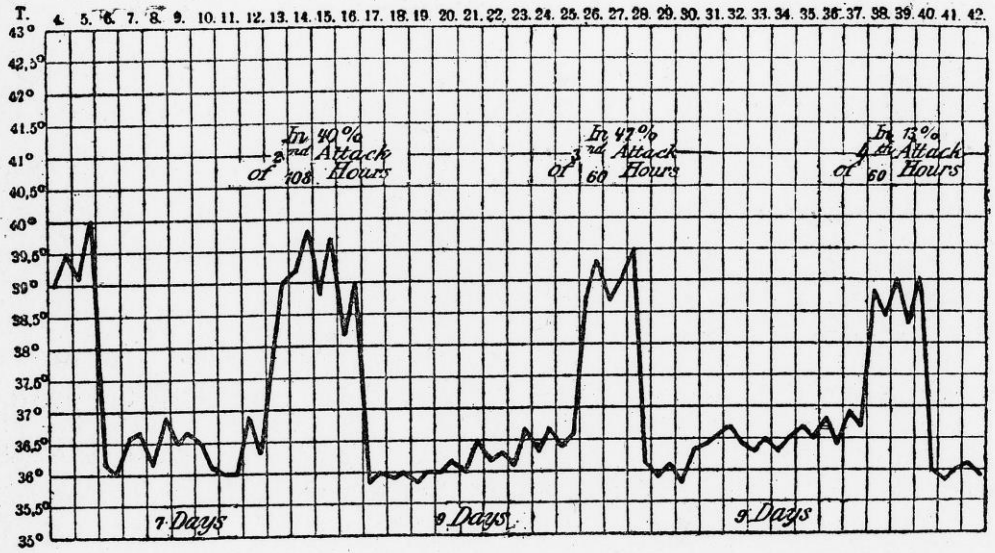

# Striscio sottile e goccia spessa

Cosa possiamo diagnosticare (oltre alla malaria?)



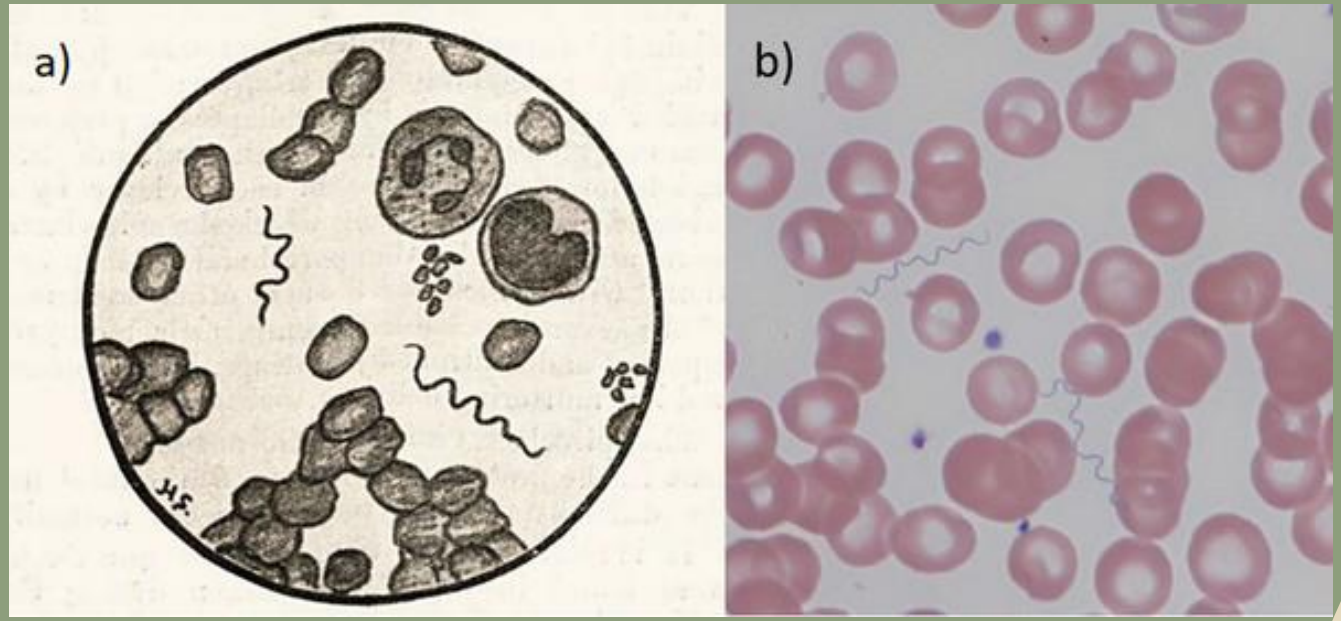

https://apps.who.int/iris/bitstream/handle/10665/163782/9789241549219_eng.pdf;sequence=1

# Periodic fever




CURVE 1.—Combination Curve from Thirty symptomatically treated Cases.

Microscopic detection of B. recurrentis in blood films.




Kahlig P, Paris DH, Neumayr A (2021) Louse-borne relapsing fever—A systematic review and analysis of the literature: Part 1—Epidemiology and diagnostic aspects. PLOS Neglected Tropical Diseases 15(3): e0008564. https://doi.org/10.1371/journal.pntd.0008564
https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0008564

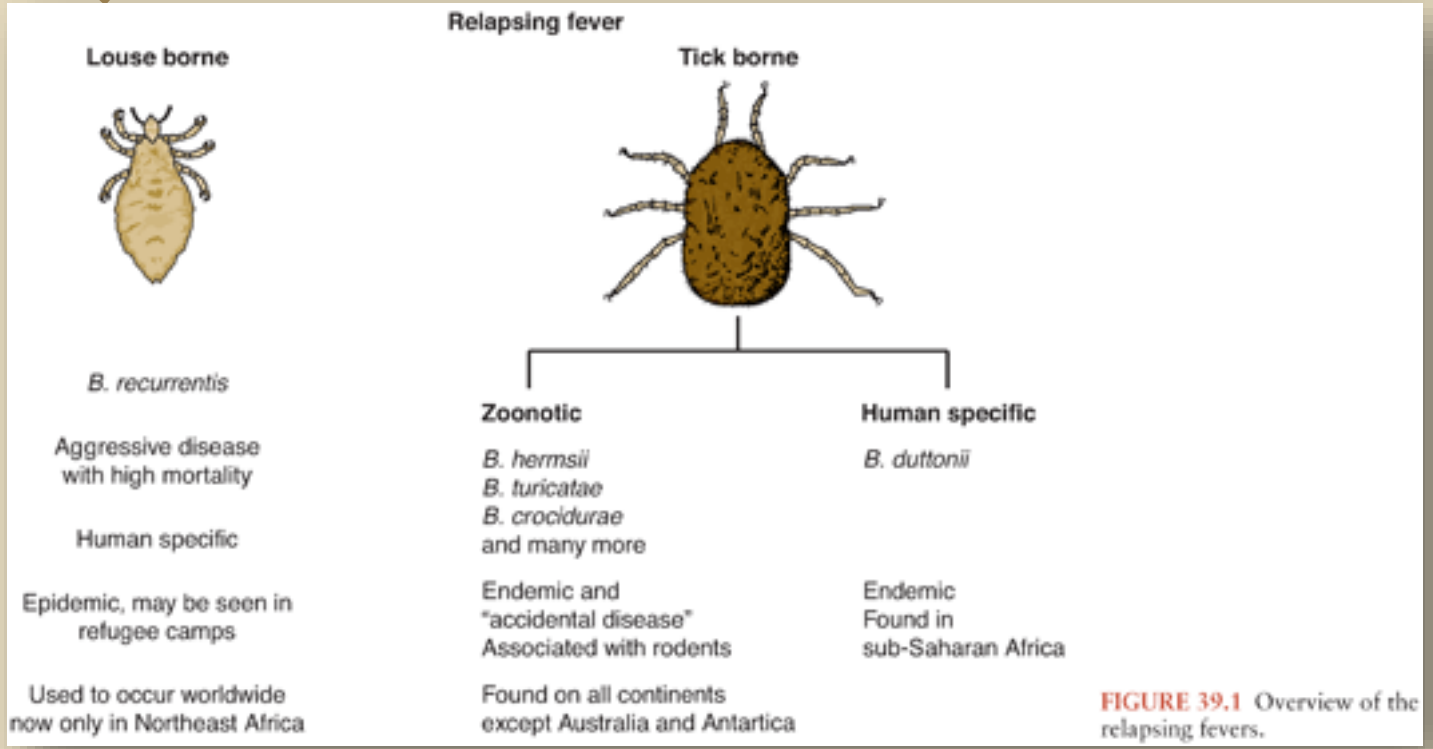



FIGURE 39.1 Overview of the relapsing fevers.

https://oncohemakey.com/neuroborreliosis-nervous-system-involvement-with-borrelia-species/

Geographic visualization of all identified LBRF cases published from 1907 to 2019

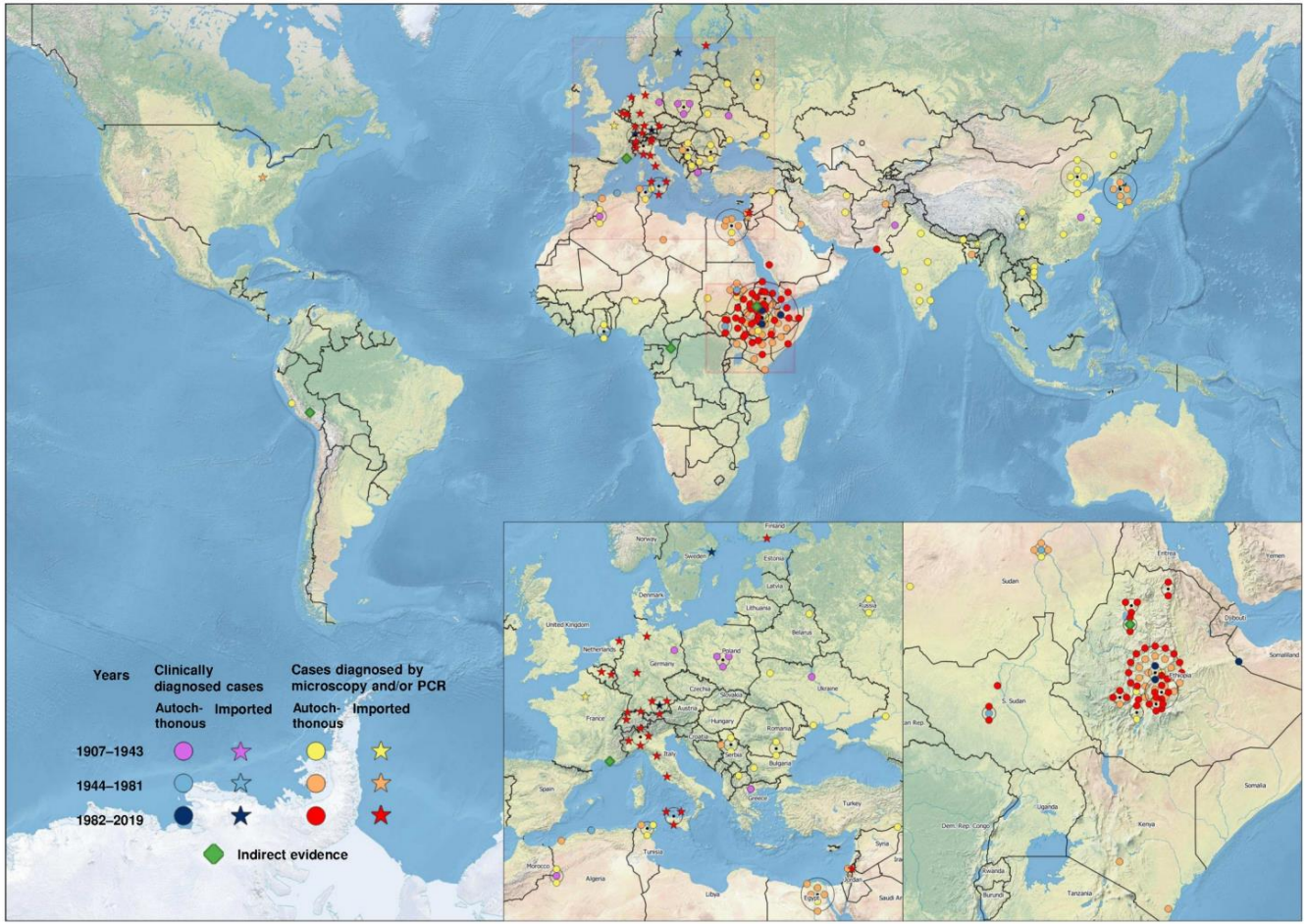



**Fig 4. Geographic visualization of all identified LBRF cases published from 1907 to 2019.** Each data point on the map corresponds to one of the analyzed 184 publications. If 2 or more studies reported cases from the same location, the dots representing these studies are connected by a circle with its center corresponding to this location. LBRF, louse-borne relapsing fever; PCR, polymerase chain reaction. (Map data: Natural Earth).

https://doi.org/10.1371/journal.pntd.0008564.g004

# Louse-borne relapsing fever

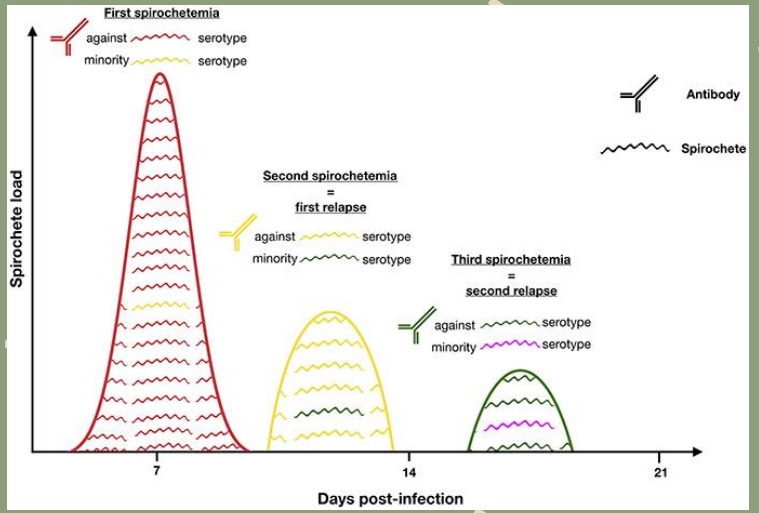
Incubation period: from 4 to 18 (average 7) days.

1st attack: abruptly fever (nearly 40˚C in a few days), rigors. Early symptoms include headache, dizziness, pains nausea, vomiting, and diarrhea. A petechial or ecchymotic rash (trunk), in 2% to 8% of patients, and 7% to >70% of patients develop jaundice. Subconjunctival hemorrhages and epistaxis are common (25%), hemoptysis, gastrointestinal bleeding, and retinal hemorrhages less so.

Severe cases: neurological involvement, myocarditis, acute respiratory distress syndrome, hepatic failure, spleen rupture, disseminated intravascular coagulation leading to intracranial, massive gastrointestinal, pulmonary or peripartum hemorrhage may occur.

Case fatalities between 30% and 80% in untreated patients, but with antibiotic treatment mortality is reduced to 2% to 5%.

Untreated attacks resolve by crisis after 4 to 10 (average 5) days. This is followed by an afebrile remission of 5 to 9 days and succeeded by up to 5 relapses of diminishing severity.



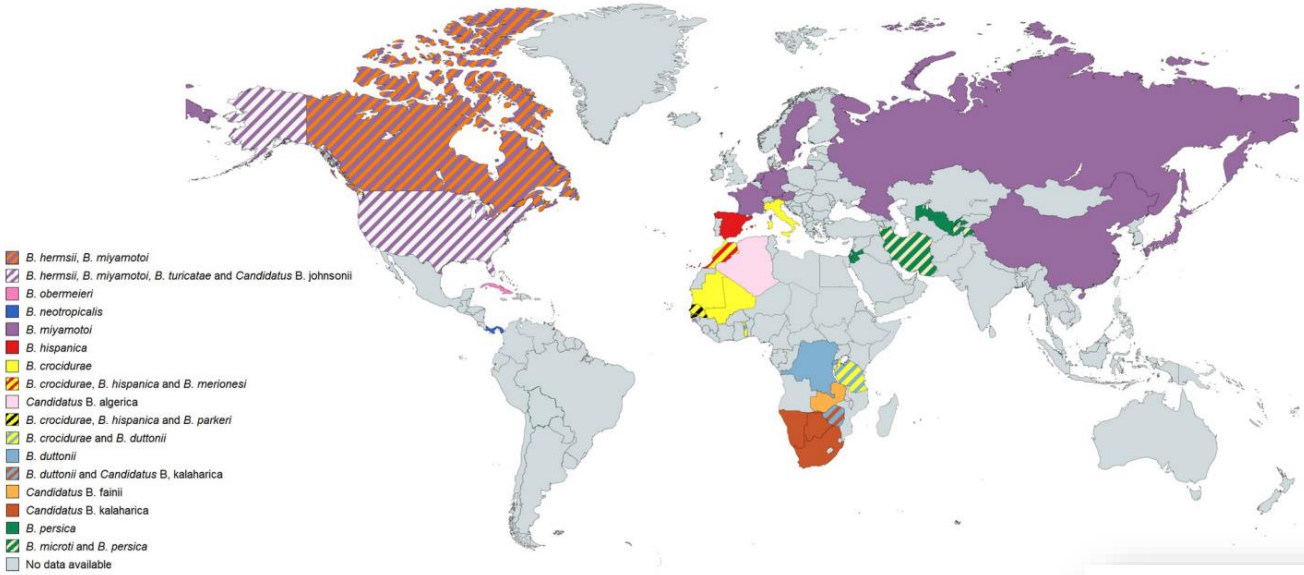



**Fig 5. Reported TBRF cases by country and causative *Borrelia* species.** B., *Borrelia*. Map created on www.mapchart.net.

https://doi.org/10.1371/journal.pntd.0010212.g005

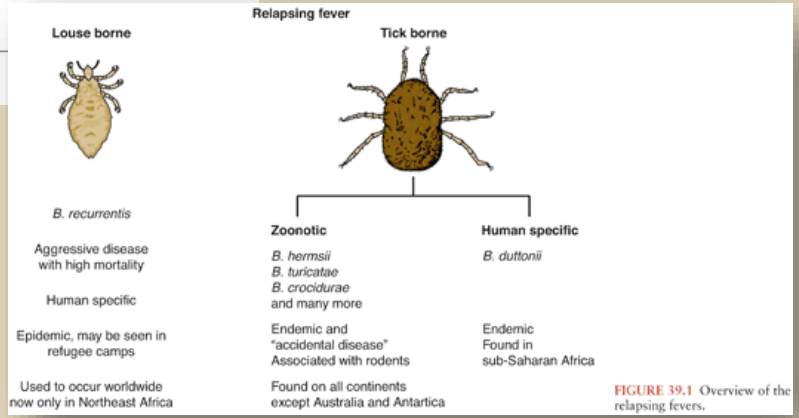
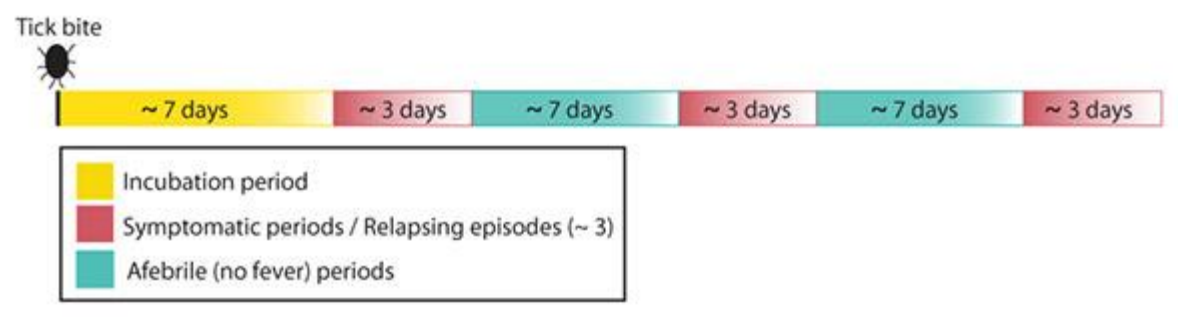



FIGURE 39.1 Overview of the relapsing fevers.

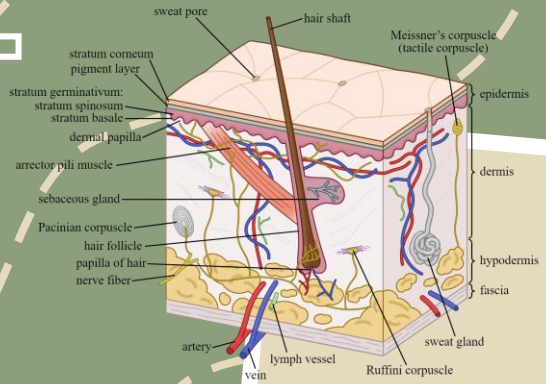
https://oncohemakey.com/neuroborreliosis-nervous-system-involvement-with-borrelia-species/

# Tick-borne relapsing fever

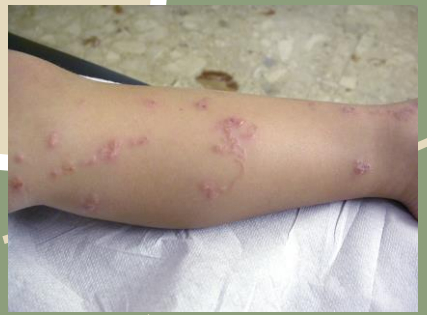
Tick-borne relapsing fever is characterized by recurring febrile episodes that last ~3 days and are separated by afebrile periods of ~7 days duration. Along with fever, patients may experience a wide range of nonspecific symptoms. Each febrile episode ends with a sequence of symptoms collectively known as a “crisis.” During the “chill phase” of the crisis, patients develop very high fever (up to 106.7°F or 41.5°C) and may become delirious, agitated, tachycardic and tachypneic. Duration is 10 to 30 minutes. This phase is followed by the “flush phase”, characterized by drenching sweats and a rapid decrease in body temperature. During the flush phase, patients may become transiently hypotensive. Overall, patients who are not treated will experience several episodes of fever before illness resolves.



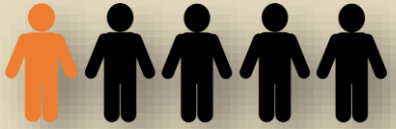

https://www.cdc.gov/relapsing-fever/clinicians/index.html




# Skin disorders: subacute or chronic/recurrent



# Skin problems in travellers



1/5

## Need hospitalization

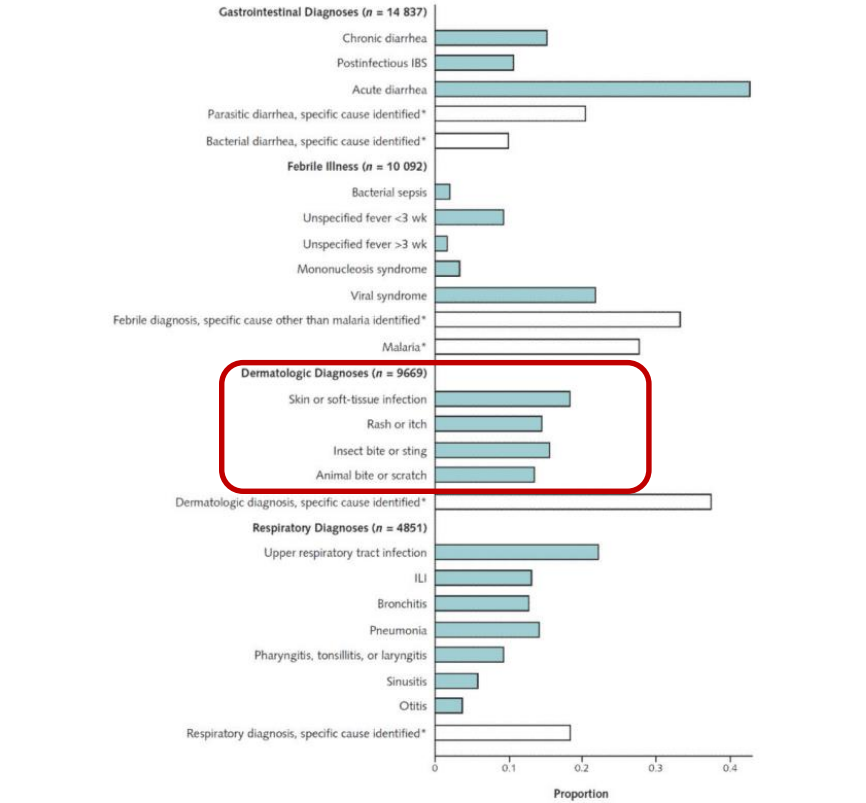
10% of all cases

## Ambulatory

90% of all cases;

Among around 47000 travellers (Geosentinel 2007-11) **19,5%** have skin diseases

GeoSentinel Surveillance of Illness in Returned Travelers, 2007– 2011
doi:10.7326/0003-4819-158-6-201303190-00005



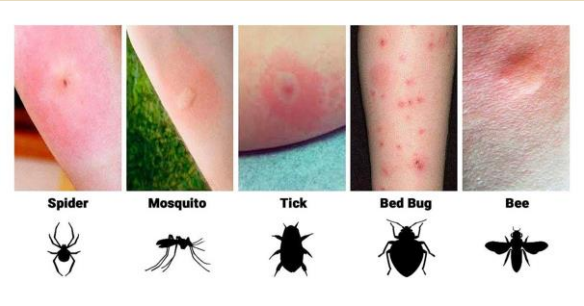

IBS = irritable bowel syndrome; ILI = influenza-like illness.
* Each bar represents a mutually exclusive classification. Green bars depict the proportion of each diagnostic category with the given syndromic grouping. White bars depict the proportion with the given specific cause, and the top diagnoses within each of these categories are shown by region in Figure 2.

**Figure 1.**
Proportion of major syndromic groupings for gastrointestinal, febrile, dermatologic, and respiratory illnesses among ill returned travelers.

# Main skin problems – travellers (Geosentinel)

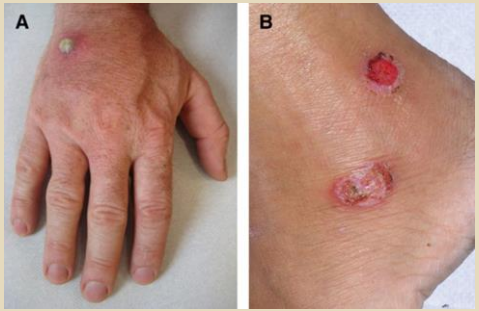
## 1st skin problem

Animal bites/scratches, insect bite or stings



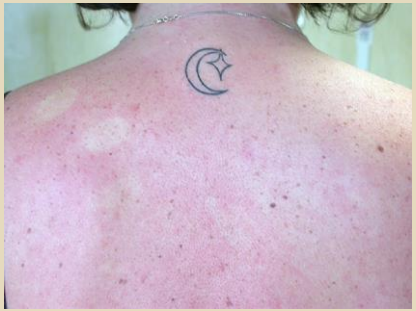

## 2nd skin problem

Skin or soft tissue infection




## 3rd skin problem

Rash, itch



2800 Israeli travellers, 19% skin problems; 1/360 leishmania; 1/190 myasis

# Skin diseases and travel destination

Latin America worse destination for skin disorders in travellers

Am. J. Trop. Med. Hyg., 85(5), 2011, pp. 868–872
doi:10.4269/ajtmh.2011.10-0471


Tropical Skin Infections Among Israeli Travelers

Michal Solomon, Shmuel Benenson, Sharon Baum, and Eli Schwartz*

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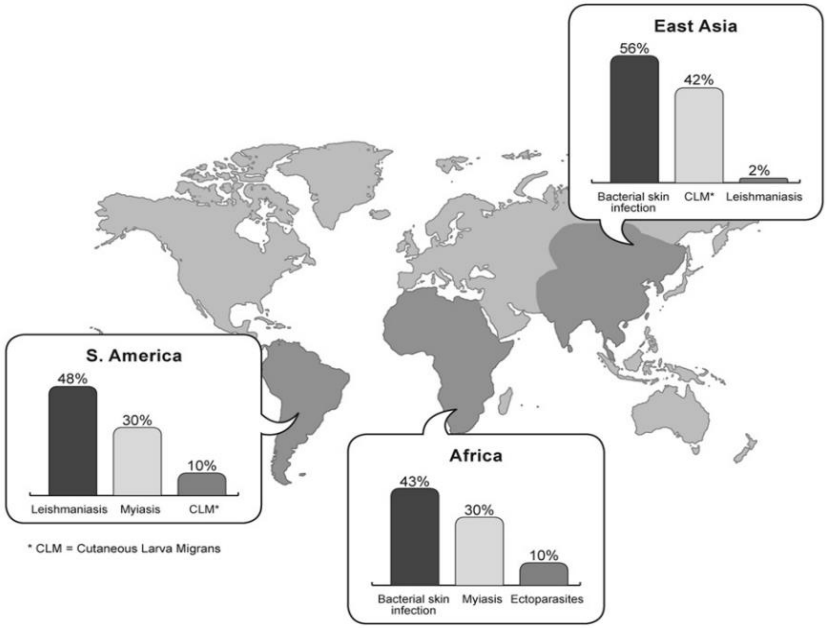



FIGURE 1. Diseases and destinations: the three most common skin infections in each continent visited.

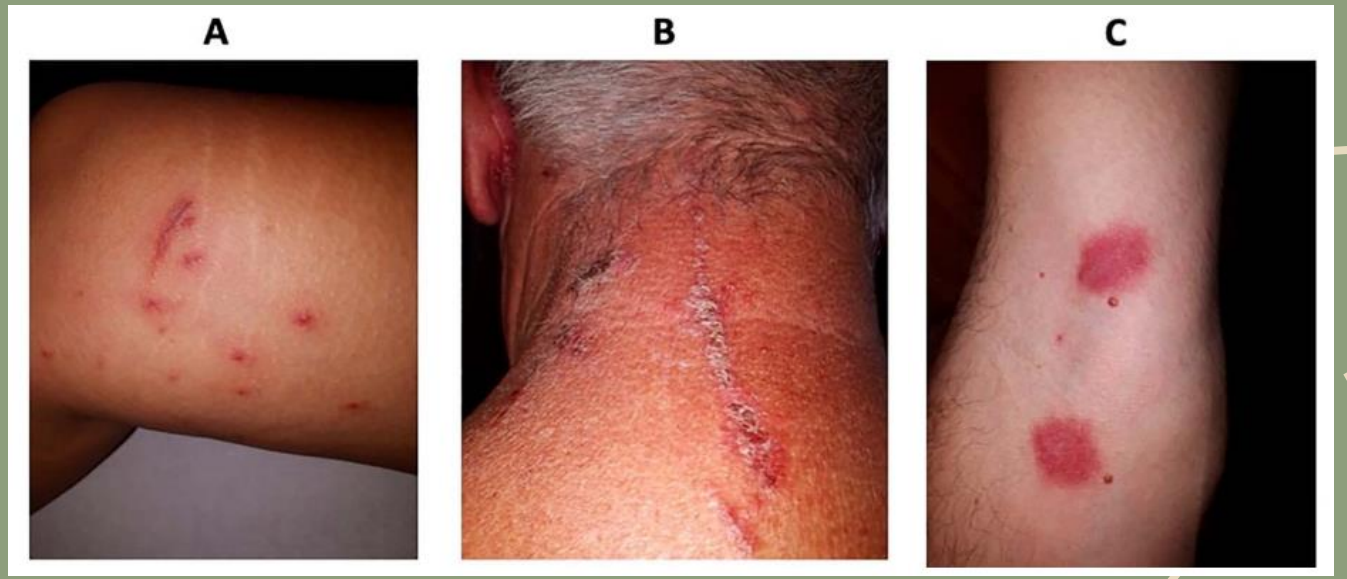
# PEP for rabies

| Diagnoses | Cases, *n* | Median Age, *y* | Man–Woman Ratio | Reason for Travel, %* | | | Reported Pretravel Visit, % | Top Countries of Exposure† |
|---|---|---|---|---|---|---|---|---|
| | | | | Tourism | Visiting Friends/ Relatives | Business | | |
| Dermatologic | | | | | | | | |
| Rabies PEP after bite or scratch | 1249 | 31 | 1.0 | 68.9 | 17.7 | 7.1 | 25.5 | Thailand, Indonesia, China, and India |

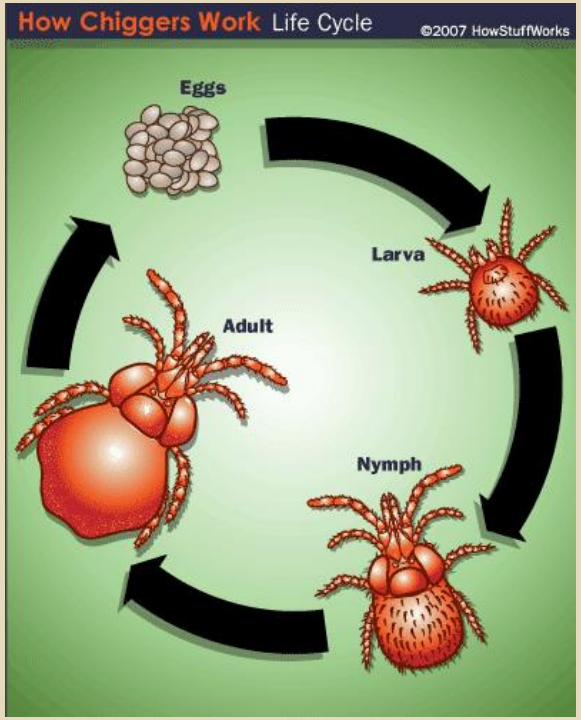
- 20% of medical problems are skin disorders; among these
- About 12% need PEP for rabies

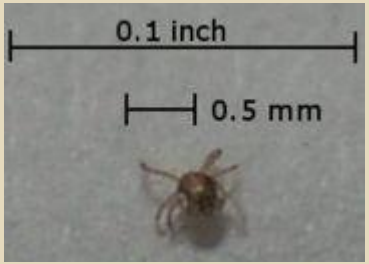
19 March 2013 | Annals of Internal Medicine | Volume 158 • Number 6

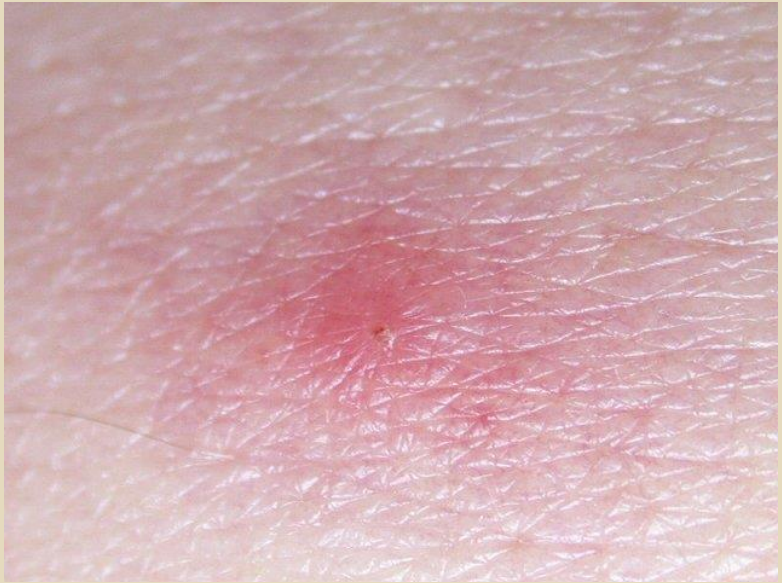
# Paederus dermatitis of beetle dermatitis



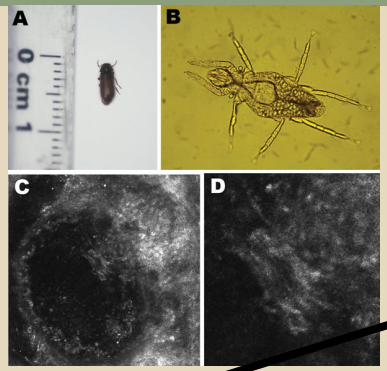
# Trombicula


How Chiggers Work Life Cycle
©2007 HowStuffWorks
Eggs
Larva
Adult
Nymph

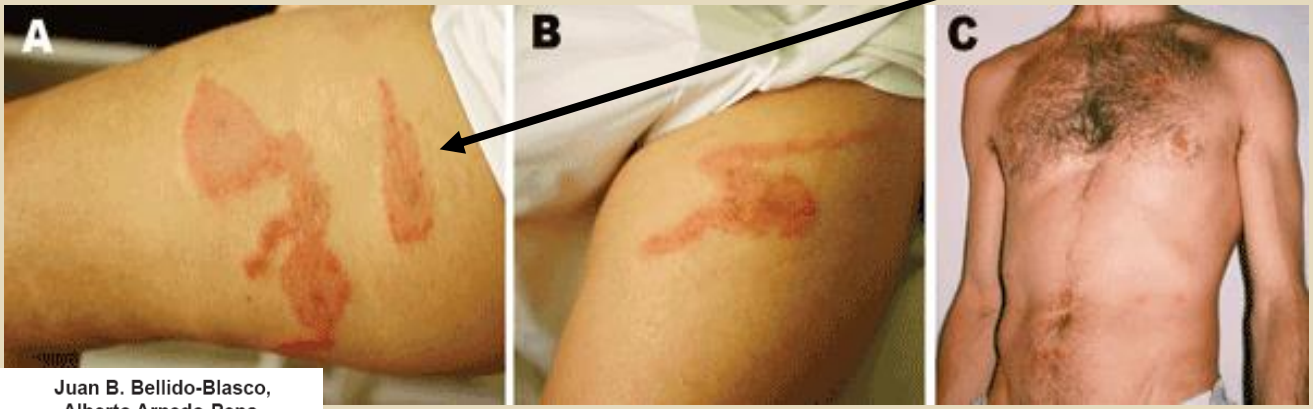

0.1 inch
0.5 mm



Punture di *Pyemotes* spp., parassita del tarlo (Francia, Spagna, Italia…)




Comet sign




**Juan B. Bellido-Blasco, Alberto Arnedo-Pena, and Francisca Valcuende**

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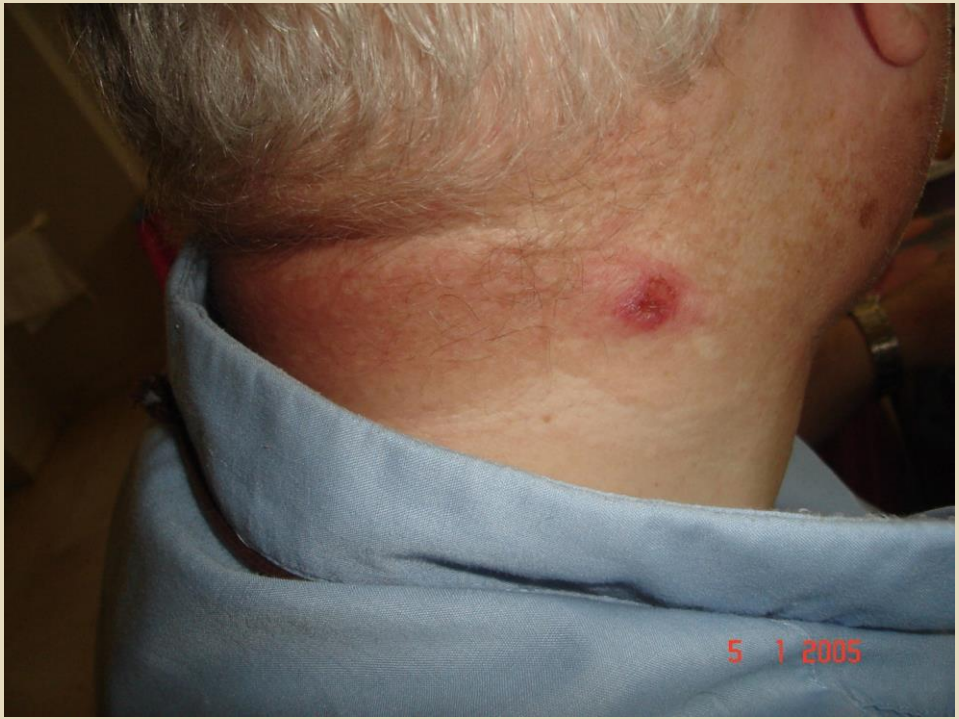
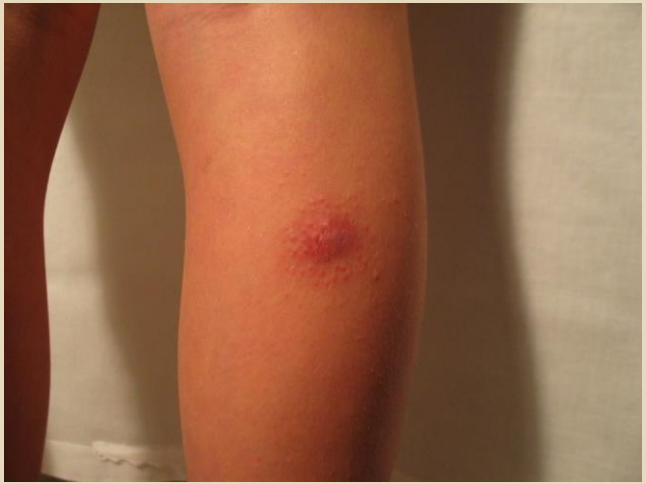
DOI: 10.3201/eid1503.081461

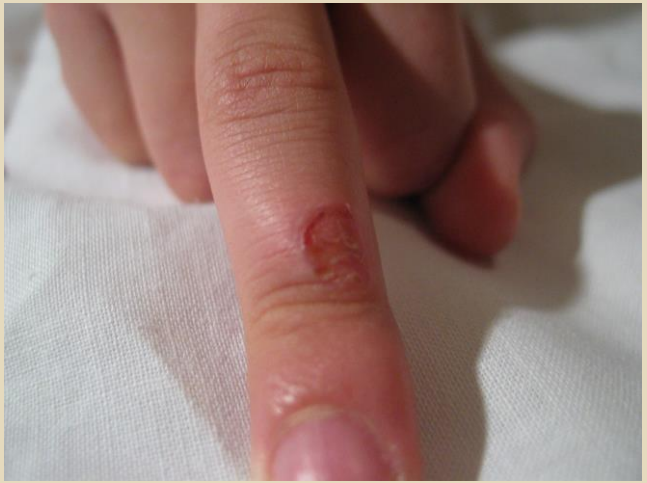
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 3, March 2009

# Leishmania

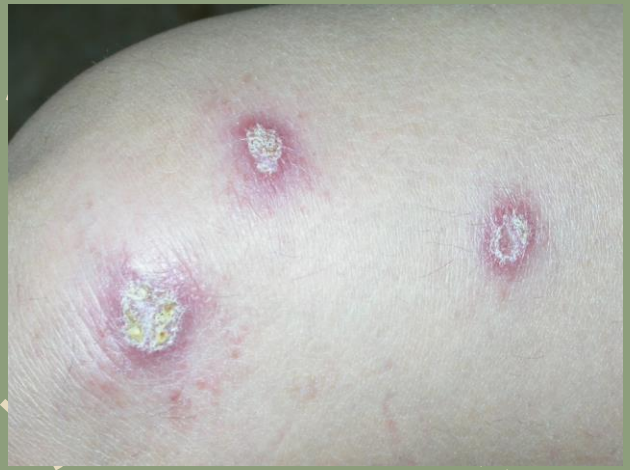


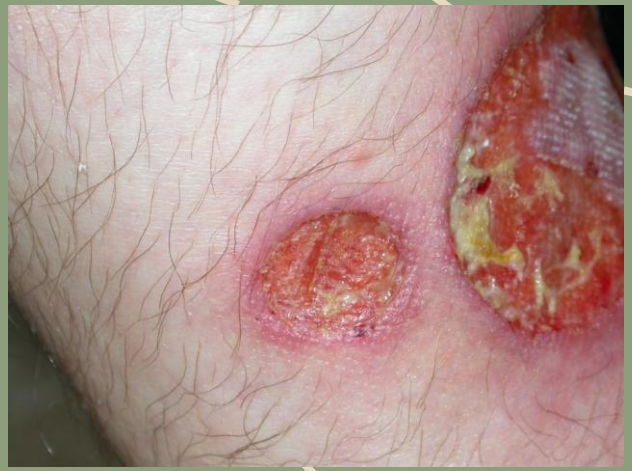
# Leishmania

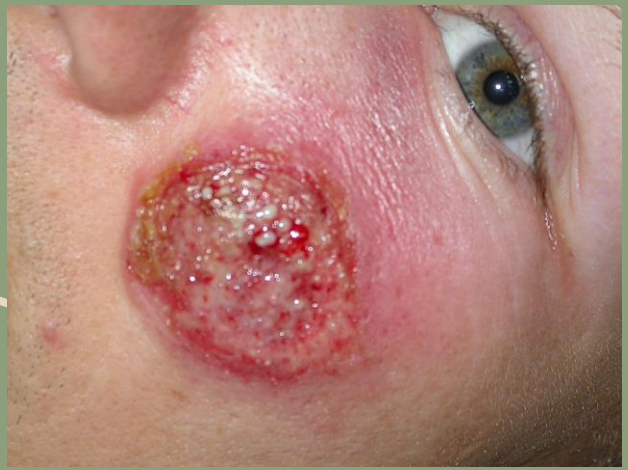




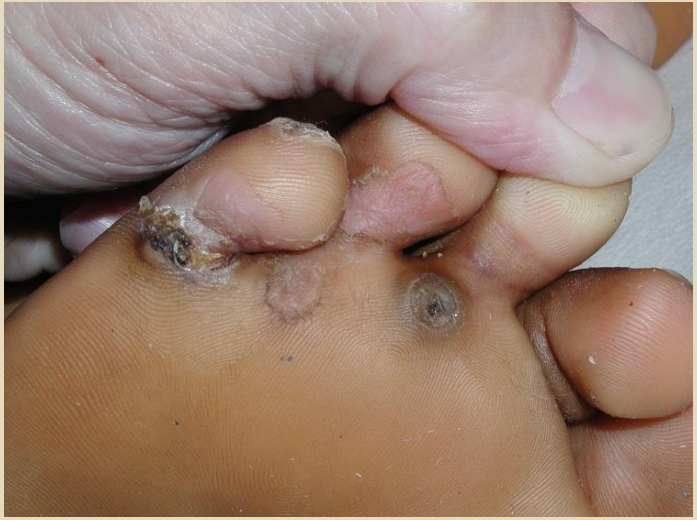
# Leishmania

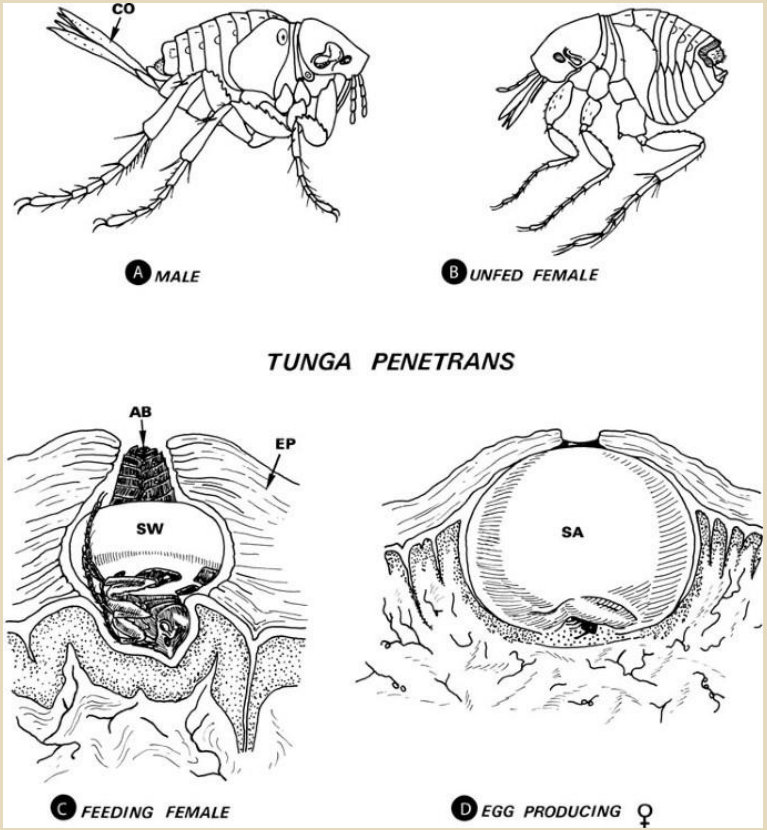


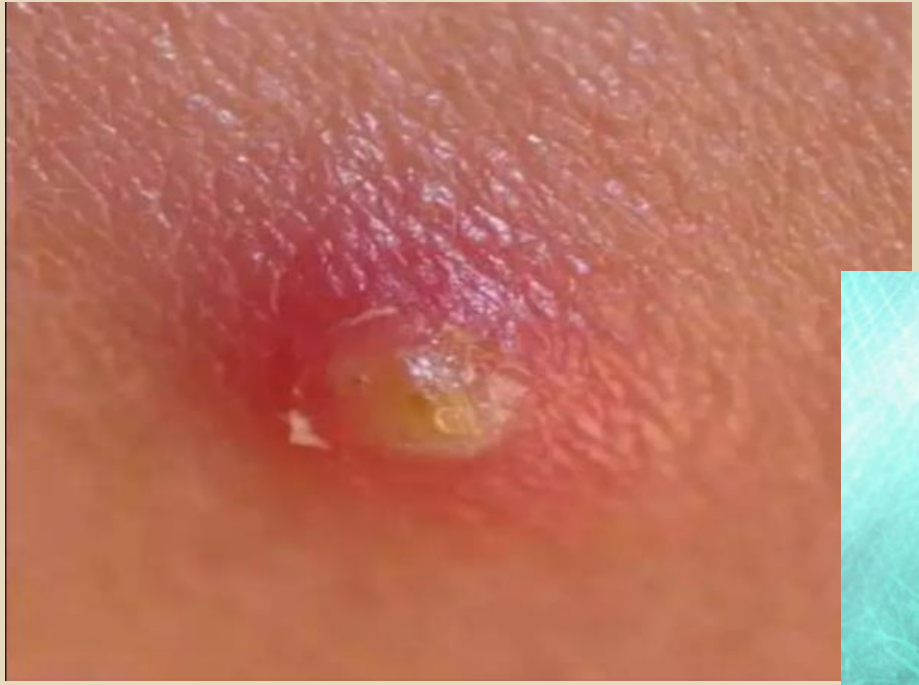


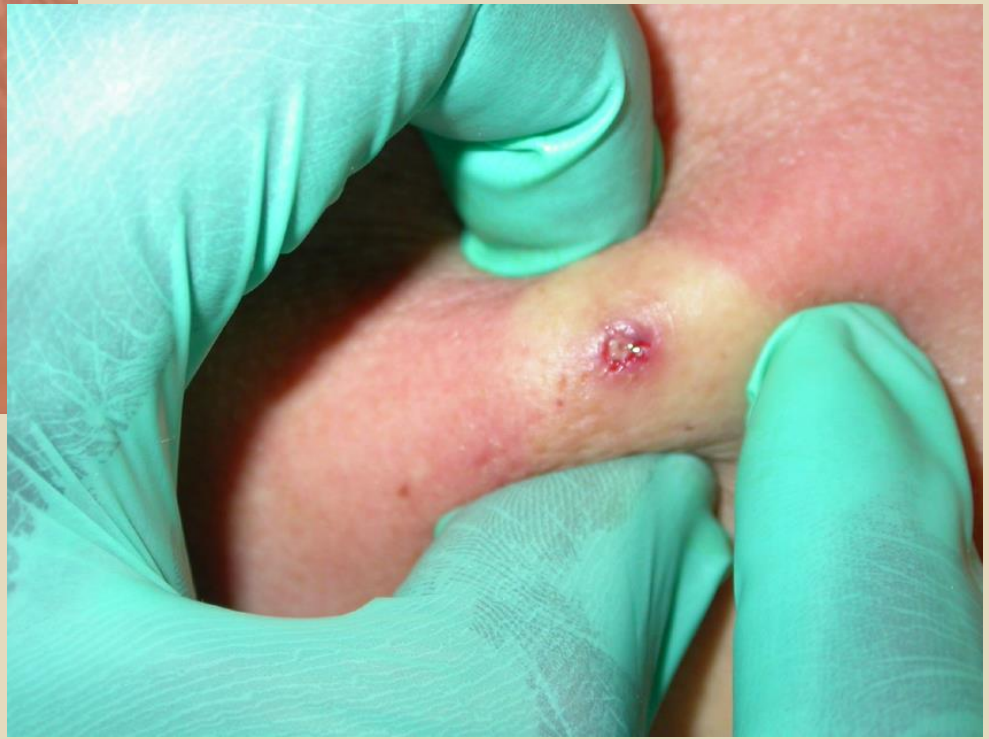


# Tungiasi o pulce penetrante









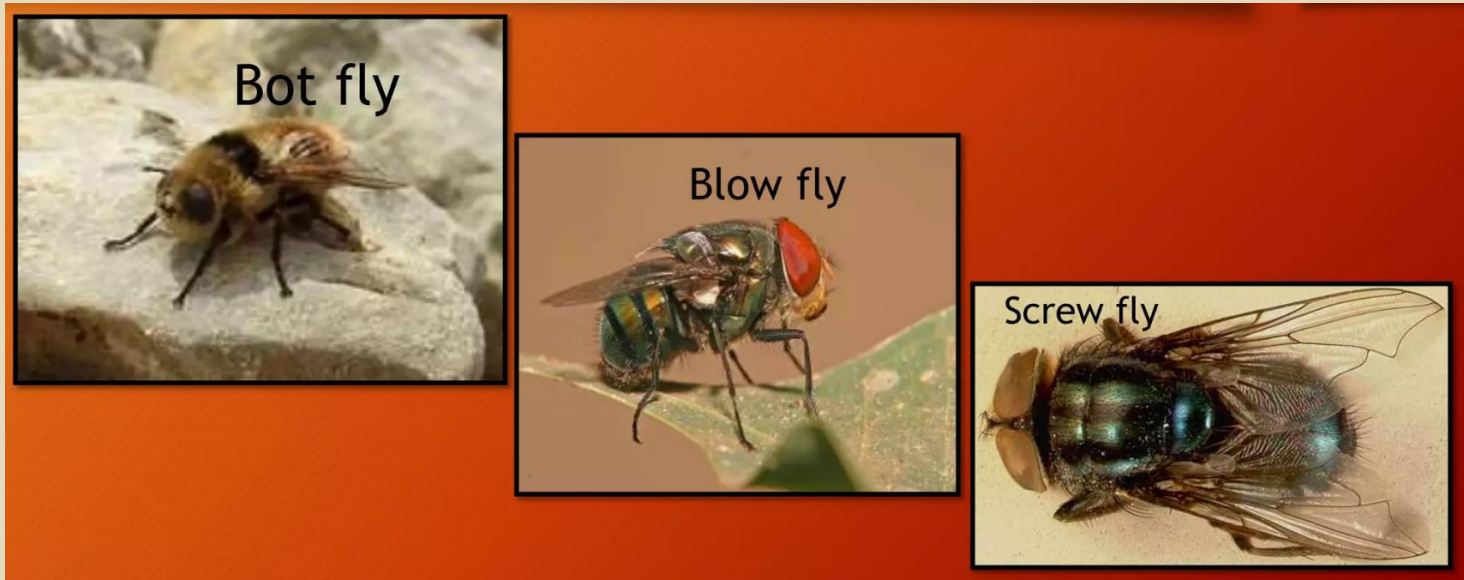
# Miasi foruncolare: *Dermatobia hominis*

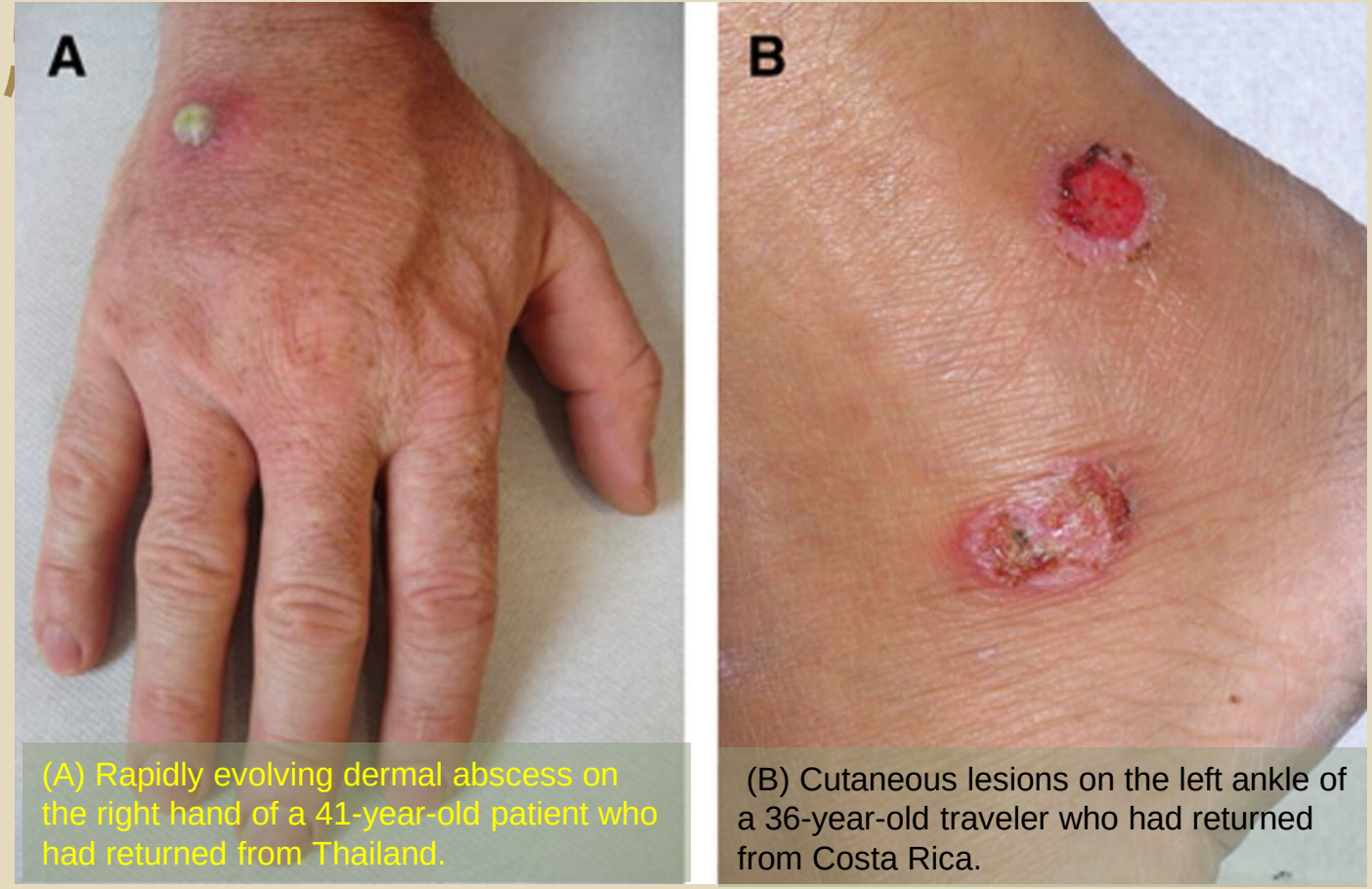

Il termine miasi è composta della parola greca che sta per mosca e malattia.

Si tratta di una parassitosi dovuta alle larve di mosca che crescono nei tessuti dell'ospite.

Benchè attratte da piaghe, urine o feci alcune mosche possono infestare l'uomo attraverso cute intatta:

(sfruttano fogliame o insetti «vettori» che depongono le uova sulla cute)



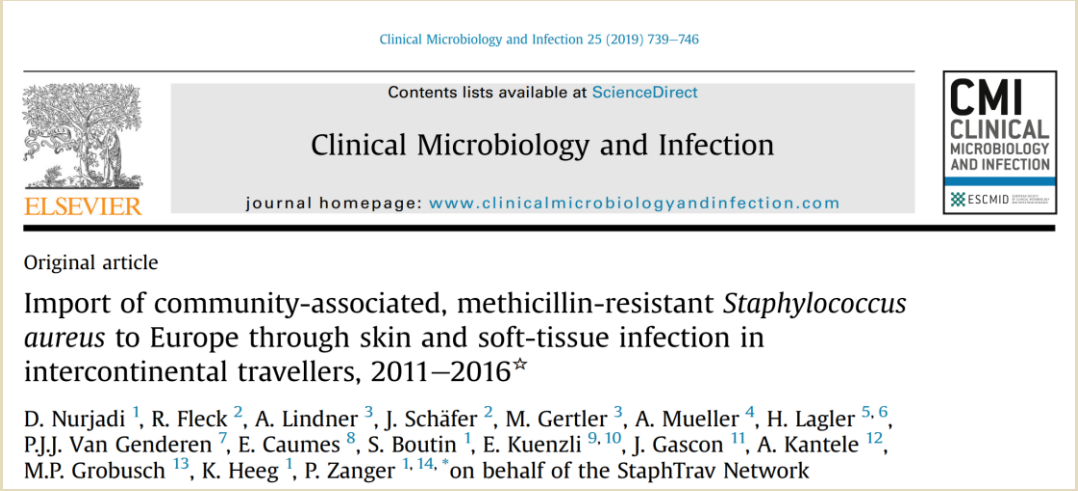



(A) Rapidly evolving dermal abscess on the right hand of a 41-year-old patient who had returned from Thailand.

(B) Cutaneous lesions on the left ankle of a 36-year-old traveler who had returned from Costa Rica.

This figure appears in color at www.ajtmh.org. Am. J. Trop. Med. Hyg., 83(4), 2010, pp. 748–750 doi:10.4269/ajtmh.2010.10-0252

A total of 564 independent case-patients with SSTI were enrolled and had 374 (67%) *S. aureus* positive lesions, of which 14% (51/374) were MRSA. The majority of CA-MRSA isolates from SSTI were Pantone Valentine leucocidin (PVL)-positive (43/51, 84%). The risk of methicillin-resistance in imported *S. aureus* varied by travel region (p <0.001) and was highest in Latin America (16/57, 28%, 95% CI 17.0e41.5) and lowest in Sub-Saharan Africa (4/121, 3%, 95% CI 0.9e8.3).



Clinical Microbiology and Infection 25 (2019) 739–746

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Import of community-associated, methicillin-resistant *Staphylococcus aureus* to Europe through skin and soft-tissue infection in intercontinental travellers, 2011–2016☆

D. Nurjadi [1], R. Fleck [2], A. Lindner [3], J. Schäfer [2], M. Gertler [3], A. Mueller [4], H. Lagler [5, 6], P.J.J. Van Genderen [7], E. Caumes [8], S. Boutin [1], E. Kuenzli [9, 10], J. Gascon [11], A. Kantele [12], M.P. Grobusch [13], K. Heeg [1], P. Zanger [1, 14, *] on behalf of the StaphTrav Network

Major epidemic clones, such as USA300, Bengal Bay and South Pacific CA-MRSA, accounted for about 37% of travel-associated MRSA SSTI.

Infections caused by these pathogens were typically acquired at endemic destinations, i.e. Latin America, India and the Philippines.

Taken together, these observations confirm that travel-associated SSTI drives the spread of epidemic CA-MRSA over long distances.

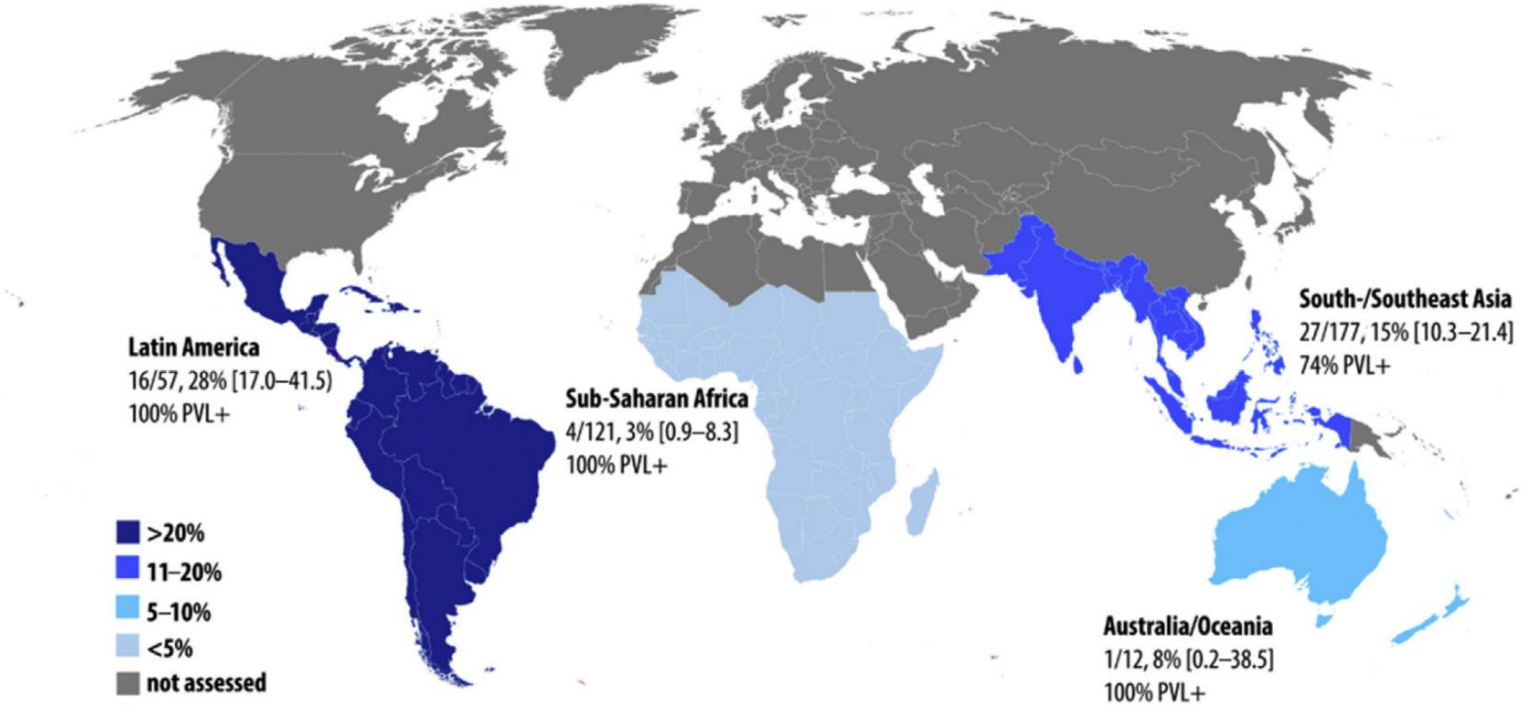
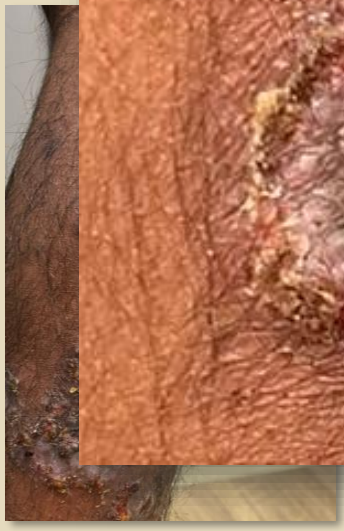



**Fig. 1.** Resistance to methicillin in *Staphylococcus aureus* imported to Europe, by region of travel destination, StaphTrav Network 2011–2016. Displayed and coded in blue are – for destinations with at least ten *S. aureus* submissions – prevalence estimates of methicillin-resistance (95% confidence interval) among *S. aureus* imported from a geographic region together with estimates of Panton–Valentine leucocidin (PVL) -positive isolates among methicillin-resistant *S. aureus*. Not displayed are estimates for regions with less than ten *S. aureus* submitted, i.e. West Asia (2/3, 67% (9.4–99.2), 100% PVL+) and North Africa (1/4, 25% (0.6–80.6), 100% PVL+). Chi-squared-test with five degrees of freedom for H0: 'The proportion of methicillin-resistant *S. aureus* is equally distributed over regions of travel destination.' gives $p < 0.001$.

- 25 year-old male from Bangladesh
-1 month and a half history of cutaneous itchy lesions.
- inguinal enlarged LNs
- no fever or other symptoms
- hiv test not available yet

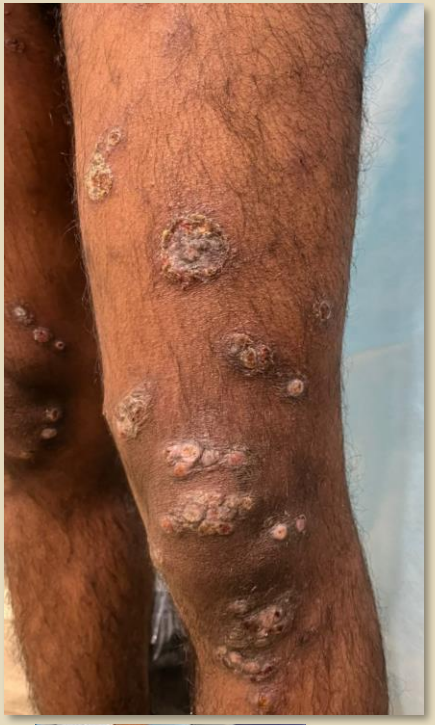
**Diagnosis**

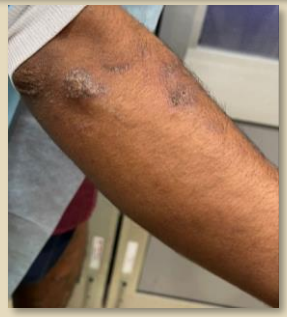
Cutaneous diphteria

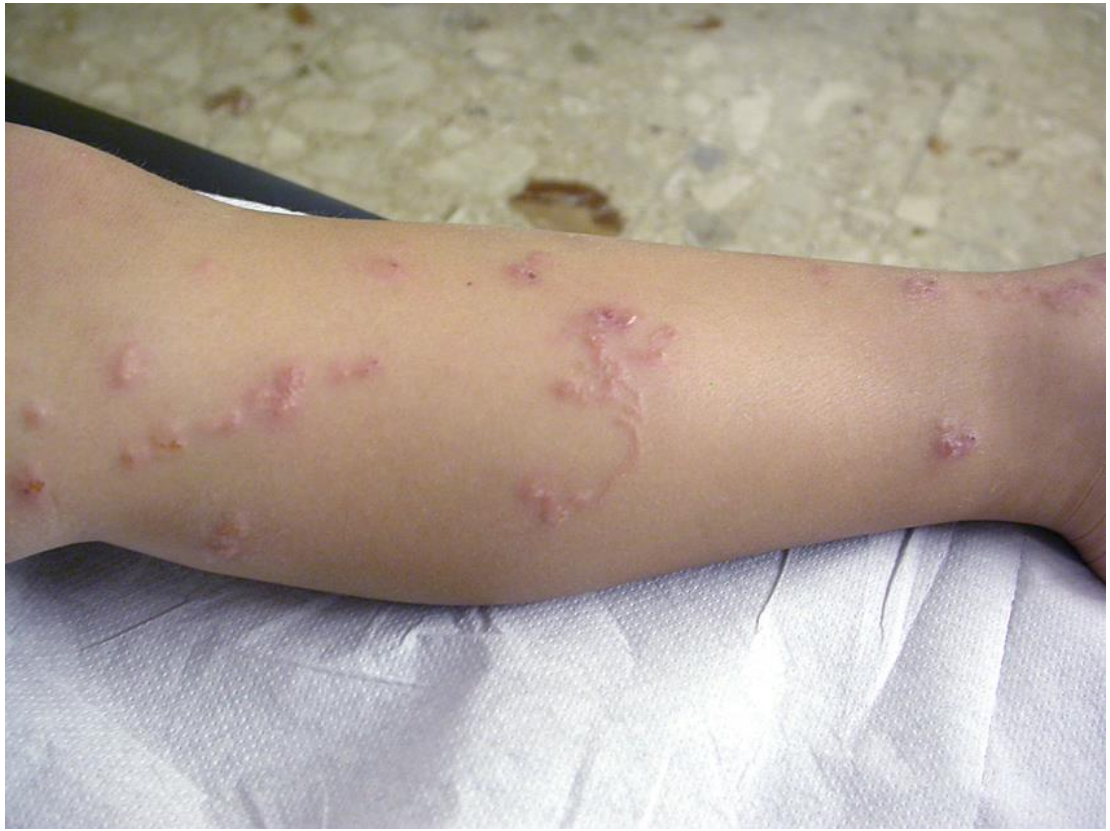



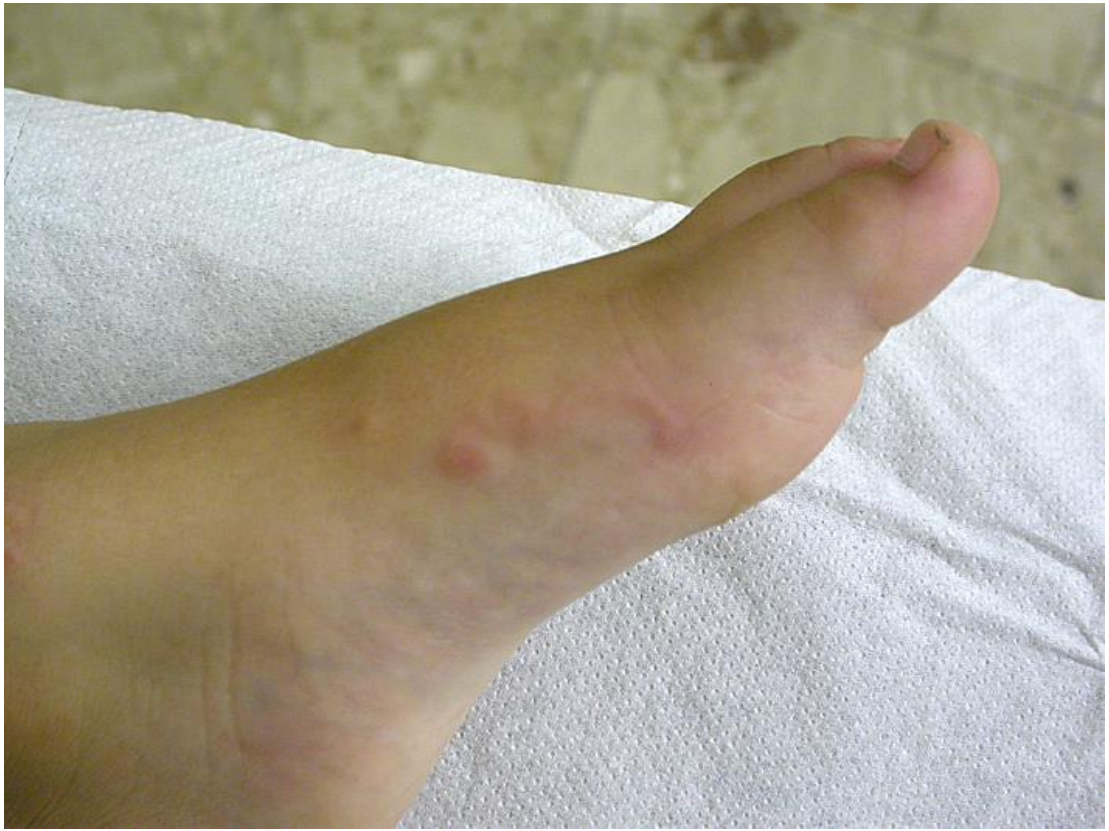


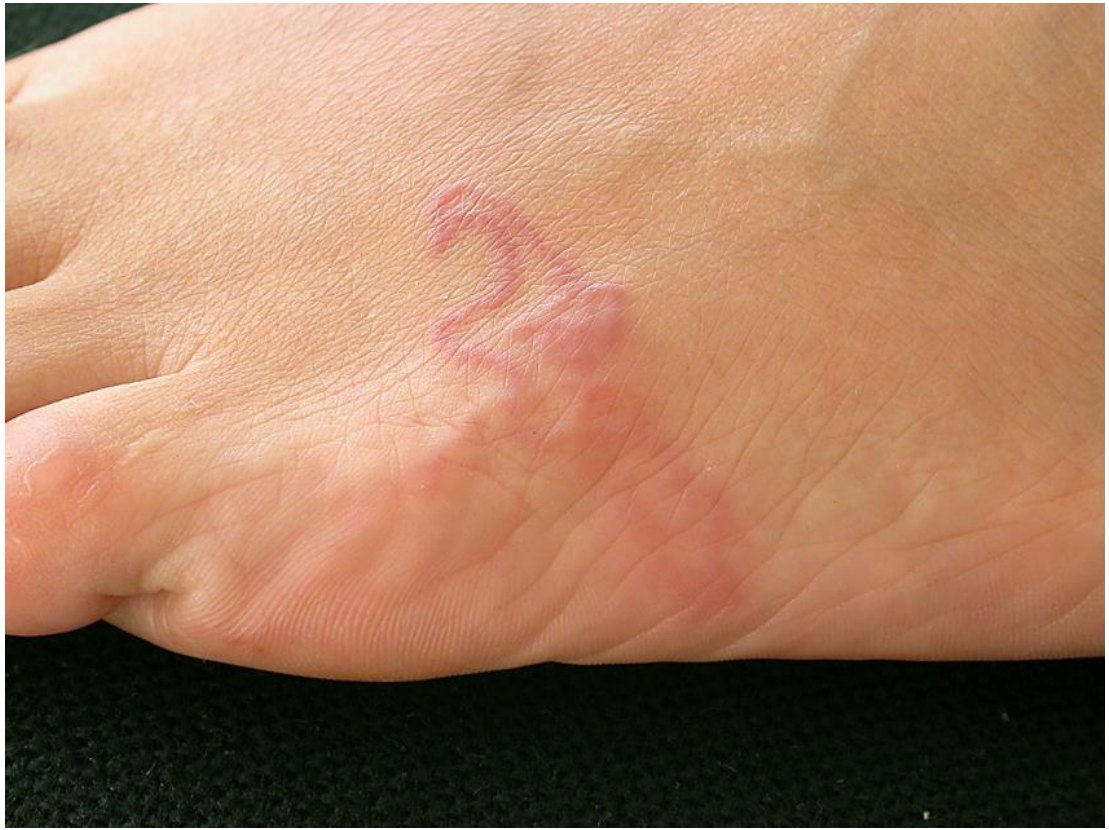


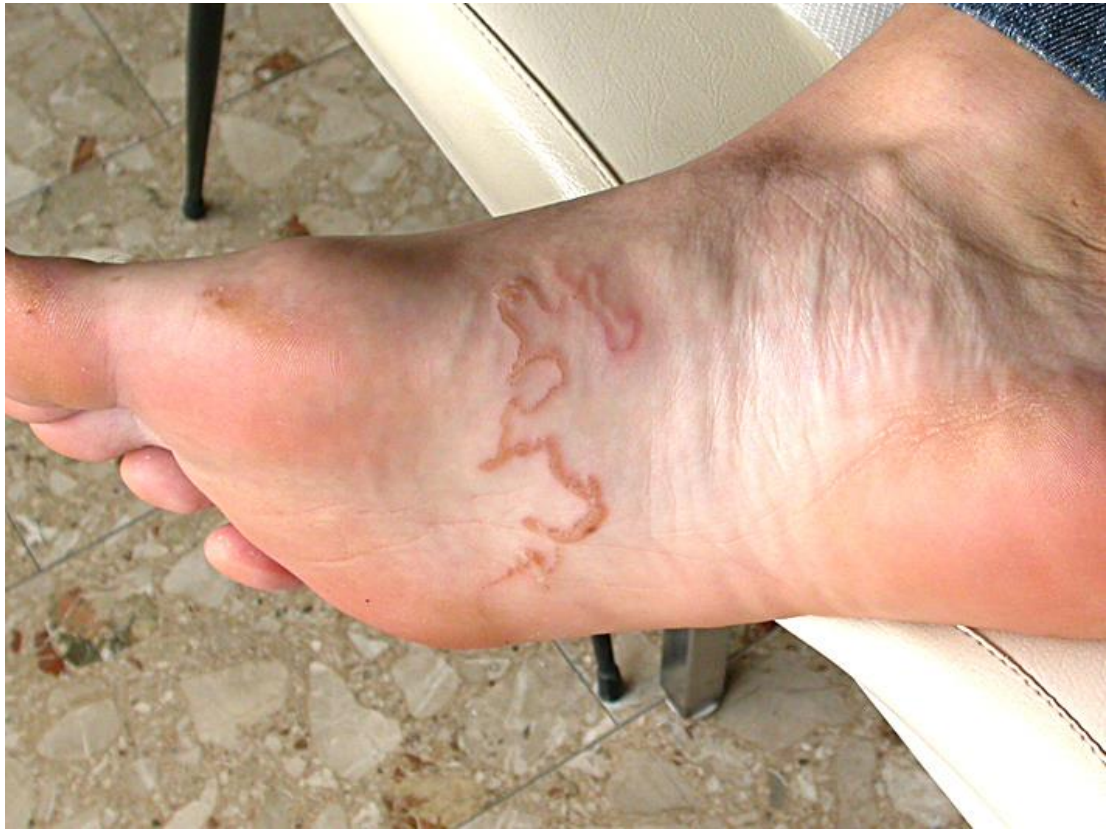


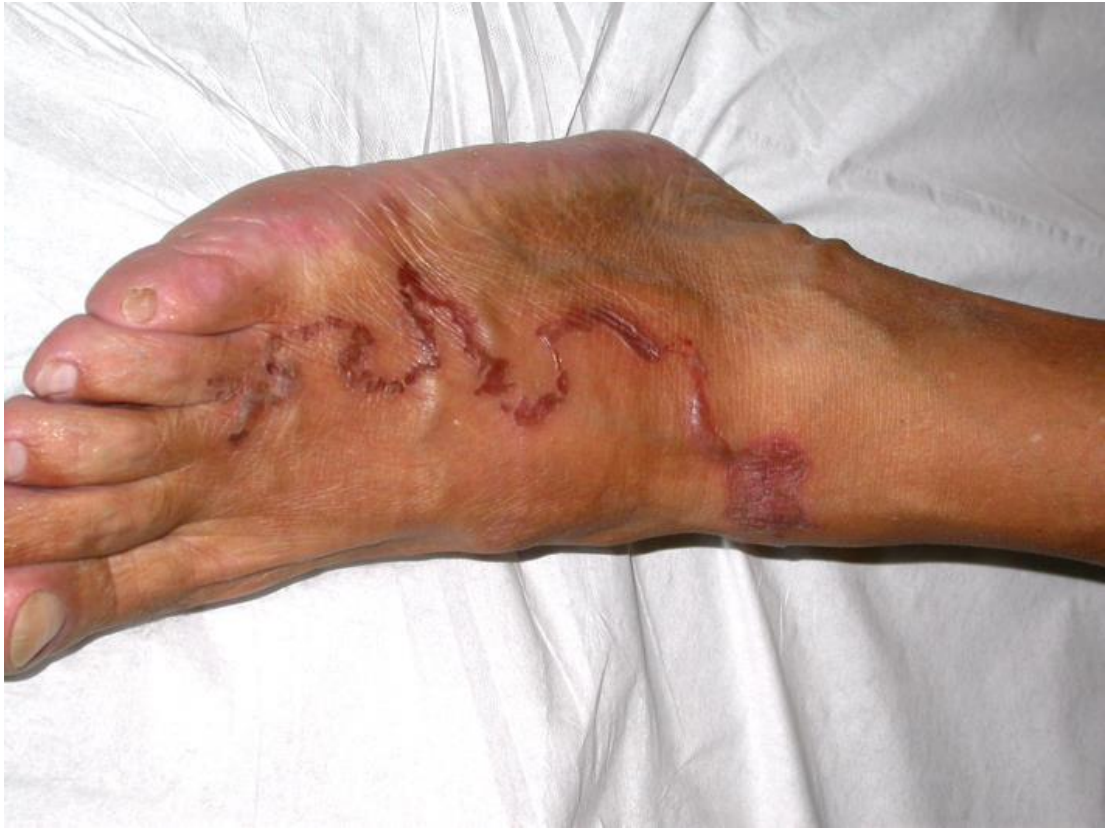


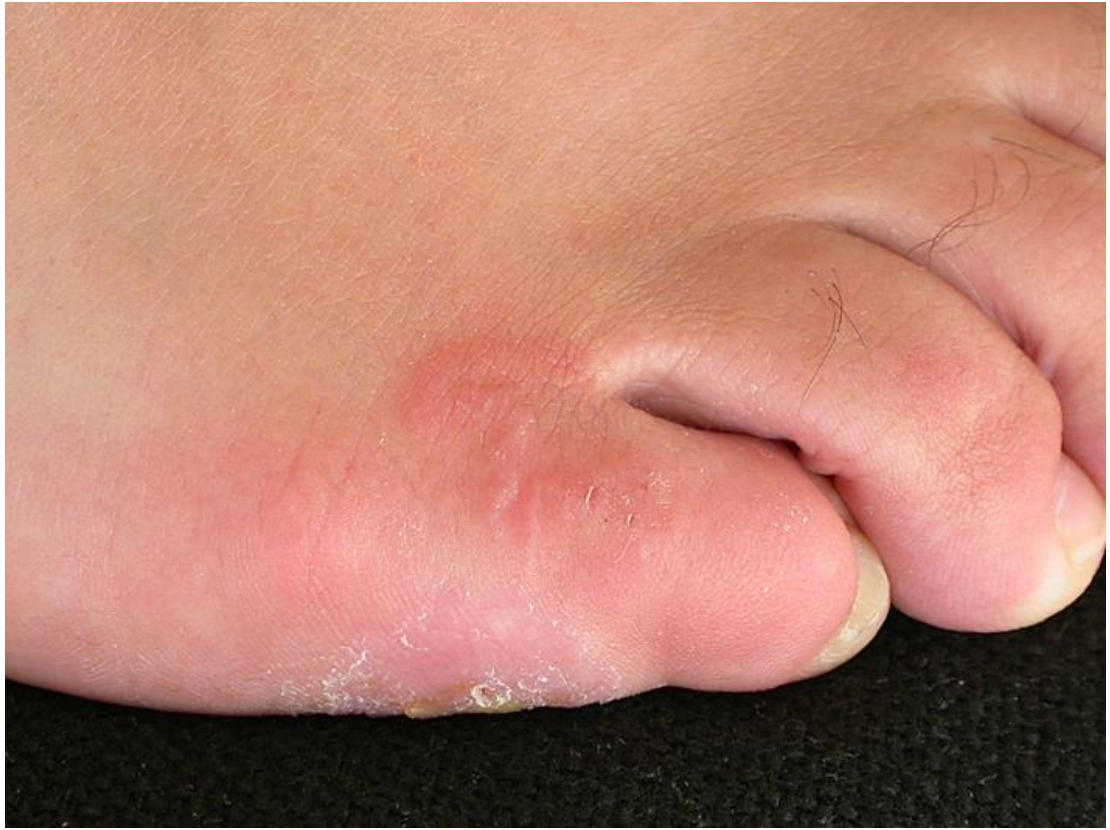


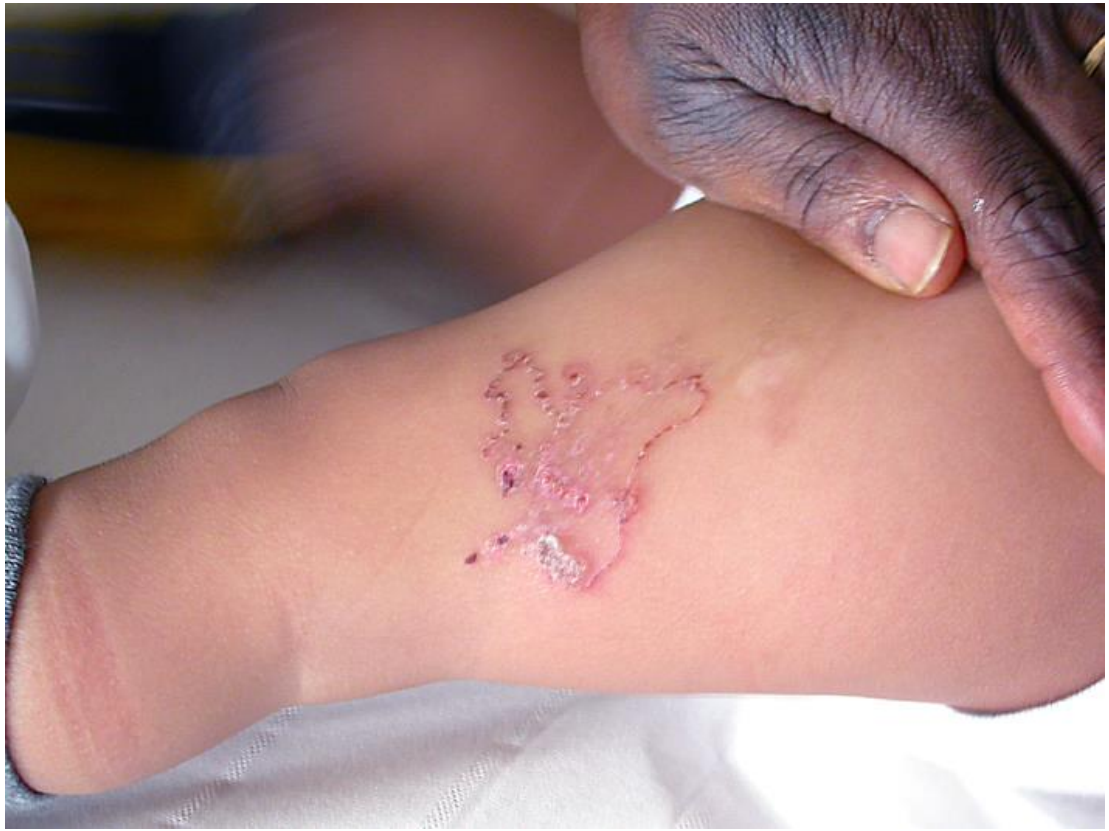


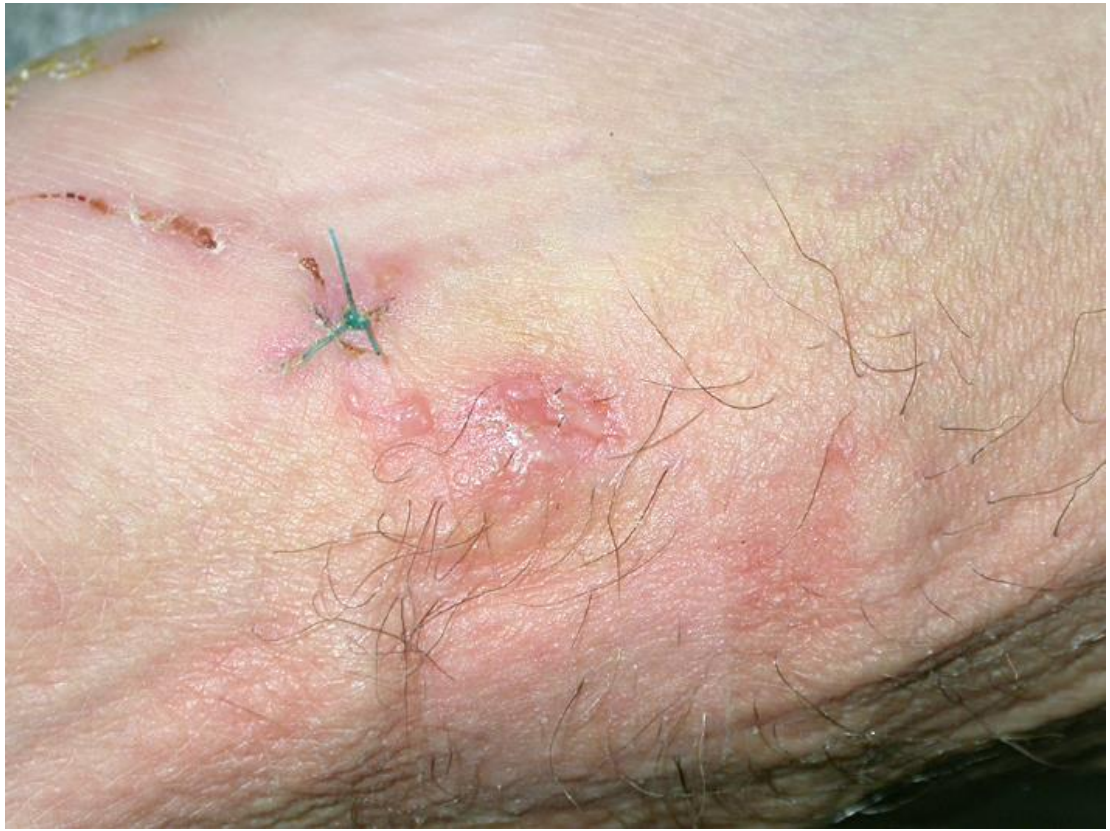


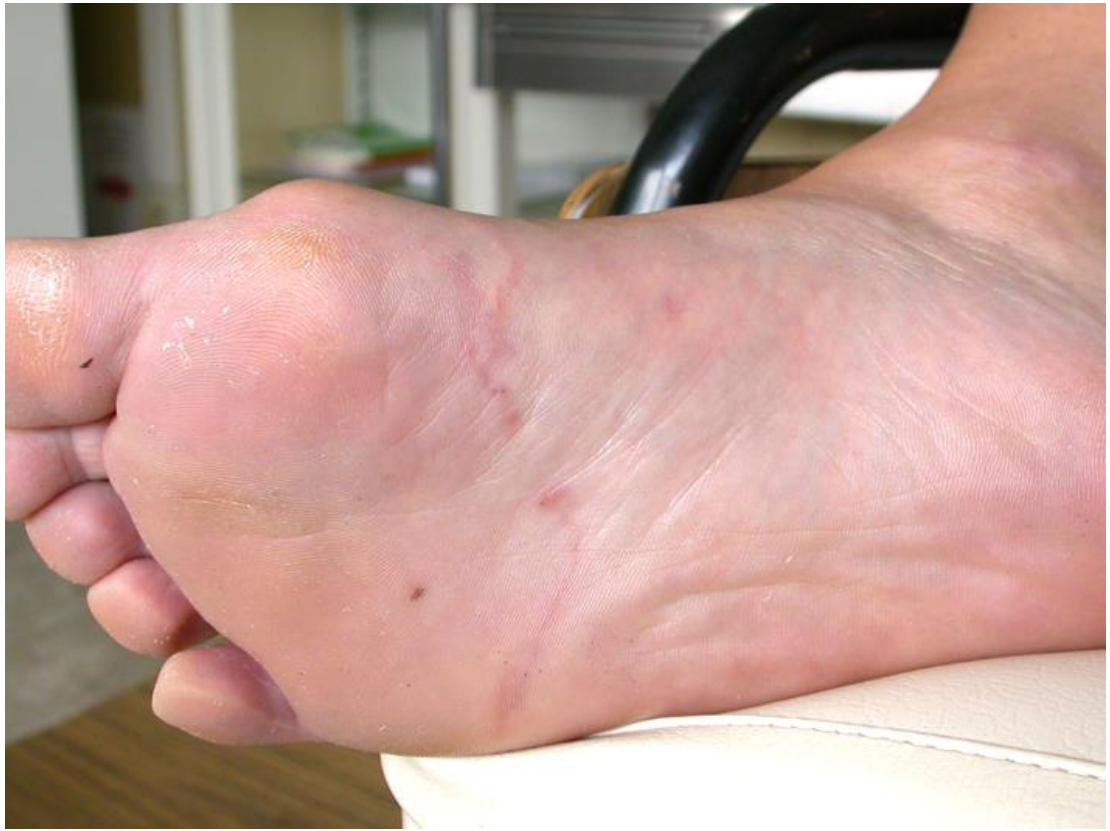


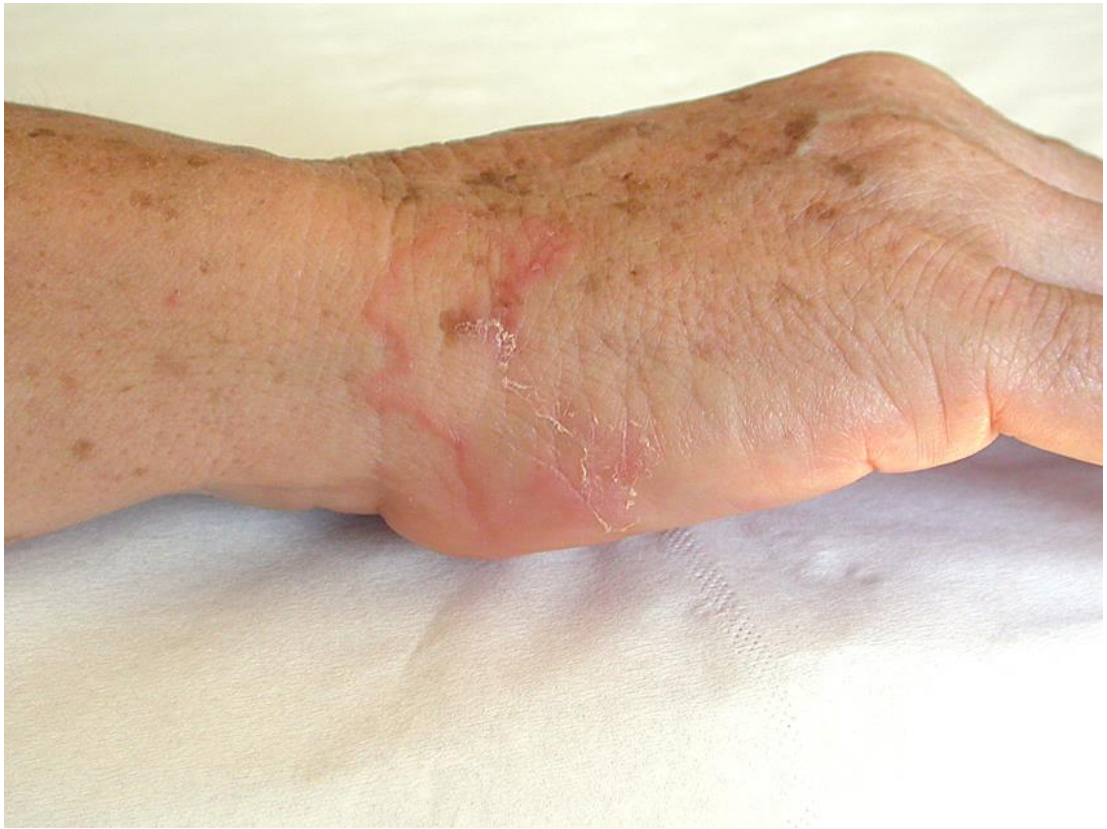


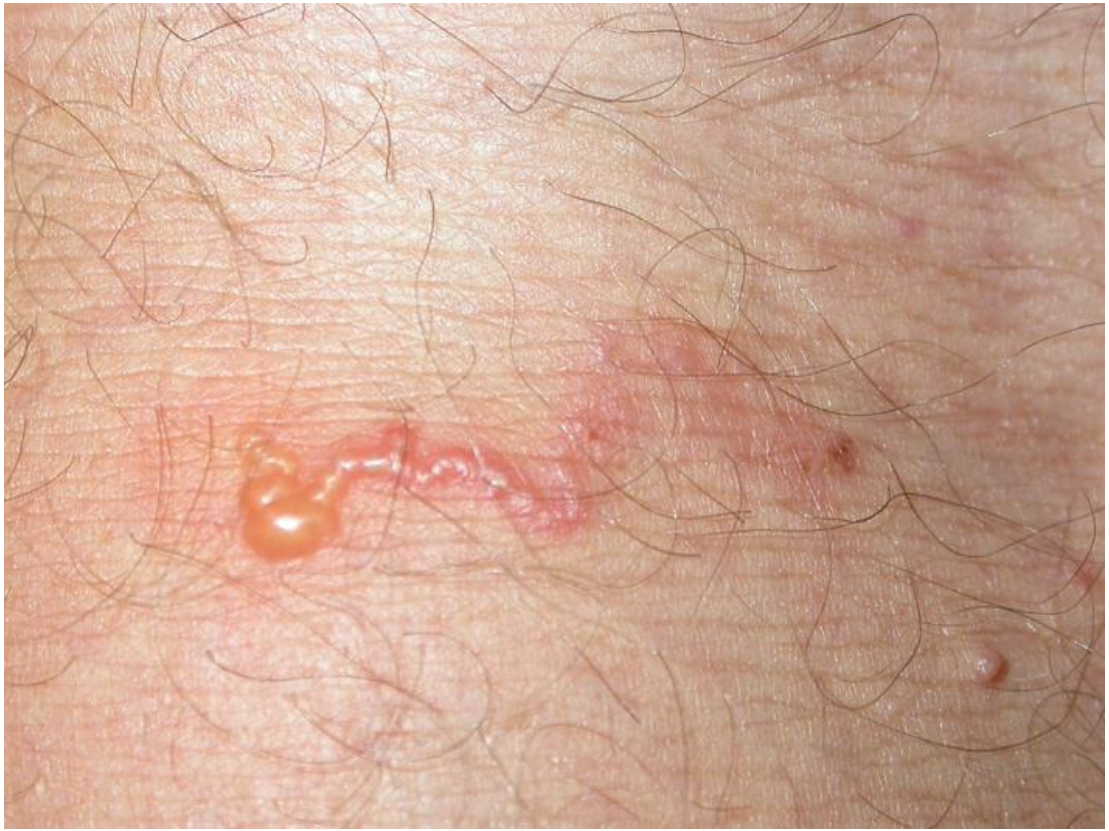


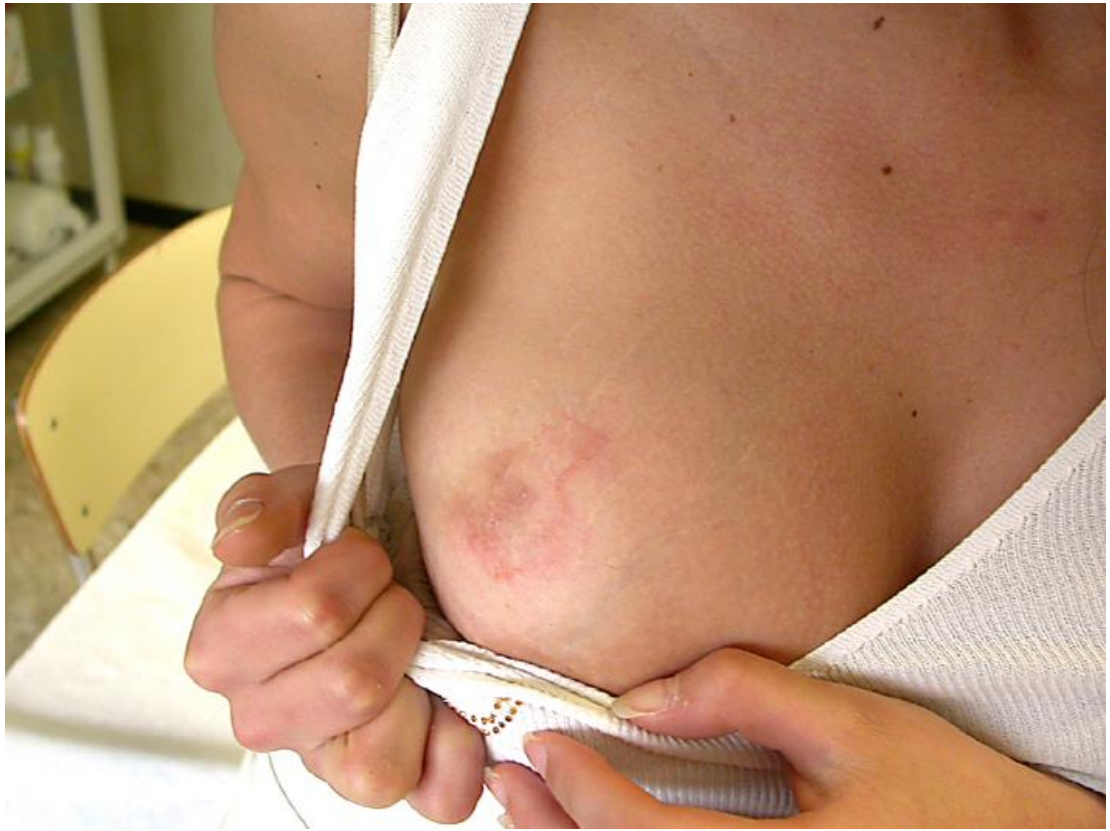


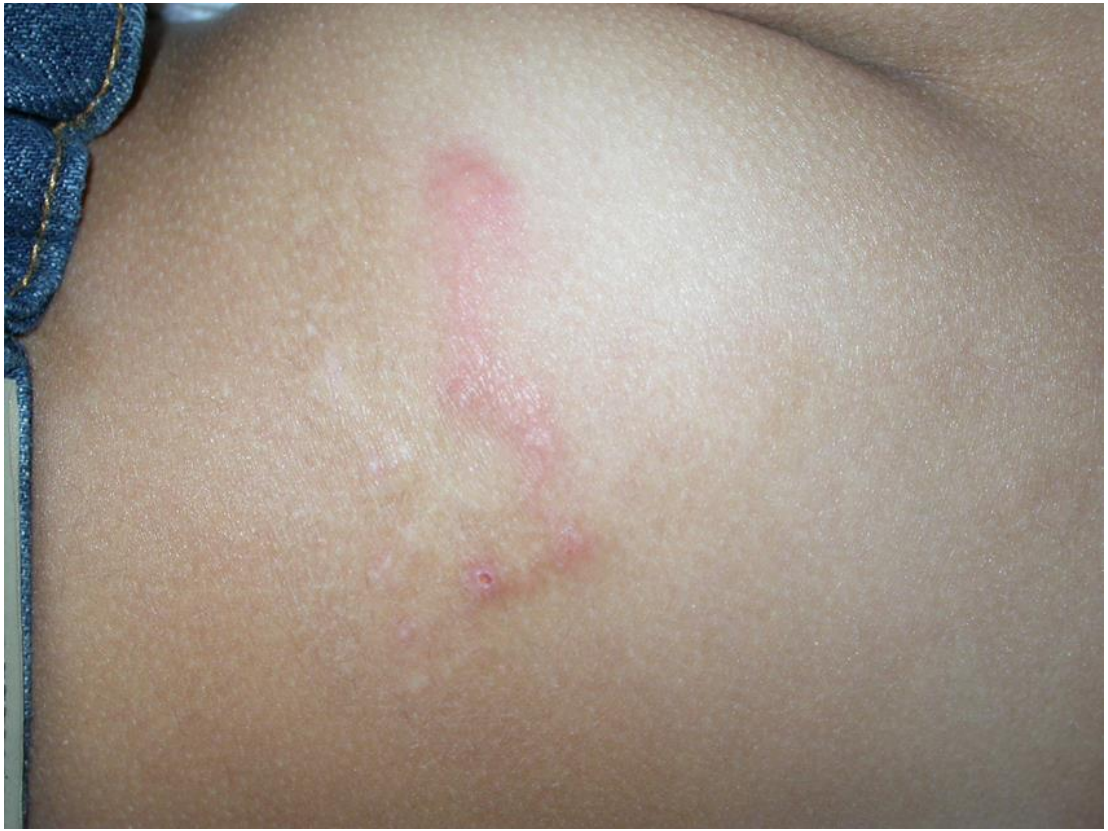


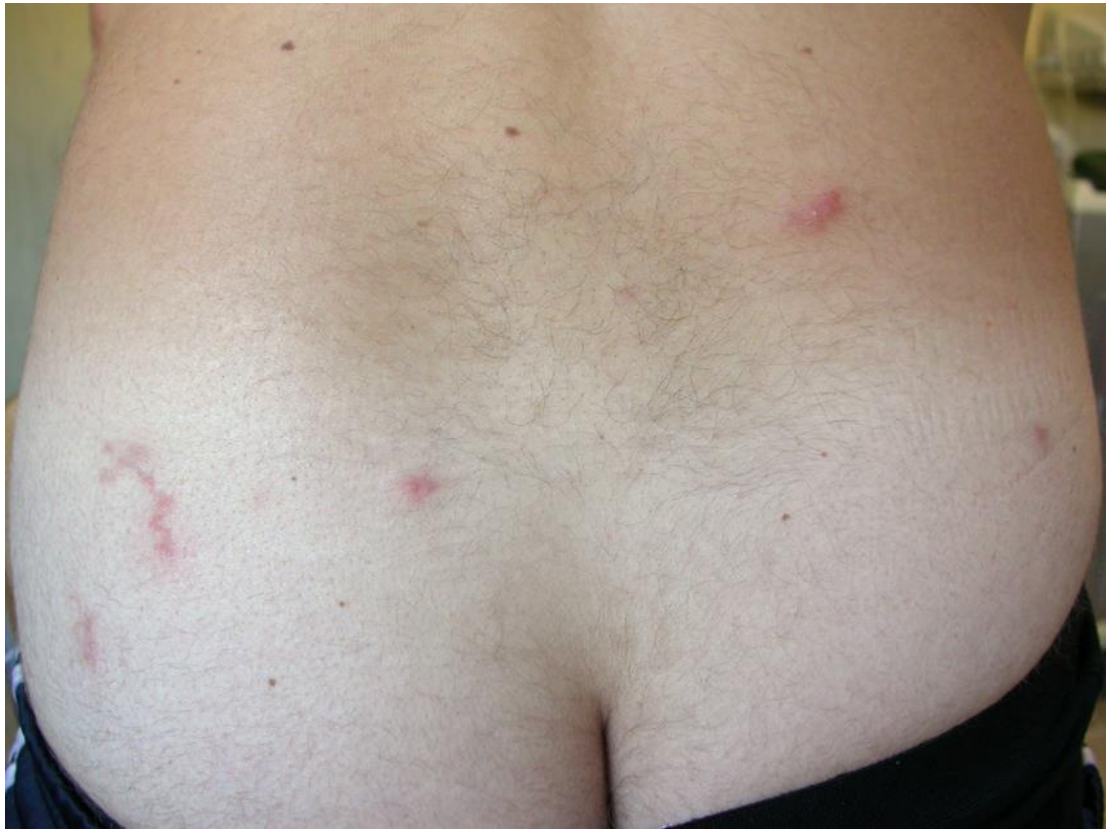




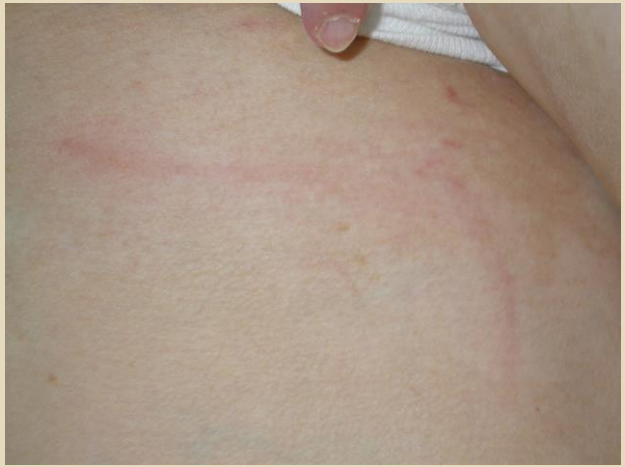


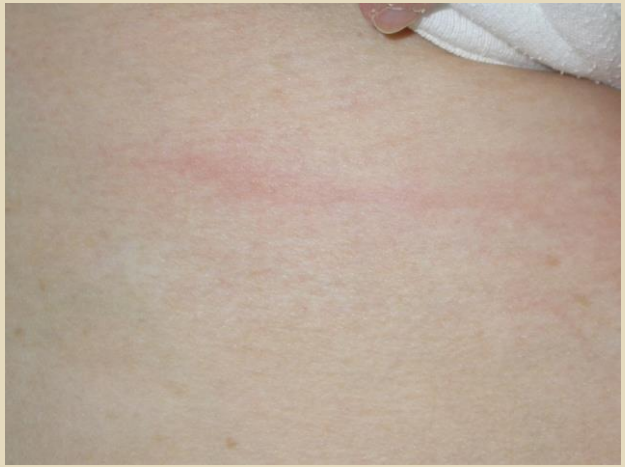




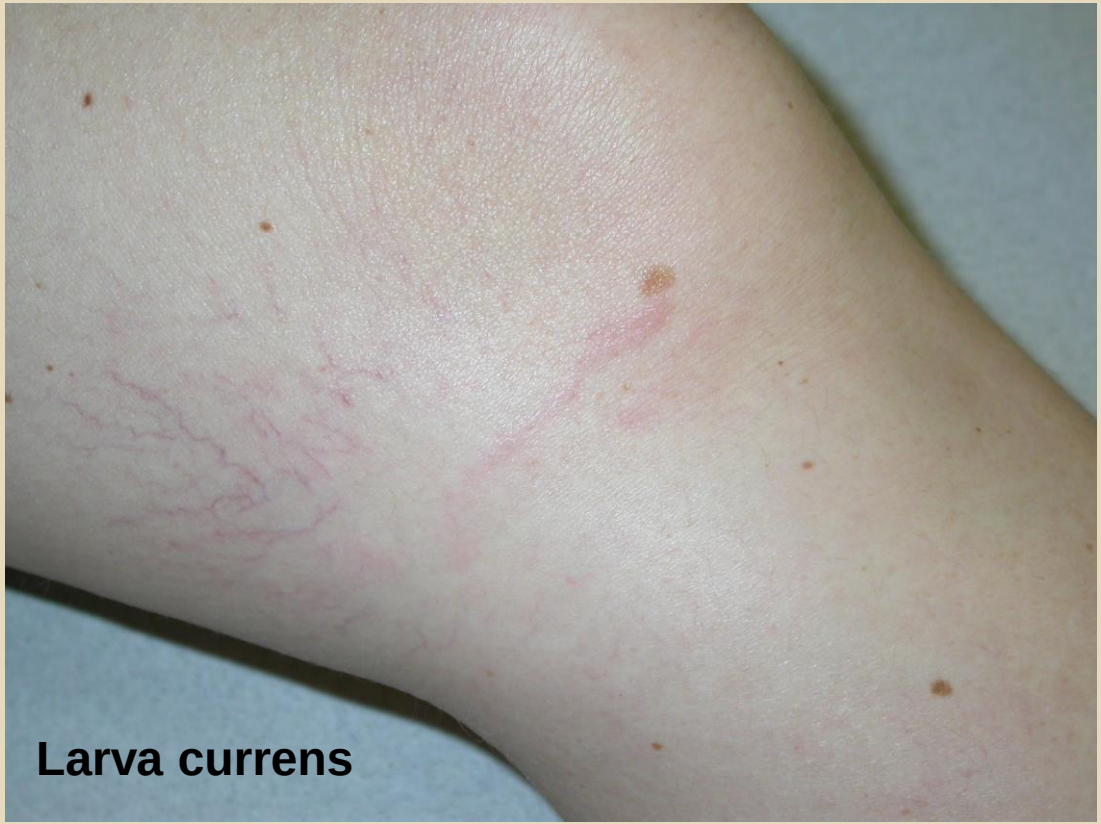


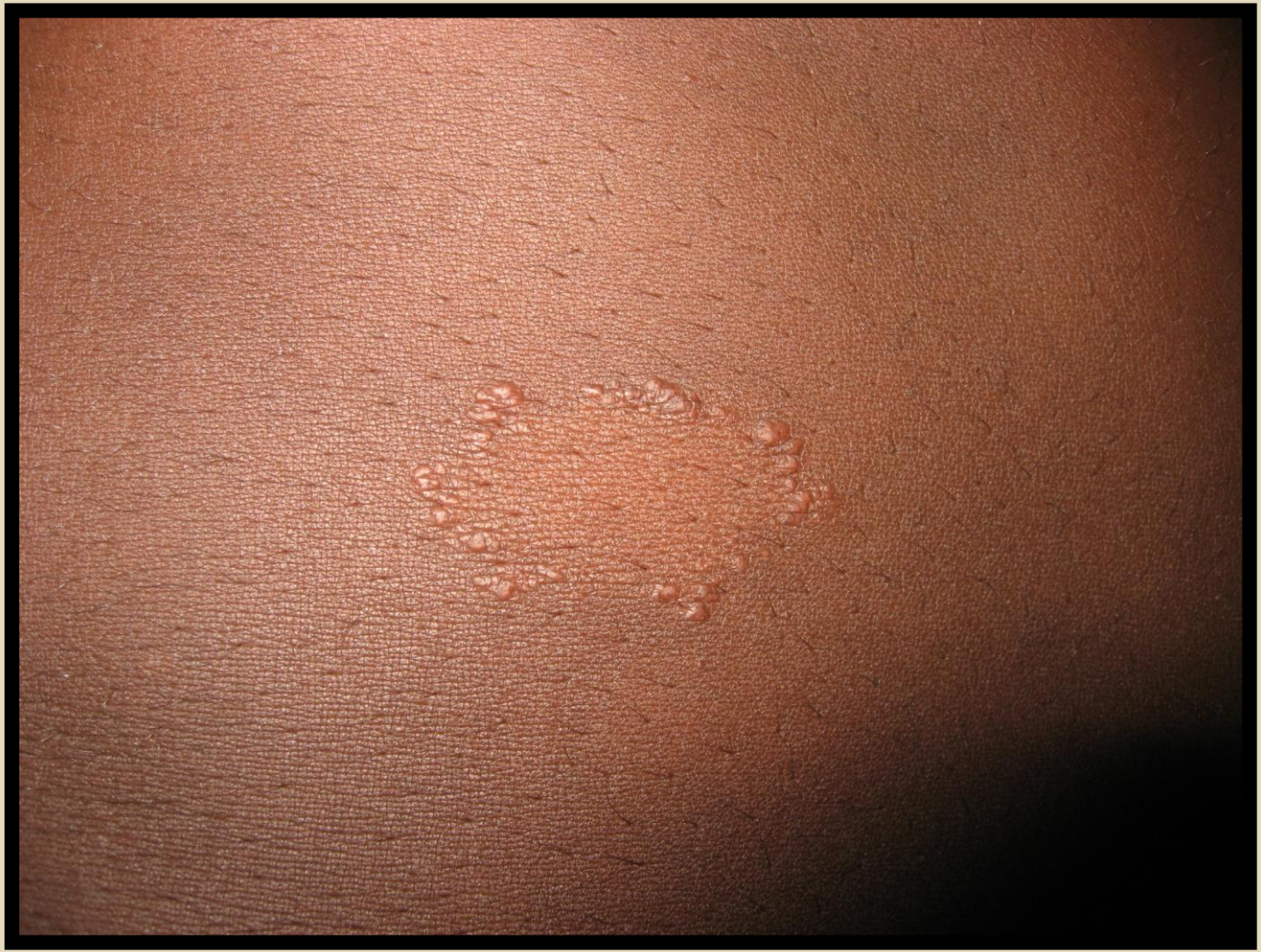
# Dura ore anziché giorni/mesi

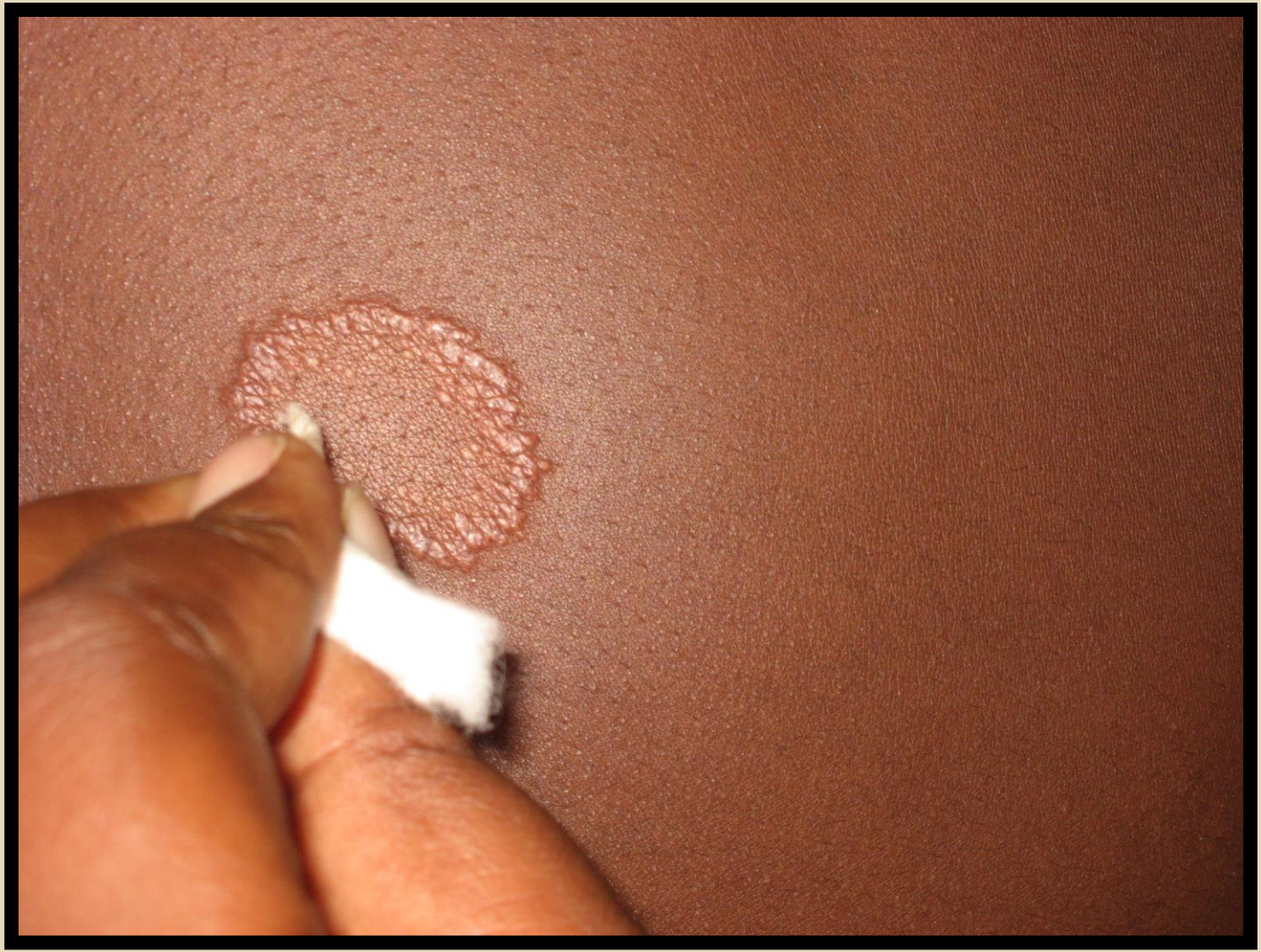




Lesione pruriginosa, fugace in paziente con eosinofilia che vive in Kenya un mese ogni anno…ama il giardinaggio







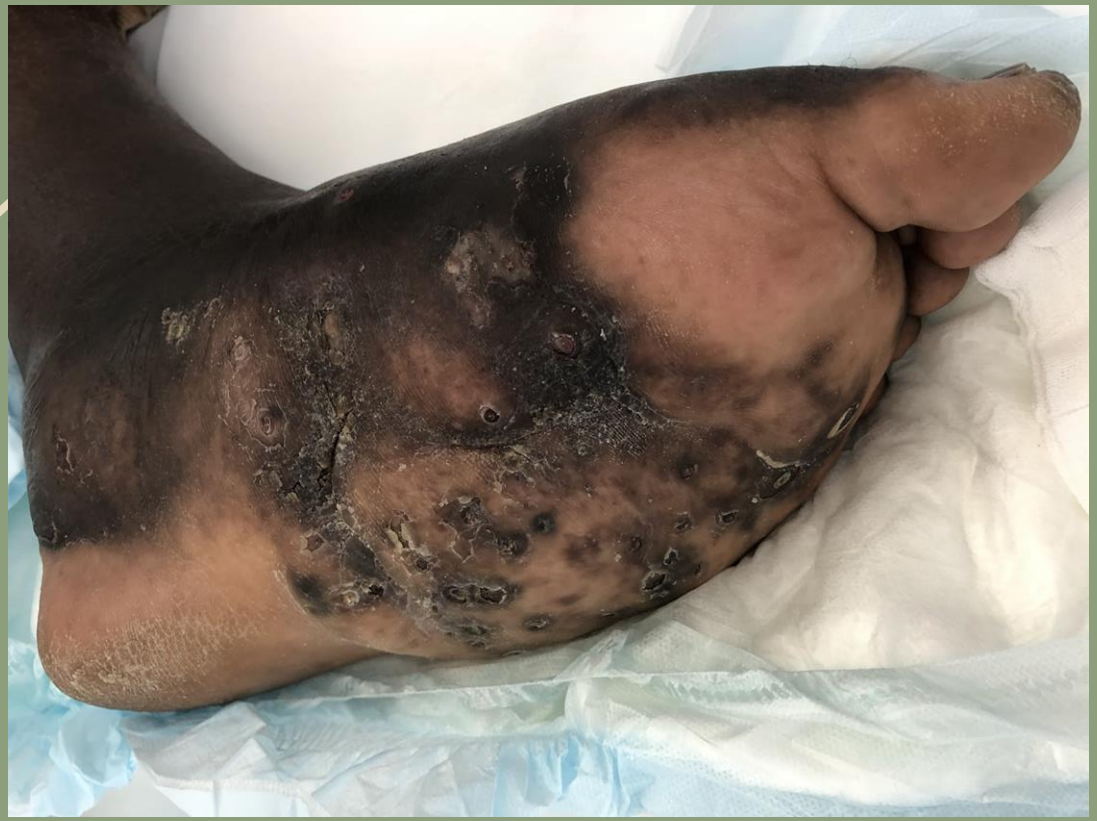
World Health Organization

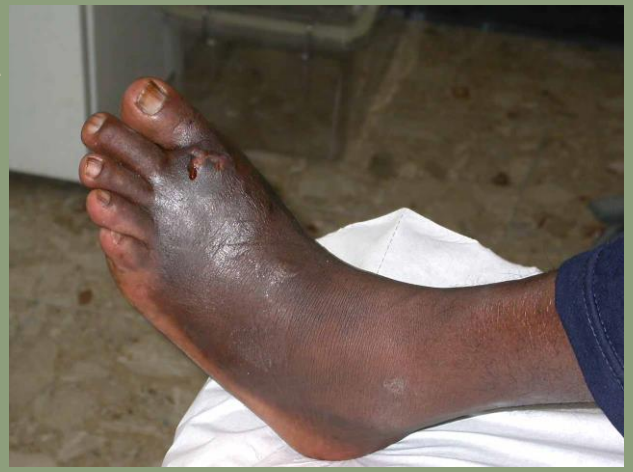
Leprosy is diagnosed by finding at least one of the following cardinal signs:

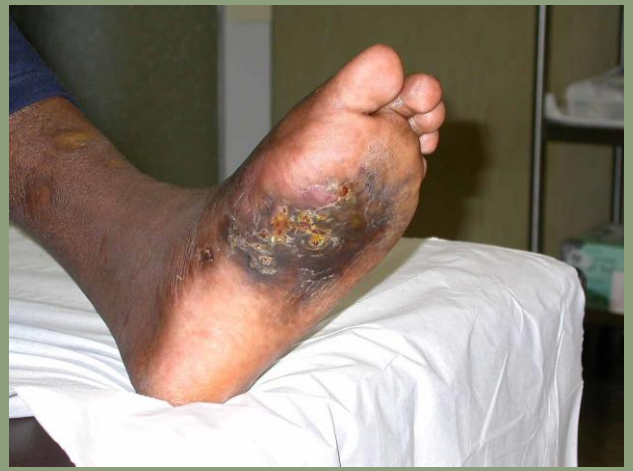
(1) definite loss of sensation in a pale (hypopigmented) or reddish skin patch;

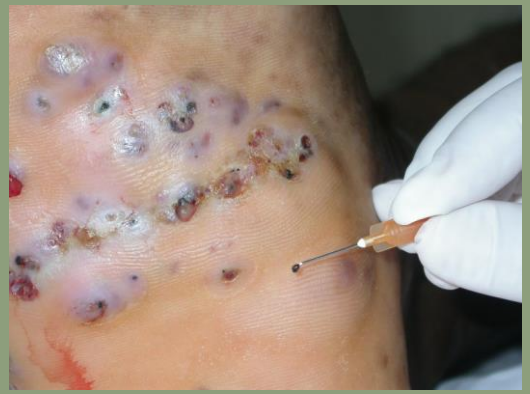
(2) thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve;

(3) microscopic detection of bacilli in a slit-skin smear.



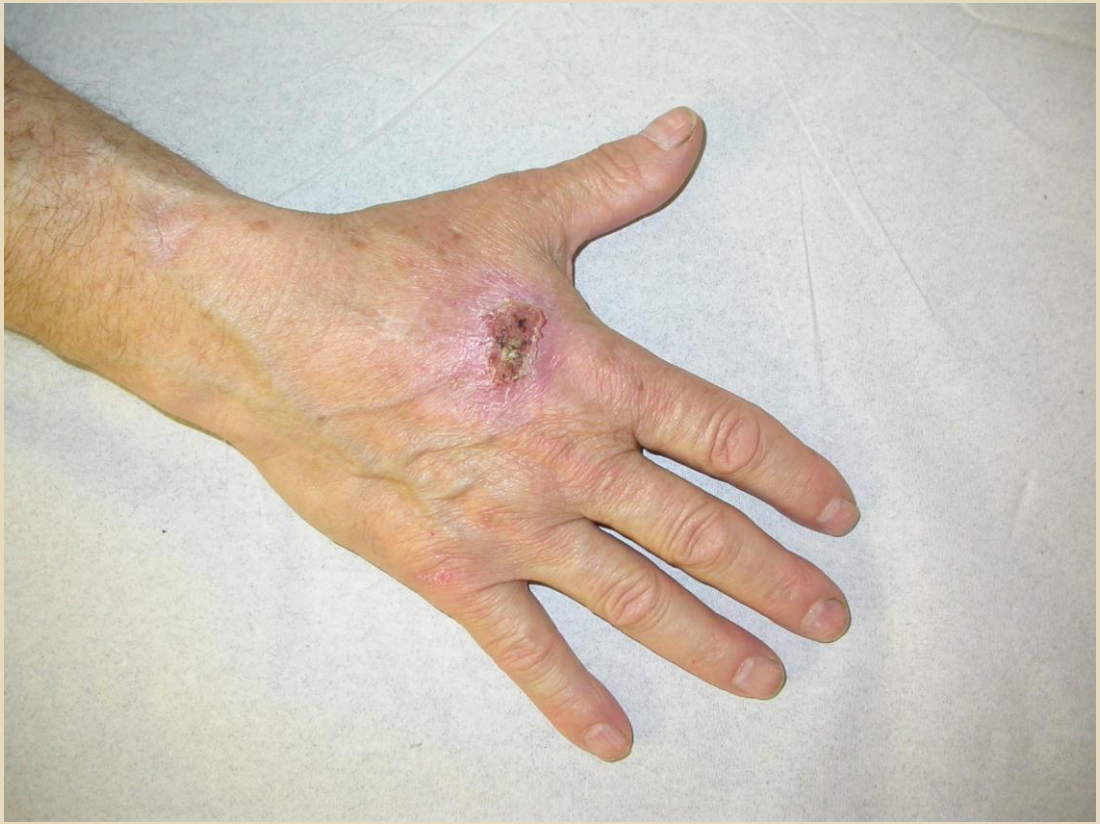


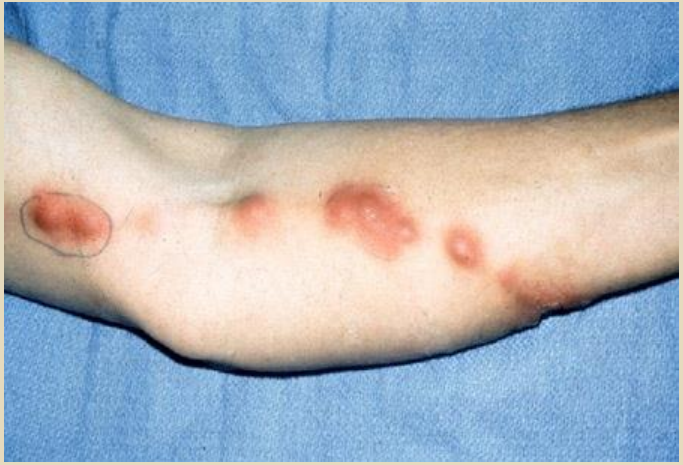




**Piede di Madura**

Lesione cronica ulcerativa comparsa un mese dopo rientro da viaggio in Brasile (volontariato)





Endemic mycosis with worldwide distribution caused by the dimorphic fungus *Sporothrix schenckii*.

The vast majority of sporotrichosis infections are lymphocutaneous or fixed cutaneous forms, although osteoarticular, pulmonary, meningeal, and disseminated sporotrichosis may occur, especially in patients with diabetes, alcoholism, HIV, and haematological malignancies, but also in normal hosts.

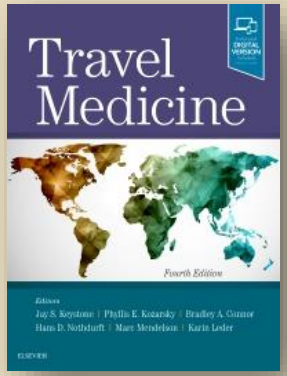
https://bestpractice.bmj.com/topics/en-gb/920

# Diarrhea/chronic GI disorder

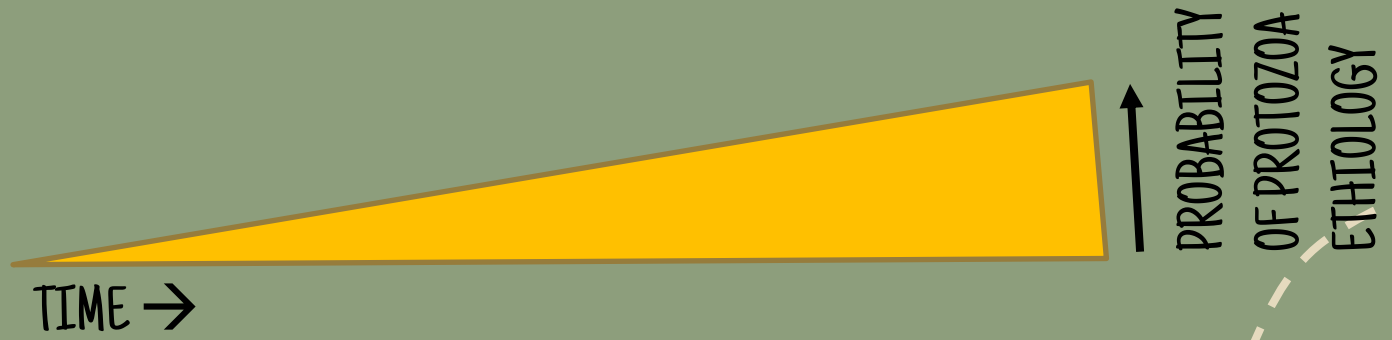
## TABLE 18.3 Distribution of Enteropathogens Among Patients With Travelers' Diarrhea, 1973–2009

| Pathogen | Latin America | Africa | South Asia (Indian Subcontinent) |
|---|---|---|---|
| Enterotoxigenic *E. coli* | 34 | 31 | 31 |
| Enteroaggregative *E. coli* | 24 | 2 | 16 |
| *Shigella* | 7 | 9 | 8 |
| *Salmonella* | 4 | 6 | 7 |
| *Campylobacter* | 3 | 5 | 8 |
| *Aeromonas* | 2 | 3 | 3 |
| *Plesiomonas* | 3 | 3 | 5 |
| *Norovirus* | 17 | 13 | 12 |
| Protozoa | 3 | 3 | 9 |
| No pathogen identified | 49 | 45 | 39 |

Data for table derived from four published studies.[136–139]



# Chronic/recurrent diarrhoea in travellers




- The most common agents for protracted diarrhea in returning travelers are parasitic infections.
- The likelihood of parasitic etiology rises commensurately with the duration of diarrheal symptoms

# Chronic diarrhea: etiology

Among travelers in Nepal with diarrhea **>14 days**, 27% were diagnosed with Giardia, in contrast to only 10% who had diarrhea <14 days. The differential for parasitic diarrhea is most likely to include *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium parvum*, *Cystoisospora belli* and *Cyclospora cayetanensis*.

Microsporidia and *Dientamoeba fragilis* are rare causes of persistent, low-grade gastrointestinal symptoms. Although the risk factors for intestinal parasites are not well defined, it appears that duration of stay is a major factor in acquiring a parasitic pathogen

# TRAVELLERS' DIARRHEA AND IBS

## COMPLICATIONS

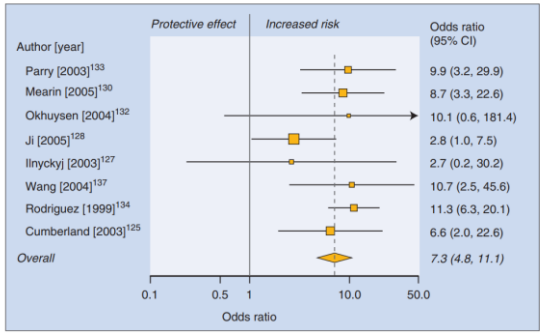
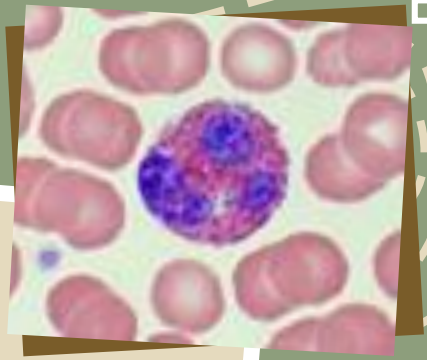



**FIG. 18.3** Risk of postinfectious irritable bowel syndrome.[136]

## CURE

Intestinal flora reconstitution

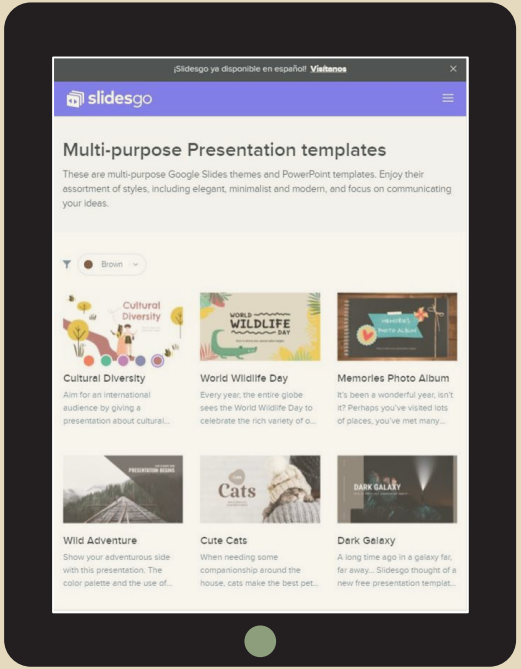


04

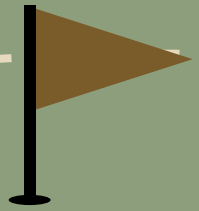
# Pre and post-travel evaluation: risk exposures/eosinophilia

# Meaningful measures

- Appropriate vaccination schedule completion
- For long-term travellers: TB IGRA evaluation, exposures evaluation?
- If asymptomatic assessment of eosinophilia?



# TBC: no please!



Peace Corps studies: in high incidence countries, risk of TST conversion overall was around 1.6% per year.

Cobelens *et al.*, in a study of Dutch travellers, found rates of TST conversion ranging between 4.28 and 5.36 per 1000 person months of travels in regions of highest risk,

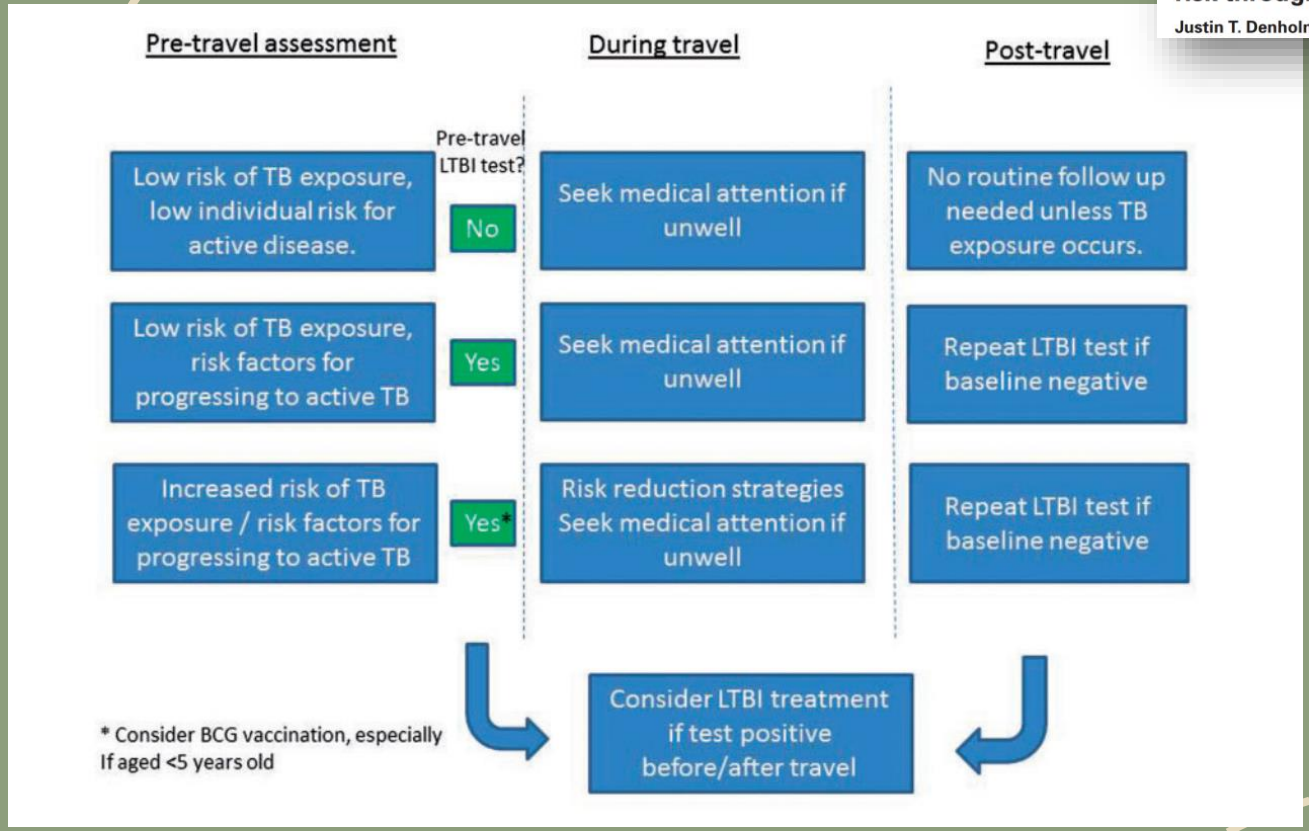
while Freeman *et al.* estimated a cumulative LTBI incidence of 2% in long-term travellers and military personnel.

Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide
Journal of Travel Medicine, 2016, 1–6
doi: 10.1093/jtm/taw008
Review

Review

# Tuberculosis and the traveller: evaluating and reducing risk through travel consultation

Justin T. Denholm[1,2,3]* and Irani Thevarajan[3,4]




Eosinophilia

# Definition of eosinophilia

Eosinophilia... defined as an absolute eosinophil count greater than 0.45 × 109/L, occurs in about 8-10% of migrants and travelers returning from the tropics who seek post-travel care.

Libman MD, MacLean JD, Gyorkos TW. Screening for schistosomiasis, filariasis, and strongyloidiasis among expatriates returning from the tropics. Clin Infect Dis 1993;17:353–9.

Checkley AM, Chiodini PL, Dockrell DH, Bates I, Thwaites GE, Booth HL, Brown M, Wright SG, Grant AD, Mabey DC, Whitty CJ, Sanderson F; British Infection Society and Hospital for Tropical Diseases. Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. J Infect. 2010 Jan;60(1):1-20.

Eosinophilia is a laboratory abnormality that is defined as a permanent increase in the number of circulating eosinophils above a generally accepted threshold of 0.5 × 109/L

Magnaval JF, Laurent G, Gaudré N, Fillaux J, Berry A. A diagnostic protocol designed for determining allergic causes in patients with blood eosinophilia. Mil Med Res. 2017 May 23;4:15.

# Eosinophilia: introduction

- Eosinophilia occurs in up to 10% of travelers and may be caused by a variety of conditions, including allergies and asthma, drug hypersensitivity, infection, neoplasm, and other miscellaneous disorders.

- Although the utility of screening for eosinophilia in returned travelers remains controversial, eosinophilia may be the first (or only) indication of a condition associated with potentially serious sequelae, such as schistosomiasis or strongyloidiasis, and is often useful in guiding the diagnostic evaluation in symptomatic patients

**TABLE 148-1** Noninfectious Causes of Peripheral Eosinophilia

| Cause | | | | | | |
|---|---|---|---|---|---|---|
| ***Atopy*** | ***Dermatologic*** | ***Drug*** | ***Gastrointestinal*** | ***Hematologic*** | ***Vasculitis*** | ***Other*** |
| Asthma | Immunobullous disorders: dermatitis herpetiformis and pemphigoid | NSAIDs | Inflammatory bowel disease | Hodgkin lymphoma | Churg–Strauss syndrome | Allergic bronchopulmonary aspergillosis |
| Eczema | Atopic dermatitis | Beta-lactam antibiotics | Eosinophilic gastroenteritis | Non-Hodgkin lymphoma | Polyarteritis nodosa | Sarcoidosis |
| Allergic rhinitis | Eosinophilic cellulitis (Well's syndrome) | Sulfa-containing antibiotics | Chronic pancreatitis | Chronic eosinophilic leukemia | Wegener's granulomatosis | Addison's disease |
| Seasonal rhinitis | | Tetracycline | Eosinophilic cholangitis | Systemic mastocytosis | Other connective tissue diseases and vasculitides | Eosinophilic myocarditis |
| | | Acetylsalicylic acid | | Chronic myelomonocytic leukemia | Rheumatoid arthritis | Familial eosinophilic syndromes |
| | | Carbamazepine | | Chronic myeloid leukemia | | Heavy metal poisoning |
| | | Colchicine | | Acute myeloid leukemia | | Idiopathic eosinophilic pneumonias |
| | | Nitrofurantoin | | Myelodysplastic syndrome | | Immunodeficiency syndromes |
| | | Dapsone | | | | Cholesterol embolization |
| | | Minocycline | | | | |

Statins and fibrates (11%)

NSAIDs, nonsteroidal anti-inflammatory drugs.

☼ In a prospective cohort study of 824 patients receiving prolonged intravenous antibiotic therapy as outpatients, 25 percent developed eosinophilia (peak absolute eosinophil count ranging from 500 to 8610/mL, median 726/mL) after a median of 15 days of therapy

# Cause parassitarie di eosinofilia

- Non tutti gli elminti si associano ad eosinofilia, ma solo quelli che in qualche stadio del loro ciclo vitale diventano tessuto-invasivi o per lo meno violano l'integrità di una barriera mucosa.

- Tra i più comuni segnaliamo *Ascaris lumbricoides* e la maggior parte dei nematodi, comprese le filarie; *Schistosoma mansoni* e altri trematodi; *Hymenolepis nana* e occasionalmente altri cestodi.

# Cause non parassitarie di eosinofilia

- Anche nella cosiddetta “patologia di importazione” ci possiamo evidentemente imbattere in cause non parassitarie di eosinofilia, alcune particolarmente gravi (linfoma di Hodgkin, alcuni tumori solidi, malattie reumatiche), altre più banali ma più frequenti (uso prolungato di alcuni farmaci, malattie allergiche).

- Cause infettive NON parassitarie: Coccidioidomicosi, Basidiobolomicosi, TBC, HIV.

- È importante studiare una eosinofilia nel viaggiatore o nel migrante;

- RISCHIO DI SEQUELE

| Malattia | Rischi/sequele |
|---|---|
| SCHISTOSOMIASI | Pseudocirrosi/ipert. portale; k vescica; aumenta trasmissione HIV |
| STRONGILOIDOSI | Rischio iperinfestazione/disseminata (immunodepresso) |
| TREMATODIASI (Fasciola, Opistorchis, Clonorchis) | Ostruzione delle vie biliari, k colecisti o vie biliari |
| ECHINOCOCCOSI | Lesioni in sede di localizzazione (fegato, SNC…), anche tumor-like |

# Eosinophilia in Infectious Diseases

Elise M. O'Connell, MD*, Thomas B. Nutman, MD

**KEYWORDS**

• Eosinophilia • Infection • Fever • Travel • Immigrant • Refugee

**KEY POINTS**

- Eosinophilia greater than 1000/μL in the setting of acute illness essentially excludes bacteria or viruses as an etiology for the acute illness.
- Strongyloidiasis is found worldwide, including in areas of the United States. Anyone with eosinophilia who comes from an endemic area should have a serologic test performed if available.
- Acute schistosomiasis should be suspected in any traveler returning from Africa with eosinophilia and fever.
- Immigrants or refugees can have very subtle or no symptoms from parasitic infections and often have very mild eosinophilia.
- Some helminth infections can persist for many years after acquisition.

Immunol Allergy Clin N Am 35 (2015) 493–522
http://dx.doi.org/10.1016/j.iac.2015.05.003

Eosinophilia is asymptomatic in 21-33% of returning travelers and migrants; common causes of asymptomatic eosinophilia are intestinal helminths, schistosomiasis, strongyloidiasis and filiariasis.

Journal of Infection (2010) 60, 1–20

ELSEVIER

BRITISH INFECTION SOCIETY

www.elsevierhealth.com/journals/jinf

CLINICAL GUIDELINES OF THE BRITISH INFECTION SOCIETY

**Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management**

Anna M. Checkley [a,*], Peter L. Chiodini [a], David H. Dockrell [b], Imelda Bates [c], Guy E. Thwaites [a], Helen L. Booth [d], Michael Brown [a], Stephen G. Wright [a], Alison D. Grant [a], David C. Mabey [a], Christopher J.M. Whitty [a], Frances Sanderson [e], On behalf of the British Infection Society and The Hospital for Tropical Diseases

Whetham J, Day JN, Armstrong M, Chiodini PL, Whitty CJ. Investigation of tropical eosinophilia: assessing a strategy based on geographical area. J Infect 2003;46:180e5.

Schulte C, Krebs B, Jelinek T, Nothdurft HD, von Sonnenburg F, Lo¨scher T. Diagnostic significance of blood eosinophilia in returning travelers. Clin Infect Dis 2002;34:407e11.


http://www.salute.gov.it/imgs/C_17_pubblicazioni_2624_allegato.pdf

## • Quesito 9 •

È indicata l'esecuzione di un esame parassitologico delle feci come screening delle parassitosi intestinali nei migranti durante il percorso di accoglienza? È indicato un programma di screening dello *Strongyloides*? È indicato un programma di screening dello *Schistosoma*?

**R9.1** – Si raccomanda di considerare, nel contesto della valutazione medica iniziale e durante tutte le fasi del percorso di accoglienza, la presenza di sintomi quali diarrea, dolori addominali, nausea, vomito, prurito, ematuria (anche anamnestica), in quanto suggestivi di parassitosi. **Grado A**

**R9.2** – Nel corso degli accertamenti clinici, il riscontro di eosinofilia deve essere considerato quale possibile marcatore indiretto di elmintiasi. **Grado A**

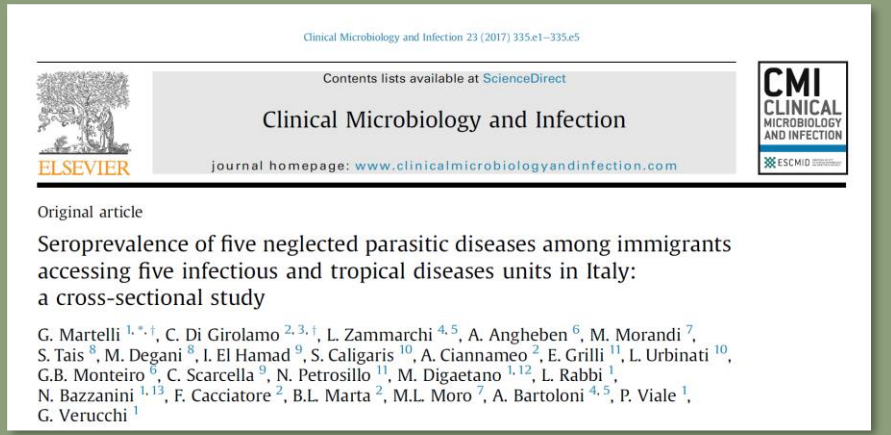
**R9.3** – In presenza di segni e sintomi compatibili con parassitosi intestinale e/o di eosinofilia, si raccomanda di offrire l'esame coproparassitologico per rilevare l'eventuale presenza di parassiti intestinali. **Grado A**

**R9.4** – Nei migranti, anche asintomatici, che hanno vissuto o viaggiato in aree endemiche per strongiloidosi * e schistosomiasi (si veda allegato 6), è raccomandato l'esame sierologico, nell'ambito della presa in carico sanitaria. Il riscontro di sierologia positiva per *Strongyloides stercoralis* e *Schistosoma spp*, in soggetti non trattati di recente, deve essere considerato come infezione in atto e come tale meritevole di trattamento. **Grado A**

* Lo *S. stercoralis* è tendenzialmente ubiquitario e comunemente distribuito nei paesi tropicali e subtropicali, con elevata endemia nel Sud-Est asiatico, in Africa e in Sud America.

http://www.salute.gov.it/imgs/C_17_pubblicazioni_2624_allegato.pdf

# Schistosomiasi e sintomi



Clinical Microbiology and Infection 23 (2017) 335.e1–335.e5

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journal homepage: www.clinicalmicrobiologyandinfection.com

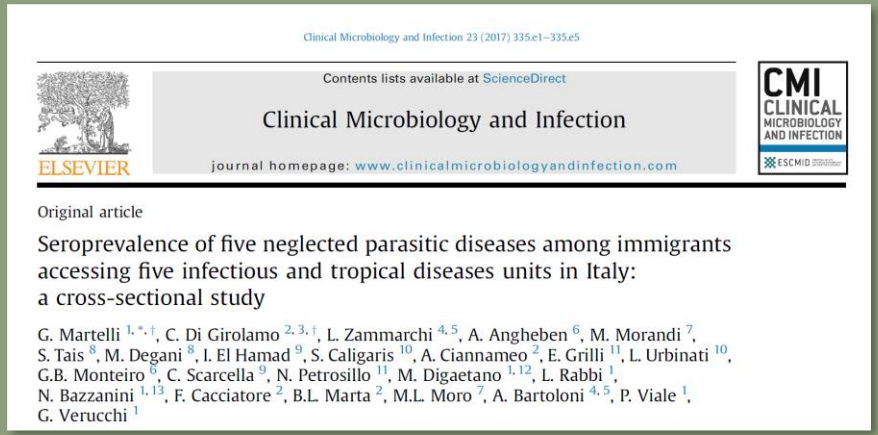
Original article

Seroprevalence of five neglected parasitic diseases among immigrants accessing five infectious and tropical diseases units in Italy: a cross-sectional study

G. Martelli [1,*,†], C. Di Girolamo [2,3,†], L. Zammarchi [4,5], A. Angheben [6], M. Morandi [7], S. Tais [8], M. Degani [8], I. El Hamad [9], S. Caligaris [10], A. Ciannameo [2], E. Grilli [11], L. Urbinati [10], G.B. Monteiro [6], C. Scarcella [9], N. Petrosillo [11], M. Digaetano [1,12], L. Rabbi [1], N. Bazzanini [1,13], F. Cacciatore [2], B.L. Marta [2], M.L. Moro [7], A. Bartoloni [4,5], P. Viale [1], G. Verucchi [1]

- 57,1% asintomatici/sintomi aspecifici

# Eosinofilia e schistosomiasi



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- Schistosomiasi nei pazienti con eosinofilia

  6/82 (7,3%)

- Schistosomiasi nei pazienti senza eosinofilia

  29/489 (5,9%)

*Trans R Soc Trop Med Hyg*
doi:10.1093/trstmh/tru195

# Schistosomiasis presenting in travellers: a 15 year observational study at the Hospital for Tropical Diseases, London

**Cordelia E. M. Coltart[a,b,*], Anastasia Chew[a], Neill Storrar[a], Margaret Armstrong[a], Natalie Suff[a], Leila Morris[c], Peter L. Chiodini[a,b] and Christopher J. M. Whitty[a,b]**

*[a]The Hospital for Tropical Diseases, UCLH, Capper Street, London WC1E 6JB, UK; [b]The London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK; [c]University College London Medical School, Gower Street, London, WC1E 6BT, UK*

**Table 3.** *Schistosoma haematobium* vs *Schistosoma mansoni* microscopy positive cases: a comparison of eosinophilia, serology results, country of acquisition, and type of patient (i.e., tourist vs other)

| | S. *haematobium* | S. *mansoni* |
|---|---|---|
| Number (n=275)[a] | 204 (74.2%) | 61 (21.8%) |
| Proportion of tourists vs other[b] | 98 (48.0%) tourists vs 97 (47.5%) other | 18 (29.5%) tourists vs 43 (70.5%) other |
| Eosinophilia | 86/167 (51.5%)<br>No difference observed between tourists and other subgroups | 22/47 (46.8%)<br>No difference observed between tourists and other subgroups |
| Serology | Tourists 86/93 (92.5%)<br>Other 73/93 (78.5%)<br>p=0.007 | Tourists 14/14 (100%)<br>Other 34/40 (85.0%)<br>p=0.12 |
| Country of travel[c] (no. of cases) | Malawi (109), Zimbabwe (43), Ghana (25)<br>Countries with 1–10 cases:<br>Somalia, Kenya, Nigeria, Zambia, South Africa, Uganda, Sudan, Botswana, Egypt, Tanzania, Angola, Mozambique, Mali, Sierra Leone, Namibia, Nepal, Madagascar, Swaziland | Uganda (19), Malawi (8)<br>Countries with 1–5 cases:<br>Kenya, Sudan, Ethiopia, Sierra Leone, Zimbabwe, Nigeria, Congo, Rwanda, Tanzania, Ghana, Zaire, Angola, Benin, Brazil, Egypt, Eritrea, Liberia, PNG, Somalia, South Africa, Thailand |

[a] Mixed infection with *S. haematobium* and *S. mansoni* was seen in 3 cases (Ghana and Zimbabwe). *S. japonicum* was detected in two cases (both from Philippines). The species of infection was not stated in 2 cases.
[b] Where reason for travel known.
[c] Where patients travelled to more than one endemic country all countries are listed.

*Trans R Soc Trop Med Hyg*
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# Schistosomiasis presenting in travellers: a 15 year observational study at the Hospital for Tropical Diseases, London

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**Table 2.** Symptoms reported in cases of imported schistosomiasis

| Symptoms | No. patients n=1020 | Ova-positive haematobium cases n=181 | Ova-positive mansoni cases n=60 | Time from exposure to presentation (weeks: mean and range) n=409 |
|---|---|---|---|---|
| Asymptomatic | 368 (36.1%) | 37 (20.4%) | 15 (25.0%) | 28 (16–104) |

RESEARCH ARTICLE

# Epidemiology of *Strongyloides stercoralis* in northern Italy: results of a multicentre case–control study, February 2013 to July 2014

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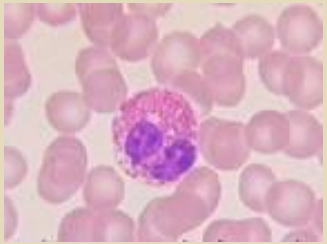

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# Positivi: soggetti con e senza eosinofilia

**Pazienti sottoposti a screening: 2714**

- Nelle province esaminate, la prevalenza di strongiloidosi negli **italiani** nati prima del 1951 e con **eosinofilia** è rilevante (**8%**)
- La prevalenza risulta ancora maggiore negli **immigrati** (**17%** dei soggetti con **eosinofilia**)
- In entrambi i gruppi (italiani e immigrati), i soggetti con eosinofilia presentano probabilità significativamente maggiore (**O.R: 8,82**) di essere affetti da strongiloidosi, rispetto ai soggetti senza eosinofilia

| Sottogruppo | Eosinofilia | Positivi | No eosinofilia | Positivi | Odds Ratio (95% C.I.) |
|---|---|---|---|---|---|
| Italiani | 1145 | 93 (8%) | 1181 | 13 (1%) | **7,49** (4,39-15,56) |
| Immigrati | 216 | 37 (17%) | 172 | 3 (1.7%) | **11,64** (3,57-59,85) |

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## Tempi di latenza e durata dell'eosinofilia per alcune elmintiasi

| Specie elmintica | Latenza eosin. | Massima eosin. | Normaliz. | Possibile diagnosi diretta | Vita media (max) |
|---|---|---|---|---|---|
| *A. lumbricoides* | ca. 7 gg. | 10-30 gg. | Mesi | 60-75 gg. | 1 a. (2-3) |
| Ancilostomi (*A. d., N. a.*) | 10-15 giorni | 1-2 mesi | Anni | 40-60 gg. (*N. a.*) | 5 a. (15) |
| *S. stercoralis* | 7-10 gg. | Picchi ciclici | Anni o mai | >=20 gg. | ? |
| *S. mansoni* | 7-15 gg. | 3 - 8 sett. | Anni | 60-90 gg. o più | 3-10 a. (20-30) |

# Indagini parassitologiche in caso di eosinofilia

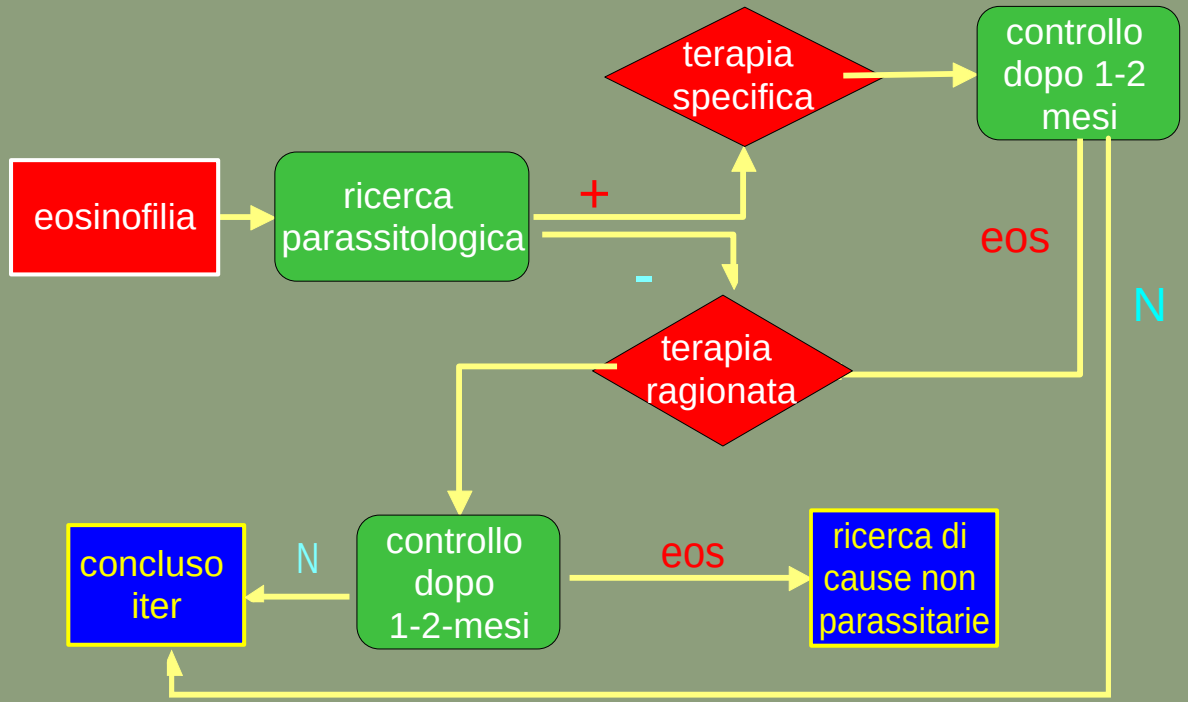
## I Livello

- Esame copromicroscopico (3 campioni, con arricchimento sec Ritchie o equivalente)
- Esame uroparassitologico (epidemiologia!)
- Sierologia per filaria
- (Coprocoltura e) sierologia per *Strongyloides stercoralis*
- Sierologia per schistosoma (epidemiologia!)

## II Livello

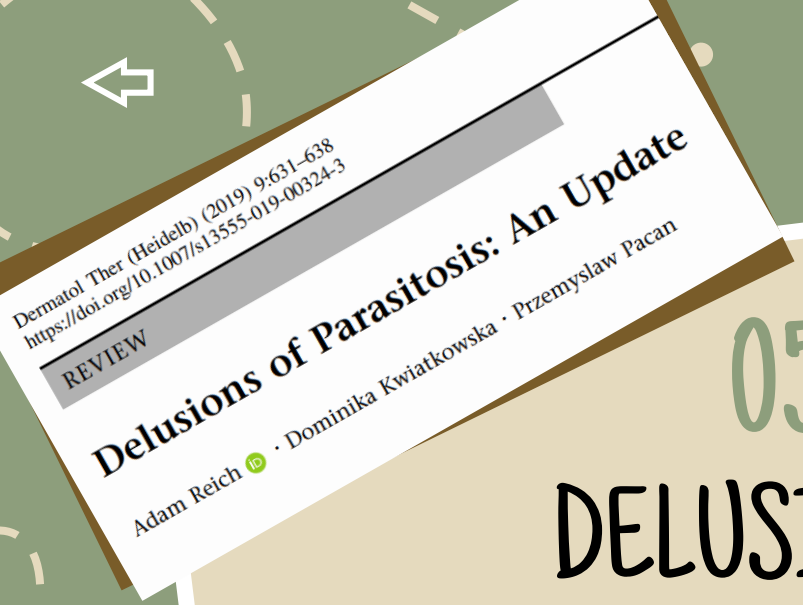
- Sierologia per *Toxocara*
- Altre sierologie su indicazione specifica (fasciola, gnatostoma…)
- Ricerca microfilarie notturne e diurne, dopo leuco-concentrazione di 10 cc. di sangue (epidemiologia!)
- Ricerca microfilarie cutanee (epidemiologia!)

# Approccio all'eosinofilia asintomatica



# Tx antielmintica ad ampio spettro

- Combinazione di praziquantel 40 mg/Kg in due dosi refratte (4 ore) → I giorno
- Ivermectina 200 mcg/Kg (o 400 mcg/Kg se zona di filarie)
- Albendazolo 400 mg bid per cinque giorni

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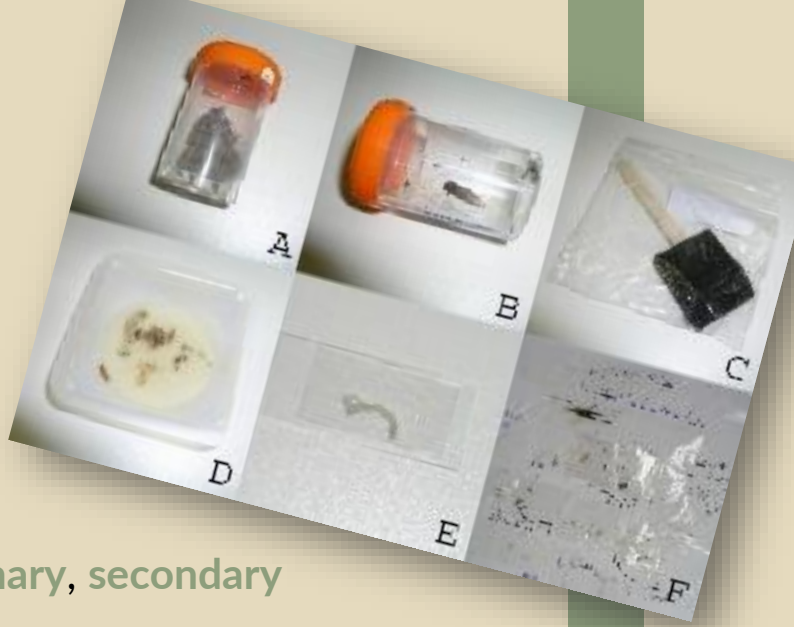
# DELUSIONAL PARASITOSIS


**Delusional parasitosis (DP), also known as delusional infestation or Ekbom syndrome**, is a relatively infrequent* psychotic disorder characterized by an unwavering false belief that there is a parasitic infestation of the skin, despite the absence of any medical evidence that could support this claim.

The disorder is most frequently seen in middle-aged, often socially isolated, women (the average age is 57 ± 14 years).

*The mean number of cases of DP per institution or hospital per year has been found to range from 0.6 to 20.




Delusional parasitosis can be categorized into primary, secondary (functional), and organic forms.

1) In **primary** delusional parasitosis, the patient has the delusion of being infested with parasites but no other psychiatric or organic disorders is present.
2) The **secondary (functional)** and **organic forms** of delusional parasitosis occur secondarily to other disorders, namely **psychiatric** and **organic disease**, respectively.

# DP: features

- Patients suffering from this delusion
  sensation of movement under the sk
  that the symptoms are caused by th
  tactile hallucinations or paresthesias
- Excoriation, discreet bruises, erosion
  attempts to remove parasites. Addit
  application of aggressive chemical o
- To prove the infestation, patients m
  which the patient has placed various
  sent many times to various laborato
  sign," or, more recently, "specimen s
- Sometimes, close relatives also expe
  15% of cases and is known as share


FIG. 1. Specimen sign. Patients provide all kinds of proof of infestation, in this case a matchbox filled with skin particles and crusts on a piece of white cotton.

# DP

- Patients with delusional parasitosis frequently seek help from **many** physician.

- For many patients, a sense of a lack of understanding leads to isolation and the development of depression symptoms, which is why it is crucial **to earn the trust of these patients** while taking care of them.

Before starting pharmacological treatment, patients with mild symptoms should try cognitive behavioral therapy (CBT).

# Treatment

Currently, second-generation antipsychotics such as **risperidone** or **olanzapine** are considered first-line therapies, mostly due to their safer profiles and better tolerabilities.

A good alternative could be **aripiprazole**, which has the smallest side effect profile and does not cause weight gain. However, only seven case reports have described its efficacy in delusional parasitosis

- The patient should be made aware that the antipsychotics are not prescribed to treat schizophrenia, and that many of the medications commonly used in psychiatry are also used in dermatological practice due to the presence of an antihistaminic component. The majority of the symptoms of delusional parasitosis disappear when the patient is receiving psychopharmacological therapy. However, with delusional disorders, there is always a risk of recurrence

## Tricks

- Effective treatment requires a good physician–patient relationship. Patients should always feel that their disease is being taken seriously; any discussion of the reality of the alleged parasite infestation is inadvisable

# THANKS!

Do you have any questions?
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