Infectious diseases during wartime:
Re-emergence of Cutaneous Leishmaniasis
among refugees in North Lebanon

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Infectious diseases = the “THIRD ARMY”
Geographic distribution of recent emerging or reemerging infectious disease outbreaks and countries affected by conflict, 1990–2006

War and Famine

Butler CD. 2012. Infectious disease emergence and global change. Inf Dis Poverty 1:5
39% of total displaced people come from Middle East and North Africa (MENA Region)

57% of refugees worldwide come from three countries

Syria
Afghanistan
South Sudan
15 March 2011
Starting of crisis

SYRIAN REFUGEE CRISIS
Massive Displacement
Syrians are now the largest refugee population in the world.
SYRIAN REFUGEE CRISIS
MILLIONS OF PEOPLE FORCED FROM THEIR HOMES

Syrians are now the largest refugee population in the world.

Source: www.unocha.org/syria
Where the world’s displaced people are being hosted

About 80 per cent of refugees live in countries neighbouring their countries of origin.

bbc.co.uk/newsbeat/article/35470894
More than 1 million refugees have fled the civil war in Syria and moved into Lebanon.
THE WORLD’S TOP 10 REFUGEE HOST COUNTRIES

- TURKEY (3.7M+)
- IRAN (979,400)
- PAKISTAN (1.4M)
- GERMANY (1M+)
- LEBANON* (1.4M+)
- SUDAN (908,700)
- JORDAN* (2.9M+)
- BANGLADESH (906,600)
- ETHIOPIA (921,000)
- UGANDA (1.1M+)

WHO HOSTS THE MOST REFUGEES PER 1,000 INHABITANTS?

- **LEBANON (156)**
- **TURKEY (45)**
- **UGANDA (26)**
- **SOUTH SUDAN (23)**
- **DJIBOUTI (19)**
- **SUDAN (26)**
- **MALTA (20)**
- **CHAD (29)**
- **SWEDEN (25)**

GLOBAL EMERGENCY PREPAREDNESS: DISEASE KNOWS NO BORDERS

An outbreak that starts in another country can hit our shores in a matter of hours. As we protect across the globe, we also protect here at home.
Numbers of papers identified by infection type in Syrian and Eritrean migrants 2014-2017

Isenring et al. Travel Med Inf Dis 2018; 25: 65-76
Cutaneous Leishmaniasis (CL)

- Aleppo boil, Baghdad boil, Delhi boil, Kandahar sore, Oriental sore, Balkan sore, Tropical sore, ..

Ranking of NTDs in the MENA region by prevalence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated or Reported Number of Cases</th>
<th>Percentage of Global Burden of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascariasis</td>
<td>22.3 million</td>
<td>3%</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>12.7 million</td>
<td>6%</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>9.0 million</td>
<td>1%</td>
</tr>
<tr>
<td>Hookworm</td>
<td>4.7 million</td>
<td>1%</td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>0.9 million</td>
<td>36%</td>
</tr>
<tr>
<td>Trachoma</td>
<td>0.6 million</td>
<td>1%</td>
</tr>
<tr>
<td>Anthroponotic cutaneous leishmaniasis (L. tropica)</td>
<td>0.04 million</td>
<td>Not determined</td>
</tr>
<tr>
<td>Zoonotic cutaneous leishmaniasis (L. major)</td>
<td>0.03 million</td>
<td>Not determined</td>
</tr>
<tr>
<td>Leprosy</td>
<td>&lt;0.01 million</td>
<td>3%</td>
</tr>
</tbody>
</table>


- Infects >100 000 refugees, migrants and displaced persons annually
Cutaneous Leishmaniasis (CL)

Number of CL cases reported in 2018

WHO, 2012
Cutaneous Leishmaniasis (CL)

New World

Old World

Lutzomyia sp.

Phlebotomus sp.

WHO, 2012
Cutaneous Leishmaniasis (CL)

Sand fly

Mosquito
Cutaneous Leishmaniasis (CL)

Protozoan parasite *Leishmania* sp.

**Promastigote form** found in the sand fly midgut

**Amastigote form** found in the macrophages of humans
Promastigotes injected into skin upon sand fly bite

Promastigotes differentiate into amastigotes

Amastigotes released in the sand fly gut differentiate into promastigotes

The sand fly ingests parasitized macrophages

Macrophages phagocytose the promastigotes

Amastigotes replicate until the macrophage burst

Released amastigotes infect more macrophages
Cutaneous Leishmaniasis (CL)

In the Old World:

- **Phlebotomus sergenti**
  - *Leishmania tropica*
  - Anthropo-otic cycle

- **Phlebotomus papatasi**
  - *Leishmania major*
  - Zoonotic cycle

Cutaneous Leishmaniasis (CL)

Polymorphic skin lesions

Cutaneous Leishmaniasis (CL)

- Treatment with chemical drugs is the only effective way to treat all forms of disease

VACCINES

- Toxic
- Expensive

Emergence of resistance

Search for new anti-leishmanial agents
Cutaneous Leishmaniasis (CL)

First choice of treatment = Pentavalent antimonials

Second choice of treatment = amphotericin B, pentamididine, miltefosine and paromomycin
First choice of treatment

Intralesional injections

0.5-5 ml of antimonials twice weekly for 3-4 weeks until the complete cure of lesions.

Cutaneous Leishmaniasis (CL)

First choice of treatment

Systemic treatment

- Presence of numerous lesions (>5 lesions),
- large lesions (>5 cm)
- disfiguring or disabling lesions.

20 mg/kg/day for 20 days

Childrensmn.org
Risk factors of CL during conflicts

- Mass movement of populations
- Environmental conditions
- Lack of health services
- Deterioration of health care infrastructures
- Poor nutritional status
- Decrease in health workforce

Vector control
Current CL situation in Syria

Number of CL cases reported by different surveillance systems in Syria (2007-2018)

Incidence rate in 2010: 20.08 per 10,000 population
in 2018: 44.99 per 10,000 population (X2)

Current CL situation in Syria

6.6 M internally displaced (Internal Refugees)

- Raqqa (100 cases in 2007 – 3502 cases in 2018)

Turkey:

- Introduction of non-endemic parasite strains *L. major* and *L. donovani* by incoming refugees.

Syrian Refugees and CL situation in neighboring countries

Lebanon:

→ only 6 CL cases in Lebanon

After Syrian war: 2013 alone
→ 1,033 new cases were reported

Figure: Cumulative numbers of monthly reported Leishmania cases 2013-2014

MoPH, 2014
- No formal refugee camps for Syrians
- Open borders with Syria during the 1st four years of war
  - No medical examination at refugee entrance
CL Infected Host + Reservoir + Sand fly

High risk for CL local transmission

Appropriate control measures
Assessment of CL situation in Lebanon

Epidemiological study in North Lebanon
(1st December - 1st June 2017)

- Contains 25% of the total number of refugees in Lebanon
- Geographic location proximal to CL endemic hotspots
Assessment of CL situation in Lebanon

Patients

Recruitment of 48 Syrian patients (18 females and 30 males) clinically diagnosed by dermatologists according to symptoms

Bachaer Medical Center
Assessment of CL situation in Lebanon

Samples – Needle Aspiration technique

[Image of sample with needle aspiration]

[Image of microscopic view of sample]

[Diagram of needle aspiration process]

[Youtube.com/editor]
Assessment of CL situation in Lebanon

Samples – Lesion Swab rubbing

DNA extraction from Swab and smears samples

Genotyping of Leishmanial isolates
Molecular characterization of *Leishmania* sp. isolates?

Determine the main CL type for a better epidemiological understanding and control planning.

- *L. tropica*
  - Anthroponotic cycle
  - Early diagnosis and treatment
  - Long-lasting Insecticidal bed nets
  - Education of community
  - Use of insecticides in houses
  - Destruction of sand fly breeding ground
  - Biological control of sand flies

- *L. major*
  - Zoonotic cycle
  - Detect the animal reservoir species
  - Application of insecticides directly to implicated animals if possible
  - Insecticidal dog collars

- Human Reservoir
  - • Early diagnosis and treatment
  - • Long-lasting Insecticidal bed nets
  - • Education of community

- Vector population

- Animal Reservoir

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L. major

Zoonotic cycle

L. tropica

Anthroponotic cycle
Assessment of CL situation in Lebanon

Swabs

DNA Extraction

Run ITS1-PCR

Gel Electrophoresis

Positive PCR products

Digestion with HaeIII enzyme

Gel Electrophoresis

Geneotyping of Leishmania sp.

Primers used:
5’ CTG GAT CAT TTT CCG ATG 3’
5’ TGA TAC CAC TTA TCG CAC TT 3’

Band of 320 bp

Bands of L. major: 200 bp & 132 bp
Bands of L. tropica: 185 bp & 57 bp
Assessment of CL situation in Lebanon

CL treatment

Follow treatment response for 6 months

Treatment failure

(Lack of complete re-epithelialization after receiving one course of treatment (12 doses) within 6 weeks of treatment starting).

Megulamine antimonate

(300 mg/ml equivalent to 85 mg/ml pentavalent antimonate)
Assessment of CL situation in Lebanon

Results:
Lesion location

Facial area (67%; 32/48)

Trunk (4%; 2/48)

Shoulder (4%; 2/48)

Arms (31%; 15/48)

Legs (14.5%; 7/48)
Assessment of CL situation in Lebanon

CL Lesion forms

67% of lesions were nodular with/without ulceration

Range of lesion size = 0.5 to 7 cm with average mean of 1.3 cm
Assessment of CL situation in Lebanon

Age distribution of patients

67% of infected patients were young children ≤ 12 years → Terrible social stigma

Necessity of future studies aiming to assess the mental health burden of the CL patients in refugee settings
Assessment of CL situation in Lebanon

Anti-leishmanial treatment response (6 months):

- Two patients (5%) receiving systemic drug treatment → cured after one course of treatment over a period of 20 days.

- 43 patients receiving intra-lesional drug injections

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Number of intralesional Glucantime courses

<table>
<thead>
<tr>
<th>Nb. of patients</th>
<th>Number of intralesional Glucantime courses</th>
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</thead>
<tbody>
<tr>
<td>46%</td>
<td>One course (12 doses)</td>
</tr>
<tr>
<td>42%</td>
<td>Two courses (24 doses)</td>
</tr>
<tr>
<td>7%</td>
<td>Three courses (&gt; 24 doses)</td>
</tr>
</tbody>
</table>
Assessment of CL situation in Lebanon

Molecular Data:

*L. tropica* = 91.7% (Mainly Edleb and Hama)
*L. major* = 8.3% (Mainly Rakka and Aleppo)
Three CL cases with no history of recent travel to Syria → Possible CL local transmission!

Assessment of CL situation in Lebanon

Map indicating areas in Syria and Lebanon with cases of cutaneous leishmaniasis, including infected individuals and probable local transmission.
Assessment of CL situation in Lebanon
Possible local transmission? Sandflies in Lebanon?

- Last entomological data concerning sandflies is related to a collection realized in 1995.

- Big gap of information on the distribution and dispersion of the sand fly fauna in Lebanon.

- No data on the role of indigenous sandflies in CL transmission among refugees.

*Les phlébotomes du Liban*

*Inventaire faunistique*

HADDAD N*, LÉGER N.**, & SADEK R. ***

Parasite, 2005, 10, 99-110
High priority to perform further entomological studies:

- To assess the distribution and dispersion of sand fly fauna in North Lebanon.

- To determine a possible existence of CL autochthonous transmission by xenodiagnosis of wild-caught sand flies.
Syrian refugees are coming back to a destroyed and unsafe country!

High density of Sand flies vector → increase the risk of CL contracting → dissemination of disease on a large scale
Summary

• The re-emergence of CL in North Lebanon represents a case study of other war-infectious disease around the globe.

• The Molecular Epidemiological studies are a necessary to understand the circulation of infectious diseases and their ways of prevention especially in emergency context.

• War and violent conflicts are one of the main recent causes for the spreading of infectious diseases.
Thanks for your attention