Splenomegaly in Congolese Refugees: Common and complicated

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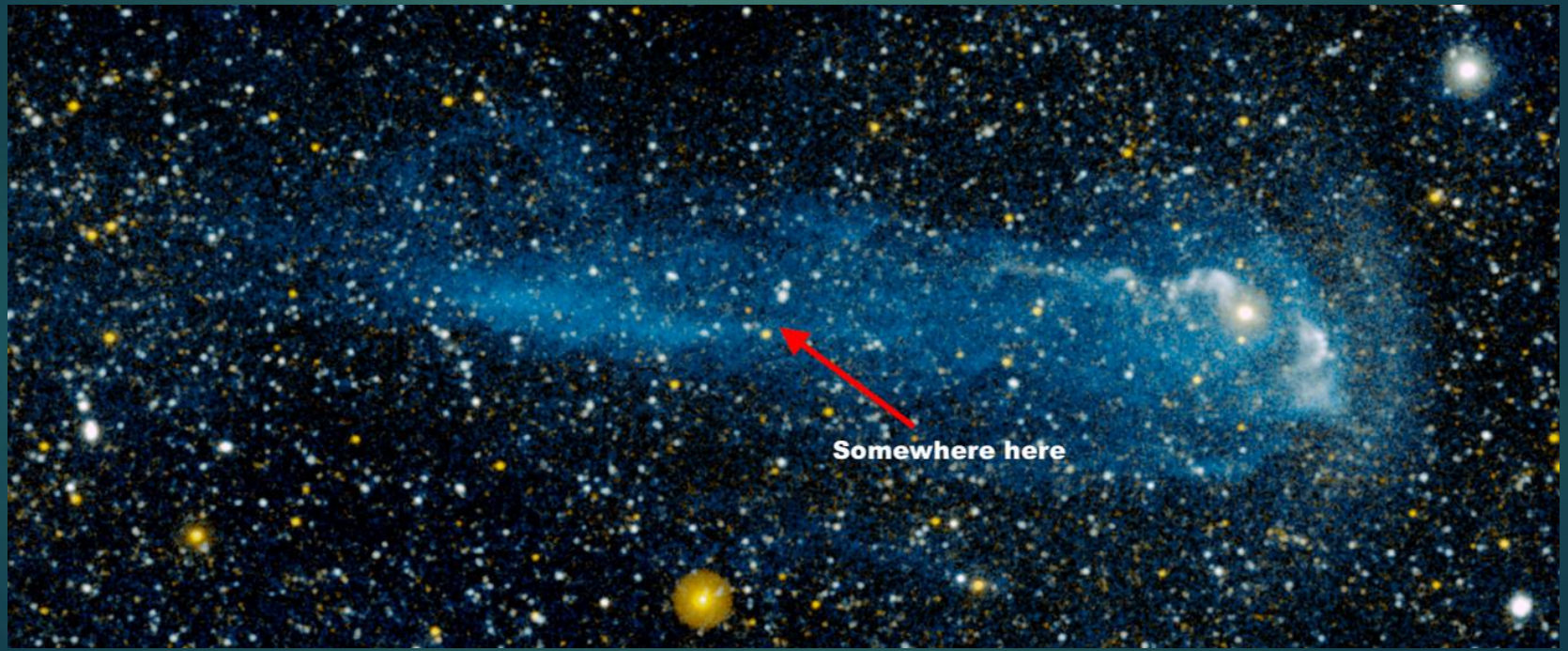
•Perspectives provided are my opinion only and are not necessarily those of the CDC

• No financial disclosures but 3 disclaimers

Disclaimer #1: I am a clinician primarily

Disclaimer #2: I use the word "We" a lot…most the actual work is not me…



Disclaimer #3
I know less than when I started about splenomegaly

If I am successful, so will you ☺

Case Scenario

- 15 y/o Ethiopian female referred from pediatric heme/onc for enlarged spleen. Extensive heme/onc evaluation negative (excluding bone marrow bx).

- ID question, is this infectious?

15 y/o Ethiopian female with a large spleen

- HPI
  - Patient immigrated from Kenya 14 months previous. Reports "feeling hot": tactile fevers? Originally from southern Ethiopia (near Awassa)
  - Abdominal discomfort…fullness.
  - No weight loss or night sweats but weakness and fatigue, difficulty with walking one block.
  - Uncle states she has had "a big stomach since she was ~5 years of age"

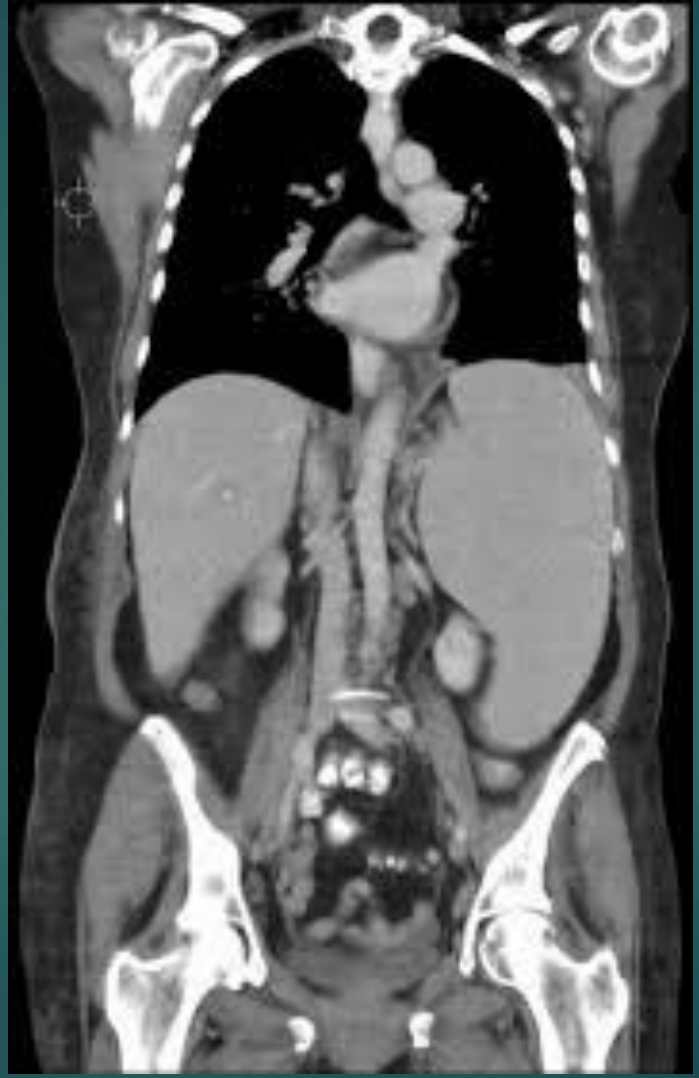
15 y/o Ethiopian female with a large spleen

- Physical Examination
  - VSS, afebrile
  - RRR, flow murmur
  - CTA B
  - Abd +BS, Right palpable mass/spleen to umbilicus and to left pelvic gutter, uncomfortable but not tender. Liver 7 cm in span

15 y/o Ethiopian female with a large spleen

- Laboratory
  - WBC 1.1 (N abs: 700, L 400)
  - Hgb 8 (MCV 78)
  - Platelets 21
  - LFT's normal

- CT:



Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

- 23 yo Ethiopian male with 3-4 weeks of drenching fevers

- Migrant, working in sorghum fields in NW corner (near Sudan) of Ethiopia
- Daily nose bleeds
- Very weak, ambulatory (but barely), lost ~9 kg over last month
- Similar presentation 1 year ago, treated at MSF with daily injections and got better

Special Thanks: Ann Settgast for case

Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

- Physical Examination
  - Cachectic (BMI 12), Temp 101
  - O/P dried blood
  - Abdomen grossly enlarged (and visible) spleen
  - Epitrochlear and inguinal LAD
- Laboratory
  - Rapid malaria test negative; Hbg 7.6

Special Thanks: Ann Settgast for case

Case 3: 7 yo Congolese male with “stone” in abdomen

- 7 yo Congolese male being screened for US refugee resettlement

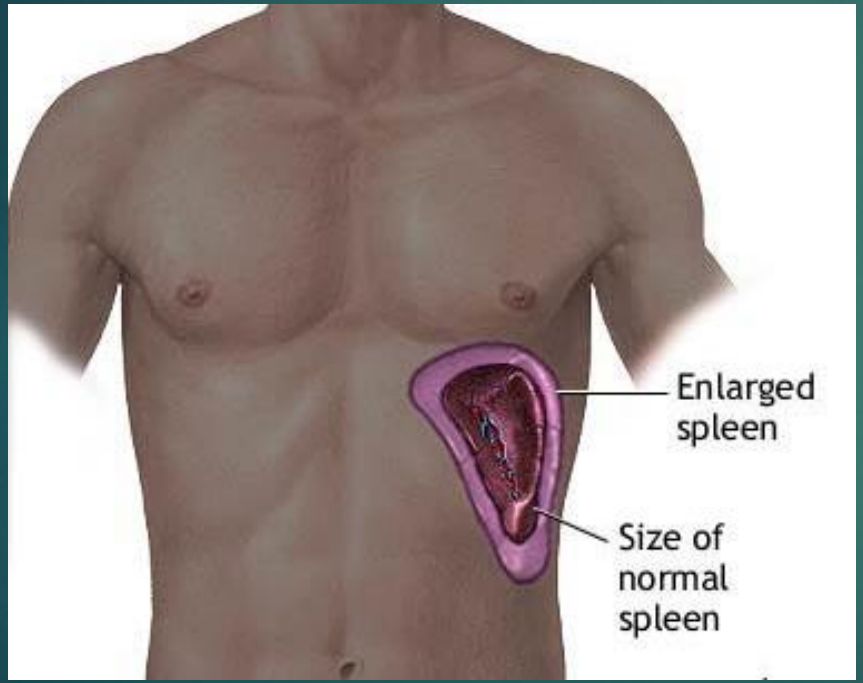
- Living outside Hoima, Uganda
- Migrated to Uganda when 4 years old
- Asymptomatic, but when asked, his parents say he has a “stone”

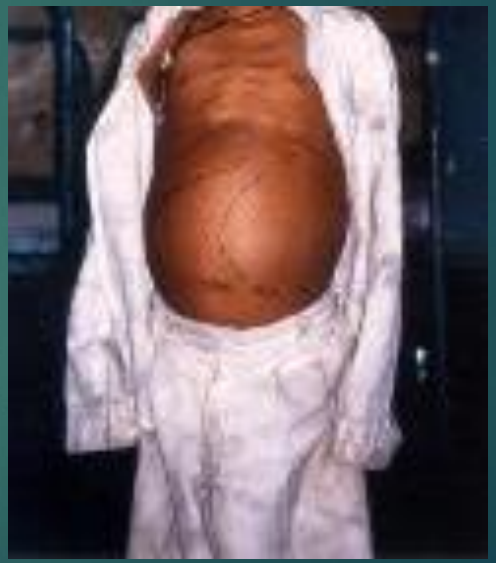
Case 3: 7 yo Congolese male with "stone" in abdomen

- Physical Examination
  - Normal except for abdomen—liver span normal, spleen grossly enlarged, uncomfortable with palpation
- Labs
  - Hgb 10; Plts 125, WBC 4.3
  - Rapid malaria test negative

Differential diagnosis (in particular, tropical infections)?

Splenomegaly





Splenic Function

- Clearance of microorganisms and antigens
- Synthesis of immunoglobulin G (properdin)
- Removal of RBCs
- Extramedullary hematopoiesis

Differential diagnosis—by mechanism

- Immune response
  - Infection (endocarditis, mononucleosis)
- RBC destruction leading to hypertrophy
  - Hereditary spherocytosis or thalassemia's (major)
- Congestion
  - Splenic vein thrombosis
  - Portal hypertension
- Neoplasms
  - E.g. leukemia/lymphoma
- Myeloproloferative
  - Chronic myeloid metaplasia
- Infiltrative
  - Sarcoidosis, Gauchers, amyloidosis
- Misc
- Structural
  - Cysts
  - Hemangiomas
  - Metastasis
  - Abscess (giant)
  - Drugs (RhoGam)/Toxins
  - Etc…

Splenomegaly

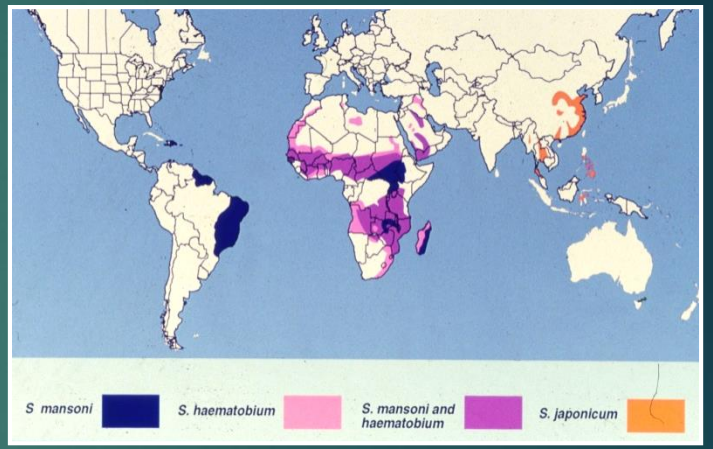
- Tropical Differential Diagnosis (top four I think about first)

  - Malaria
  - Schistosomiasis (mainly liver disease sequalae, can be immune mediated)
  - Visceral Leishmaniasis

  - Brucellosis, (any common cause of chronic liver disease (e.g. viral chronic hepatitis, toxins), TB?

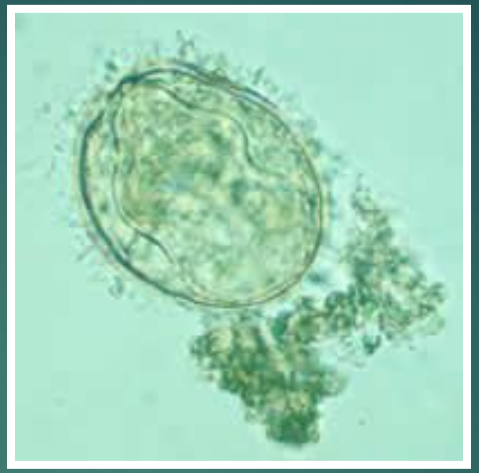
Schistosomiasis

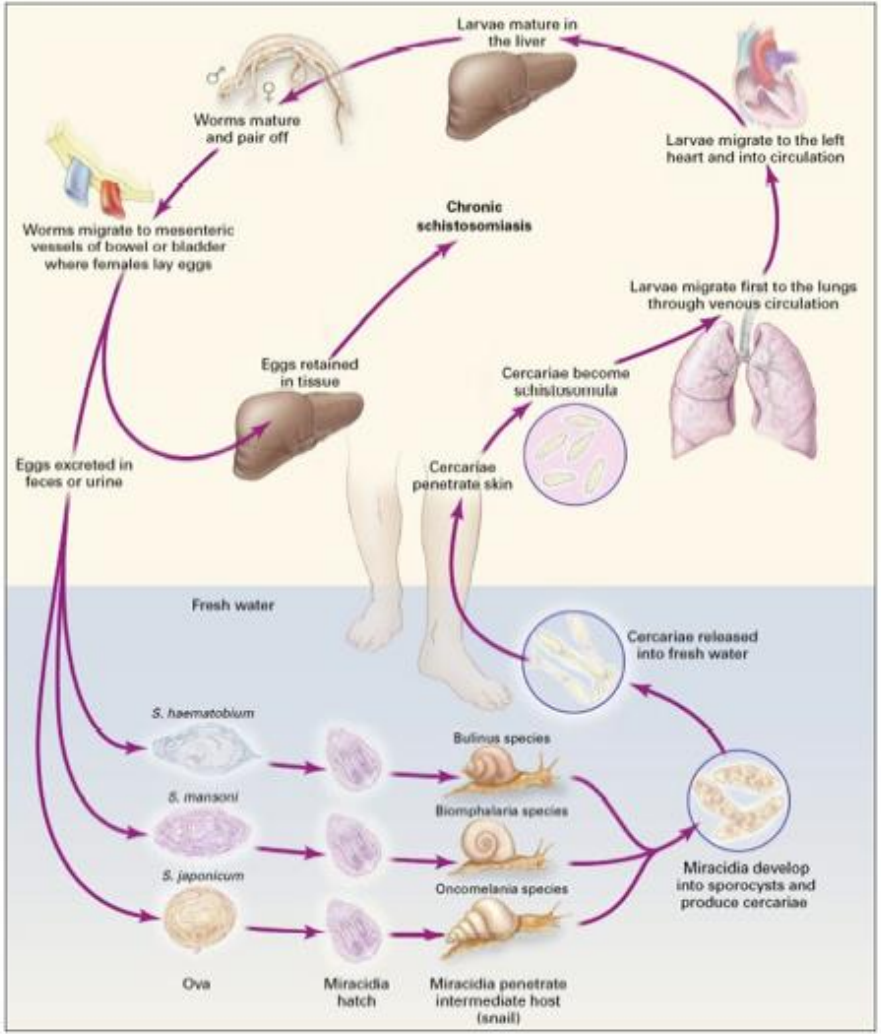
- Epidemiology
  - Endemic in 74 countries
  - 600-800 million at risk, ~200 infected, ~120 symptomatic, ~20 million with severe disease
  - 85% in Africa

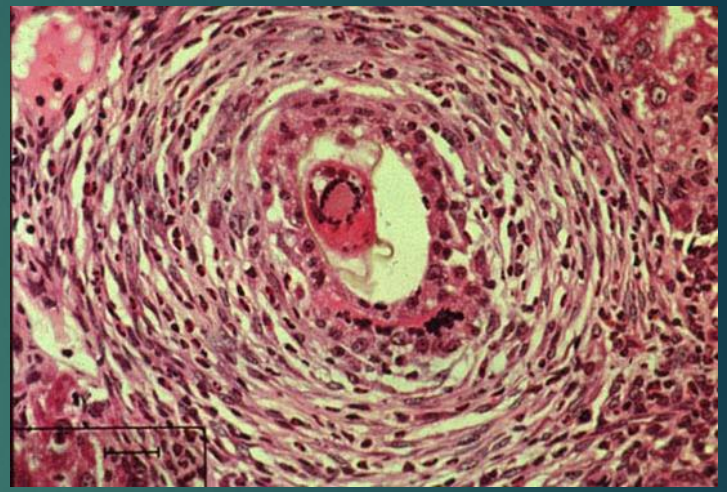


Species

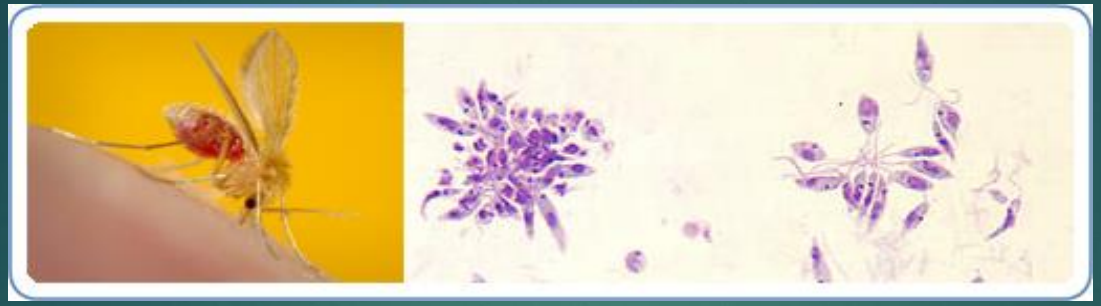
- Intestinal
  - *S. mansoni*
  - *S. japonicum*
  - *S. mekongi*
  - *S. intercalatum*
- Urinary
  - *S. Haematobium*
- *Rare Zoonotic*
  - *S. bovis*
  - *S. mattheei*
  - *S. margrebowiei*
  - *S. curassoni*
  - *S. rodhaini*




Larvae mature in the liver
Worms mature and pair off
Larvae migrate to the left heart and into circulation
Worms migrate to mesenteric vessels of bowel or bladder where females lay eggs
Chronic schistosomiasis
Larvae migrate first to the lungs through venous circulation
Eggs retained in tissue
Cercariae become schistosomula
Eggs excreted in feces or urine
Cercariae penetrate skin
Fresh water
Cercariae released into fresh water
S. haematobium
Bulinus species
S. mansoni
Biomphalaria species
S. japonicum
Oncomelania species
Miracidia develop into sporocysts and produce cercariae
Ova
Miracidia hatch
Miracidia penetrate intermediate host (snail)



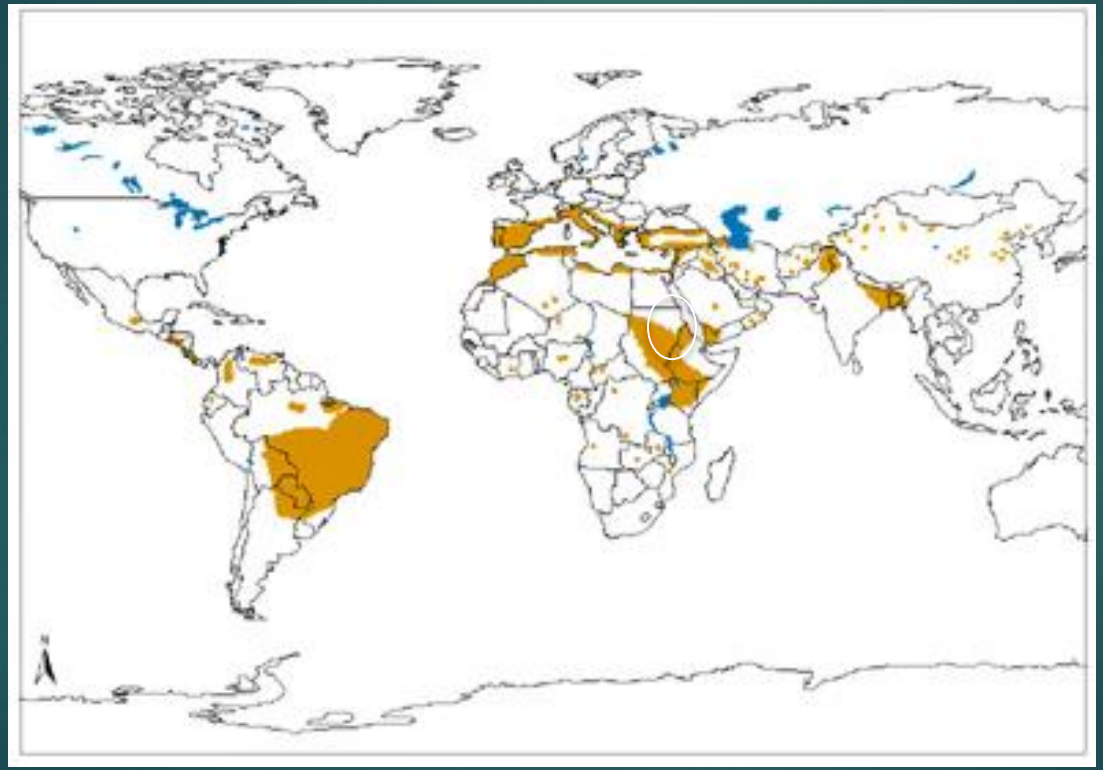
Leishmaniasis (Visceral)



- 90% in six countries: Bangladesh, Brazil, Ethiopia, India, Sudan, South Sudan

- *L. donovani* and *L. infantum* and affects internal organs (particularly, spleen, liver, and bone marrow).

Leishmaniasis (Visceral)



Leishmaniasis (Visceral)

- Kala-azar ("black fever" in Hindi)

- Typical symptoms
  - fever
  - weight loss (cachexia; wasting)
  - hepatosplenomegaly (usually, the spleen is more prominent than the liver)
  - pancytopenia—i.e. anemia, leukopenia, and thrombocytopenia
  - a high total protein level and a low albumin level, with hypergammaglobulinemia

Diagnostic evaluation?

Non-clinicians: you can Go to your happy place

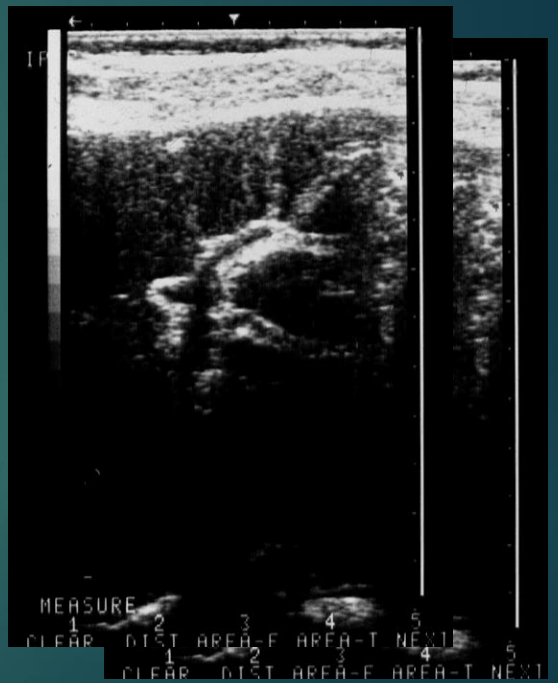
15 yo Ethiopian female with splenomegaly

- Most pertinent test results
  - Liver CT normal, LFTs normal
    - Malaria
      - Peripheral smear negative
      - RDT (weak positive for non-falciparum—aldolase; negative for falciparum—HSP1)
      - Malaria serology (IgG negative); Total IGM slightly high
      - Malaria PCR negative
    - Schistosomiasis
      - Stool ova and parasite (*S. mansoni* ova in 1/3 —H. nana 1/3)
      - Schistosomiasis serology negative
    - Leishmaniasis serology negative
    - Other serologies negative: brucella, hep B and C, EBV

15 yo Ethiopian female with splenomegaly

- What do you think the most likely diagnosis is?

A. Malaria (hyper-reactive splenomegaly syndrome
B. Schistosomiasis
C. Visceral Leishmaniasis
D. Brucellosis



- Reminder:
- Malaria
  - Peripheral smear negative
  - RDT (weak positive for non-falciparum—aldolase; negative for falciparum—HSP1)
  - Malaria serology (IgG negative); Total IGM slightly high
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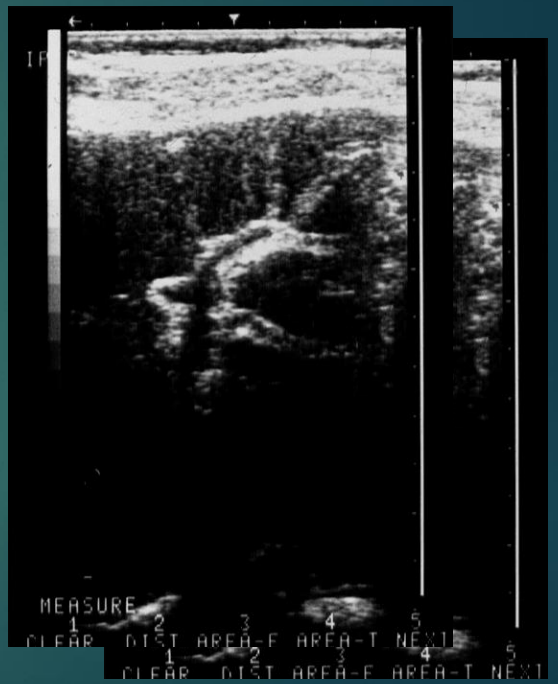

- Schistosomiasis
  - Stool ova and parasite (*S. mansoni* ova in 1/3 —H. nana 1/3)
  - Schistosomiasis serology negative (call from outside lab, postivie)

Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

- Most Likely Diagnosis?
  - A. Malaria (hyper-reactive splenomegaly syndrome)
  - B. Schistosomiasis
  - C. Visceral Leishmaniasis
  - D. Brucellosis

Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

DAT +, HIV +

Direct agglutination test

- Direct agglutination test (DAT) based on agglutination of the trypsenized whole promastigotes is useful in endemic regions. Its sensitivity ranges from 91-100% and specificity from 72 to 100%.

Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly

- Most Likely Diagnosis?
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  - B. Schistosomiasis
  - C. Visceral Leishmaniasis
  - D. Brucellosis

Case 2: 23 yo Ethiopian male with 3-4 weeks of fevers and splenomegaly (DAT +, HIV +)

- A few learning points
  - Highly geographically determined (as with most infectious diseases, but even more so…)
  - Description of sodium stibogloconate--hint (30 days IM)
  - Recurrence: hint for HIV
  - Epistasis is very common (amastigotes replace BM causing thrombocytopenia)
  - Epitrochlear nodes very common

Case 3: 7 yo Congolese male with "stone" in abdomen

- Most Likely Diagnosis?
  - A. Malaria (hyper-reactive splenomegaly syndrome)
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  - C. Visceral Leishmaniasis
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- Most Likely Diagnosis?
  - A. Malaria (hyper-reactive splenomegaly syndrome)?
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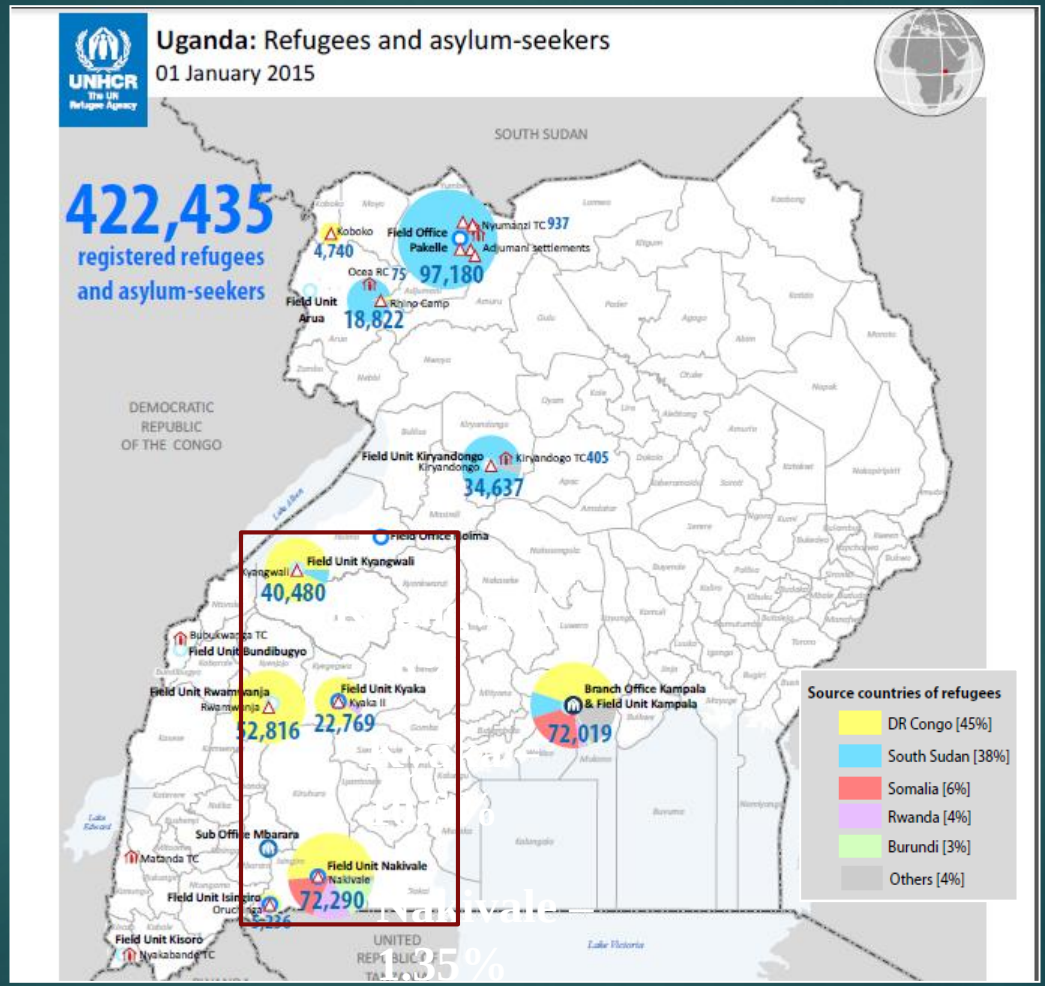
Splenomegaly among Congolese refugees from Uganda

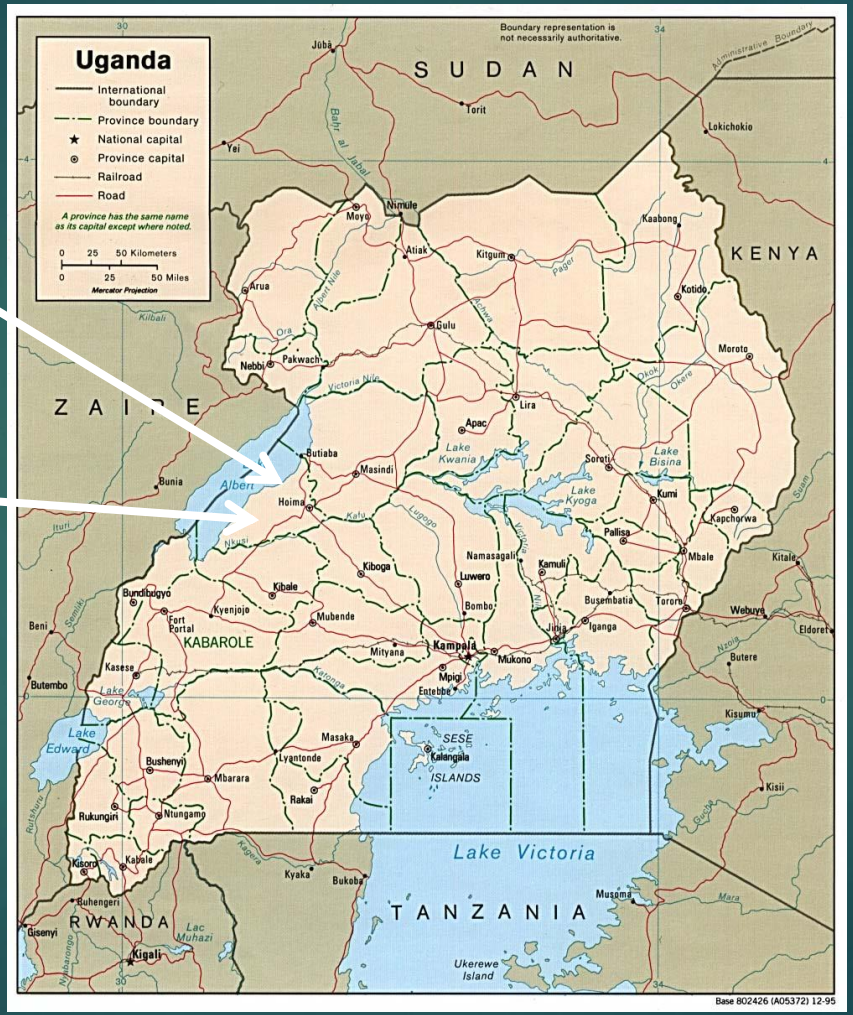

Uganda: Refugees and asylum-seekers
01 January 2015
422,435
registered refugees and asylum-seekers
SOUTH SUDAN
DEMOCRATIC REPUBLIC OF THE CONGO
Koboko 4,740
Field Office Pakelle 97,180
Nyumanzi TC 937
Adjumani settlements
Ocea RC 75
Rhino Camp
Field Unit Arua 18,822
Field Unit Kiryandongo
Kiryandongo
Kiryandongo TC 405
34,637
Field Office Moima
Field Unit Kyangwali
Kyangwali 40,480
Bubukwanga TC
Field Unit Bundibugyo
Field Unit Rwamwanja
Rwamwanja 52,816
Field Unit Kyaka
Kyaka II 22,769
Branch Office Kampala & Field Unit Kampala 72,019
Sub Office Mbarara
Matanda TC
Field Unit Nakivale
Nakivale 72,290
Field Unit Isingiro
Field Unit Kisoro
Nyakabande TC
UNITED REPUBLIC
Lake Victoria
Source countries of refugees
DR Congo [45%]
South Sudan [38%]
Somalia [6%]
Rwanda [4%]
Burundi [3%]
Others [4%]

Investigation Context

- Kyangwali Refugee Settlement:
  - Hoima, Uganda
  - Most refugees are from DRC
  - Higher than expected number of splenomegaly cases

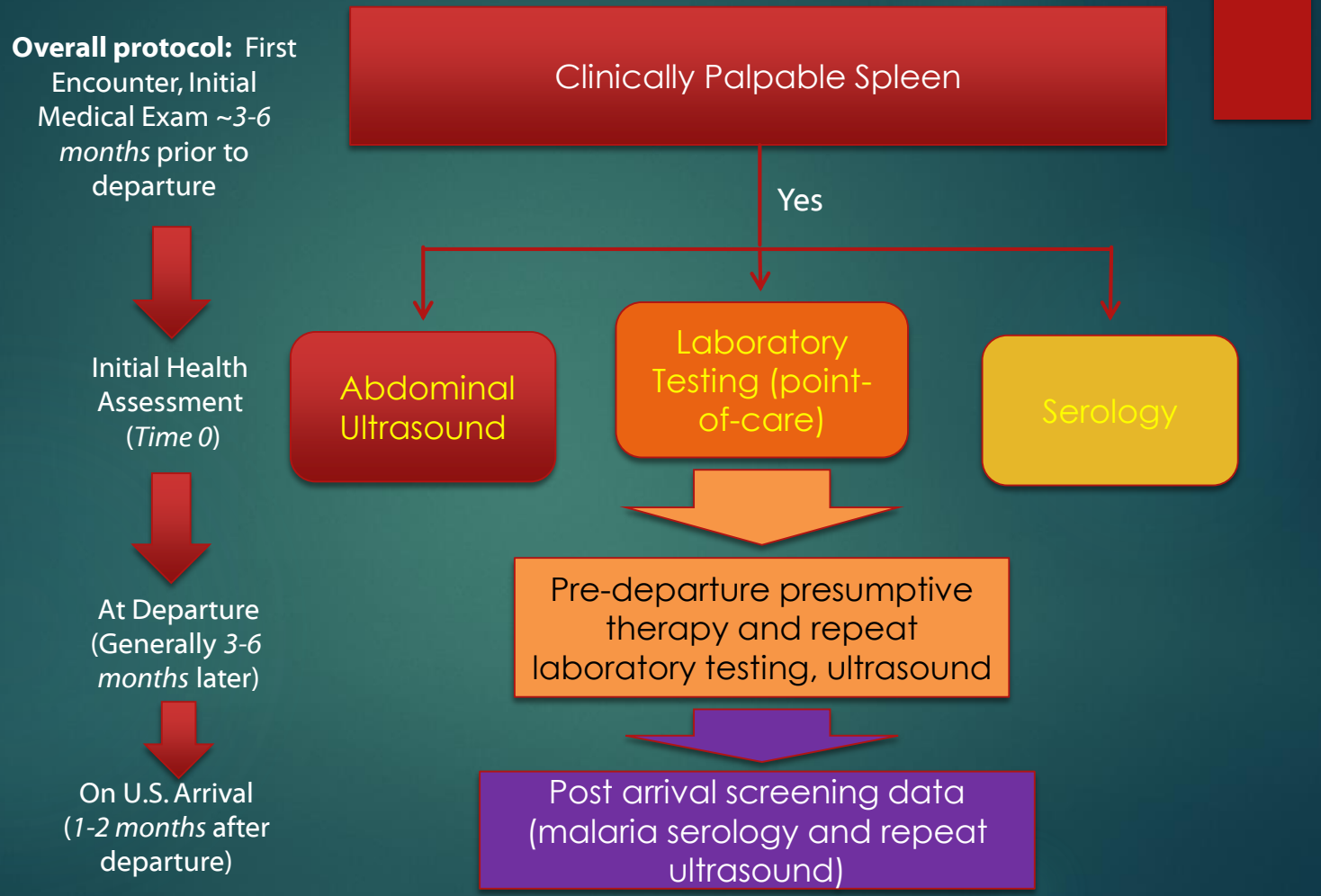
Hoima, Uganda

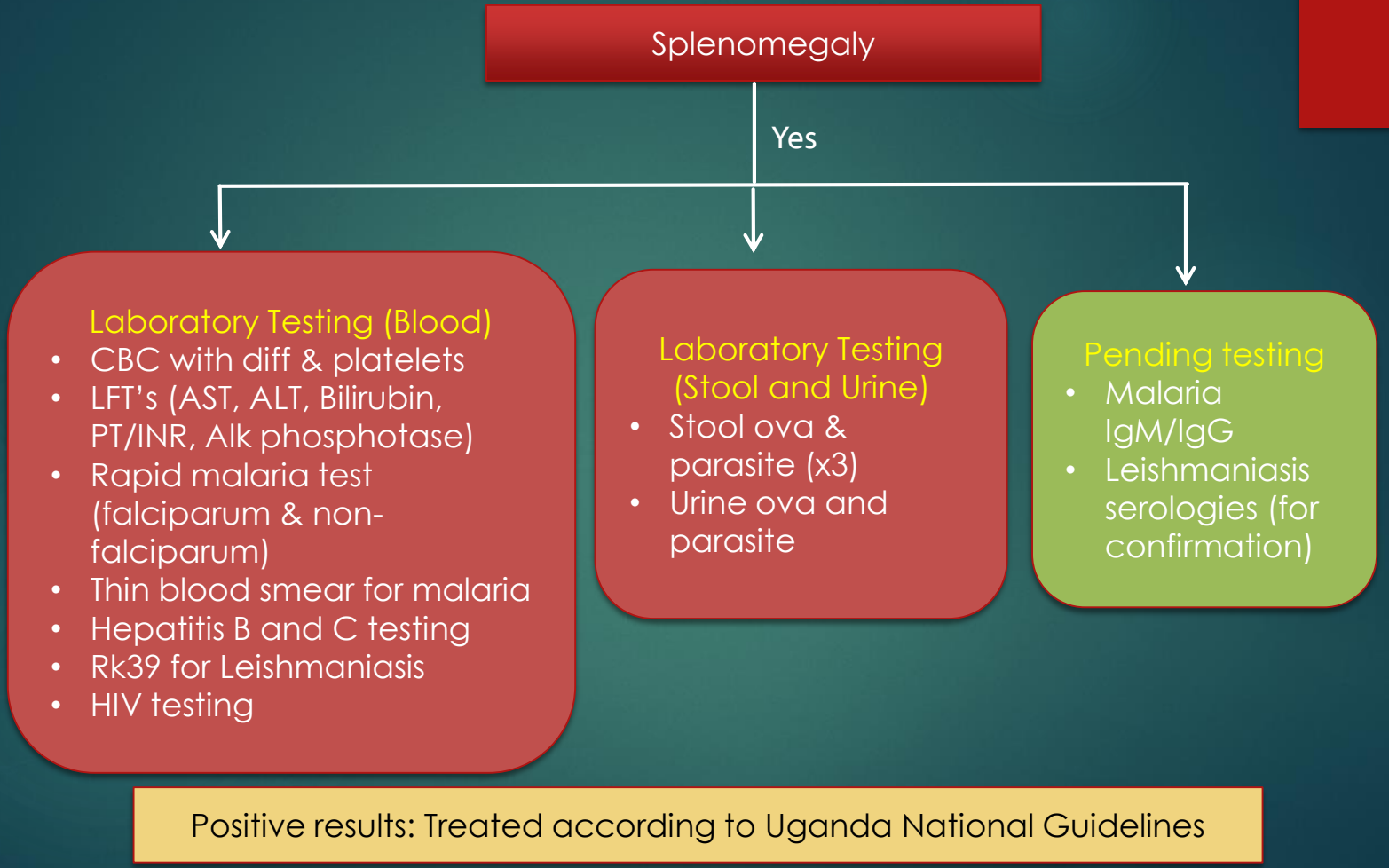
Kyangwali Refugee Settlement



Evaluation

- With assistance of CDC, IOM implemented a diagnostic and treatment protocol:
  - Additional screening and diagnostic testing
  - Questionnaire, Survey data
  - Ultrasonography
  - Treatment


Overall protocol: First Encounter, Initial Medical Exam ~*3-6 months* prior to departure
Clinically Palpable Spleen
Yes
Initial Health Assessment (*Time 0*)
Abdominal Ultrasound
Laboratory Testing (point-of-care)
Serology
At Departure (Generally *3-6 months* later)
Pre-departure presumptive therapy and repeat laboratory testing, ultrasound
On U.S. Arrival (*1-2 months* after departure)
Post arrival screening data (malaria serology and repeat ultrasound)


Splenomegaly
Yes
Laboratory Testing (Blood)
• CBC with diff & platelets
• LFT's (AST, ALT, Bilirubin, PT/INR, Alk phosphotase)
• Rapid malaria test (falciparum & non-falciparum)
• Thin blood smear for malaria
• Hepatitis B and C testing
• Rk39 for Leishmaniasis
• HIV testing
Laboratory Testing (Stool and Urine)
• Stool ova & parasite (x3)
• Urine ova and parasite
Pending testing
• Malaria IgM/IgG
• Leishmaniasis serologies (for confirmation)
Positive results: Treated according to Uganda National Guidelines
Record all results on DS Form

Procedure at Departure (all refugees)

Routine Presumptive Treatment
Praziquantel
Albendazole
Co-artem

Additional Testing (as indicated,)
-- Malaria Serologies
-- Repeat ultrasound (measurements)
-- Other testing as clinically indicated

Tracking system:
Notify states and provide written treatment advice and/or clinical consultation

RK39 (amastigote antigen)

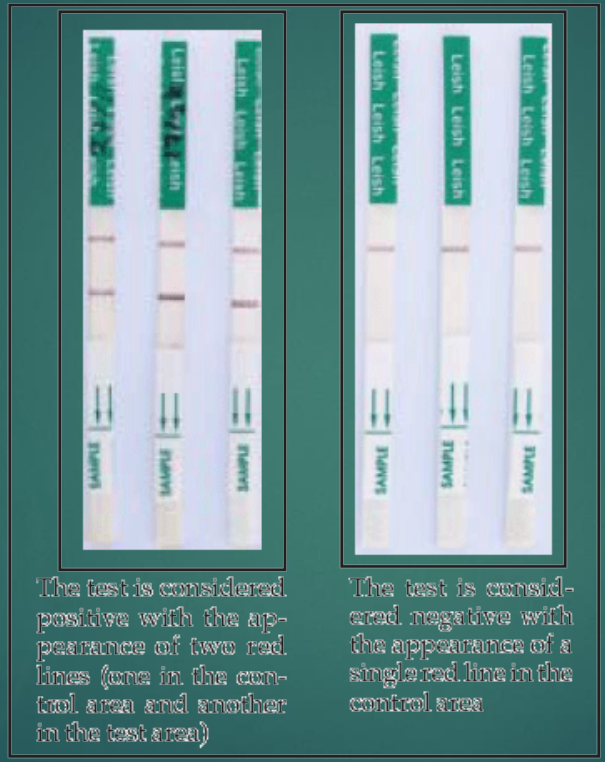


Figure-1: rK39 Immunochromatographic dipstick test for kala-azar


1 . Malaria(P.f)
2 . Malaria(P.v)
1 . Malaria(P.f)
2 . Malaria(P.v)
1 . Malaria(P.f)
2 . Malaria(P.v)

Perceptions in local communities

Splenomegaly is a well known

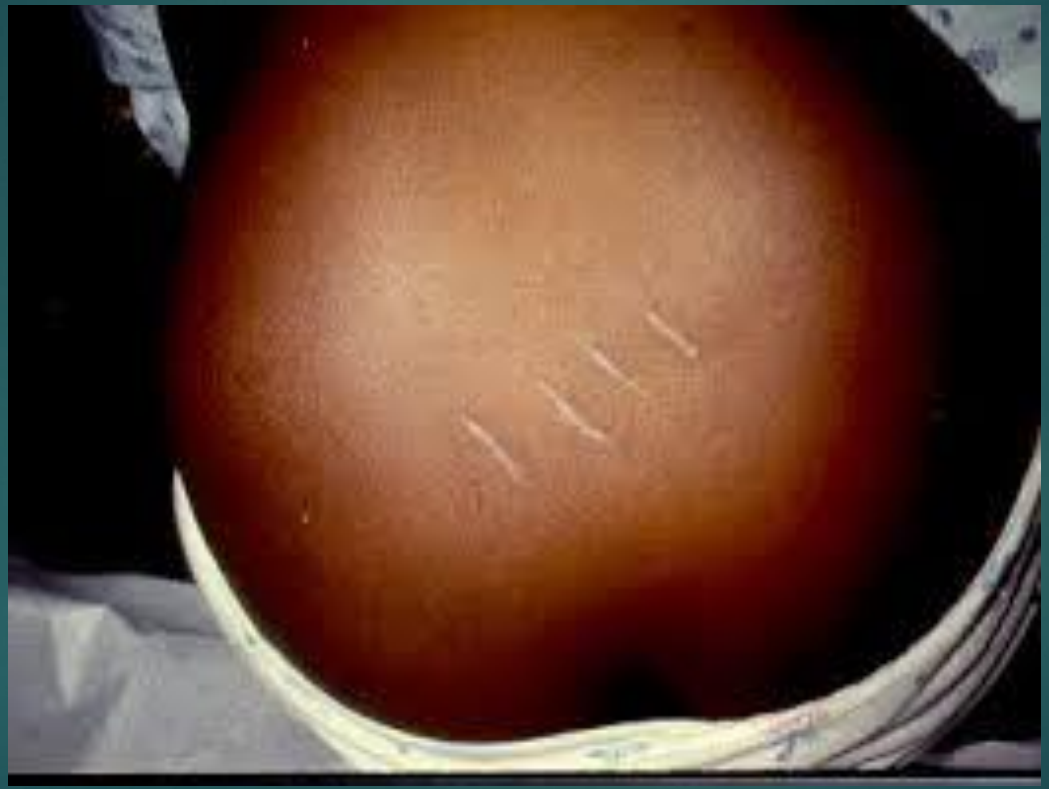
There is a name in all the major language local languages

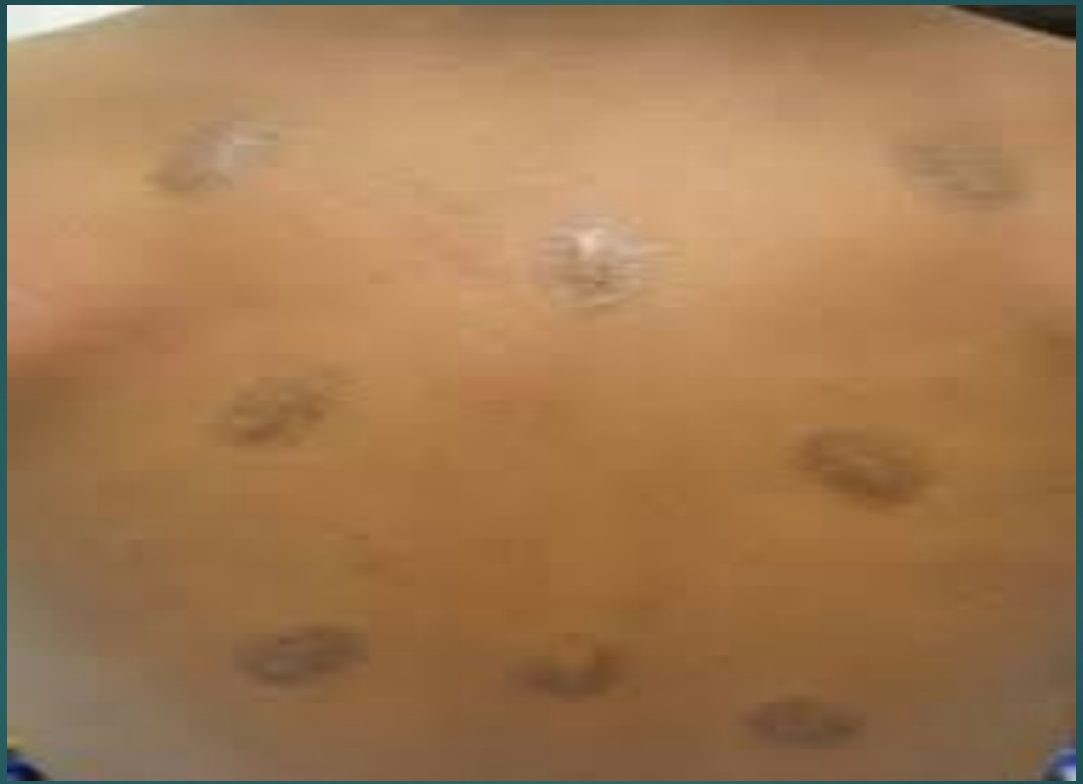
“Ekibaare” in local language (Runyakitara) which can be literally translated in English as a “big stone”

It is perceived as:

- Non-fatal
- Mainly a childhood illness
- Associated with malaria
- Not routinely associated with witchcraft

- Treated traditionally with herbs or through traditional practices (pictures to come)





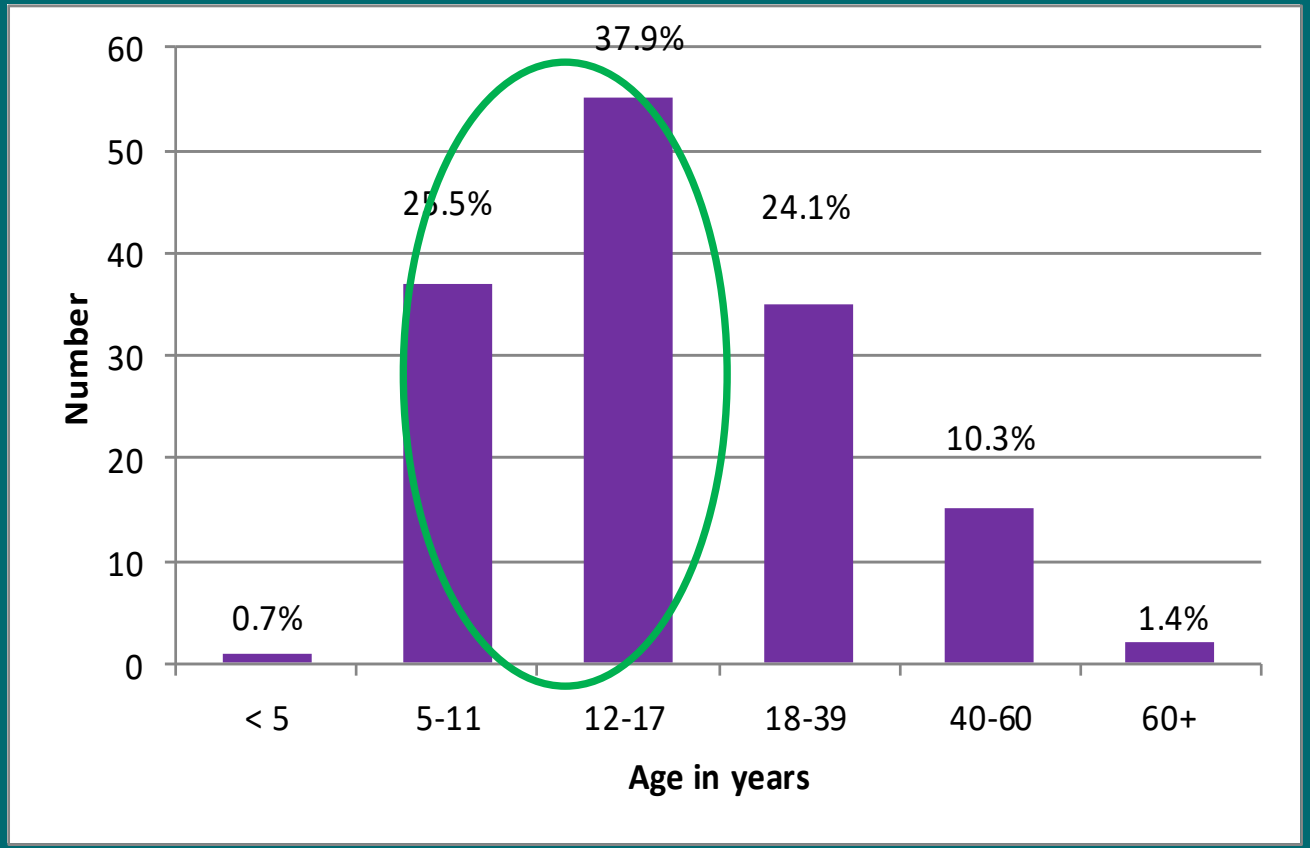
Local Care:

- Unlikely to seek medical care
- Some clinicians treat using a weekly dose of quinine for 6 months.
- Rarely clinically investigated beyond malaria testing Hb estimation.

Results

- Refugees: 145/987 (14.7%)
  - Signs/Symptoms
    - 85% massive, 14% moderate, 1.4% mild
    - >98% born in Congo, clustered in families

Splenomegaly cases by age group



Laboratory Characteristics

	Number (%)
Full Hemogram	
Anemia (Hb <12 g/dl)	82 (57.3)
Leucopenia (WBC<4)	23 (15.9)
Thrombocytopenia (<150,000)	55 (37.9)
Pancytopenia	14 (9.7)
Ova for *Schistosoma mansoni*	3 (2.1)
Leischmaniasis Antibody test	1 (0.7)
Rapid Diagnostic Test for HIV	
Negative	143 (98.6)
Indeterminate	2 (1.4)
Malaria RDT positive	39 (26.9)
Hepatitis B surface Antigen positive	5 (3.5)

Splenomegaly post-arrival

- Post-arrival management
  - Test for G6PD, treat with Primaquine x 2 weeks
  - Repeat ultrasound and monitoring of splenomegaly and any associated abnormalities (e.g. hematologic abnormalities)
  - Avoid contact sports or activities place at risk for abdominal trauma
  - CDC clinical assistance in management and follow-up

Last few words on “Hyperreactive Malarial Syndrome”

- Common manifestation of repeated malarial infections
  - Familial clustering, potential genetic predisposition
  - Prevalence ranges 0.16% (Gambia) to 80% (PNG)
    - Pathogenesis poorly understood, largely immune mediated..

Hyperreactive Malarial Syndrome

Table 2 Treatment outcome: studies conducted in malaria endemic countries with >10 patients and follow up data available

Study	Country	N patients	Type of treatment	Duration	Follow up	Outcome
Prior 1967 [49]	*New Guinea*	99	CLQ 1500 mg/3 days, then 300 mg/wk	NR	average 4.1 mths in hospital plus 6-23 mths out	No change in spleen size, general benefit
Sagoe 1970 [57]	*Nigeria*	43	PG 100 mg /day	≥6 mths	6 mths	32 improved 11 worsened
Bagshawe a.f. 1970 [13]	*Kenya*	28	PG 100 mg /day	1 - 26 mths	1 -6 mths	16 improved 11 worsened 8 unchanged
Stuvier 1971 [27]	*India*	14	PQ 15 days, then CLQ 300 mg/wk	6-14 mths	once/mths for ≥6 mths	11/14 spleen size ↓50%
Stuvier 1974 [71]	*Uganda*	41	CLQ 300 mg/wk or PG 100 mg /day	NR	4- 20 mths	all improved
Bryceson 1976 [60]	*North Nigeria*	30	PG 100 mg /day	3 - 12 mths	3 mths	12/13 improved (17 lost)
Fakunle 1980 [64]	Nigeria	69	PG 100 mg /day	3 mths	10 wks	2 /40 died plus 8/29 defaulters
De Cock 1986 [52]	Kenya	38	PG 100 mg /day or CLQ 300 mg/wk	NR	NR	13/18 improved (20 lost)
Crane 1986 [2]	Papua NG	148	CLQ 300 mg/wk	lifelong	12-18 mths	146 improved (2 lost)
Gupta 1987 [31]	India	54	CLQ 300 mg, 1 or 2/wk	2 yrs	2 yrs	54 Improved
Mac Onuigbo 1992 [76]	Nigeria	39	PG 100 or 200 mg	2 - 12 mths	2 - 12 mths	All improved (10 cured)
Manenti 1994 [79]	Tanzania	312	PMT 25 mg/wk	1 mths	3 mths	208 improved 104 unchanged
A Elgayoum 2011 [18]	Sudan	54	Single short term treatment (various regimens)	1 d to 1 wk (often repeated)	15 –24 mths	36 improved 12 worsened 6 unchanged
Alkadarow, 2013 [69]	Sudan	33	CLQ 300 mg/wk	3 mths	3 mths	14/21 improved (12 lost)

(*CLQ* = chloroquine; *PG* = proguanil; *PQ* = primaquine; *PMT* = pyrimethamine; *NR* = not reported).

Leoni S, et al. The hyper-reactive malaria splenomgaly: a systemic review of the literature. Malar J 2016;15:278.

Key messages from original *MMWR* article (Goers *et al*., 2016)

- Potential etiologies:
  - 26.9% positive for malaria (RDT or thick smear)
  - 2.1% positive for *Schistosoma mansoni* ova (by stool)
  - 0.7% positive for previous *Leishmania* exposure (by serology)
  - 3.5% positive for HepBsAg.
- Recommendations
  - Pre-departure ACTs
  - Further laboratory and radiology testing after relocation
  - Empiric treatment with primaquine

Ongoing Issues/Analysis

--Many reports of cases not resolving, a few worsening

--Reports of complications (e.g. traumatic splenic rupture, surgical splenectomy

--Non-falciparum malaria reports (particularly *P malaraie*)

--Continued new cases, including from Tanzania

Investigation Timeline

Allison *et al.* (2017)

Sept 2016: MMWR published on initial cases (Goers *et al.*)

Epi-Aid 2018-014 initiated

OVERSEAS EXAM March – July

U.S. RESETTLEMENT June 2015 – Jan 2017

CLINICIAN REPORTS Oct 2016 – Present

2015 | 2016 | 2017

Goers, et al. (2016). Splenomegaly of Unknown Etiology in Congolese Refugees Applying for Resettlement to the United States – Uganda, 2015

Ongoing analytic projects

- MMWR
  - Follow-up to original MMWR, describe clinical characteristics and explore other potential etiologies:
    - Clinical progression associated with splenomegaly cases (and controls)
      - matched on age, sex, time of arrival, refugee camp, country of origin, and state of resettlement

*D*escriptive analysis

Clinical course of disease

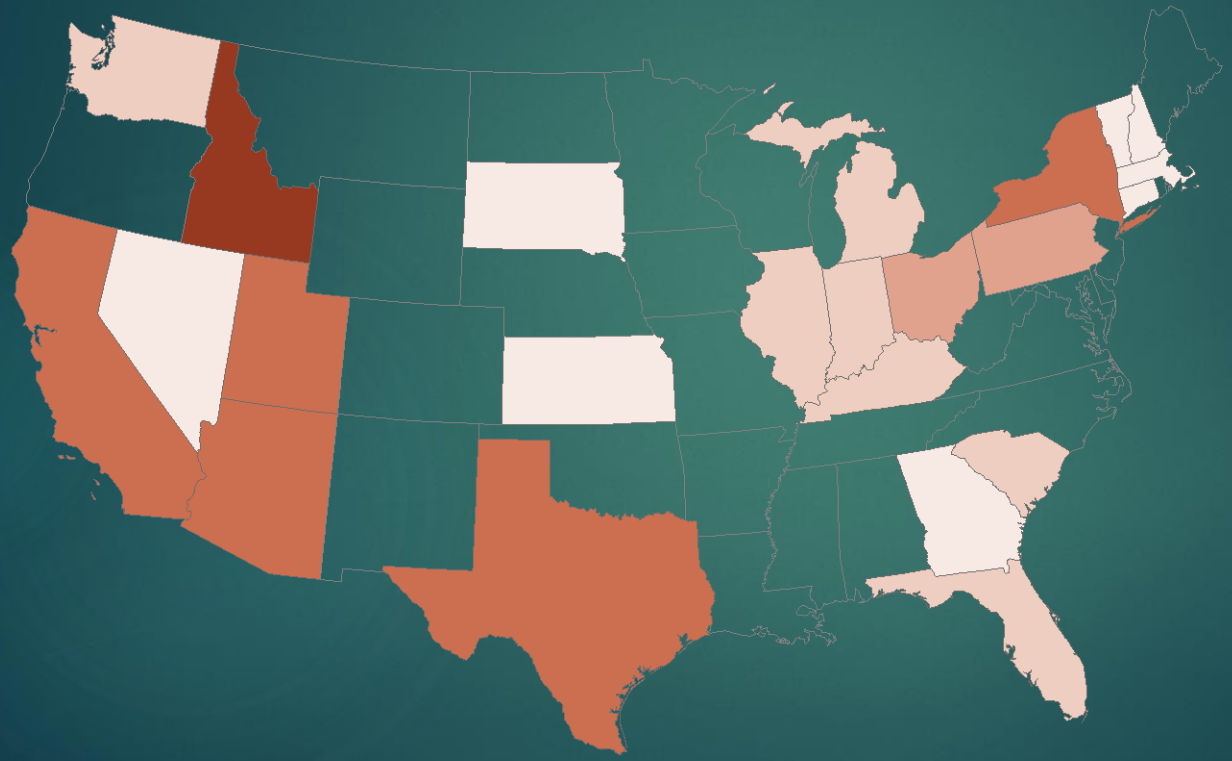
Objectives

- Describe any diagnostic tests and alternative etiologies
- Characterize clinical progress
- Provide ongoing recommendations based on findings

Methods

- Engage state/local health departments, initial screening clinics, and refugee health providers
- Perform medical chart abstractions from initial screening, primary care, and referral care visits
- Calculate descriptive

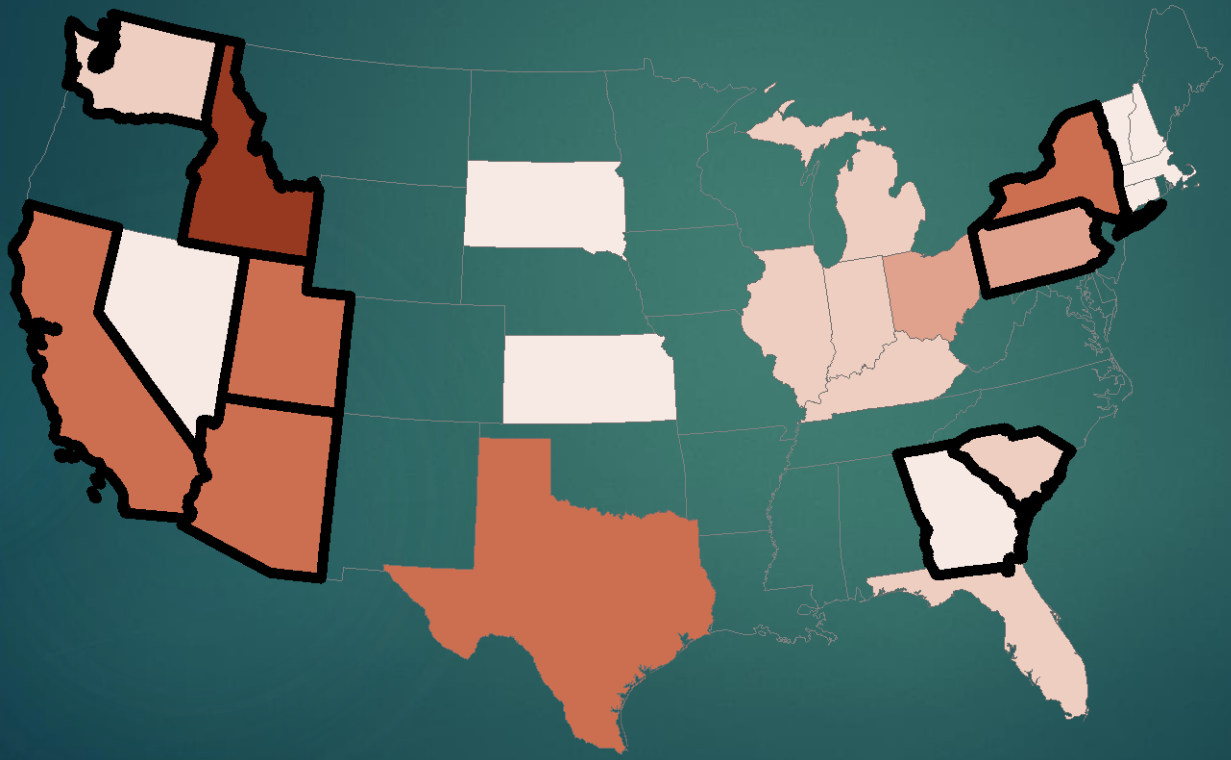
Participating States



Original MMWR

- **145 cases, 23 states**

Participating States



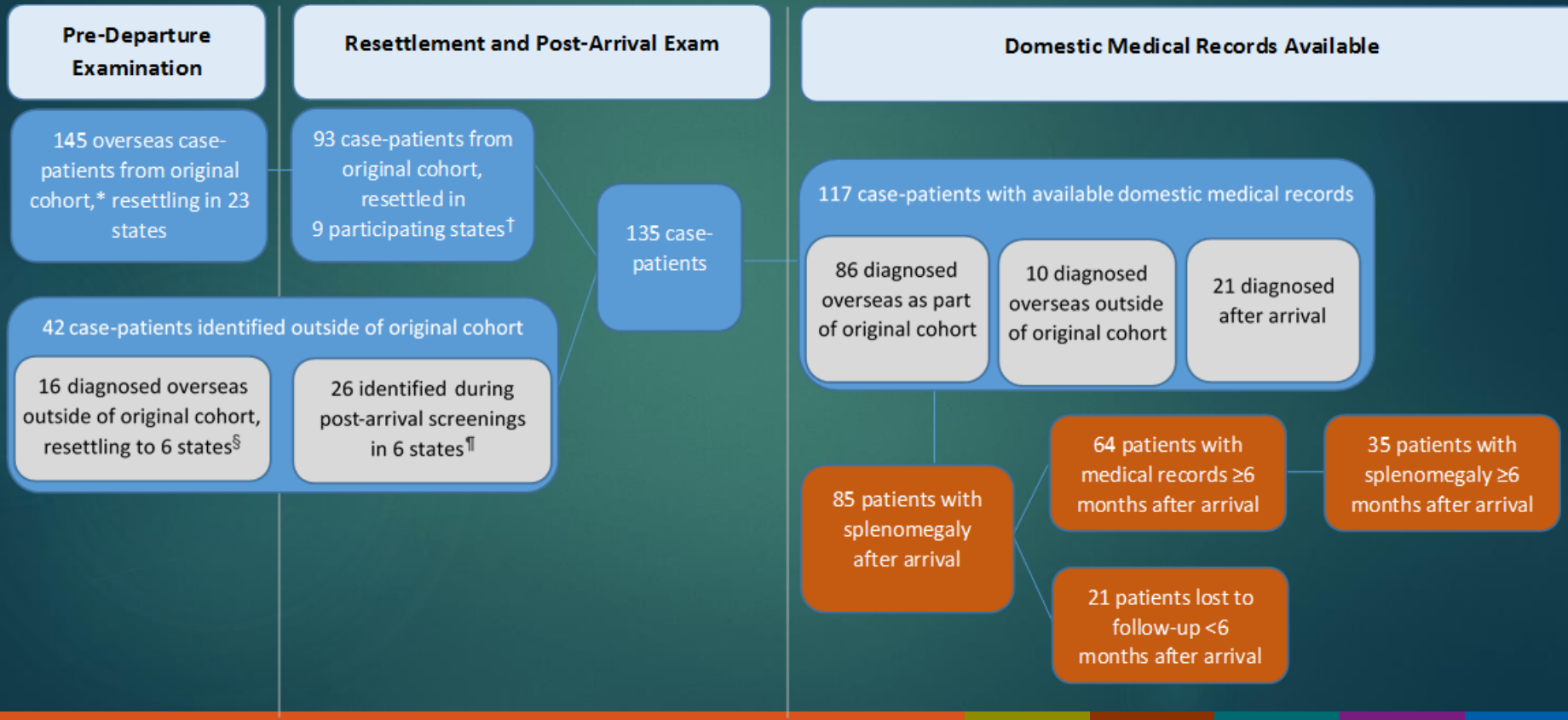
Original MMWR

- **145 cases, 23 states**

Current Epi-Aid

- **93 cases, 9 states**

Flow algorithm of patient inclusion in follow-up investigation



Persistence

- 85 patients had splenomegaly at initial examination
- 64 patients had follow-up data beyond 6 months after arrival
- Median duration: 9.0 months (range: 0.3 – 27.9 months)
- 35 (54.7%) out of 64 patients had persistent splenomegaly

Familial clustering

- Ninety patients (66.7%) clustered in 22 families
- In New York State, clinicians identified six cases by proactively screening family members of known cases
  - Cases were detected by ultrasound, not by abdominal palpation

Treatment regimens

- All patients were treated with praziquantel (for schistosomiasis) and one dose of artemethur-lumefantrine before departure
- Only 26.5% of patients received primaquine after arrival as recommended
  - No one had documented completion of the 14-day regimen
- Among patients who received primaquine, there was still some evidence of persistent splenomegaly

Pre-departure malaria PCR studies

PCR-positive	No. of positive specimens (n=144)	Percent
P. falciparum	83	58%
P. malariae	29	20%
P. ovale	12	8%
P. vivax	2	1%
Mixed infection	35	24% (21% for P fal/mal)
Any malaria detected	**92**	**64%**

Overall PCR in Hoima (different time)
--P. fal ~15% (vs 64%)
--P mal ~2% (vs 20%)

Limitations

- Irregular clinic visit intervals and loss to follow-up likely resulted in underestimates of splenomegaly duration
- Multiple data collectors across several states could have yielded some inconsistencies
- Standard of care (including diagnostic and prognostic tests) differs between clinics. This analysis used all available data.

Cohort study

Methods

- Controls of Congolese origin are matched to splenomegaly cases by:
  - Age (+/- 5 years)
  - Sex
  - Date of arrival (+/- 12 months)
  - State
  - Refugee camp
- Chart abstractions performed as before
- **Cohort** study because we knew that information on exposures would be inconsistent – easier to collect information on clinical manifestations to justify a subsequent case-control investigation.

Status

- Nearing completion of data collection
- Data collection has been completed in Arizona, California, Georgia, New York, Pennsylvania, South Carolina, Utah, and Washington
- Ongoing in Idaho, but should be complete in the next week or two
- Analyses are forthcoming

Future projects/questions

- Analyze cohort study (upon data collection completion)
- Case-control study to help identify etiology (perhaps in refugee settlement)?
- Epidemiology studies in refugee camps/settlements

Take-home points

- Come back from your happy place

Take-home points

- Splenomegaly etiology is still uncertain, malaria playing a role but it might be multi-factoral
- Persistence beyond 6 months was common, despite literature
- Health providers should proactively screen family members of known cases

Take-home points

- Health providers should provide primaquine after arrival (if G6PD levels are normal)
- Aware that there is break-through malaria
- Testing for other etiologies may be important (e.g. infections (schistosomiasis), non-infectious)

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It is time for parents
to teach young people
early on that in diversity
there is beauty and
there is strength

Maya Angelou

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