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Faculté de biologie et de médecine

Policlinique Médicale Universitaire CH-Lausanne

Epidemiology of febrile illnesses – beyond malaria

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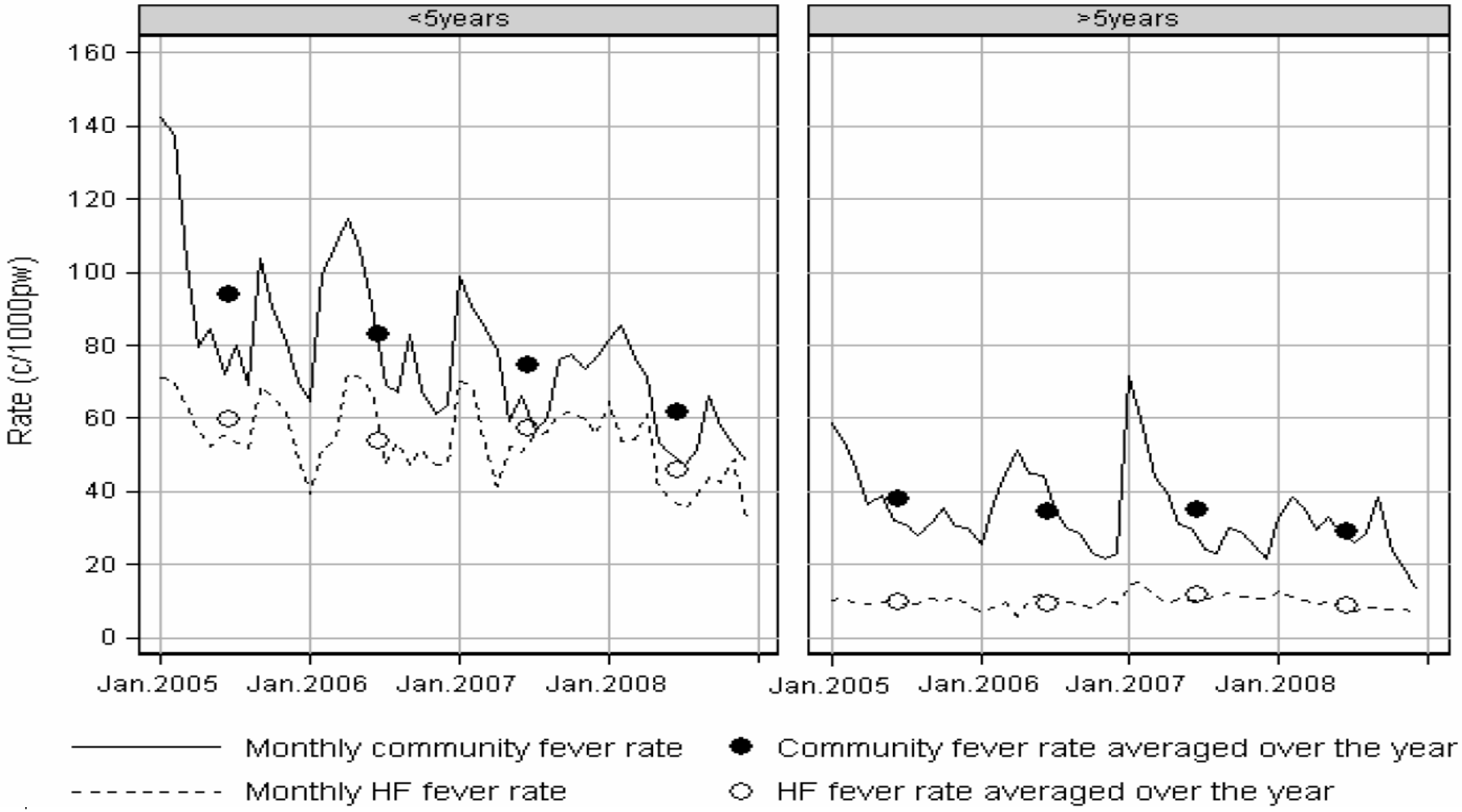
The size of the problem: Typical incidence of febrile episodes in Africa

	Children	Adults
At community level	4.9 → 3.2	2.0 → 1.5 episodes/person/year

2/3 ↓

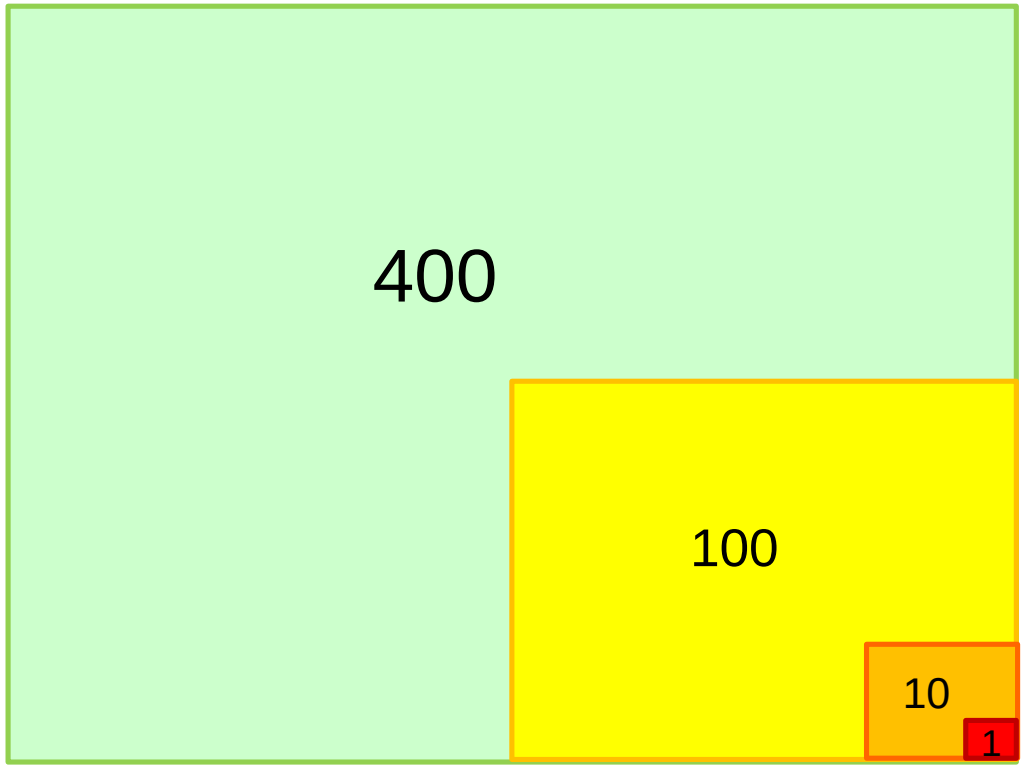


↓ 1/4

Sandra Alba, Int J Epid 2011

The size of the problem: Typical incidence of febrile episodes in Africa

Number of patients



Level of care

Community

Primary care

Hospital

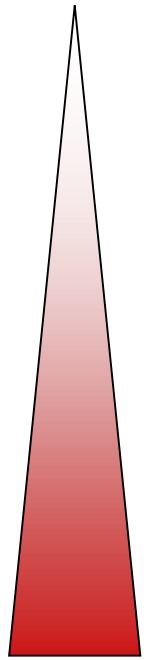
OPD

Ward

2/3 Moderate

1/3 Severe

Type of infection



Mild

Localized

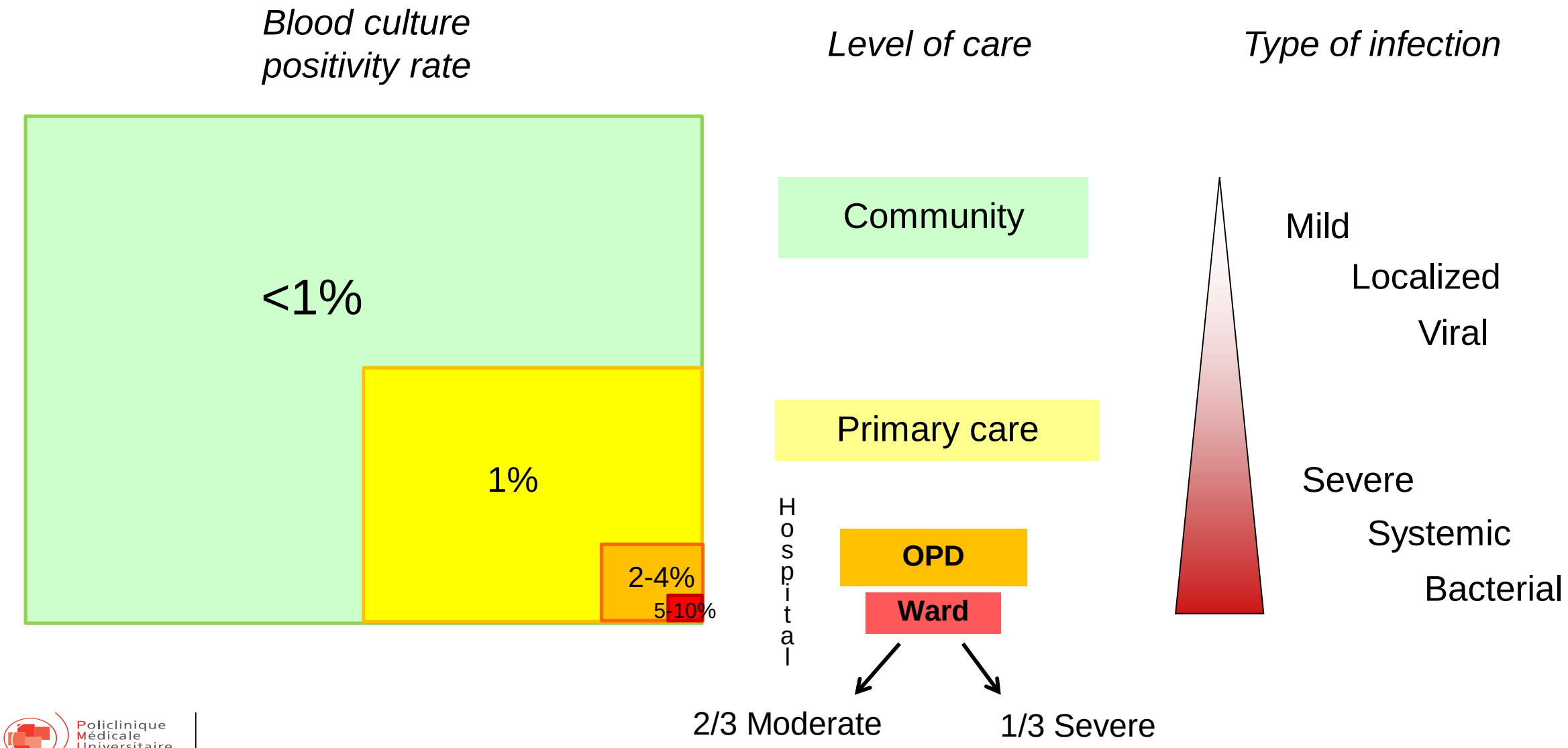
Viral

Severe

Systemic

Bacterial

The size of the problem: Typical incidence of febrile episodes in Africa



Challenges for summarizing and comparing etiology of fever studies

- Age profile
- Inclusion criteria (all fevers versus undifferentiated fever)
- Seasonality and year to year variation
- One disease – one syndrome vs all fevers
- Patient population: characteristics and level of health care
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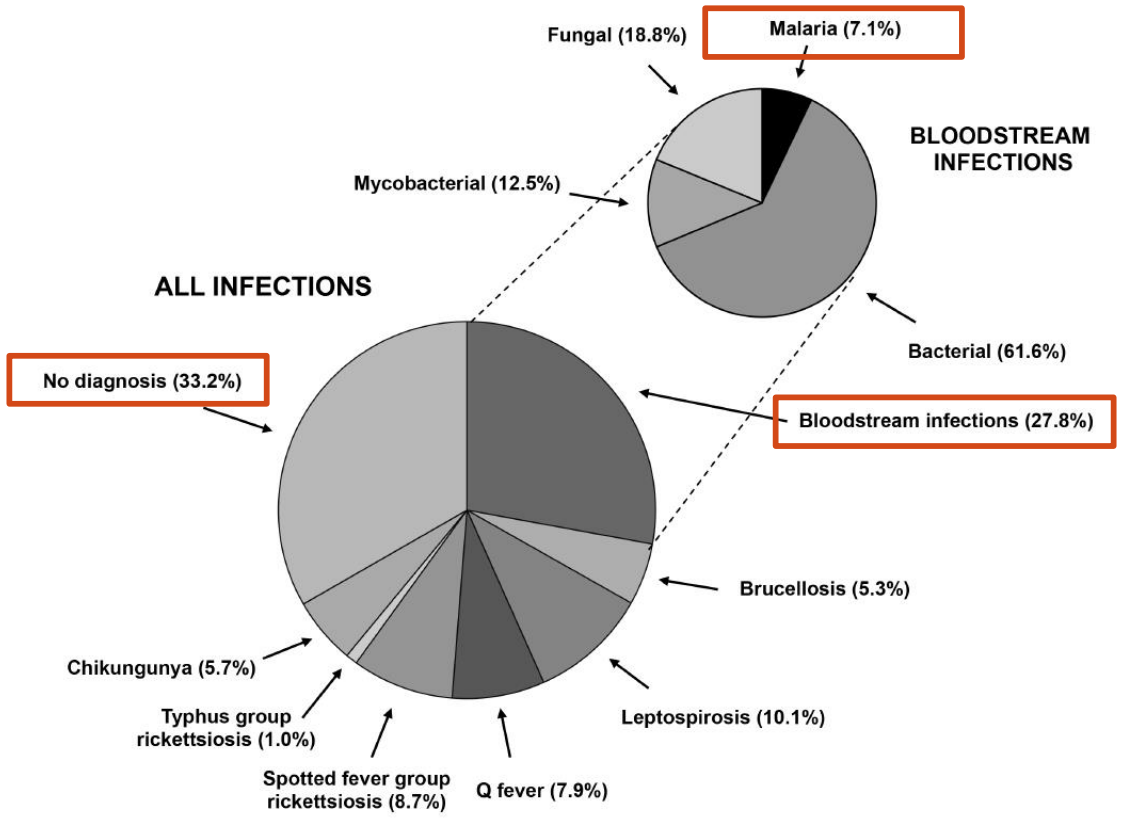
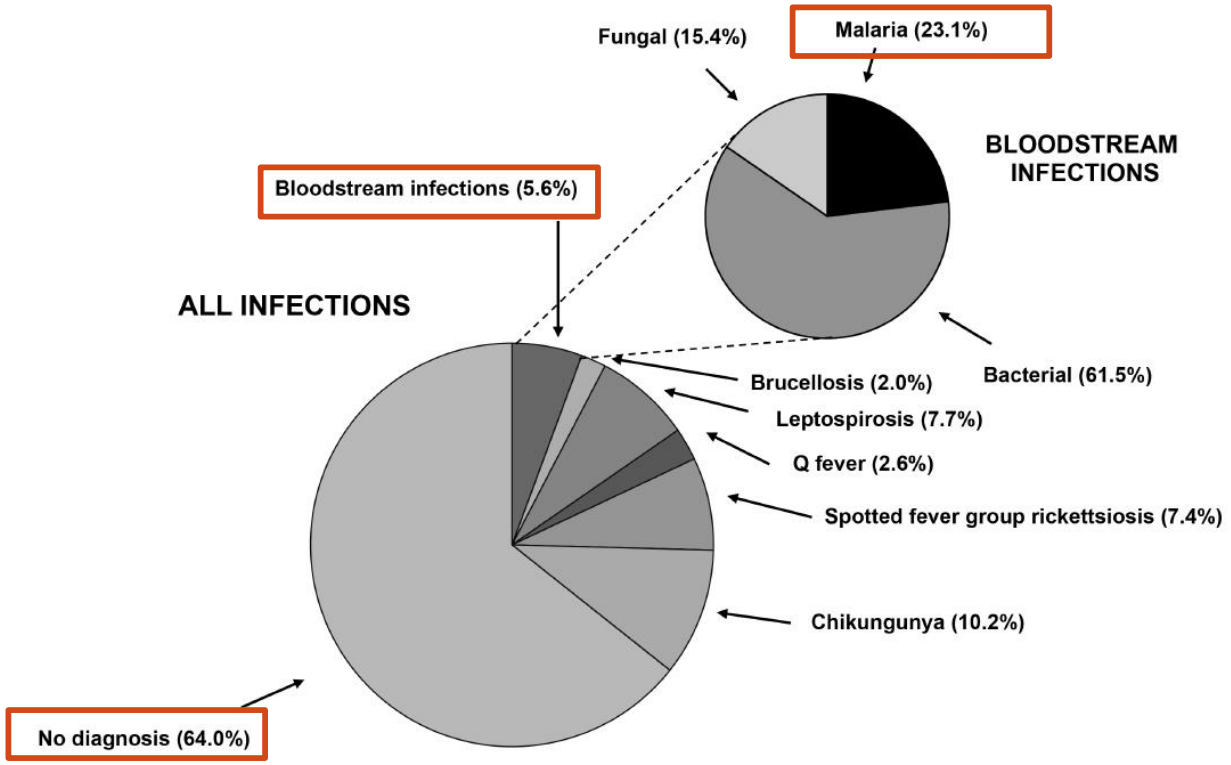
Fever etiology according to age (Northern Tanzania)

Adolescents and adults

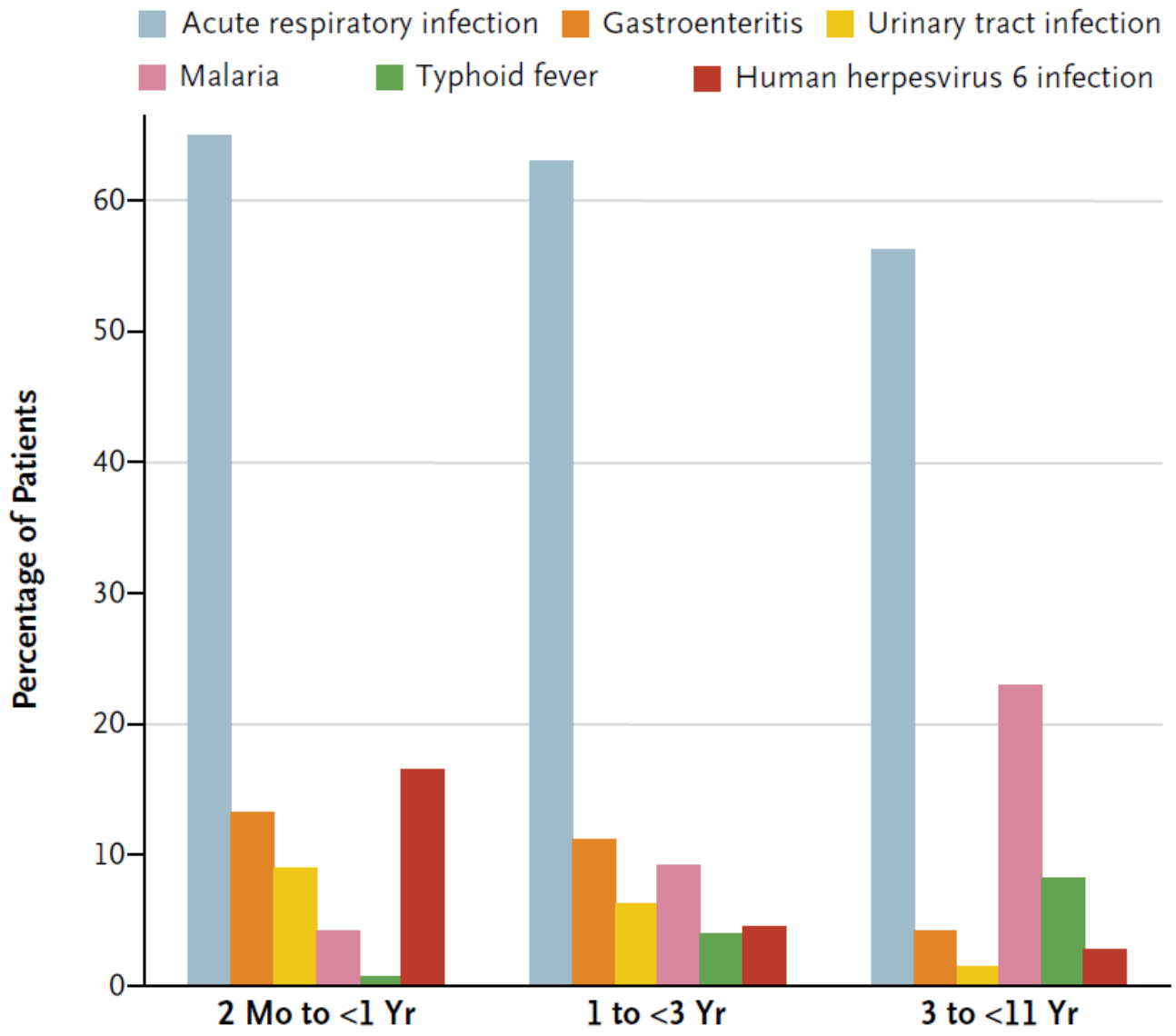


Infants and children



Crump et al, Plos Neg Trop Dis 2013

Fever etiology according to age (Kilombero, Dar es Salaam)



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D'Acremont et al, New Engl J Med 2014

Blood stream infections by PCR according to age (Kilombero)

PLOS ONE | A diagnostic and epidemiologic investigation of acute febrile illness (AFI) in Kilombero, Tanzania

Table 3. Detections of viral, bacterial and parasitic agents by acute febrile illness (AFI) and respiratory TAC.

Agent Detected	Younger Children (1<5yrs)	Older Children (5<14yrs)	Adults (≥15yrs)	All ages
	n (%)	n (%)	n (%)	n (%)
Blood Stream Agents	**N = 58**	**N = 156**	**N = 628**	**N = 842**
Plasmodium	7 (12)	53 (34)	339 (54)	399 (47)
Leptospira	0 (0)	2 (1)	20 (3)	22 (3)
Bartonella	0 (0)	0 (0)	4 (1)	4 (1)
Salmonella non-Typhi	0 (0)	2 (1)	2 (1)	4 (1)
Coxiella burnetii	0 (0)	0 (0)	2 (1)	2 (1)
Rickettsia	0 (0)	0 (0)	2 (1)	2 (1)
West Nile virus	0 (0)	0 (0)	1 (1)	1 (1)
Total number of bloodstream detections	*7*	*57*	*370*	434

No Chikungunya, dengue, Crimean-Congo Hemorrhagic fever, Hepatitis E, Marburg, Rift Valley fever, Yellow fever

Hercik et al, Plos one 2017

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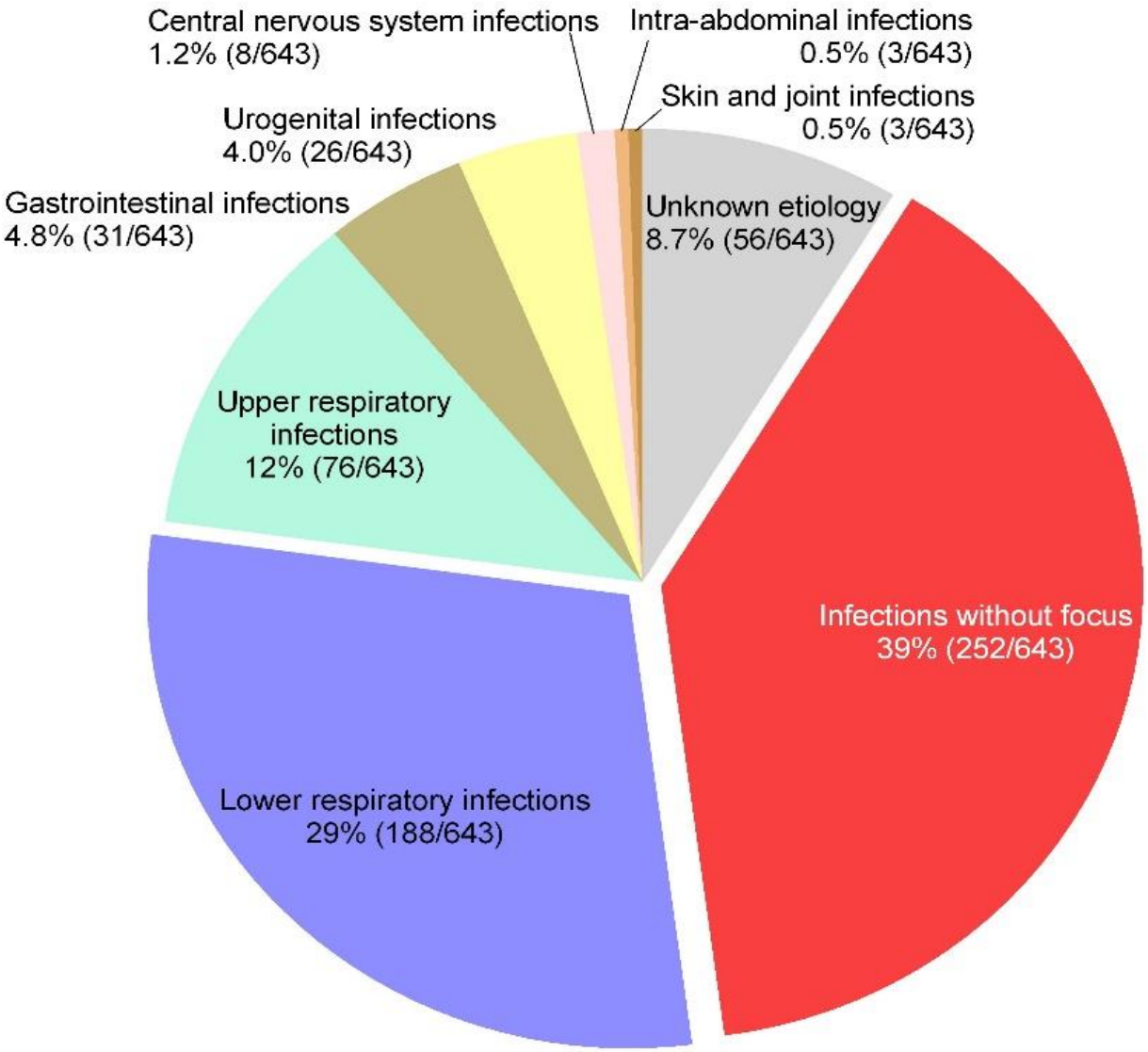
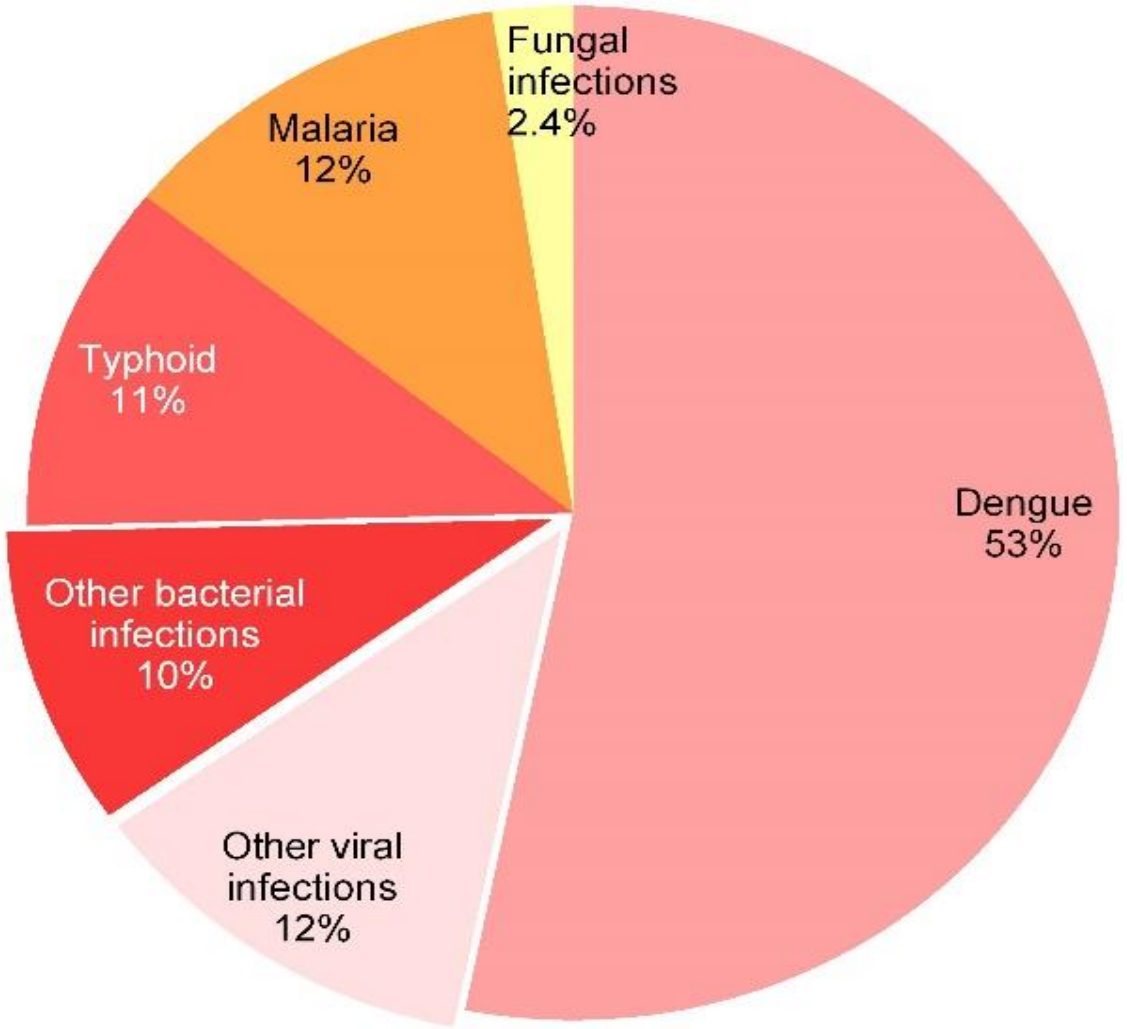
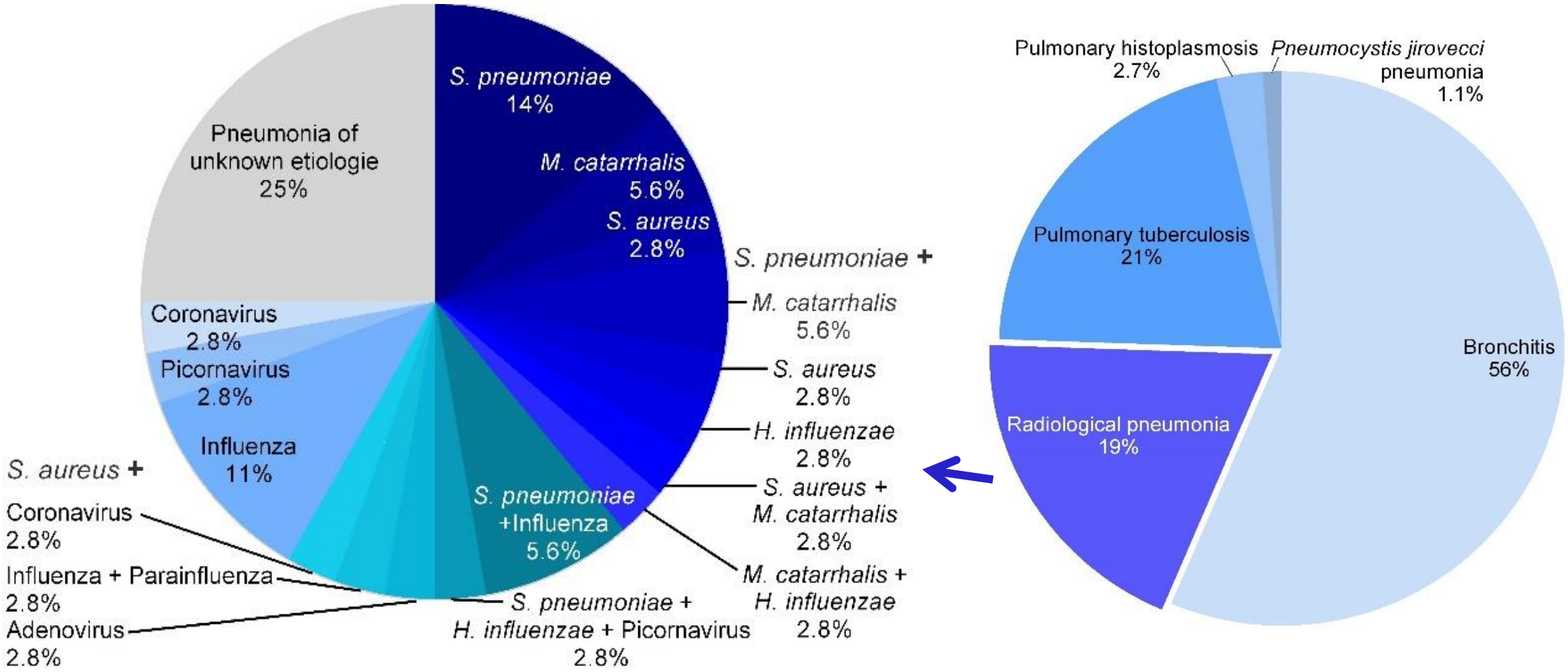
643 diagnoses identified in 519 adults in Dar es Salaam, Tanzania: all fevers versus Acute Undifferentiated fever





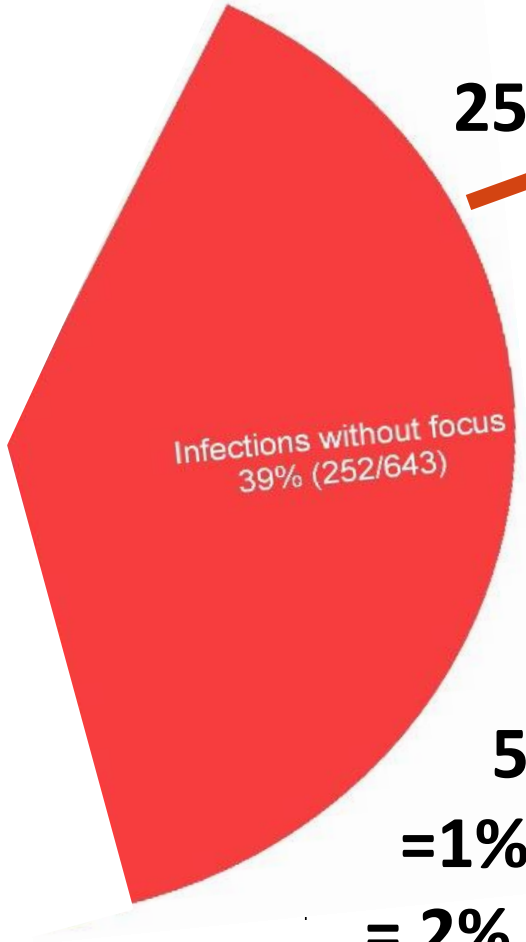
Boillat *et al*, in preparation

Lower respiratory tract infections in 188/643 (29%) diagnoses by PCR of NP swabs

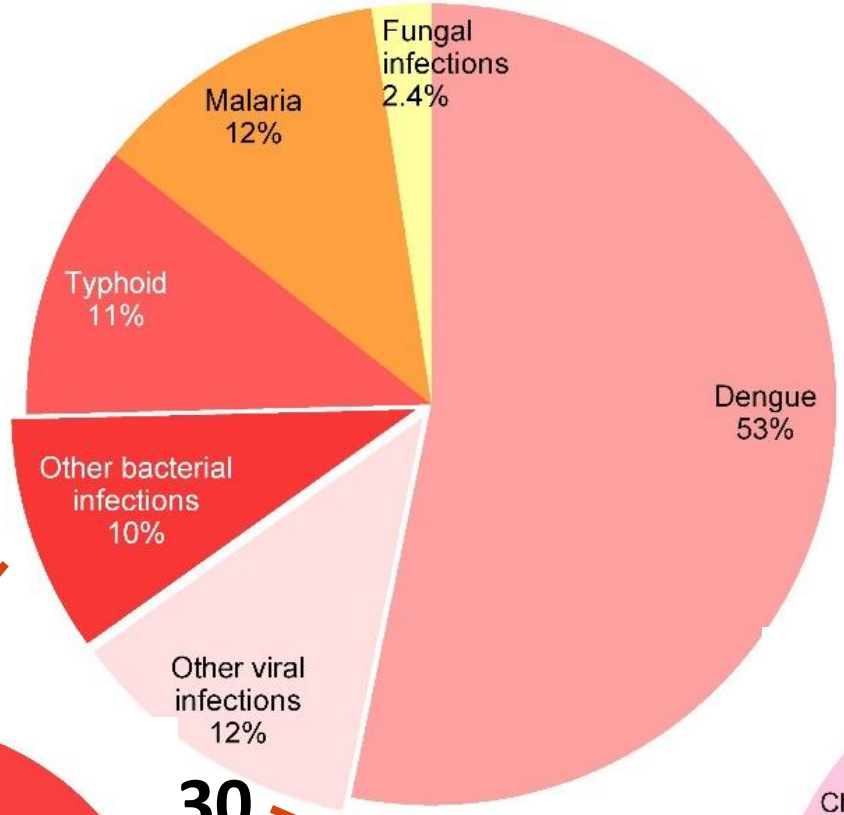


Boillat *et al*, in preparation

643 diagnoses identified in 519 adults in Dar es Salaam, Tanzania: all fevers versus AUF

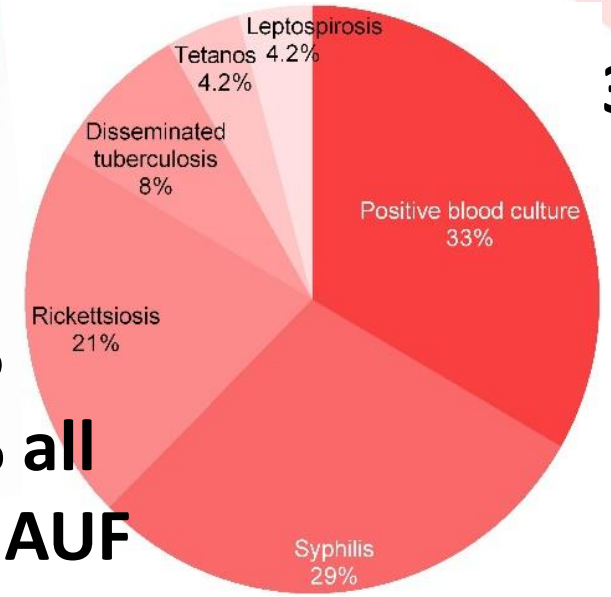


252



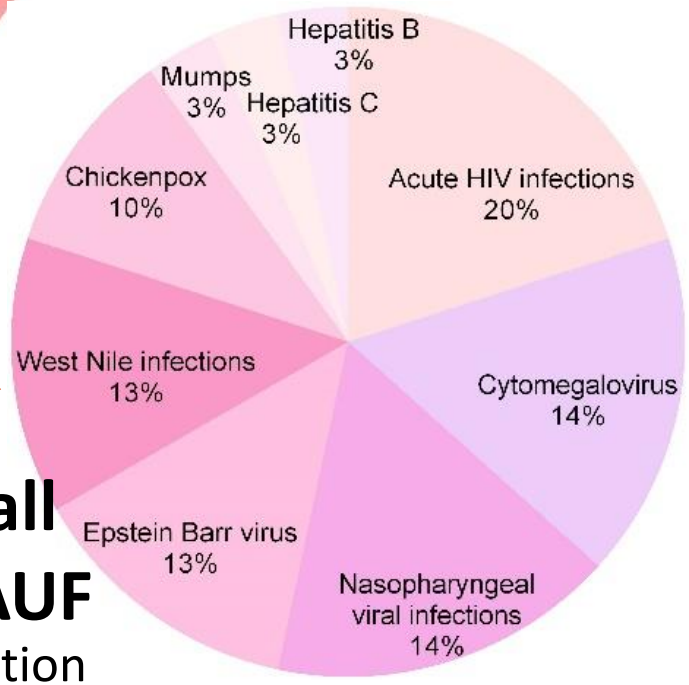
25

1



5
=1% all
= 2% AUF

30



4
=1% all
= 2% AUF

Boillat *et al*, in preparation

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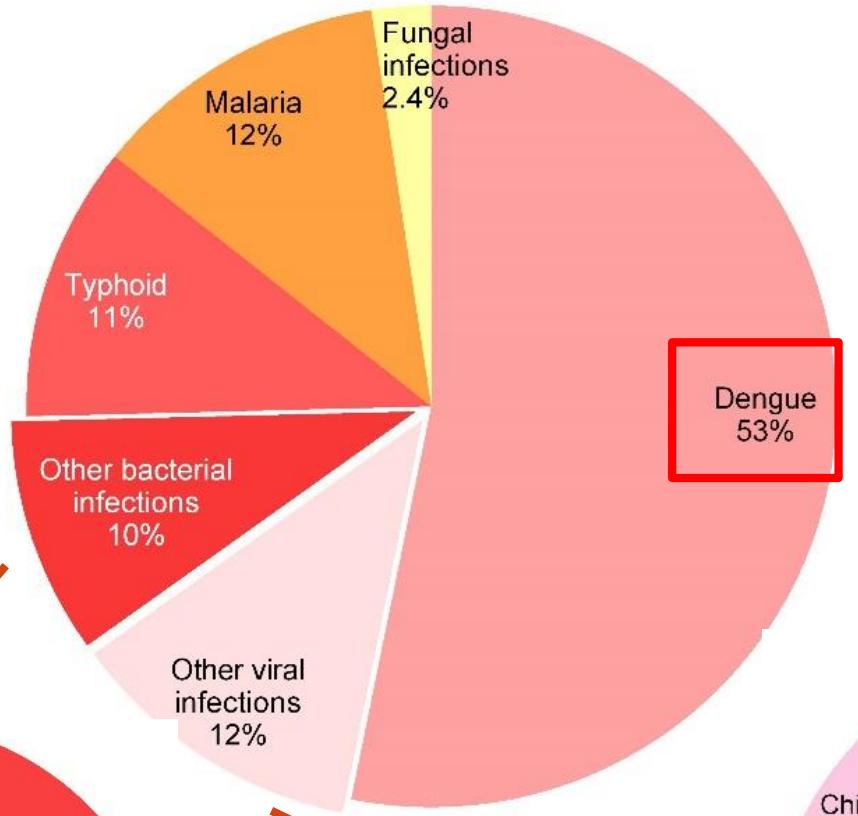
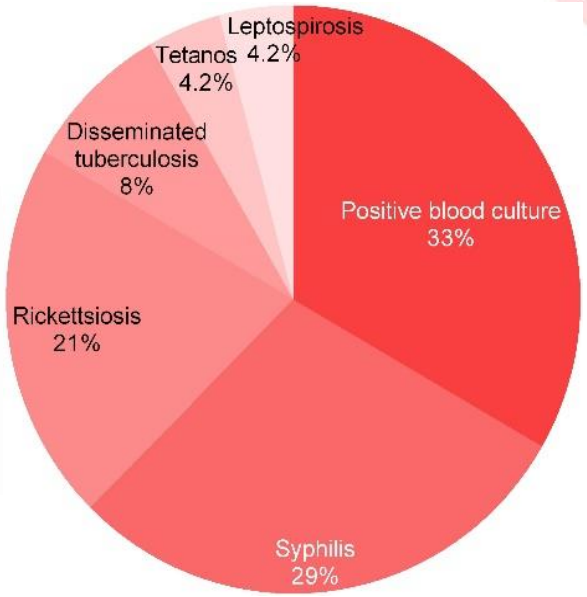
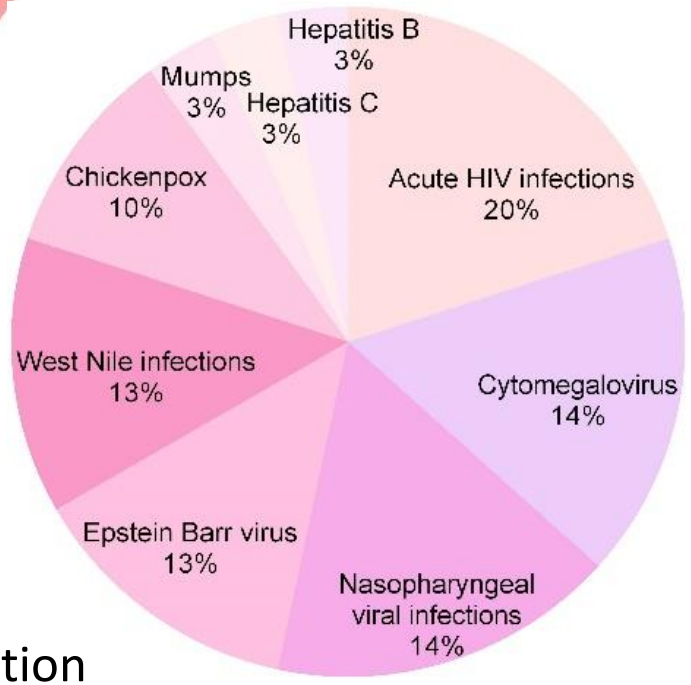
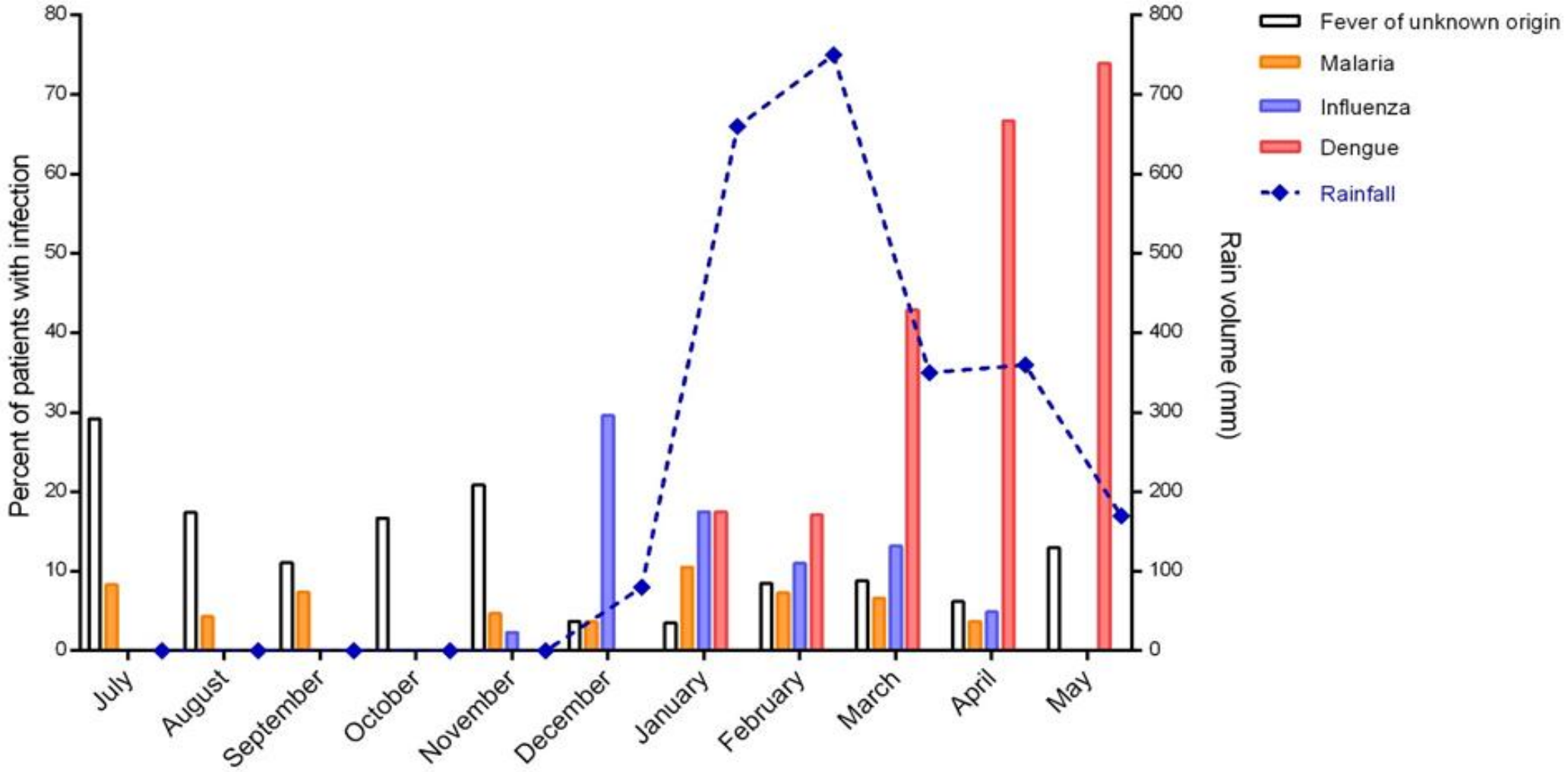






Boillat *et al*, in preparation

Influenza seasonality and Dengue epidemic in 519 adults in Dar es Salaam

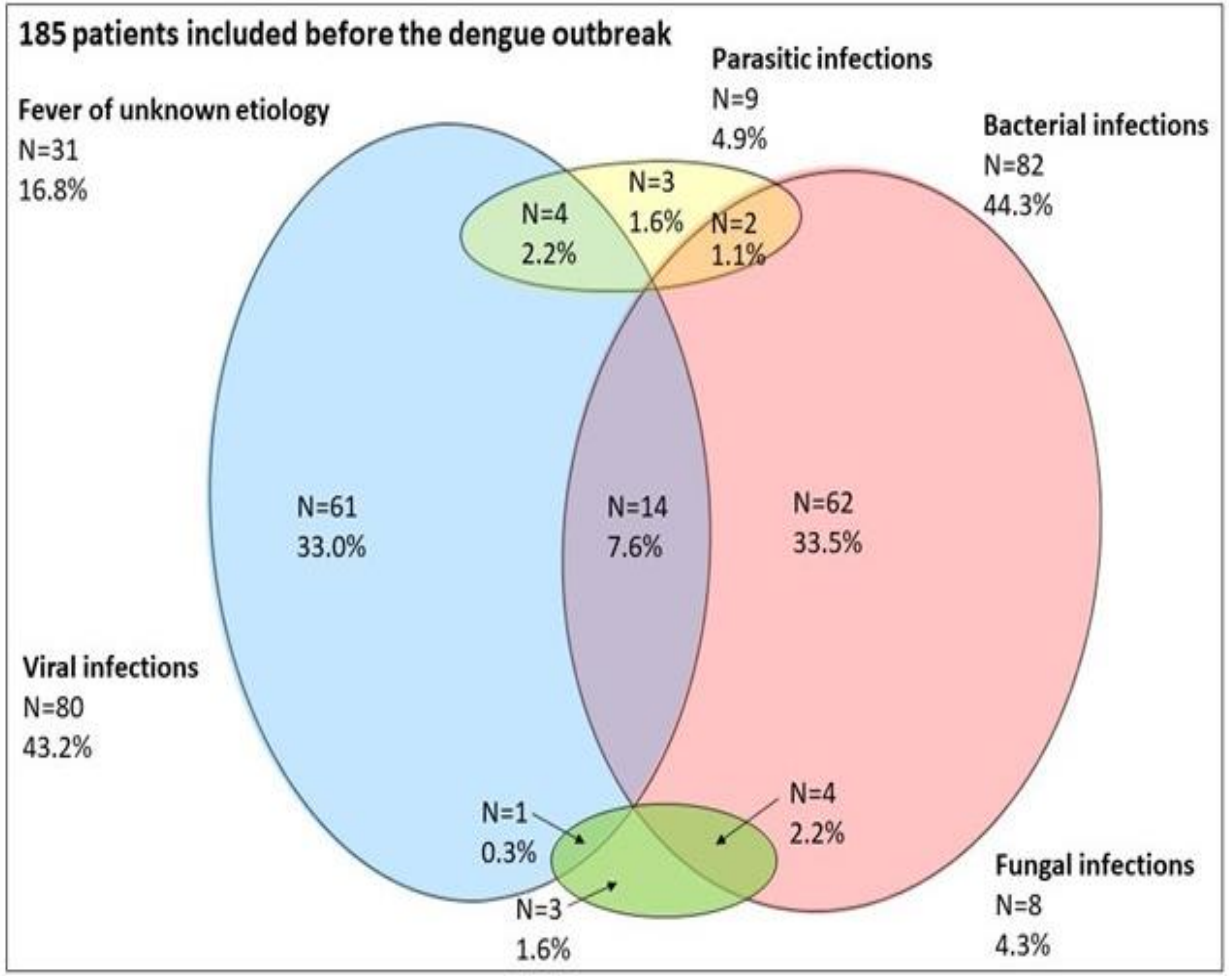


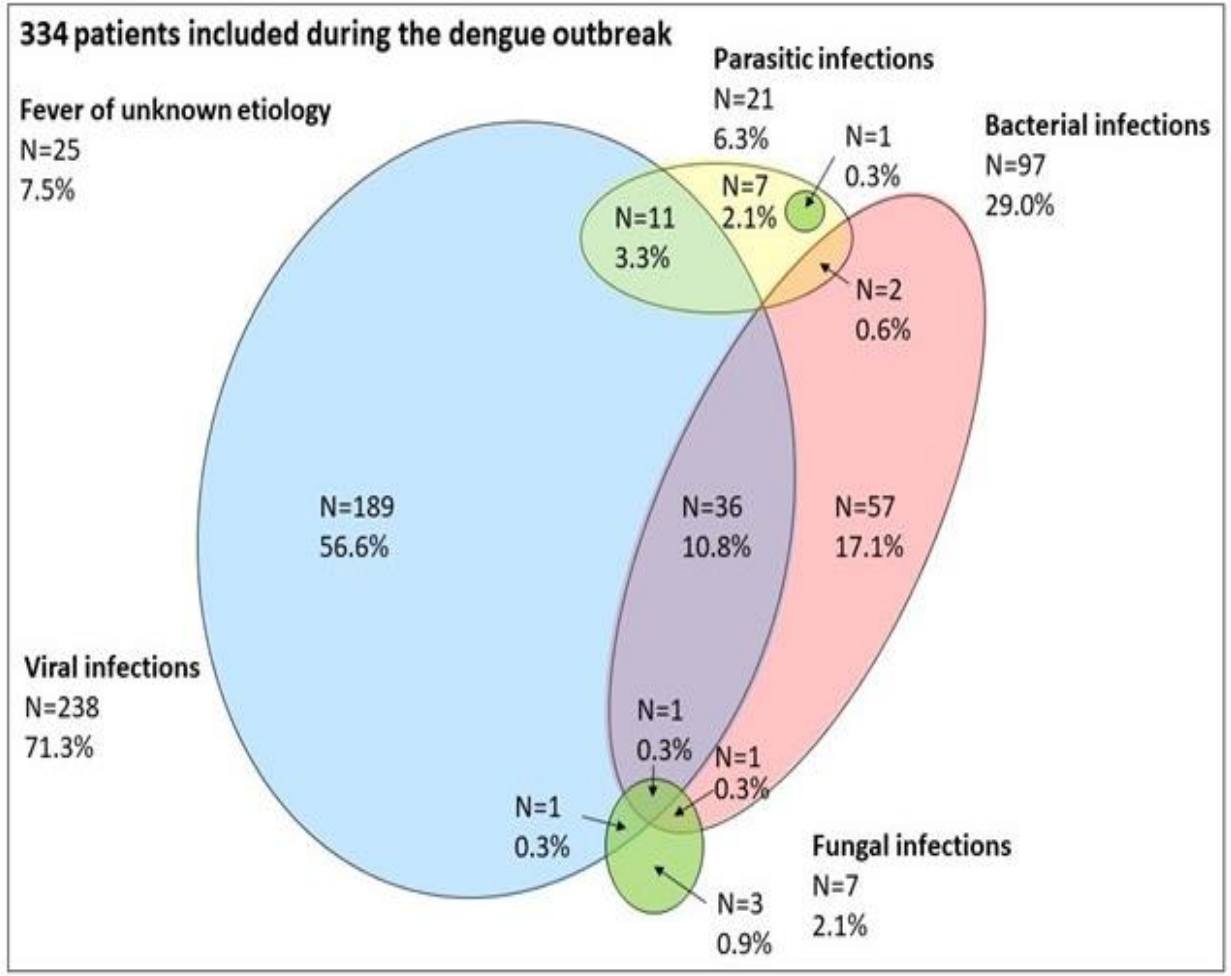
Number of patients with infection	24	46	27	18	43	27	57	82	91	81	23

Boillat *et al*, in preparation

Influence of a Dengue epidemic on fever etiologies in adults in DSM

185 patients before Dengue outbreak 334 patients during Dengue outbreak





Boillat *et al*, in preparation

Seasonality of etiologies of AUF in adults in Northern Thailand

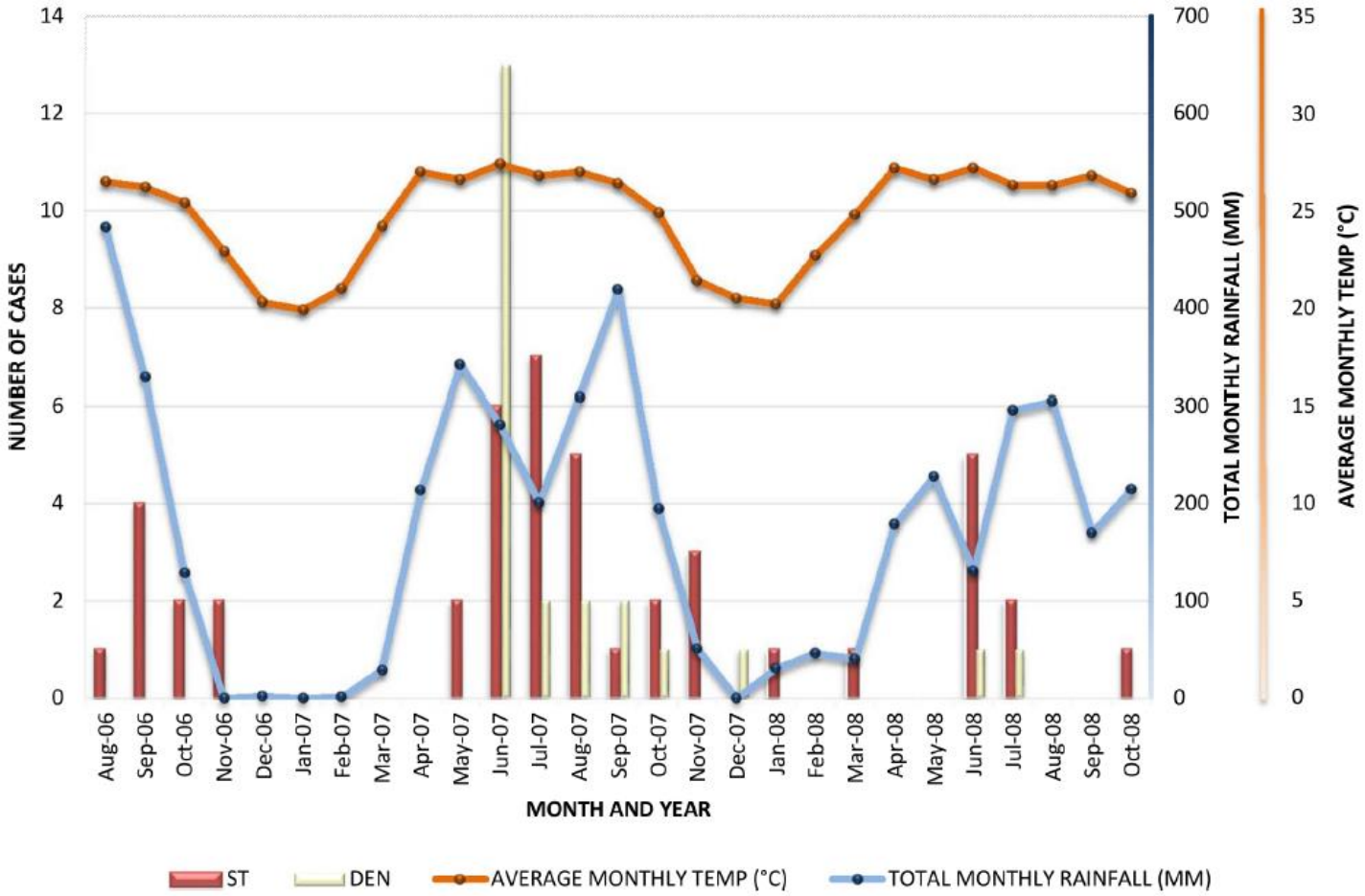
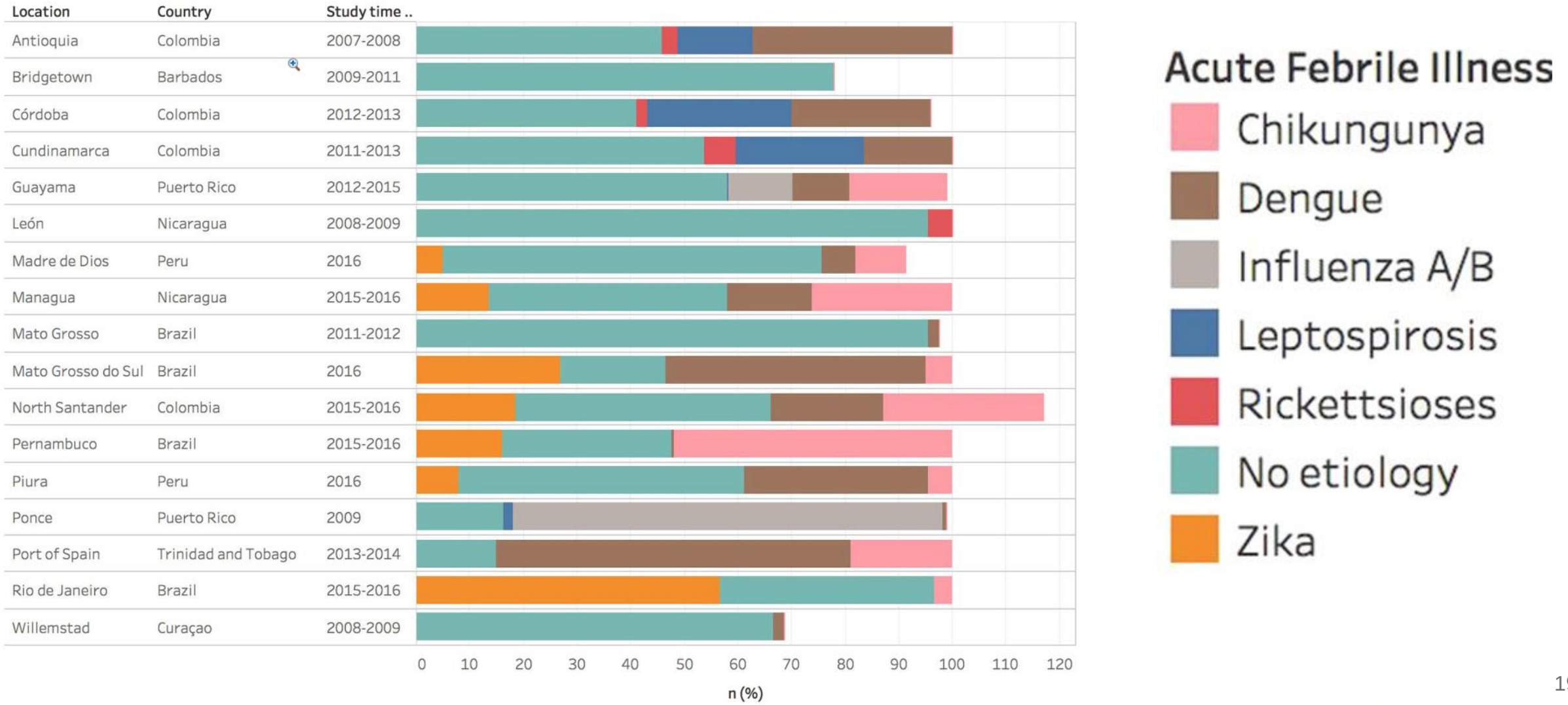


Fig 1. The temporal spread of scrub typhus and dengue cases and monthly meteorological data for Mueang district, Chiangrai province (Thai Meteorological Department, Chiangrai).

https://doi.org/10.1371/journal.pntd.0006477.g001

Wangrangsimaku et al, Plos Negl Trop Dis 2018

Year to year variation in etiology of acute febrile illness in Latin America



Moreira et al, Clin Microbiol Inf 2018

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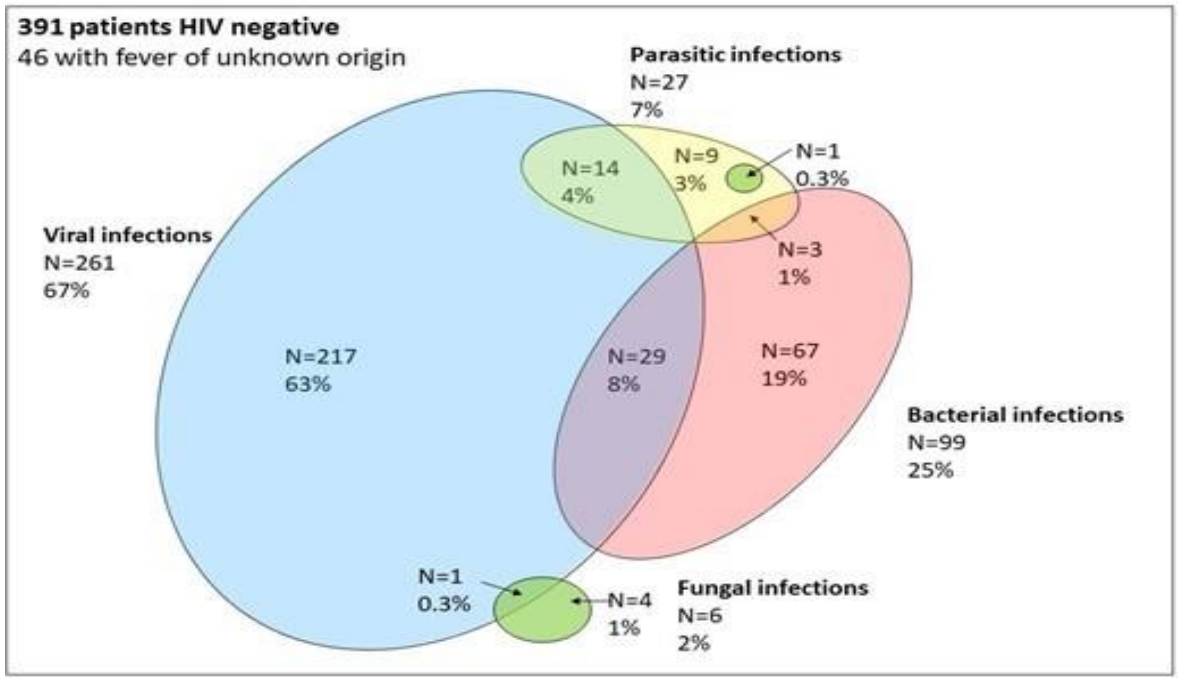
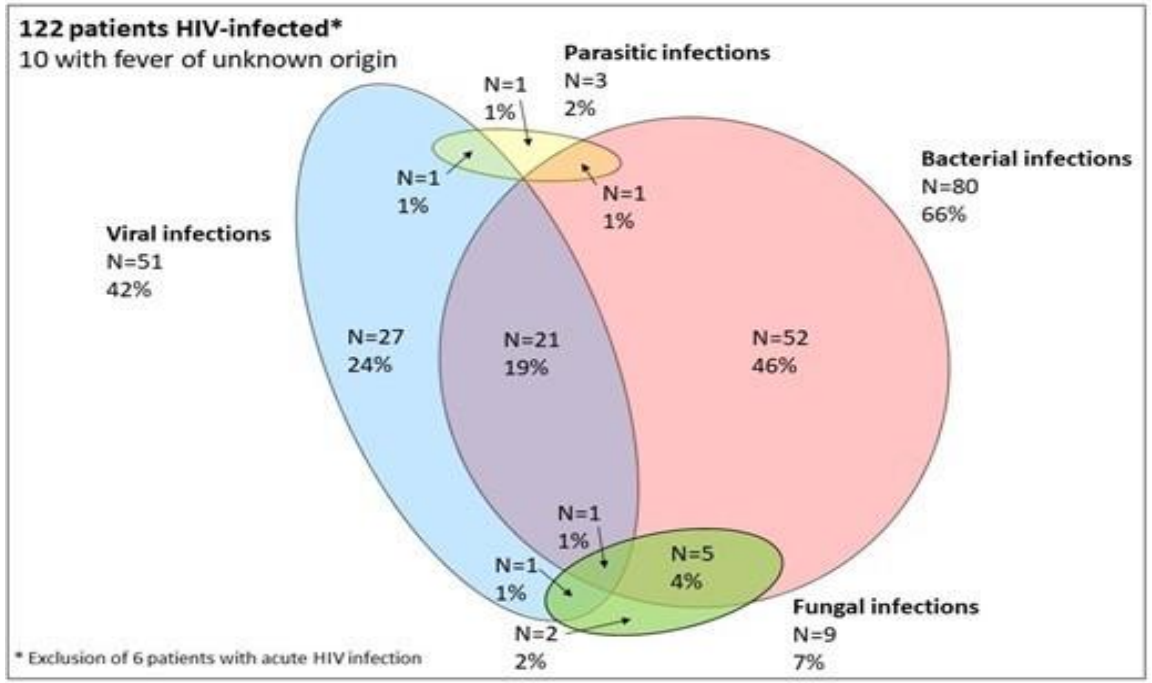
Patient characteristics: co-morbidity (HIV status)
519 adults in Dar es Salaam, Tanzania

27% bacterial in 391 HIV negatives

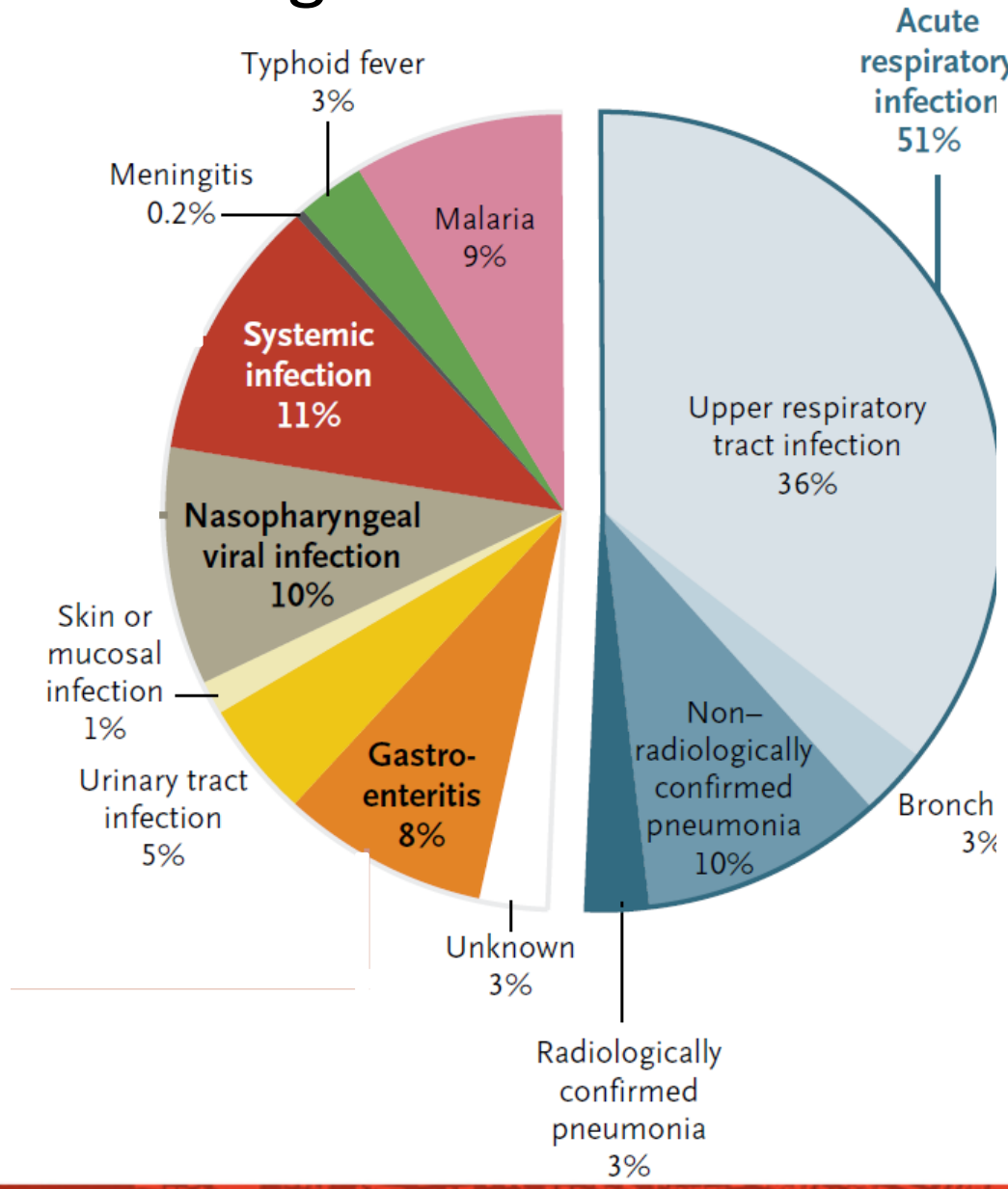


65% bacterial in 122 HIV positives

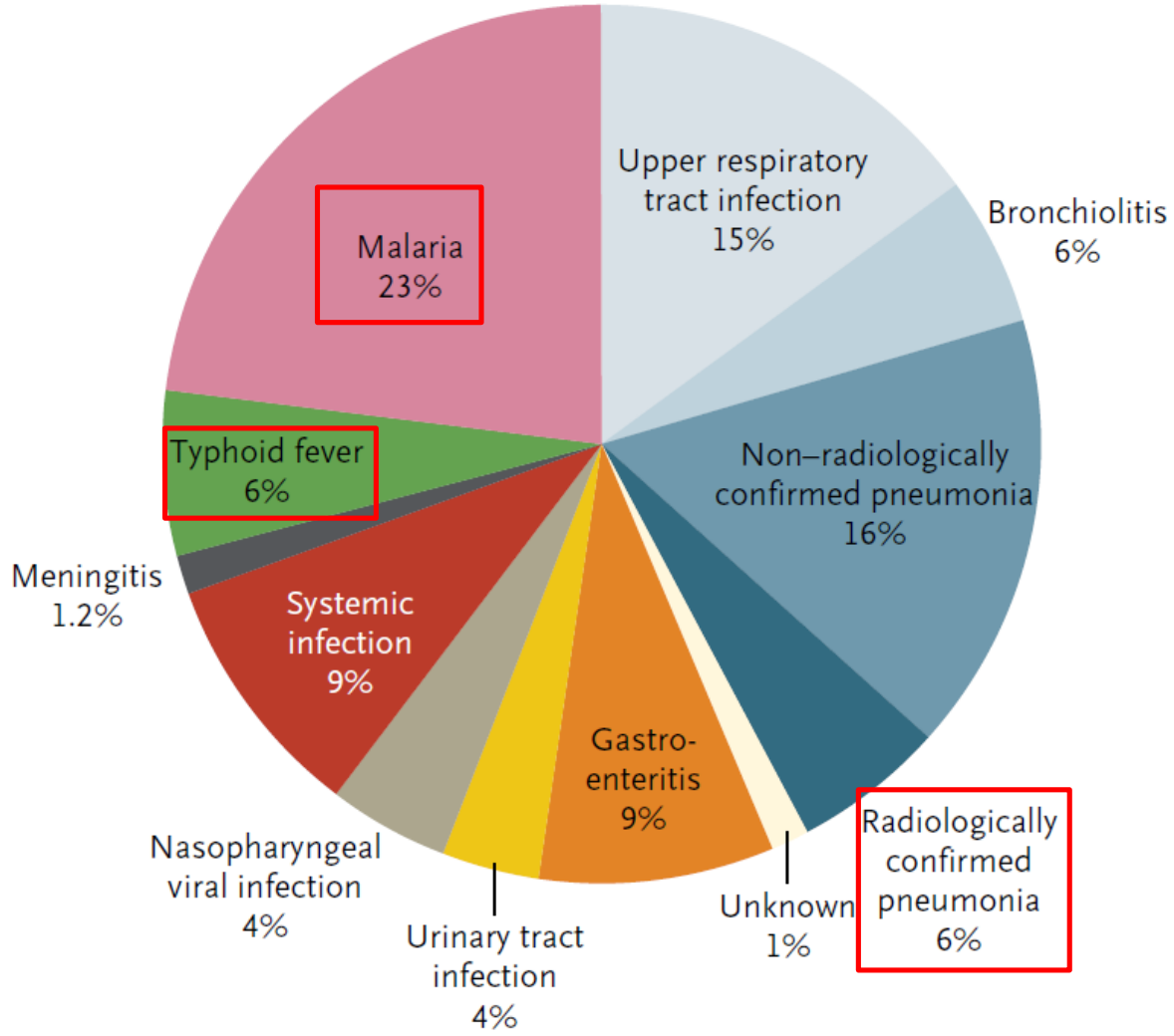


Boillat *et al*, in preparation

1232 diagnoses in all 1005 cases



160 diagnoses in 133 severe cases



D'Acremont et al, New Engl J Med 2014

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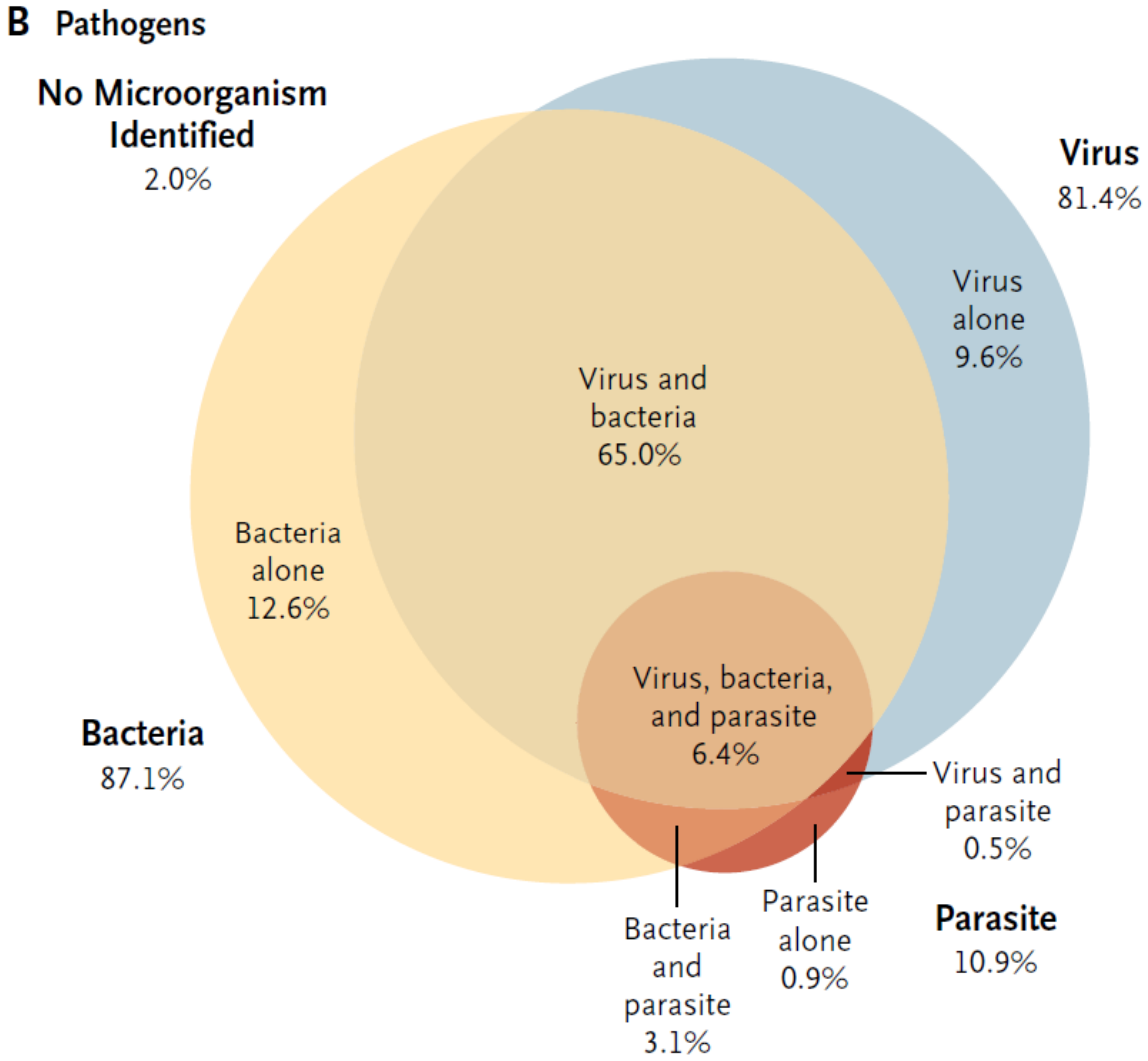
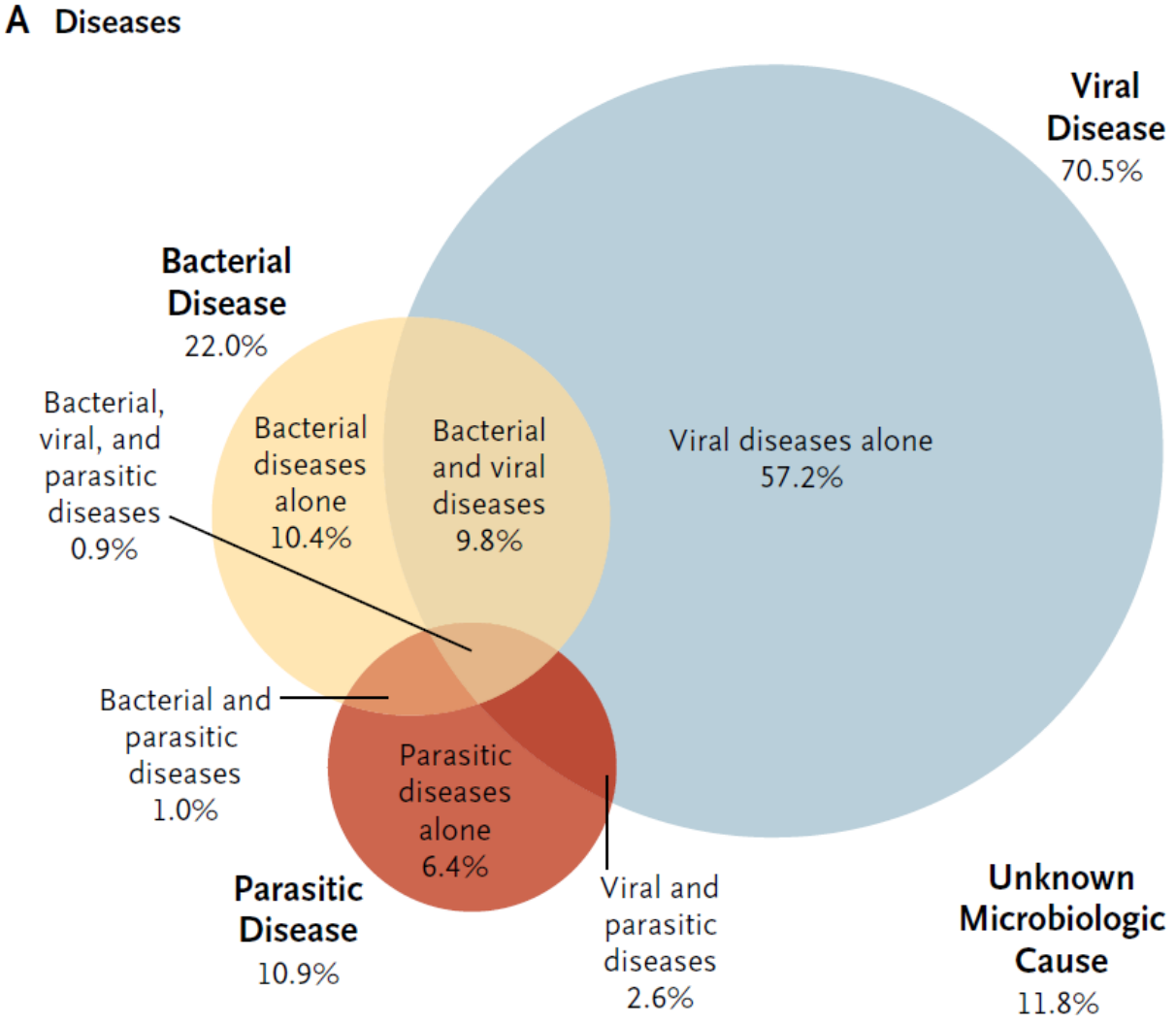
Botanical garden: microbiology

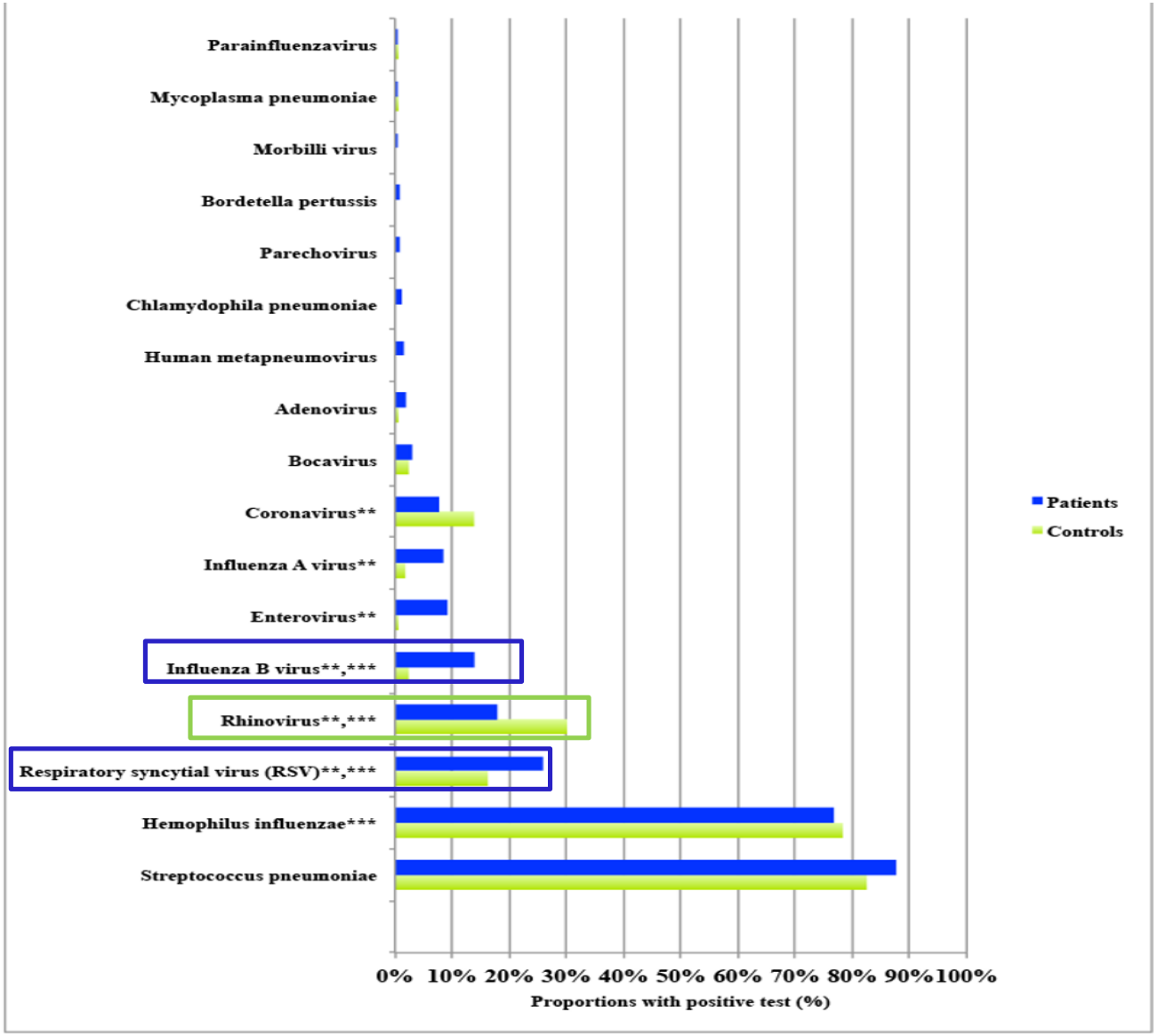
Diseases: clinical + microbiology



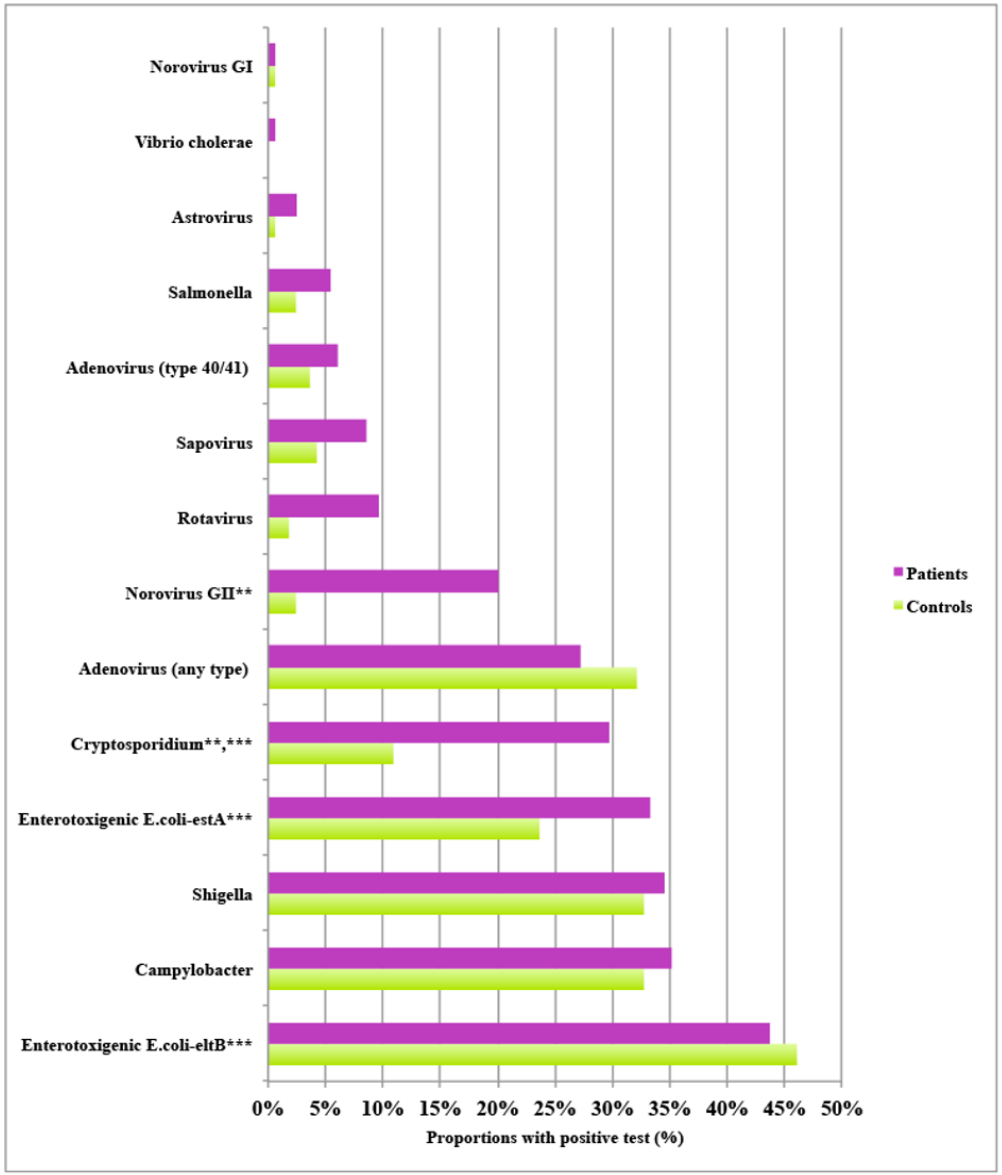


D'Acremont et al, New Engl J Med 2014

Pathogen attributable fraction (NP and rectal PCR swabs in ZNZ children)



. **p<0.05 by Fisher´s test (comparison of proportions)
***p<0.05 by Mann-Whitney U test (comparison of Ct-values)



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Elfving et al, Plos One 2016

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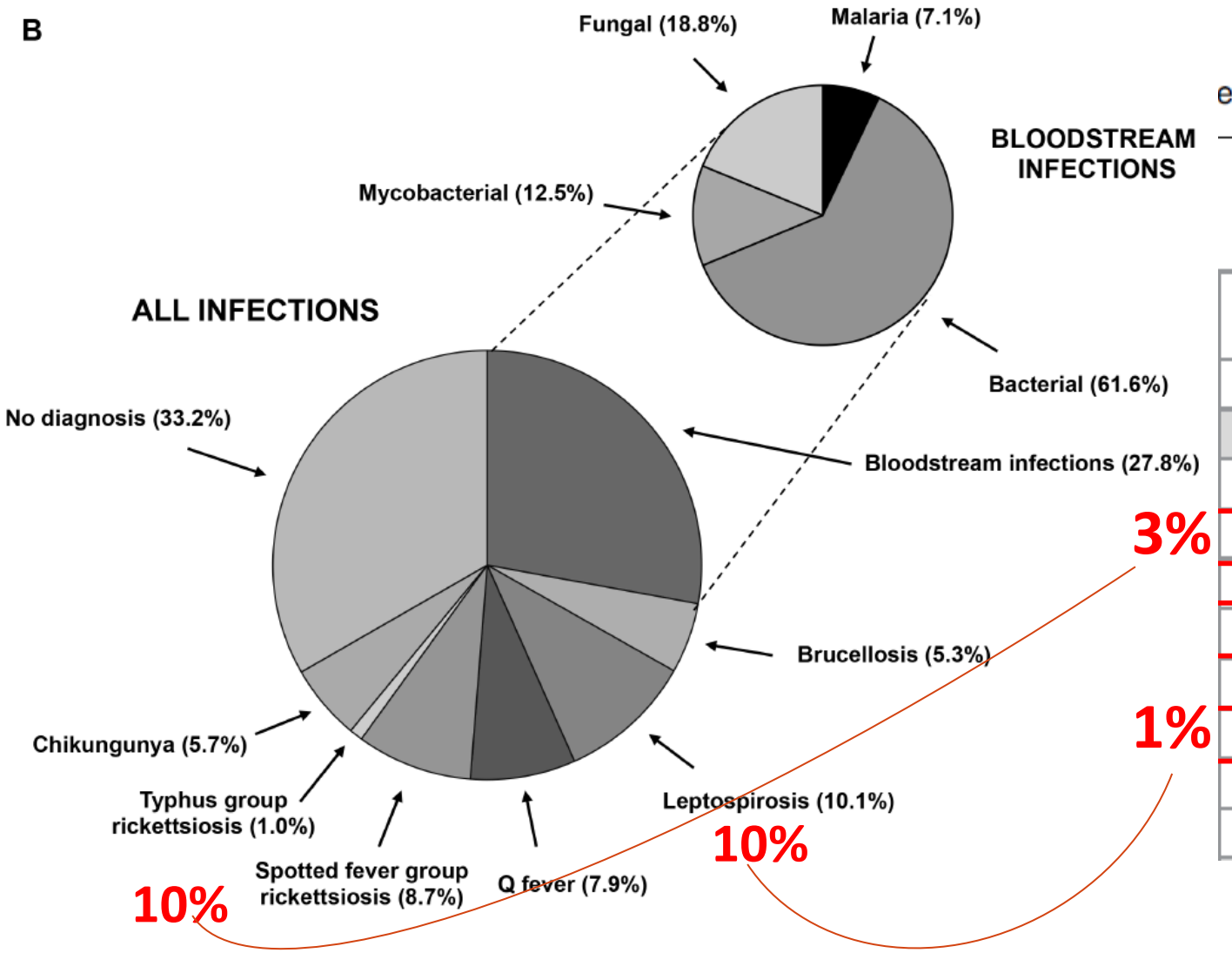
Blood stream infections by PCR or serological methods in hospitalized patients

PLOS

B



ebrile illness (AFI) in Kilombero, Tanzania

Table 3. Detections of vi

Agent Detected	Adults (≥15yrs)	All ages
	n (%)	n (%)
Blood Stream Agents	N = 628	N = 842
Plasmodium	339 (54)	399 (47)
Leptospira	20 (3)	22 (3)
Bartonella	4 (1)	4 (1)
Salmonella non-Typhi	2 (1)	4 (1)
Coxiella burnetii	2 (1)	2 (1)
Rickettsia	2 (1)	2 (1)
West Nile virus	1 (1)	1 (1)
Total number of blood	*370*	434

Crump et al, Plos Trop Negl Dis 2013

Hercik et al, Plos one 2017

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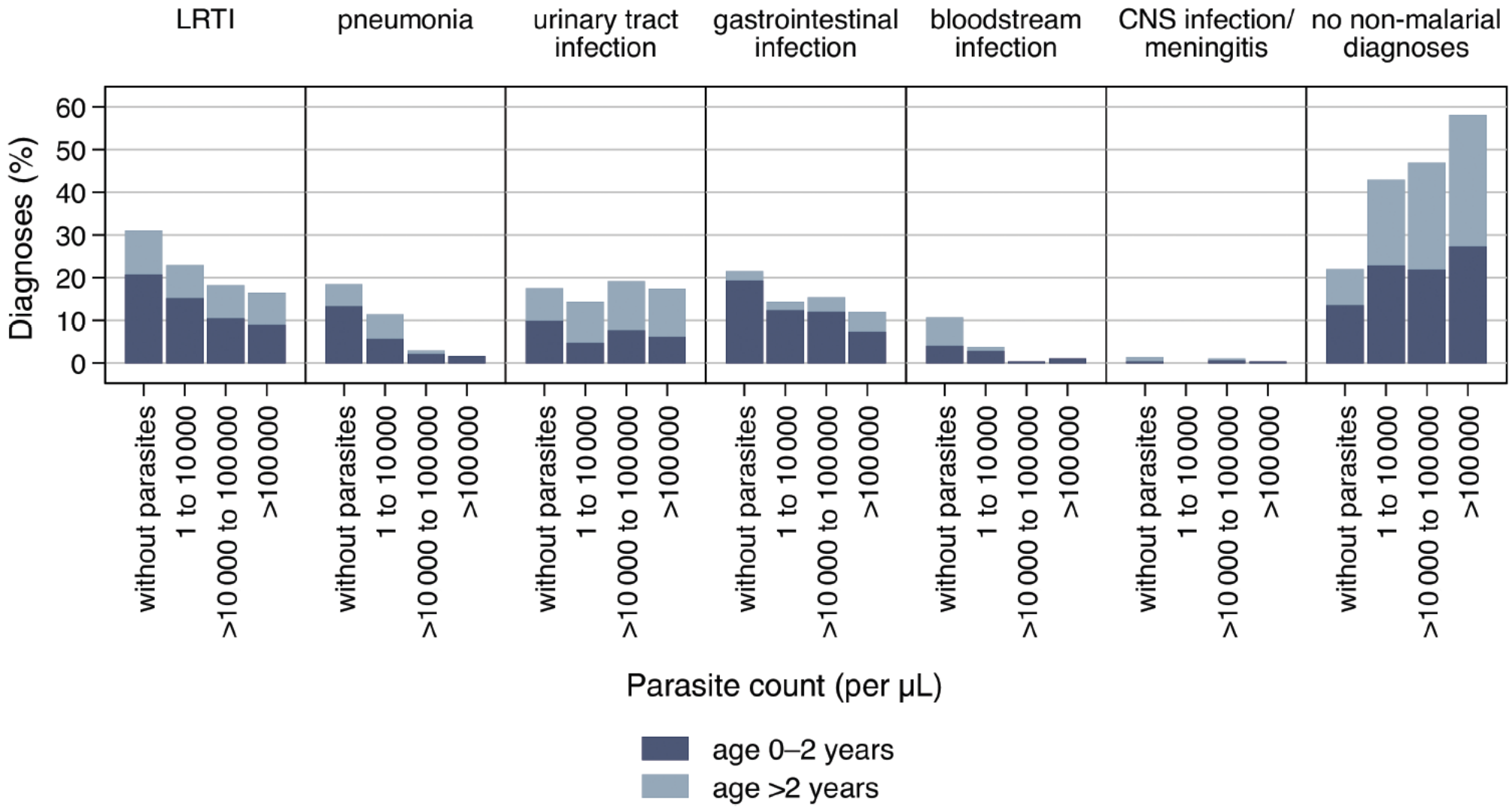
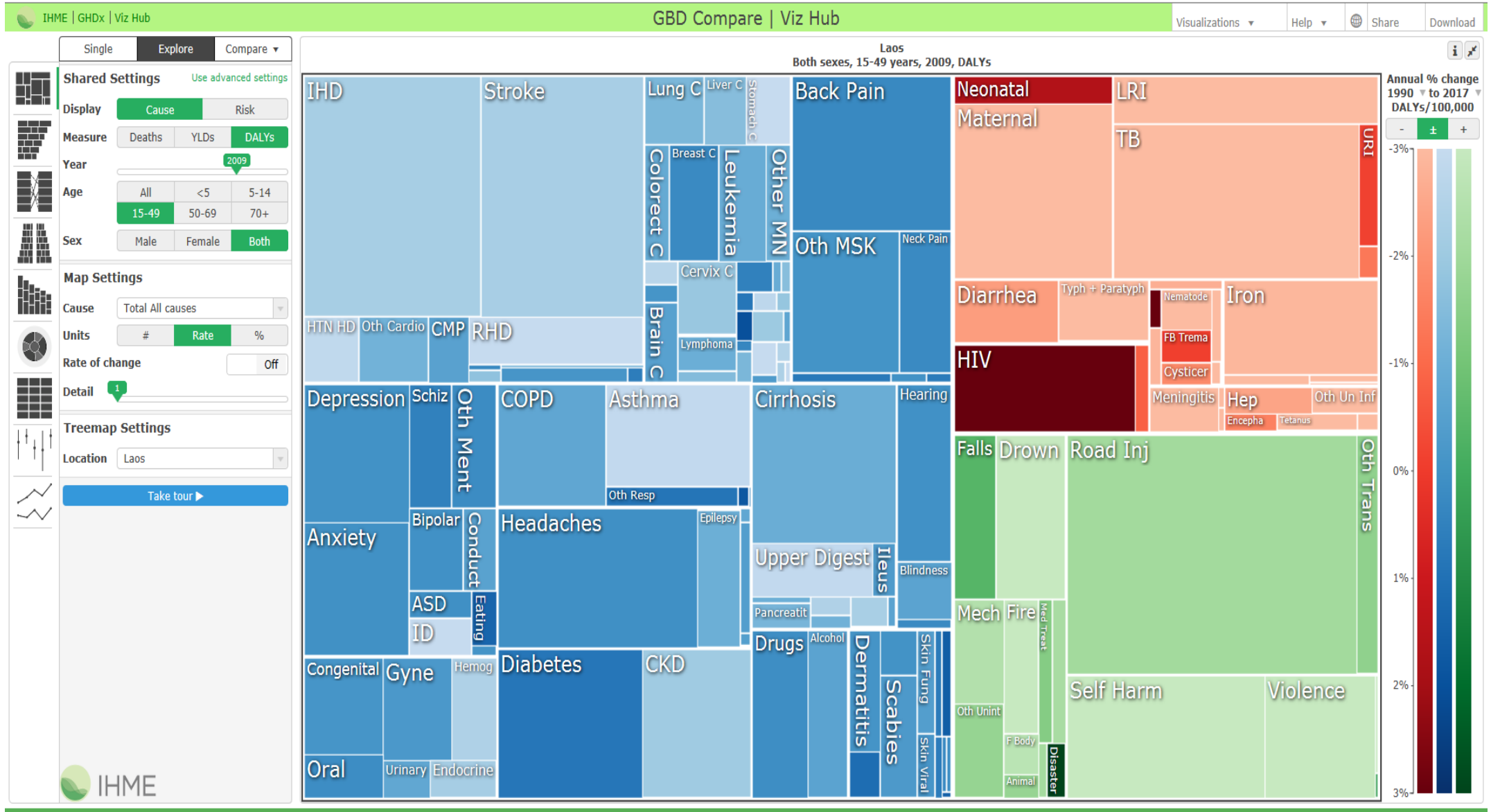
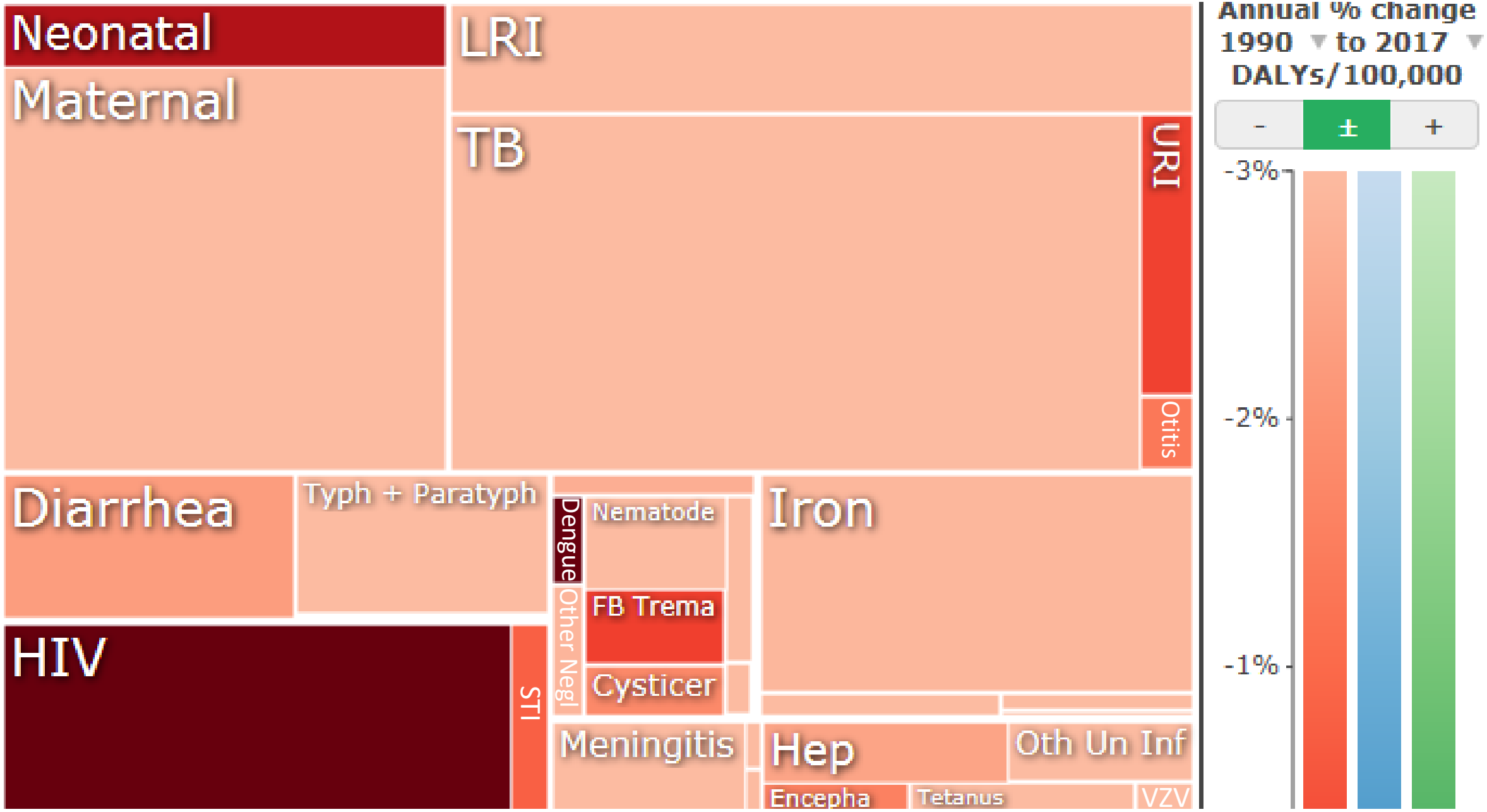
Pathogen detection according to malaria parasitaemia



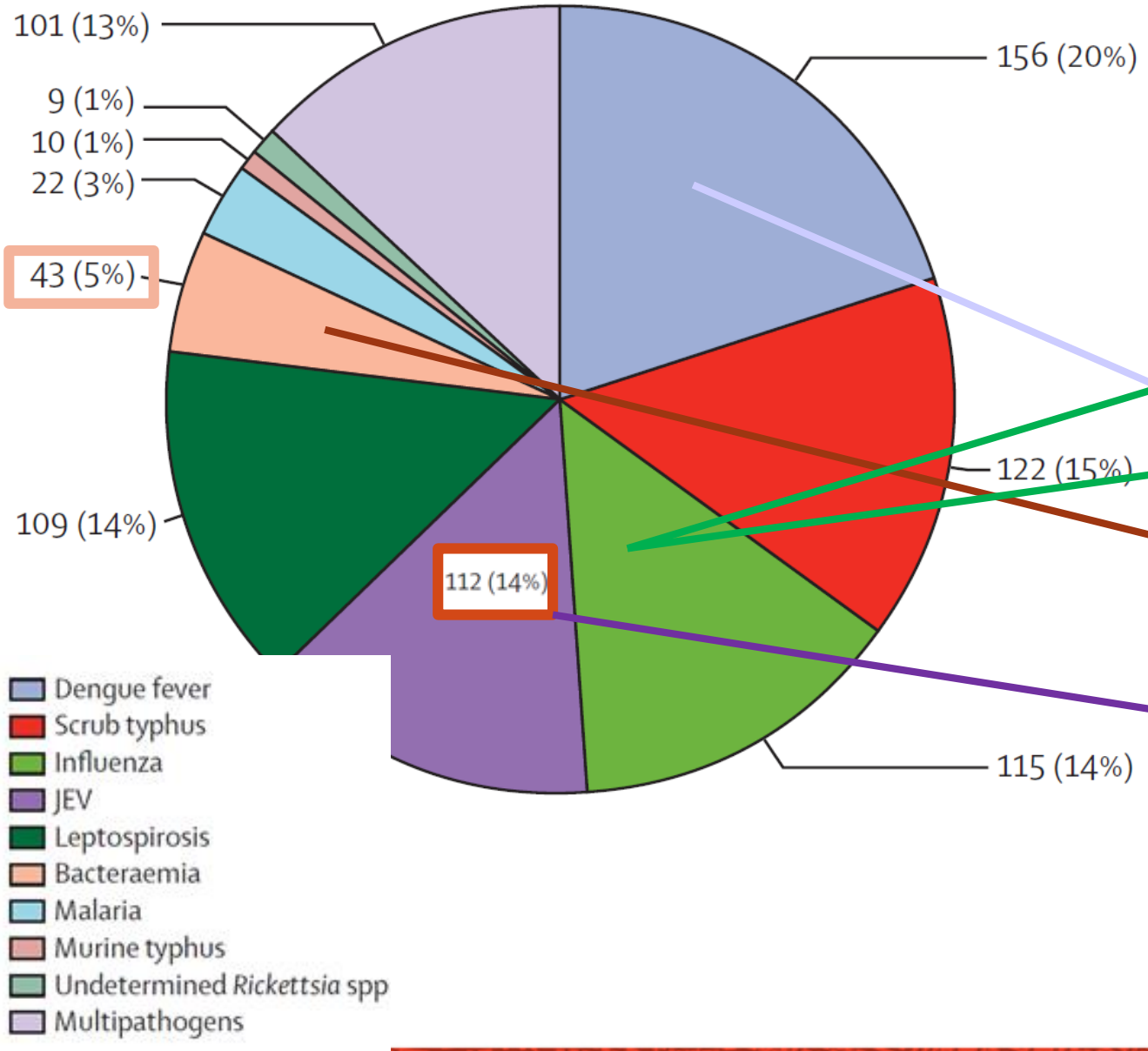
Hogan et al, Clin Inf Dis 2018

What about burden of diseases?

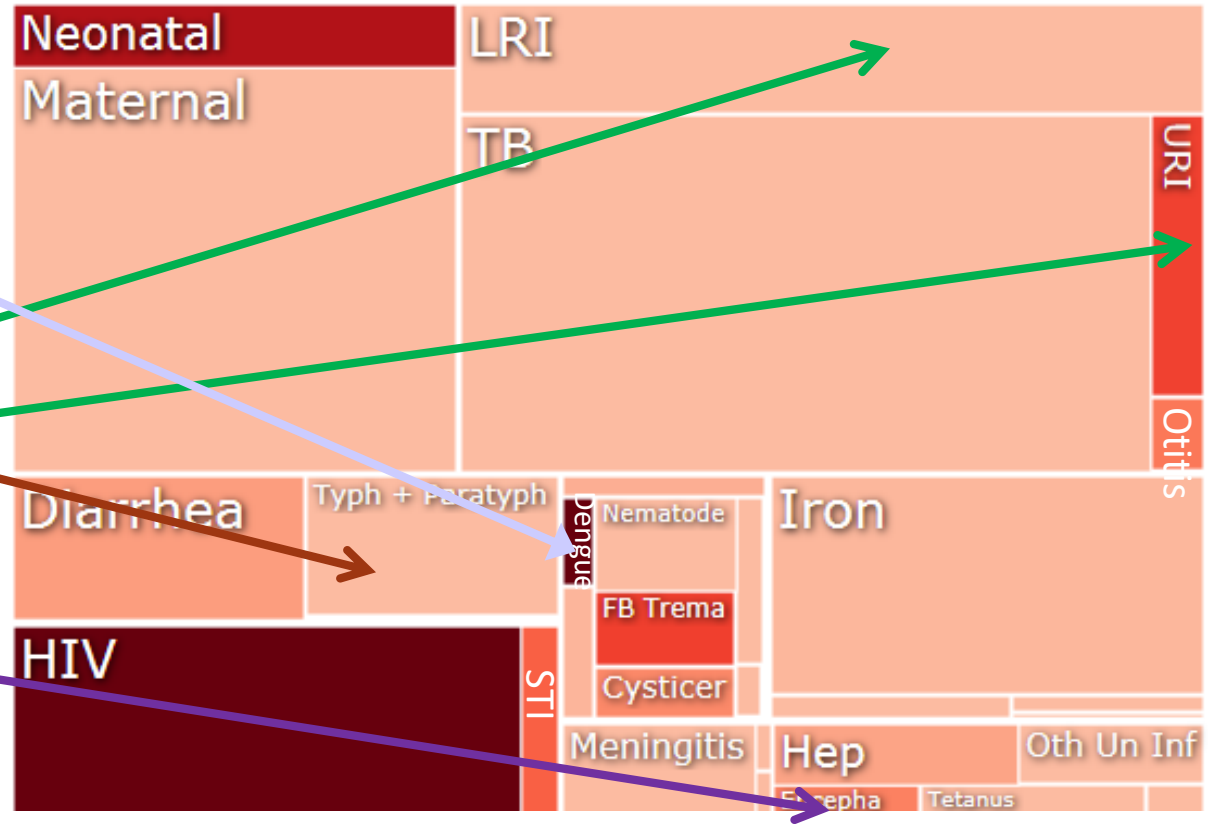



Neonatal
Maternal
LRI
TB
URI
Otitis
Diarrhea
Typh + Paratyph
Dengue
Nematode
Other Negl
FB Trema
Cysticer
Iron
HIV
STI
Meningitis
Hep
Oth Un Inf
Encepha
Tetanus
VZV
Annual % change
1990 to 2017
DALYs/100,000
-
±
+
-3%
-2%
-1%

Diagnoses in 799 patients in Laos



Burden of diseases (DALY) 15-49y Laos 2009



Mayxay et al, Lancet Glob Health 2013; Crump & Kirk, Plos Negl Trop Dis 2015 http://vizhub.healthdata.org/gbd-compare/

Key messages

- Not possible at this stage to have an overall picture of etiologies of fever in different geographical regions due to considerable heterogeneity between studies
- Systematic reviews are difficult to interpret due to heterogenity
- Case definitions should include composite diagnostic criteria (clinical and laboratory)
- Epidemics render etiology of fevers studies highly variable
- To reflect the true burden of acute fevers, all patients should be included (malaria, Tb etc.), at all levels of health care

The question

Febrile illness: a unified approach to protocol design for multicentered studies

Organized by Fondation Merieux

Do we really need other etiology studies? … After FIEBRE

Febrile Illness Evaluation in a Broad Range of Endemicities

What will we gain more? When to stop?

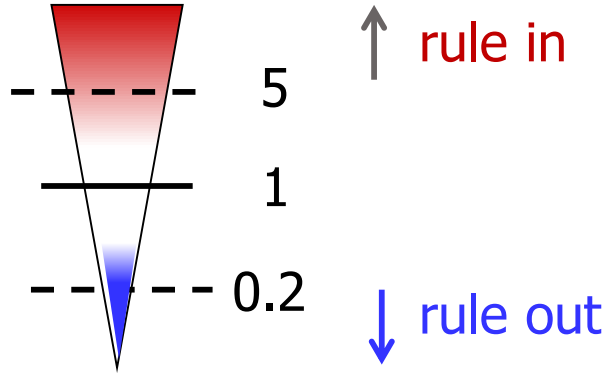
The question

Do we really need other etiology studies?

or should we rather focus on other types of studies?

- Studies of disease predictors to improve pre-test probabilities?

Predictors for typhoid fever

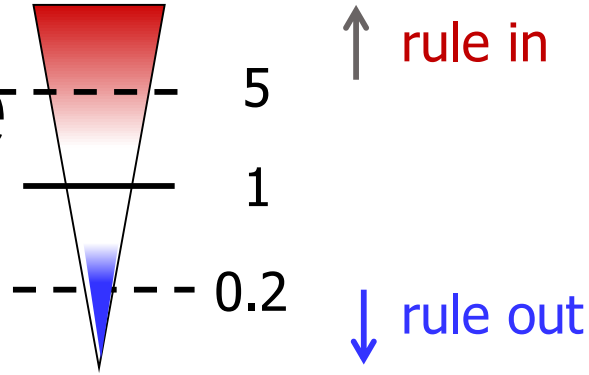


Typhoid fever n = 37

Predictors variables	**n**	**aLR+**	**(95% CI)**	**aLR-**	**(95% CI)**
Abdominal tenderness	33	**5,9**	**(2,5-11)**	**0,84**	**(0,71-0,96)**
Liver pain	11	3,9	(0-8,4)	0,95	(0,89-1,0)
Lymphadenopathy	48	3,1	(0,68-6,1)	0,90	(0,78-1,0)
High alanine aminotransferase	43	3,0	(0,86-5,5)	0,91	(0,80-1,0)
Mouth ulcer	39	2,9	(0,62-6,7)	0,92	(0,81-1,0)
Temperature ≥40˚C	37	2,7	(0,80-5,1)	0,93	(0,83-1,0)
Jaundice	42	**2,5**	**(1,6-3,6)**	**0,90**	**(0,80-0,97)**
Rainy season (vs dry season)	576	**1,3**	**(1,1-1,5)**	**0,56**	**(0,25-0,89)**

De Santis et al, Plos One 2017

Predictors for bacterial disease



Bacterial disease n = 221

Predictors variables	n	aLR+	(95% CI)	aLR-	(95% CI)
Chest indrawing	27	**19**	**(8,2-60)**	**0,90**	**(0,86-0,94)**
Nasal flaring	22	**11**	**(5,4-22)**	**0,94**	**(0,91-0,96)**
Severe anemia	14	**9,7**	**(2,8-48)**	**0,96**	**(0,93-0,98)**
Seizures	16	**5,9**	**(1,5-26)**	**0,96**	**(0,92-0,99)**
Low weight	29	**4,6**	**(2,2-9,4)**	**0,94**	**(0,90-0,97)**
Lymphadenopathy	48	**3,5**	**(1,9-6,3)**	**0,92**	**(0,88-0,97)**
White mouth	13	3,4	(0,73-15)	0,98	(0,95-1,0)
Temperature>40˚C	37	2,4	(0,95-5,5)	0,96	(0,92-1,0)
Jaundice	42	**2,0**	**(1,3-3,0)**	**0,96**	**(0,93-0,99)**
Fever duration >3 days	97	**1,6**	**(1,3-2,1)**	**0,94**	**(0,89-0,98)**
Recent travel	953	0,42	(0,11-1,0)	1,0	(1,0-1,1)

De Santis et al, Plos One 2017

Examples of predictors?

Excluders and predictors
in clinical findings and basic laboratory tests

	Malaria	Enteric fever	Scrub typhus	Leptospirosis	Dengue
Rule out features Presence of these features suggest alternative diagnosis	Rash and lymphadenopathy	Generalised rash or generalised lymphadenopathy			Fever >12 days, combination of normal tourniquet test and normal leucocyte count (LR- 0.12)
Rule in features Associated with an increase in probability of disease	Fever >40 degrees. Splenomegaly, thrombocytopenia and hyperbilirubinemia are associated with moderate to large increase in probability of disease	Fever in endemic areas >3 days duration & presence of abdominal tenderness is associated with moderate increase in probability of disease	Eschar virtually pathognomonic for scrub typhus (OR 46). Eschar seen in 17–86% of patients in recent series	Combination of suffusion, icterus and conjunctival hemorrhage is characteristic of leptospirosis.	Leukopenia and thrombcytopenia. Positive tourniquet test is a good predictor of infection (OR: 4.86) and ascites is a good predictor of severe dengue (OR:13.91)

Bhargava et al, BMJ 2018

The question

Do we really need other etiology studies?

or should we rather focus on other types of studies?

- And/or sentinel sites with ongoing ‘syndromic’ surveillance and in-depth investigation when necessary

The question

Do we really need other etiology studies?

or should we rather focus on other types of studies?

- Targetted intervention studies to kill two birds with one stone? e.g. *haemophilus influenzae type b* vaccine =>20% of pneumonia in infants are due to Hib

The question

Do we really need other etiology studies?

or should we rather focus on other types of studies?

- Targetted intervention studies ?

  with a focus on health outcome rather than etiology

  since at the end we want to improve health of children and adults in LMIC…

thebmj Visual summary

Fever identification charts

A quick guide to differentiation and diagnosis in tropical and subtropical regions

This document is designed to be printed on three sheets of ordinary A4 paper, which can be mounted vertically

Acute undifferentiated febrile illnesses (AUFIs) are characterised by fever of less than two weeks duration without organ-specific symptoms at the onset. This document provides an approach to the diagnosis of common AUFIs in children older than five years as well as in adults in low resource settings, with a focus on early recognition of the most severe non-malarial illnesses.

Local Disease Prevalence

	North Africa	South Africa	East Africa	West Africa	Central Africa	Latin America and Caribbean	South and South-East Asia	East Asia	Australia and New Zealand	Oceania
Protozoal	Malaria Limited risk	Malaria	Malaria East African trypanosomiasis	Malaria Acute African trypanosomiasis	Malaria West African trypanosomiasis	Malaria Limited risk Acute American trypanosomiasis	Malaria	Malaria Parts of China		Malaria Some countries
Bacterial	Enteric fever Brucellosis Q fever	Enteric fever Brucellosis	Enteric fever Brucellosis Meningococcal disease (epidemic)	Enteric fever Brucellosis Meningococcal disease (epidemic)	Enteric fever Brucellosis Meningococcal disease (epidemic)	Enteric fever Brucellosis Oroya fever (Bartonellosis)	Enteric fever Brucellosis Melioidosis	Enteric fever Brucellosis Melioidosis	Melioidosis	Melioidosis
Rickettsial	Murine Typhus Mediterranean spotted fever	Murine Typhus African tick bite fever	Murine Typhus African tick bite fever	Murine Typhus	Murine Typhus Epidemic Typhus African tick bite fever	Murine Typhus Scrub typhus African tick bite fever Rocky Mountain spotted Fever	Murine Typhus Scrub typhus In Asia, Scrub typhus is more common than Murine typhus	Murine Typhus Scrub typhus	Australian tick typhus Q fever	
Spirochetal	Leptospirosis	Leptospirosis	Leptospirosis Tick/louse-borne relapsing fever Q fever	Leptospirosis African tick bite fever	Leptospirosis Tick-borne relapsing fever	Leptospirosis Tick-borne relapsing fever	Leptospirosis		Leptospirosis	Leptospirosis
Arboviruses	No yellow fever risk, limited risk of other arboviral infections	Dengue Chikungunya	Dengue Chikungunya Yellow fever	Dengue Chikungunya Zika Yellow fever	Dengue Chikungunya Zika Yellow fever	Dengue Chikungunya Zika	Dengue Chikungunya Zika	Dengue	Chikungunya (limited) Ross River virus	Dengue Chikungunya Zika Ross River virus
Other viruses			Crimean-Congo Hemorrhagic Fever Rift valley fever	Crimean-Congo Hemorrhagic Fever Ebola Lassa	Crimean-Congo Hemorrhagic Fever Ebola Marburg	Hantavirus pulmonary syndrome Hemorrhagic fever with renal syndrome Other viral hemorrhagic fevers: Junin, Machupo, Sabia, Guanarito	Crimean-Congo Hemorrhagic Fever Kyasanur Forest disease	Crimean-Congo Hemorrhagic Fever Hemorrhagic fever with renal syndrome Hantavirus		
Helminthic	Filariasis Acute schist-osomiasis	Filariasis Acute schist-osomiasis Trichinosis	Filariasis Acute schist-osomiasis	Filariasis Acute schist-osomiasis	Filariasis Acute schist-osomiasis Trichinosis	Filariasis Acute schist-osomiasis Trichinosis	Filariasis Acute schist-osomiasis (SE Asia)	Filariasis Acute schist-osomiasis		Filariasis

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