Understanding Fever and the Acute Febrile Illness Landscape

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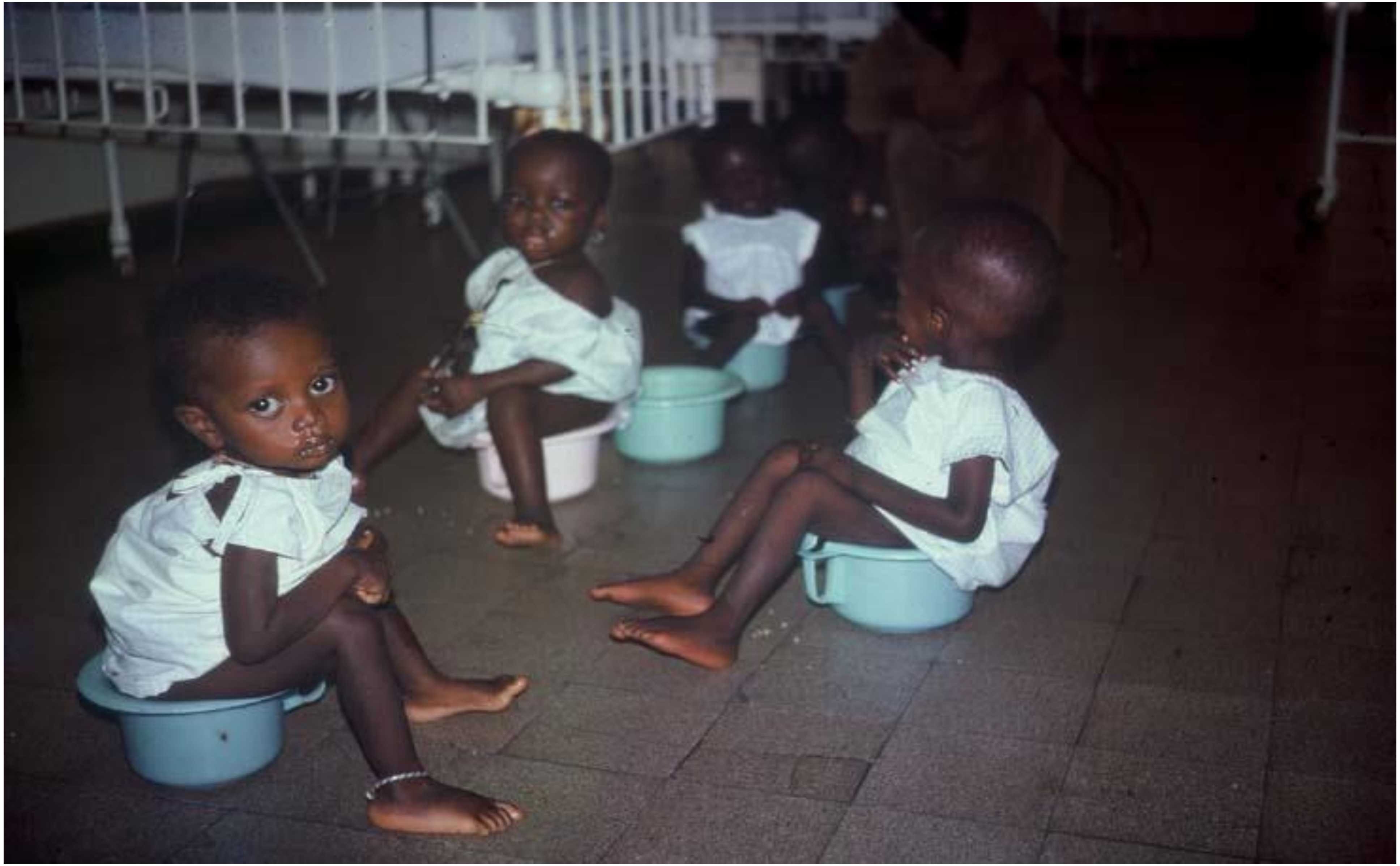
The “Gate Clinic”, MRC Labs, The Gambia, 1978

The ward at MRC Labs, The Gambia, 1978



Association between malaria and non-typhoid *Salmonella* (NTS) bacteraemia in The Gambia

Mabey D, Brown A, Greenwood BM. J Infect Dis 1987; 155: 1319-21

- 71 cases of NTS bacteraemia; 30 had malaria (42%)
- 45 cases of typhoid; 5 had malaria (11%)

Mean haemoglobin

- In NTS cases: 6.7
- In typhoid cases: 10.3

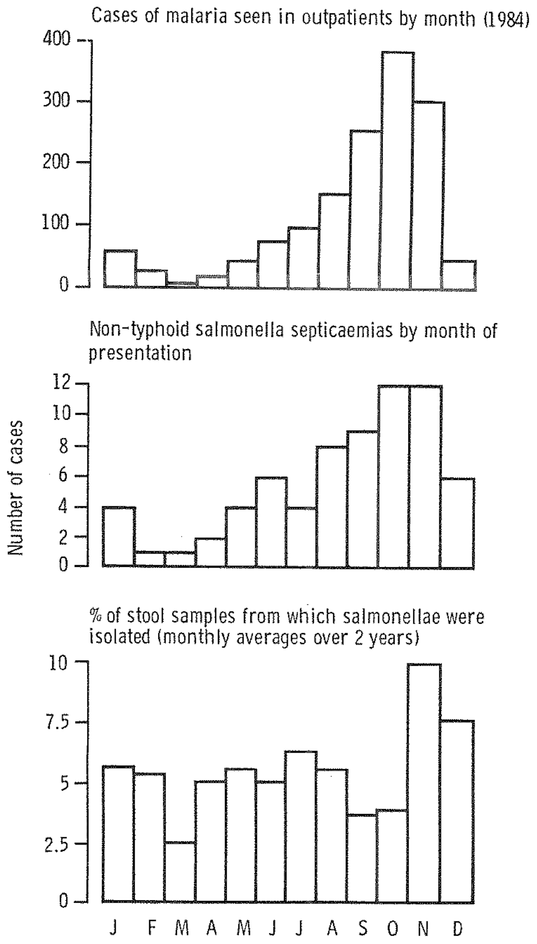


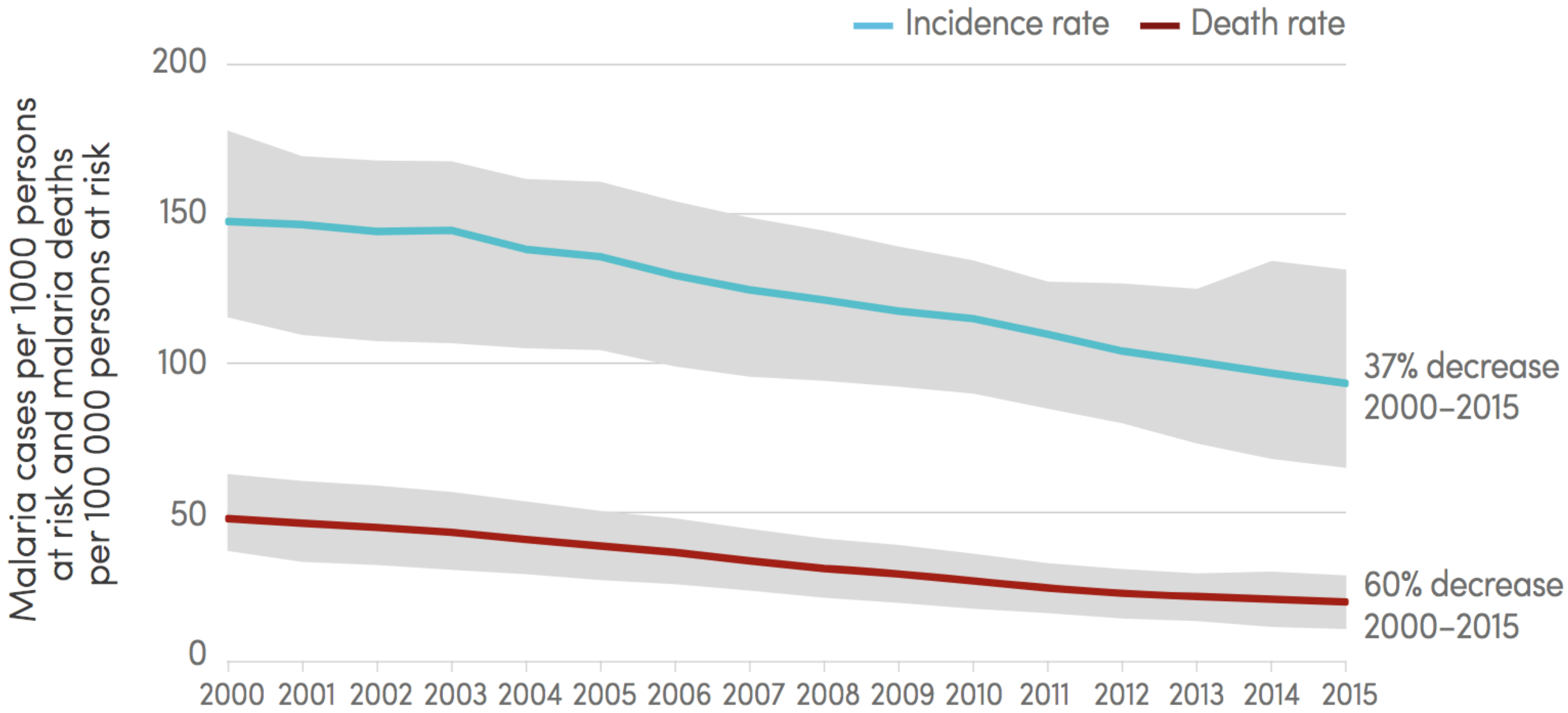
Figure 1. A comparison of the monthly incidence of cases of malaria, nontyphoid salmonella septicemia, and positive stool cultures for salmonellae at the Medical Research Council hospital, Fajara, The Gambia.

The Effect of Insecticide-treated Bed Nets on Mortality in Gambian Children

Alonso PL et al. Lancet 1991; 337: 1499-502

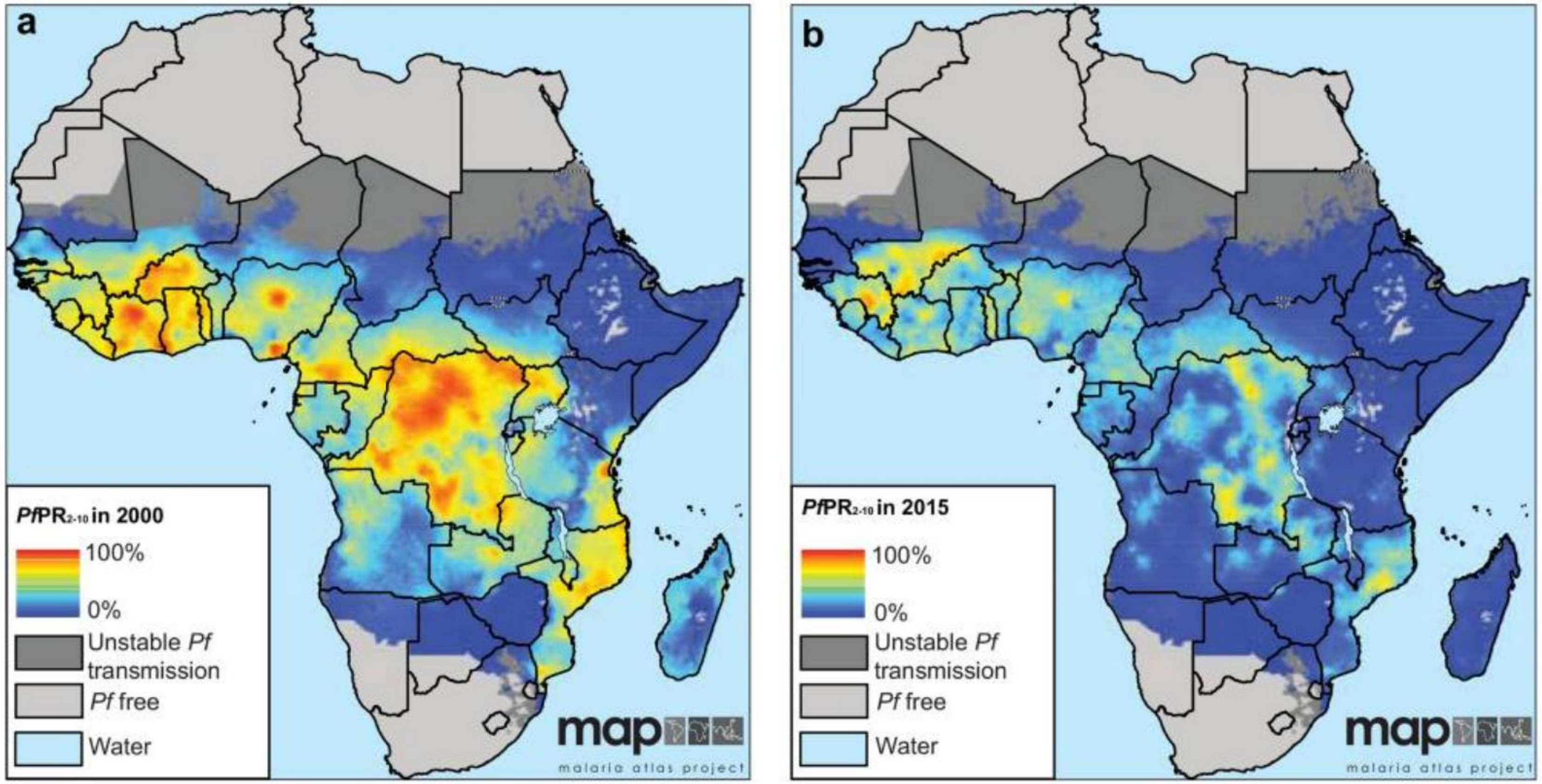
Permethrin-impregnated bednets + weekly malaria chemoprophylaxis during the rainy season reduced mortality of children aged 1-4 years by 63%

Figure 2.1 Estimated malaria case incidence and death rate globally, 2000–2015



Source: *WHO estimates*

Decline in malaria 2000 - 2015

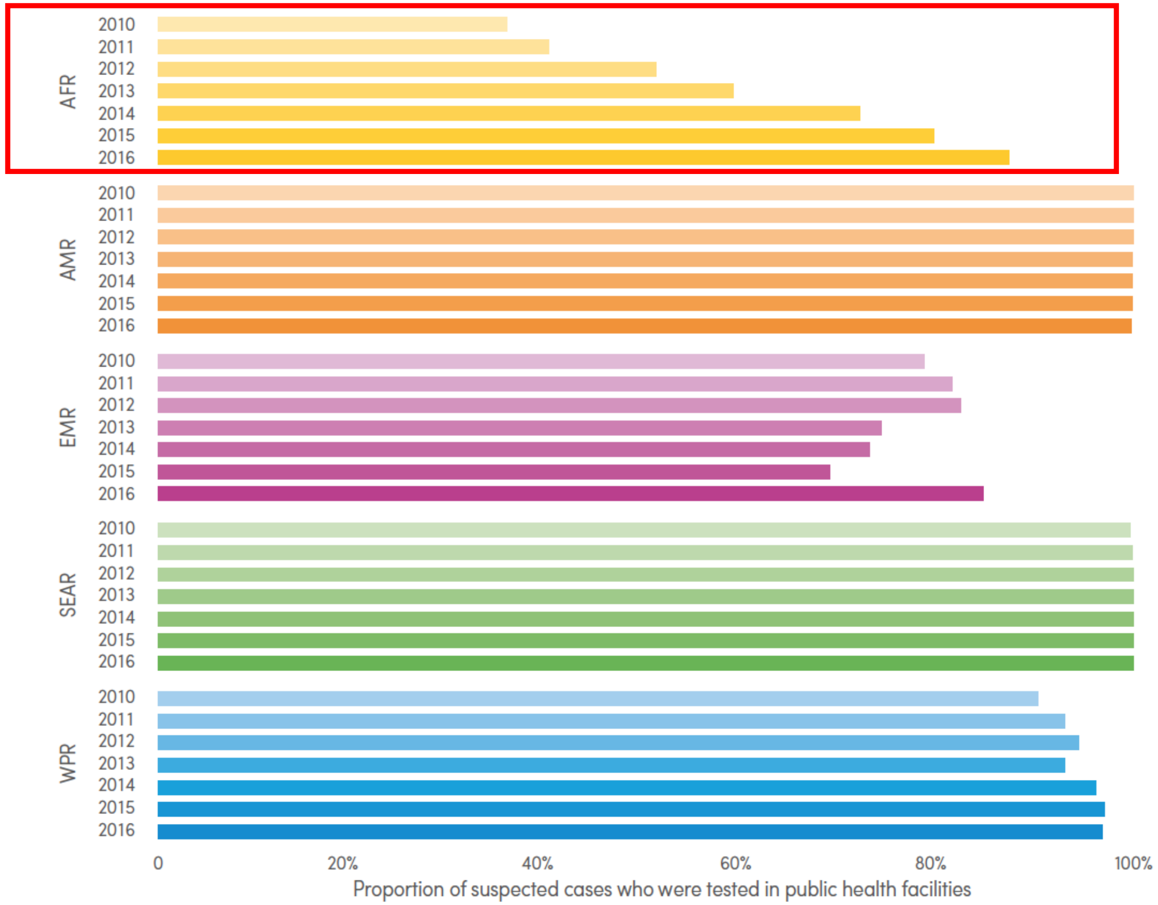


Bhatt S et al Nature 2015

Increase in use of malaria Rapid Diagnostic Tests (mRDTs)

FIG. 4.4.

Proportion of suspected malaria cases attending public health facilities who received a diagnostic test by WHO region, 2010–2016 *Source: National malaria control programme reports*



AFR, WHO African Region; AMR, WHO Region of the Americas; EMR, WHO Eastern Mediterranean Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region

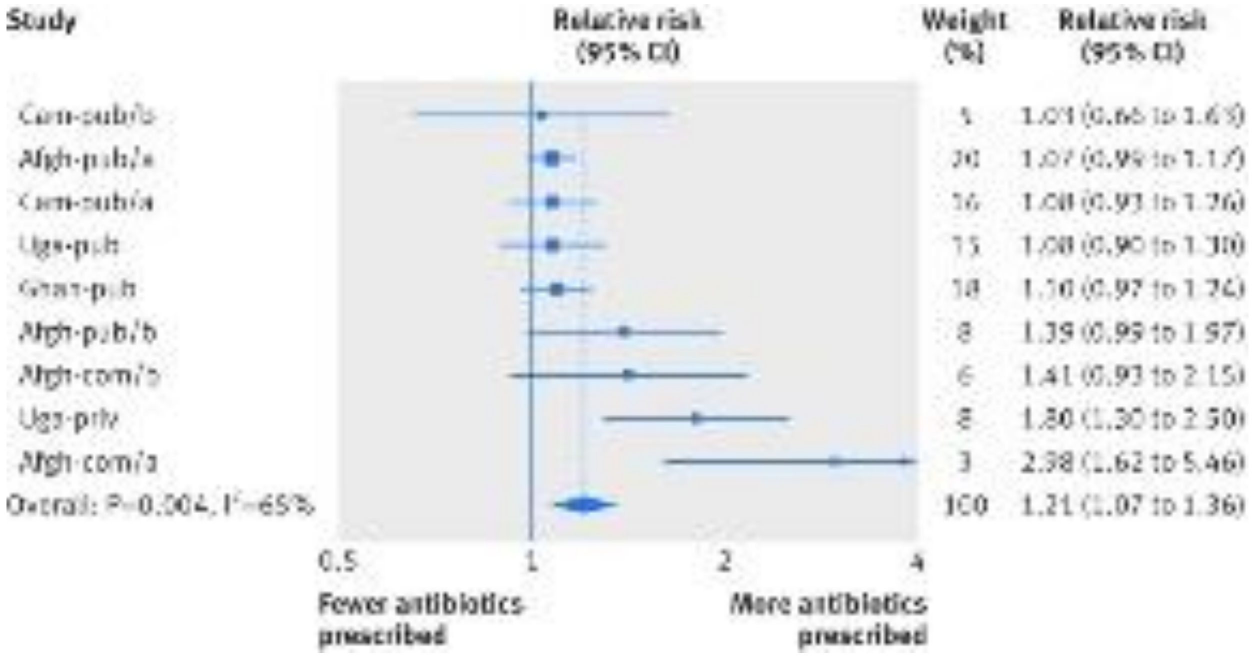
WORLD MALARIA REPORT 2017

IMCI guidelines

• Any general danger sign or • Stiff neck.	***Pink:*** **VERY SEVERE FEBRILE DISEASE**	■ **Give first dose of artesunate or quinine for severe malaria** ■ **Give first dose of an appropriate antibiotic** ■ **Treat the child to prevent low blood sugar** ■ **Give one dose of paracetamol in clinic for high fever (38.5°C or above)** ■ **Refer URGENTLY to hospital**
• Malaria test POSITIVE.	***Yellow:*** **MALARIA**	■ **Give recommended first line oral antimalarial** ■ **Give one dose of paracetamol in clinic for high fever (38.5°C or above)** ■ Give appropriate antibiotic treatment for an identified bacterial cause of fever ■ Advise mother when to return immediately ■ Follow-up in 3 days if fever persists ■ If fever is present every day for more than 7 days, refer for assessment
• Malaria test NEGATIVE • Other cause of fever PRESENT.	***Green:*** **FEVER:** **NO MALARIA**	■ **Give one dose of paracetamol in clinic for high fever (38.5°C or above)** ■ **Give appropriate antibiotic treatment** for an identified bacterial cause of fever ■ Advise mother when to return immediately ■ Follow-up in 3 days if fever persists ■ If fever is present every day for more than 7 days, refer for assessment

Introduction of Malaria RDTs increases prescription of antibiotics

Hopkins H et al. BMJ 2017; 356:1054



Ratios for antibiotic prescription in randomised studies comparing patients in control settings with patients in settings where malaria rapid diagnostic test intervention was implemented.

The NEW ENGLAND JOURNAL of MEDICINE

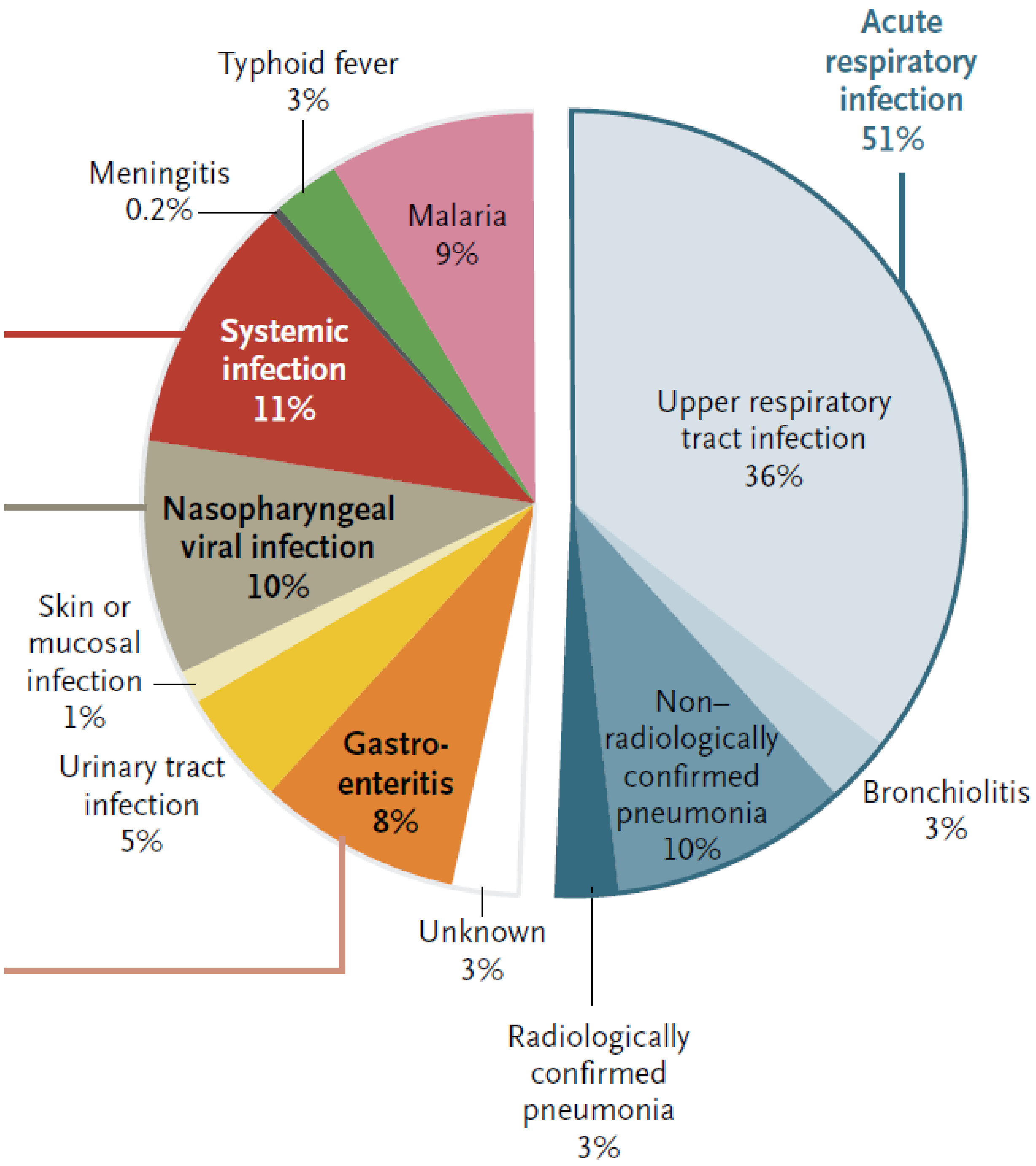
ORIGINAL ARTICLE

Beyond Malaria — Causes of Fever in Outpatient Tanzanian Children

Valérie D'Acremont, M.D., Ph.D., Mary Kilowoko, M.P.H., Esther Kyungu, M.D., M.P.H., Sister Philipina, R.N., Willy Sangu, A.M.O., Judith Kahama-Maro, M.D., M.P.H.,* Christian Lengeler, Ph.D., Pascal Cherpillod, Ph.D., Laurent Kaiser, M.D., and Blaise Genton, M.D., Ph.D.

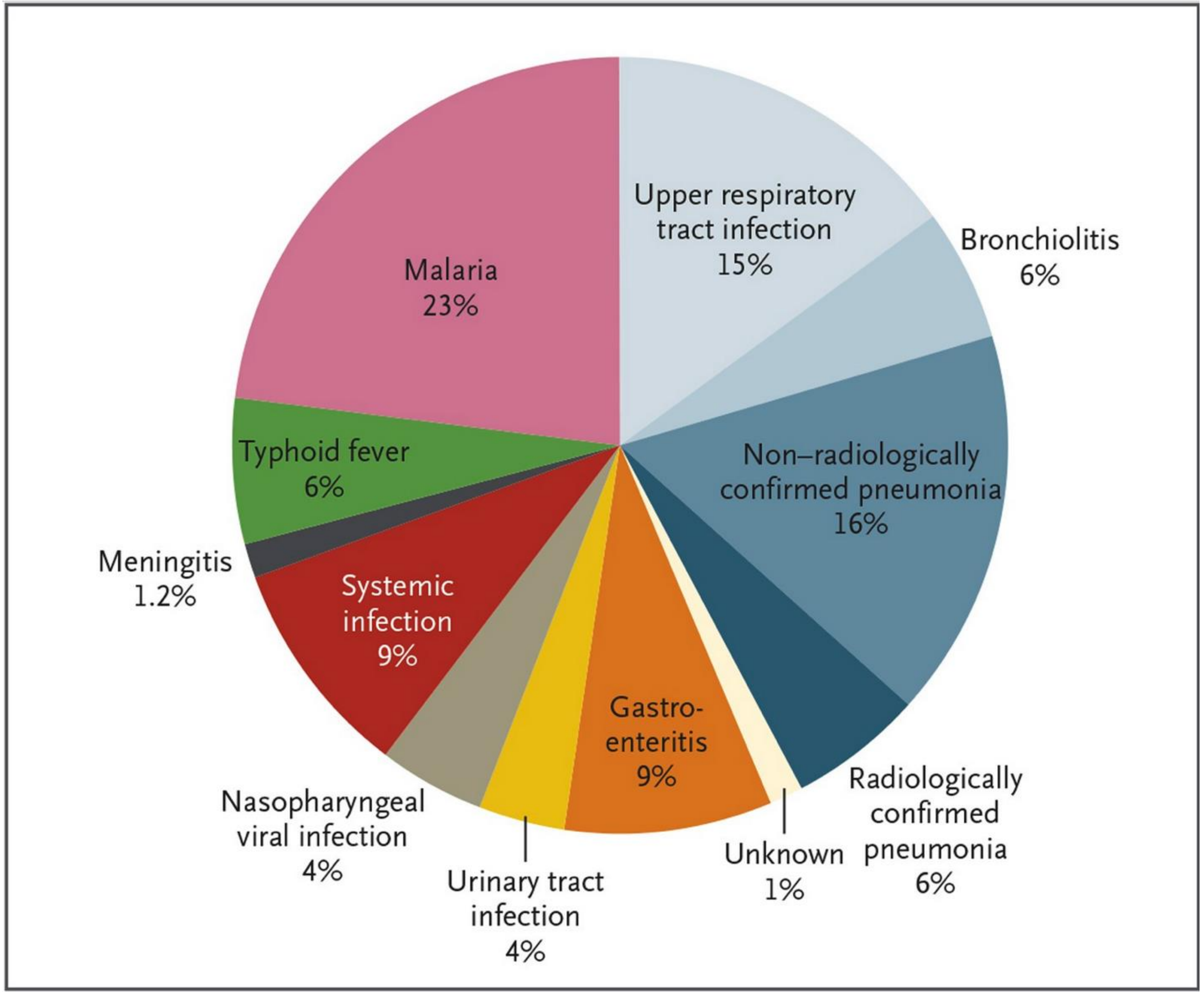
- 2 sites (Ifakara and Dar es Salaam)
- 2 months – 10 years
- Low malaria endemicity (around 9% in febrile children)
- Recorded temperature >38^0C
- 23 symptoms, travel history, risk factors, 49 clinical signs
- 5 ml blood and pooled nasal and throat
- Final diagnosis based on predefined clinical and micro criteria using computer

1005 children – 1232 diagnoses



D'acremont et al NEJM 2014

133 children with severe illness - 160 diagnoses



D'acremont et al NEJM 2014

ORIGINAL ARTICLE

Bacteremia among Children Admitted to a Rural Hospital in Kenya

Berkley JA *et al.*, N Engl J Med 2005;352:39-47

Table 1. Prevalence and Outcome of Community-Acquired Bacteremia among Hospitalized Children, According to Age.*

Age	All Patients	Patients with Bacteremia		Patients without Bacteremia		Patients with Bacteremia (95% CI)	Deaths Involving Bacteremia (95% CI)
		Total	Deaths	Total	Deaths		
						percent	
<7 days	867	117	65	750	247	13.5 (11.5–16.0)	20.8 (16.5–25.8)
7–59 days	916	111	29	805	51	12.1 (10.1–14.4)	36.2 (25.8–47.8)
60–364 days	4,354	301	86	4,053	152	6.9 (6.2–7.7)	36.1 (30.0–42.5)
≥1 yr	10,433	565	128	9,868	426	5.4 (5.0–5.8)	23.1 (19.7–26.8)
All ages	16,570	1094	308	15,476	876	6.6 (6.2–7.0)	26.0 (23.5–28.6)

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28%

6%

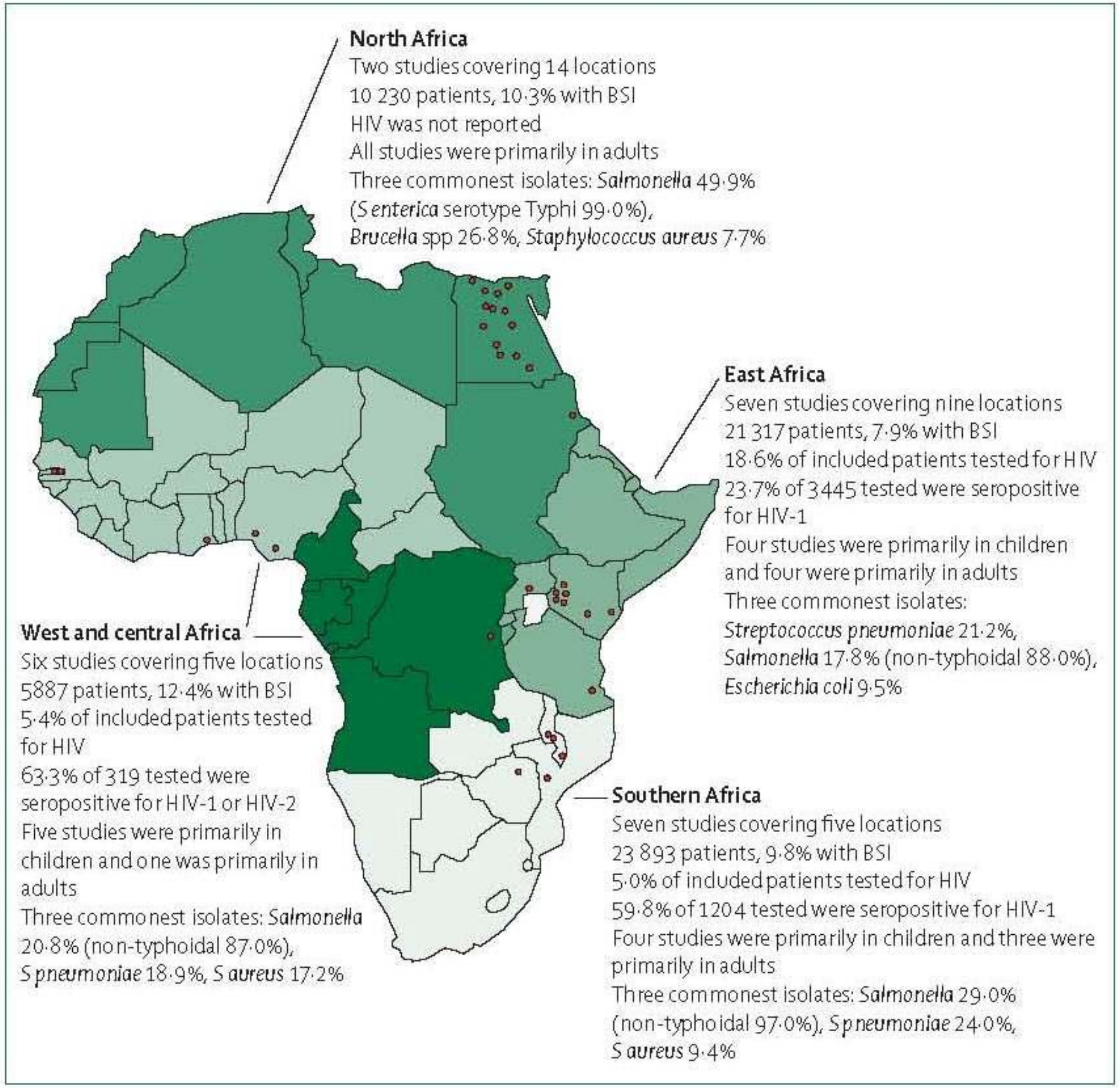
Table 4. Odds Ratio for Community-Acquired Bacteremia in Children with Malnutrition and Those with HIV Infection.

Pathogen	Odds Ratio (95% Confidence Interval)*	
	Malnutrition	HIV Infection†
None‡	1.00	1.00
Any organism	2.02 (1.65–2.47)	3.22 (2.34–4.44)
Streptococcus pneumoniae	1.85 (1.36–2.52)	5.84 (3.98–8.56)
Staphylococcus aureus	1.31 (0.76–2.26)	1.93 (0.87–4.27)
Group A streptococci	3.28 (1.75–6.15)	2.24 (0.82–6.14)
Group B streptococci§	1.15 (0.45–3.00)	—
Nontyphoidal salmonella species	1.68 (1.15–2.44)	3.21 (1.95–5.28)
Haemophilus influenzae	1.16 (0.75–1.79)	2.97 (1.71–5.17)
Escherichia coli	4.73 (3.15–7.10)	2.24 (1.19–4.22)

Berkley, J. et al. N Engl J Med 2005;352:39-47

Bacterial bloodstream infections in Africa

Reddy EA, et al. Lancet Infect Dis 2010; 10: 417



Organisms isolated from Blood Cultures in Blantyre, Malawi, 1998-2016

Musicha P et al. Lancet Infect Dis 2017; 17: 1042

194,539 blood cultures, of which 29,183 (15%) were positive

	Total	1998-2001	2002-5	2006-9	2010-13	2014-16
Salmonella (non-typhi)	36%	30%	50%	40%	18%	11%
Strep. pneumoniae	15%	17%	17%	20%	10%	3%
S. typhi	10%	1%	1%	1%	27%	43%
E.coli	9%	9%	7%	10%	9%	9%
S. aureus	7%	7%	5%	5%	8%	9%
Klebsiella	4%	7%	3%	4%	4%	5%
Cryptococcus	3%	1%	3%	6%	5%	4%

Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case–control study

Thomas N Williams, Sophie Uyoga, Alex Macharia, Carolyne Ndila, Charlotte F McAuley, Daniel H Opi, Salim Mwarumba, Julie Makani, Albert Komba, Moses N Ndiritu, Shahnaaz K Sharif, Kevin Marsh, James A Berkley, J Anthony G Scott

	Isolates from children without sickle-cell anaemia (%)	Isolates from children with sickle-cell anaemia* (%)	Proportion of isolates in children with sickle-cell anaemia (%)
Gram positive			
Streptococcus pneumoniae	425 (25·9%)	44 (40·7%)	10·4%
Staphylococcus aureus	173 (10·5%)	6 (5·6%)	3·5%
Group A streptococci	82 (5·0%)	0	0
Group B streptococci	35 (2·1%)	1 (0·9%)	2·9%
Other gram-positive organisms†	82 (5·0%)	4 (3·7%)	4·9%
Gram negative			
Non-typhi *Salmonella* species	192 (11·7%)	19 (17·6%)	9·9%
Haemophilus influenzae type b	100 (6·1%)	13 (12·0%)	13·0%
Haemophilus influenzae other	27 (1·6%)	2 (1·9%)	7·4%
Escherichia coli	138 (8·4%)	7 (6·5%)	5·1%
Acinetobacter species	136 (8·3%)	7 (6·5%)	5·1%
Pseudomonas species	81 (4·9%)	0	0
Klebsiella species	57 (3·5%)	1 (0·9%)	1·8%
Other gram-negative organisms‡	113 (6·9%)	4 (3·7%)	3·5%
Overall			
Any organism	1641 (100·0%)	108 (100·0%)	6·6%

Sickle Cell Disease

- OR 26.3 for bacteraemia
- Bacterial etiology similar to non-Sickle children
- Association strongest for:
  - *Streptococcus pneumoniae*
  - Non-Typhi *Salmonella*
  - *Haemophilus influenzae*

Williams TN *et al.*, Lancet 2009
DOI:10.1016/S0140- 6736(09)61374-X

Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study

	Nosocomial (total [%])	Health-care-associated* (total [%])	Community-acquired (total [%])
Gram-negative organisms			
Escherichia coli	44 (21%)	16 (11%)	144 (9%)
Proteus mirabilis	3 (1%)	1 (1%)	6 (<1%)
Klebsiella pneumoniae	43 (20%)	2 (1%)	37 (2%)
Klebsiella spp (other)	9 (4%)	1 (1%)	5 (<1%)
Pseudomonas aeruginosa	16 (8%)	8 (6%)	31 (2%)
Pseudomonas spp (other)	3 (1%)	1 (1%)	24 (2%)
Acinetobacter spp	19 (9%)	12 (9%)	159 (10%)
Non-typhi *Salmonella* spp	3 (1%)	10 (7%)	136 (9%)
Salmonella typhi	2 (1%)	0 (0%)	12 (1%)
Other enterobacteriaceae	8 (4%)	4 (3%)	26 (2%)
Haemophilus influenzae	2 (1%)	4 (3%)	99 (6%)
Other Gram-negative organisms	4 (2%)	0 (0%)	59 (4%)
Gram-positive organisms			
Staphylococcus aureus	20 (9%)	22 (16%)	198 (13%)
Streptococcus pneumoniae	3 (1%)	23 (16%)	459 (29%)
Group A streptococci	1 (1%)	5 (4%)	71 (5%)
Group B streptococci	2 (1%)	18 (13%)	26 (2%)
Group D streptococci	18 (9%)	12 (9%)	53 (3%)
Other gram-positive organisms	1 (1%)	2 (1%)	37 (2%)
Fungi			
Yeasts	11 (5%)	1 (1%)	8 (1%)
Total pathogens†	212 (100%)	141 (100%)	1590 (100%)

Data are number of episodes. *Health-care-associated infection was defined as bacteraemia within the first 48 h of admission to hospital when within 28 days of discharge from hospital or hospital birth. †Contaminants were grown from 19·5% of samples collected in the first 48 h after admission and 18·1% of samples obtained 48 h or more after admission. These proportions did not differ significantly (p=0·11).

Table 3: Pathogens causing paediatric bacteraemia in Kilifi District Hospital, 2002–09

Nosocomial bacteraemia

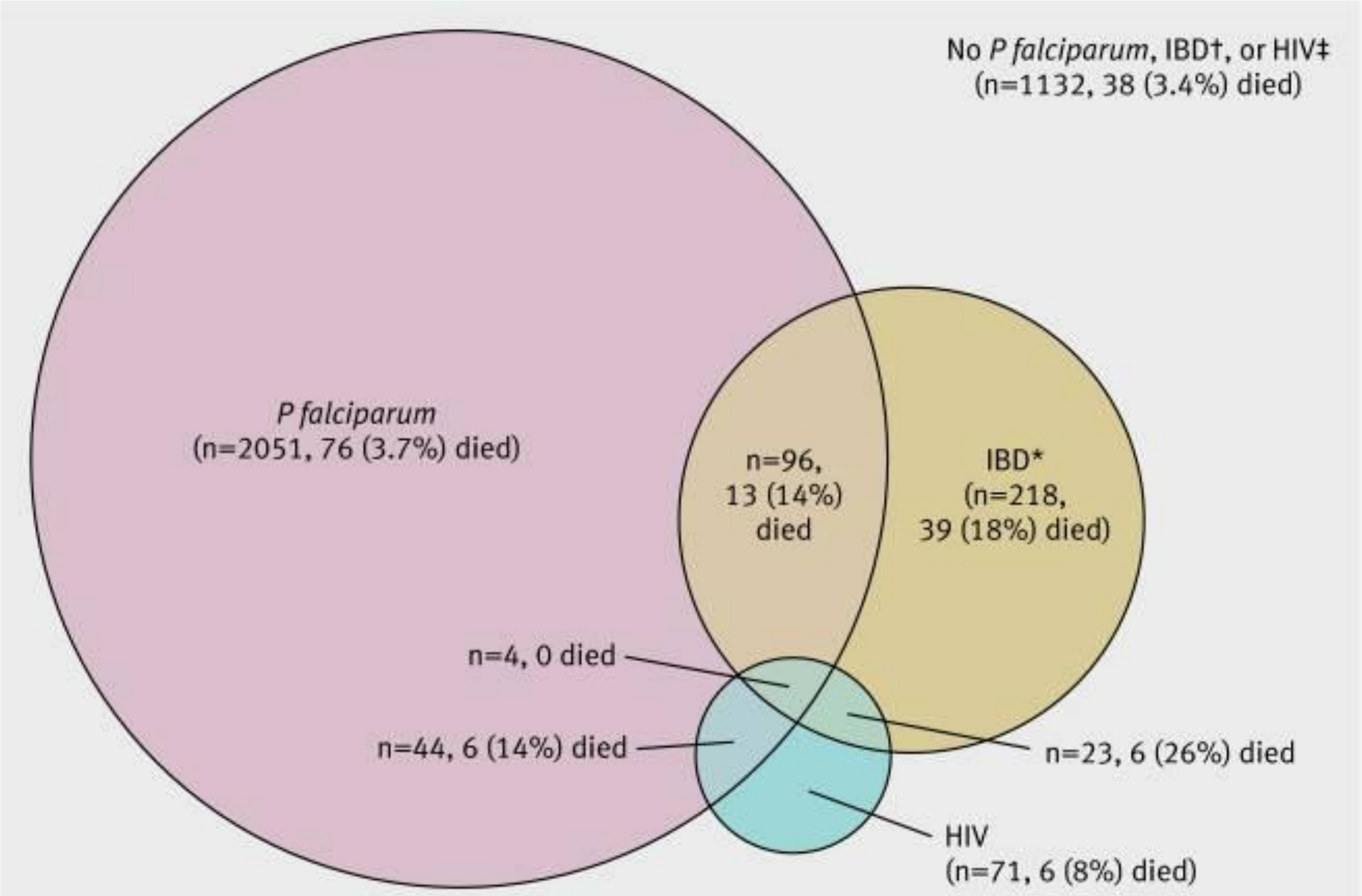
- Incidence 40x higher than community acquired bacteraemia
- Risk increasing 27%/year
- Mortality twice as high as community acquired bacteraemia (53% vs 24%)
- Longer hospital stay

Aiken A *et al.*, Lancet 2011

DOI:10.1016/S0140- 6736(11)61622-X

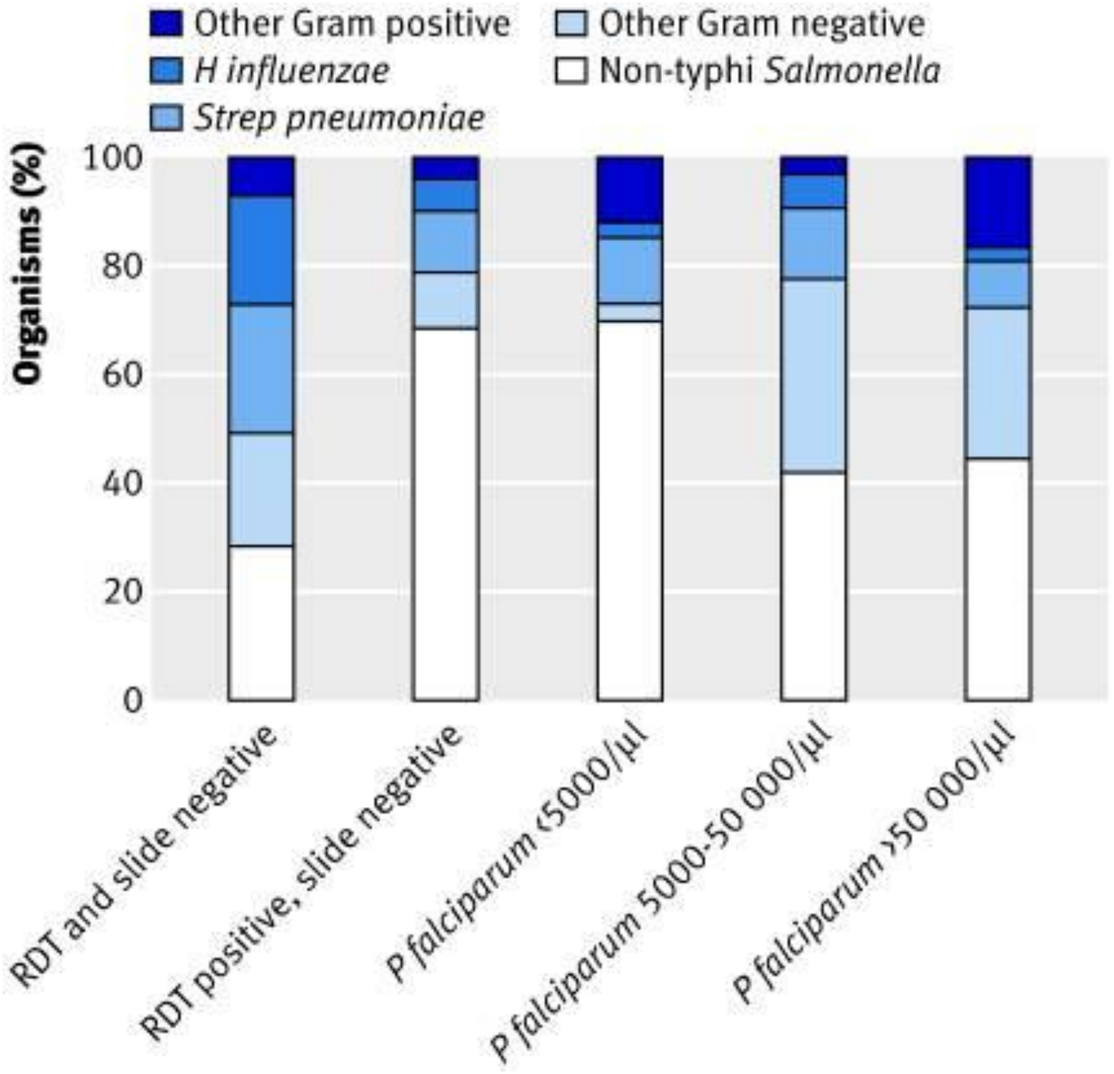
Febrile Paediatric Admissions to Muheza Hospital

Nadjm B et al BMJ 2010;340:c1350



Muheza Hospital

Nadjm B et al BMJ 2010;340:c1350



Risk factors for bacteraemia in African children

- Malnutrition
- HIV infection
- Sickle cell disease
- Admission to hospital
- ? Malaria

Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study

J Anthony G Scott, James A Berkley, Isaiah Mwangi, Lucy Ochola, Sophie Uyoga, Alexander Macharia, Carolyne Ndila, Brett S Lowe, Salim Mwarumba, Evasius Bauni, Kevin Marsh, Thomas N Williams

Lancet 2011; 378: 1316-23

Case-control study

- Children aged 3 months to 3 years
- Recruited between Sept 1999 and July 2002
- 292 cases admitted with bacteraemia
- 2 healthy controls for each case, matched for age, sex and location
- Sickle haemoglobin phenotype determined for cases and controls by electrophoresis

Results of case-control study

Bacteraemia was associated with

- HIV
- Malnutrition
- Sickle cell disease
- Leucocyte haemozoin pigment

Sickle trait (HbA/S) was negatively associated with bacteraemia (OR 0.36, 95% CI 0.20-0.65)

Is this because sickle trait protects against malaria?

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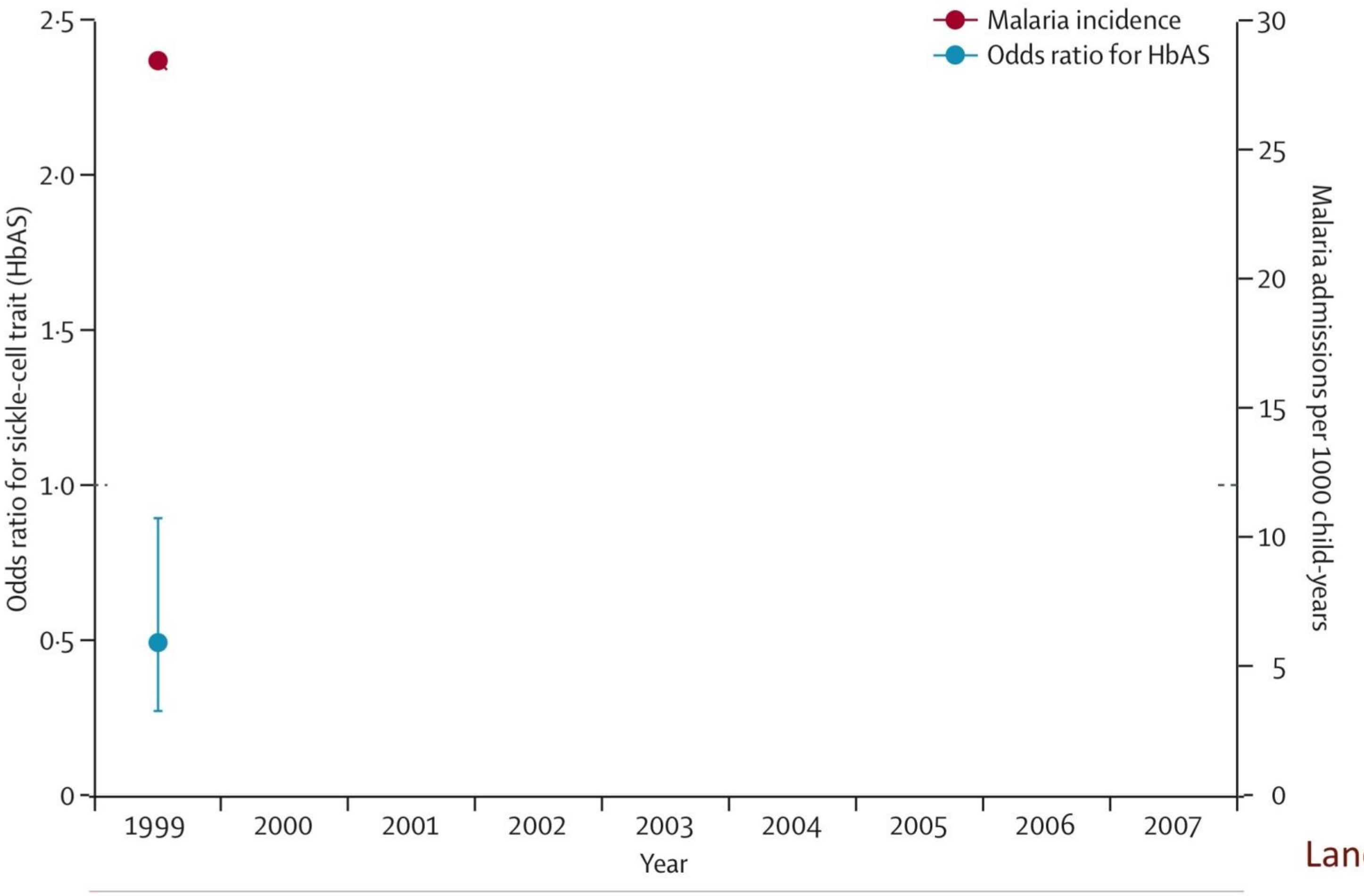

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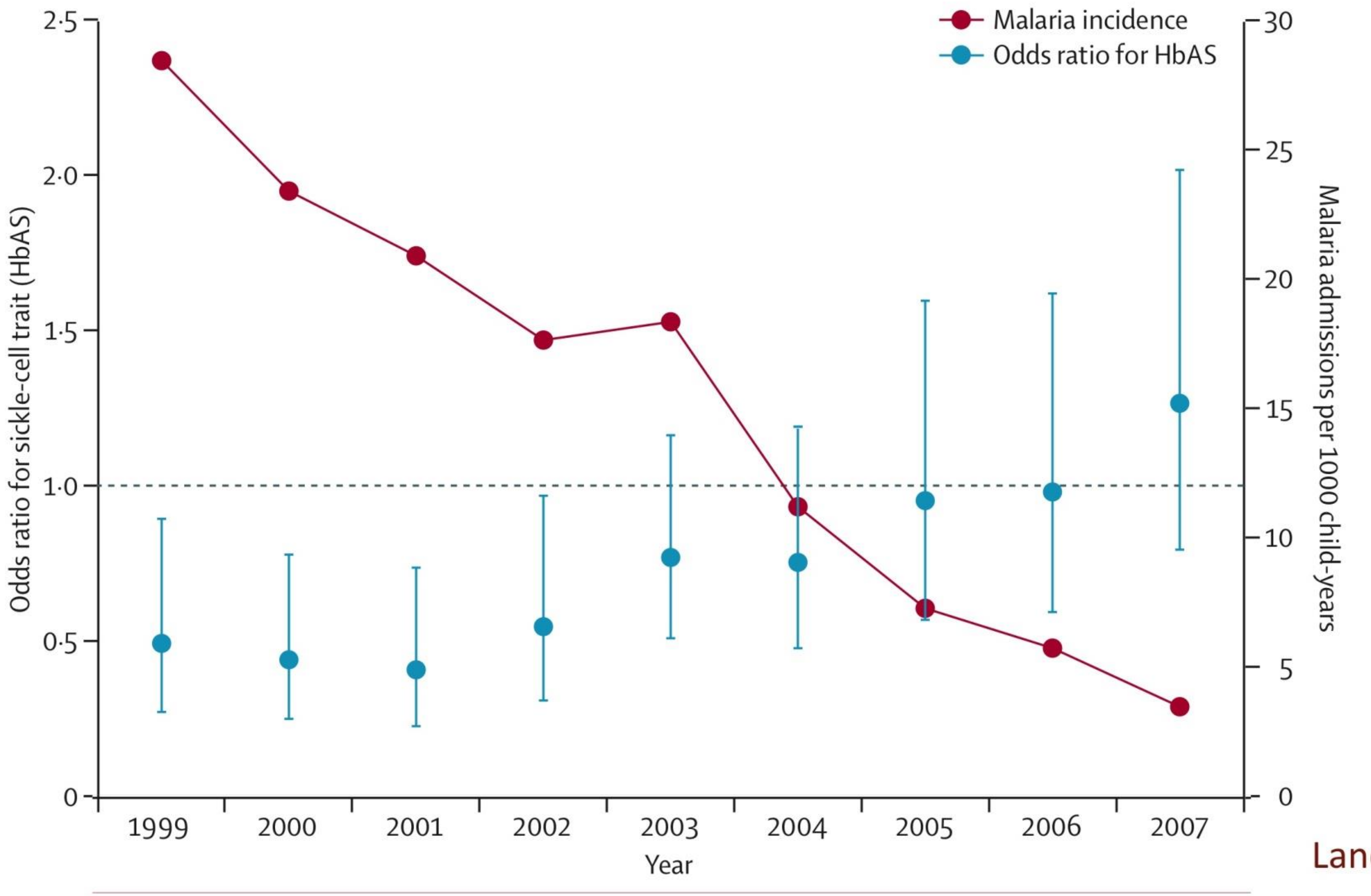


Lancet 2011;378:1316-23.

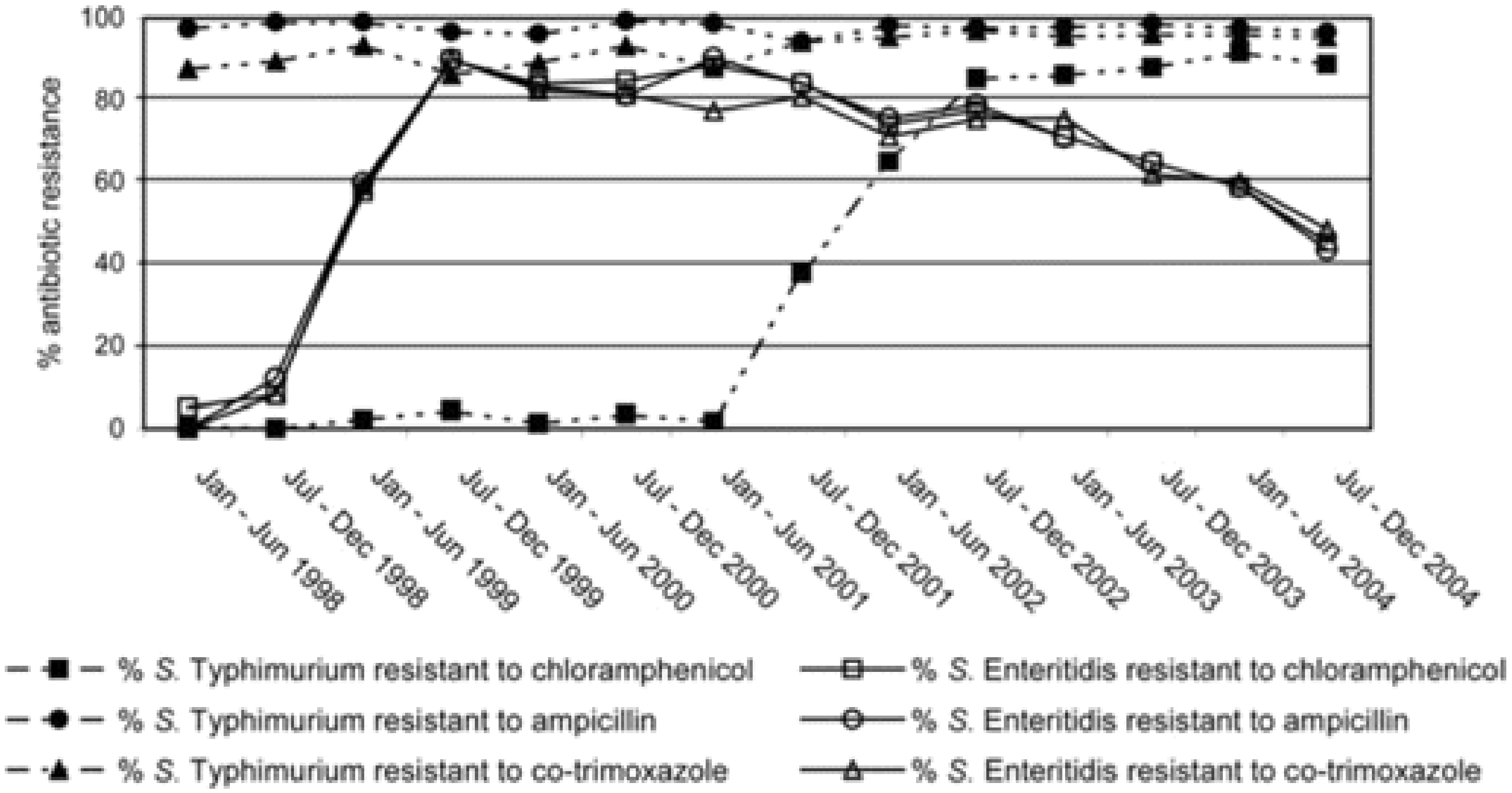
Conclusions

- Malaria is a risk factor for invasive bacterial infection
- Therefore a severely ill febrile child with or without malaria should be given an antibiotic

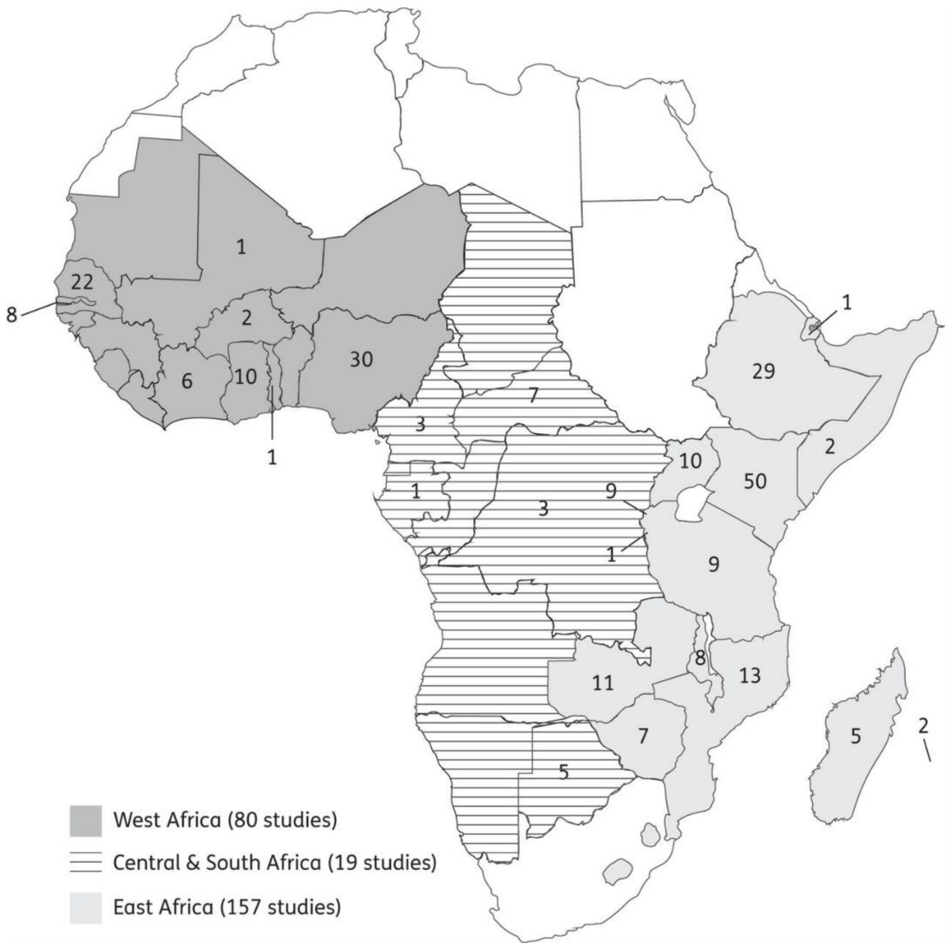
Which one?

Emergence of resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole among *Salmonella enteritidis* and *S. typhimurium* in Malawi, 1998–2004

Gordon MA et al Clin Infect Dis 2008; 46: 963



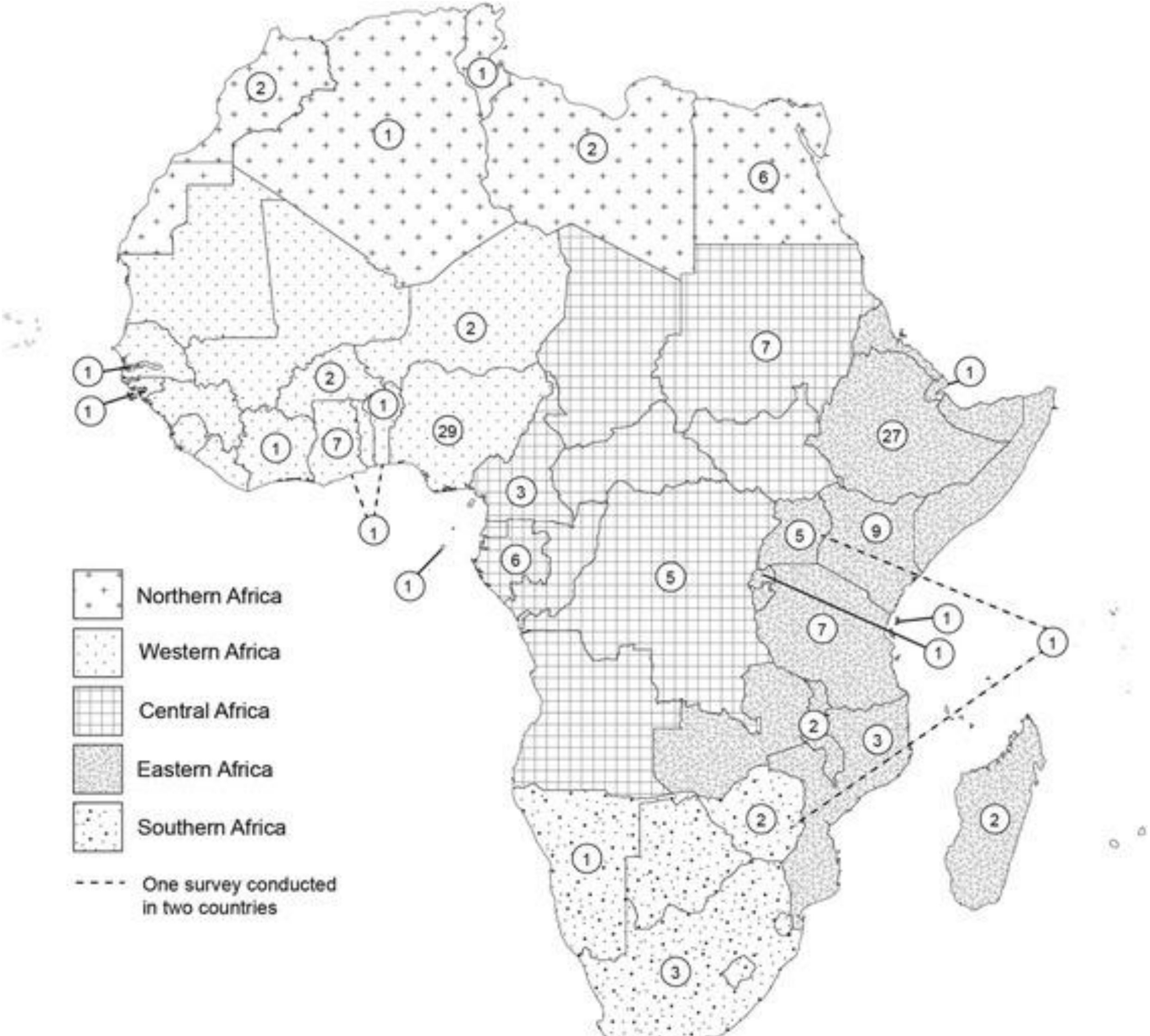
Publications on AMR in Africa 1990-2013



Leopold SJ et al. Antimicrobial drug resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a systematic review J Antimicrob Chemother. 2014;69(9):2337-2353

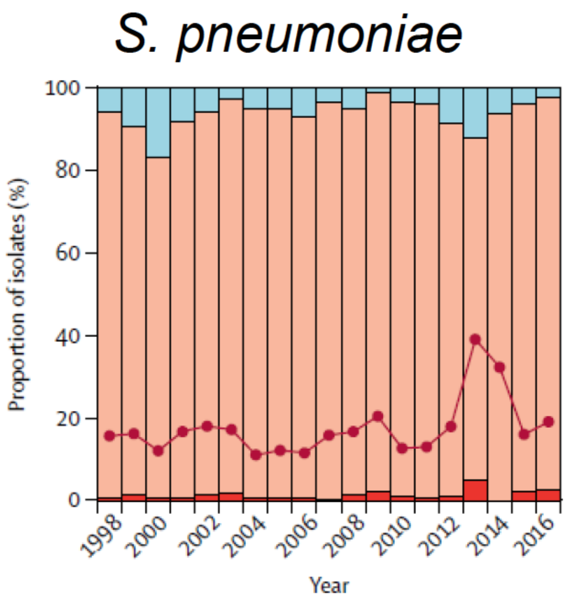
Publications on AMR in Africa 2013-6

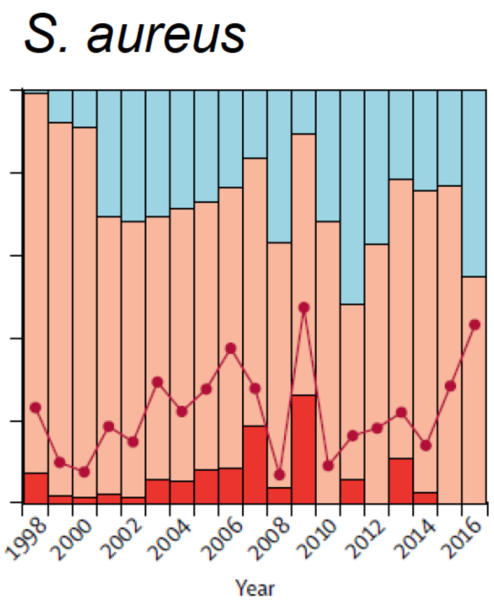
Tadesse BT et al. BMC Infectious Diseases 2017; 17: 616



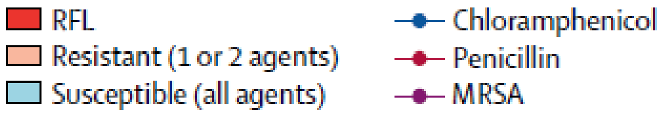
Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study

Patrick Musicha, Jennifer E Cornick, Naor Bar-Zeev, Neil French, Clemens Masesa, Brigitte Denis, Neil Kennedy, Jane Mallewa, Melita A Gordon, Chisomo L Msefula, Robert S Heyderman, Dean B Everett, Nicholas A Feasey





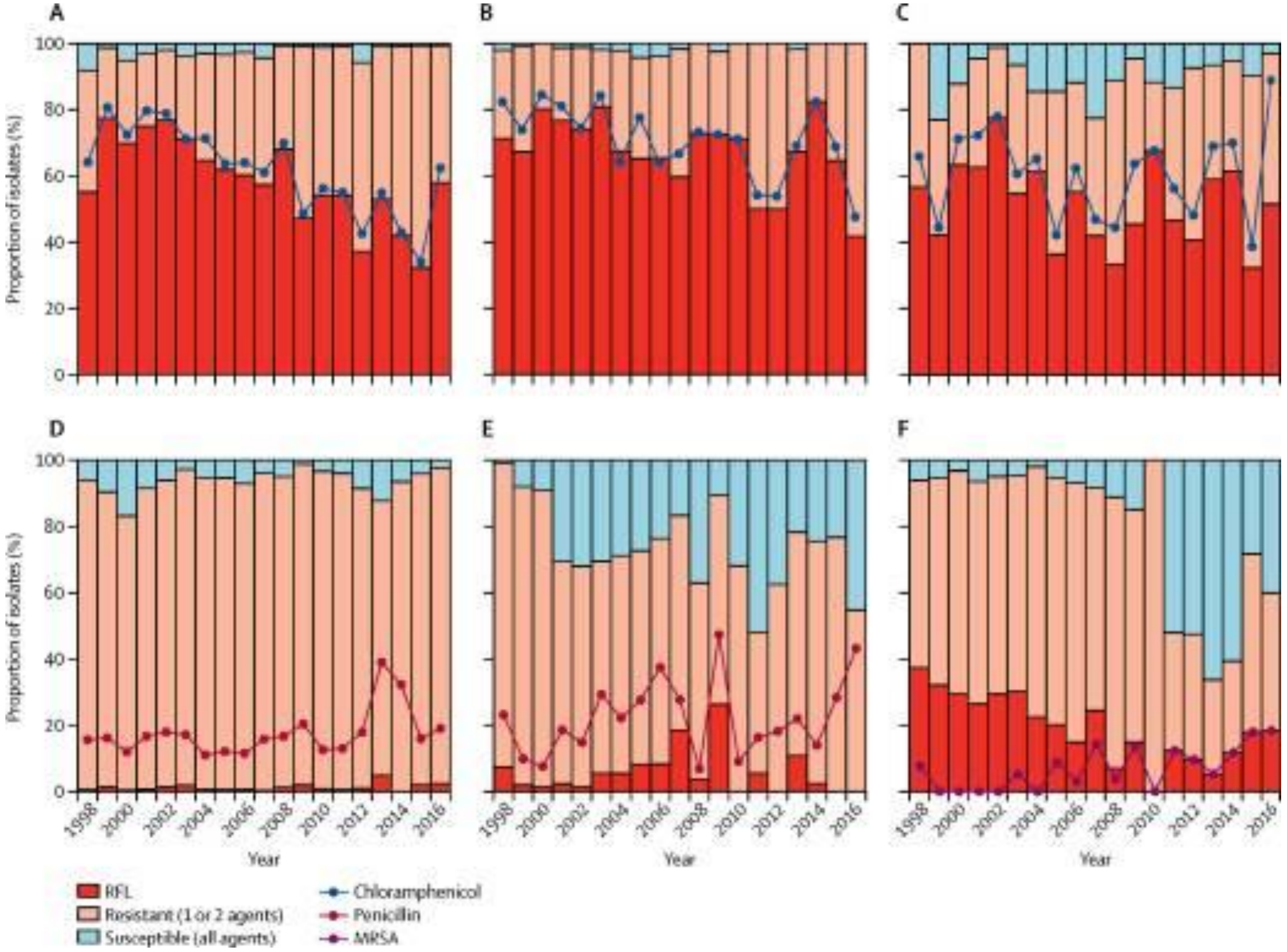
First –line antibiotics



RFL = resistant to penicillin, cotrimoxazole, chloramphenicol

Trends in Antimicrobial Resistance in Bloodstream Isolates in Malawi 1998-2016: 29,183 isolates from 194,539 blood cultures

Musicha P et al. Lancet Infect Dis 2017; 17: 1042



A) *Escherichia coli.* (B) *Klebsiella* spp. (C) Other Enterobacteriaceae.
(D) *S pneumoniae.* (E) *Staphylococcus aureus.* (F) Other *Streptococcus and Enterococcus* spp.

RFL=resistant to all first-line antimicrobials, which include chloramphenicol and co-trimoxazole, plus ampicillin for Gram-negative pathogens and penicillin for Gram-positive pathogens.

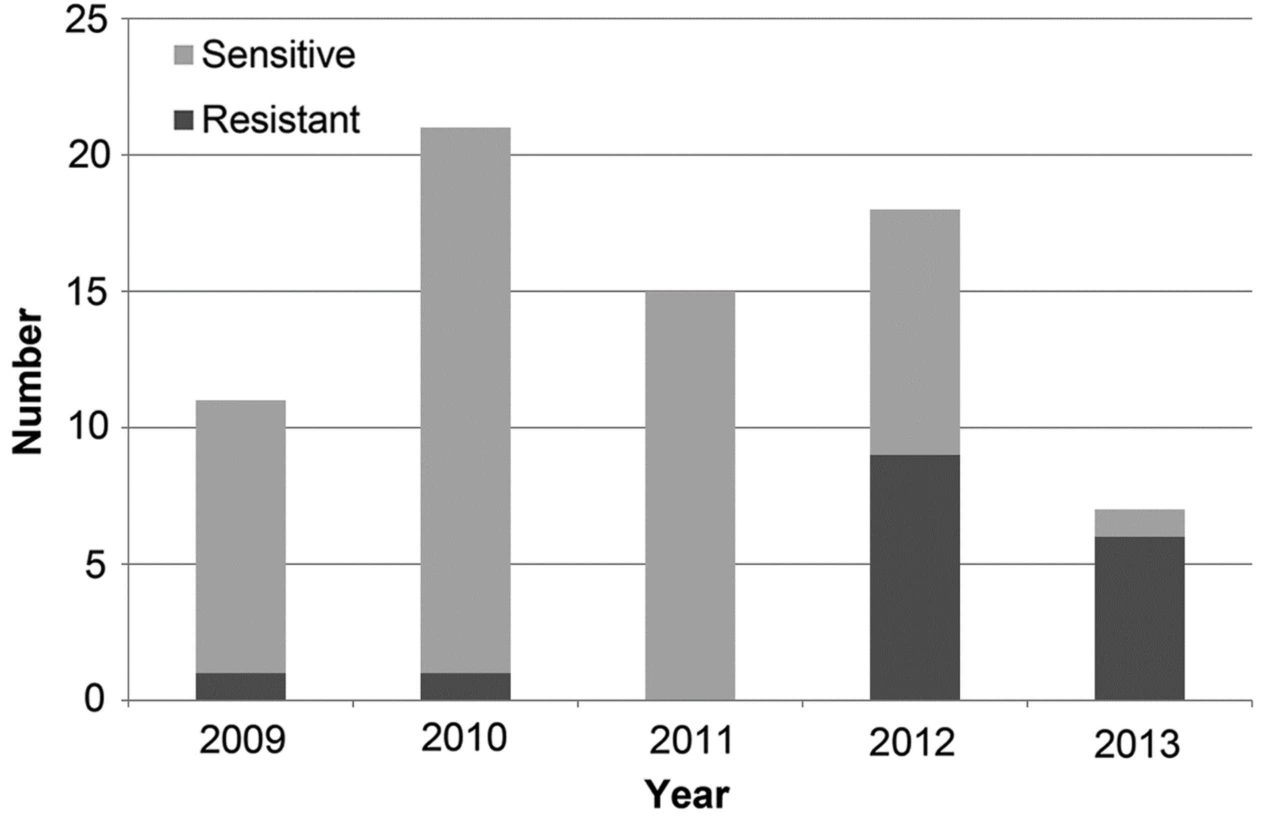
Resistance in NTS from Blood Cultures in Western Kenya

Oneko M et al. Clin. Infect. Dis 2015; 61 (supp 4)

Antibiotic	Resistant/Tested, No. (%)	
	Salmonella B (n = 72)[a]	*Salmonella* D (n = 30)
Ampicillin	64/68 (94.1)	27/30 (90)
Chloramphenicol	54/72 (75)	28/30 (93.3)
Amoxicillin + clavulanate	44/67 (65.7)	13/27 (48.1)
Ceftriaxone	17/72 (23.6)	0/30 (0)
Ciprofloxacin	1/71 (1.4%)	0/30 (0)
Imipenem	0/42 (0)	0/15 (0)
A, Au, C	36/64 (56.3)	13/30 (43.3)
A, Au, C, Gen, Cx	17/64 (26.6)	0/30 (0)

Ceftriaxone Resistant *Salmonella* from Blood Cultures in Western Kenya

Oneko M et al. Clin Infect Dis. 2015;61(suppl_4):S310-S316.



ensibilité

Antibiotic Susceptibility of *Salmonella* Strains from Blood Cultures in Bukavu, DRC

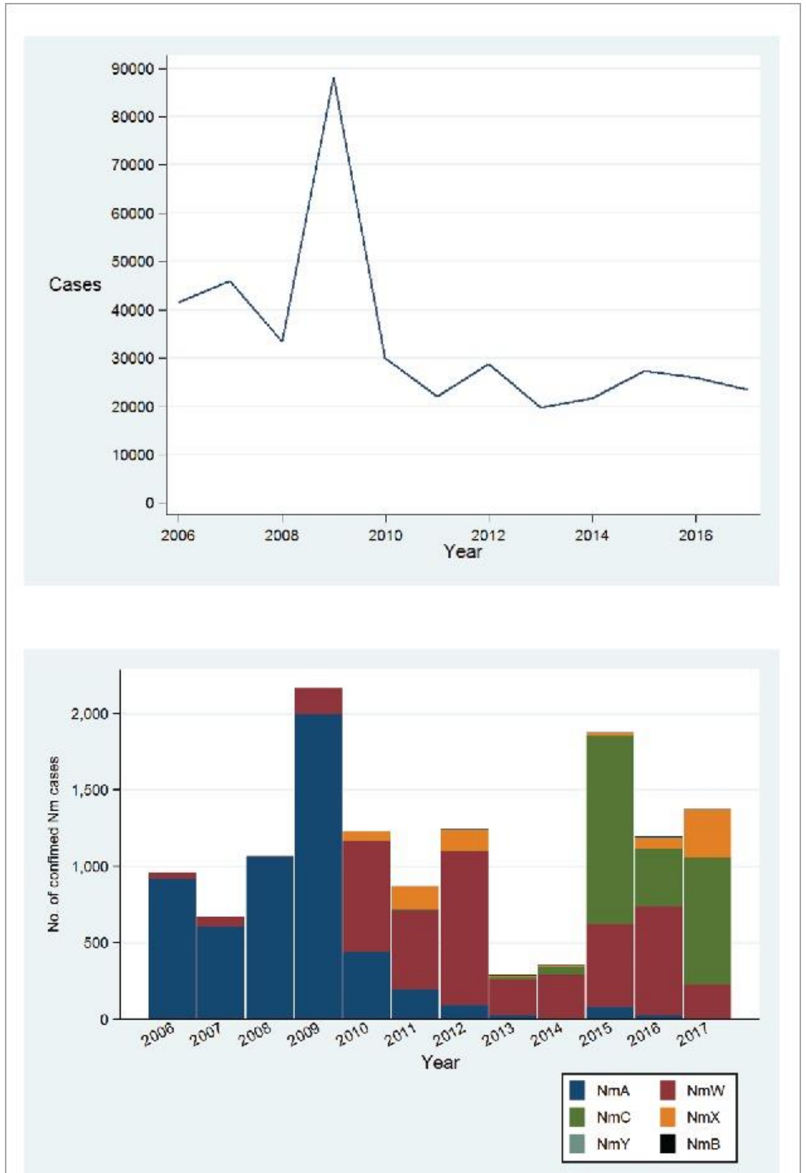
Kashosi TM et al. Pan Afr Med J 2018 Jan 17;29:42

Antibiotiques	Sensitive (%)	Intermediate (%)	Resistant (%)
Amikacine	46(76,6)	1(1,7)	13(21,7)
Amoxicilline	7(11,7)	-	53(88,3)
Augmentin	3(5)	-	57(95)
Ceftazidime	49(81,7)	-	10(18,3)
Ceftriaxone	48(80)	2(3,3)	10(16,7)
Cefuroxime	44(73,3)	-	16(26,7)
Chloramphénicol	5(8,3)	-	55(91,7)
Ciprofloxacine	55(91,7)	-	5(8,3)
Cotrimoxazole	6(10)	-	54(90)
Doxycycline	12(20)	4(6,7)	44(73,3)
Gentamicine	7(11,7)	-	53(32)
Négram	1(1,7)	-	59(98,3)
Norfloxacine	48(80)	-	12(20)

The African Meningitis Belt

Meningococcal Meningitis in the Meningitis Belt

Mustapha M and Harrison L. Hum Vaccin Immunother 2018; 14: 1107



Serogroup A conjugate vaccine rolled out in 2010

Febrile illness in Moshi

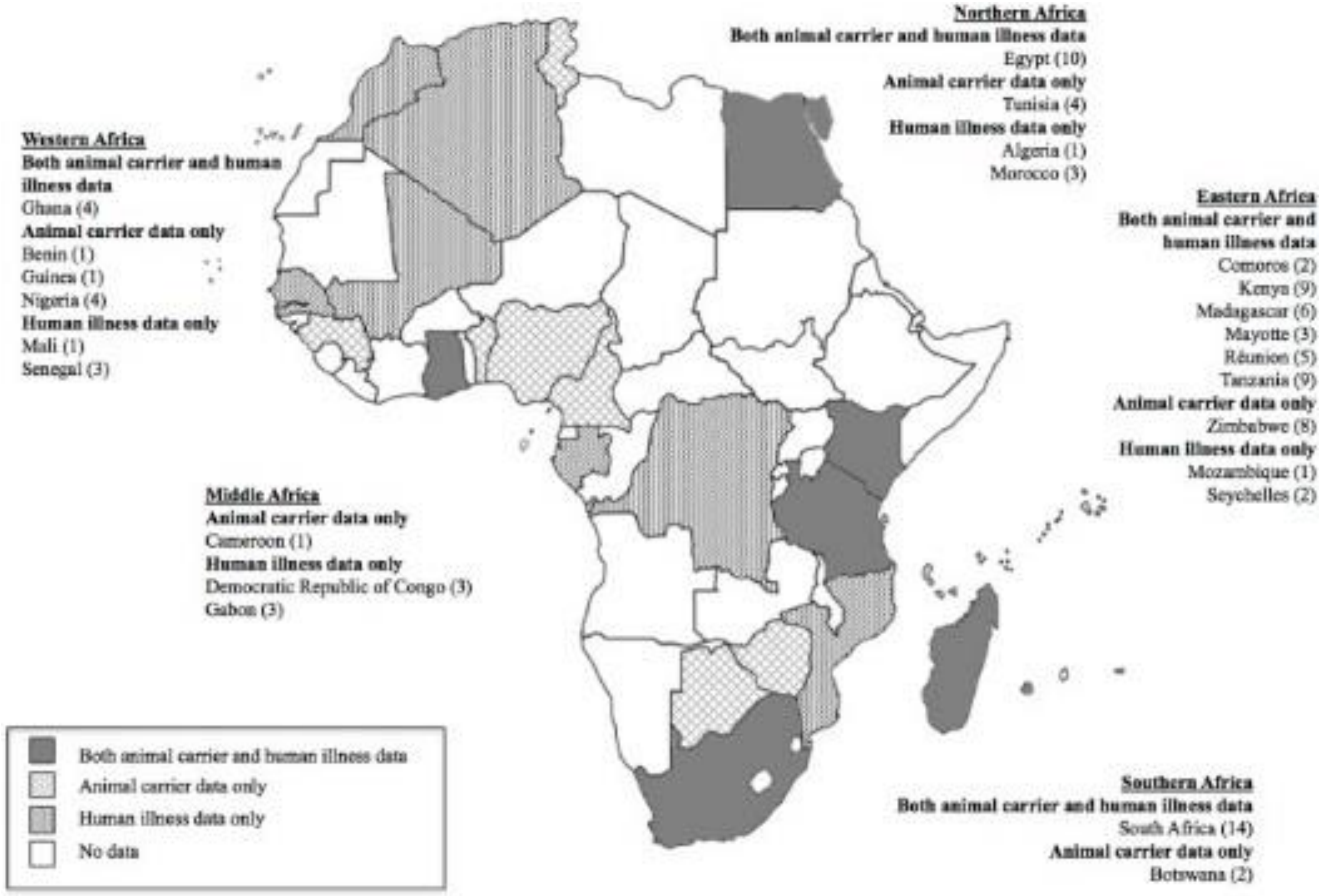
Crump J et al PLoS NTD 2013; 7(7): e2324

- Prospective study, 2 hospitals
- 870 consecutive admissions with fever (children and adults)
- 528 clinical malaria (60%)
- 14 confirmed (1.6%)
- 118 bacterial zoonoses (26%)
  - 16 brucellosis
  - 40 leptospirosis
  - 24 Q fever
  - 36 Rickettsia
- 55 chikungunya

None of the above were included in the differential diagnosis

Leptospirosis in Africa

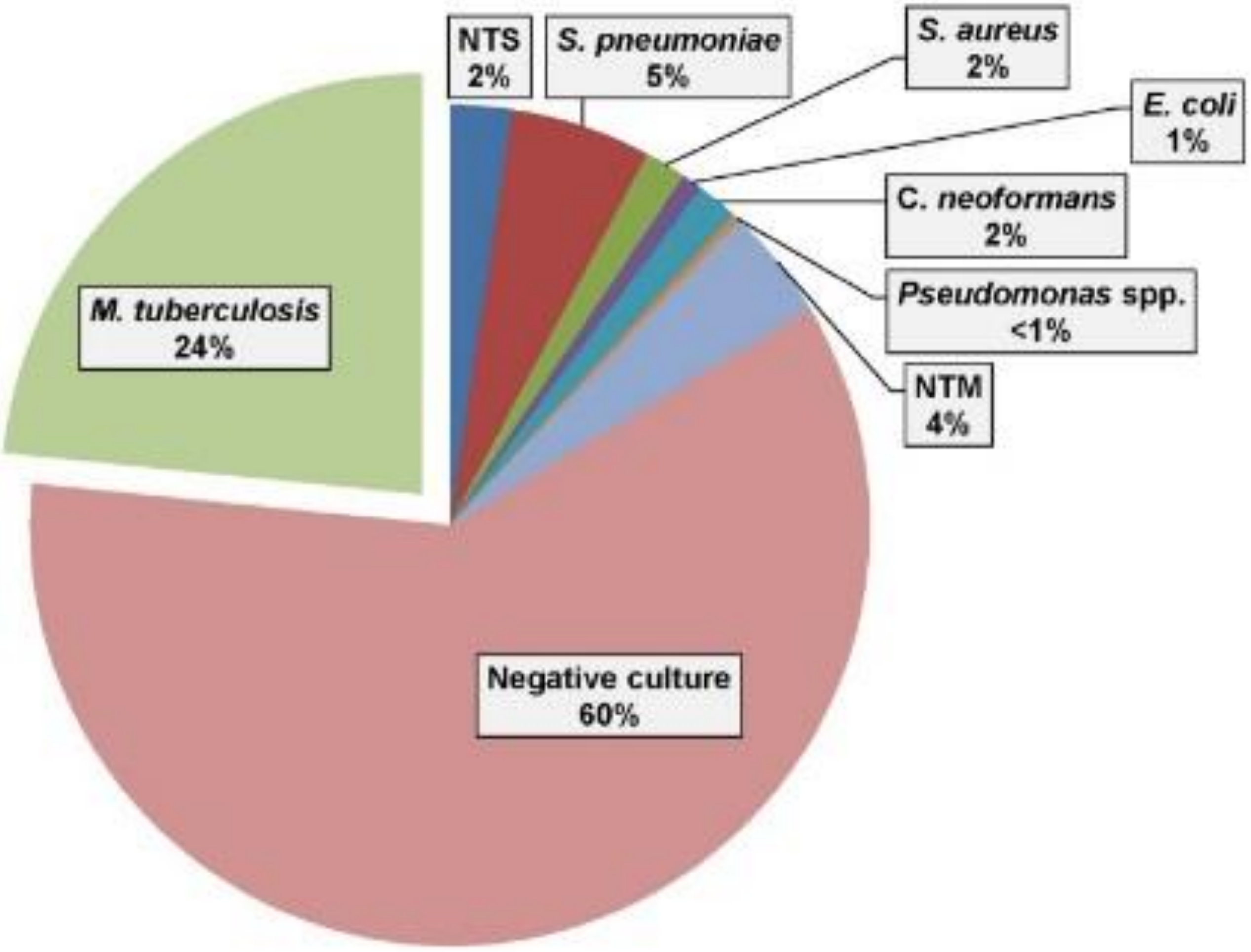
Allan KJ et al. Epidemiology of leptospirosis in Africa. PLoS NTDs 2015; 9: e0003899



2..3% -19.8% of inpatients with non-specific febrile illness had leptospirosis
(Data from 11 studies)

Ugandan HIV+ Patients admitted with severe sepsis

Jacob ST et al. PLoS One 2013; 8: e70205

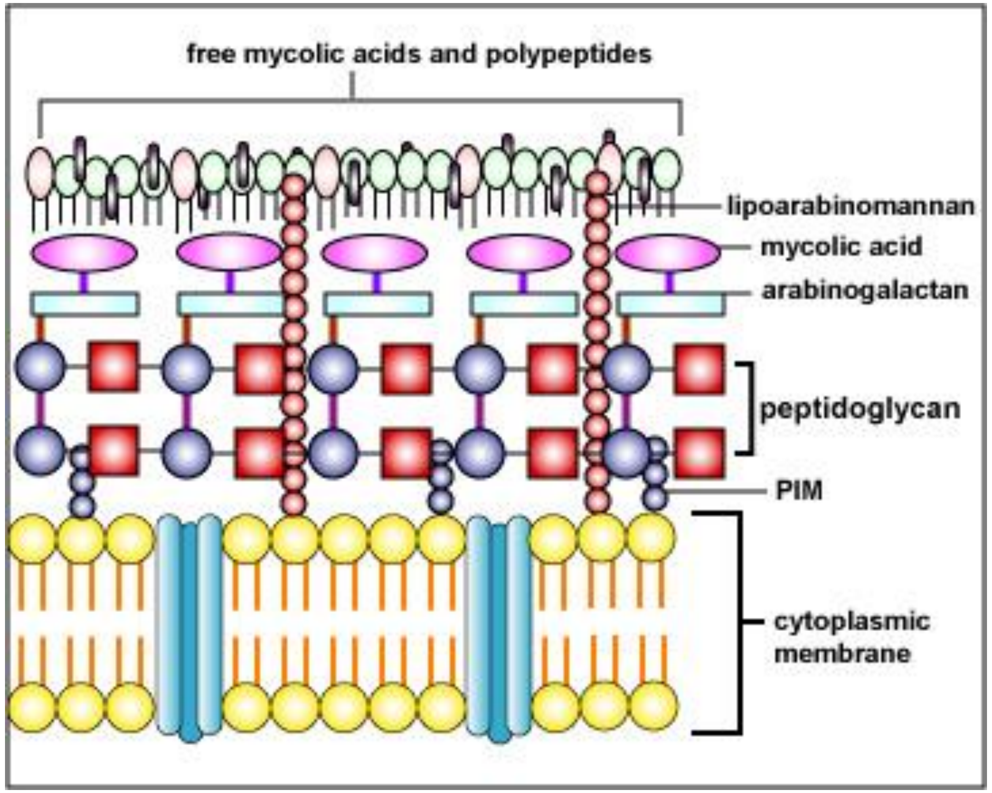


368 patients

Median CD4 count

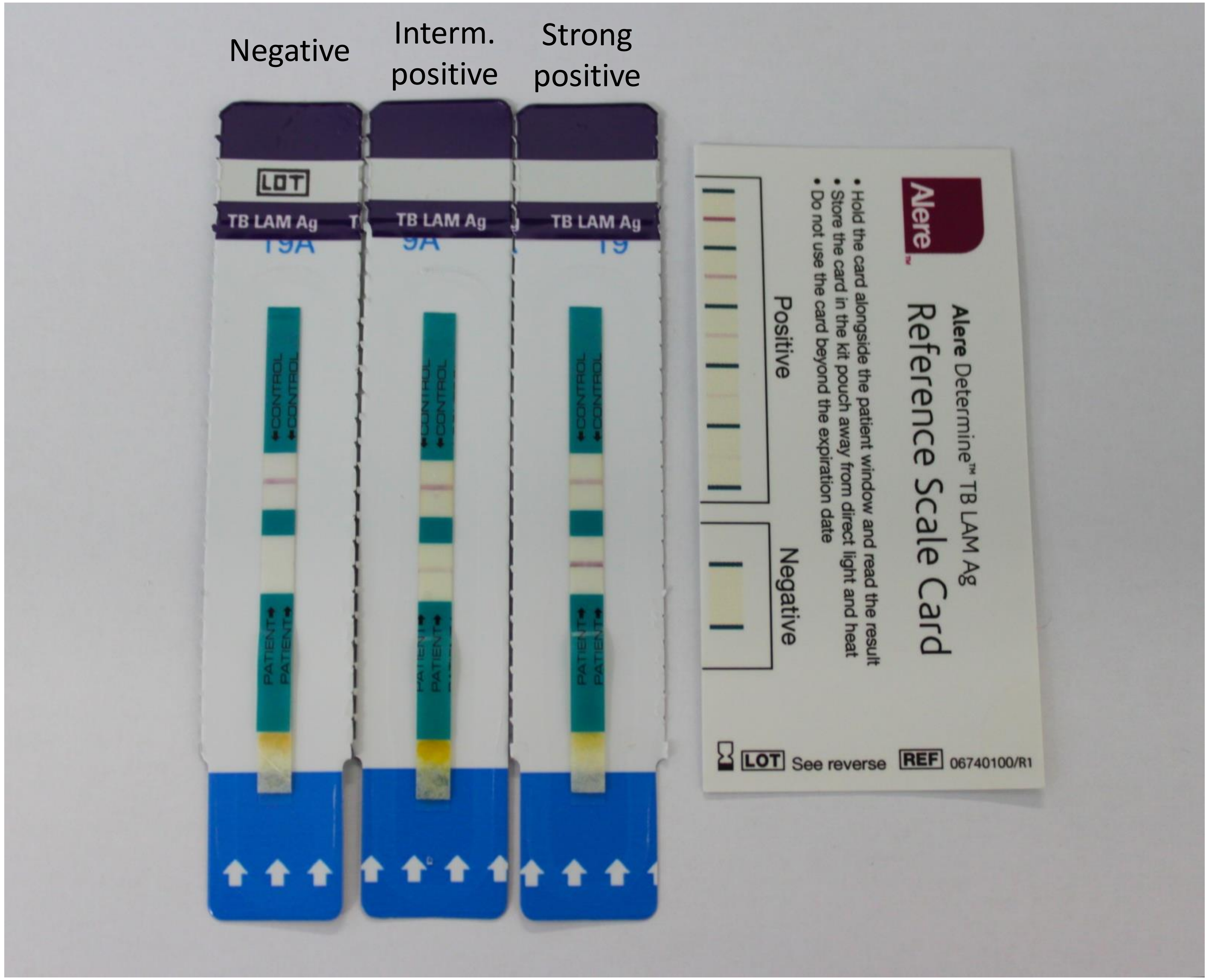
- 17 in *MTb* + cases
- 64 in others

Urine Antigen Detection to diagnose TB



Lipoarabinomannan (LAM)

Determine TB-LAM Ag

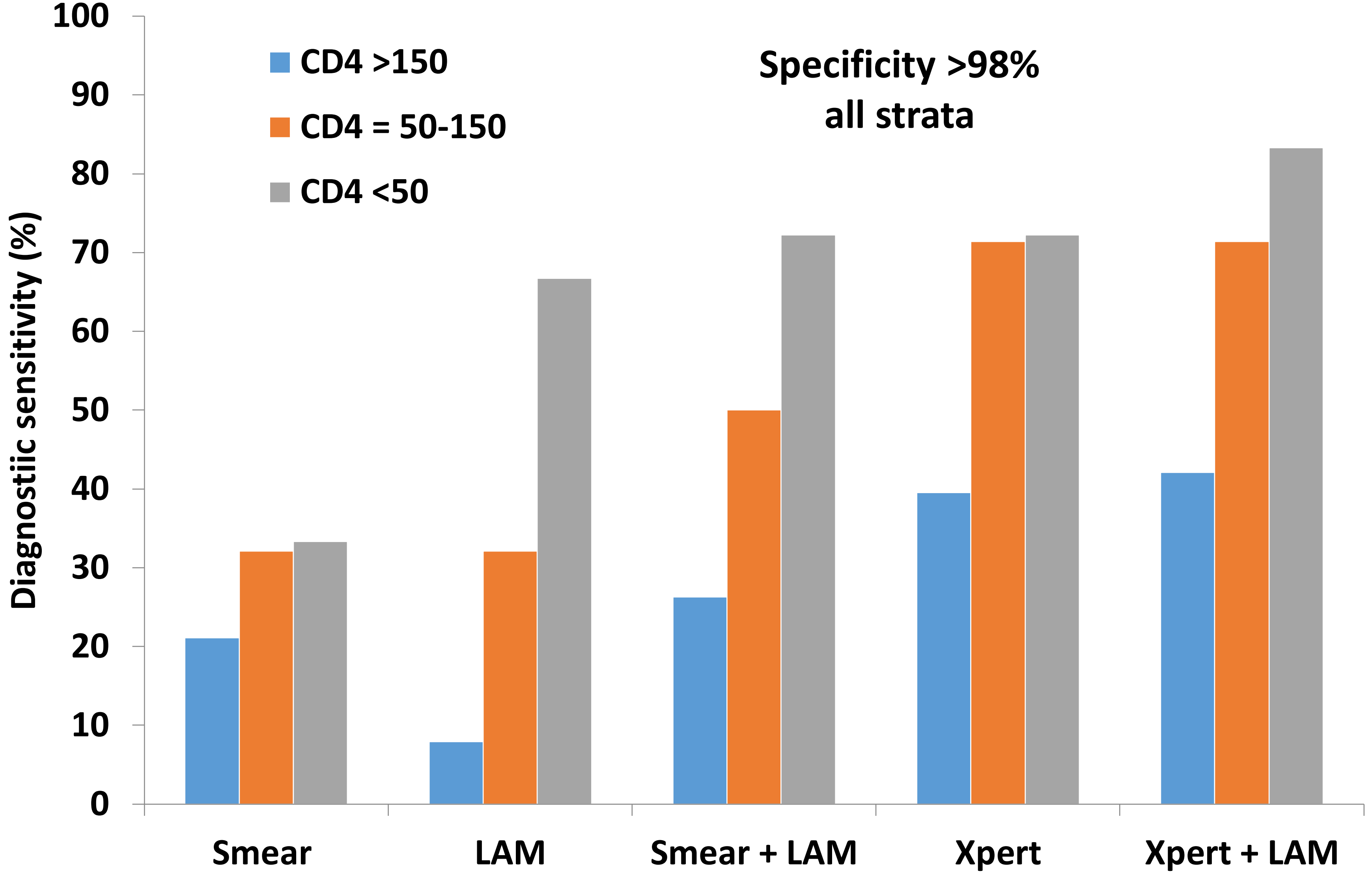


Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study

Stephen D Lawn, Andrew D Kerkhoff, Monica Vogt, Robin Wood

Sensitivity of LAM POC test

Lawn SD et al. Lancet Infect Dis. 2012;12:201-9.



Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial

***Lancet* 2018; 392: 292–301**

Ankur Gupta-Wright, Elizabeth L Corbett, Joep J van Oosterhout, Douglas Wilson, Daniel Grint, Melanie Alufandika-Moyo, Jurgens A Peters, Lingstone Chiume, Clare Flach, Stephen D Lawn, Katherine Fielding*

- RCT comparing standard of care with standard of care + urine testing by LAM POCT and GenExpert
- 2600 HIV + adults admitted to hospital in Malawi and South Africa
- Primary outcome: Mortality at 56 days

Results

- 72% of study subjects taking ART
- Median CD4 count 227
- Mortality overall was 21% in the standard of care group vs 18% in the intervention group (p=0.074)
- Mortality significantly reduced in the intervention group in those with CD4<100 (p=0.036)
- And in those with severe anaemia (p=0.021)

Invasive bacterial infections in Africa

- High incidence, especially in children
- High mortality
- Risk factors
  - HIV
  - Malnutrition
  - Sickle cell disease
  - Hospital admission
  - Malaria

Conclusions

Great progress has been made in the past 20 years

- 40% reduction in incidence of malaria between 2000 and 2015
- Vaccinations rolled out (Hib, pneumococcus, meningococcus)
- Antiretroviral treatment rolled out
- POC tests for malaria, HIV, TB, cryptococcal meningitis
- Identification of biomarkers associated with bacterial infections
- Clinical algorithms shown to reduce antibiotic prescription without affecting outcomes

Many challenges remain

- Rapid spread of antimicrobial resistance in major pathogens
- Incidence of malaria is no longer declining
- Serotype replacement when vaccines are rolled out
- Difficult access in regions with conflict
- Uncertain funding environment

<u>For the clinician</u>

Which febrile outpatients need an antibiotic?

Which antibiotic should I give to a febrile inpatient?

The Way Forward

- Further studies on causes of fever in different populations
- Roll out of global surveillance for antimicrobial susceptibility
- Development and evaluation of new vaccines
- Evaluation of new biomarkers to identify patients who need antibiotics in different settings
- Development and evaluation of new POC diagnostic tests
- Development and evaluation of new clinical algorithms for the management of fever in different settings
- New strategies for the control and elimination of malaria