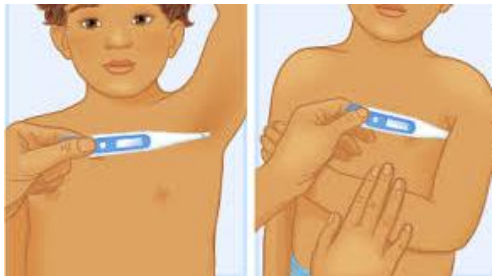
Management of Fever

- without (obvious) Cause
- without a focus
- with no obvious source of infection

SAPA, Cape Town Sept 2014

U Hallbauer

Fever

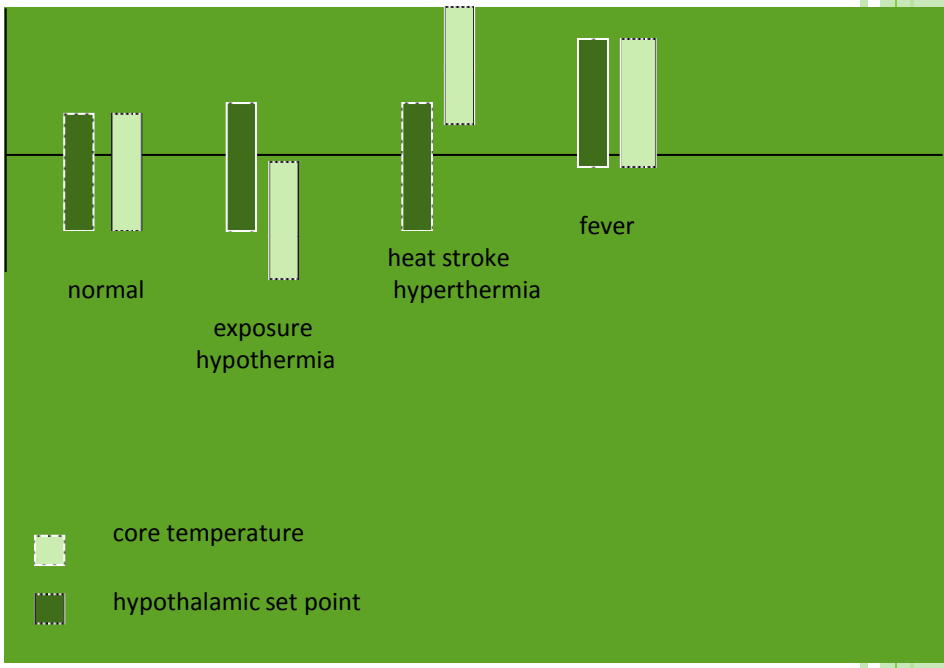


- ≥ 38°C
- Rectal – reflects core temp
- Axillary, tympanic membrane, temporal artery thermometry to measure
- Subjective determination by caretaker
  - moderately accurate
  - sensitivity 89.2%, specificity 50% (Teng et al)
  - ‘rule in’ rather than ‘rule out’ fever

Disadvantages of treating fever

Fever – Benefit

- Do no harm



- Fever may protect, has antimicrobial action
- May delay recovery from illness (eg malaria, varicella)
- Most fever is short-lived and benign
- Obscure diagnostic signs
- If the child is dehydrated, may induce renal failure
- Can induce hypothermia
- Attain lower antibody level if give antipyretic before or within 2 hrs of vaccination

Causes of fever

- Viral infections – usually self-limiting
- Fever without identifiable focus – a diagnostic problem
  - *Occult bacteraemia*
  - Serious bacterial infection

  Serious bacterial infections (SBI) – diagnosis usually clear
    - Meningitis
    - Pneumonia
    - Urinary tract infection
    - Bacterial gastroenteritis, enteritis
    - Osteomyelitis, septic arthritis
- Non-infectious causes
  - Kawasaki disease
  - Toxins
  - Malignancy

Fever in children

- Neonates
- 1 – (2) 3 months age
- 3 - 36 months
- > 36 months

- Risk of SBI decreases with age

NEONATES

- Immature immune system: greater risk of systemic infection, haematogenous spread
- Clinical signs not helpful

- UTI
- Meningitis
- Bacteraemia
  - grp B strep, E coli, Listeria,
- Viral infection and HSV

Incidence of SBI

- Neonates : up to a quarter
- < 3 months age: 6-10%
  - Relatively immature immune system
    - Decreased opsonin activity, decreased macrophage function, decreased neutrophil activity
- 3 - 36 months: 5-7%

Occult bacteraemia (OB)

- 1970's defn: "Bacteria in blood of otherwise well-appearing febrile child in absence of identifiable focal bacterial source of infection"
- At risk of developing focal disease
- Risk – febrile infants
  - < 36 months age

- In pre-vaccine era prevalence of OB 2-11% in fever without source : *S pneumoniae, H influenza b, Salmonella, Neisseria meningitidis*

The post-vaccine era

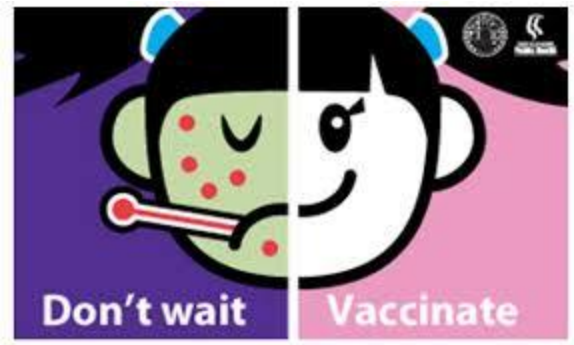
- Routine vaccinations : changed epidemiology

  Strep pneumoniae and *Haemophilus influenza b*

  Effect of conjugate vaccines greatest on 3-36 month old

Overall incidence of bacteraemia dropped to 0.17 – 0.36%

- Benefit also on unvaccinated if vaccine coverage > 80% (herd protection)



Occult bacteraemia 1 - 3 months – advances in medical practice, prenatal screening

- *E coli* (>50%)
- Less *Grp B strep* (antepartum identification and Rx)
- *Staph aureus*
- *Strep viridans*
- *S pneumoniae*
- *Klebsiella*
- *Salmonella*

Occult bacteraemia - age: 3-36 months – post conjugate vaccine era

- *Strep pneumoniae* non-vaccine serotypes, 19A
- *Strep pyogenes*
- *Enterococcus spp*
- *N meningitidis*
- *Non-type b H influenzae*
- *E coli*
- *Moraxella catarrhalis*
- *Salmonella spp*
- *Staph aureus*

Most are obviously sick, 12-16% unsuspected, consider risk factors (outbreaks, contacts)

most have diarrhoea

Fever – are there clues to diagnosis from the character of fever

- Hyperpyrexia (≥ 40 ^{o}C) - ↑ rates SBI in young
- Height of fever and SBI - do not correlate
- Duration and SBI - do not correlate
- Response to antipyretics does not differentiate bacterial or viral causes
- Bundling does not increase core temperature
- Teething does not cause fever

History and clinical examination

- Symptoms: not feeding or feeding well, convulsions

- Underlying medical conditions
- Exposure / contact to other ill people
- Immunizations : recent and immunization status

SBI

- Ill-appearing, *toxic*
- Abnormal mental status, lethargy
- Weak peripheral pulse
- Cool extremities, delayed capillary refill, hypotension
- 'Marbled' appearance
- Tachypnoea >60/min, chest indrawing

- Most well-appearing children do not have SBI
- Focus of infection

Parental concern
Clinician instinct

Lancet 2010;375:834-845

"Parental anxiety should not be discounted: it is often of significance even if the child does not appear especially unwell"

Other factors on examination

Less likely to have SBI if

- Clearly recognizable viral condition
- Lower risk stratification
- Tested positive for viruses (eg RSV, influenza, adeno, rota)

Often assumed if no bacterial source found,

but prevalence of SBI in the presence of these viral infections:

RSV: 1.1-7.0%

Influenza: 2.5%

Other investigations
sensitivity 0-69%, specificity 53-80%

- WCC : imperfect screening tool for meningitis and bacteraemia
  - 15000-20000/mm^3 -> sens 50-69%, spec 53-80%; of limited value to 'rule in/out' SBI
  - >15000 or <5000/mm^3 -> sens 42-86%, spec 74-77%, PPV 1.5-3.2%
  - Post PCV era: >15000/mm^3 -> PPV 1.5 – 3.2%
  - NT Salmonella: 54% had median WBC 10000/mm^3
  - Absolute neutrophil count
  - Diff count
  - Band counts – sensitivity 58% [95% CI 49-67]
  - Band : neutrophil ratio > 0.2

Other investigations

sensitivity 0-69%, specificity 53-80%

- CSF < 8wbc/mm^3
- Urine culture and

  ≥10wbc/HPF or bacteria on unspun urine or both
  dipstick leukocyte esterase or nitrites: sensitivity 88%
- CXR – for those with signs of lung disease
- Stool WCC < 5wbc/HPF – with diarrhoea

- C-reactive protein – sensitivity 74% [95% CI 49-67]
  - Screen for bacterial vs viral infection

- Procalcitonin – sensitivity 83% [95% CI 79-91]
  - Not sensitive enough? Does not 'rule out'
  - Increases more rapidly in bacterial infections compared to CRP and interleukins
  - Correlate with severity and mortality

- Interleukins
  - IL-6, IL-1, IL-8

The blood culture – the gold standard – Limited ? Cost effective

- Sample collection technique, time collection to incubation, culture media, previous antibiotics

- Time to growth: use antibiotics till show lack of growth of pathogen
- True positive = 1%
- False negative = ?; transient or intermittent bacteraemia
- False positive: high rate of contamination

  (62.5% - 70% - 87.8%) → increased treatment, cost and iatrogenic complications

- The future
  - – PCR assays (multisystem, short tat)
  - – assess host responses (pathogens induce distinct transcriptional 'biosignatures' in RNA of leukocytes which can be measured)

Viral pathogen detection

- New pathogen detection techniques will affect way SBI is evaluated
- Rapid testing for viral pathogens: ↓ other tests, ↓antibiotic use, ↓hospital days
- Most common: adeno, HH6, entero
- Does not exclude SBI (in conjunction with RSV and infl)

- Future studies important

Guidelines and research

- Excluded children with pre-existing medical conditions
- Excluded infants born prematurely
- Assume that children appear non-toxic

- No single biomarker, clinical sign, other lab test or in combination, can reliably identify SBI in febrile child

- → clinical decision rules

Risk stratification rules

- Have in common:
  - Infants must appear well
  - No focal infection on clinical examination
  - WCC in normal range
  - Urine testing no evidence of UTI

- Low risk infants discharged home

Risk stratification rules (identifies those with low risk of SBI)

- Rochester criteria (<60 days)
  - Low-risk: appear well, previously healthy, WCC 5000-15000, normal absolute band counts (<1500), <10wbc/HPF spun urine, *CSF not mandatory (but consider strongly),* CXR
  - Negative predictive value 98.9%

- Philadelphia criteria (29-56 days)
  - Appear well, WCC<15000, band:neutro≤0.2, normal CXR, urine <10wbc/HPF, CSF < 8 wbc/HPF, stool no wbc's (if diarrhoea)
  - 8.7% had SBI

- Boston criteria (1-3mths)
  - Appear well, no abnormal clinical findings, CSF < 10 wbc/HPF, urine <10wbc/HPF, dipstick leuko esterase neg, WCC 5000 - 20000/mm^3, normal CXR
  - 5.4% still have SBI

Risk classification and SBI: neonates

- Rochester criteria: neonates meeting low risk criteria
  - 1% (2/227) SBI
  - 6% had SBI
- Philadelphia criteria
  - High risk: 18.6% SBI
  - Low risk: 4.6% SBI

Other investigators had similar findings

Therefore: All neonates should receive antibiotics

Hospitalization strongly recommended in neonates

Lab score

- Procalcitonin <0.5 >0.5 >2
- C-reactive protein <40 40-99 ≥100
- Urine dipstick (leuko esterase or nitrite) neg / pos

- Scores for each age group (<3m, 3-12m, >12m), add up
- → sens, spec, PPV, NPV,LR+, LR-

Evaluation of neonates

- Up to a quarter with fever may have SBI:
- History: maternal fever, prematurity
- Physical findings – limited and unreliable:

  high / low temperature, lethargy, seizures, rash, respiratory distress

ALL NEED WORK-UP

- Blood, urine (catheter or supra-pubic), CSF (HSV-PCR), CXR
- WCC – value insignificant to discriminate SBI or non-bacterial disease
- ↓platelets, ↑liver enzymes – HSV
- U-cultures necessary - faster tests don't detect all UTI

Evaluation of 1 – (2) 3 month old infant

- Clinical examination may miss SBI
- Need lab testing
- Not apparent SBI in this age group (esp <6wks)
  - UTI : urine – females <24 m, uncircum males <12m, circum males < 6m
  - Bacteraemia : blood / CSF cultures as indicated
  - Pneumonia : CXR if indicated

- Advice will continue to vary in comprehensiveness
- Depends on setting
- Depends on rapid screening panels

- No single algorithm recommended
- Investigate, 3rd gen cephalosporins until culture negative
- Follow-up in 24 hours if not hospitalized

Fever and.....

- …are healthy, appear well
  - Term
  - Normal results on screening
  - Follow-up within 24 hours
  - Easy access to health care
  - Agreement with parents on plan of action
  - Withholding antibiotics is acceptable
  - →manage on outpatient basis
- …abnormal results, appear ill
  - Require inpatient care

Evaluation of > (2) 3 months – 36 months

- No single guideline, algorithm, combination lab tests

Compared to the younger infant:

- History more useful
- Assess immunization history
- Physical examination more informative
- Well vs ill vs toxic: SBI 3% vs 26% vs 92%

The older child >36 months

- If no focal source of infection, do not require antibiotics
- Pneumonia: consider macrolides for *M pneumonia* or amoxicillin for moderate pneumonia
- Moderate – severe pneumonia: resp distress, hypoxia, <3-6 mths, virulent pathogen, poor feeding, inability to take oral Rx
- Staph: consider vanco or clindamycin
- Antibiotics: UTI, pneumonia, suspected bacteraemia – but not all need admission
- No antibiotics if no blood cultures taken

Evaluation and management – varies among children

- Limitations of history
- Limitations of physical examination
- Changing epidemiology of SBI
- New diagnostic tests
- Lack of expert consensus
- Varying acceptance of risk by parents
- Differences in populations (developed vs underdeveloped; high vs low social class; rich vs poor)

- Child's age
  - Neonate
  - 1-(2) 3 months
  - (2) 3 – 36 months
  - > 36 months

Implications

Variation in guidance : fever young infant

- Cost
- Safety (eg iatrogenic overuse : LP)
- Empiric antibiotics
- Unnecessary hospitalizations

- Many studies done in single centres or small groups
- Retrospective study design
- Different inclusion criteria
- Clinical and lab criteria differ slightly
- Screening tests: reliability of differentiating bact / viral
- New pathogen detection techniques evolving

Fever in africa

- Prevalence of bacteraemia (8.2%) of inpatients more than in wealthier areas and differs whether malaria area or not
- Gram positives more than Gram negatives:

  Strep pneumonia, *Staph aureus*;

  Salmonella enterica, *E coli*, *H influenzae*
- Blood culture positive more likely if also has malaria

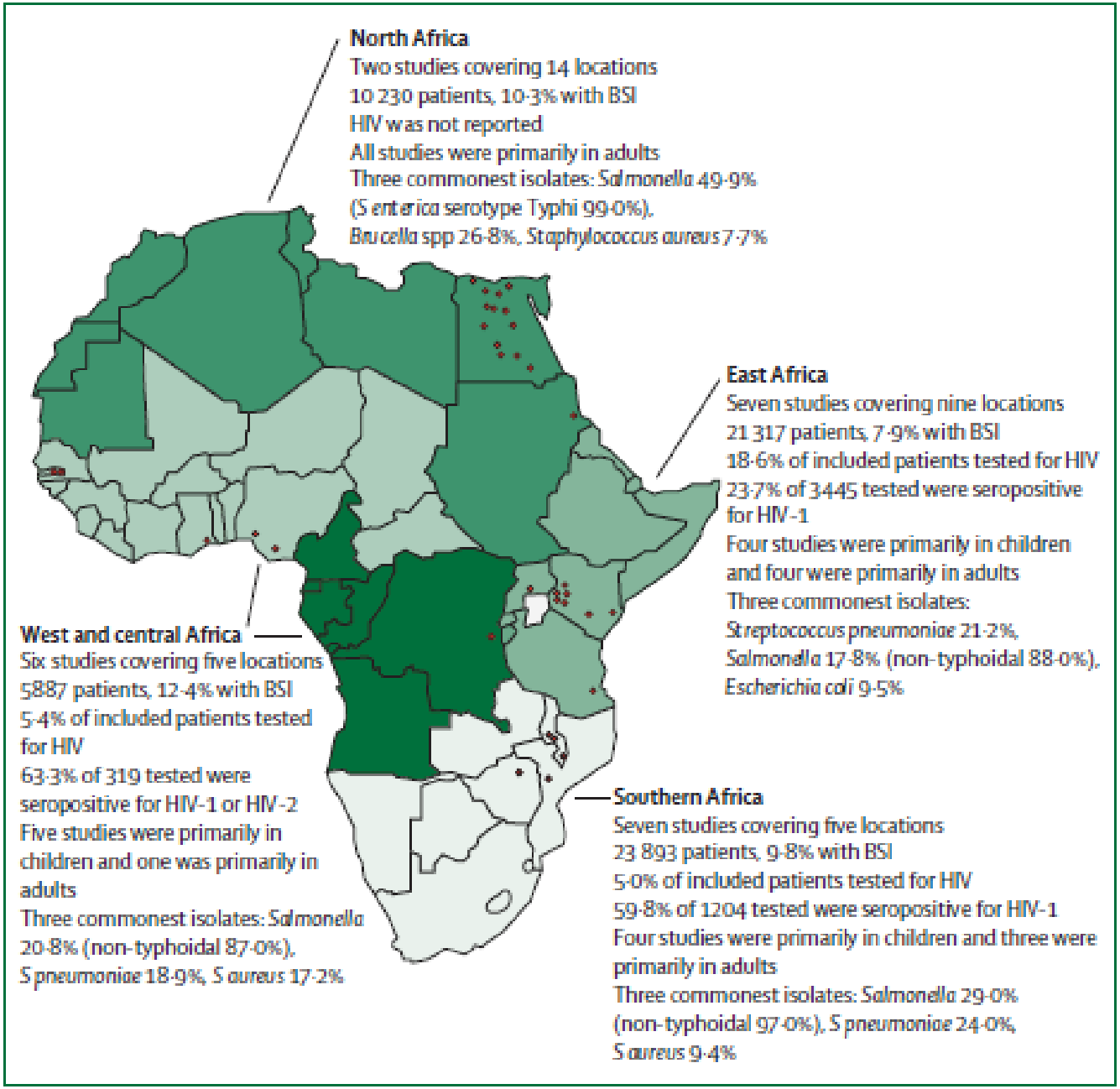


Figure 2: **Study locations and summary findings including prevalent pathogens**
Mycobacterium tuberculosis was excluded because adequate comparison of its relative importance could not be made since several study sites did not use culture media capable of isolating mycobacteria.

Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. Lancet Inf Dis 2010;10:417-32 [studies from 1984-2006]

Isolates and HIV infection

	Total isolates (proportion of patients with BSI)	Number of patients infected with HIV (proportion of patients with BSI)	Number of patients not infected with HIV (proportion of patients with BSI)	OR for those infected with HIV
Bloodstream infection[4,21,26,38,48,66,73]	596 (26·6%)	486 (34·5%)	110 (13·1%)	3·4 (p<0·001)
Staphylococcus aureus[21,26,38,73]	38 (4·5%)	18 (2·0%)	20 (3·6%)	p>0·05
Streptococcus pneumoniae[4,21,26,38,73]	66 (3·7%)	48 (4·1%)	18 (3·0%)	p>0·05
Non-typhoidal *Salmonella*[4,21,38,73]	99 (6·7%)	92 (9·7%)	7 (1·3%)	8·2 (p<0·001)
Salmonella enterica serotype Typhi[21,26,38,73]	8 (0·7%)	1 (0·1%)	7 (1·8%)	0·07 (p<0·001)
Non-*Salmonella* Enterobacteriaceae[4,21,26,38,52,73]	50 (3·8%)	34 (3·8%)	16 (3·8%)	p>0·05
Escherichia coli[4,21,26,38,52,73]	30 (1·6%)	21 (1·8%)	9 (1·5%)	p>0·05
Mycobacterium tuberculosis complex[4,21,26,38,66]	166 (12·4%)	161 (17·9%)	5 (1·1%)	23·4 (p<0·001)

BSI=bloodstream infections. *Archibald et al[38] included 30 infants <18 months with HIV seropositivity alone; Nathoo et al[26] included 61 infants <18 months seropositive for HIV with clinical immunosuppression; Vugia et al[73] included 139 patients infected with HIV-1, 22 infected with HIV-2, and with 41 co-infected HIV-1 and HIV-2.

Table 3: Causes of bloodstream infection by HIV serostatus* in seven African studies, 1993–2004

	Reported positive association (p<0·05)	OR range, where reported*	Reported negative or no association
Lethargy or restlessness	Four paediatric studies[14,15,25,43]	OR 2·4–4·4[14,25,43]	--
Oral candidiasis	Two paediatric studies[14,25]	OR 1·8–7·2[4,14,25,46]	--
	2 adult studies[4,46]	--	--
Jaundice	One paediatric study[2]	OR 2·3–7·8[2,46]	--
	Two adult studies[4,46]	--	--
Splenomegaly	One paediatric study[2]	OR 1·7–2·5[2,4]	No association: three paediatric studies[14,25,43]
	One adult study[4]	--	--
Hepatomegaly	Two paediatric studies[4,14]	OR 2·0–5·0[4,14]	No association: one adult study[4]
Malnutrition or wasting	Four paediatric studies[14,25,48,52]	OR 1·8–7·3[14,25,48,52]	No association: one paediatric study[73]
		--	One adult study[73]
		--	Negative association: one paediatric study[2]
Fever >38·9°C	Two paediatric studies[14,15]	OR 2·1–4·4[4,14,46]	--
	Two adult studies[4,46]	--	--
Anaemia	Any BSI:† two paediatric studies[2,52]	Any BSI: OR 2·0[2,52]	--
	One adult study[73]	--	--
	Mycobacterial BSI: two adult studies[4,76]	Mycobacterial BSI: OR 9·5[4]	--
Leucopenia	White blood cells <5000 cells per mL: one adult study[4]	OR 2·1[4]	--
	White blood cells <1000 cells per mL: one adult study[73]	--	--
Leucocytosis >15 000 cells per mL	Two paediatric studies[14,43]	OR 2·4[14]	--

BSI=bloodstream infection. * Comparison of the prevalence of the following findings among patients with BSI versus those without BSI; data from adult and paediatric studies are both presented in these ranges. †Sigauque et al[52] found anaemia significant in multivariate, but not univariate, analysis.

Table 5: **Clinical and laboratory associations with non-malaria bloodstream infection from 12 studies, Africa, 1991–2006**

Beyond Malaria — Causes of Fever in Outpatient Tanzanian Children

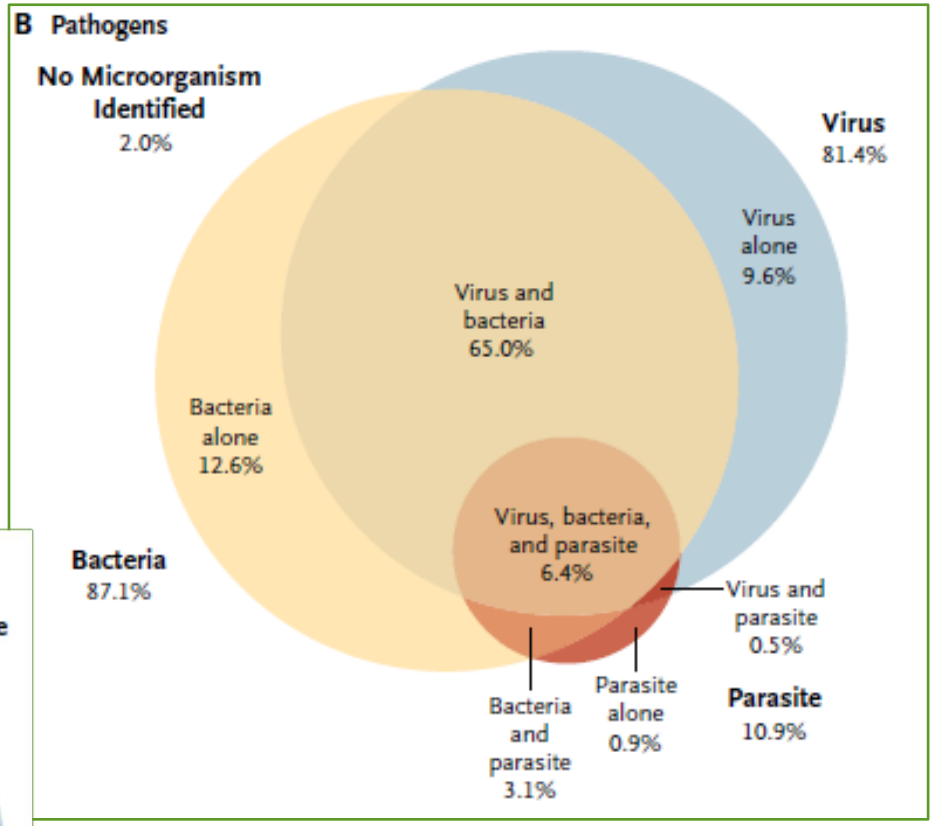
Valérie D'Acremont, M.D., Ph.D., Mary Kilowoko, M.P.H., Esther Kyungu, M.D., M.P.H., Sister Philipina, R.N., Willy Sangu, A.M.O., Judith Kahama-Maro, M.D., M.P.H.,* Christian Lengeler, Ph.D., Pascal Cherpillod, Ph.D., Laurent Kaiser, M.D., and Blaise Genton, M.D., Ph.D.

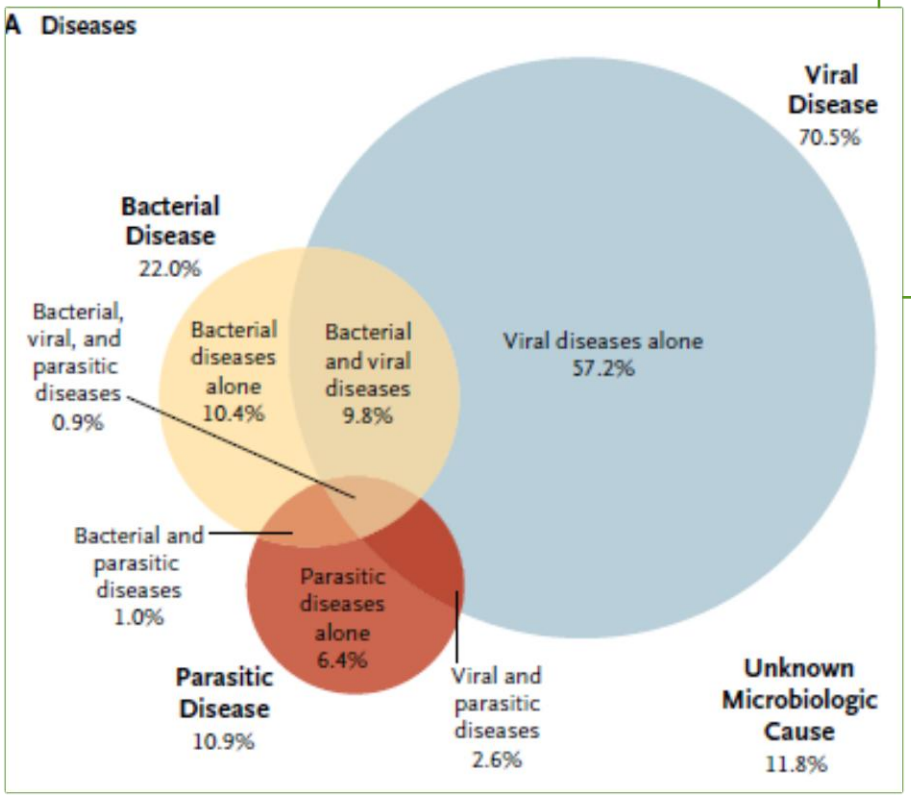
NEJM 2014;370:809-817

- 1005 children 2mths to <10 yrs. Urban and rural site. 2008
  - Excluded severe malnutrition and with emergency signs
- Malaria 10.5% (point of care tests available)
- Acute respiratory 62.2% of whom <13% required antibiotics
- Gastroenteritis 10.2%
- UTI 5.9%
- Multiple diagnoses in a quarter

- Cause of fever undetermined in 3.2%
- 88% had at least one microbe identified, 2/3 had at least two
- 70.5% had viral disease
- 22.0% had bacterial disease
- 10.9% had parasitic disease
- 13.2% had severe disease
- 22.6% had multiple conditions

Disease and pathogens





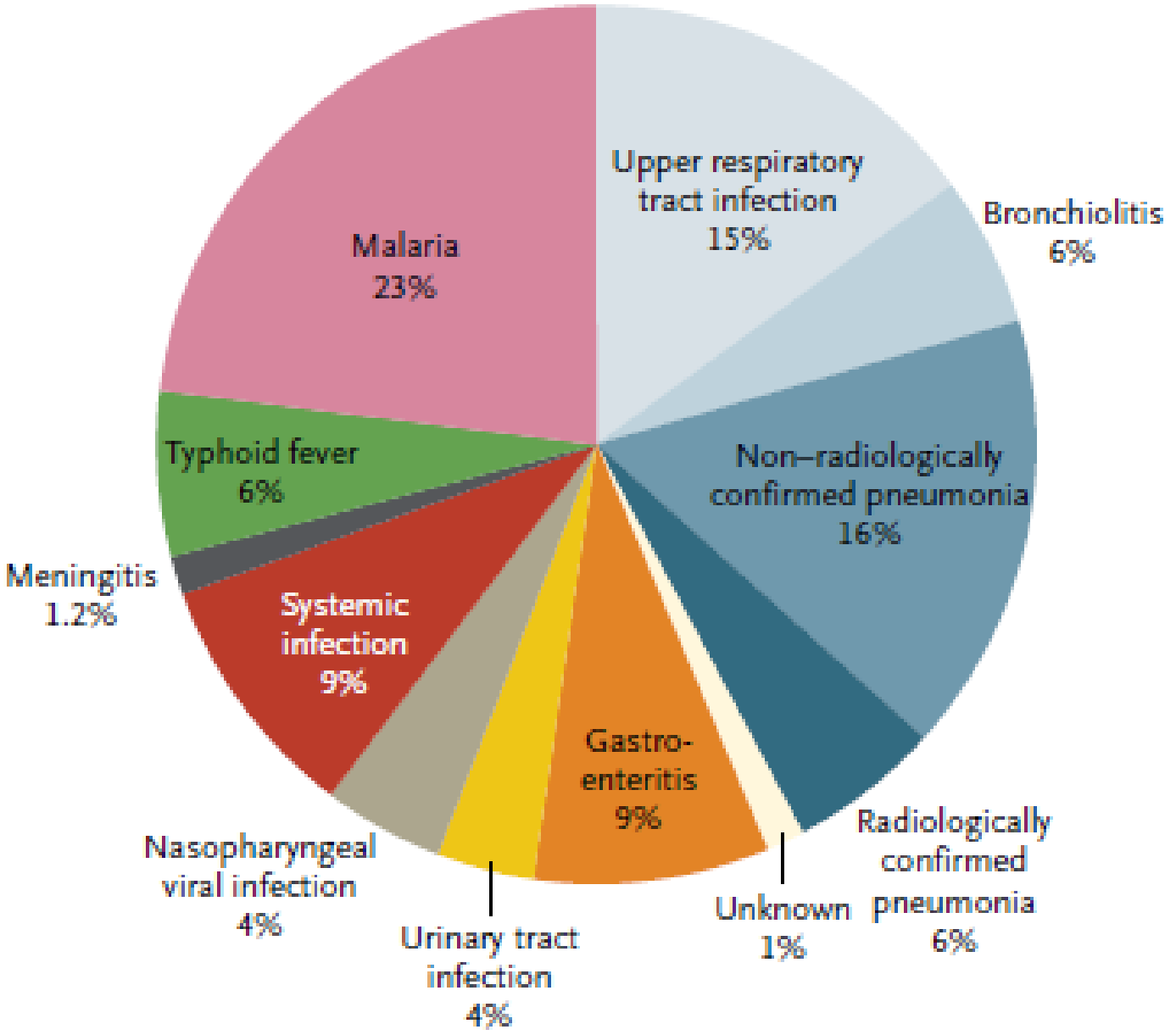


Figure 3. Distribution of All 160 Diagnoses among 133 Febrile Children with Severe Illness.

- Support to send children home without anti-malarials if not indicated
- Support to send children home without antibiotics if not indicated
- Call for more point-of-care tests

Bacteremia among Children Admitted to a Rural Hospital in Kenya

James A. Berkley, M.D., Brett S. Lowe, M.Phil., Isaiah Mwangi, M.B., B.Ch., Thomas Williams, Ph.D., Evasius Bauni, M.Sc., Saleem Mwarumba, H.N.D., Caroline Ngetsa, H.N.D., Mary P.E. Slack, F.R.C.Path., Sally Njenga, H.N.D., C. Anthony Hart, F.R.C.Path., Kathryn Maitland, Ph.D., Mike English, M.D., Kevin Marsh, F.R.C.P., and J. Anthony G. Scott, M.R.C.P.

N Engl J Med 2005;352:39-47.

- Bacteraemia 0-60 days : 12.8%
- E coli, Grp B Strep

- Bacteraemia > 60 days : 5.9%
- Strep pneumoniae, NT Salmonella, H infl, E coli

- Community-acquired bacteraemia
- 1457/100000 <1yr
- 1080/100000<2yrs
- 505/100000 <5yrs

- 26% in-hospital death: bacteraemia
- 33% on day of admission, 70.5% within 2 days

S Afr Med J 2013 Cape Town 2008-12

- pathogens isolated in 6.2%
- contaminated 5.9 – 7.2%, esp from infants <1yr, CoNS

- Less *Strep pneumonia*
- More Gram neg's: Klebsiella, Enterobacteriacae

Community acquired bacteraemia among hospitalized children in rural mocambique 2001-2006

Ped Inf Dis J 2009; 28:108-113

- 8% of admissions
- 1730/100000 child years < 1yr (16% bld cultures pos)
- 782/100000 child years 1-4 yrs (8% bld cultures pos)
- 49/100000 child years ≥ 5yrs (7% bld cultures pos)
- NT Salmonella, pneumococcus (26%, 25%)
- Neonates: Staph aureus (39%), grp B strep (20%)

- Accounted for 21% hospital deaths
- Resistance to antibiotics high among H infl, NTS, E coli

The child with other problems – higher risk of bacteraemia

- Malnutrition – found in more studies (4 vs 2)
- HIV-infection – community-acquired infections
- Not breastfed or non-exclusive breastfeeding
- Unhygienic environment
- Concomitant malaria

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