

MMed and DCH Lectures

Fever in children

February 15th, 2021

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Summary

- Pathogenesis of fever
 - Pyrogens
 - Hypothalamus
 - Prostaglandins
 - Effector mechanism (parasympathetic, sympathetic, behavioral)
- Classification of fever
- Aetiology of fever in PNG and other tropical countries
- Why is (some) fever good
- Heat stroke

Causes of fever

- **Pyrogenic**

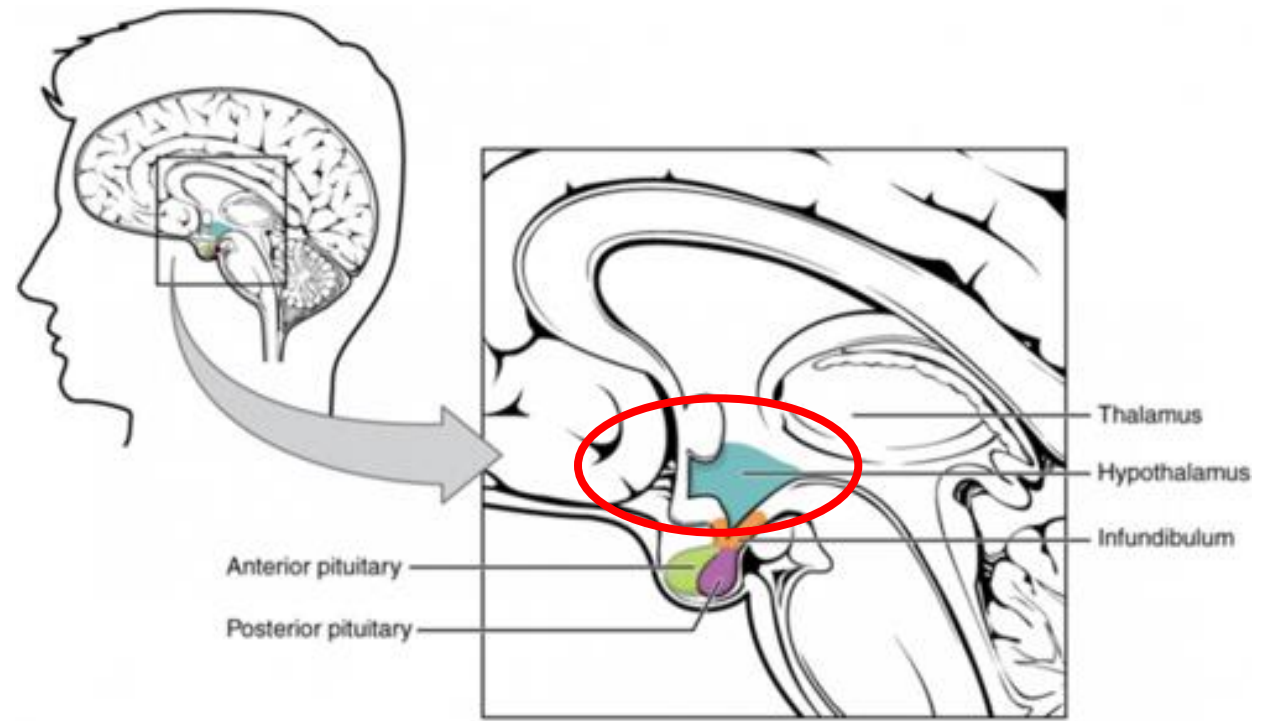
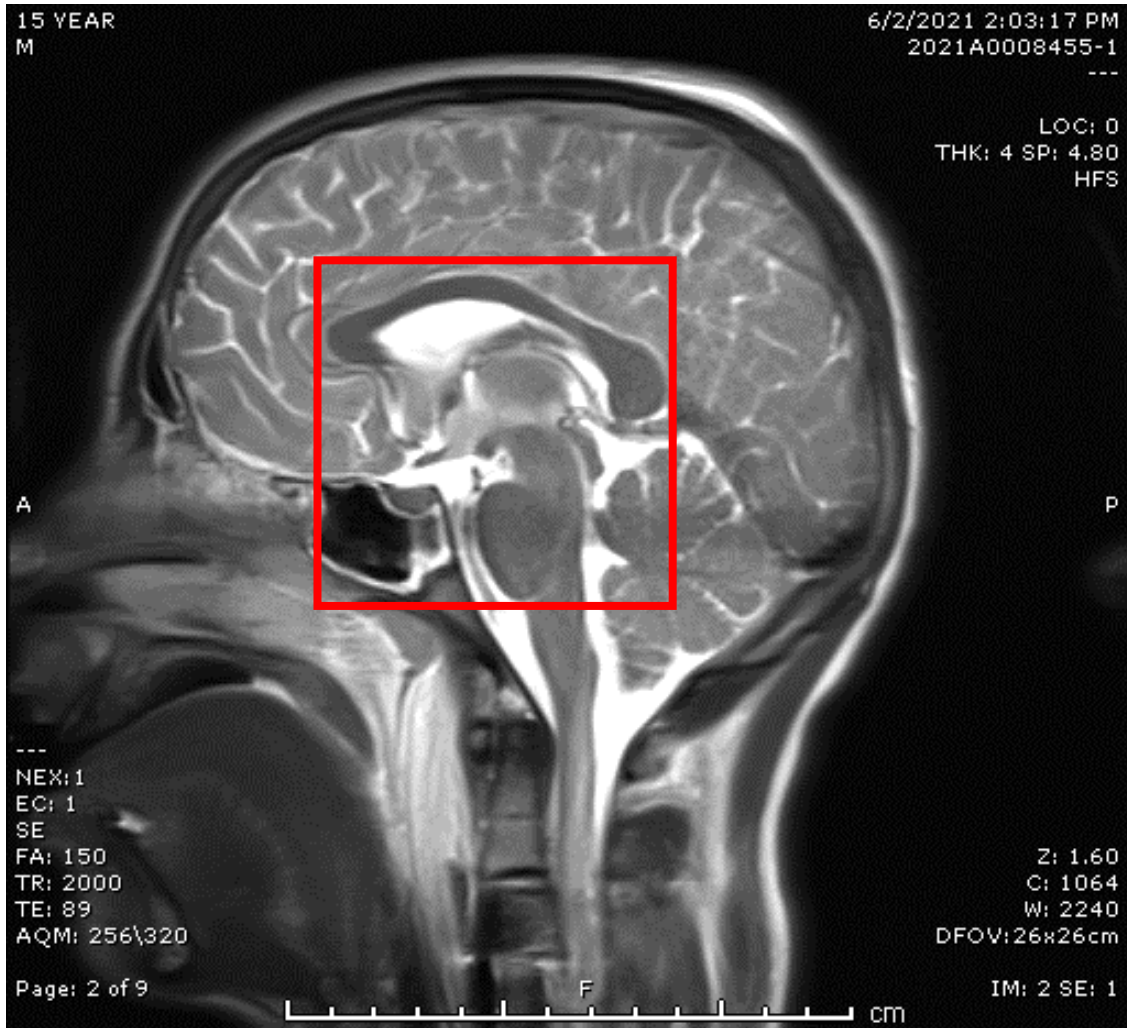
- Virus, bacteria, fungi, endotoxin, impurities in drugs
- Resetting of the set-point of the core body temperature (CBT)

- **Non-pyrogenic (heat exhaustion or heat stroke)**

- Set-point of CBT is unchanged
- Other factors that interfere with the “efferent” mechanisms of heat loss
 - Vasodilatation
 - Sweating
 - Reducing clothes
 - Decreasing activity
 - Move to shade / cool area

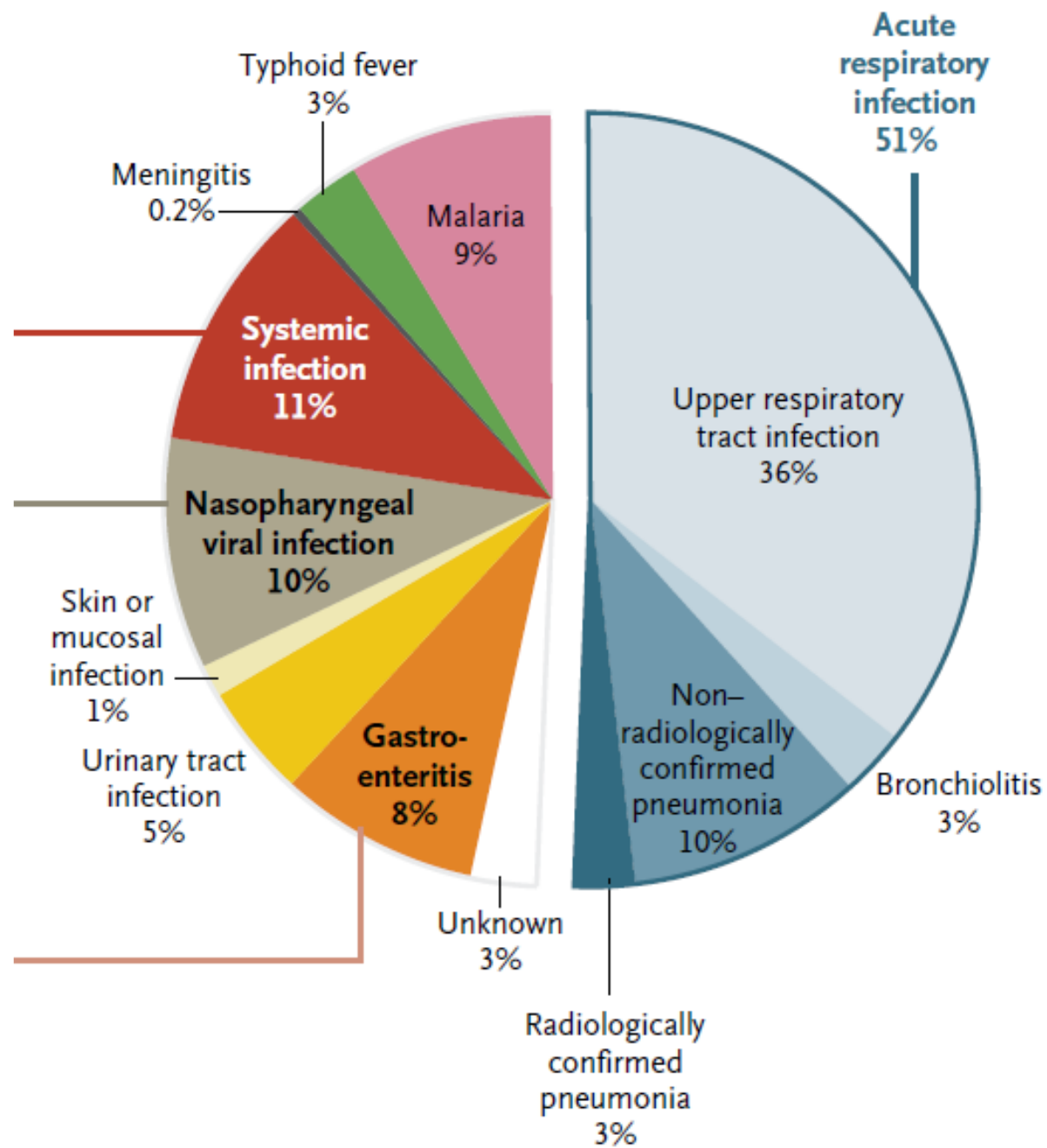
Pyrogens, the hypothalamus, prostaglandins and fever

- Exogenous pyrogens → phagocytosed by neutrophils → IL-1, IL-6, TNF- α (endogenous pyrogen) → hypothalamus → prostaglandins (and ceramide) → slows the firing rate of “warm sensitive” neurons of posterior hypothalamus (resetting the core body temperature)
- (LPS → direct action on Kupffer cells of liver → prostaglandins)
- **Prostaglandins → ↑↑↑ heat production, ↓↓↓ heat loss**
- (Aspirin and other NSAIDS counteract fever inhibiting synthesis of PGE2 in hypothalamus)



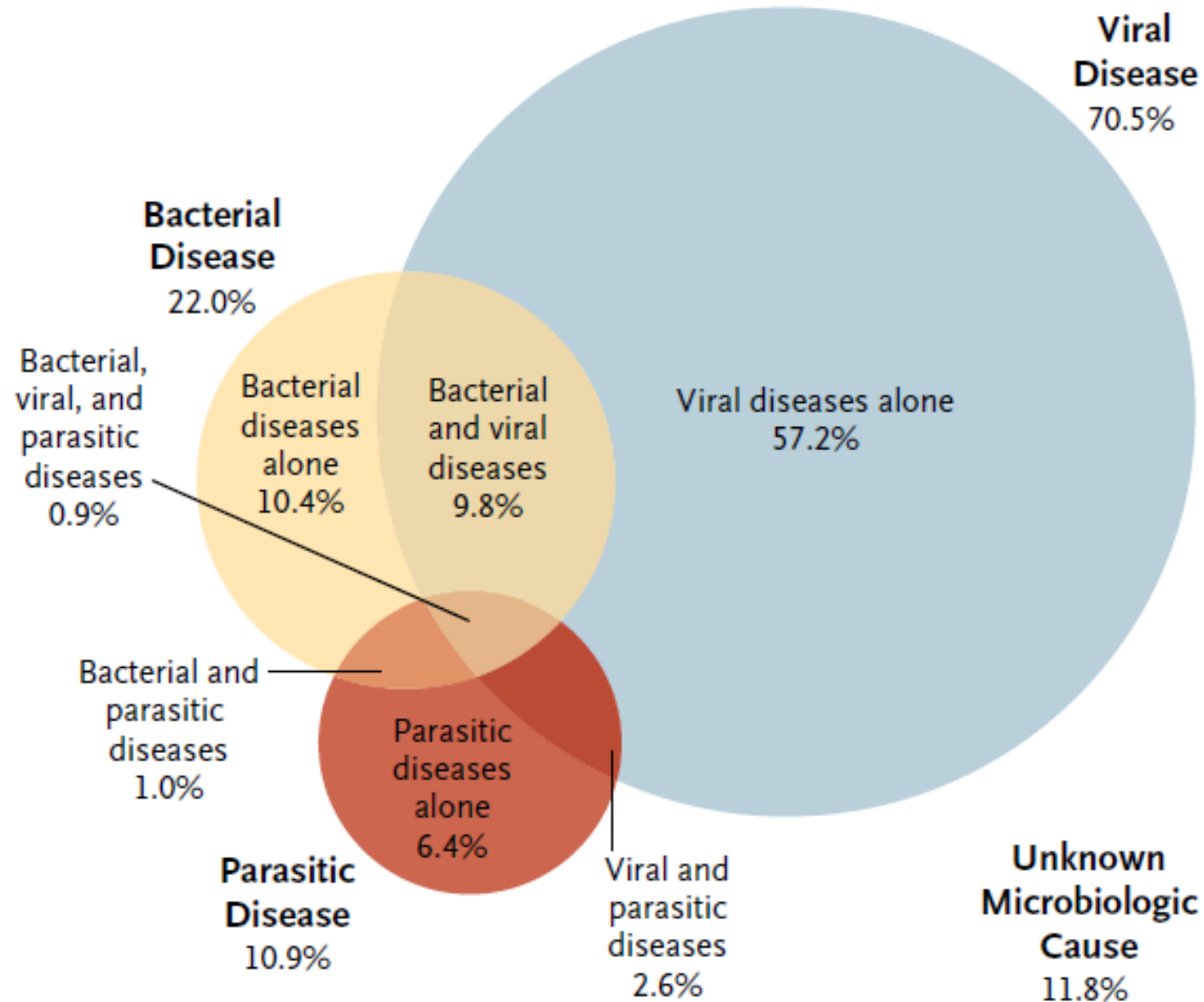
Autonomic nervous system

- Activation of **cold** receptors
 - **Activation of sympathetic NS** – ↑ cutaneous vasoconstriction, ↑ metabolic rate ↑ piloerection (hairs stand on end) ↑ thermogenesis (metabolism)
 - → **Heat production**
 - (and inhibition of parasympathetic NS)
- Activation of **warm** receptors
 - **Activation of parasympathetic NS** – ↑ peripheral vasodilatation and sweating
 - → **Heat loss**
 - (and inhibition of sympathetic NS)



Beyond Malaria — Causes of Fever in Outpatient Tanzanian Children
 N Engl J Med 2014;370:809-17.
 DOI: 10.1056/NEJMoa1214482

A Diseases

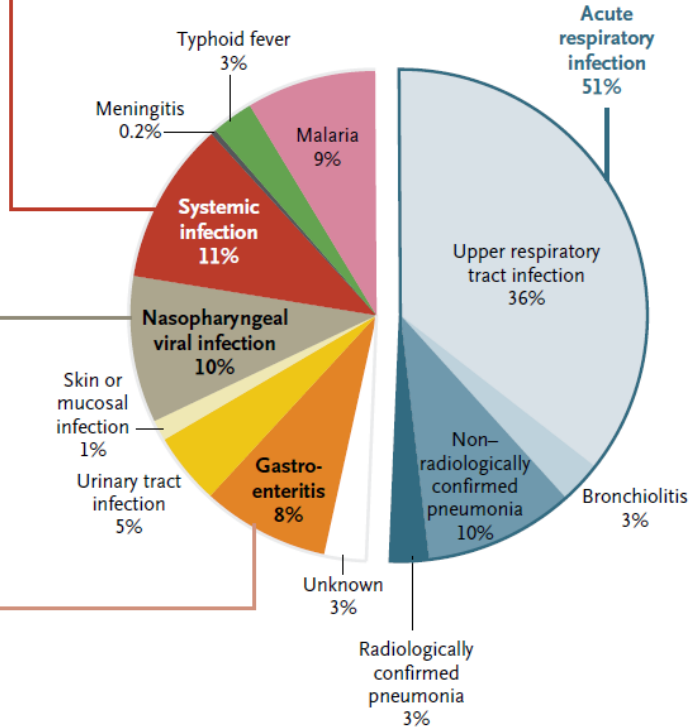
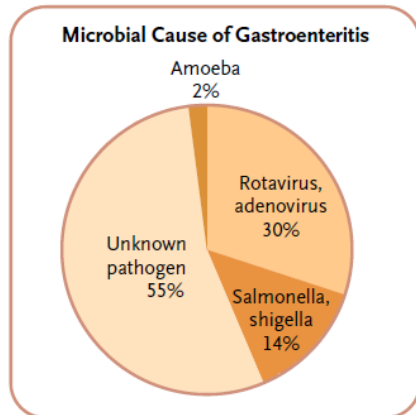
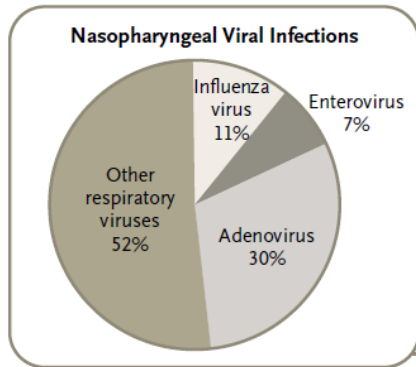
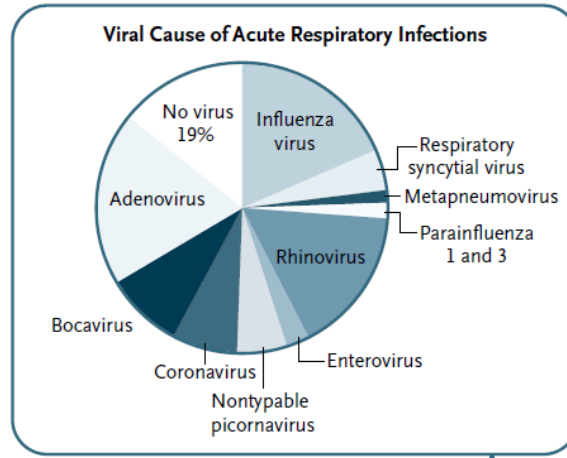
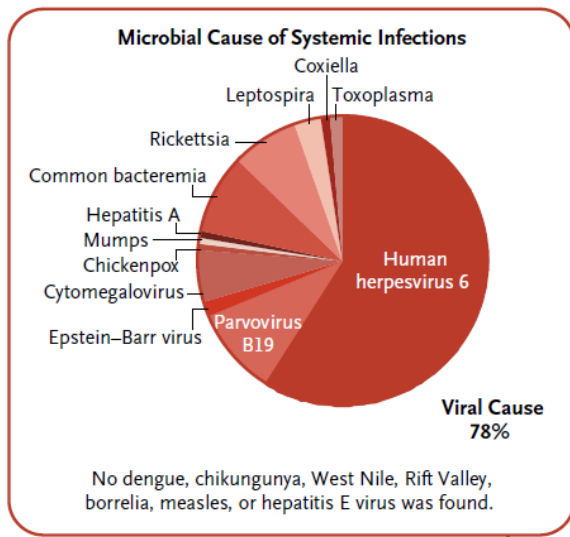


Viral: 70.5%
Bacterial: 22%
Parasitic: 10.9%

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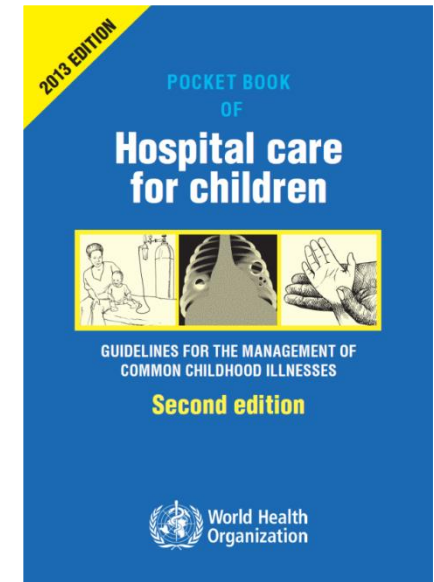


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- Commonest cause of fever with generalized systemic symptoms?
 - Human herpesvirus 6
 - Parvovirus
- Malaria
 - 10% (105/1005) children with fever had malaria
 - 51% of these 105 children with malaria also had another infection (acute respiratory infection, gastro, systemic viral syndrome, bacteraemia)

Classification of fever

- Fever without localizing signs
- Fever with localizing signs
- Fever with rash
- Fever lasting >7 days



Fever without localizing signs

- Malaria
- Septicaemia
- Typhoid
- UTI
- HIV

Table 16. Differential diagnosis of fever without localizing signs

Diagnosis	In favour
Malaria (in endemic area)	<ul style="list-style-type: none">– Positive blood film or rapid diagnostic test for malaria parasites– Anaemia– Enlarged spleen
Septicaemia	<ul style="list-style-type: none">– Seriously ill with no apparent cause– Purpura, petechiae– Shock– Hypothermia in a young infant or severely malnourished child
Typhoid	<ul style="list-style-type: none">– Seriously ill with no apparent cause– Abdominal tenderness– Shock– Confusion
Urinary tract infection	<ul style="list-style-type: none">– Abdominal pain– Loin or suprapubic tenderness– Crying on passing urine– Passing urine more frequently than usual– Incontinence in previously continent child– White blood cells and/or bacteria in urine on microscopy, or positive dipstick
Fever associated with HIV infection	<ul style="list-style-type: none">– Signs of HIV infection (see Chapter 8, p. 225)

Fever with localizing signs



Table 17. Differential diagnosis of fever with localized signs

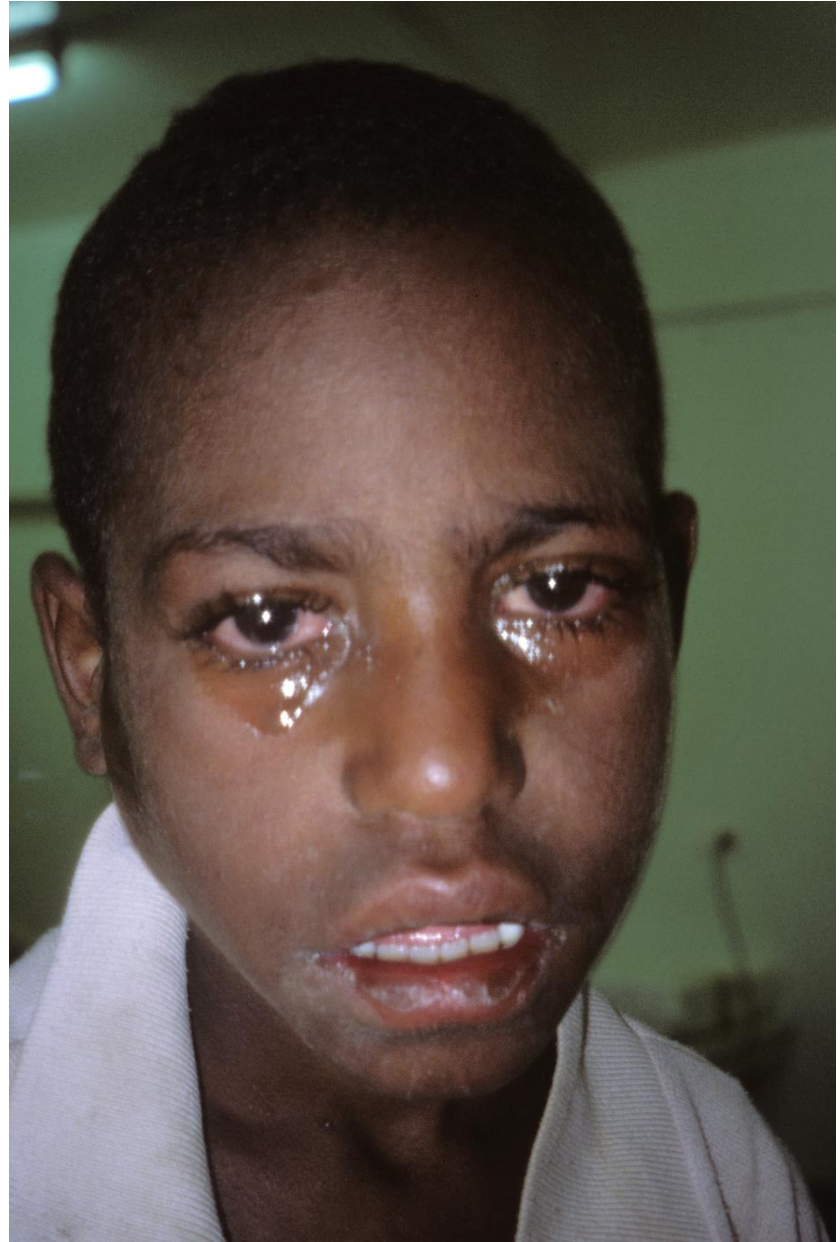
Diagnosis	In favour
Meningitis	<ul style="list-style-type: none"> – Multiple or complicated convulsions – Altered level of consciousness – Lumbar puncture positive – Stiff neck – Bulging fontanelle in infancy – Meningococcal rash (petechial or purpuric)
Otitis media	<ul style="list-style-type: none"> – Red immobile ear-drum on otoscopy – Pus draining from ear – Ear pain
Mastoiditis	<ul style="list-style-type: none"> – Tender swelling behind the ear
Osteomyelitis	<ul style="list-style-type: none"> – Local tenderness – Refusal to move the affected limb – Refusal to bear weight on leg
Septic arthritis	<ul style="list-style-type: none"> – Joint hot, tender, swollen
Acute rheumatic fever	<ul style="list-style-type: none"> – Migratory joint pains – Heart murmur(s)
Skin and soft tissue infection	<ul style="list-style-type: none"> – Cellulitis – Skin boils – Pustules – Pyomyositis (purulent infection of muscles)
Pneumonia (see 4.2 and 4.3, pp. 80–90 for other clinical findings)	<ul style="list-style-type: none"> – Cough with fast breathing – Lower chest wall indrawing – Grunting – Nasal flaring – Coarse crackles, consolidation, effusion
Viral upper respiratory tract infection	<ul style="list-style-type: none"> – Symptoms of cough or cold – No systemic upset
Retropharyngeal abscess	<ul style="list-style-type: none"> – Sore throat in older child – Difficulty in swallowing, drooling of saliva – Tender cervical nodes
Sinusitis	<ul style="list-style-type: none"> – Facial tenderness on percussion over affected sinus – Foul nasal discharge
Hepatitis	<ul style="list-style-type: none"> – Severe anorexia – Abdominal pain – Jaundice with dark urine

Fever with rash

- Measles
- Rubella
- Viral infection (e.g. parvovirus, HHV-6, enterovirus, varicella)
- Relapsing fever (*Borrelia*, Lyme disease – not in Pacific)
- Typhus
- Dengue fever

Table 18. Differential diagnosis of fever with rash

Diagnosis	In favour
Measles	<ul style="list-style-type: none">– Typical rash (see p. 174)– Cough, runny nose, red eyes– Mouth ulcers– Corneal clouding– Recent exposure to a measles case– No documented measles vaccination
Viral infections	<ul style="list-style-type: none">– Mild systemic upset– Cough or cold– Mild systemic upset– Transient non-specific rash
Relapsing fever	<ul style="list-style-type: none">– Petechial rash, skin haemorrhages– Jaundice– Tender enlarged liver and spleen– History of previous episode of relapsing fever– Positive blood smear for <i>Borrelia</i>
Typhus ^a	<ul style="list-style-type: none">– Epidemic of typhus in region– Characteristic macular rash– Muscle aches
Dengue haemorrhagic fever ^b	<ul style="list-style-type: none">– Bleeding from nose or gums or in vomitus– Bleeding in stools or black stools– Skin petechiae or purpura– Enlarged liver and spleen– Shock– Abdominal tenderness





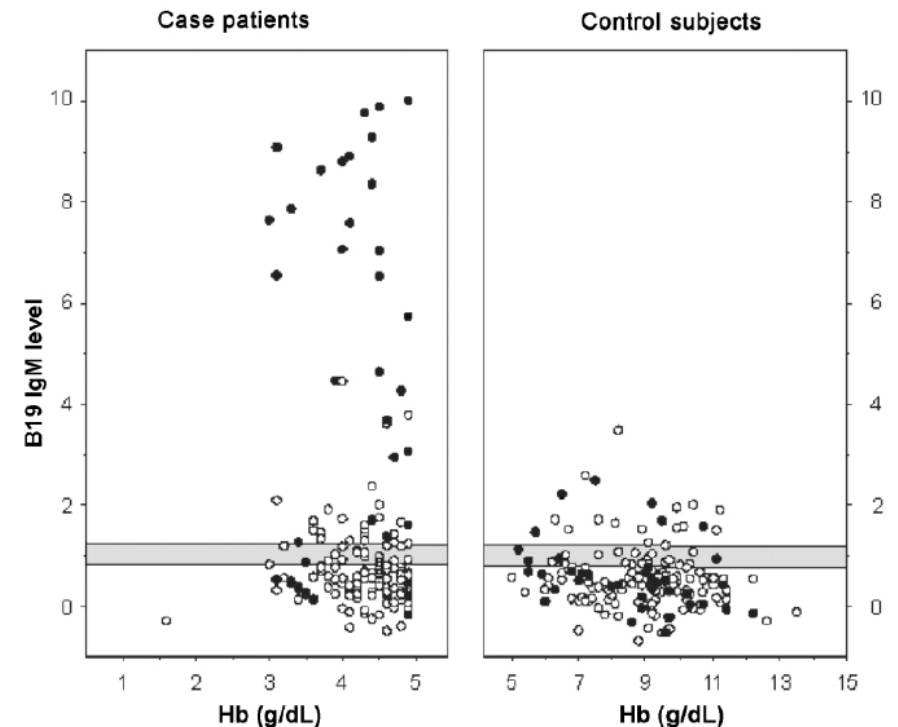
Parvovirus B19 “Fifth disease”

- Febrile illness, rash (“slap-cheek”), on face and limbs 7-10 days
- Usually mild
- Adults can have painful swollen joints
- **Strongly linked to severe anaemia in PNG**, interaction with malaria, thalassaemia, G6PD



Parvovirus B19 Infection Contributes to Severe Anemia in Young Children in Papua New Guinea

The Journal of Infectious Diseases 2006;194:146–53



Human herpes virus-6 “Sixth disease”

- HHV-6 the commonest virus causing systemic viral infection (79 cases / 1005 = 8%) - typically 6 months-3 years
- “Roseola infantum”: **high temperature (often 40 C) for 3- 5 days, followed by the rash**
- Hepatitis, febrile convulsions, encephalitis, myelosuppression
- Nearly 100% of people exposed to HHV-6 by 3 years of age
- 30% of febrile seizures in children younger than 2 years
- CSF and salivary glands: a source of latency after the primary infection
- Causes many cases of temporal lobe epilepsy. HHV-6 can reactivate in immunosuppressed patients, including HIV.



Human herpes virus-6

Typhus - Scrub typhus (*Orientia tsutsugamushi*)

- Gram negative rod, transmitted by mites to humans (arthropod born), primary hosts are wild rodents.
- Fever, cough, tachypnoea, hepatomegaly, lymphadenopathy, constipation, abdominal pain, oedema, splenomegaly, vomiting, petechial rash
- Myocarditis, meningoencephalitis
- Described in PNG during WWII, and in Southern Highlands and West Sepik in 2011, Cairns and NT in Australia
- Doxycycline / chloramphenicol



Distribution of scrub typhus



Fever > 7 days

- Abscess
- Salmonella
- Infective endocarditis
- Rheumatic fever
- Tuberculosis – especially disseminated
- Brucellosis

Table 19. Additional differential diagnoses of fever lasting longer than 7 days

Diagnosis	In favour
Abscess	<ul style="list-style-type: none">– Fever with no obvious focus of infection (deep abscess)– Tender or fluctuant mass– Local tenderness or pain– Specific signs depend on site, e.g. subphrenic, psoas, retroperitoneal, lung, renal
<i>Salmonella</i> infection (non-typhoidal)	<ul style="list-style-type: none">– Child with sickle-cell disease– Osteomyelitis or arthritis in infant
Infective endocarditis	<ul style="list-style-type: none">– Weight loss– Enlarged spleen– Anaemia– Heart murmur or underlying heart disease– Petechiae– Splinter haemorrhages in nail beds– Microscopic haematuria– Finger clubbing
Rheumatic fever	<ul style="list-style-type: none">– Heart murmur, which may change over time– Arthritis or arthralgia– Cardiac failure– Persistent, fast pulse rate– Pericardial friction rub– Chorea– Recent known streptococcal infection
Miliary TB	<ul style="list-style-type: none">– Weight loss– Anorexia, night sweats– Enlarged liver and/or spleen– Cough– Tuberculin test negative– Family history of TB– Fine miliary pattern on chest X-ray (see p. 85)
Brucellosis (local knowledge of prevalence is important)	<ul style="list-style-type: none">– Chronic relapsing or persistent fever– Malaise– Musculoskeletal pain– Lower backache or hip pain– Enlarged spleen– Anaemia– History of drinking unboiled milk

Typhoid fever in children

- Ingestion of an infecting dose of *S. typhi*
- Through contaminated water or food
- Poor hygiene and sewage contamination of water supply
- Diarrhoea, vomiting, anorexia, abdominal pain, headache, splenomegaly, and hepatomegaly, mental confusion



Usually 2-3 weeks into the illness

Blanching, **papular**, 2-8 mm

Typically between the level of the nipples and umbilicus, proximal extremities and back.

Each lasts 3-5 days

Bacterial emboli into the skin – can aspirate fluid with a fine needle, do Gram stain and see Gram negative bacilli

Typhoid fever in children - diagnosis

- Clinical – most GI symptoms non-specific, but mental state changes, Typhoid facies (adolescents)
- FBC
 - Leukocytosis or leukopenia
 - Thrombocytopenia
- Blood culture the Gold Standard for diagnosis
- Widal's test (low specificity): leads to high number of children treated inappropriately → widespread use of antibiotics usually preserved as second- or third-line therapies → antimicrobial resistance

Typhoid - treatment

Antimicrobial agent	% resistance
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• Ampicillin	55
• Cotrimoxazole	57
• Chloramphenicol	57
• Ciprofloxacin	0.0
• Ceftriaxone	2.0

Multi-drug resistance (MDR)

Typhoid: resistance to the three first-line agents commonly used to treat typhoid fever,

- Chloramphenicol
- Ampicillin
- Co-trimoxazole

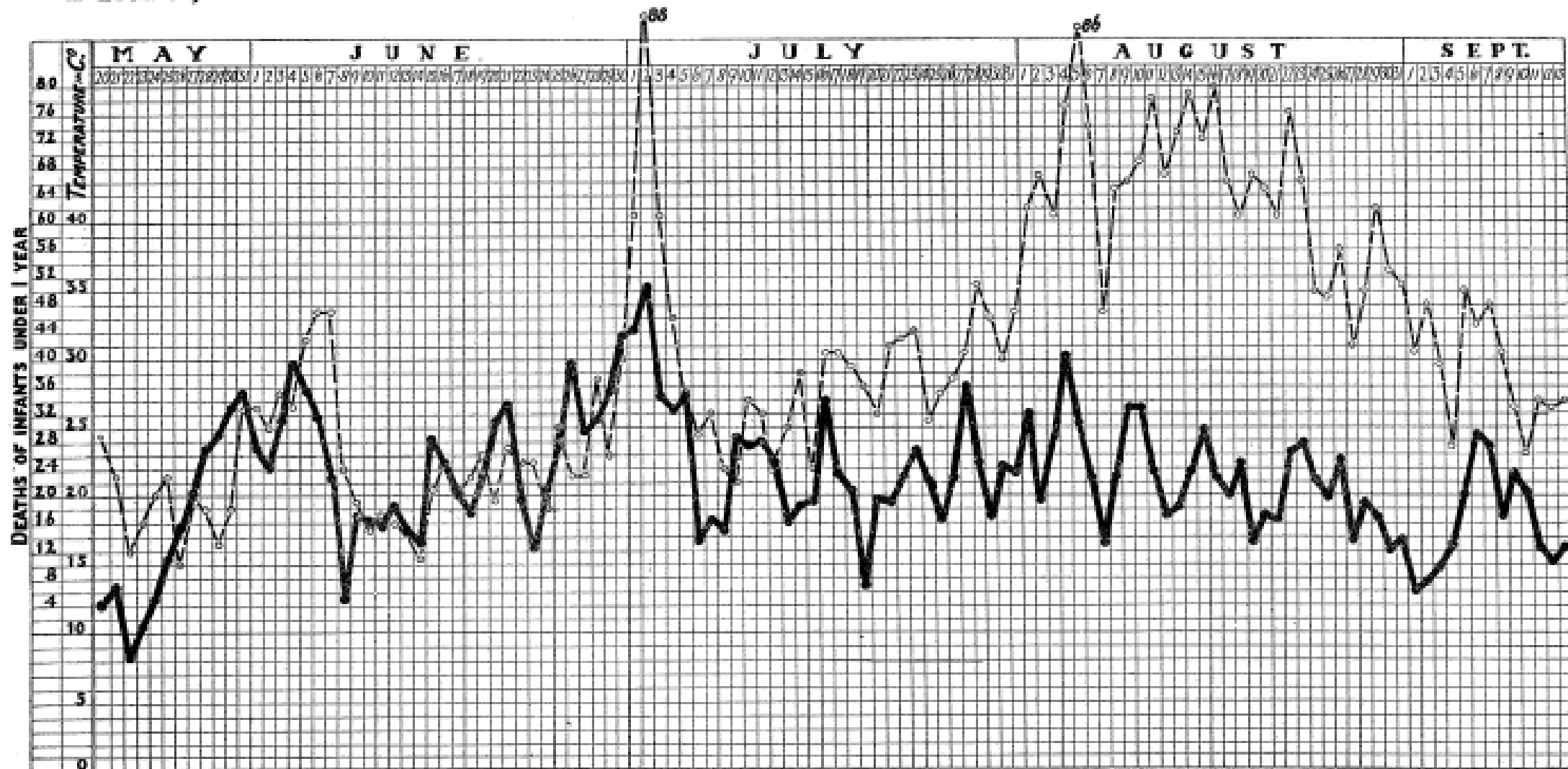
MDR typhoid endemic in India and Asia – now **fluoroquinolone R** and **naladixic acid R**

Bacteremic Typhoid Fever in Children in an Urban Slum, Bangladesh
Emerg Infect Dis. 2005 Feb; 11(2): 326–329.

Fever – why (a little) is it good for you in infection

- Mortality rates
 - Lower in patients with moderate fever (37.5-38.8) than no-fever or hypothermia
 - Higher in patients with very high fever (>39-40 C)
- Why?
 - Optimal replication of some pathogens below 37 C, therefore fever reduces pathogen replication
 - Antibiotics work better if temperatures are higher
 - Increased temperature linked to stronger immunity

BERLIN, 1905.—DAILY DEATHS OF CHILDREN UNDER 1 YEAR COMPARED WITH THE DAILY TEMPERATURE AT 2 P.M.



(See Legend on next page)

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—— TEMPERATURE.

- - - - INFANT MORTALITY.

December 5, 1913

2598

Berlin 1905

- 4-fold increase in infant deaths over summer
- **Bottle fed babies** had a much higher death rate than breast fed babies
 - No refrigeration, bacterial contamination of cow's milk
 - Diarrhoea and dehydration
- Babies living in basements and cellars had a *much lower* death rate
 - Protection from heat stroke

Heat stroke

- Very high body temperature (above 40°C)
- Red, hot, and dry skin (no sweating)
- Tachycardia, strong pulse
- Headache
- Dizziness
- Nausea, vomiting
- Confusion, unconsciousness

Heat stroke (environmental)

- Autonomic regulatory mechanisms overwhelmed
- Heat → increased skin blood flow to lose heat
- Dehydration → vasoconstriction (sympathetic tone) → lack of heat loss mechanism
- Impaired behavioral responses (infant, disabled child, elderly person)
- Dehydration → reduced gut blood flow → translocation of bacteria and sepsis
- Reduced cerebral blood flow - lethargy, convulsions
- Renal failure, coagulopathy (bleeding)

Prevention of heat stroke

- In other countries in Asia clusters of deaths occur during extreme hot weather
 - Especially among **chronically ill children**
- **Teach mothers to give more fluid when a child has a fever, or on a hot day**
- **Stay in the shade or a cool location, cool wet towels**
- Treatment
 - Rehydration with *cold* IV fluids
 - Rapid cooling with ice packs, cold wet towels
 - Anticonvulsant