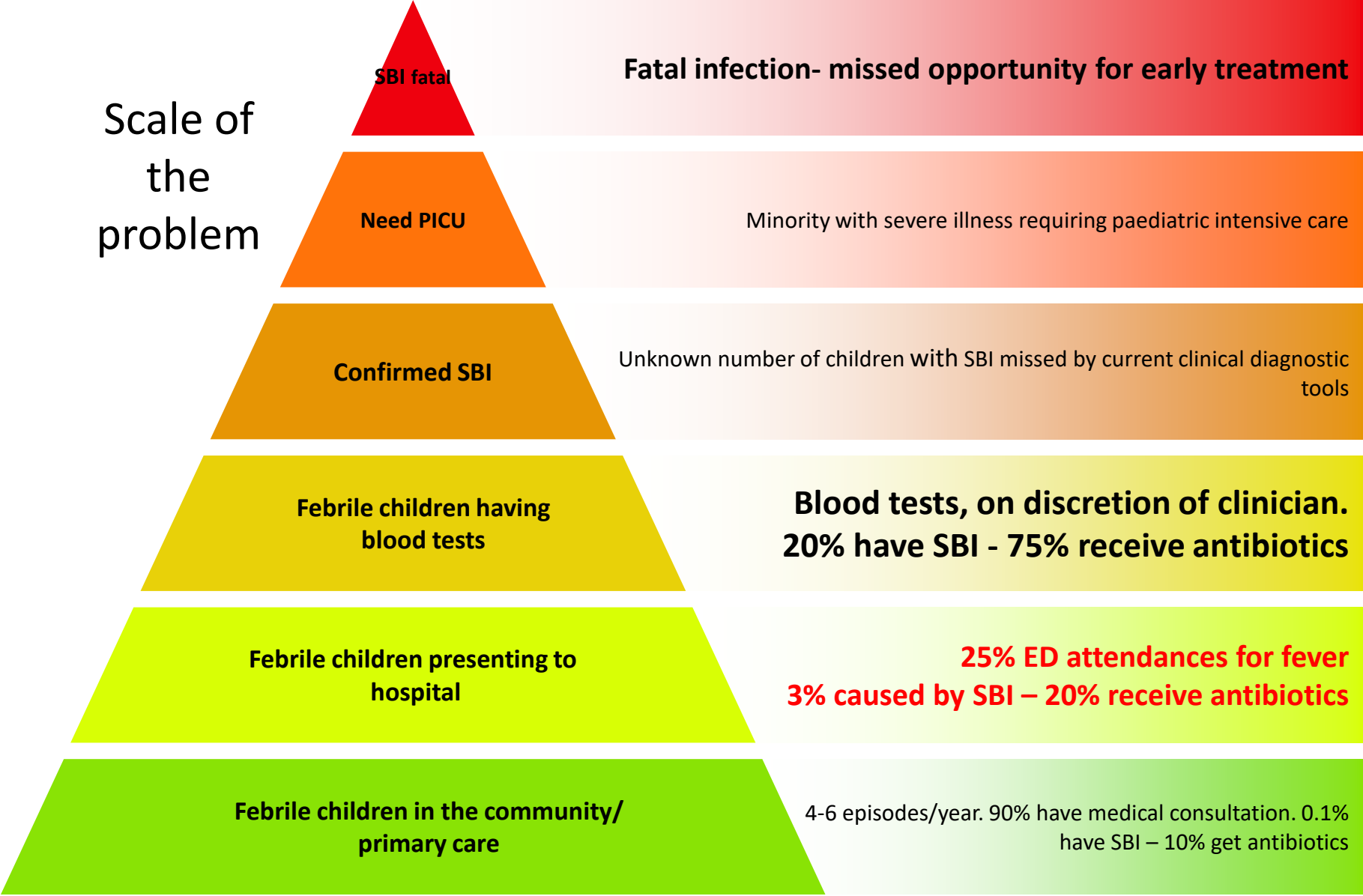


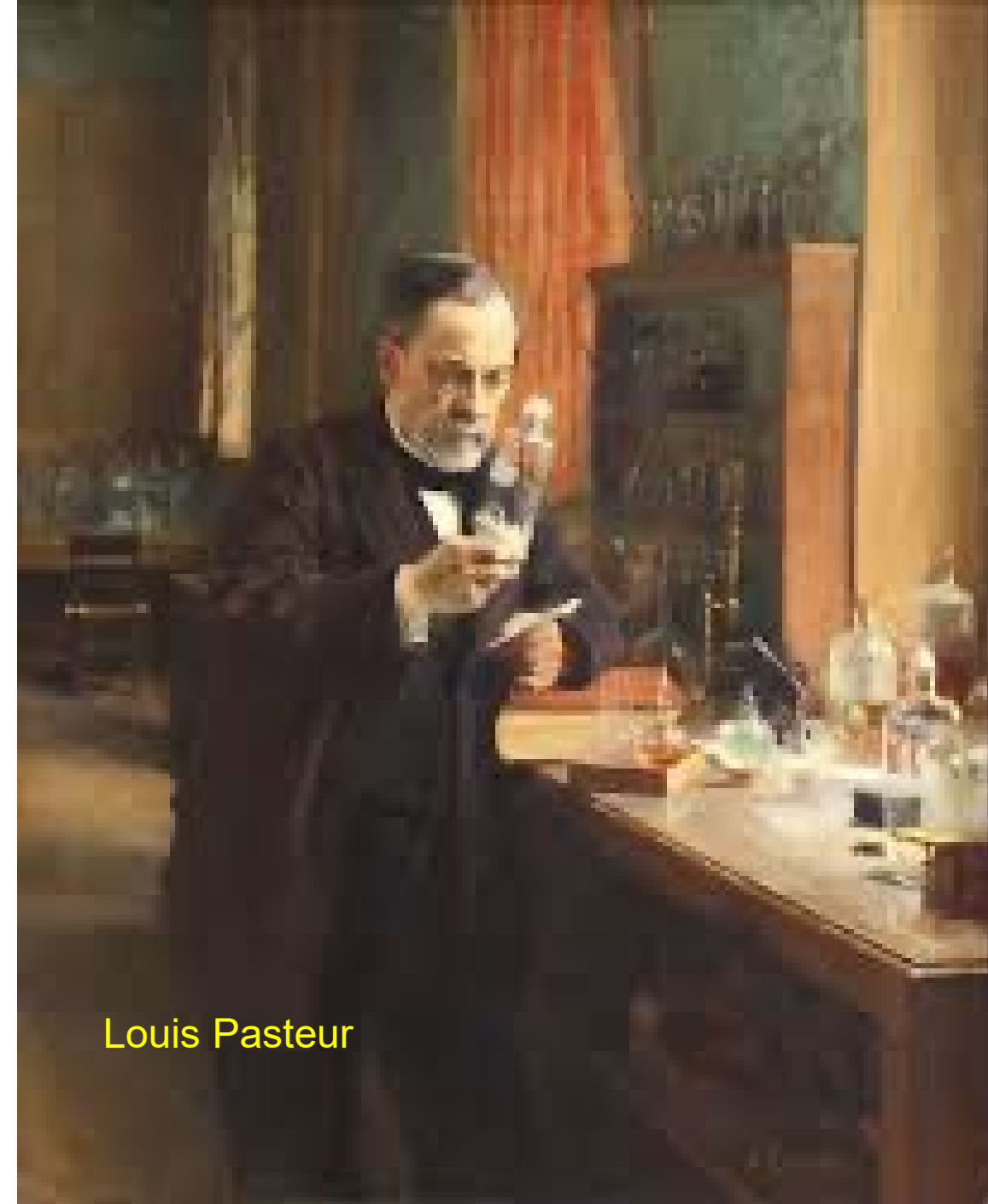
IMPERIAL

Why do we need new diagnostic *approaches* for infectious diseases?

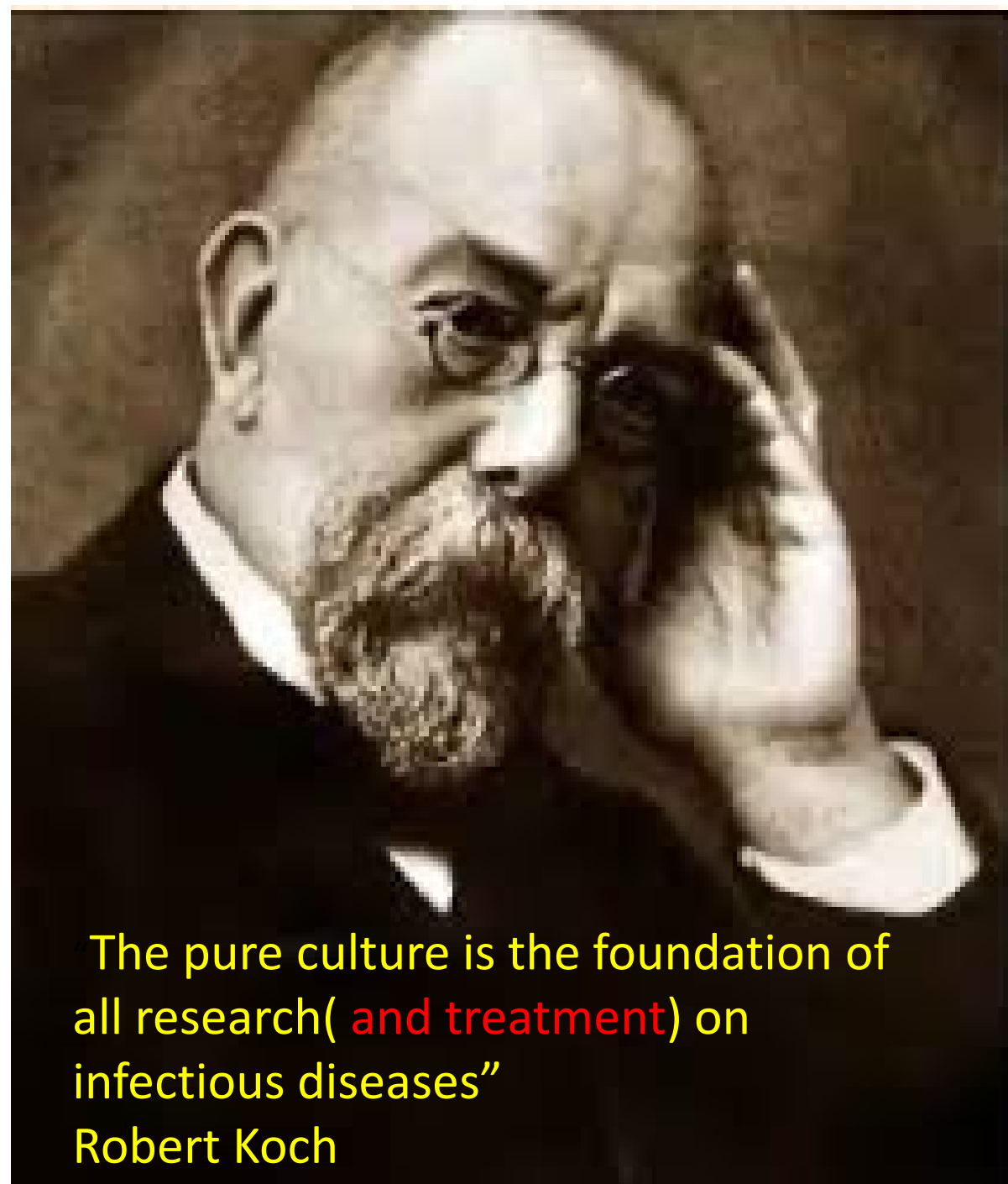
Professor Michael Levin
Section for Paediatrics
Department of Infectious diseases
Imperial

Fever and Infection in Children and adults - a Global child health problem



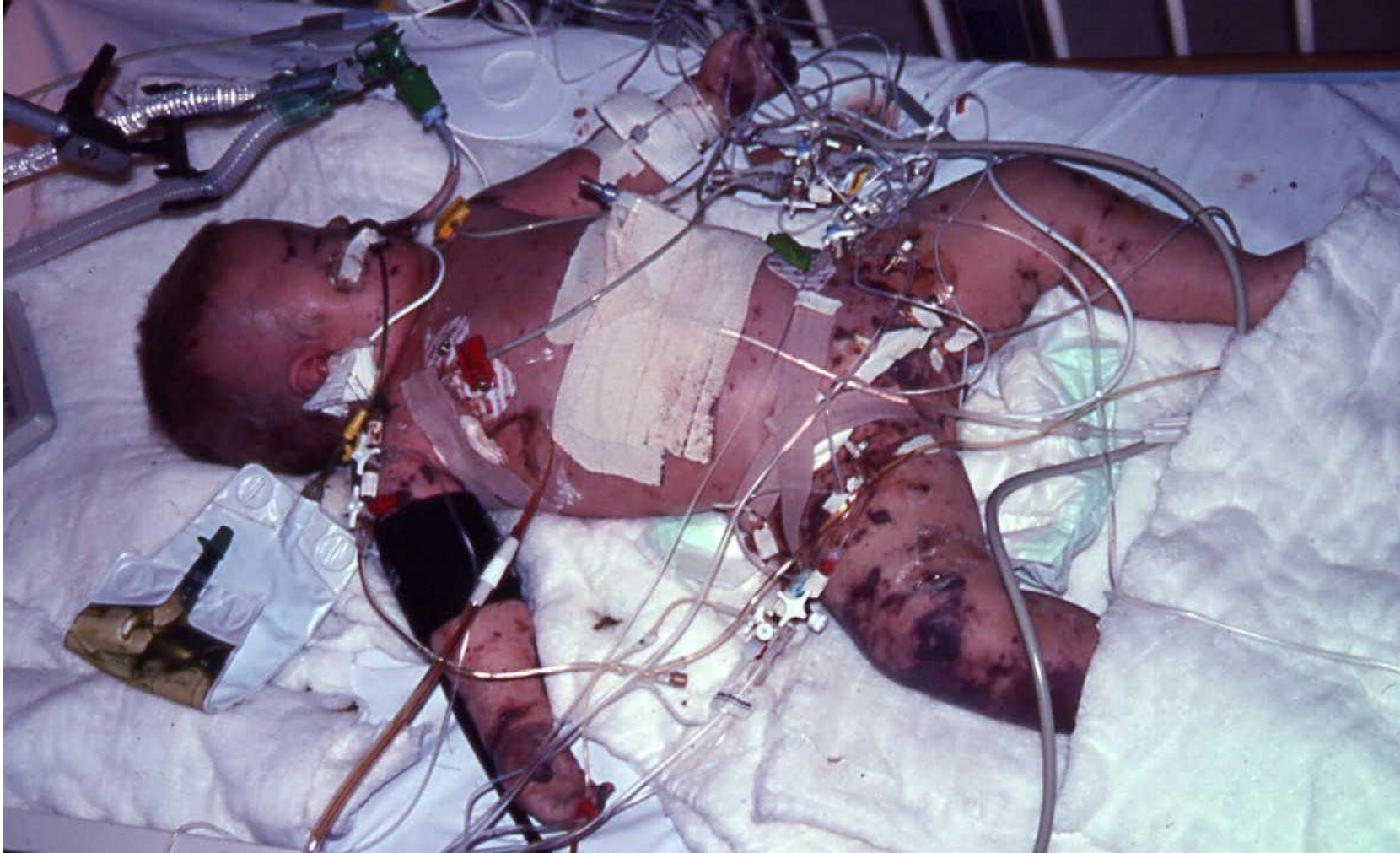


Louis Pasteur



The pure culture is the foundation of
all research(and treatment) on
infectious diseases”
Robert Koch

Early recognition of critical illness



Patient A

Sent home from London
Casualty department 12 hours
earlier

Seen by Family doctor 24
hours previously

**Parents told “It’s a
virus”**

Returned critically ill with
meningococcal meningitis



What diseases does this child have?

meningococcal sepsis
Staphylococcal Toxic shock
Group A Streptococcal infection
“Sepsis”
Disseminated Herpes
Haemorrhagic varicella
Ebola Virus
Dengue
Rickettsial infection
Multisystem inflammatory syndrome

If immunocompromised a wider range of possibilities

Immunosuppressed patient presenting with Respiratory failure

Bacterial pneumonia

Gram positive/Negative? Resistant pathogen

Viral ? Respiratory virus, CMV, HSV

COVID

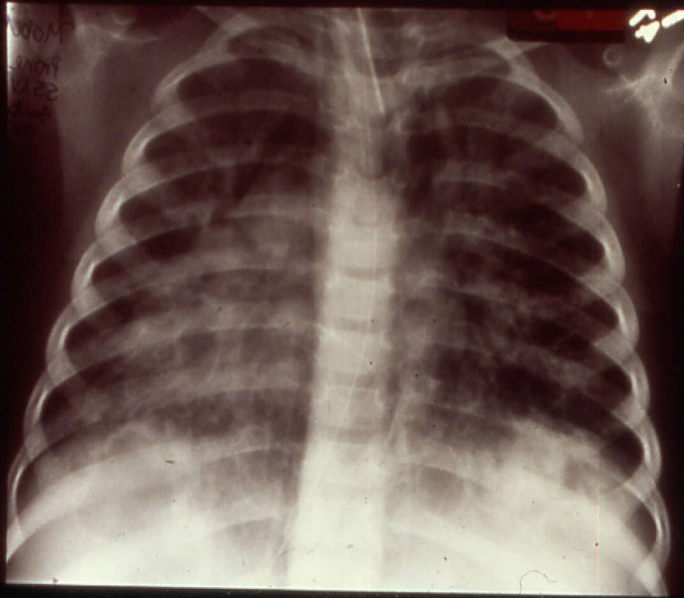
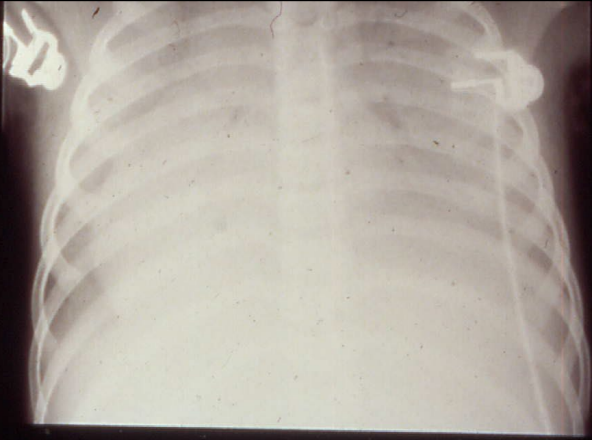
Mycoplasma/Legionella

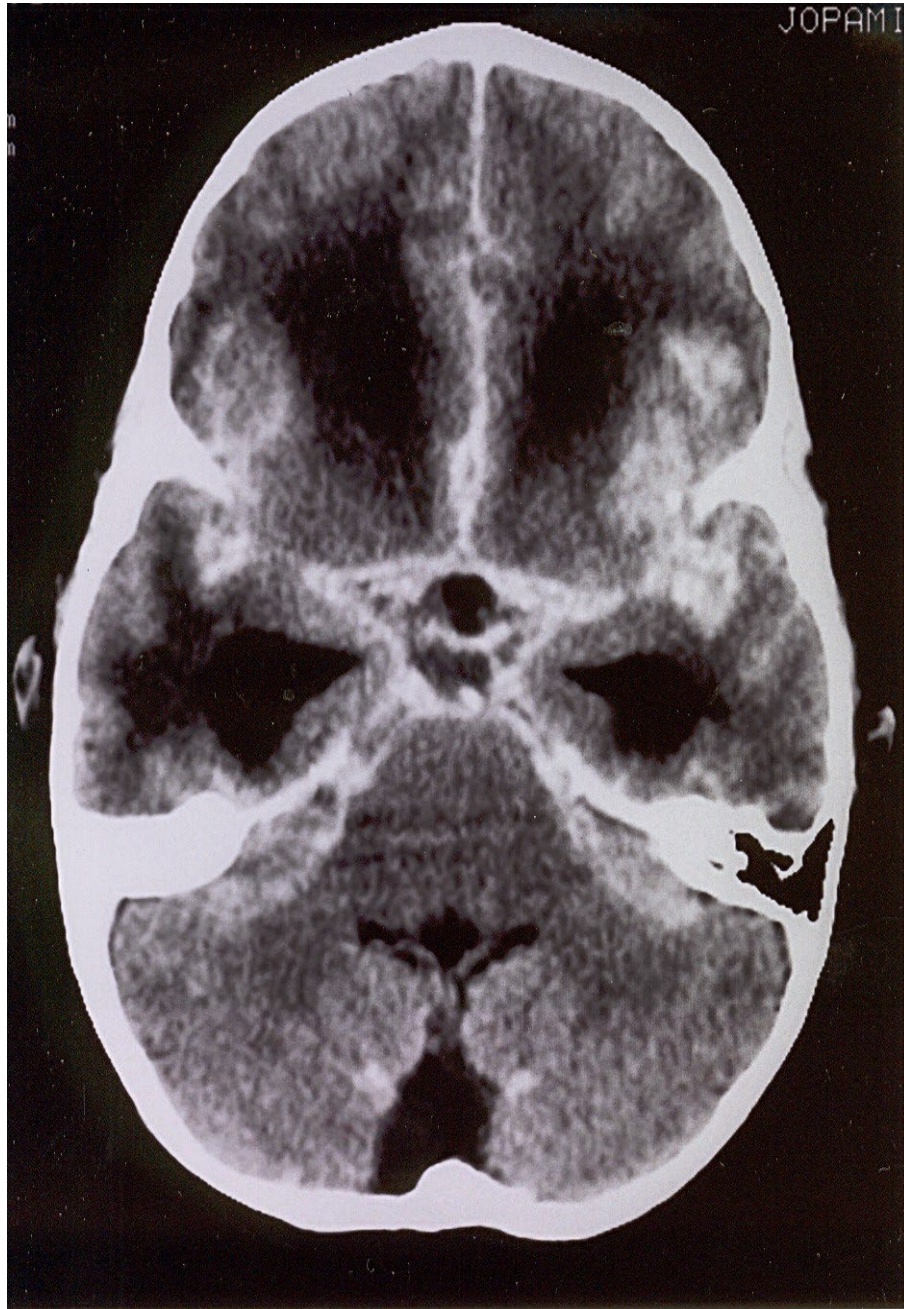
TB

Fungal

PJP

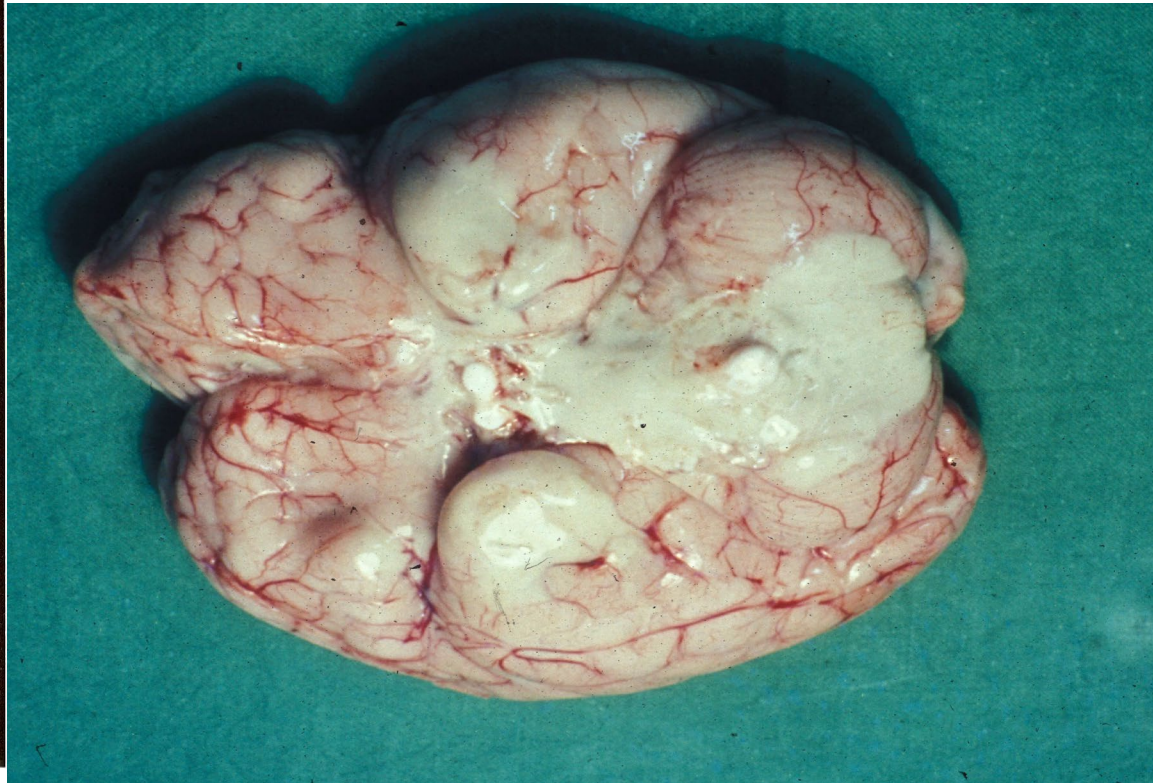
Immunological disorders





Patient x Neurological Symptoms

- Low grade fevers, irritable, cough for 6 weeks
- Presented in Coma
- Seen by multiple doctors without the Diagnosis being made



TB
meningitis



Kawasaki disease



Staphylococcal Toxic Shock syndrome



Streptococcal disease



MIS-C/PIMS-TS



Systemic JRA

**Wide Differential
Diagnosis of fever and
red rash remains**



Adenovirus infection



Measles



Stevens Johnson Syndrome



Rickettsial Infection



enterovirus/Parvovirus infection



If the causative organism is not known Treatment is Blind- or polypharmacy

Antibiotics???

- Which ones

- Antiviral

- Cover for resistant pathogens

- Anti fungal

- Anti malarials

- Anti Rickettsia

- Immune modulators

- Steroids

- Monoclonal antibodies

Is the illness contagious ?

Do we need prophylaxis for family members and contacts

Are hospital staff and patients at risk

Do we need to isolate the patient

Control of Infection difficult if pathogen unknown

Overuse of antimicrobials and AMR



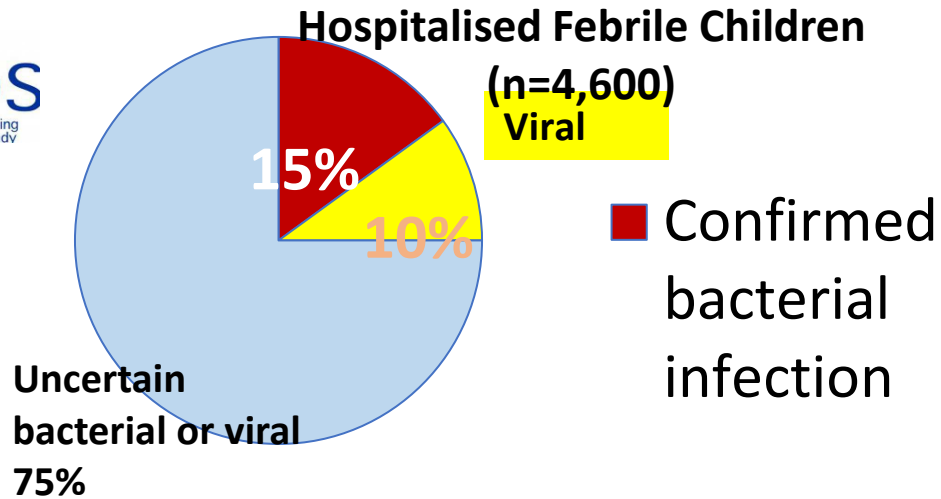
Identification of the causative agent is fundamental to all treatment and management decision

Most Research to improve Diagnosis has focused on Pathogen detection using molecular approaches

**Despite huge efforts to improve rapid pathogen detection
Pathogen identification fails in 80% of hospitalized cases
Diagnosis rarely achieved in LMIC where cultures largely unavailable**



Pathogen Detection Does not help in decision to administer antibiotics



5,000 febrile children presenting to hospitals in UK and EU
Confirmed bacterial or viral infection in 25%
75% have no clear diagnosis

Shah et al Lancet Regional Health Europe 2023

Molecular pathogen detection has not improved situation

Martinon Torres 2018 Lancet Paediatric and adolescent medicine medicine

We need Better Accurate and rapid Diagnostics for infectious and inflammatory disease

Febrile patient meeting entry criteria for study
 With available samples for biomarker discovery (RNA, proteomic, metabolomic)

Categorization of patients based on clinical data

BACTERIAL
 cellulitis, appendicitis, abscess, bone infection, cellulitis, CLABSI, empyema, endocarditis, HUS, impetigo, Lyme, mastoiditis, necrotising fasciitis, peri/orbita infection
 I cellulitis, peritonitis, pneumonia, purp. fulminans, pyelonephritis, scarlet fever, staph scalded skin, TB, TSS, UTI, wound infection

Viral OR Bacterial
 adenitis, conjunctivitis, encephalitis, febrile convulsion, FWS, gastroenteritis, meningitis, myositis, otitis media, pharyngitis, pleural effusion, PUO, sepsis, septic shock, severe sepsis, sinusitis, stomatitis, tonsillitis, undefined LRTI, URTI

VIRAL syndrome
 bronchiolitis, EBV/glandular fever, viral-induced wheeze, croup, varicella, herpes simplex, flu-like illness, hand-foot-mouth, roseola/HHV6, mumps, erythema infectiosum/parvovirus

Other febrile syndrome
 Infection (not viral or bacterial) eg malaria
 Inflammatory eg ADEM, GBS, HLH, HSP, IBD, JIA, KD, reactive arthritis, SJS, SLE, sJIA, rheumatic fever, Other eg bronchospasm, seizure, sickle crisis, asthma

Review clinical investigation results
 Bacteriology, virology, radiology, hematology, chemistry

Sterile-site pathogenic bacteria, match syndrome

Bacterial syndrome but no bacteria identified

Unclear features OR microbiology does not fit syndrome

Viral syndrome but no virus identified

Virus identified that matches syndrome

Minor illness, & insufficient clinical information

Other infection, eg malaria

Unclear features – infection or inflammatory

Matches criteria for inflammatory syndrome

CRP > 60 mg/l

no

yes

CRP ≤ 60 mg/l
neutrophils ≤ 12 x 10⁹/ml

no

yes

Definite Bacterial *

Probable Bacterial *

Bacterial syndrome
low or no inflamm, markers*

Unknown bacterial or viral*

Viral syndrome
high or no inflamm, markers*

Probable Viral

Definite Viral

Trivial

Other infection

Infection or inflammation

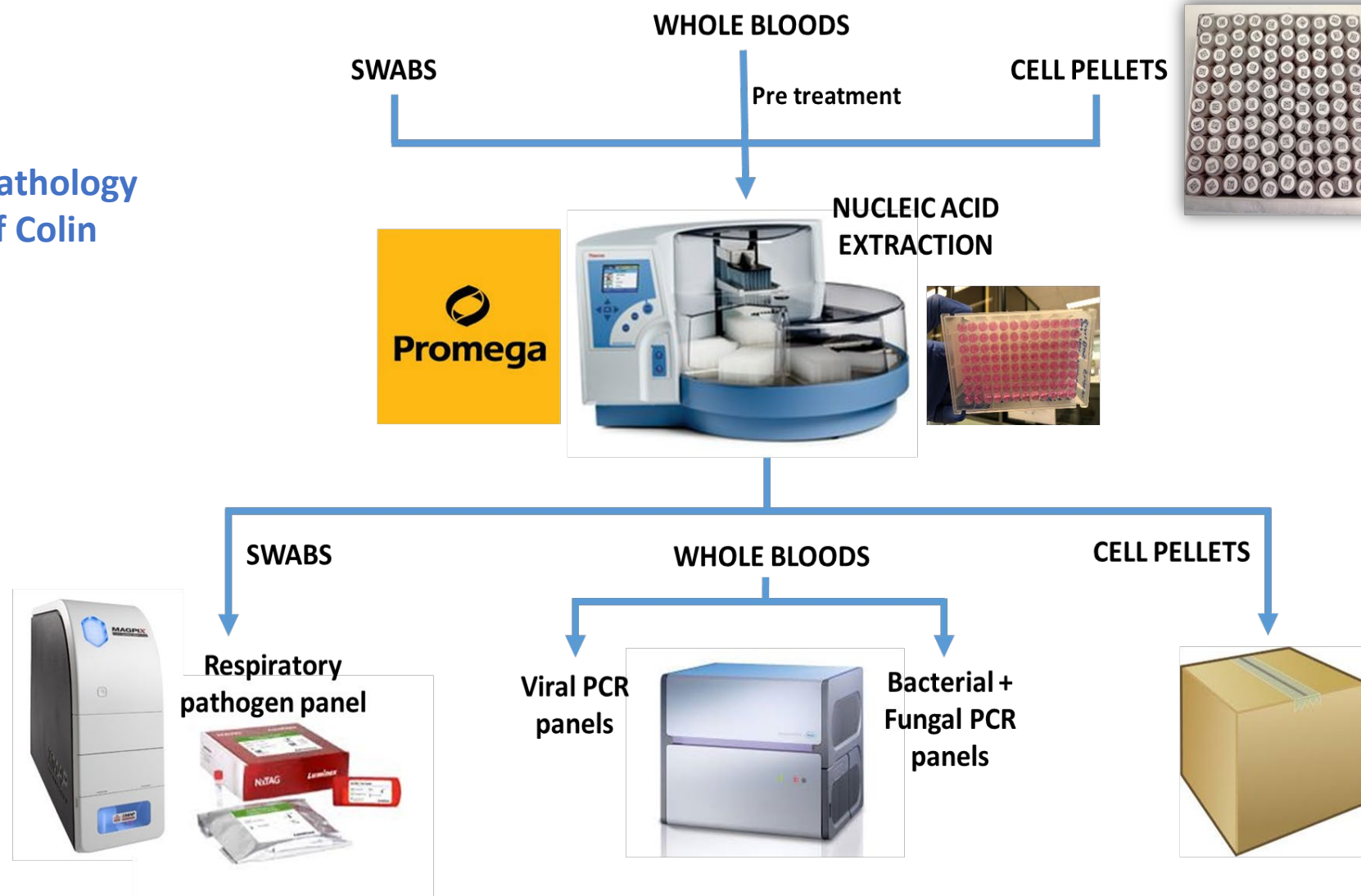
Inflammatory syndrome

Diagnostic phenotyping of patients with suspected infection

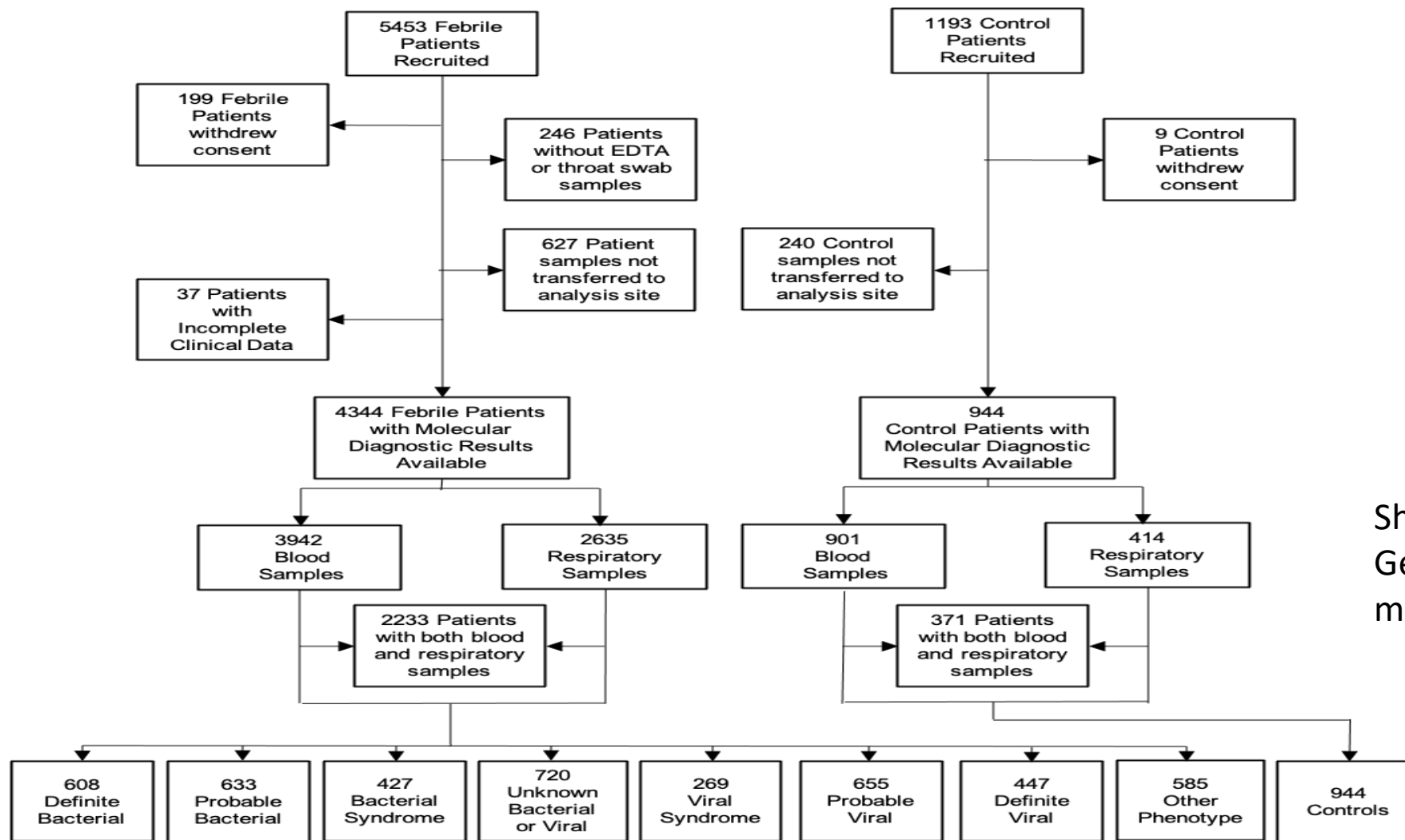


Can molecular pathogen detection improve Diagnosis ?

Micropathology
Ltd Prof Colin
Fink



Best practice clinical diagnosis **AND** molecular pathogen detection



Shah et al Lancet
Geographic
medicine 2023

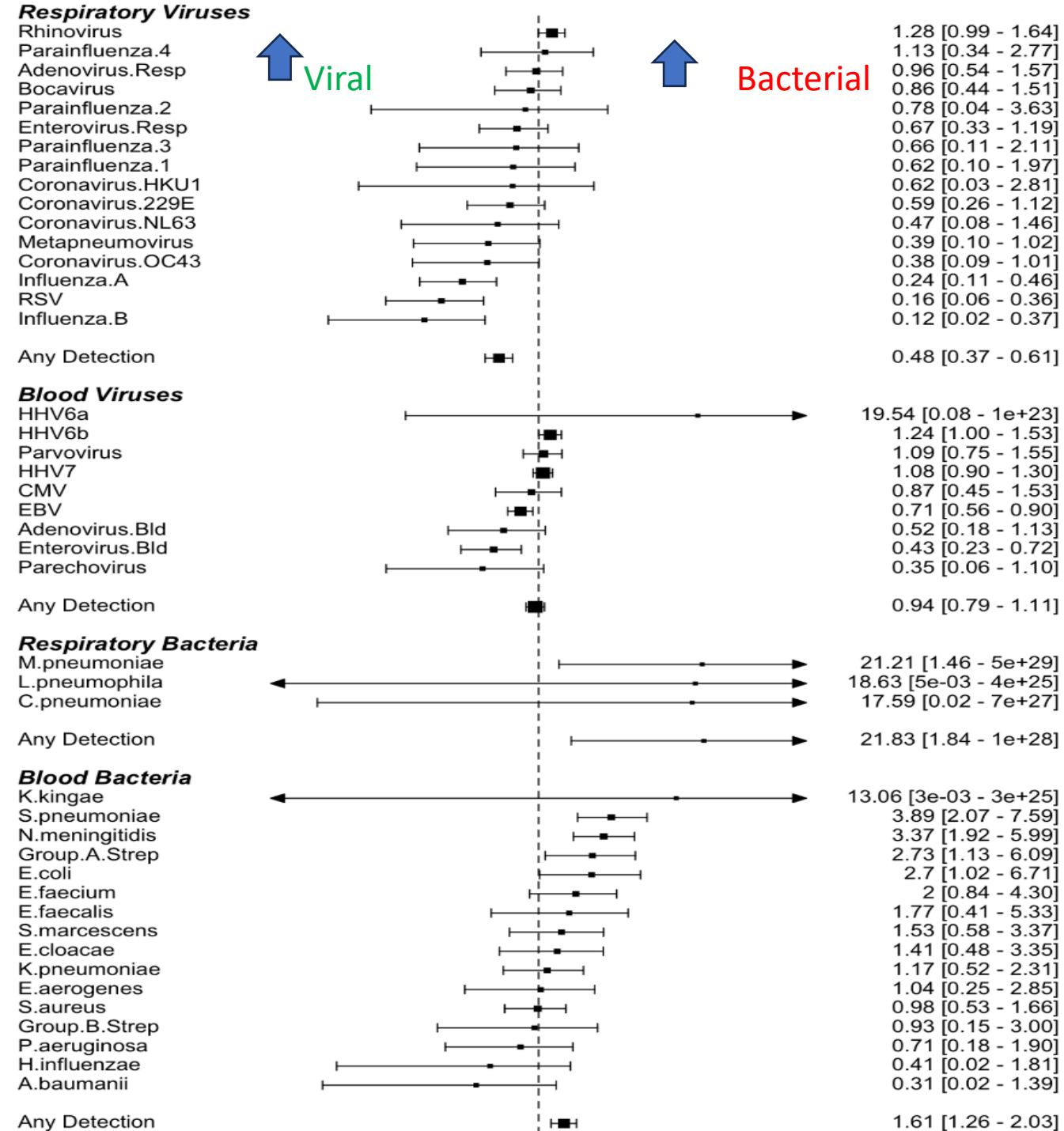


Diagnosis uncertain 75%

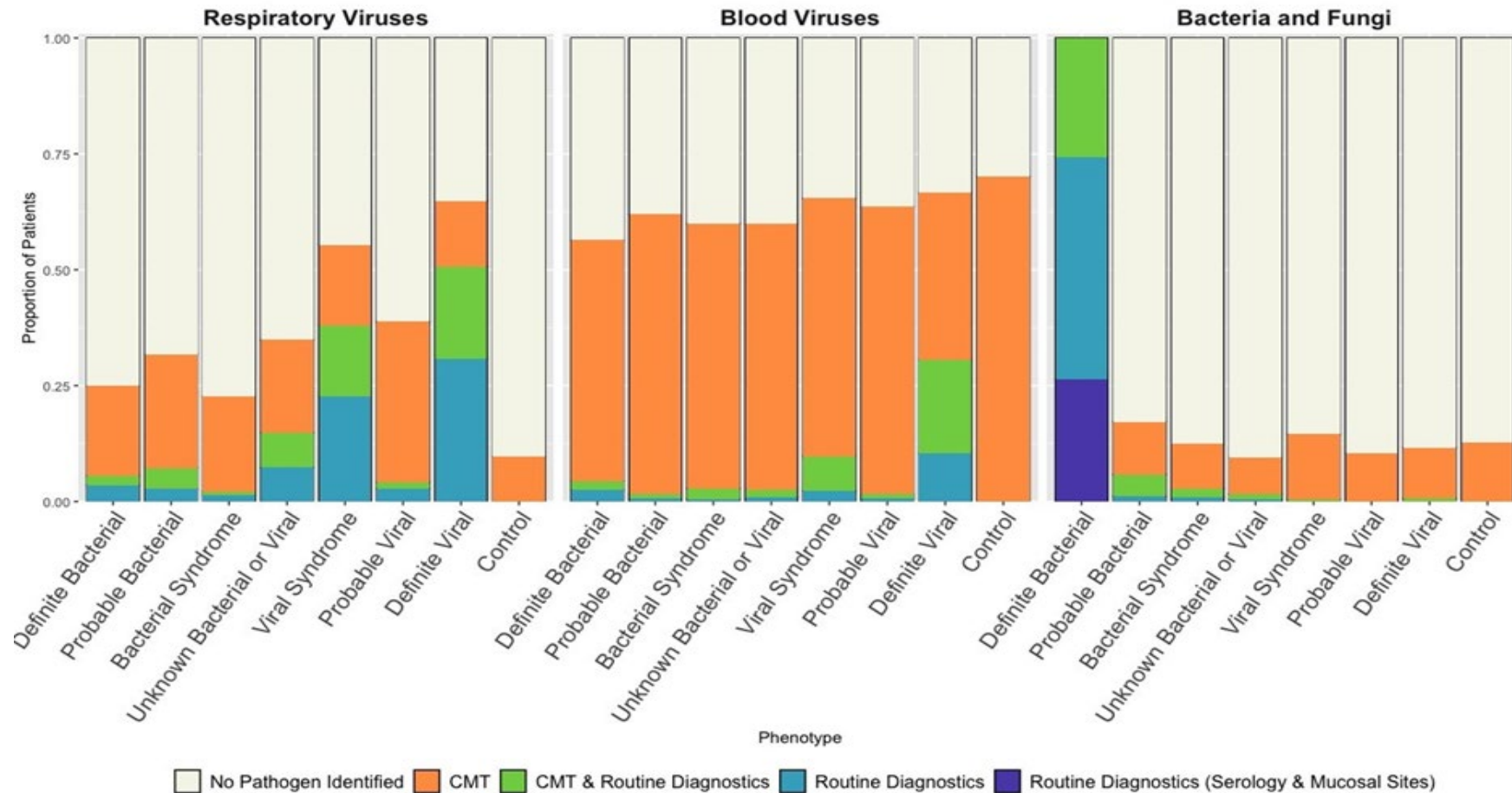


Odds ratio for detection of pathogen by PCR in viral or bacterial infection

Shah et al Lancet geographic medicine Europe 2023



Molecular Pathogen detection on PERFORM Cohort



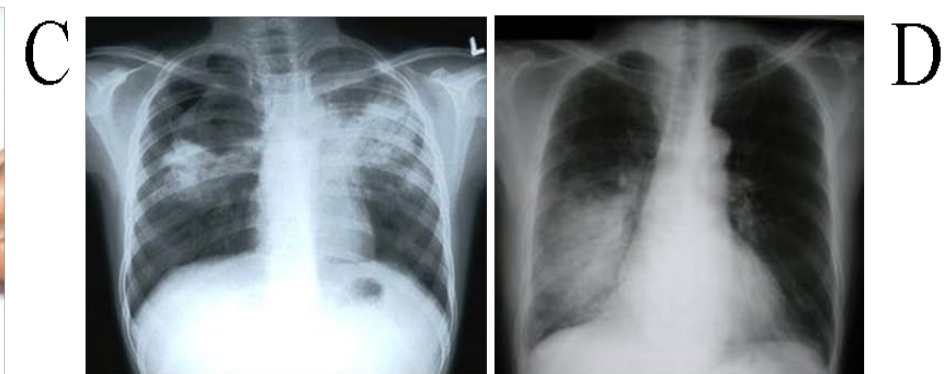
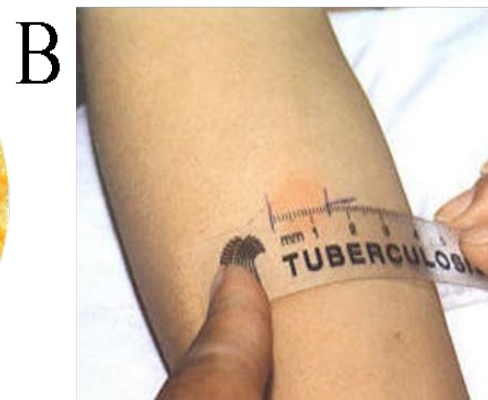
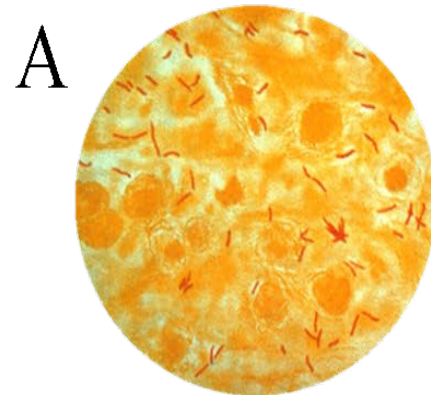
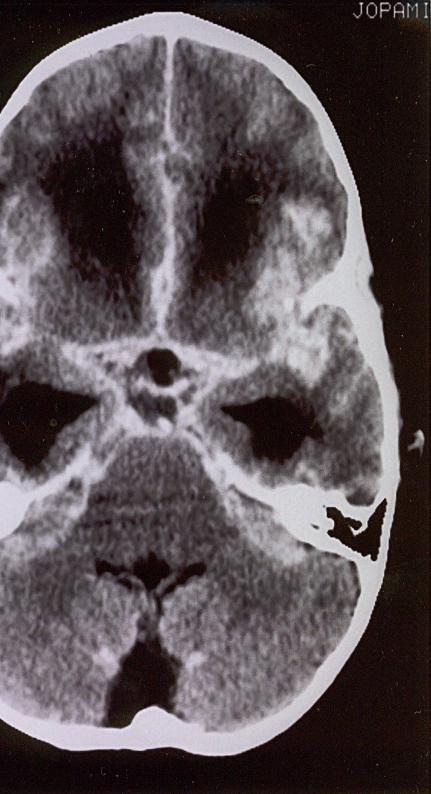
Respiratory Viruses found in 25% and blood viruses in 50% of children with proven bacterial infection

Shah lancet geographic medicine 2023

Pathogen detection fails to identify cause of illness in majority



DIAGNOSIS of TB



Microbiological diagnosis possible in only 20% of treated cases of childhood TB (even with Gene expert)
Diagnosis most difficult in HIV infected individuals
Most childhood TB treated with no microbiological confirmmration

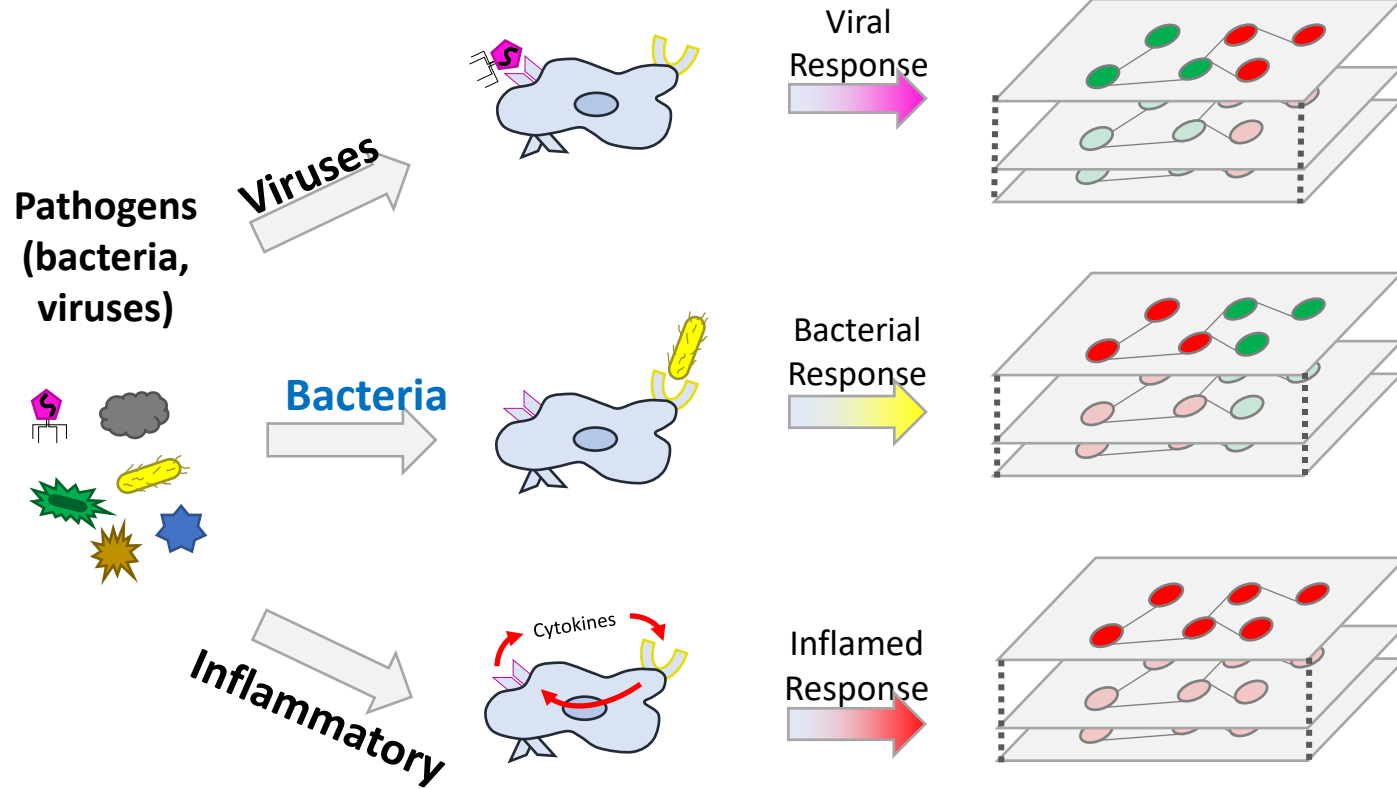
Can we improve the diagnosis of infectious and inflammatory diseases through alternative approaches ??

Diagnosis using Host RNA(or protein) expression

- **A Paradigm shift.** Instead of attempting to identify Pathogens or diagnose disease by clinical features
- **can we use the pattern of genes switched on or off in the blood as diagnostic signatures of each disease**

Genes/proteins switched on or off in inflammatory cells

Unique pattern of on/off genes(or proteins) in each disease



Each disease is characterized by unique pattern of immune genes switched on or off

Building on long term EU funding



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 668303 and . 848196

EU Horizon 2020 program grant 23 million Euro 2020-2025

Lead from Imperial

Partners in 11 EU countries, Gambia, Nepal , Taiwan, South Africa/Malawi



Thanks

and over to Professor Aubrey Cunnington