Kent / East Sussex / South-East London Paediatric AMS Network
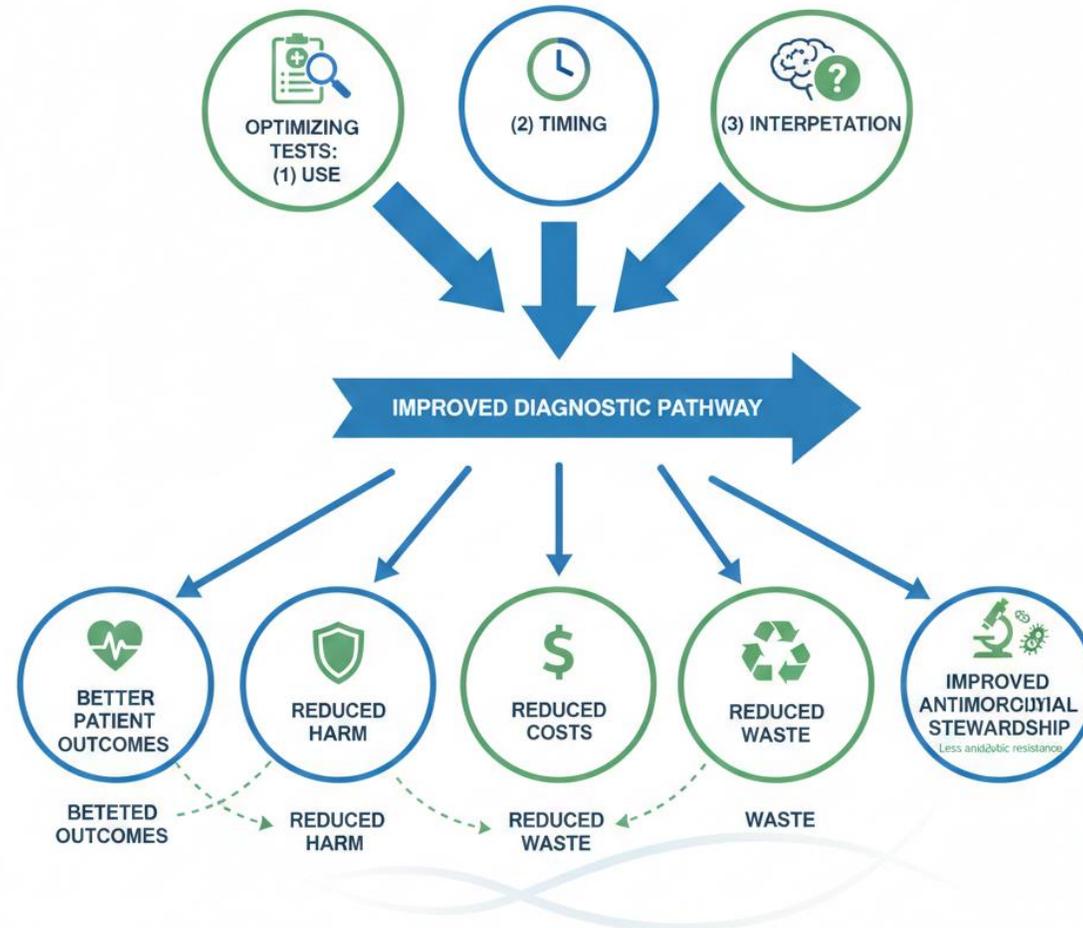
Diagnostic Stewardship

Dr Jonathan Cohen
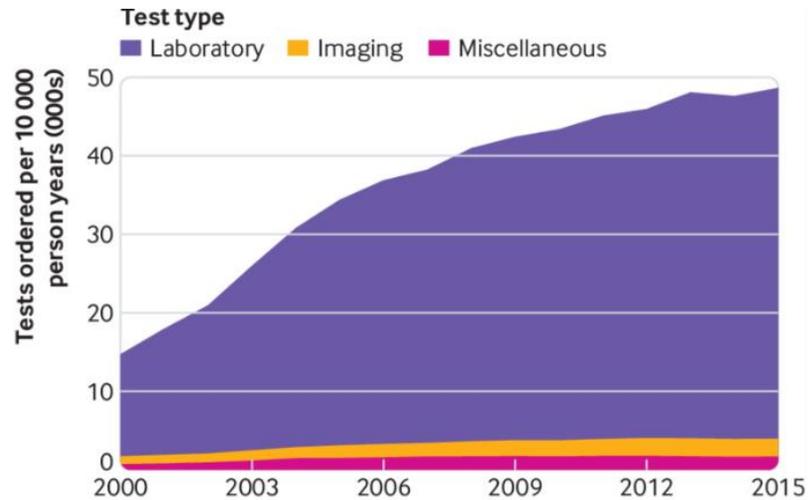## Evelina London

What is diagnostic stewardship?

OPTIMIZING DIAGNOSTIC STRATEGIES:
FOR ENHANCED HEALTHCARE VALUE

OPTIMIZING TESTS: (1) USE
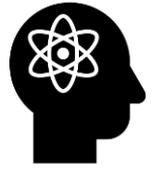
(2) TIMING

(3) INTERPETATION

IMPROVED DIAGNOSTIC PATHWAY

BETTER PATIENT OUTCOMES

REDUCED HARM

REDUCED COSTS

REDUCED WASTE

IMPROVED ANTIMORCIJYIAL STEWARDSHIP
Less anid2ubic resistance

BETETED OUTCOMES

REDUCED HARM

REDUCED WASTE

WASTE

Why we need better diagnostic stewardship?

Right test, right child, right time

Diagnostic pathway

| Decision to test | Order test | Collect specimen | Transport specimen | Test processing | Reporting of result | Clinician interpretation |
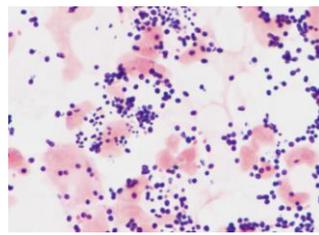
Pretest probability

Is test likely to change management?

Will the test be successful?

Requesting on order comms – access to computers

Communication with laboratory / discussion with experts

Avoid contamination

Collect enough volume

Sample quality (i.e. not bloodstained)

Mode of transport: risk of getting lost?

Transfer time duration: degradation of sample

Specimen accepted?

Time to process

Quality of processing / test performance

Selective reporting

Frame results

Knowledge re: test performance and characteristics

Decision support for interpretation
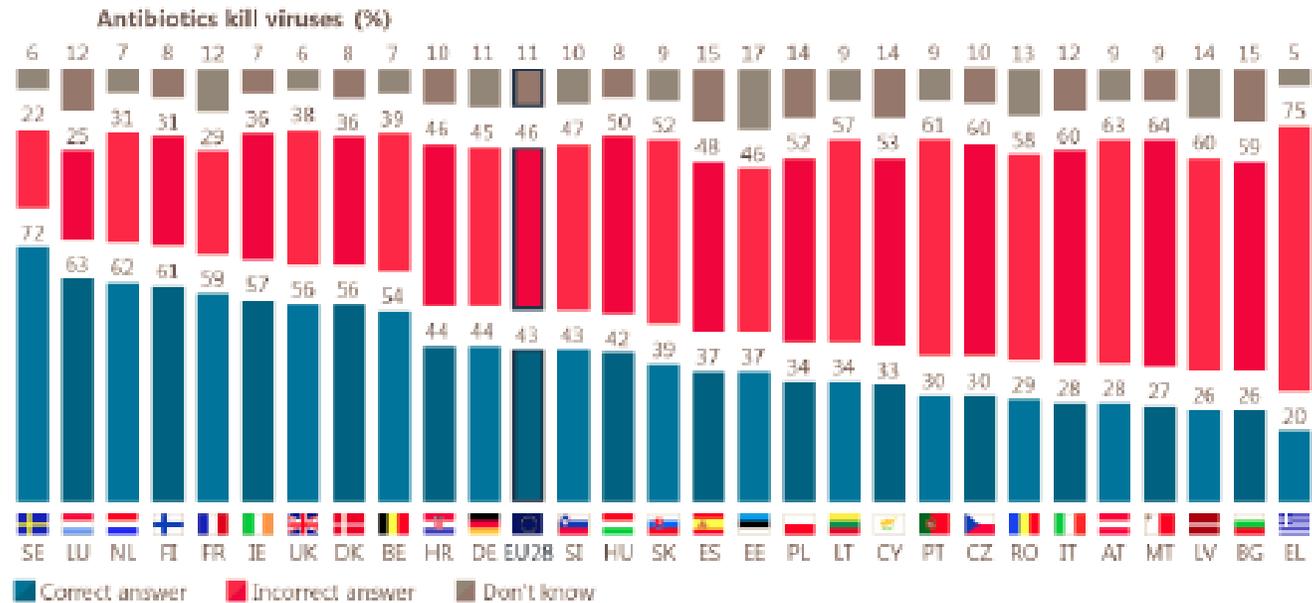
The paediatric ED….

- Limited volumes – prioritisation

- Contamination

- Trauma to child vs diagnostic yield

- Parental pressure for tests / for no tests

Understanding gap

Eurobarometer 2016:
46% of Europeans think that antibiotics kill viruses

QB4.1 For each of the following statements, please tell me whether you think it is true or false.

Antibiotics kill viruses (%)

Don't know row: 6 12 7 8 12 7 6 8 7 10 11 11 10 8 9 15 17 14 9 14 9 10 13 12 9 9 14 15 5

Incorrect answer row: 22 25 31 31 29 36 38 36 39 46 45 46 47 50 52 48 46 52 57 53 61 60 58 60 63 64 60 59 75

Correct answer row: 72 63 62 61 59 57 56 56 54 44 44 43 43 42 39 37 37 34 34 33 30 30 29 28 28 27 26 26 20

SE LU NL FI FR IE UK DK BE HR DE EU28 SI HU SK ES EE PL LT CY PT CZ RO IT AT MT LV BG EL

■ Correct answer   ■ Incorrect answer   ■ Don't know

Correct Answer=False

Total base (N=27,569)

Survey conducted by TNS opinion & social at the request of the European Commission, Directorate-General for Health and Food Safety

2016.4325
Special Eurobarometer 445 - April 2016
"Antimicrobial Resistance"
Report

I think I need antibiotics for my col…   IT'S A VIRUS!

Case Scenario: Jacey

- 3yo coryza for 2 days, now febrile and coughing more
- T 38.5 / HR 150 / RR 35 / SaO2 97% in room air

- Tolerating oral intake
- Crepitations and coarse breath sounds in left lower zone

- Blood tests? Which?
- Chest x-ray?
- Antibiotics?

Case Scenario: Jacey
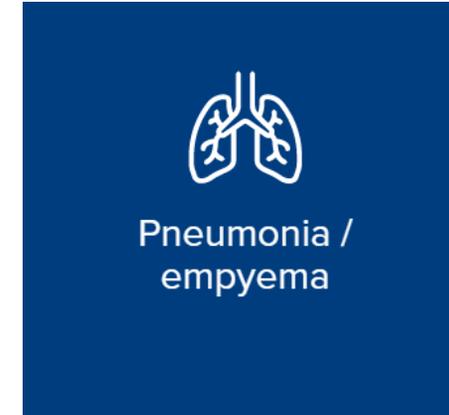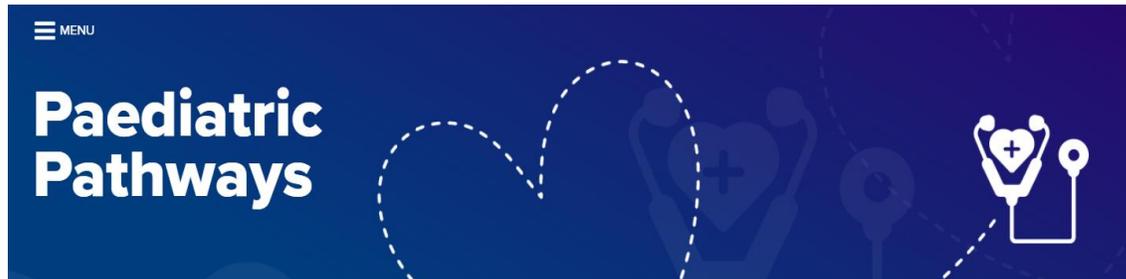
- Blood tests? Which?

- Chest x-ray?

- Antibiotics?

- Likely diagnosis and pre-test probability...?

- Will diagnostic tests change management?

- How to gain confidence to treat without investigations?

Pathways and guidelines to support test use

• BSAC paediatric pathways

Pneumonia / empyema

INVESTIGATIONS

If no features of severe disease, no investigations routinely indicated.

If features of SEVERE respiratory distress:

- FBC, U&E, creatinine, CRP & blood culture
- Consider respiratory viral testing if diagnosis of bronchiolitis considered
- Consider other appropriate microbiological investigations
- Consider performing a CXR (AP film), especially if hypoxia or significant respiratory distress. Also consider if no improvement in symptoms despite >48 hours of adequate oral Ab therapy.

Case Scenario: Sana

- 5 years old
- Chickenpox – started 2 days ago

- Now fever 39.6, miserable and quiet
- HR 140 / RR 35 / CRT 3 sec central / SaO2 91% in air
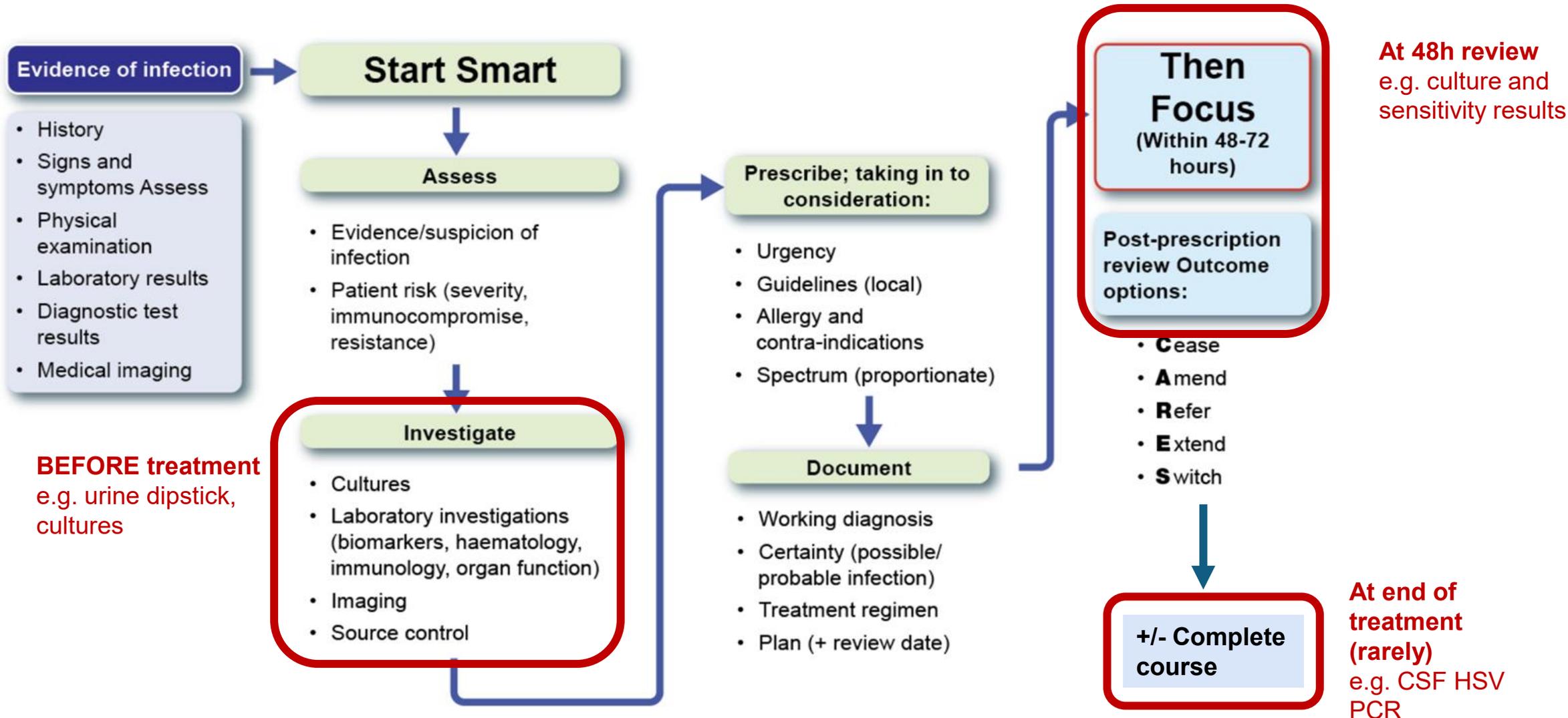
- Investigations?
- Management?

Case Scenario: Sana

- 5 years old
- Chickenpox – started 2 days ago

- Now fever 39.6, miserable and quiet, not drunk much today
- HR 140 / RR 35 / CRT 3 sec central / SaO2 91% in air

- Investigations?   Blood gas, CRP, FBC, U&E, blood culture
- Management?   Antibiotics? Antivirals? Other?   Skin swab?

Antimicrobial stewardship: Start Smart then Focus Clinical management algorithm

Evidence of infection → **Start Smart**

- History
- Signs and symptoms Assess
- Physical examination
- Laboratory results
- Diagnostic test results
- Medical imaging

Assess

- Evidence/suspicion of infection
- Patient risk (severity, immunocompromise, resistance)

BEFORE treatment
e.g. urine dipstick, cultures

Investigate

- Cultures
- Laboratory investigations (biomarkers, haematology, immunology, organ function)
- Imaging
- Source control

Prescribe; taking in to consideration:

- Urgency
- Guidelines (local)
- Allergy and contra-indications
- Spectrum (proportionate)

Document

- Working diagnosis
- Certainty (possible/ probable infection)
- Treatment regimen
- Plan (+ review date)

Then Focus
(Within 48-72 hours)

At 48h review
e.g. culture and sensitivity results

Post-prescription review Outcome options:

- **C**ease
- **A**mend
- **R**efer
- **E**xtend
- **S**witch

+/- Complete course

At end of treatment (rarely)
e.g. CSF HSV PCR

Antimicrobial stewardship: Start smart - then focus

Blood culture

Avoid unnecessary use if not seriously ill

Collection during fever does not increase yield

Aerobic and anaerobic bottles where possible

Take BEFORE antibiotics

Fill volumes
- Aim at least 1ml in babies
- 5ml in children
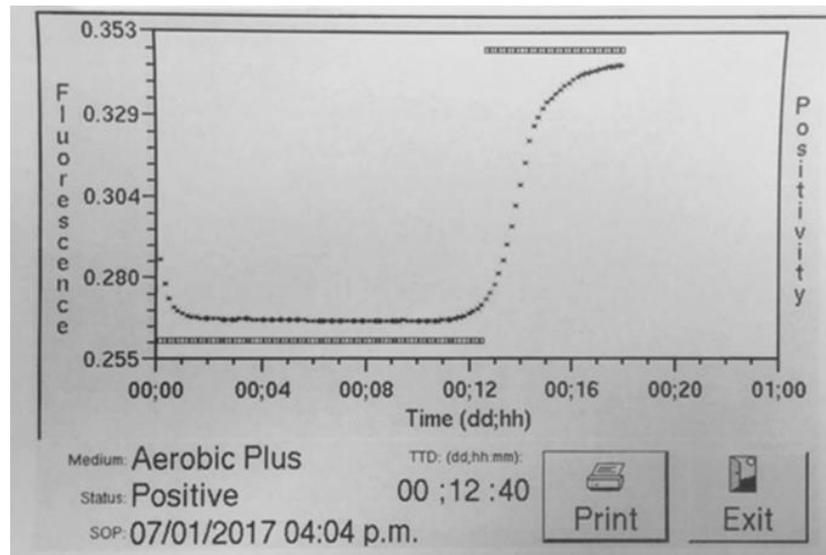- 10ml in teenagers (5ml each bottle)

Minimise chance of rejection (sample labelling)
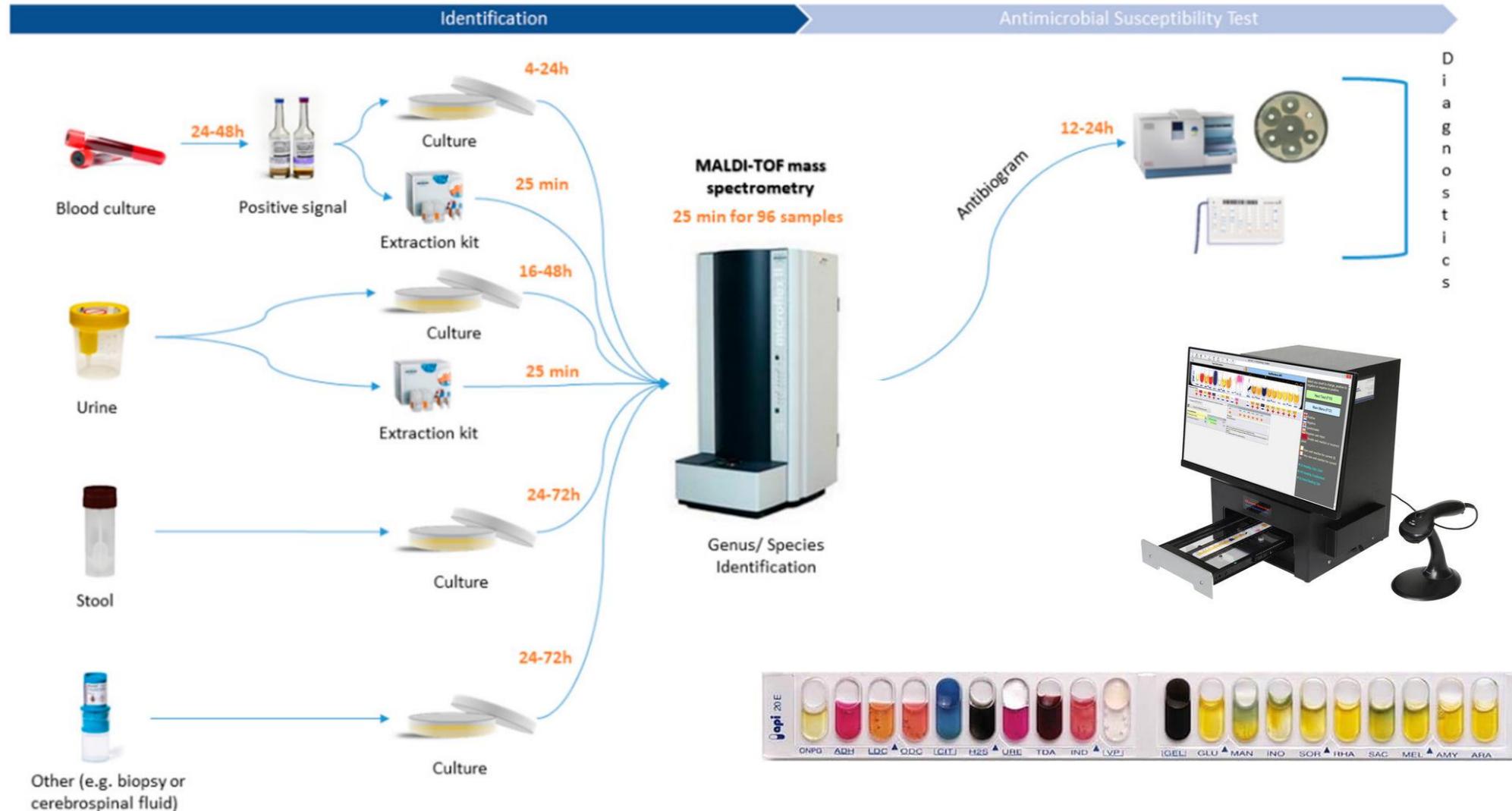
Problem with eczematous skin!

QI Fill volumes of blood cultures

How do we find out what we find out?
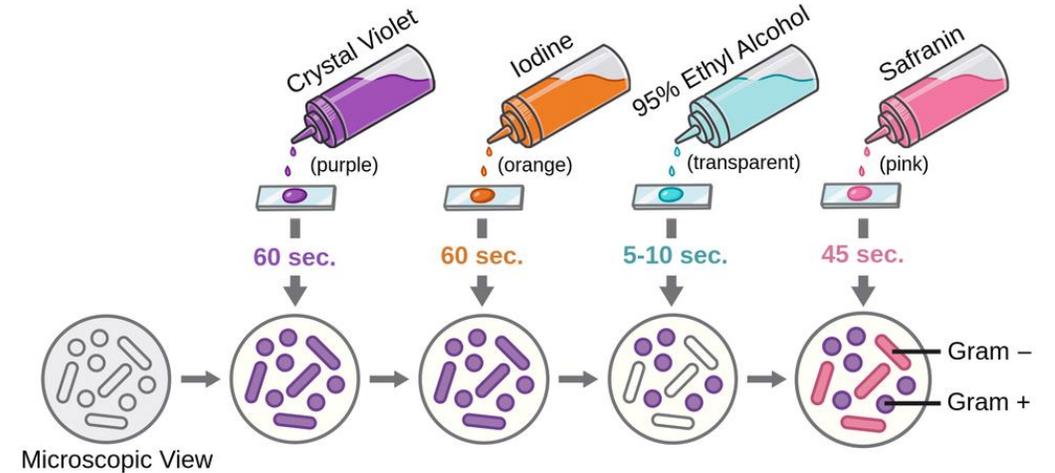
- Most clinically significant organisms grow within 24-36 hours

How do we find out what we find out?

Case Scenario: Archie

- 5 months old

- Cough and coryza for 2 days

- Now fever and breathing hard

- Its December

- Mother declined RSV vaccine in pregnancy

- T 38.2 / HR 130 / RR 40 / SaO2 97% in RA

- Widespread wheeze and crepitations

- Tolerating feed in ED

Case Scenario: Archie

- 5 months old

- Cough and coryza for 2 days

- Now fever and breathing hard

- Its December

- Mother declined RSV vaccine in pregnancy

- T 38.2 / HR 130 / RR 40 / SaO2 87% in RA

- Widespread wheeze and crepitations

- Increased work of breathing

- Struggling with oral intake in ED

Imaging

- When can it be harmful?

Reducing unwarranted chest x-rays in bronchiolitis: Importance of a robust analysis

Joanna Lawrence ✉, Harriet Hiscock, Alice Voskoboynik, Ramesh Walpola, Anurag Sharma

"antibiotic use increased five-fold if a CXR was performed, concerning given the increased risk of side effects and potential contribution to global antibiotic resistance.

CXRs also result in unnecessary radiation exposure at the beginning of an infant's lifetime cumulative exposure.

The costs of the CXR and unnecessary downstream consequences represent an opportunity cost for higher value healthcare."

Respiratory virus PCR testing

- What can be tested for?
- How sensitive is it?
- What do results mean?

How PCR works

So the virus is there...is it the cause of the illness?

- 350 children < 5yo
- In Europe
- Acute respiratory infection vs Controls

- Likely for RSV

- Possibly for others (HMPV / flu / paraflu)

- Unlikely for others

Lower respiratory samples in PICU

234 samples tested for both

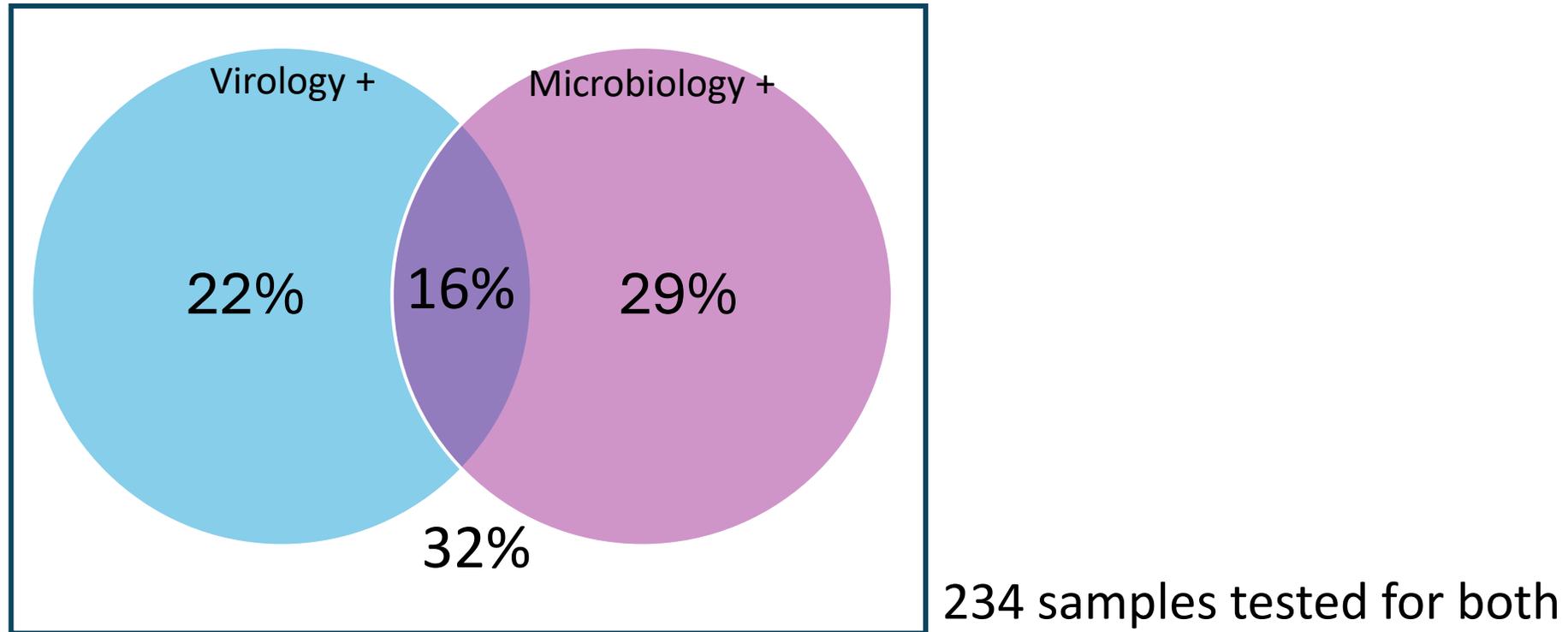- 36% of those with positive microbiology cultures are also virus positive

Evelina PICU, 2024 data

Respiratory virus PCR testing

- **Too much information!**
- **Not enough meaning?**

1 Test. 21 Pathogens. 45 minutes.

The FilmArray® Respiratory Panel 2 (RP2)

Sample type: Nasopharyngeal Swab

Viruses
Adenovirus
Coronavirus HKU1
Coronavirus NL63
Coronavirus 229E
Coronavirus OC43
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza A/H1
Influenza A/H1-2009
Influenza A/H3
Influenza B
Parainfluenza Virus 1
Parainfluenza Virus 2
Parainfluenza Virus 3
Parainfluenza Virus 4
Respiratory Syncytial Virus

Bacteria
Bordetella parapertussis
Bordetella pertussis
Chlamydia pneumoniae
Mycoplasma pneumoniae

45 MIN

An unprecedented run time of about 45 minutes enables **higher efficiency and throughput** on the FilmArray® 2.0 and the FilmArray® Torch Systems with only 2 minutes of hands-on time.

21 | 1
Pathogens | Test

With 21 pathogen targets in one test, including *Bordetella parapertussis*, the FilmArray RP2 is **more comprehensive** than ever.

97.1% Sensitivity*
99.3% Specificity*

*Data on file.

Higher overall sensitivity across a broader spectrum of pathogens means that the FilmArray RP2 offers the world the fastest way to better results in the detection of respiratory pathogens.

Case - PCR hinderance

6 year girl presents with fever, cough and respiratory distress. CRP 58
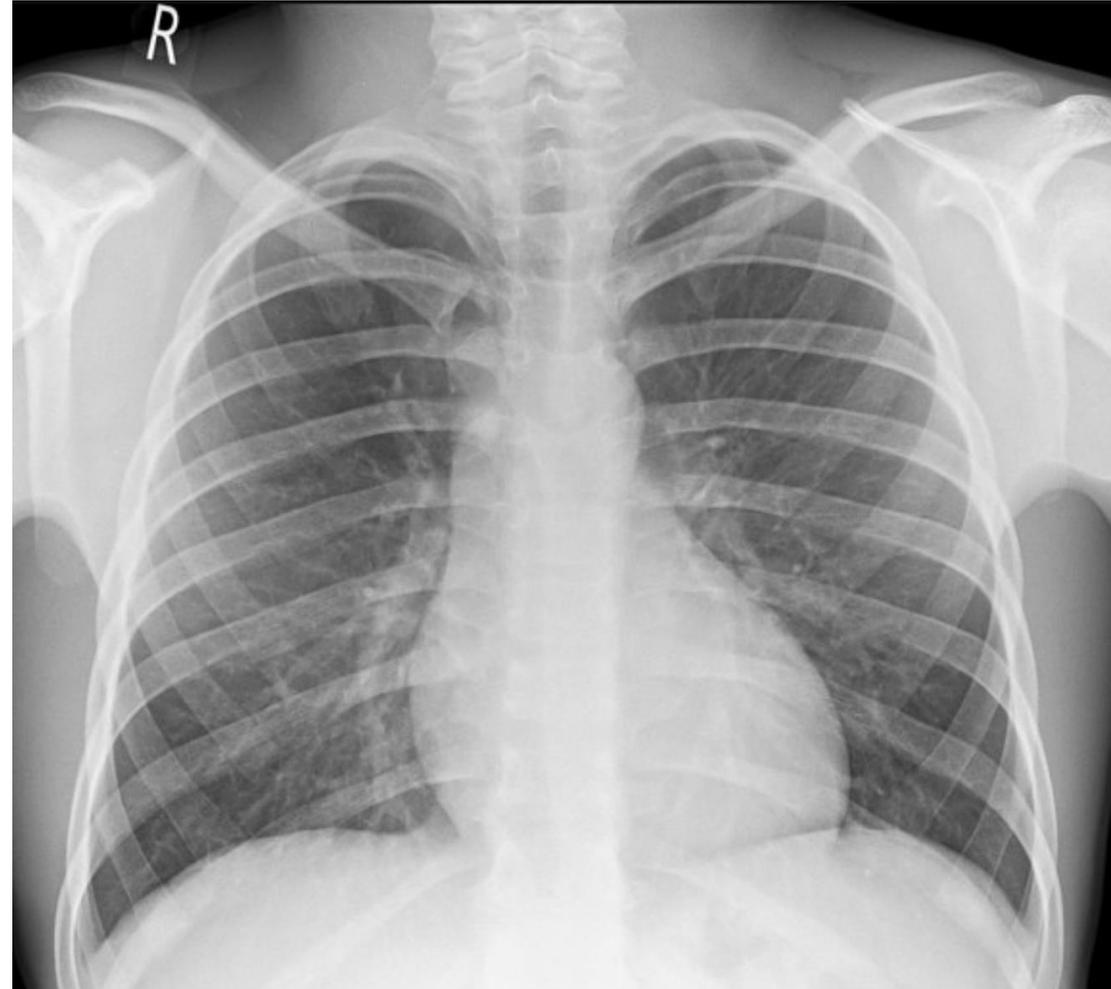
Clinically LRTI

Respiratory viral PCR sent routinely

- Mycoplasma pneumoniae +
- Rhinovirus +

Prescribed azithromycin

Likely mycoplasma colonisation
Overtreatment, parental anxiety, future expectation for antibiotics

Urine samples

QI

24 h   **48 h**

Urine dip (urgent microscopy if <3m)

Urine culture & sensitivities result

Empirical antibiotics → Targeted therapy

Contamination or Colonisation or Infection?

Method of collection	Contamination rate
Clean catch	26%
Catheter sample	12%
Suprapubic aspiration	1%
Bag sample	**46%**

Tosif S, Baker A, Oakley E *et al*. Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. *J Paediatr Child Health* 2012; 48: 659-64.

Can host biomarkers tell us what is going on?

Inflammatory markers

- CRP
- FBC
- ESR

- Procalcitonin (better than above [bacterial vs viral] though expensive and often unavailable)

- Just because test works doesn't mean people are guided by it
  (e.g. BATCH study)

Better decisions by looking at host response
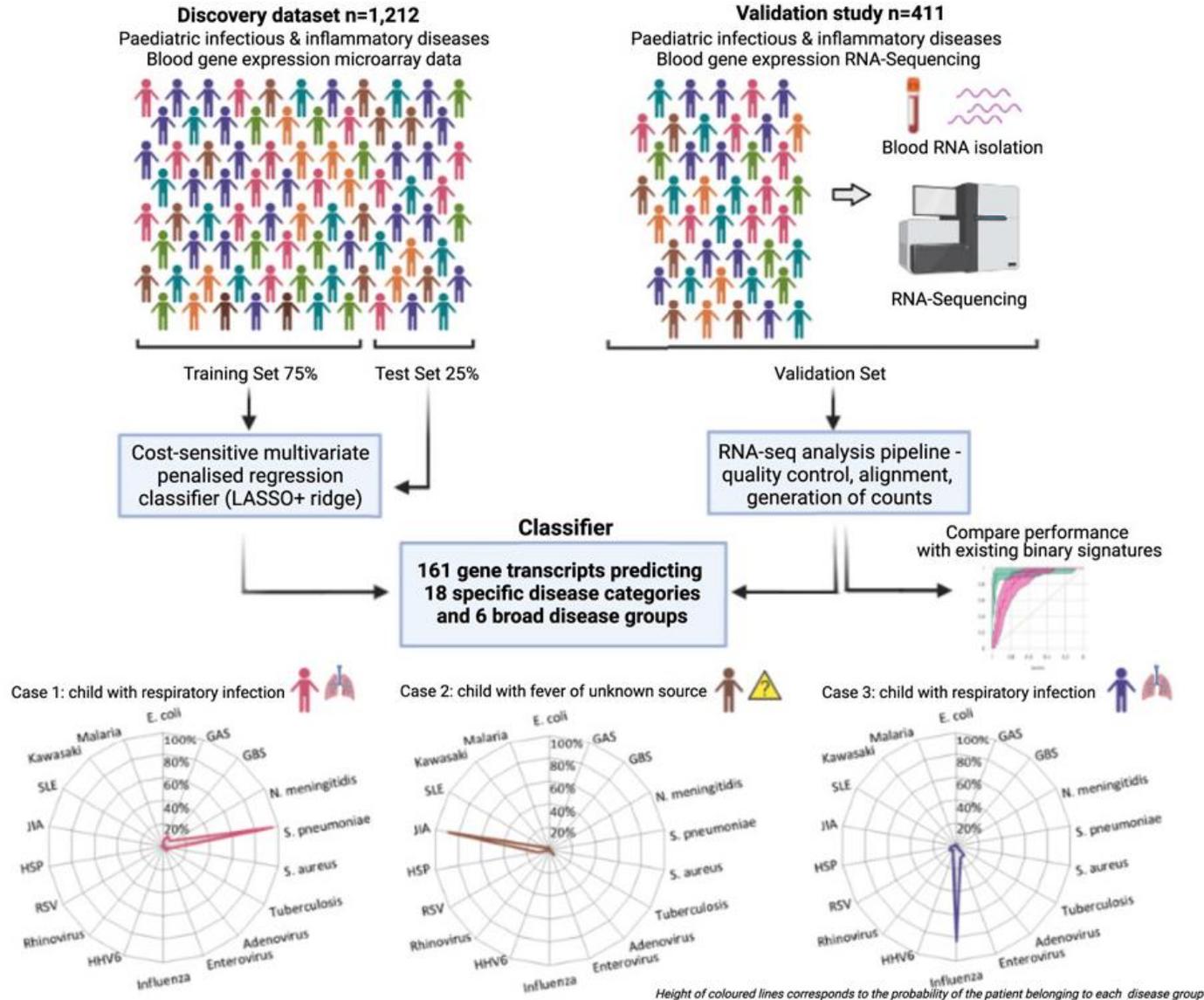
Clinical and Translational Article

Diagnosis of childhood febrile illness using a multi-class blood RNA molecular signature

Habgood-Coote et al., Med 4, 635–654
September 8, 2023 © 2023 The Author(s).

How to Read Your MeMed BV® Score

V (Viral/Other)

B (Bacterial)

10 < score < 35
Moderate
likelihood of **viral** infection
(or other non-bacterial etiology)

65 < score < 90
Moderate
likelihood of **bacterial** infection
(or co-infection)

0   10   35   65   90   100

0 ≤ score ≤ 10
High
likelihood of **viral** infection
(or other non-bacterial etiology)

35 ≤ score ≤ 65
Equivocal

90 ≤ score ≤ 100
High
likelihood of **bacterial** infection
(or co-infection)

CSF

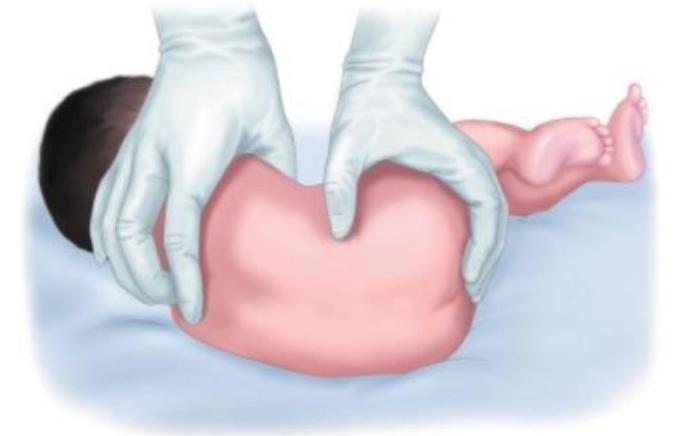%age LP before AB
Time **sample** →
process

CSF: **prior** to antibiotics
- LP post-antibiotics prolongs hospital stay 5d → 12.5d (no pathogen found) [1]

- CSF sterilizes within 2h (*N.meningitidis);* 6h (pneumococcus); 8h (GBS) [2]

Delay in specimen collection → processing
- CSF WCC progressively reduces after 4 hours

1. Ramasany et al. Arch Dis Child 2018
2. Kanegaye et al. 2001. Pediatrics

Sterile site PCRs for causative bacteria

Broad range PCR
- Can detect lots of things
- Less sensitive

Requested Test
We strongly recommend the addition of targeted real-time PCR alongside broad-range bacterial PCR in order to maximise sensitivity. **Please tick this box if you do not want additional tests to be performed** ☐

Please tick desired testing:
☐ Broad Range Bacterial PCR (16S rRNA gene)

☐ Broad Range Fungal PCR (ITS)

☐ Enterobacteriacae real-time PCR

☐ Kingella kingae real-time PCR

☐ Mycobacterium tuberculosis / Mycobacterium spp. real-time PCR

☐ Neisseria meningitidis real-time PCR

☐ Staphylococcus aureus real-time PCR
☐ Streptococcus pyogenes real-time PCR

☐ Streptococcus agalactiae real-time PCR

☐ Streptococcus pneumoniae real-time PCR

☐ Haemophilus influenzae real-time PCR

☐ Tropheryma whipplei (Whipples) real-time PCR

Targeted specific PCR
- Can detect lots of things
- More sensitive

Culture >>> Targeted PCR >>> Broad-spectrum PCR (e.g. 16S)

HIGHER-----------------------SENSITIVITY-----------------------**LOWER**

Sterile site PCRs for causative bacteria

Requested Test
We strongly recommend the addition of targeted real-time PCR alongside broad-range bacterial PCR in order to maximise sensitivity. **Please tick this box if you <u>do not</u> want additional tests to be performed** ☐

Please tick desired testing:		
☐ Broad Range Bacterial PCR (16S rRNA gene)	☐ Mycobacterium tuberculosis / Mycobacterium spp. real-time PCR	☐ Streptococcus agalactiae real-time PCR
☐ Broad Range Fungal PCR (ITS)	☐ Neisseria meningitidis real-time PCR	☐ Streptococcus pneumoniae real-time PCR
☐ Enterobacteriacae real-time PCR	☐ Staphylococcus aureus real-time PCR	☐ Haemophilus influenzae real-time PCR
☐ Kingella kingae real-time PCR	☐ Streptococcus pyogenes real-time PCR	☐ Tropheryma whipplei (Whipples) real-time PCR

Targets for bone/joint samples

Targets for CSF samples

CSF PCR Panels (e.g. BioFire)

Paediatric meningitis in the conjugate vaccine era and a novel clinical decision model to predict bacterial aetiology

N.G. Martin [a,b], S. Defres [c], L. Willis [a], R. Beckley [a], H. Hardwick [c], A. Coxon [a], S. Kadambari [d,e], L.-M. Yu [f], X. Liu [a], U. Galal [a], K. Conlin [a], M.J. Griffiths [c,g], R. Kneen [g], S. Nadel [h], P.T. Heath [i], D.E. Kelly [a], T. Solomon [c,j], M. Sadarangani [k,l,*,1], A.J. Pollard [a,1], on behalf of the UK-ChiMES and ENCEPH-UK study groups [2]

3002 children <16y hospitalized with *suspected* meningitis/encephalitis in 31 UK hospitals

36.7% had diagnosis of meningitis (pathogen detection on CSF or raised CSF WCC)

Bacterial pathogen found in 6%
Most common pathogen in 6m-10 years = Enterovirus

Positive enterovirus/parechovirus result = supports stopping antibiotics

Negative PCR supports stopping antibiotics in culture negative CSF

BUT:

1. Sensitivities for Listeria, H.influenzae, E.coli and HSV-1 suboptimal [2]

2. HSV PCR can be false negative in 1st 72h in 25% of cases

PRE-TEST PROBABILITY EDUCATION

1. Tansarli GS, Chapin KC. Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. Clin Microbiol Infect. 2020 Mar;26(3):281-290.
2. Trujillo-Gómez J, Tsokani S, et al. Biofire FilmArray Meningitis/Encephalitis panel for the aetiological diagnosis of central nervous system infections: A systematic review and diagnostic test accuracy meta-analysis. EClinicalMedicine. 2022 Feb 14;44:101275.

Rapid pan-microbial metagenomics for pathogen detection and personalised therapy in the intensive care unit: a single-centre prospective observational study
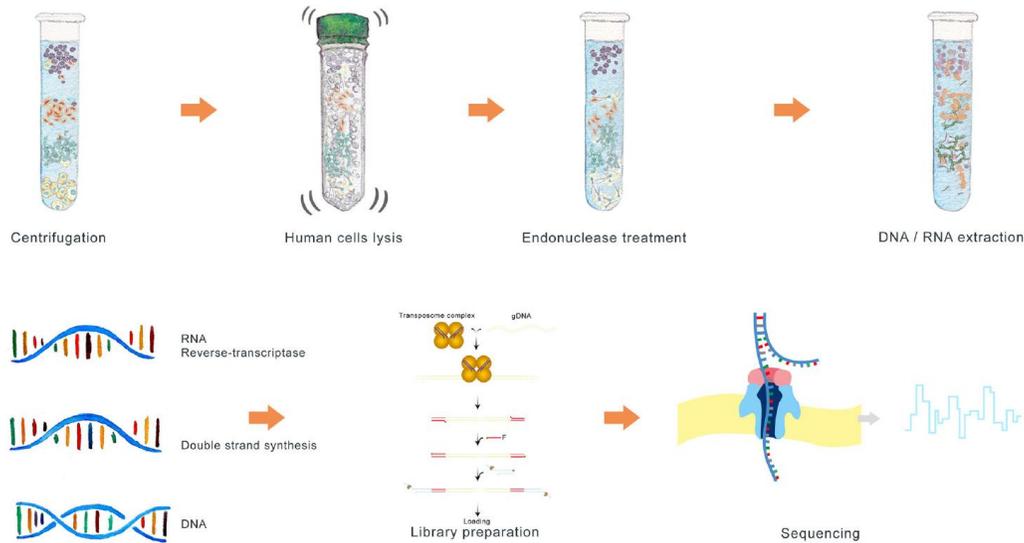
- Detection of all DNA/RNA in a sample – deplete human material
- Match genetic sequences to pathogen databases
- Same day results in ICU settings

- Genomics England Network of Excellence

- Being rolled out to several NHS settings

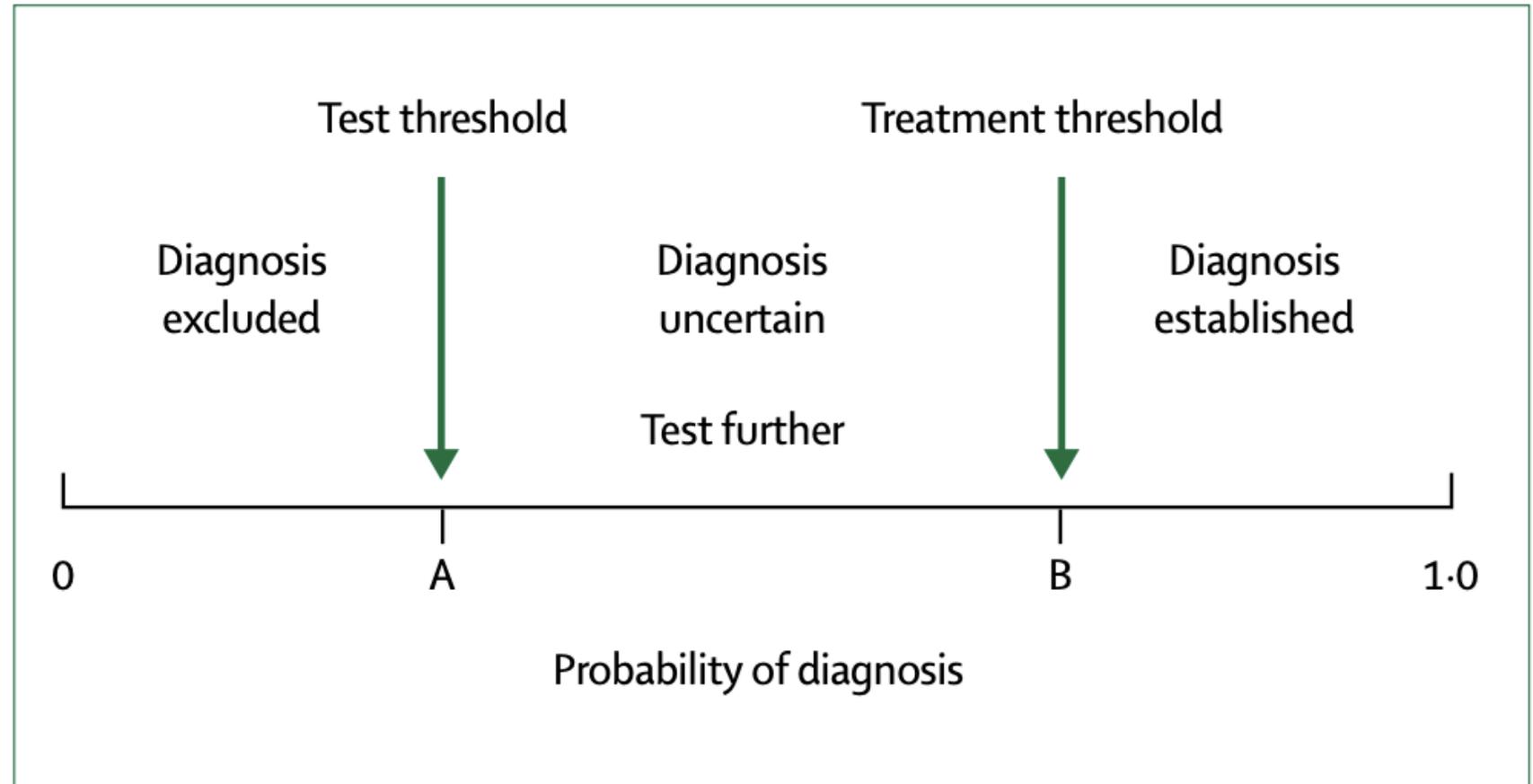|	Number of samples	True positive	True negative	False positive	False negative	Sensitivity	Specificity	Negative predictive value	Positive predictive value
All samples									
Bacteria	104	45	57	1	1	98% (88–100)	98% (91–100)	98% (89–100)	98% (87–100)
Viruses	83	28	52	0	3	90% (74–98)	100% (93–100)	95% (86–98)	100% (88–100)
Fungi	104	17	85	0	2	89% (67–99)	100% (96–100)	98% (92–99)	100% (80–100)
Lower respiratory tract samples									
Bacteria	89	38	49	1	1	97% (87–100)	98% (89–100)	98% (89–100)	97% (85–100)
Viruses	74	24	47	0	3	89% (71–98)	100% (92–100)	94% (84–98)	100% (86–100)
Fungi	89	16	71	0	2	89% (65–99)	100% (95–100)	97% (91–99)	100% (79–100)

Data are n or % (95% CI).

Table 2: Performance characteristics of all samples and lower respiratory tract samples after 24-h results on a per-sample basis and separated by microbial kingdom

Alcolea-Medina, 2025

Consider pre-test probability

The lower the pre-test probability, the higher the likelihood of a false positive

Grimes & Schulz. Refining clinical diagnosis with likelihood ratios. 2005. *The Lancet. 365*;9459, p 1500-05

Improving diagnostic stewardship

Core Elements of Hospital Diagnostic Excellence

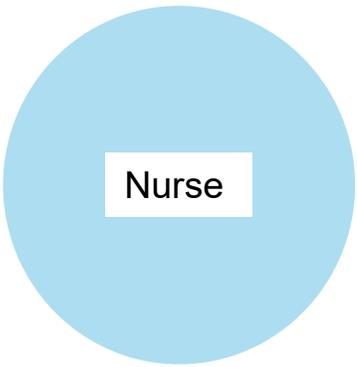**Assessment Tool Priority Examples**

1. Identify the problem
2. Obtain baseline data
   - Safety events
   - Audit of laboratory data / medical records
   - Interviews with clinicians / laboratory staff / patients
3. Engage stakeholders
4. Educate
5. Monitor and report

Toolkit to support diagnostic excellence: CDC Hospital Diagnostic Excellence

How to evaluate diagnostic stewardship?

- Blood culture volumes
- Urine sampling methods (%age clean catch)
- Time from sample collection to test result
- Time from test result to antimicrobial review

QI

| Decision to test | → | Order test | → | Collect specimen | → | Transport specimen | → | Test processing | → | Reporting of result | → | Clinician interpretation |

Nursing education

Urine sampling

Box 1

Urine collection and preservation
- Clean catch is recommended method. Gentle suprapubic cutaneous stimulation using gauze soaked in cold fluid helps trigger voiding*
- If absolutely unavoidable pads / bags must be put on clean skin and checked very regularly to minimise contamination risk
- Unless urine can get straight to lab preservation in a boric acid (red top) container will allow 48 hours delay
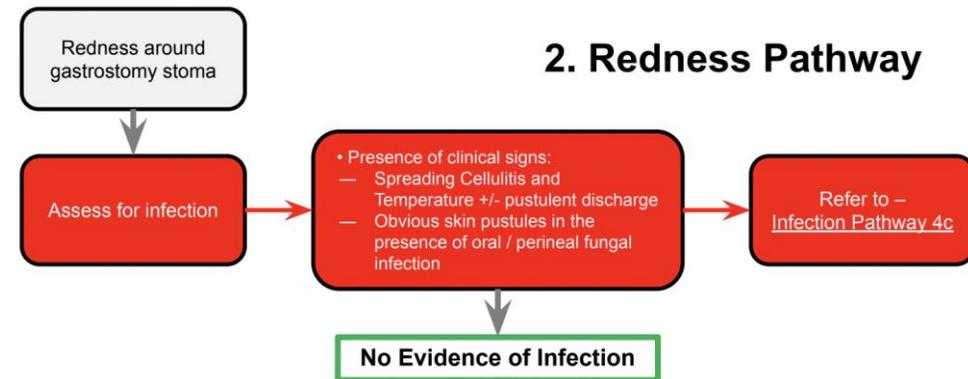
*Urine collection in infants
Kaufmann et al BMJ open

Correct swabs

Gastrostomy assessment

Redness around gastrostomy stoma

2. Redness Pathway

Assess for infection

- Presence of clinical signs:
  — Spreading Cellulitis and Temperature +/- pustulent discharge
  — Obvious skin pustules in the presence of oral / perineal fungal infection

Refer to –
Infection Pathway 4c

No Evidence of Infection

Summary

Performing the right test for the right patent at the right time is foundational to antimicrobial stewardship

Diagnostic pathway can be used to target quality improvement efforts

Education of appropriate use of diagnostics is key