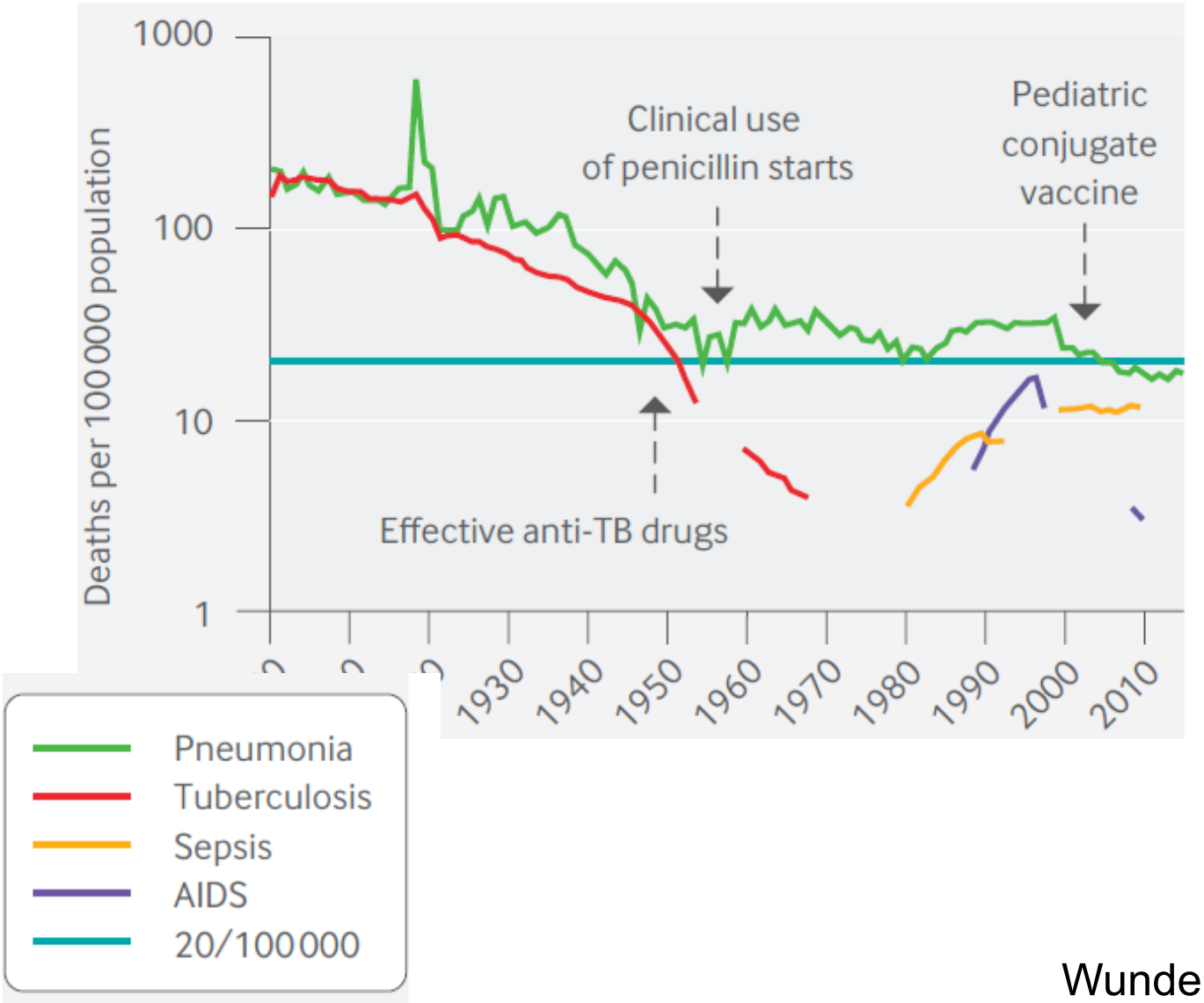
Respiratory tract infections: diagnostic tests which make a difference

Kate Templeton

NHS Lothian

Pneumonia



- CAP is the most frequent cause of death due to infection.

Wunderink BMJ 2017;358:j2471

Pathogens

- S.pneumonia
- H. influenza
- Moraxella
- Staphyloccoci
- Gram Neg bacteria
  - E.coli
  - A.baumanii
  - P.aeruginosa
  - K.pneumoniae
- Mycoplasma
- Legionella
- Chlamydia
- Viruses
  - Influenza
  - RSV
  - Adenovirus
  - Parainfluenza
  - Metapenumovirus
  - Rhinovirus
  - Coronavirus

Diagnosis

Conventional Diagnosis

	Conventional
S. pneumoniae	22
H. influenzae	6
Other	3
L. pneumophila	2
Legionella sp.	0
Chlamydophila sp	2
M. pneumoniae	5
Influenza A	8
Influenza B	2
RSV	2
Adenovirus	0
PIV	1
HCOV	0
HRV	2

- 50% diagnosis of etiological agent

LUMC

Validation in CAP study: 105 patients

Qualitative Multiplex Applications

Bacteria

- Mycoplasma pneumoniae
- Chlamydophila spp.
- PhHV

- Legionella sp.
- L. pneumo
- PhHV

- B. pertussis / B. holmesii
- B. parapertussis / B. holmesii
- PhHV

Viruses

- Influenza A
- RSV
- Influenza B

- Parainfluenza 1, 2, 3, 4

- Rhinovirus, hMPV, EA V

- CoV 229E, OC43, NL-63, HKU1

- ADV / hBoCV

- MERS-CoV

FAM	HEX/YY	TEXAS RED	CY5 : ICs

9 Tubes; 1 sample; 26 targets; 10 samples per plate

Validation in CAP study: 105 patients

	Conventional	real-time PCR
S. pneumoniae	22	nt
H. influenzae	6	nt
Other	3	nt
L. pneumophila	2	3
Legionella sp.	0	3
Chlamydophila sp	2	3
M. pneumoniae	5	10
Influenza A	8	9
Influenza B	2	3
RSV	2	3
Adenovirus	0	4
PIV	1	8
HCOV	0	14
HRV	2	18

80 % diagnosis

8.5% > 18%

14% > 56 %

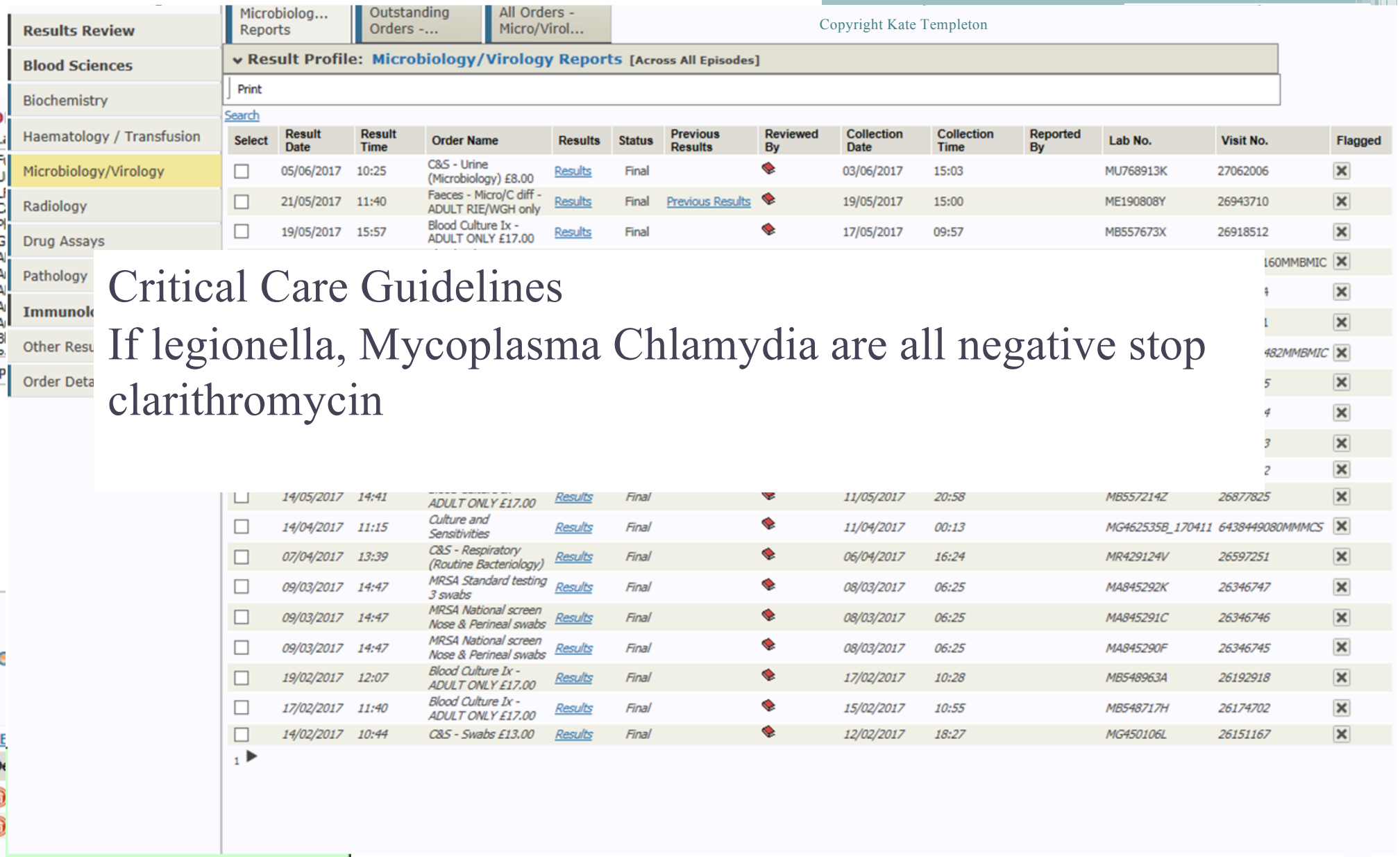
Templeton et al., CID 2005; 41: 345

ITU Protocol

Lower respiratory tract sample
Urine sample for legionella

Adherence to protocols – 44 CAP

LRT sample testing	Number of patients
Throat Swab	17
Sputum PCR	16
BAL PCR	14
Urinary Antigen legionella	12
Urine requested, not performed and nil sputum sent	2
Treated with antibiotics	44
Change with PCR result	25 (56%)



Critical Care Guidelines

If legionella, Mycoplasma Chlamydia are all negative stop clarithromycin

Adherence to protocols – 50 CAP

LRT	Number of patients
Throat swab	5
Sputum PCR	16
BAL PCR	23
Urinary Antigen legionella	40
No samples -	7
Mycoplasma/Legionella/ Chlamydia pos	0
Result noted in EPR- with treatment decision to stop clarithromycin	39 (78%)
Microbiology ward round	9 (18%)
No decision noted -	2 (4%)

Pediatric ICU

- Regular ward

"pertussis PCR through and neg
Can now stop clarithromycin"

- Infection prevention control nurse
- Virology
- Microbiology
- Infectious diseases

"Straightforward bronch-
(A virus pos) can stop all
Antibiotics"

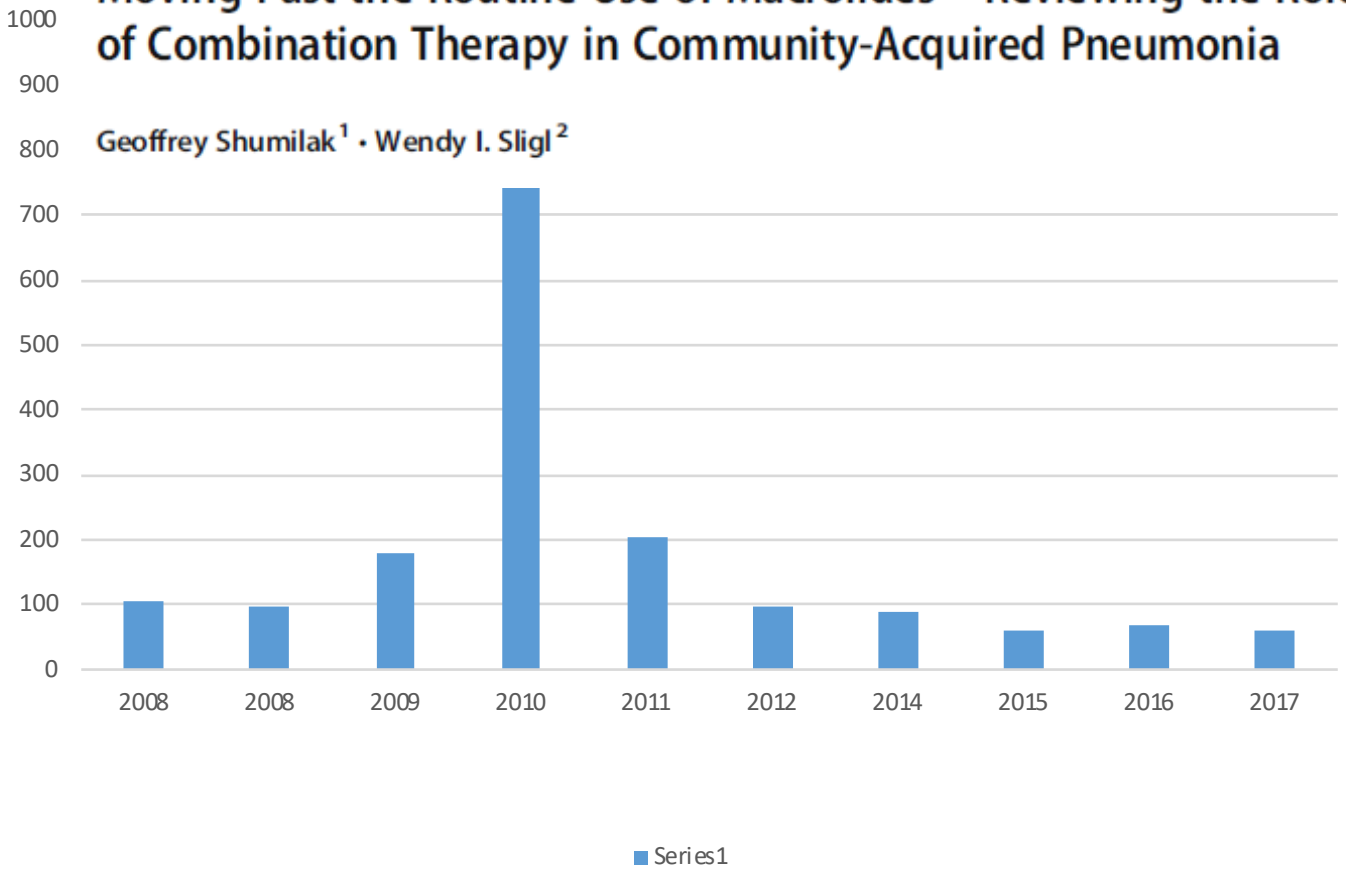
KNOW EPIDEMIOLOGY TO INFORM DIAGNOSIS AND MANAGEMENT

Current Infectious Disease Reports (2018) 20: 45
https://doi.org/10.1007/s11908-018-0651-8

RESPIRATORY INFECTIONS (F ARNOLD, SECTION EDITOR)

Moving Past the Routine Use of Macrolides—Reviewing the Role of Combination Therapy in Community-Acquired Pneumonia

Geoffrey Shumilak [1] · Wendy I. Sligl [2]

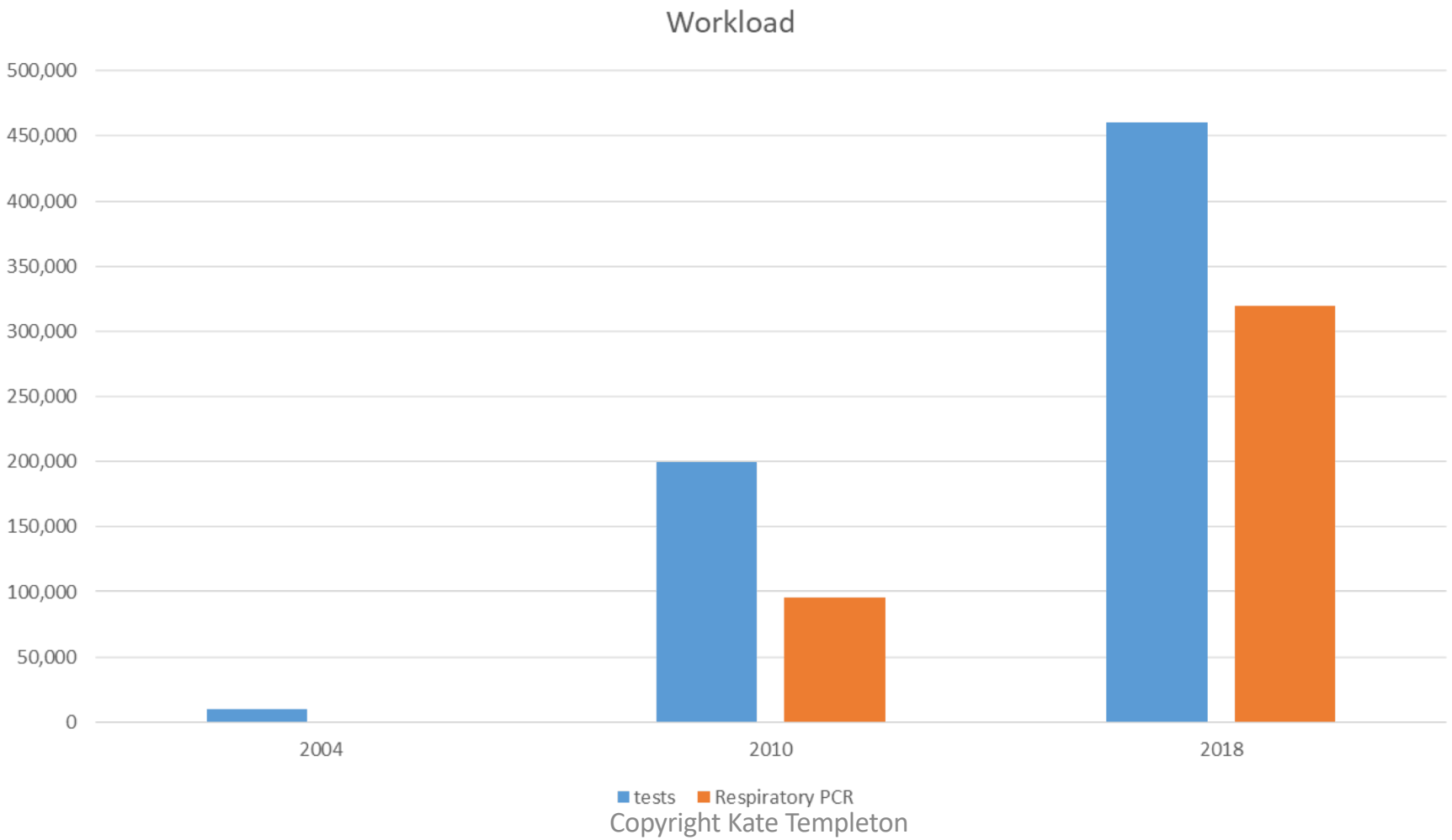


MYCOPLASMA CASES - SCOTLAND

Why include macrolides in all severe CAP?

The approach – we need to use resources carefully

Workload Over Time



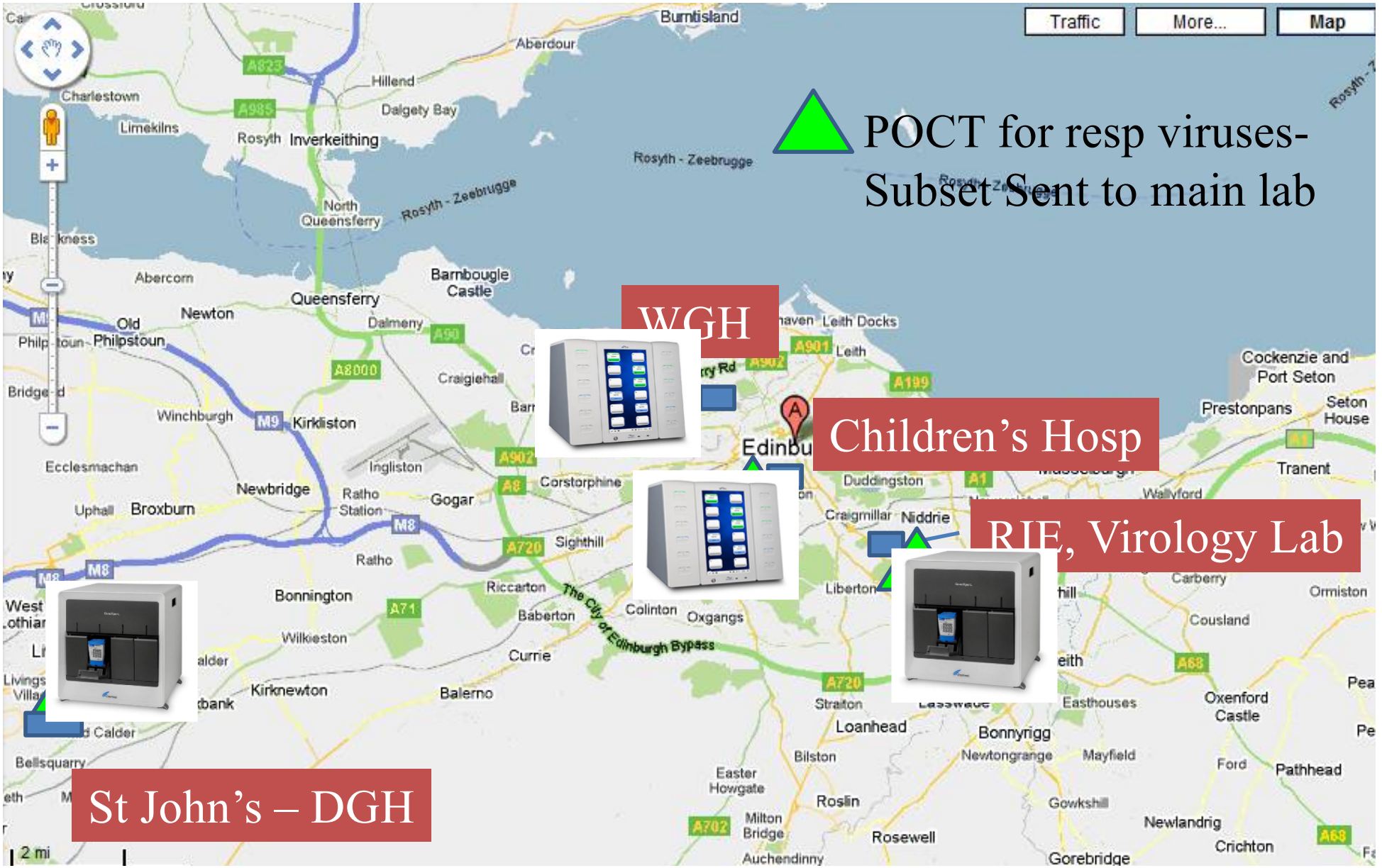
PoCT to guide treatment

Alere™ i Influenza A & B

- Now CLIA Waived!
- Results in Less Than 15 Minutes

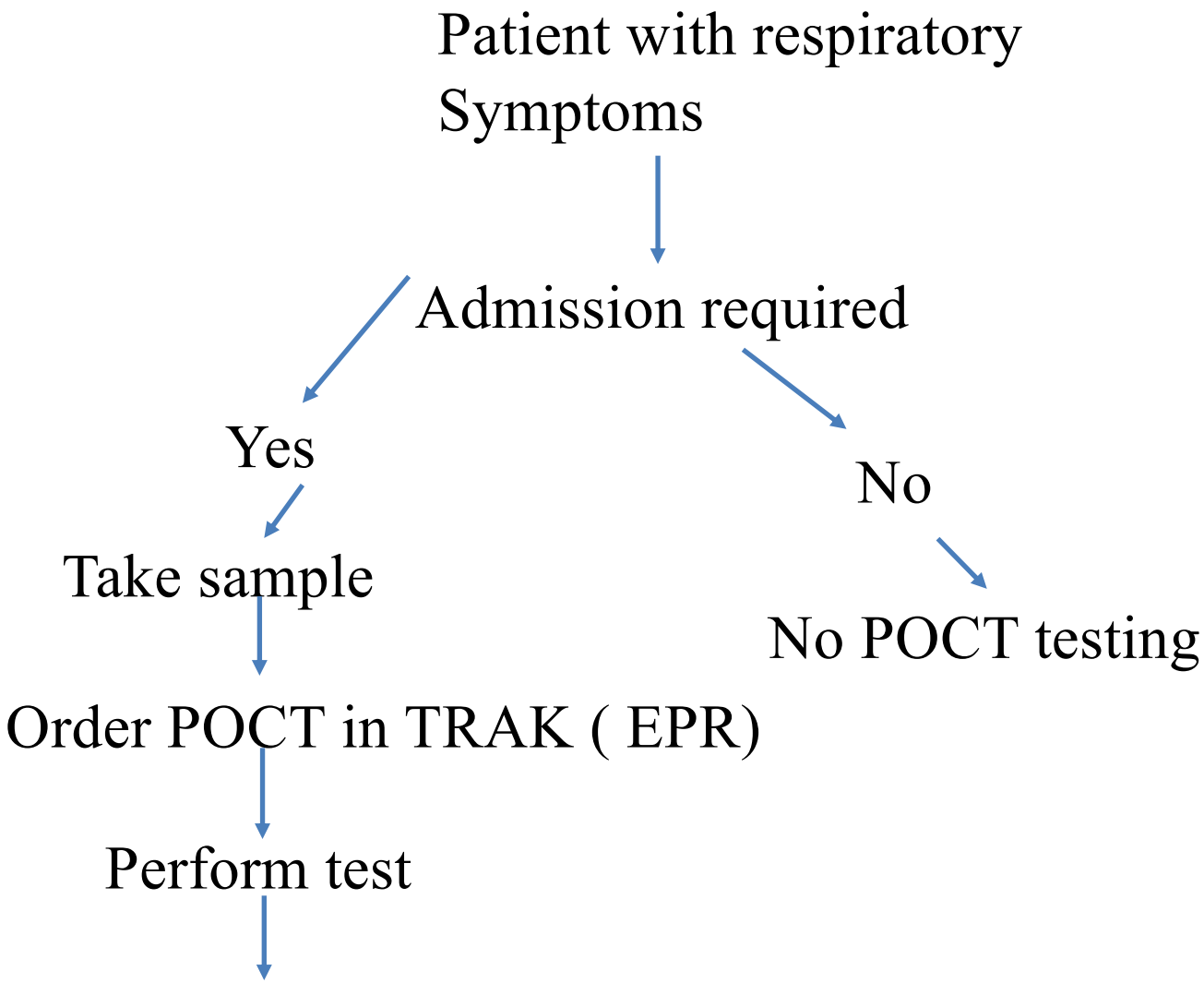
cobas® Liat PCR system

BIOFIRE® | FilmArray® BIOMÉRIEUX



Stages to implementation

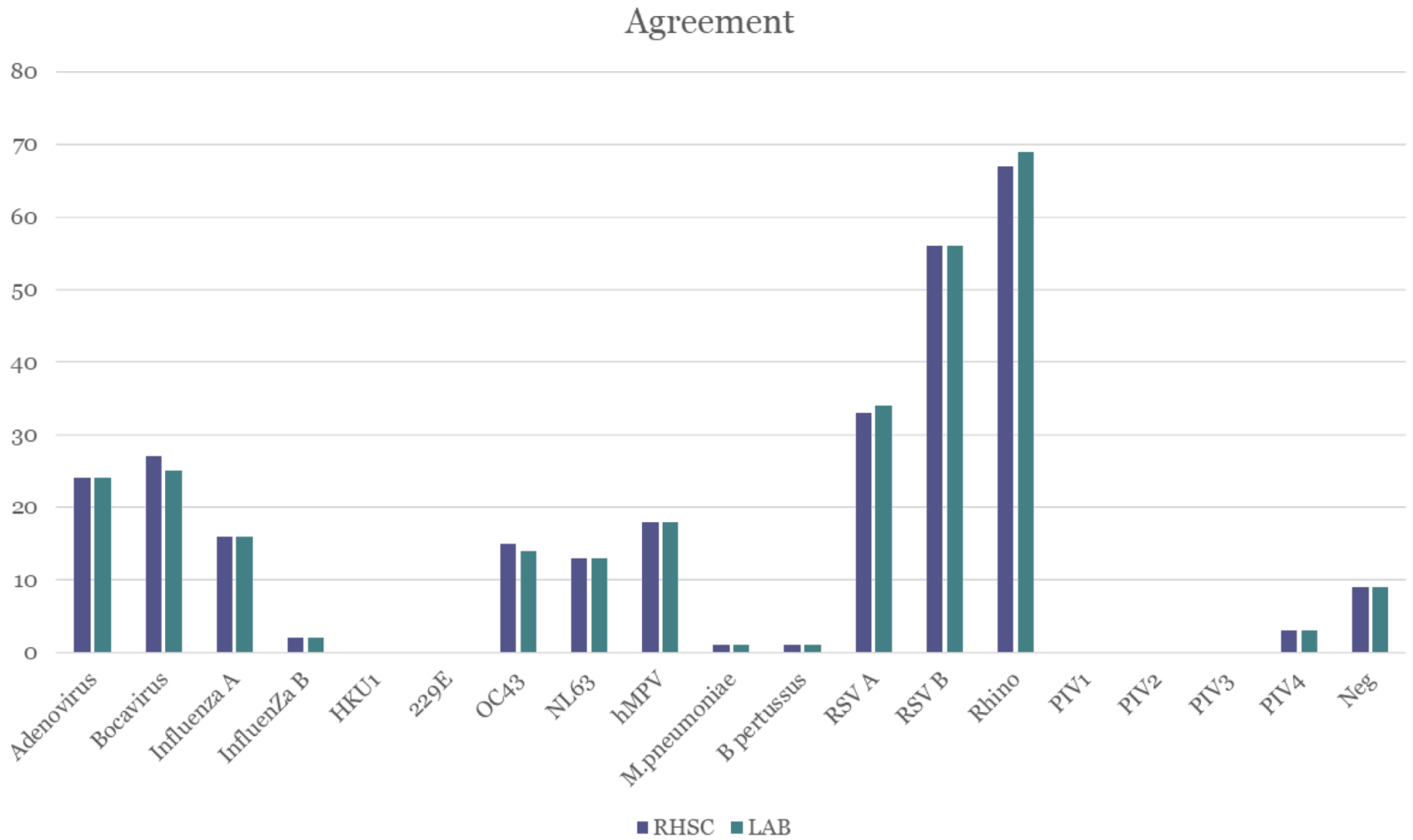
- Validation
- Business case
- Training
  - Cascade by teams
  - Recording and competency
- SOPs
- Algorithm
- IT set up
- Duplicate testing in Lab
- EQA - NEQAS



Pathogen – In **bold requires isolation**
Adenovirus
Influenza A H1
Influenza A 2009 H1
Influenza A H3
Influenza B
Parainfluenza virus 1
Parainfluenza virus 2
Parainfluenza virus 3
Parainfluenza virus 4
Human Metapneumovirus
Coronavirus NL63
Coronavirus OC43
Coronavirus HKU1
Coronavirus 229E
MERS coronavirus
Human Bocavirus
Rhnovirus/enterovirus
Respiratory syncytial virus A
Respiratory syncytial virus B
Bordetella pertussis
Legionella pneumophila
Chlamydophila pneumoniae
Mycoplasma pneumoniae

1st 400 tests RHSC

99% agreement
Stopped testing in Lab
Just duplication



Link Treatment and testing

Treatment

Tests and Results

Link Treatment and testing

Treatment

Tests and Results

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia

Naomi J. Gadsby,[1] Clark D. Russell,[1,2] Martin P. McHugh,[1] Harriet Mark,[1] Andrew Conway Morris,[3] Ian F. Laurenson,[1] Adam T. Hill,[4] and Kate E. Templeton[1]

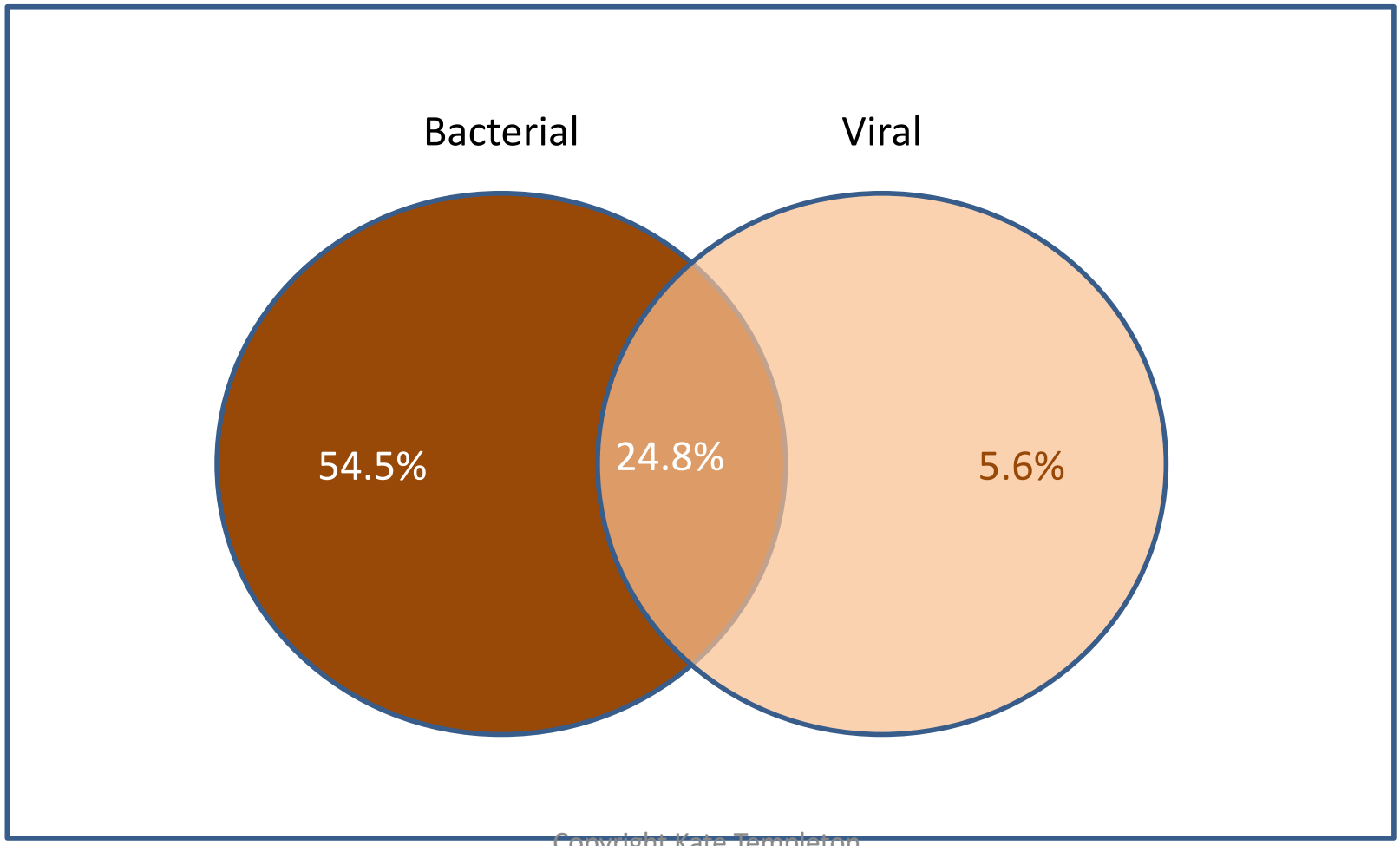
[1]Medical Microbiology, Department of Laboratory Medicine, Royal Infirmary of Edinburgh, [2]College of Medicine and Veterinary Medicine, University of Edinburgh, [3]Department of Anaesthesia, University of Cambridge, and [4]Respiratory Medicine, Royal Infirmary of Edinburgh, United Kingdom

(See the Editorial Commentaries by Musher on pages 824–5 and Jain and Pavia on pages 826–8.) **2016;62(7):817–23**

- To improve microbiological diagnosis in patients hospitalised with CAP
  - Develop new comprehensive test (MiCAP)
  - Evaluate on Cohort.
  - 26 tests – covers all main bacteria
  - Includes quantification

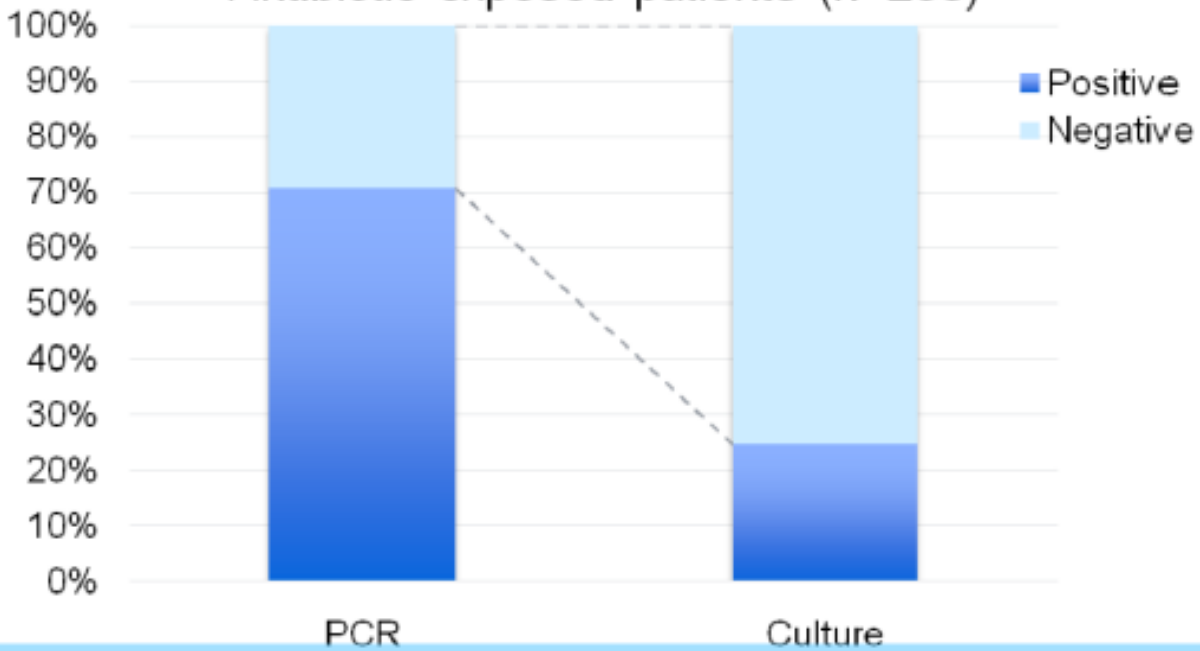
Etiology of CAP by Syndromic PCR Testing

90% with diagnosis



Antibiotic exposure on Sputum

Antibiotic exposure prior to sputum sampling occurred in 84.8% of patients and was significantly associated with culture negativity (OR = 9.1, 95% CI 4.1-22.4, p<0.0001)



Antibiotic exposure did not affect PCR positivity but the mean combined bacterial load was significantly higher in non-exposed patients (p=0.0001)

Antibiotic management

Potential modification	N (%)
De-escalation	247 (77.2)
Escalation	19 (5.9)
No change	54 (16.9)

Real – syndromic management – link with antimicrobial stewardship

Clinical studies

MIDAS

26 Pathogen test
Guide patient antibiotic treatment

26 Pathogen test
Guide patient antibiotic treatment

Plan to recruit 851 patients across 5 sites

Single site – 600 patients – sputum only

Can we follow guidelines ??

Pneumonia Severity

Confusion
Urea >7mmol/l
Respiratory rate ≥30
Blood pressure: systolic <90mmHg *or* diastolic ≤60mmHg
Age ≥**65** years

(Give score of 1 for each feature present)

CURB-65 score	Severity	Where to treat
0	Low	Home
1	Low	Home
2	Moderate	Hospital
3-5	High	Hospital: assess for ITU admission

Important:
Pneumonia severity scores (such as the CURB-65) must be used in conjunction with **clinical judgement** when assessing the severity of a pneumonia case.

NH

NHS Lothian Joint Formulary- Treatment of Community Acquired Pneumonia

Severity	*1st Line*	*2nd Line/Penicillin Allergy*	Duration
CURB65 0-1 (Low Severity)	**Amoxicillin** 500mg tds *oral*	**Clarithromycin** 500mg bd *oral* OR **Doxycycline** 200mg day 1 and then 100mg daily *oral*	**7 days**
CURB65 2 (Moderate Severity)	**Amoxicillin** 500mg tds *oral* AND **Clarithromycin** 500mg bd *oral or IV*	**Clarithromycin** 500mg every 12 hours oral or iv OR **Doxycycline** 200mg day 1 and then 100mg daily *oral*	**7-10 days**
CURB65 3-5 (High Severity)	**Co-amoxiclav** 1.2g every 8 hours *IV* AND **Clarithromycin** 500mg every 12 hours *IV*	**Ceftriaxone** 2g daily IV AND **Clarithromycin** 500mg every 12 hours IV	**7-10 Days**

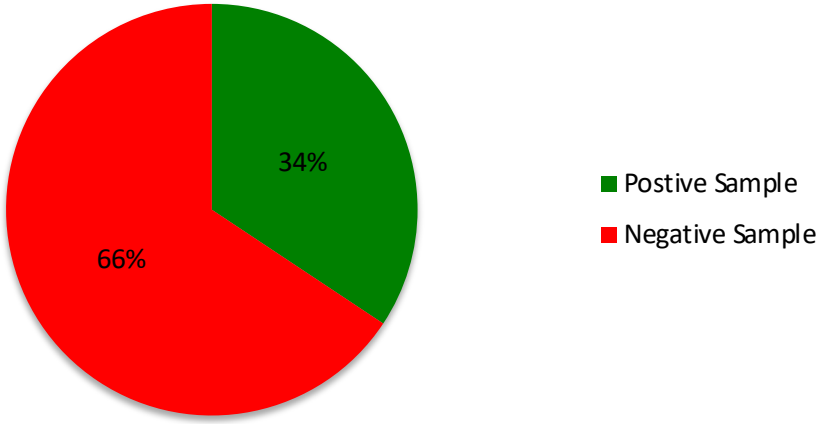
IV therapy is only indicated in those who are severely ill or cannot tolerate oral therapy. Patients should be switched to oral therapy when temperature is <38.°C for 48 hours, CRP and WBC have improved and patient is clinically improving.

Microbiological samples should be done prior to antibiotic administratio

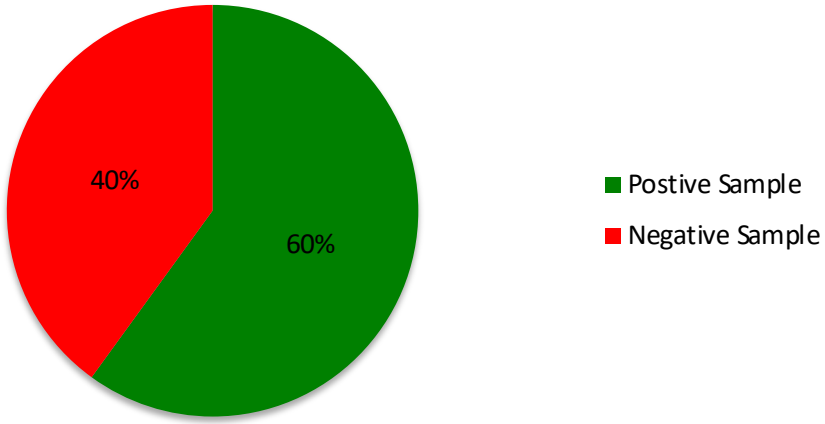
A audit-Antibiotics and Sampling

- 87% Sample collected post antibiotic administration.
- 40% had antibiotics for more than 24 hours prior to admission
- 31% were compliant with NHS Lothian Guidelines

Sputum bacterial microbiology in those receiving antibiotics prior to sampling



Sputum bacterial microbiology in those not receiving antibiotics prior to sampling



GAP – how to get message to those treating

Vestjens *et al. Pneumonia* (2018) 10:15
https://doi.org/10.1186/s41479-018-0059-0

Pneumonia

BRIEF REPORT **Open Access**

Inter-hospital variation in the utilization of diagnostics and their proportionality in the management of adult community-acquired pneumonia

Stefan M. T. Vestjens[1*], Esther Wittermans[1], Simone M. C. Spoorenberg[1], Jan C. Grutters[2,3], Charlotte A. van Ruitenbeek[4], G. Paul Voorn[5], Willem Jan W. Bos[1,6] and Ewoudt M. W. van de Garde[7,8*]

Issuing of negative result prompt to change treatment had biggest impact

GAP –role of combined infection

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Impact of bacterial and viral coinfection in community-acquired pneumonia in adults

Yong Kwan Lim [a,c], Oh Joo Kweon [b,c], Hye Ryoun Kim [c], Tae-Hyoung Kim [d], Mi-Kyung Lee [c,*]

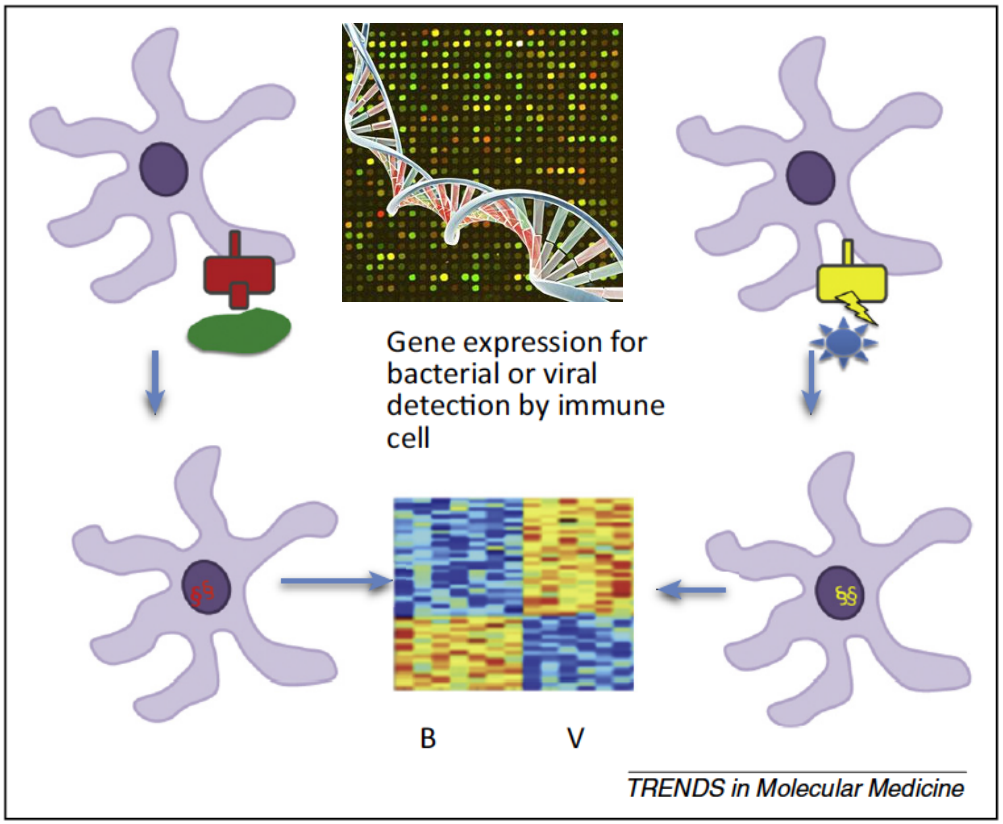
[a] Department of Laboratory Medicine, Armed Forces Capital Hospital, Gyeonggi-do, Republic of Korea
[b] Department of Laboratory Medicine, Aerospace Medical Center, Chungcheongbuk-do, Republic of Korea
[c] Department of Laboratory Medicine, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[d] Department of Urology, Chung-Ang University College of Medicine, Seoul, Republic of Korea

Mortality rate 18% in combined infections vs 6% in bacteria only

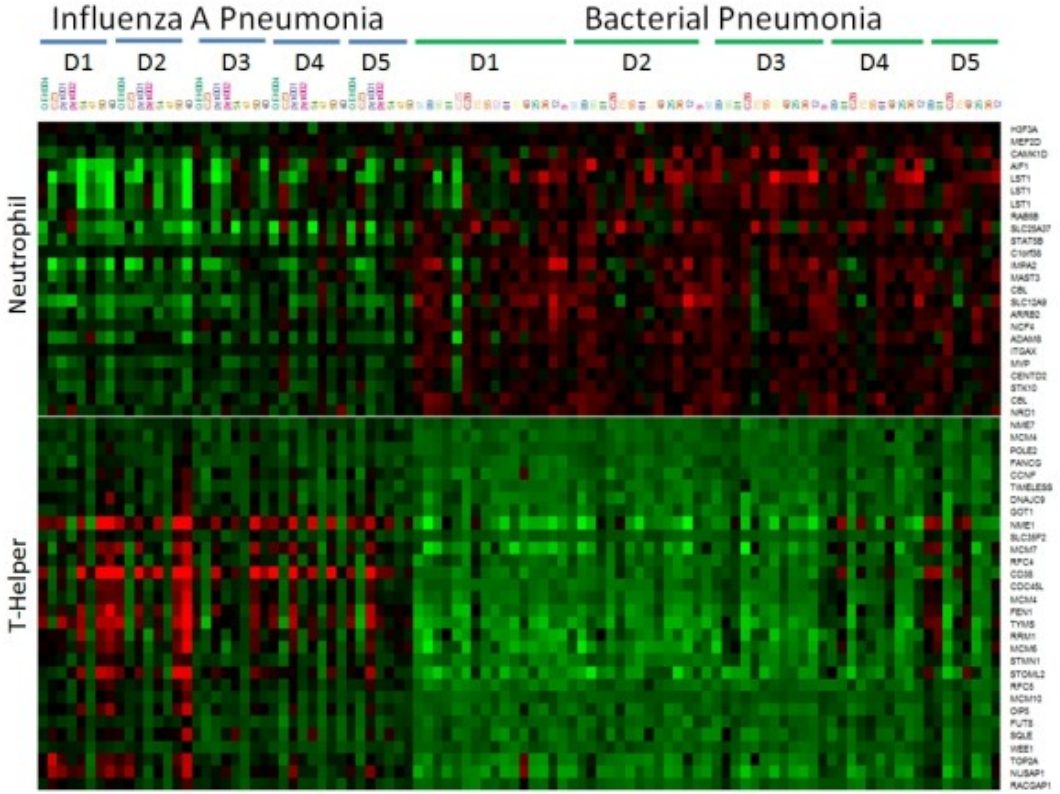
GAP –Add host profile

Gene expression profiling:

differentiating pathogens by host responses?



Host gene transcriptional profiles differentiate between viral and bacterial pneumonia

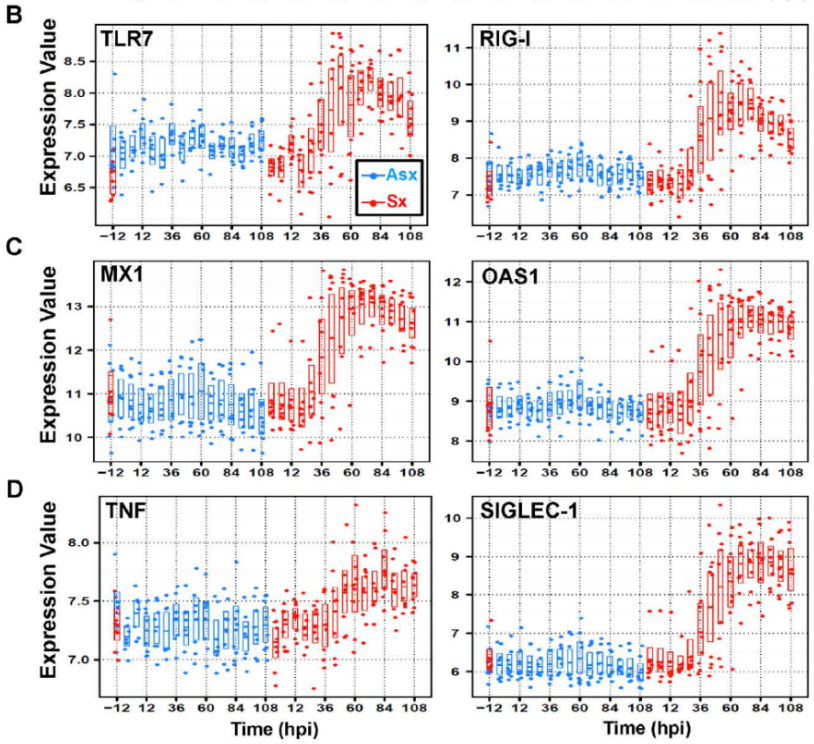


Parnell GP et al. Crit Care. 2012

Temporal Dynamics of Host Molecular Responses Differentiate Symptomatic and Asymptomatic Influenza A Infection

Yongsheng Huang[1,2], Aimee K. Zaas[3,4], Arvind Rao[5], Nicolas Dobigeon[6], Peter J. Woolf[1,7,8], Timothy Veldman[4], N. Christine Øien[4], Micah T. McClain[3,4], Jay B. Varkey[9], Bradley Nicholson[4], Lawrence Carin[10], Stephen Kingsmore[11], Christopher W. Woods[3,4], Geoffrey S. Ginsburg[3,4]*, Alfred O. Hero III[1,2,7,12]*

PLoS Genetics | www.plosgenetics.org 1 August 2011 | Volume 7 | Issue 8 | e1002234



Clinical microbiology in 2025:
CAP in a 62-year old COPD

Molecular Diagnostic report

- *Pathogens detected:*
  - **Viral**: hBoV, RSV, hRV
  - **Bacterial**:*H. influenzae* (β lactamase +), P.aeroginosa
- *Interpretation:*
  - host response profiling indicates hRV infection, no bacterial involvement, good prognosis
- *Advice:*
  - no antibiotics; supportive care

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- Daniel Guerendiain
- Luke Tysall
- Giles Edwards
- Diane Lindsay
- Liz Dickson
- Anne Holmes
- Louise Seagar
- Jurgen Haas
- Sam Griffiths
- Debby Bogaert

ESGREV

"**Survey on Point of Care testing (POCT) for seasonal influenza and other respiratory viruses**". This survey aims to capture the current status of use of point of care testing in the ESCMID community and to highlight areas of best practice and areas where further work is required. You can fill in the survey

https://www.surveymonkey.co.uk/r/ESGREVsurvey