BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

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How can the laboratory help antimicrobial stewardship?

Dr Nick Brown
Cambridge University Hospitals NHS Foundation Trust
Cambridge, UK

February 2020

‘No branch of therapeutics depends so heavily on the laboratory as antimicrobial chemotherapy.

The prescriber lacking such help has been described as a mariner (sailor) without chart or compass.’

L.P. Garrod 1978

Contribution of the laboratory to AMS

A. Optimizing management of the patient

- Diagnosis of infection or alternative
- Antibiotic susceptibility results
- Therapeutic drug monitoring
- Biomarkers to guide therapy and facilitate stopping

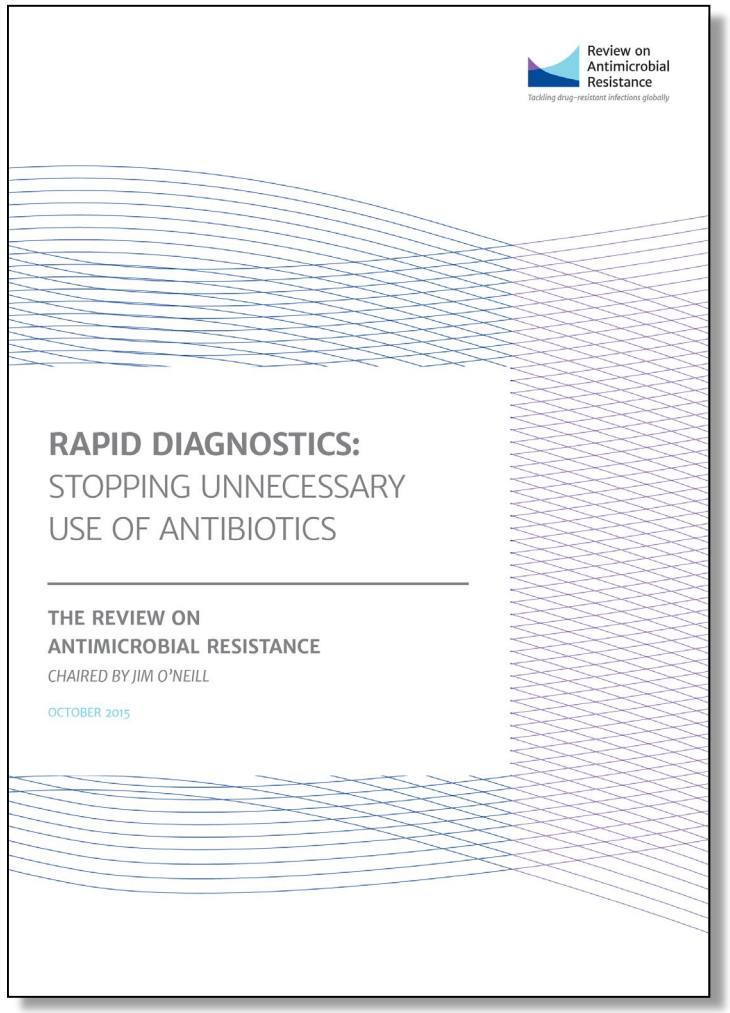
B. Surveillance

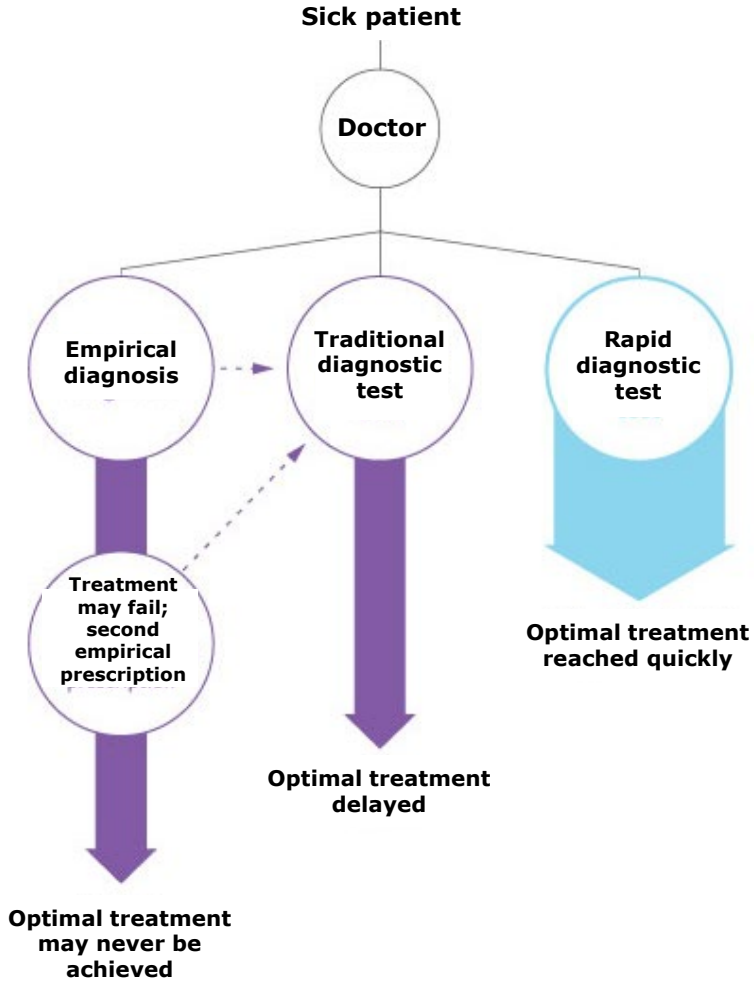
- Descriptive epidemiology and trend analysis
- Comparisons between institutions and geographical areas
- Assessment of impact of interventions

Limitations of current antibiotic prescribing

- Remains empirical (i.e. ‘best guess’)
- An assumption is made that the original diagnosis was correct
- If you have got the diagnosis wrong, how can you prescribe the right treatment?
- Potential consequences:
  - Wrong organism targeted
  - Wrong antimicrobial agent selected
  - Unnecessary exposure to side effects
  - Expenditure without benefit

AMR Review by J O'Neill





https://amr-review.org

Review on Antimicrobial Resistance

Some molecular diagnostics systems in use for rapid pathogen detection

(other systems are available…)


www.drw-ltd.com


www.biocartis.com


www.cepheid.com


www.nanosphere.com


www.molecular.roche.com


www.check-points.com


www.chipcare.ca


www.bosch-vivalytic.com


nanoporetech.com


www.optigene.co.uk


www.curetis.com


www.alere-i.com


www.epistem.co.uk


www.meridianbioscience.co.uk

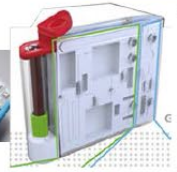

www.enigmadiagnostics.com


www.rheonix.com


www.xagenic.com


www.atlasgenetics.com


www.micronics.net


www.dnae.co.uk


www.optigene.co.uk


www.alere.com


www.quantumdx.com


www.me-med.com


gbscience.com


www.biomerieux-diagnostics.com


www.path.org


www.daktaridx.com


www.quidel.com

www.twistdx.co.uk


www.fcubed.biz


www.stat-dx.com

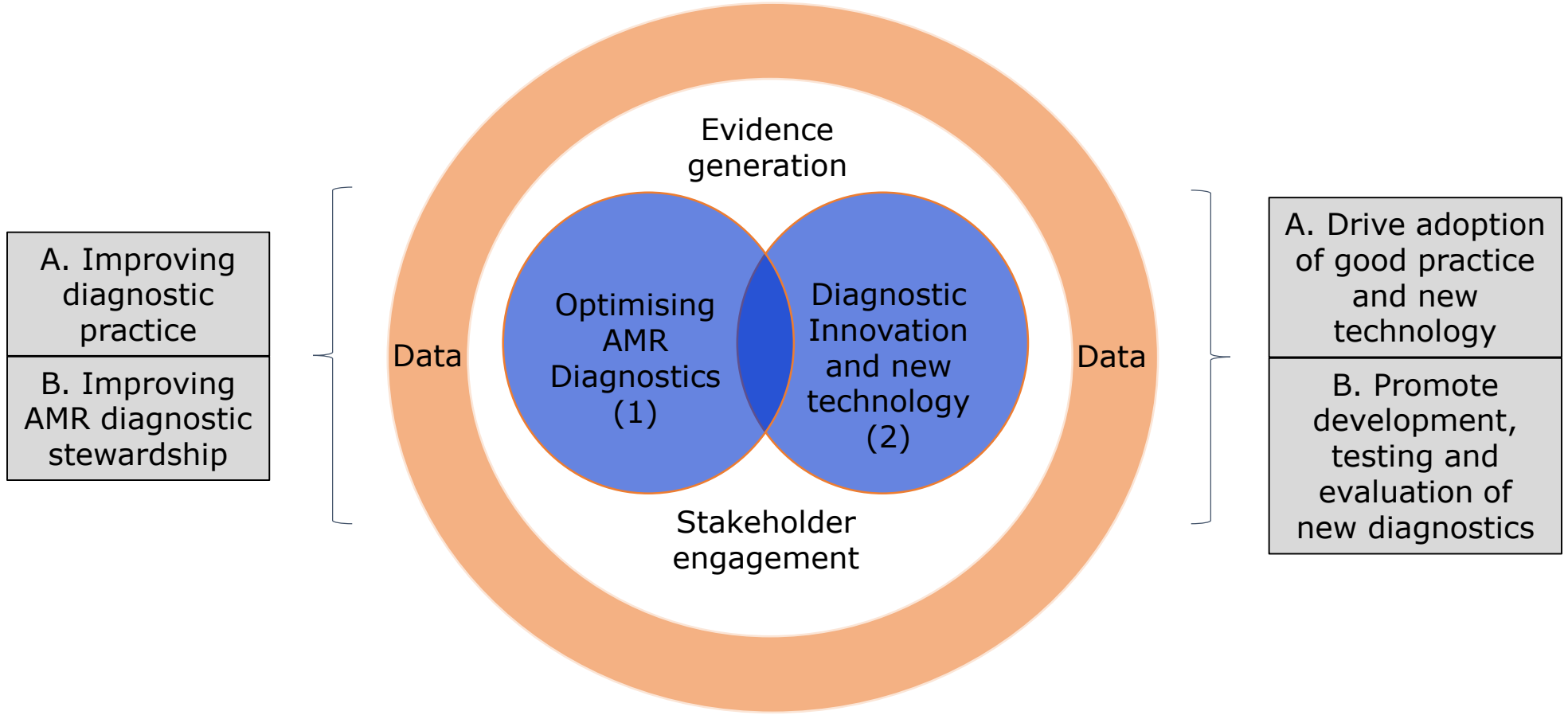

www.bigteclabs.com


spindiag.de


www.genmarkdx.com

Adapted from T. Bachmann BSAC Spring Conference 2019

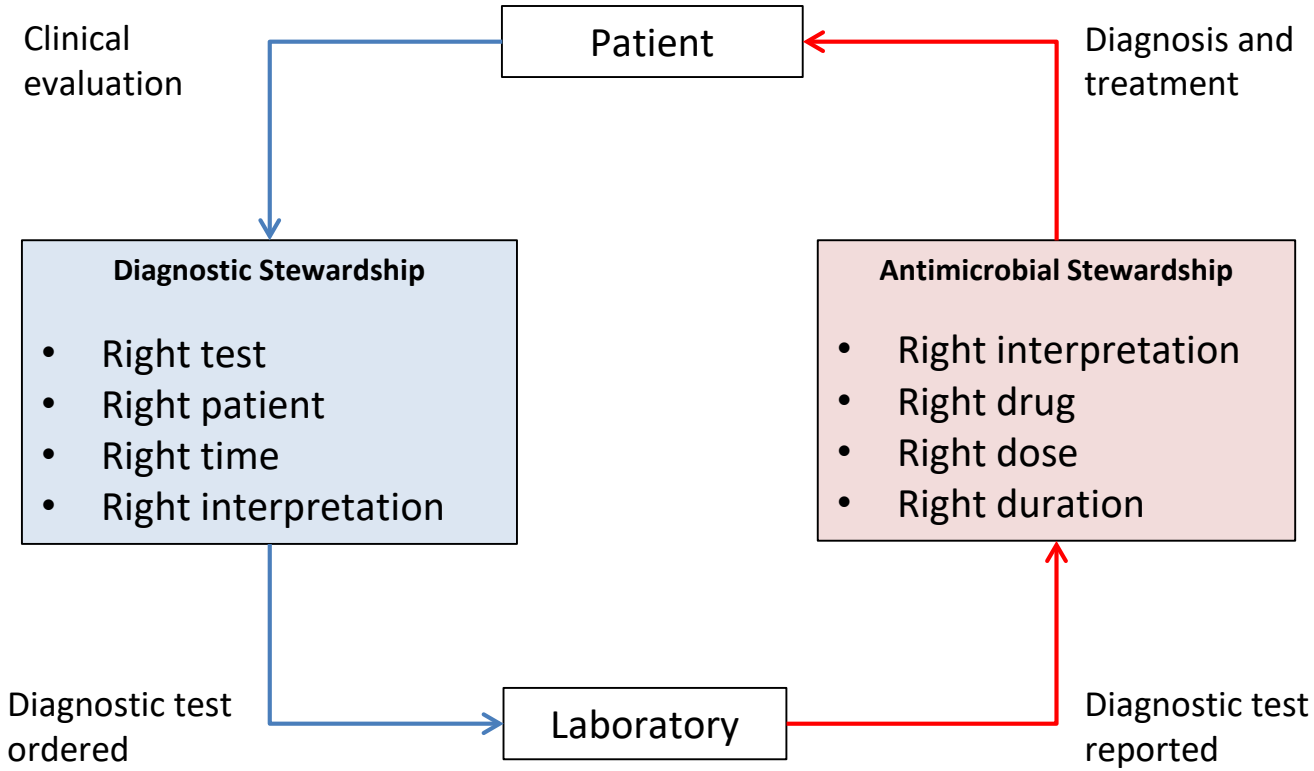
AMR diagnostic workstream clusters



Adapted from A Douglas 'UK Diagnostics Forum' Dec 2019

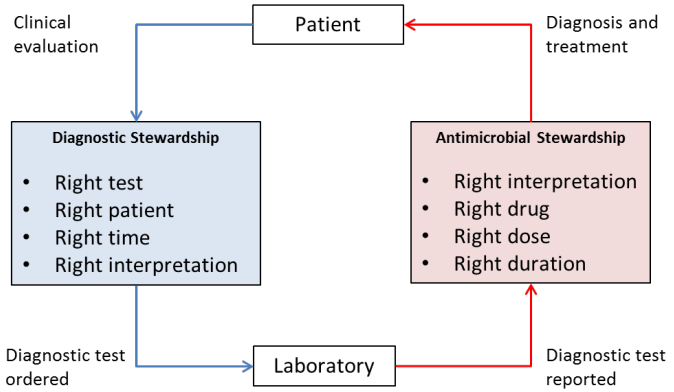
Approach to diagnostic testing

Diagnostic stewardship view



Messacar K et al. *J Clin Microbiol 2017;* 55:715–723

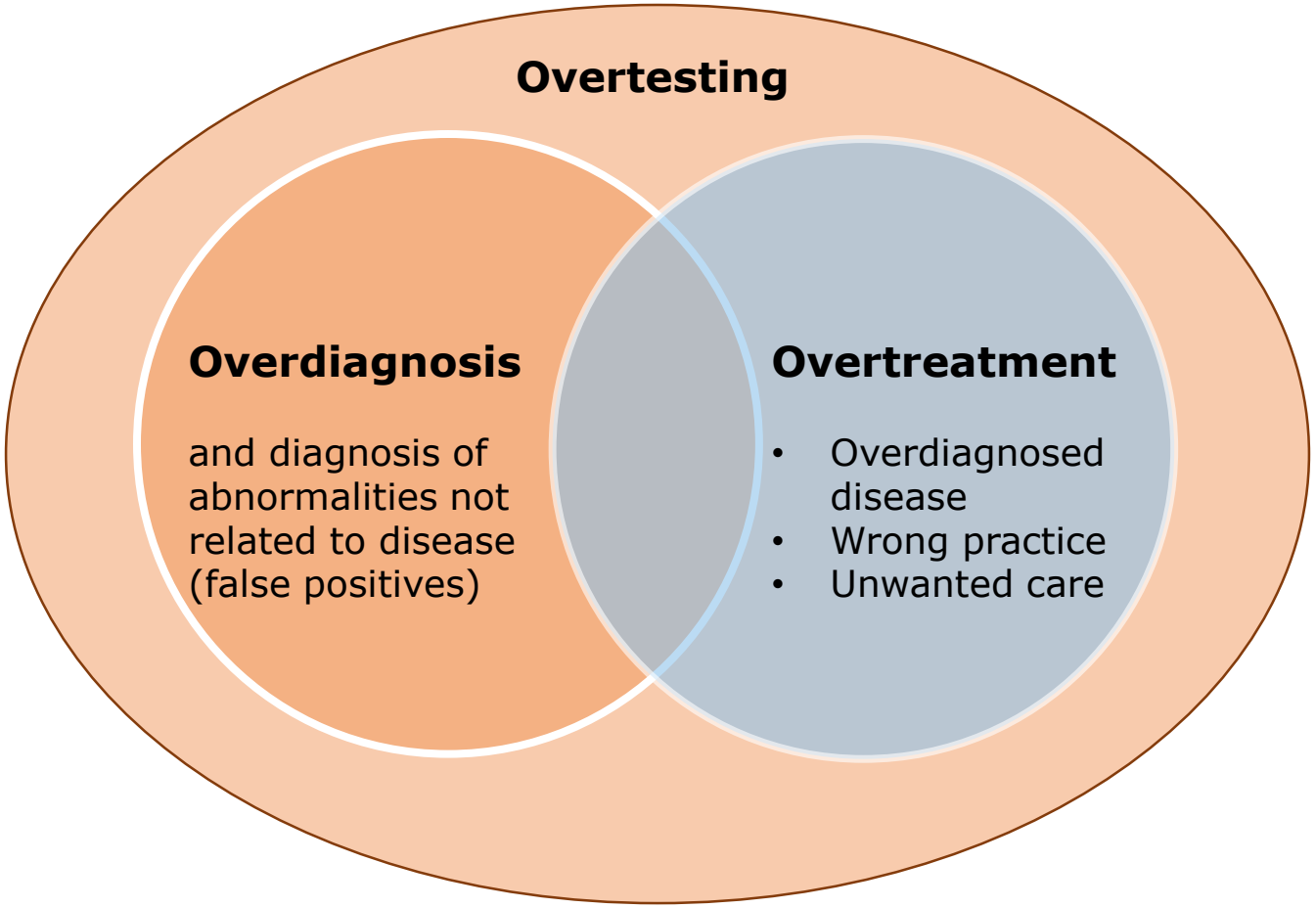
Approach to diagnostic testing



Right test	Is the test appropriate for the clinical setting?
Right patient	Will the clinical care of the patient be affected by the test result?
Right time	Will the result be available in time to affect patient care optimally?

Messacar K et al. *J Clin Microbiol 2017;* 55:715–723

Overuse of diagnostic tests



Adapted from: Morgan DJ et al. BMJ 2015; 351: h4534

Approach to diagnostic testing

The traditional laboratory science view

Pre-analytical	Analytical	Post-analytical
Test selection Ordering Collection Transport	Processing Testing Test performance	Interpretation Reporting Intervention

Approach to diagnostic testing

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Diagnosing UTI

To Dip or Not to Dip?

Results of educational intervention in elderly patients in care homes





- **56% reduction** in the proportion of residents who had an antibiotic for a UTI
- **67% reduction** in the number of antibiotic prescriptions
- **82% reduction** in the number of residents prescribed antibiotic prophylaxis
- Reduction in unplanned admissions for UTI, urosepsis and acute kidney injury
- Reduced calls to GP practices for inappropriately diagnosed UTI

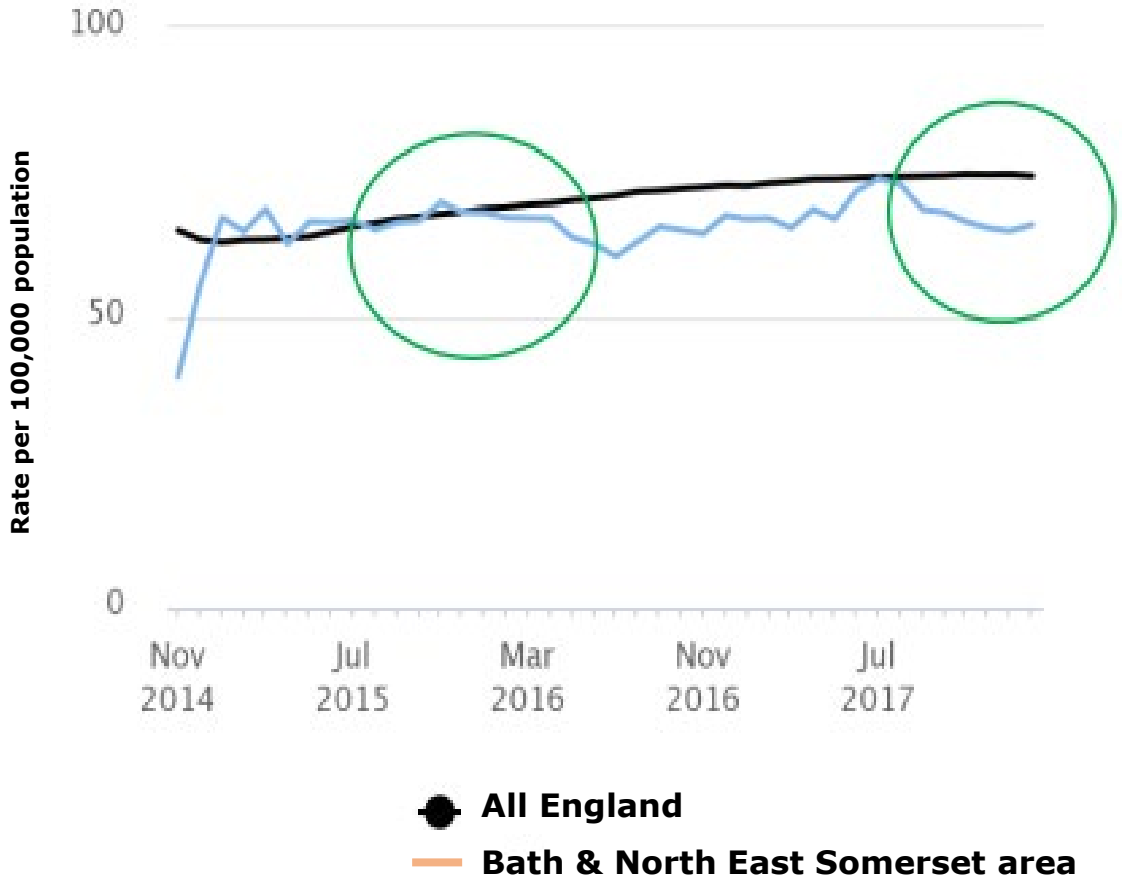
Beech E, BSAC Spring meeting 2018 available at www.bsac.org/

Analysis for evidence of harm

Rates of E. coli bacteraemia per 1000,000 population

Intervention

Educational bundle delivered to all nursing homes



Intervention to reduce treatment of urinary catheter–associated asymptomatic bacteriuria

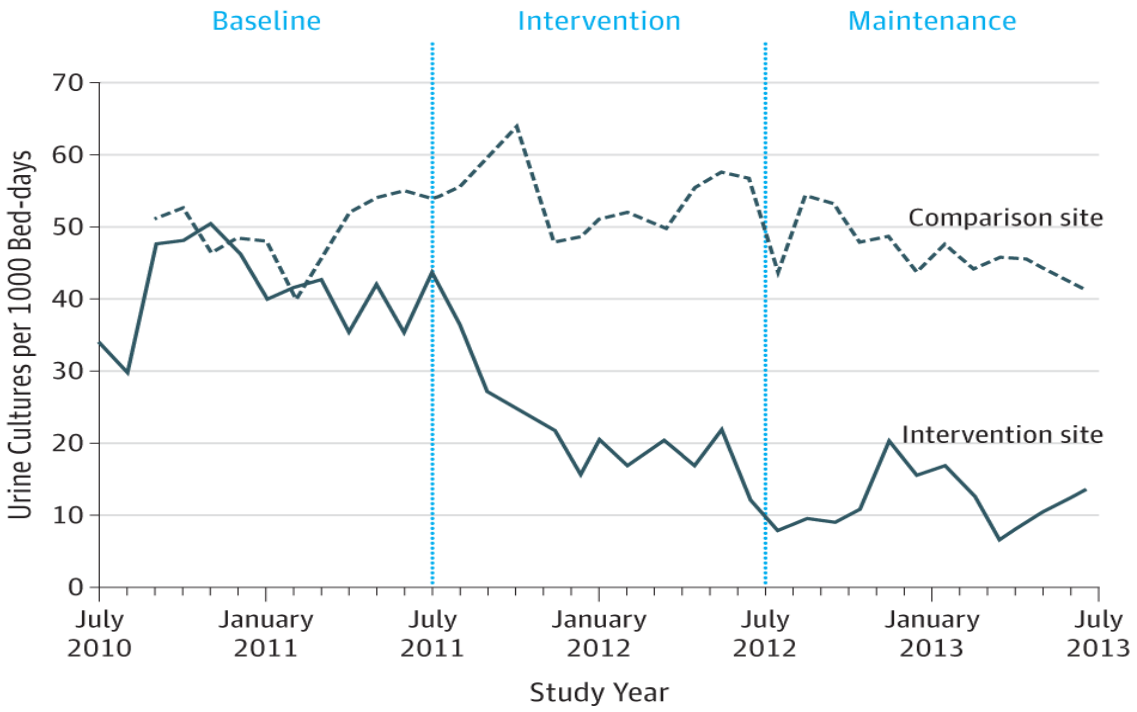
Two outcomes studied:

- Decision to send a sample (unnecessary screening)
- Decision to treat a positive result (overtreatment)

Main findings:

- Reduced sampling
- Decrease in treatment of asymptomatic bacteriuria

  (1.6 to 0.6 per 1,000 bed days)
- No change in treatment of CAUTI



Trautner BW et al. *JAMA Intern Med*. 2015;175:1120-27

Selective urine culture and antibiotic utilisation

Reflex protocol in 500 ICU patients

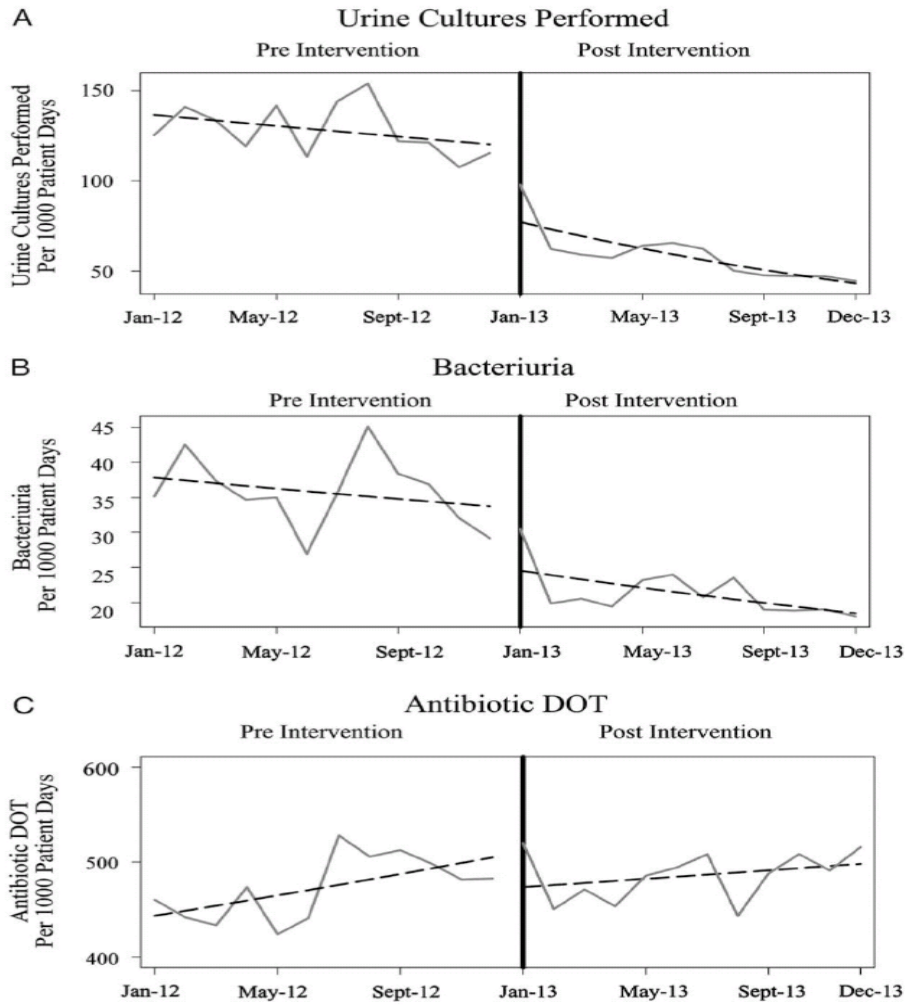
Culture only if >10 wbc/hpf

Results:

- Fewer cultures
- Lower bacteriuria rates
- No change in overall antibiotic days of therapy (DOT)
- Fewer antibiotic starts for index urine culture

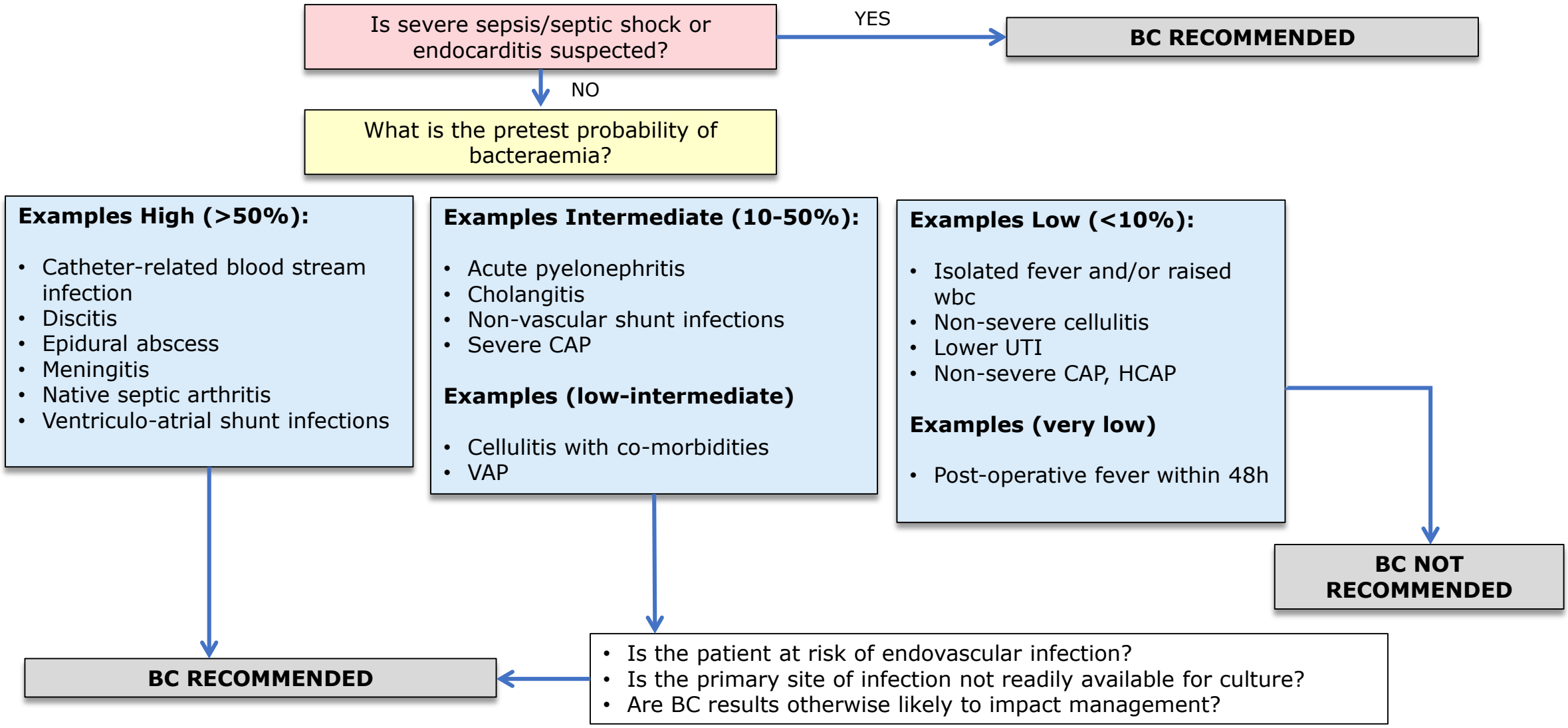
Pre: 55/134 (41%) vs.

Post: 28/123 (23%) (p=0.002)



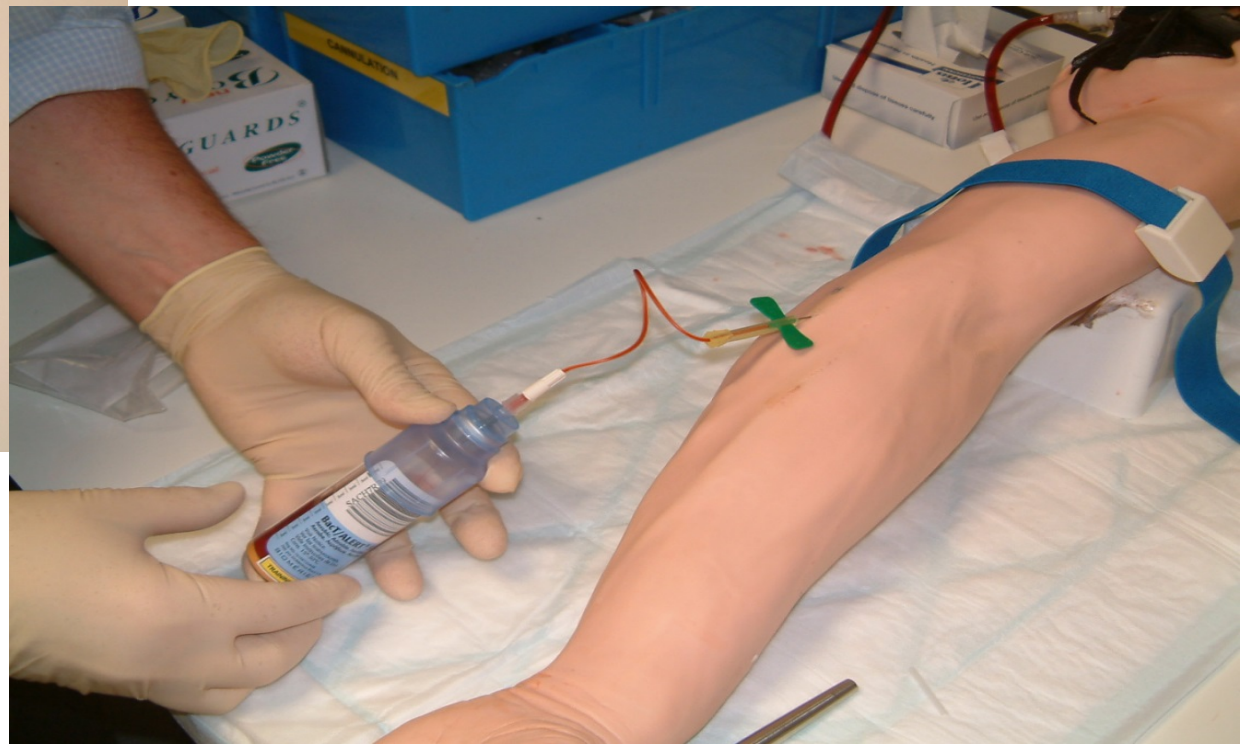
Sarg M et al. *Infect Control Hosp Epidemiol*. 2016; 37: 448–454

Does this patient need a blood culture? A review of indications in adult non-neutropenic patients

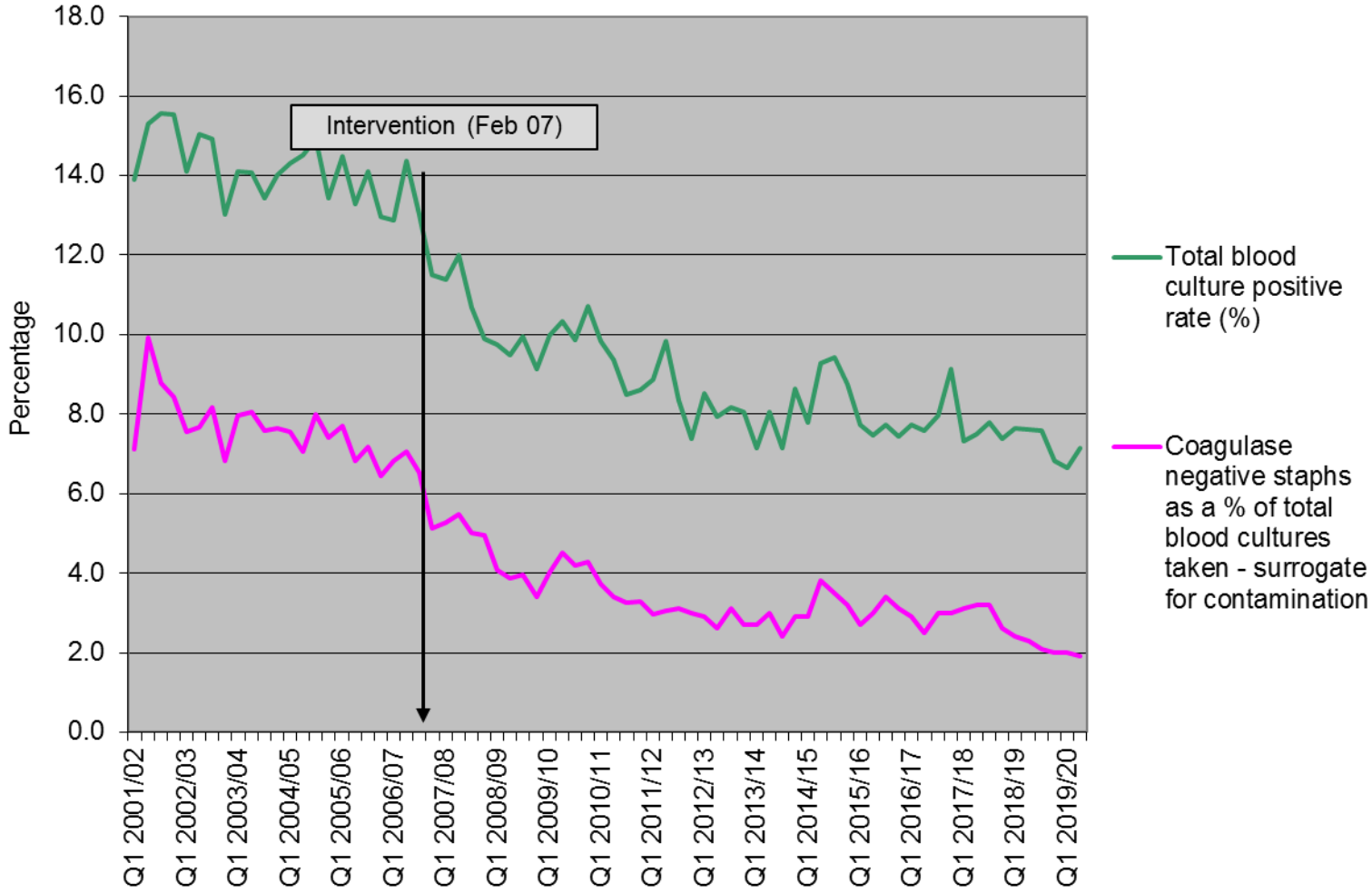


Fabre V et al *Clin Infect Dis* 2020

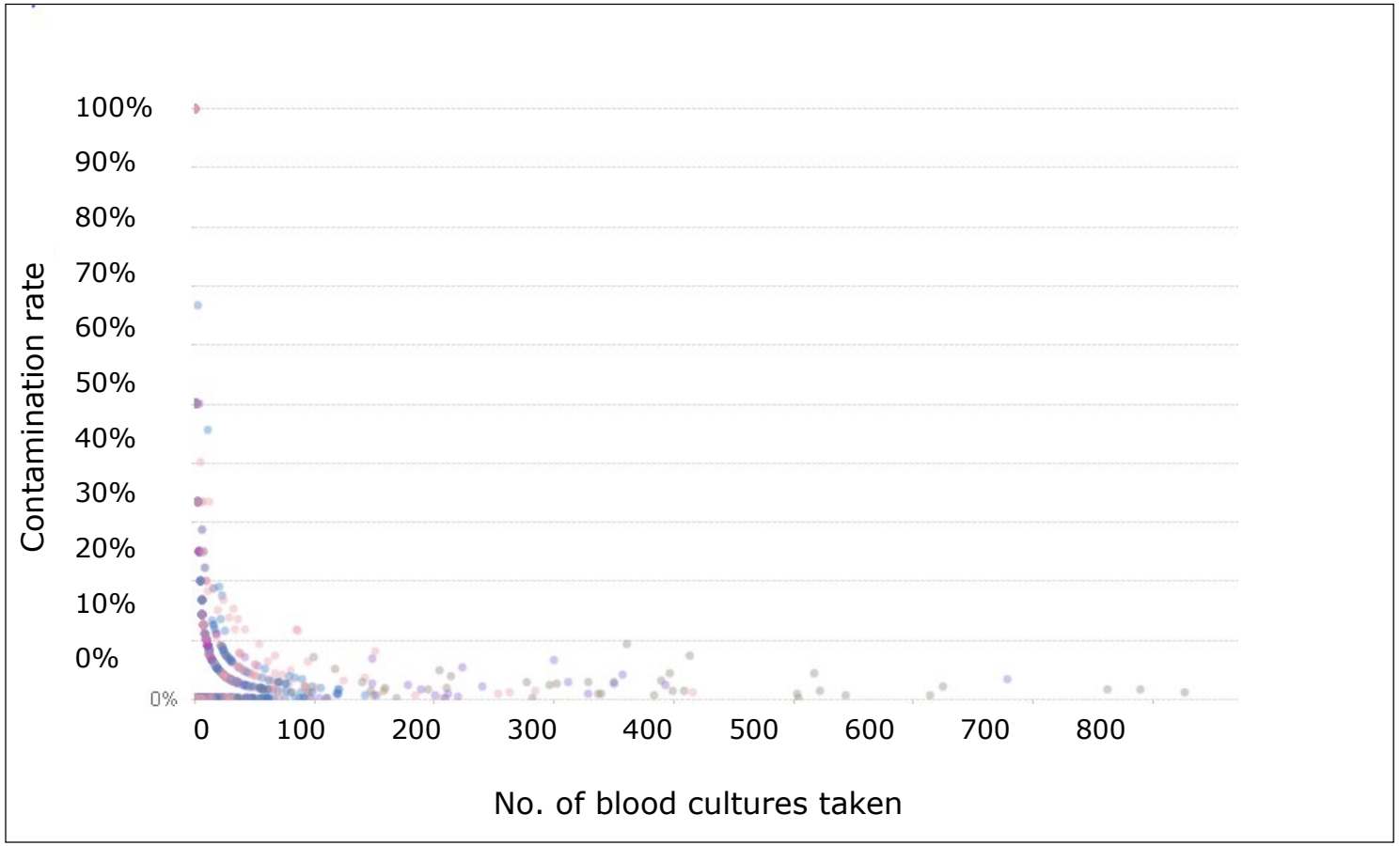
Reducing blood culture contamination



Reducing blood culture contamination



Taking blood cultures: individual performance monitoring and feedback



Automated Blood Cultures

Opportunities for service improvement and/or KPIs

- Who do you sample?
- Sampling technique
- Number of cultures taken
- Volume of blood in each bottle
- Time to incubation
- Time to flag positive on the machine
- Time to communicate initial positive result
- Rapid same-day identification
- Rapid same-day sensitivity tests
- Patient review and antibiotic optimisation

Approach to diagnostic testing

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Laboratory innovation – some recent examples

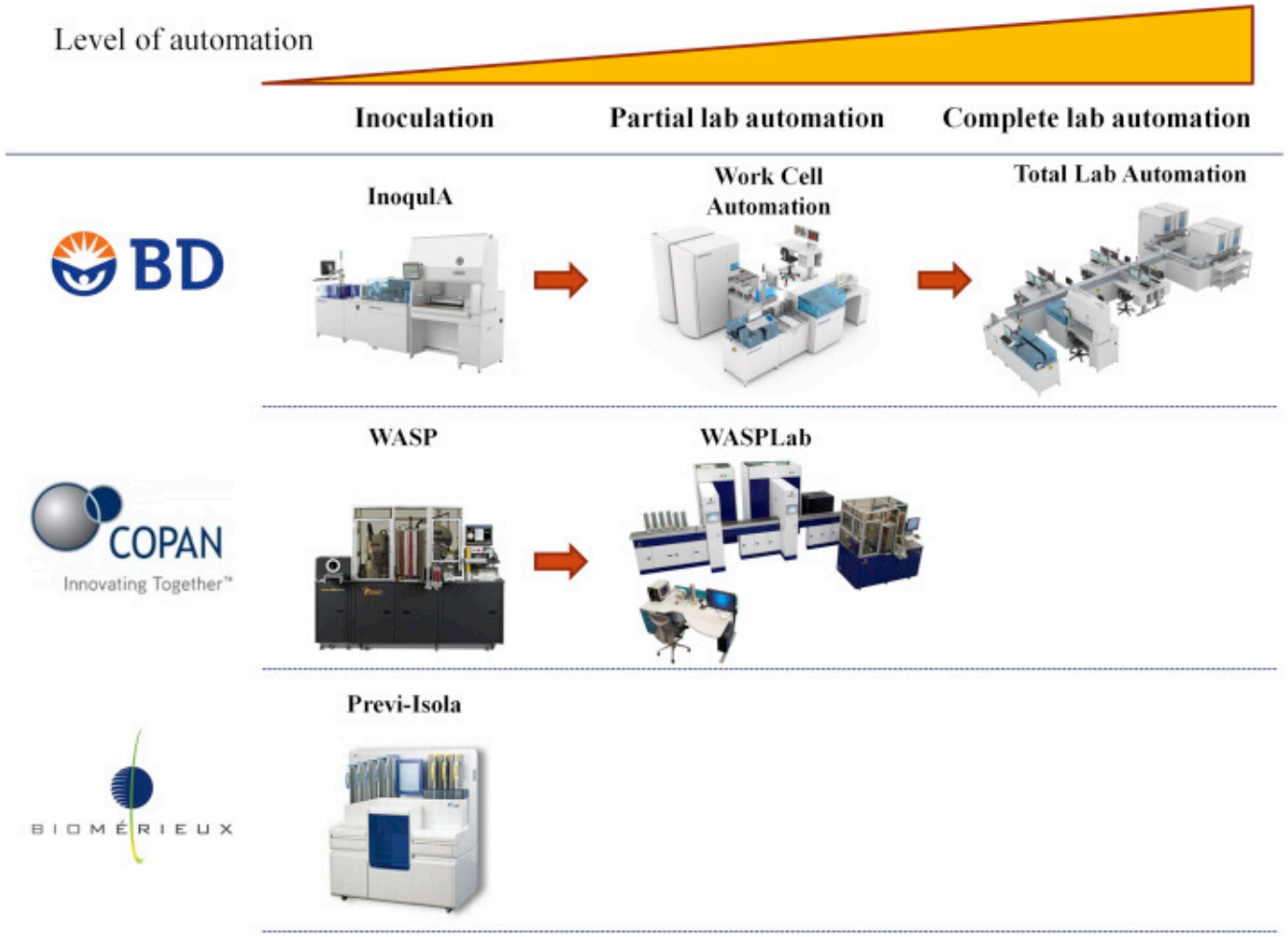
- Total laboratory automation
- Improvements to antibiotic susceptibility testing
- MALDI-TOF bacterial identification
- Syndromic testing
- Point-of-care testing
- Biomarkers
- Genomics

The Bacteriology Laboratory

Cambridge laboratory c. 1987

Fleming’s laboratory c. 1929

Levels of automation in bacteriology

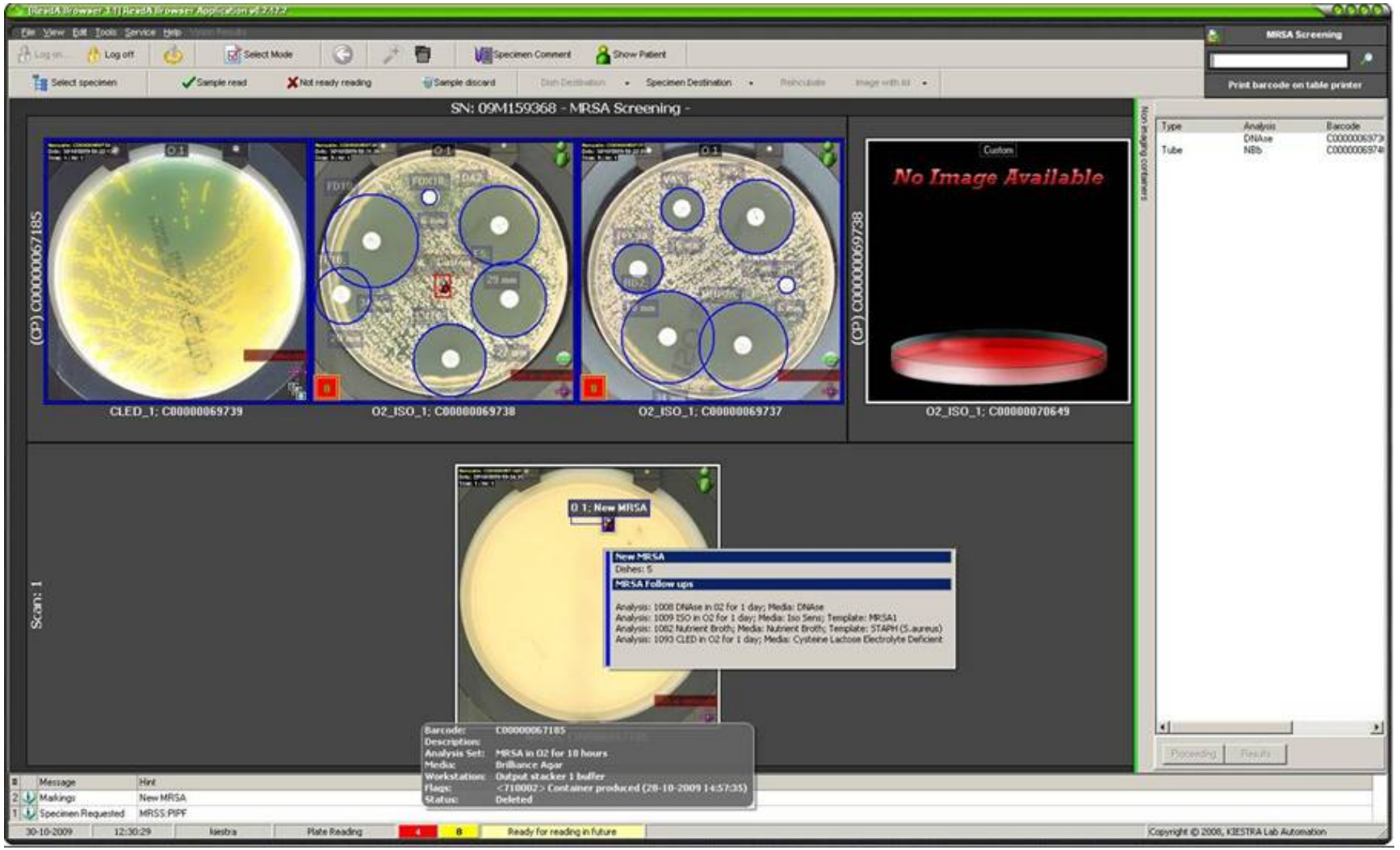


Croxatto A et al. *Clin Microbiol Infect* 2016; 22: 217-235

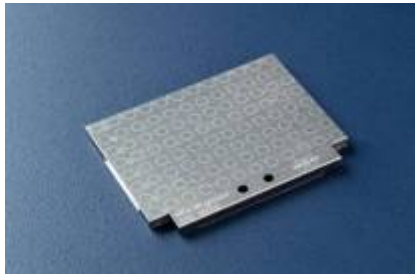
The new Bacteriology Laboratory

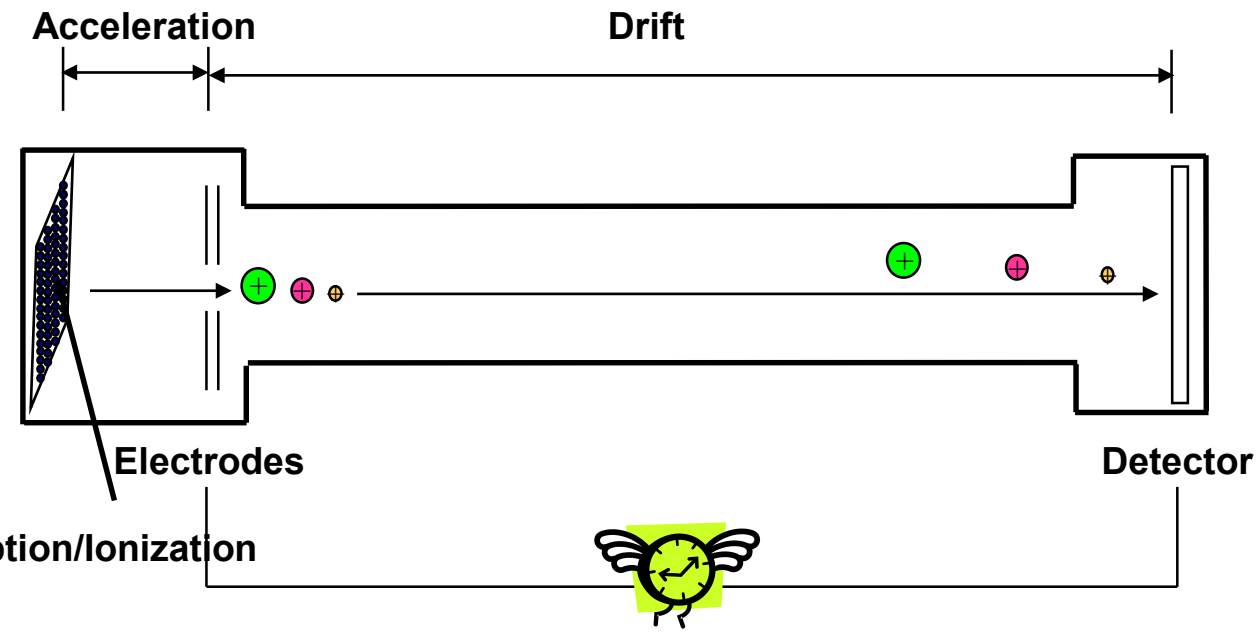
Cambridge laboratory 2013

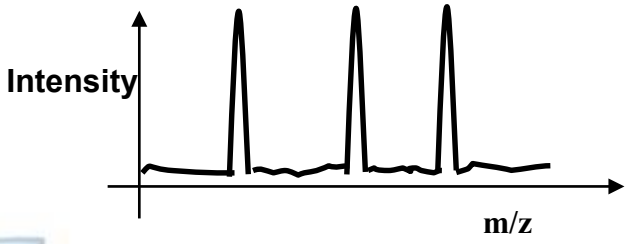
Allows us to store images and record susceptibility test zone sizes



MALDI-TOF Mass Spectrometry



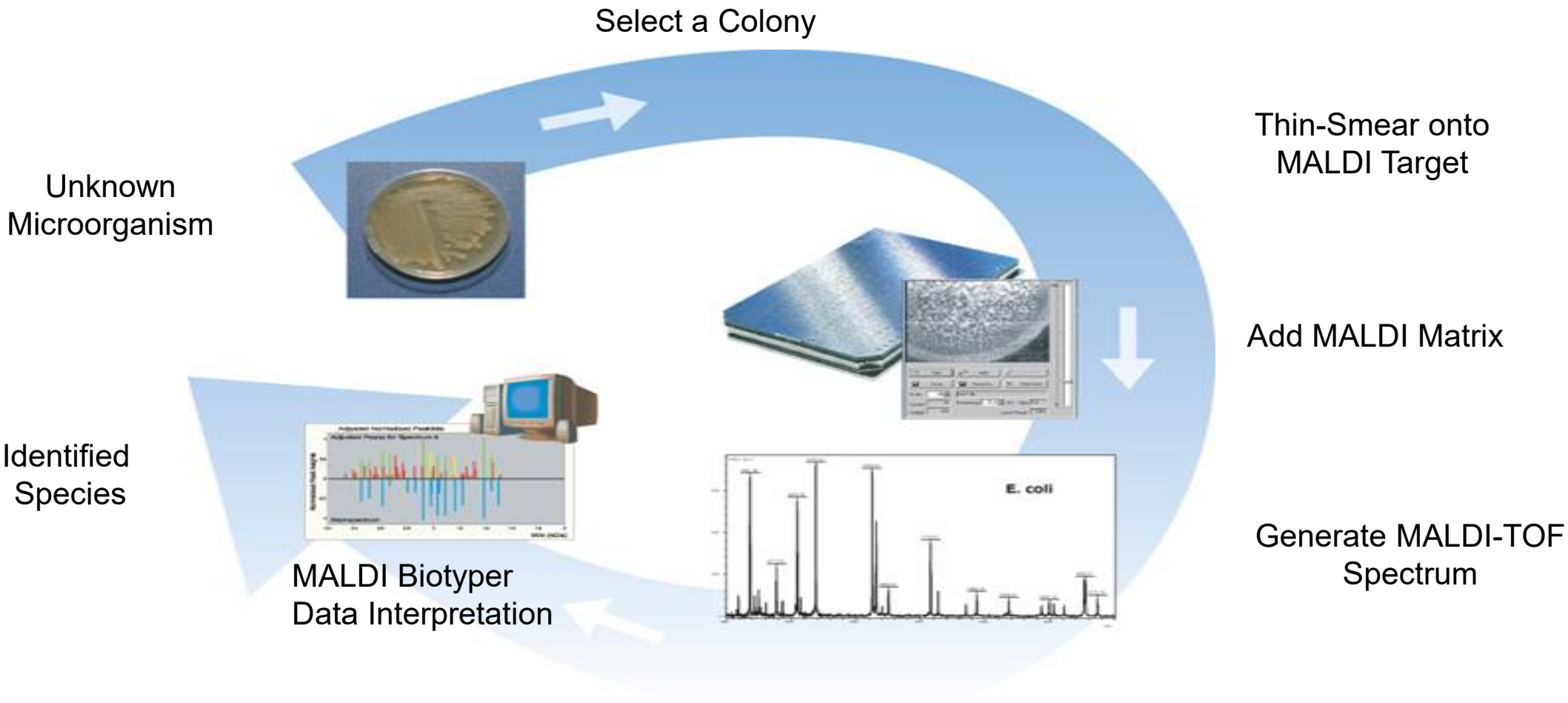




Time-of-Flight

Modified from: Lottspeich, Zorbas, eds
"Bioanalytik", Spektrum Akademischer Verlag, 1998

MALDI Biotyper - Workflow

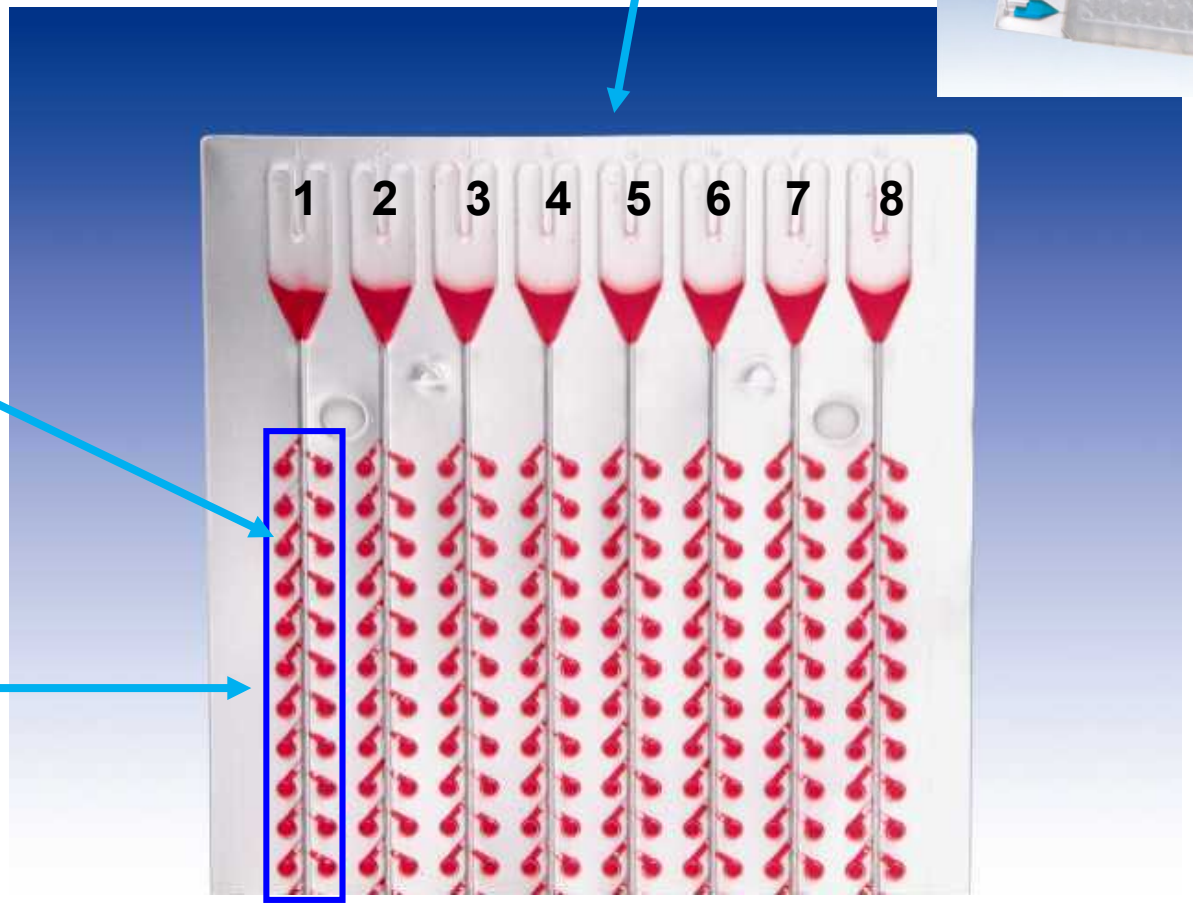


TaqMan® Array Cards

1 to 8 samples

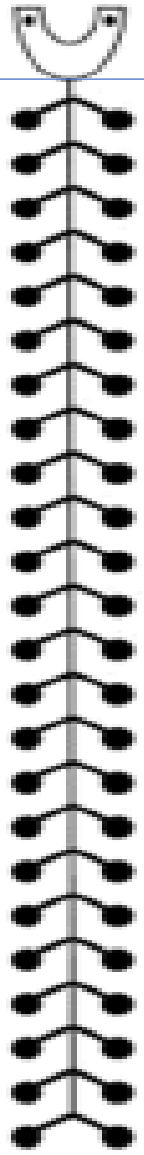
TaqMan® Assays pre-spotted

48 wells per channel



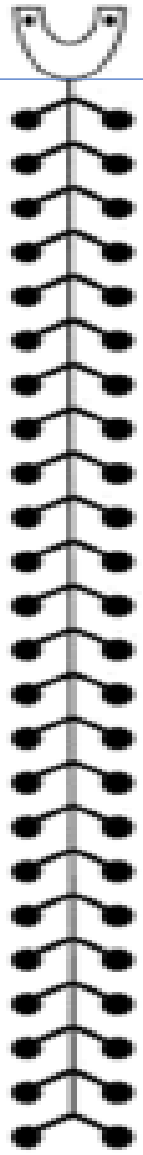
384 wells (1µL reaction volume)

Respiratory Card: Version 9 – ECMO



1. RSV A
2. RSV B
3. HPIV 1
4. HPIV 2
5. HPIV 3
6. HPIV 4
7. Enterovirus
8. Rhinovirus
9. B. pertussis ptx S1
10. HCoV OC43/HKU1
11. 18S RNA
12. HCoV NL63
13. HCoV 229E
14. hMPV
15. MS2 IC
16. Adenovirus #1
17. Bocavirus
18. Adenovirus #2
19. L. pneumophilia
20. M. pneumoniae
21. C. pneumoniae
22. Coxiella burnetii
23. C. psittaci
24. M. tuberculosis

25. Flu B #1
26. Flu B #2
27. Staph PVL
28. Flu A #2
29. Flu A #3
30. S. pneumoniae#1
31. S. pyogenes#1
32. S. aureus (Nuc)
33. Aspergillus 28S
34. Flu A H12009
35. Flu A H3
36. Legionella species#1
37. H. influenzae #1
38. Enterovirus Br
39. M. pneumoniae #2
40. B. pertussis IS481
41. Parechovirus
42. P.jiroveci #1
43. RSV #3
44. HCoV OC43
45. Rnase P IC
46. HPIV 1 #2
47. HPIV 3 #3
48. Rhinovirus #2



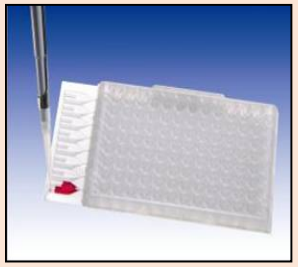
49. HSV#1
50. HSV#2
51. HSV#3
52. HSV type 1
53. HSV type 2
54. EBV#1
55. EBV#2
56. VZV#1
57. VZV#2
58. CMV#1
59. CMV#2
60. BK#1
61. BK#2
62. BK/JC
63. Aspergillus 28S
64. Measles#1H
65. Measles#2 N
66. Legionella spp # 5a
67. Tamiflu S
68. Tamiflu R
69. IS481#2
70. L. pneumophilia #2
71. S. pneumoniae #2
72. H. influenzae #2

73. S. pyogenes# 2
74. N. meningitidis
75. Mec A
76. S. aureus (Nuc)
77. TB#2
78. TB#3
79. P.jiroveci #2
80. P.jiroveci #3
81. MS2 IC
82. EVD68
83. Acanthamoeba #1
84. Acanthamoeba #2
85. Fusarium #1
86. Fusarium #2
87. A. fumigatus new
88. B19
89. MERS #1
90. MERS #2
91. MERS #3
92. Leptospirosis #1
93. Legionella spp # 6a
94. Legionella species #2
95. Legionella species #3
96. Legionella spp # 4a

TaqMan® Array Cards: Process

5 – 10 Minutes

52 Minutes



Load

Spin

Seal

Run

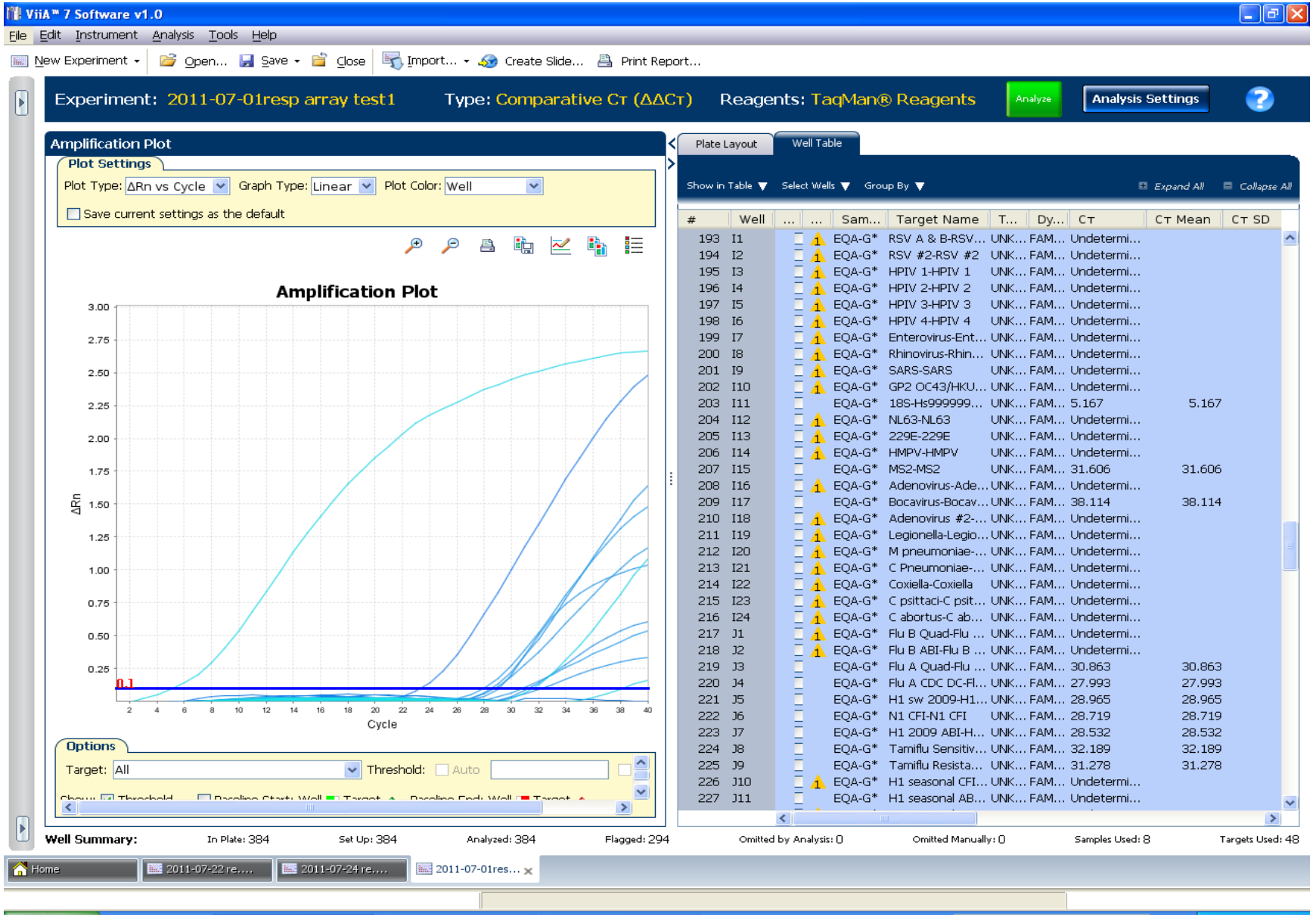
20µL NA extract
25µL Master Mix
(Fast Virus 1 step)
55µL Water

1200 rpm / 2 mins

50°C 5 min (RT)
95°C 20 sec

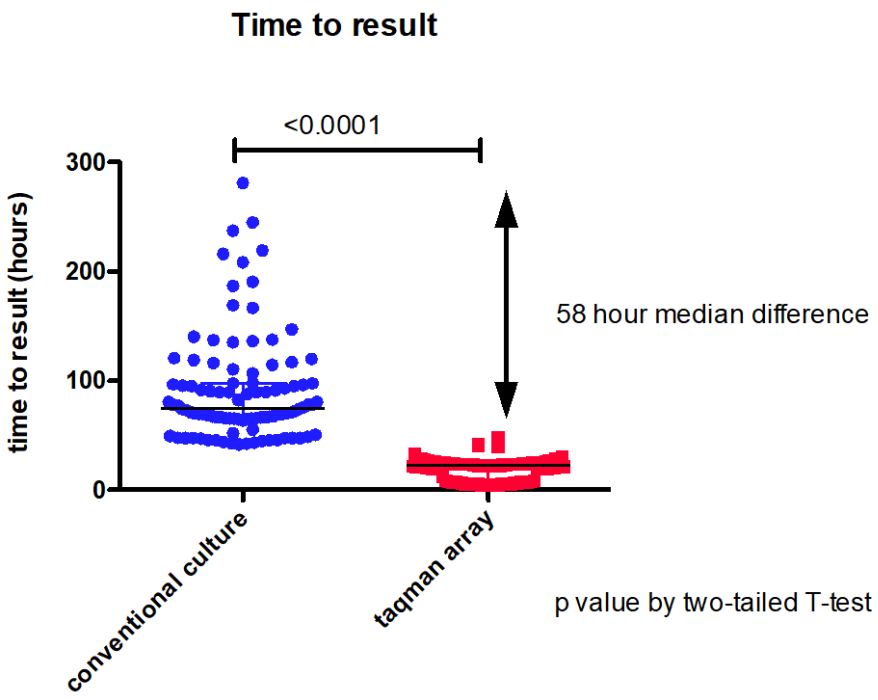
95°C 1 sec
60°C 20 sec
X 45

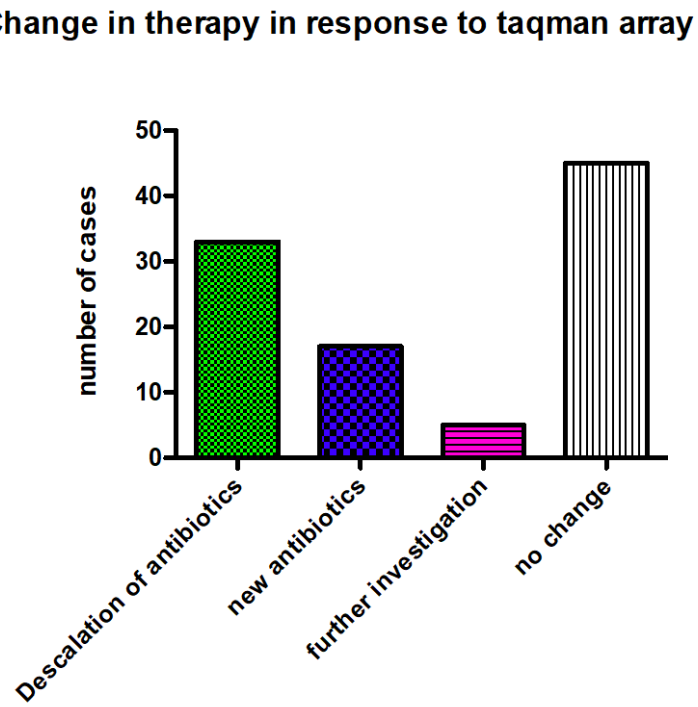
Example of respiratory array amplification curves



Comparative performance of TaqMan® array card versus conventional culture

100 ventilated ICU patients with clinically suspected pneumonia





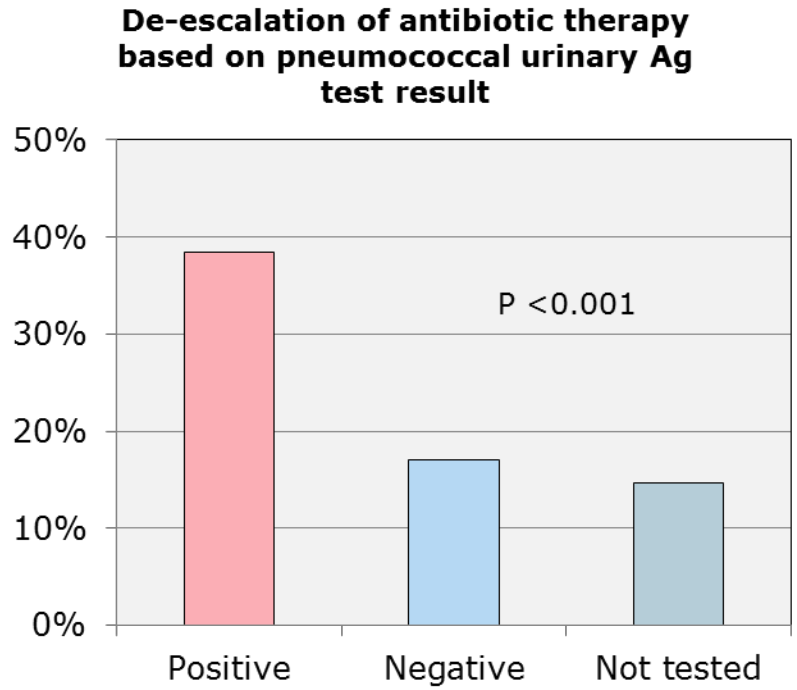
Unpublished data, Cambridge

Pneumococcal Urinary Antigen Testing in United States Hospitals: A Missed Opportunity for Antimicrobial Stewardship

- Retrospective cohort study of adults admitted to 170 US hospitals with CAP or HCAP
- 160,000 eligible admissions
- 15.5% had PUAT (range 0-69%)
- 18.4% ICU vs. 15.3% non-ICU

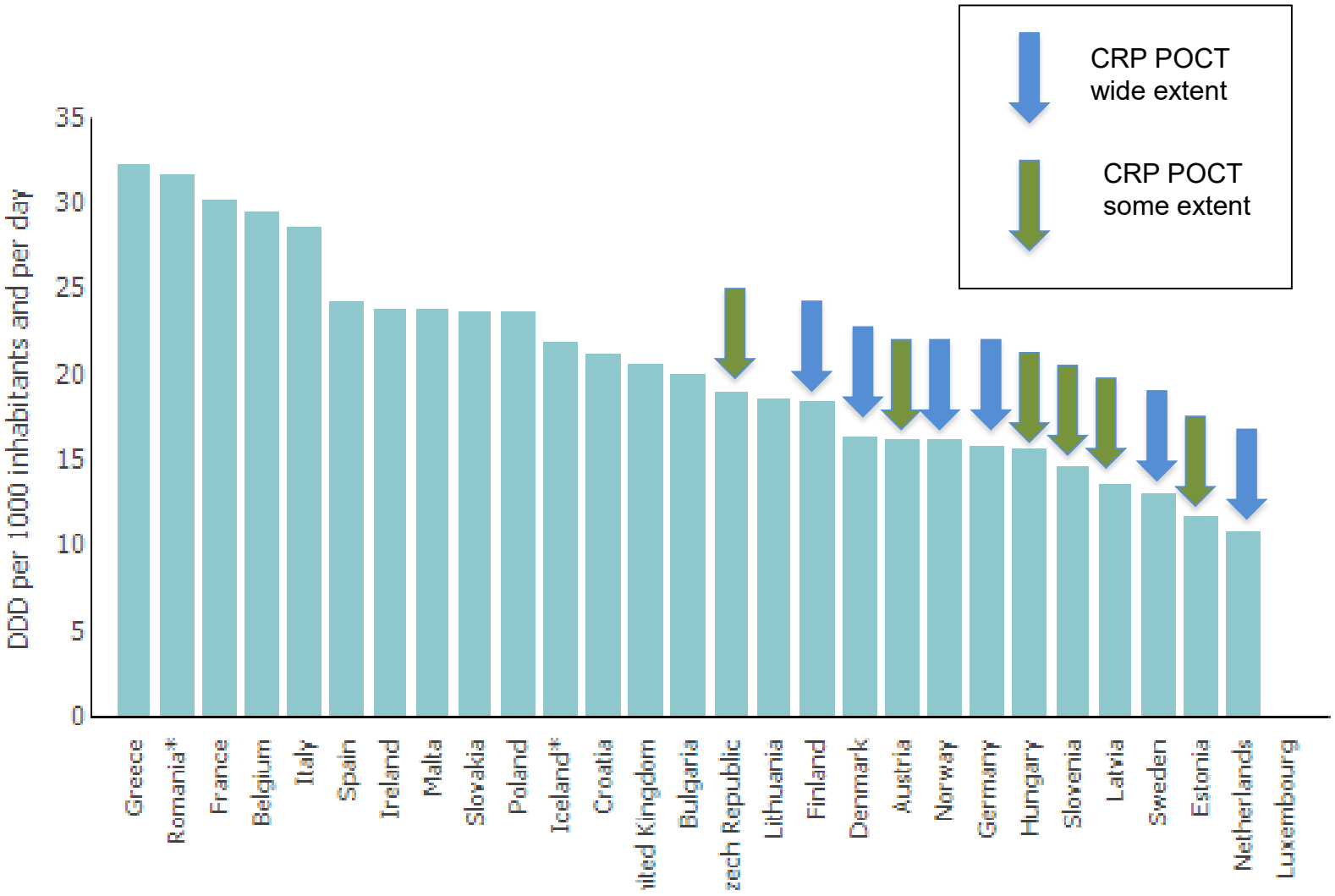
Conclusions:

- Uptake of testing poor, even on ICU
- Positive test significantly increases de-escalation of antibiotic therapy, but in the minority of patients



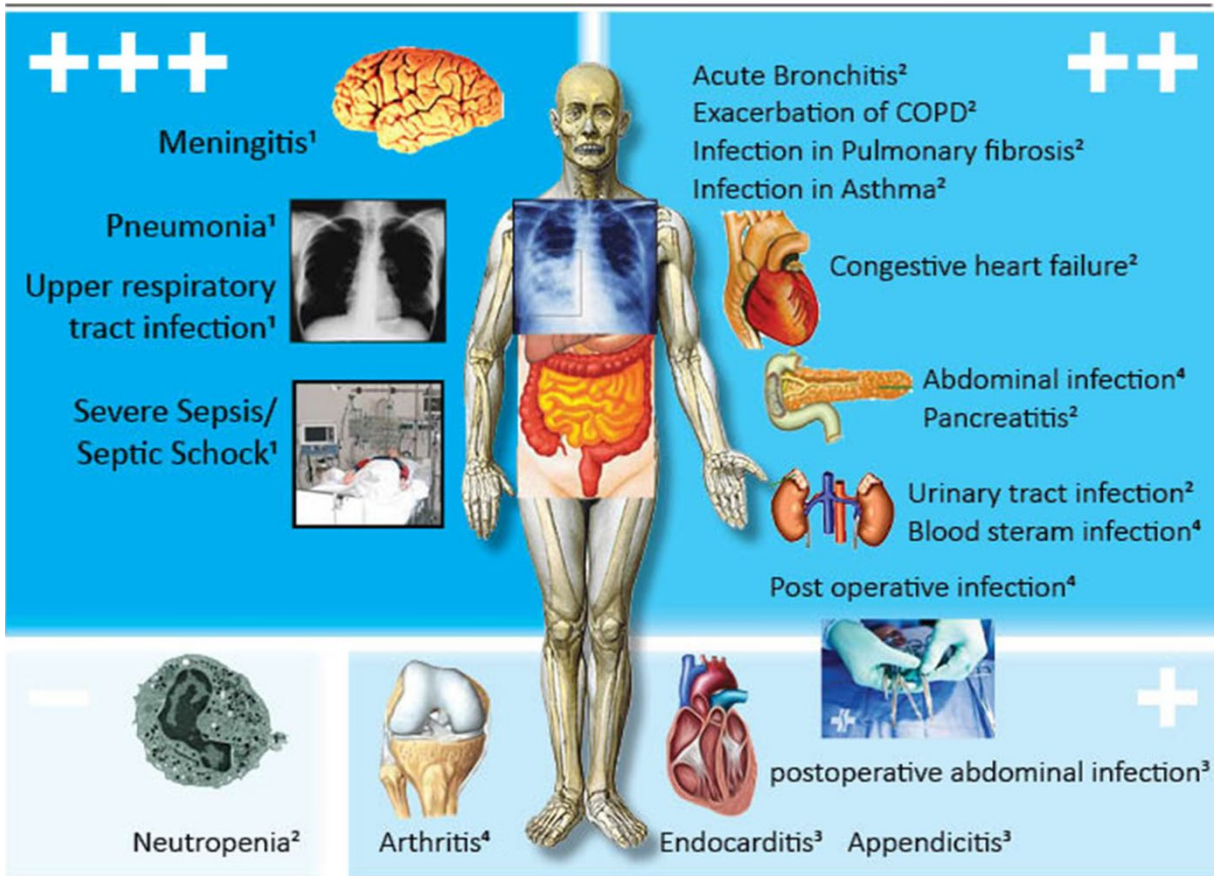
Schimmel J et al. *Clin Infect Dis 2020*

Use of CRP POCT and antibiotic prescribing in Europe



Summary of evidence regarding PCT for diagnosis and antimicrobial stewardship (AMS)

Intervention studies of benefit and harm of PCT for diagnosis and AMS



Observational studies of diagnostic utility

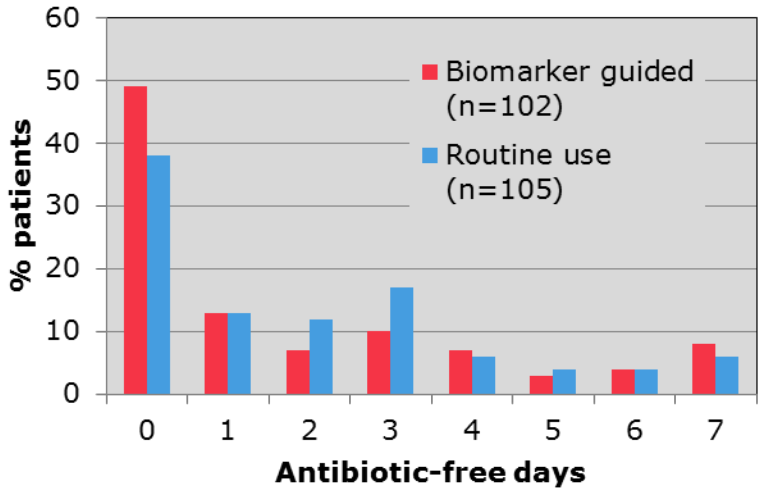
+ moderate evidence; ++ good evidence; +++ strong evidence; - no evidence in favour

Sager R et al. BMC Medicine (2017) 15:15

Biomarker-guided antibiotic stewardship in suspected ventilator-associated pneumonia (VAPrapid2): a randomised controlled trial and process evaluation

Thomas P Hellyer, Daniel F McAuley, Timothy S Walsh, Niall Anderson, Andrew Conway Morris, Suveer Singh, Paul Dark, Alistair I Roy, Gavin D Perkins, Ronan McMullan, Lydia M Emerson, Bronagh Blackwood, Stephen E Wright, Kallirroi Kefala, Cecilia M O'Kane,

"Biomarker result below cutoff. The negative predictive value is 1 and ventilator-associated pneumonia is very unlikely. Consider discontinuation of antibiotics."



Summary:

- IL-1ß and IL-8 in BAL did not reduce antibiotic use
- Process evaluation suggested that lack of adoption of the technology and clinician behaviour had a greater influence on trial outcomes than did test performance.

Hellyer TP et al. *Lancet Respir Med Published online 3 Dec 2019*

Approach to diagnostic testing

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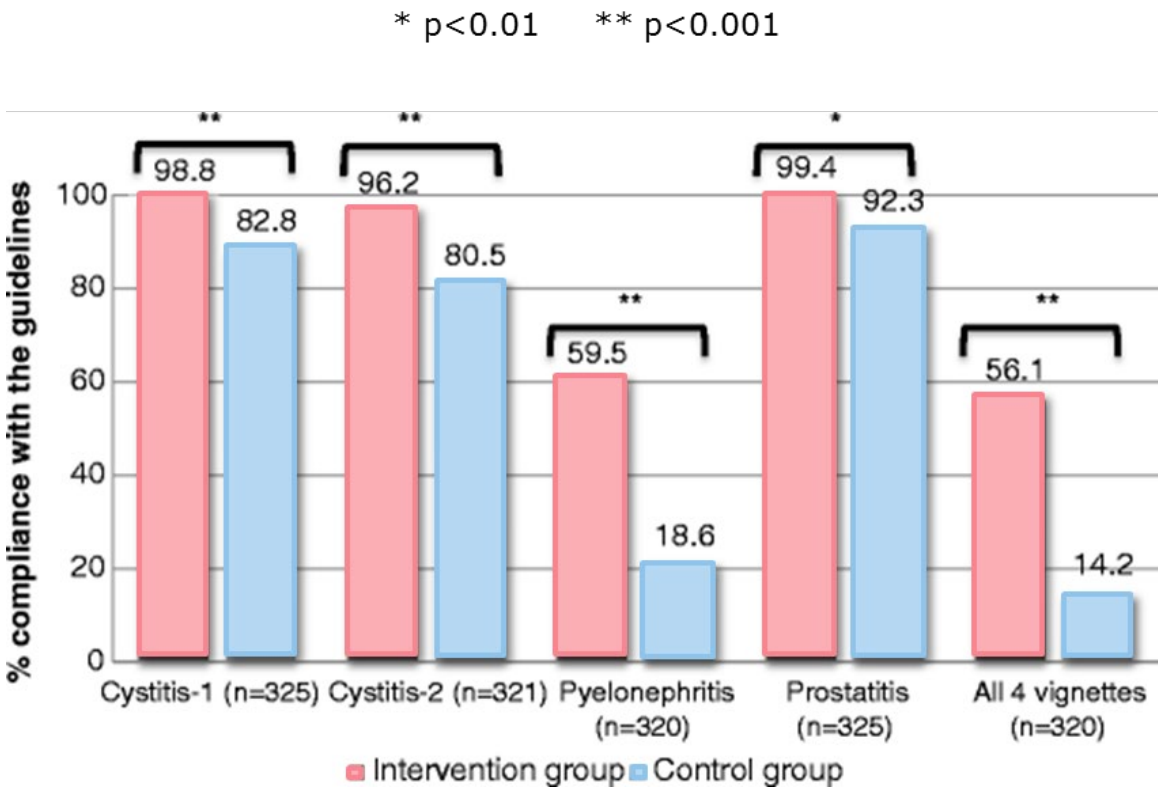
Pre-analytical	Analytical	Post-analytical
Test selection Ordering Collection Transport	Processing Testing Test performance	Interpretation Reporting Intervention

Selective antibiotic reporting

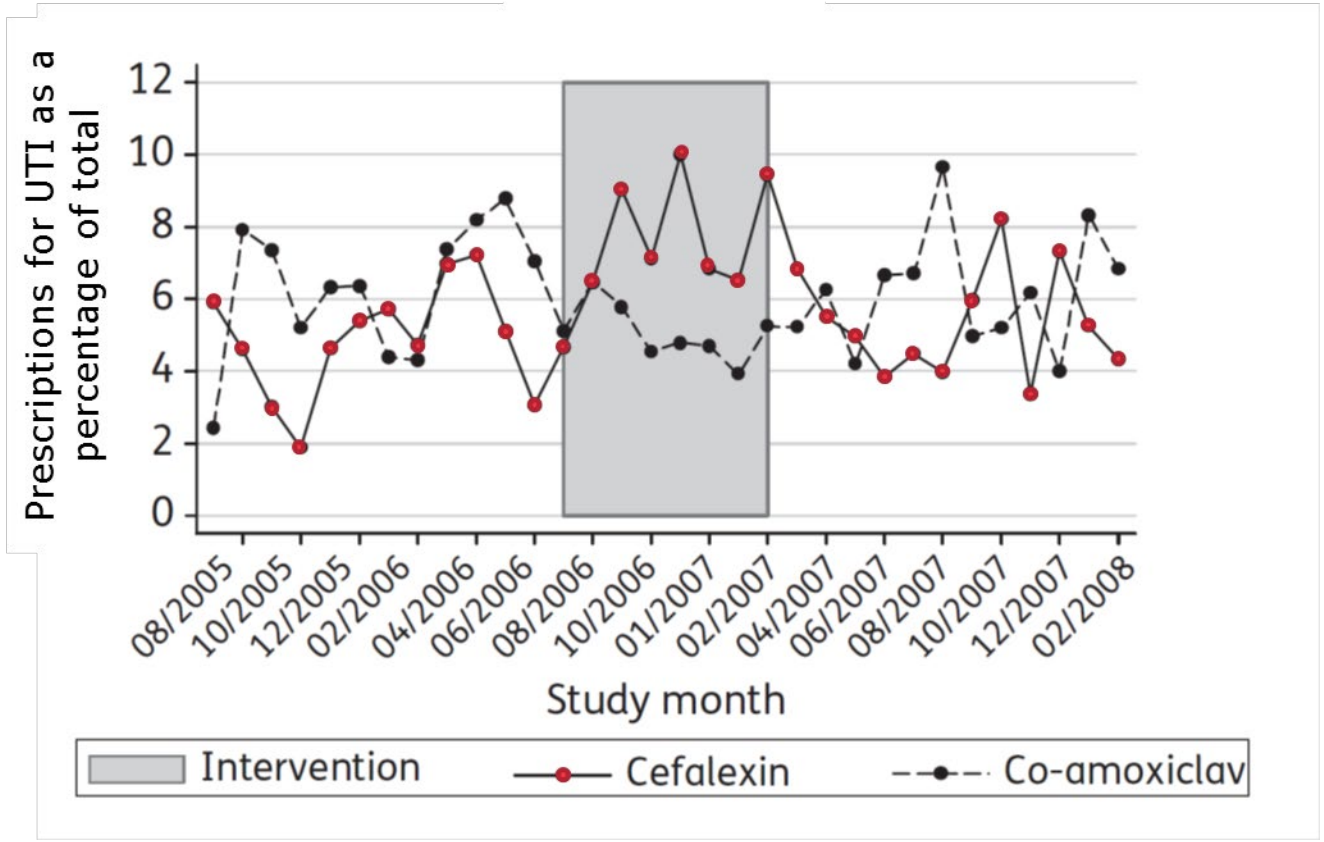
Clinical case histories presented to GPs



Coupat C et al. *Eur J Clin Microbiol Infect Dis* 2013; 32: 627–36

Selective antibiotic reporting

Change in reported antibiotic susceptibilities and impact on GP prescribing



McNulty CAM et al. *J Antimicrob Chemother* 2011; 66: 1396–1404

Key messages

- The laboratory is your chart and compass
- How can you prescribe the right treatment if you have got the diagnosis wrong?
- Right test, right patient, right time
- Over-testing will lead to harm due to treatment of infections that the patient hasn't got
- Monitor for unintended consequences of any intervention
- Implementation is difficult, even with a great test
- Clinicians will often do what the laboratory report guides them to do

Into the future…

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journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Smartphones as mobile microbiological laboratories

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[3)] *Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*