Challenges in infection diagnostics

Professor Mark Wilcox

University of Leeds

Leeds Teaching Hospitals

UK Health Security Agency

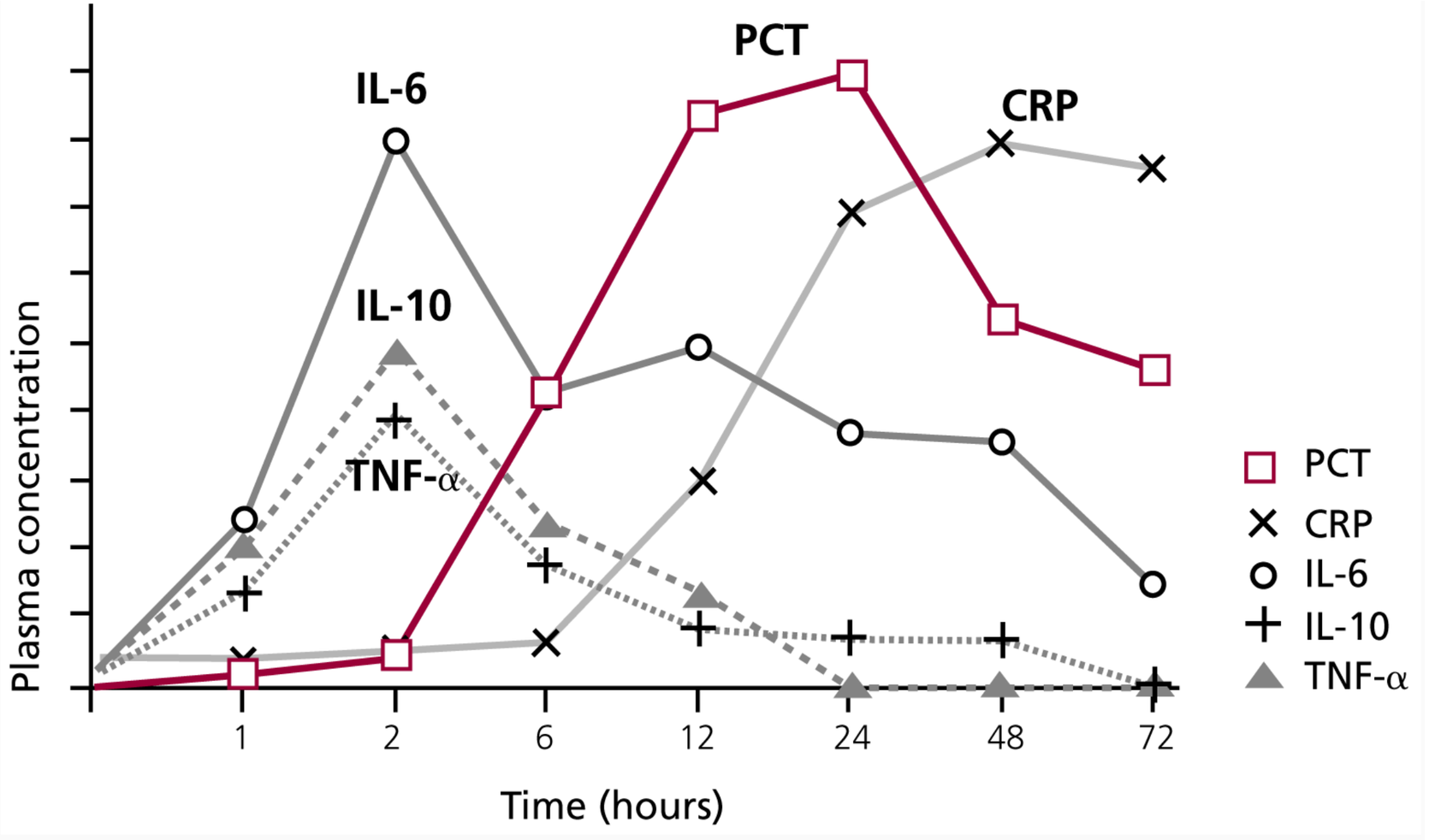
NHS England

Pandemic roles

- I am a member of UK Scientific Advisory Group for Emergencies (SAGE) - COVID-19
- Co-chair of SAGE Hospital-Onset/Nosocomial Transmission COVID-19 subgroup (HOCI)
- Member of SAGE Environment and Modelling subgroup
- Member of four nations' CMOs Senior Clinicians Group, chaired by Prof. C Whitty
- Led evidence reviews on
  - prevention of transmission of SARS-CoV-2 in UK hospitals,
  - facemask use by healthcare workers in NHS and primary care
  - respiratory protection equipment use by healthcare workers in NHS
- Member of UK NICE group: COVID-19 rapid guideline: arranging planned care in hospitals and diagnostic services
- Medical advisor to Chief Scientific Officer
- Co-chair (with Chief Scientific Officer) of NHS England/Improvement Technologies Validation group / CTDA - accuracy/utility of rapid virus tests for use/sale in UK and NHS deployment
- Member of NHS England/Improvement Rapid Turnaround and Point Of Care Testing group
- Moonshot (UK Government) Scientific Advisory Group
- **National Clinical Director Antimicrobial Resistance & Infection Prevention & Control**

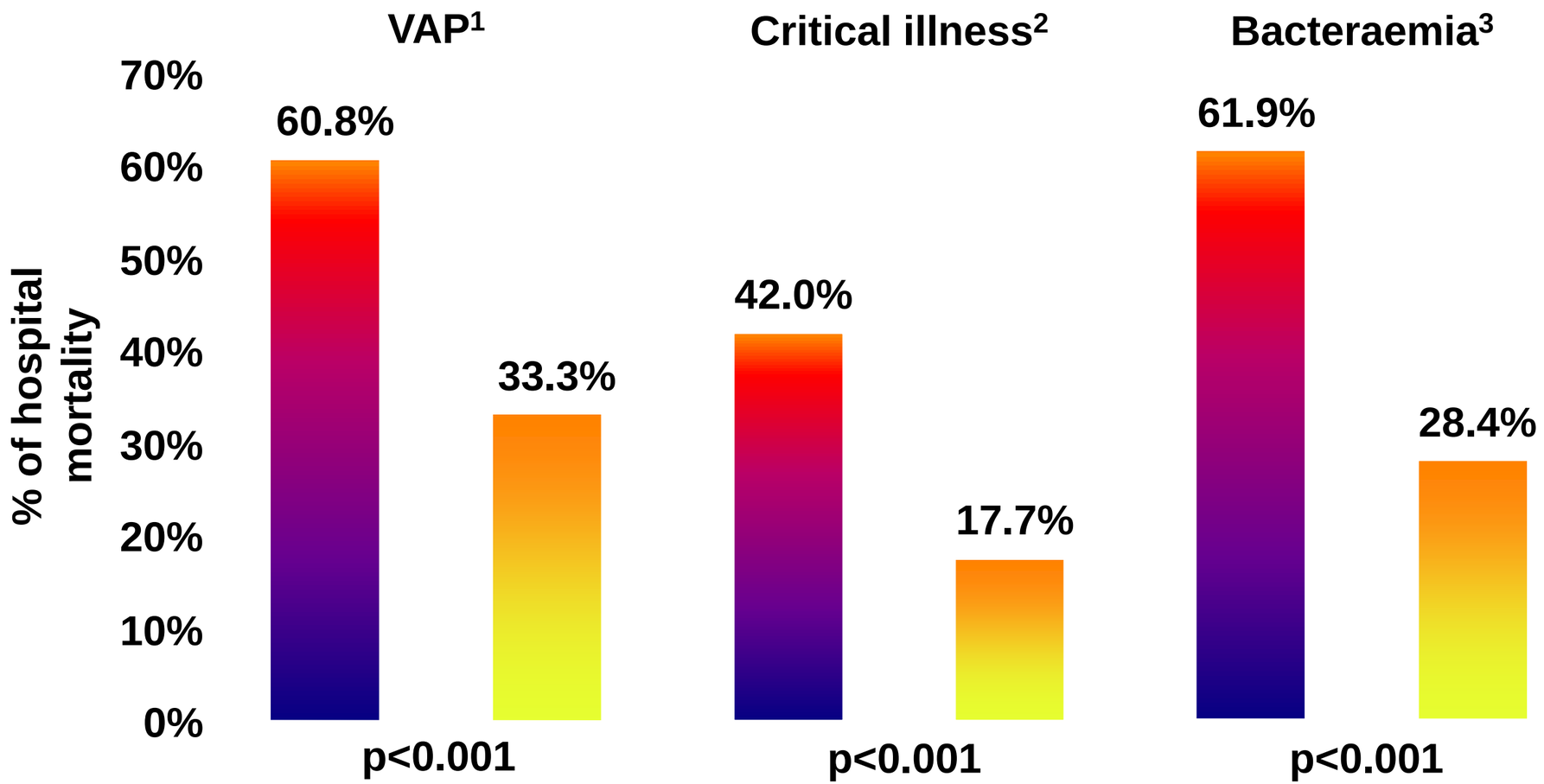
- 80% of antibiotic prescriptions are empirical (best guess)
- Once start an antibiotic, difficult to stop it
- Infection yes or no?
- Antimicrobial resistance yes or no?
- Test accuracy
  - Sensitivity
  - Specificity
  - **Positive predictive value**
  - **Negative predictive value**
- Clinical utility
- Cost effectiveness

Biomarkers associated with infection



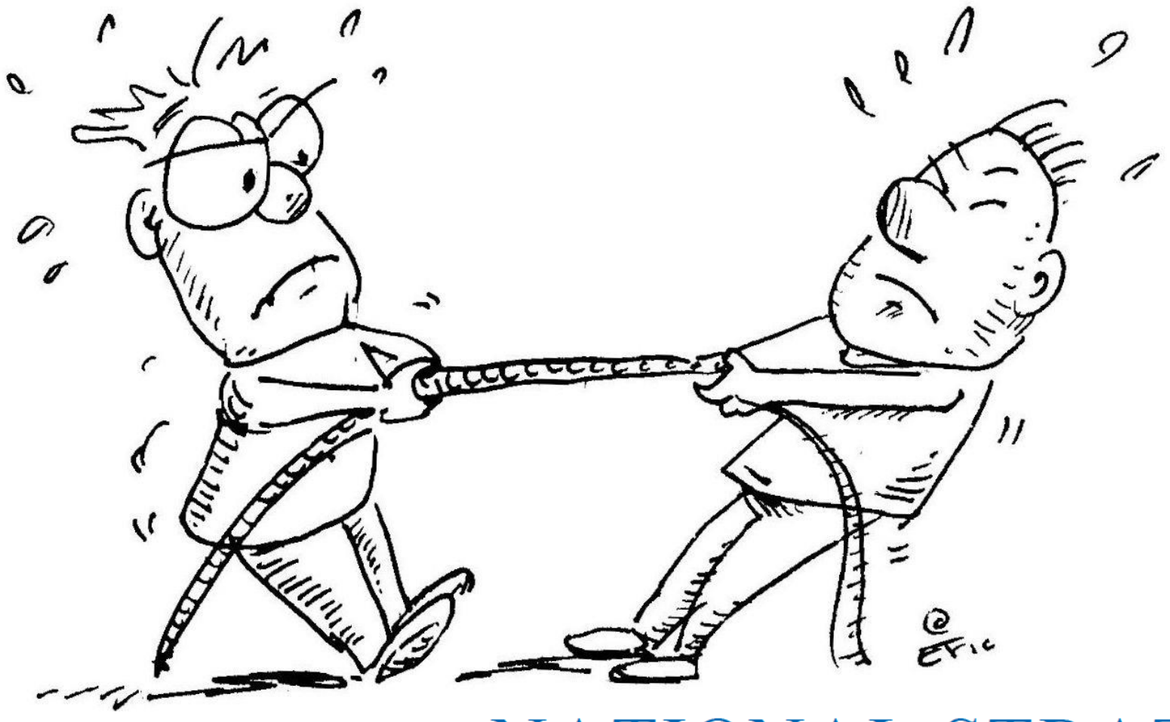
Meisner M., J Lab Med 1999;23:263-72

Consequences of inadequate initial antibiotic treatment

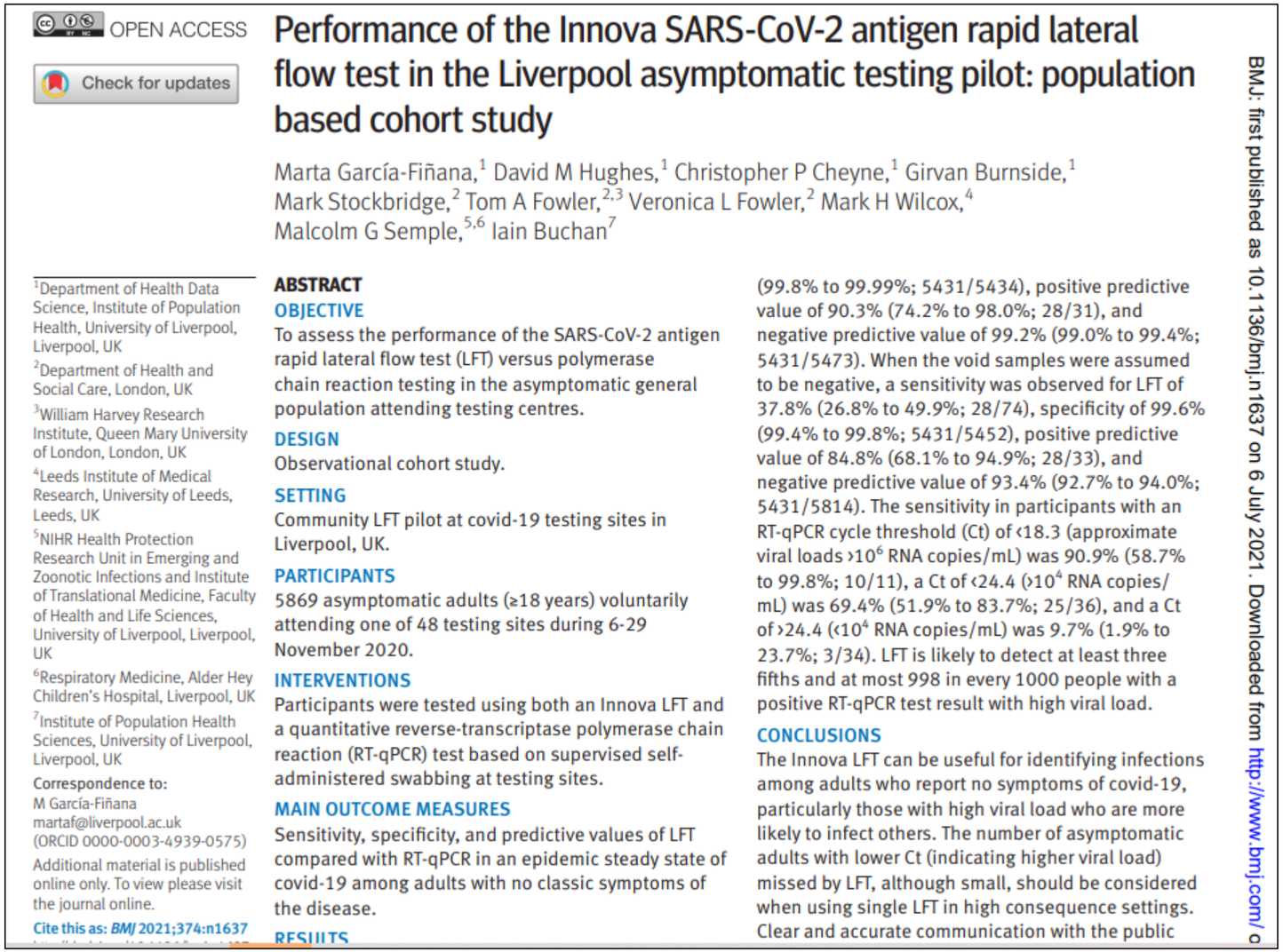


1. Kollef MH and Ward S. *Chest* 1998;113:412–20; 2. Kollef MH, *et al. Chest.* 1999;115:462–74;
3. Ibrahim EH, *et al. Chest.* 2000;118:146–55.

Surviving Sepsis Campaign



NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA



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Performance of the Innova SARS-CoV-2 antigen rapid lateral flow test in the Liverpool asymptomatic testing pilot: population based cohort study

Marta García-Fiñana,[1] David M Hughes,[1] Christopher P Cheyne,[1] Girvan Burnside,[1] Mark Stockbridge,[2] Tom A Fowler,[2,3] Veronica L Fowler,[2] Mark H Wilcox,[4] Malcolm G Semple,[5,6] Iain Buchan[7]

[1]Department of Health Data Science, Institute of Population Health, University of Liverpool, Liverpool, UK
[2]Department of Health and Social Care, London, UK
[3]William Harvey Research Institute, Queen Mary University of London, London, UK
[4]Leeds Institute of Medical Research, University of Leeds, Leeds, UK
[5]NIHR Health Protection Research Unit in Emerging and Zoonotic Infections and Institute of Translational Medicine, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK
[6]Respiratory Medicine, Alder Hey Children's Hospital, Liverpool, UK
[7]Institute of Population Health Sciences, University of Liverpool, Liverpool, UK

Correspondence to:
M García-Fiñana
martaf@liverpool.ac.uk
(ORCID 0000-0003-4939-0575)

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ABSTRACT

OBJECTIVE
To assess the performance of the SARS-CoV-2 antigen rapid lateral flow test (LFT) versus polymerase chain reaction testing in the asymptomatic general population attending testing centres.

DESIGN
Observational cohort study.

SETTING
Community LFT pilot at covid-19 testing sites in Liverpool, UK.

PARTICIPANTS
5869 asymptomatic adults (≥18 years) voluntarily attending one of 48 testing sites during 6-29 November 2020.

INTERVENTIONS
Participants were tested using both an Innova LFT and a quantitative reverse-transcriptase polymerase chain reaction (RT-qPCR) test based on supervised self-administered swabbing at testing sites.

MAIN OUTCOME MEASURES
Sensitivity, specificity, and predictive values of LFT compared with RT-qPCR in an epidemic steady state of covid-19 among adults with no classic symptoms of the disease.

RESULTS
(99.8% to 99.99%; 5431/5434), positive predictive value of 90.3% (74.2% to 98.0%; 28/31), and negative predictive value of 99.2% (99.0% to 99.4%; 5431/5473). When the void samples were assumed to be negative, a sensitivity was observed for LFT of 37.8% (26.8% to 49.9%; 28/74), specificity of 99.6% (99.4% to 99.8%; 5431/5452), positive predictive value of 84.8% (68.1% to 94.9%; 28/33), and negative predictive value of 93.4% (92.7% to 94.0%; 5431/5814). The sensitivity in participants with an RT-qPCR cycle threshold (Ct) of <18.3 (approximate viral loads >10^6 RNA copies/mL) was 90.9% (58.7% to 99.8%; 10/11), a Ct of <24.4 (>10^4 RNA copies/mL) was 69.4% (51.9% to 83.7%; 25/36), and a Ct of >24.4 (<10^4 RNA copies/mL) was 9.7% (1.9% to 23.7%; 3/34). LFT is likely to detect at least three fifths and at most 998 in every 1000 people with a positive RT-qPCR test result with high viral load.

CONCLUSIONS
The Innova LFT can be useful for identifying infections among adults who report no symptoms of covid-19, particularly those with high viral load who are more likely to infect others. The number of asymptomatic adults with lower Ct (indicating higher viral load) missed by LFT, although small, should be considered when using single LFT in high consequence settings. Clear and accurate communication with the public

The Innova LFT can be useful for identifying infections among adults who report no symptoms of covid-19, particularly those with high viral load who are more likely to infect others. The number of asymptomatic adults with lower Ct (indicating higher viral load) missed by LFT, although small, should be considered when using single LFT in high consequence settings. **Clear and accurate communication with the public about how to interpret test results is important, given the chance of missing some cases, even at high viral loads.** Further research is needed to understand how infectiousness is reflected in the viral antigen shedding detected by LFT versus the viral loads approximated by RT-qPCR

https://www.bmj.com/content/bmj/374/bmj.n1637.full.pdf

UK Response to O'Neill AMR Review - diagnostics

"No antibiotic without a diagnostic test (or clinical scoring system) by 2020"

- Longitude Prize of £10M to develop a new diagnostic test for bacterial infections that is accurate, rapid, affordable and easy-to-use anywhere in the world.
- NHS Accelerated Access Review & Innovation Accelerator Scheme
- NICE to explore the feasibility of assessing the effectiveness of existing diagnostics

https://amr-review.org/

NICE DG20 review of rapid diagnostic tests for bloodstream bacteria & fungi

- **Not recommended for routine use.** Compared to BC +/- MALDI-ToF. More evidence needed as **only 3/66 RCTs**
- ↓time to pathogen identification: 26h v 80h BC
- ↓ time to change AB tx: SeptiFast 18h v 38h MALDI; 9h v 50h BC;
- Little impact ITU LOS; shorter broad ABs SeptiFast 19h v 38h MALDI
- Mortality: poor follow-up; **no real difference**
- Cost effectiveness: MALDI-ToF MS +ve net benefit vs BC. SeptiFast best but expensive
  - **LightCycler SeptiFast Test MGRADE**: real time PCR 25 bacterial and fungal pathogens from whole blood. 6hrs. Use MecA to identify MRSA
  - **SepsiTest**: PCR test for 200 genera of bacteria and 65 genera of fungi. From whole blood. 3-4hrs.
  - **IRIDICA BAC BSI**: PCR + MALDI-ToF. 780 bacteria and candida. MecA (*MRSA*), vanA and vanB (*VRE*), and KPC (G-ve carbapenem resistance) genes. 6hrs.

2016 https://www.nice.org.uk/guidance/DG20
2020 We found nothing new that affects the recommendations in this guidance

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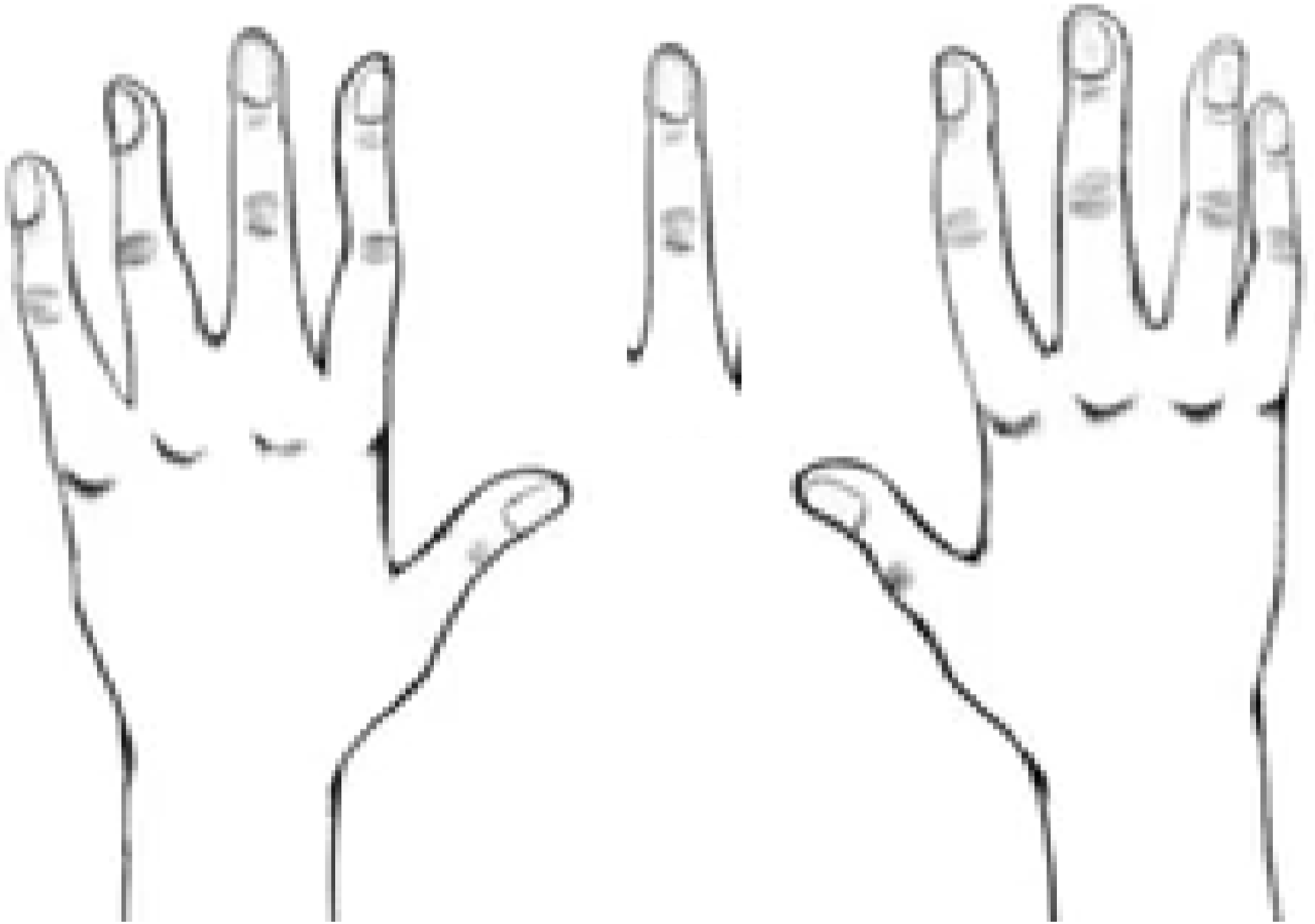

Clin Infect Dis. 2018 Jan 18;66(3):452-455. doi: 10.1093/cid/cix743.

Demise of Polymerase Chain Reaction/Electrospray Ionization-Mass Spectrometry as an Infectious Diseases Diagnostic Tool.

Özenci V[1,2], Patel R[3,4], Ullberg M[1,2], Strålin K[5,6].

Author information

Abstract

Although there are several US Food and Drug Administration (FDA)-approved/cleared molecular microbiology diagnostics for direct analysis of patient samples, all are single target or panel-based tests. There is no FDA-approved/cleared diagnostic for broad microbial detection. Polymerase chain reaction (PCR)/electrospray ionization-mass spectrometry (PCR/ESI-MS), commercialized as the IRIDICA system (Abbott) and formerly PLEX-ID, had been under development for over a decade and had become CE-marked and commercially available in Europe in 2014. Capable of detecting a large number of microorganisms, it was under review at the FDA when, in April 2017, Abbott discontinued it. This turn of events represents not only the loss of a potential diagnostic tool for infectious diseases but may be a harbinger of similar situations with other emerging and expensive microbial diagnostics, especially genomic tests.

or

?

Speed of infection diagnosis matters

Rapid ID +/- sensitivity is possible

But realistically at present only for a pre-set group of pathogens +/- resistance markers

When is it cost-effective?

Will it influence outcomes when it cannot inform 1st antibiotic dose?