

The Clinical Need for Antibiotic Resistance Related Diagnostics

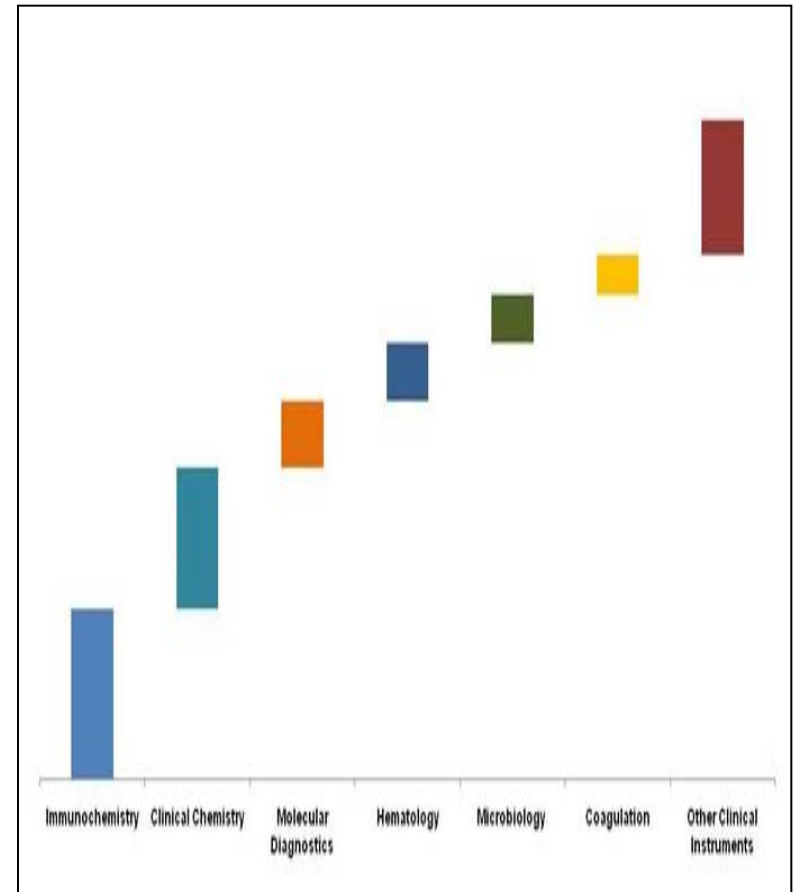
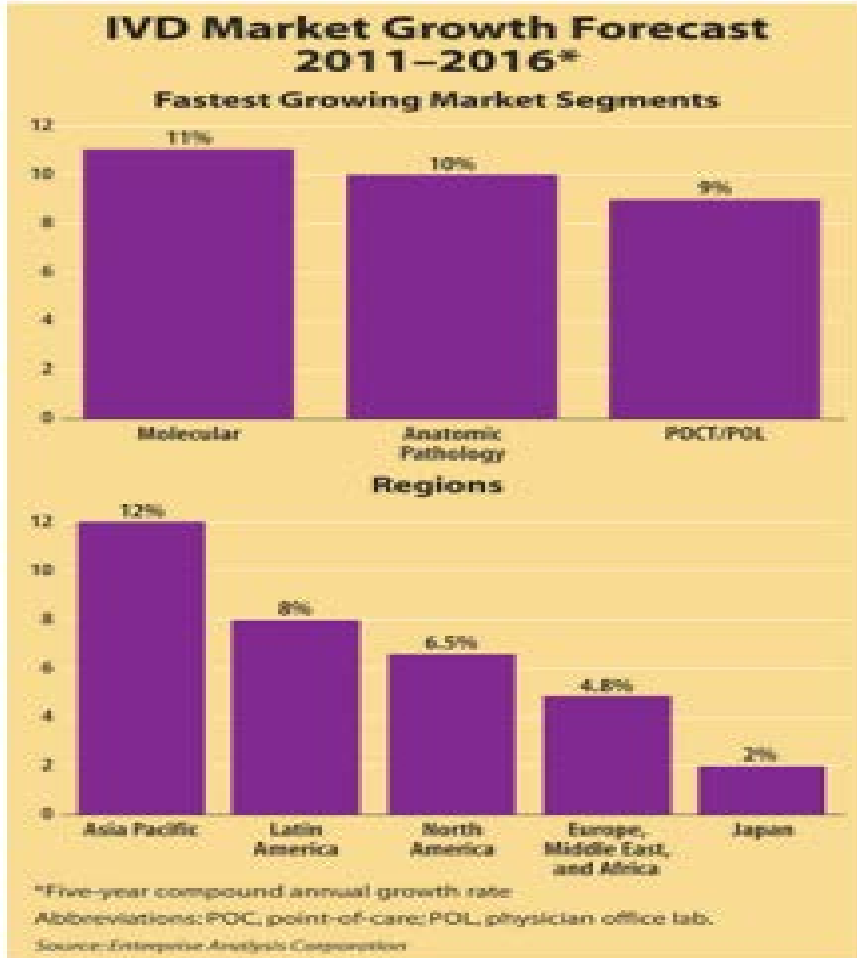
Professor Mark H. Wilcox

Leeds Teaching Hospitals, University of Leeds,
& Public Health England, UK

Facts (i)

- IVDs will be the **world's largest med-tech sector** in 2018
- Beating cardiology and diagnostic imaging to the top spot
- Annual sales of **\$54.5 billion**
- 5 yr compounded **annual growth rate 4.8%**
- Roche is the clear IVD market leader (18% market share)
- Projected 2018 sales **\$9.9 billion**

Facts (ii)



<http://www.aacc.org/publications/cln/2012/ExpolIssue/Pages/RecordBreaking2012ClinicalLab.aspx#>
<http://www.marketsandmarkets.com/Images/ivd-in-vitro-diagnostics-market.jpg>

NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC- RESISTANT BACTERIA

- GOAL 1: Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections
- GOAL 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance
- GOAL 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
- GOAL 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
- GOAL 5: Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development.....

September 2014





Department
of Health



Department
for Environment
Food & Rural Affairs

**‘diagnostics’ are mentioned 40 times in the UK’s
Five Year Antimicrobial Resistance (AMR) Strategy
2013–18.**

UK Five Year Antimicrobial Resistance Strategy 2013 to 2018

CE marking diagnostics (IVDs)

- CE Marking based **only on self-declaration**
- **No systematic safety net** to identify poor IVD performance
- **No clear requirement to demonstrate IVD has good clinical utility**

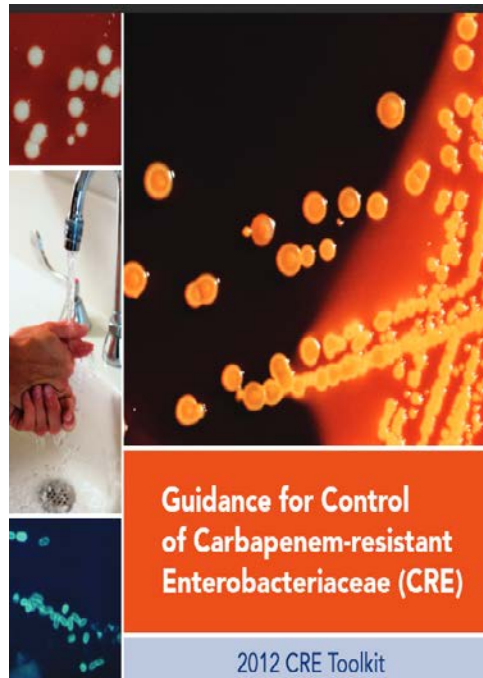


Widely used molecular pathogen detection / screening tests

- HPV 16/18
- Influenza
- HSV
- RSV

- *M. tuberculosis*
- *C. trachomatis, N. gonorrhoeae, T. vaginalis*
- MRSA screening
- *C. difficile* 'screening'
- Group A Strep


Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae



Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)

2012 CRE Toolkit

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion



https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/329227/Acute_trust_toolkit_for_the_early_detection.pdf

<http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf>

http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/guidance-infection-prevention-control/Pages/guidance-prevention-control-infections-CRE.aspx



European Centre for Disease Prevention and Control

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You are here: Portal Home > English > Health Topics > Healthcare-associated Infections > Directory: Guidance on prevention and control > CRE: Guidance on infection prevention and control

CRE: Guidance on infection prevention and control

Directory of guidance on prevention and control of Carbapenem-resistant *Enterobacteriaceae*, published by ECDC, EU/EEA Member States, international and national agencies and professional societies

Page last updated: 25 April 2013

AGENCIES

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (ECDC)

- Systematic review of the effectiveness of infection control measures to prevent the transmission of carbapenemase-producing *Enterobacteriaceae* through cross-border transfer of patients (2014)
- Risk assessment on the spread of carbapenemase-producing *Enterobacteriaceae* (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer (2011)

US CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

- CDC 2012 CRE Toolkit - Guidance for Control of Carbapenem-resistant *Enterobacteriaceae* (CRE)

US AGENCY FOR HEALTHCARE RESEARCH AND QUALITY (AHRQ)

- Carbapenem-resistant *Enterobacteriaceae* (CRE) Control and Prevention Toolkit

PROFESSIONAL SOCIETIES

EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES (ESCMID)

Supports for infection and control of carbapenemase-producing *Enterobacteriaceae* are part of the guidelines on multidrug-resistant Gram-negative bacteria (ESCMID, 2013)

- ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients

MEMBER STATES

AUSTRIA

Control of carbapenemase-producing *Enterobacteriaceae* in Austria (Ministry of Health, 2011)

- CPE – Carbapenemase produzierende Enterobakterien in Österreich – Carbapenemassen Kontrollieren

BELGIUM

Measures to apply following the emergence of carbapenemase-producing *Enterobacteriaceae* in Belgium (Hoge Gezondheidsraad/ Conseil Supérieur de la Santé, 2011)

- Mesures à prendre suite à l'émergence des entérobactéries productrices de carbapénémases (CPE) en Belgique
- Maatregelen te nemen naar aanleiding van de toename van carbapenemase producerende enterobacteriën (CPE) in België

CZECH REPUBLIC

Control of imported cases of colonization and/or infection by carbapenemase-producing *Enterobacteriaceae* (Ministry of Health, 2012)

- Kontrola výskytu importovaných případů kolonizace a/nebo infekce enterobakteriemi produkujícími carbapenemázu (CPE – Carbapenemase Producing *Enterobacteriaceae*)

FINLAND

Guidance for the handling of infections by multiresistant bacteria. This document includes guidance for infection prevention and control of carbapenem-resistant *Enterobacteriaceae* (Terveyden ja hyvinvoinnin laitos – THL, 2014)

- Orijje moniresistenttien mikrobien tartunnatortunnasta.

FRANCE

Prevention of cross-transmission of emerging highly resistant bacteria. This document includes guidance targeting carbapenemase-producing *Enterobacteriaceae* (Haut Conseil de la Santé Publique, 2013)

- Prévention de la transmission croisée des 'Bactéries Hautement Résistantes aux antibiotiques émergentes' (BHRa)

GERMANY

Infection control measures for infections or colonisation by multidrug-resistant Gram-negative bacteria. This document applies to carbapenem-resistant *Enterobacteriaceae* (Robert Koch Institute, Commission for Hospital Hygiene and Infection Prevention, 2012)

- Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stämmen

GREECE

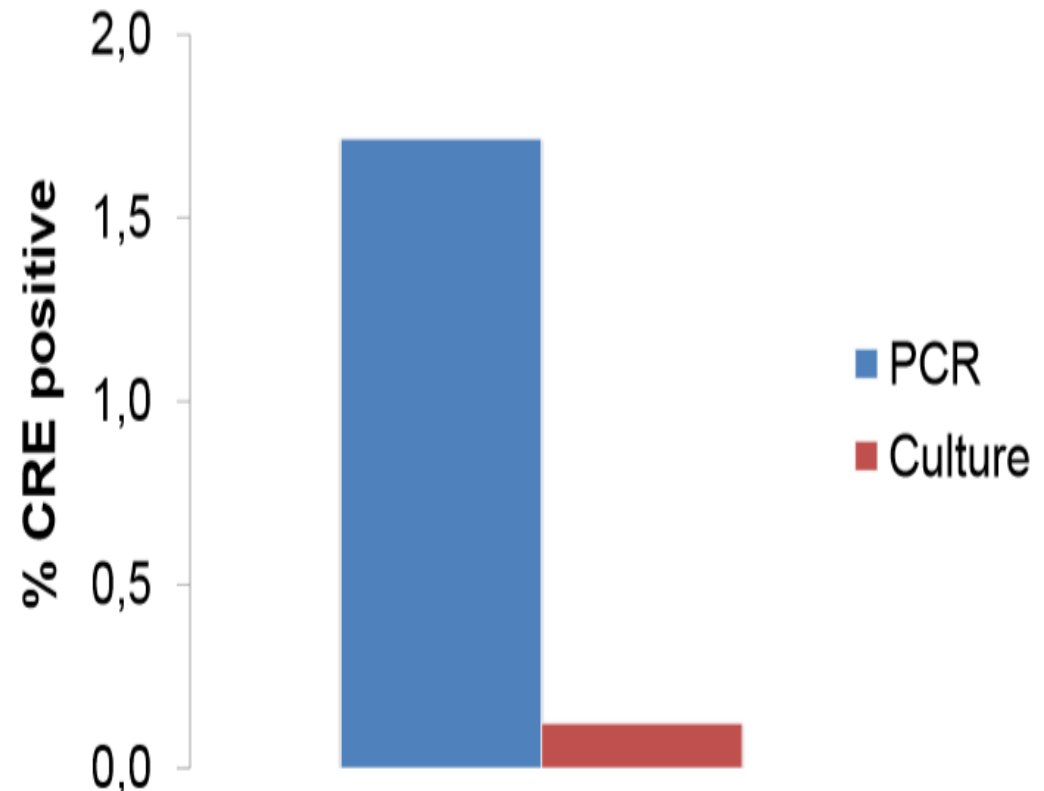
Action plan for the management of infections by multidrug-resistant Gram-negative pathogens in healthcare settings. Protroudas' Guidance on Infection Prevention and Control of carbapenem-resistant *Enterobacteriaceae* is a part of the national action plan. (Hellenic Centre for Disease Control and Prevention, 2010)

- Σχέδιο δράσης για την αντιμετώπιση λοιμώξεων από πολυανθεκτικά Gram-αρνητικά παθογόνα σε χώρους παροχής υγειονομικών υπηρεσιών (Προβούρης)

Screening for CRE – culture vs PCR

Each rectal swab (n=816)
was cultured using:

- Chromogenic media for CRI (Carba-SMART ChromID, BioMerieux)
- Non-chromogenic media (MacConkey with an ertapenem disc)
- PCR assay (CheckDirect, Checkpoints)



What could be the impact of modern and future diagnostics on antibiotics stewardship?

Which would you prefer to know?

- There is an infection
- There is not an infection

- There is a specific pathogen
- There is not a specific pathogen

- There is a specific resistance profile
- There is not a specific resistance profile

Molecular diagnostics

Rapid

Sensitivity

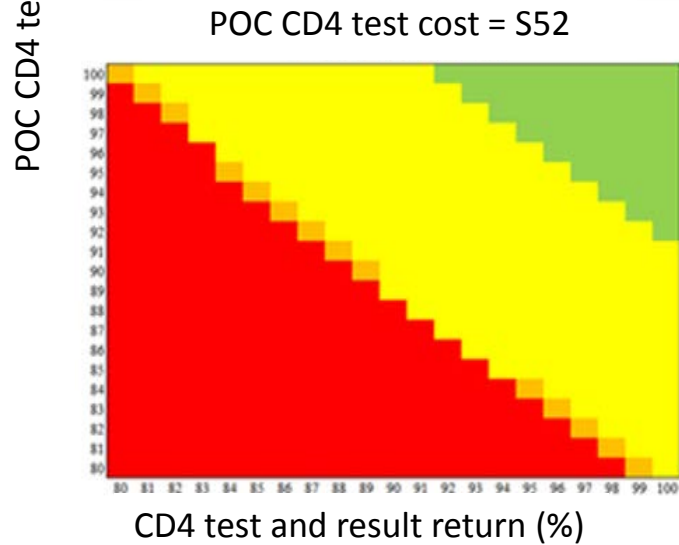
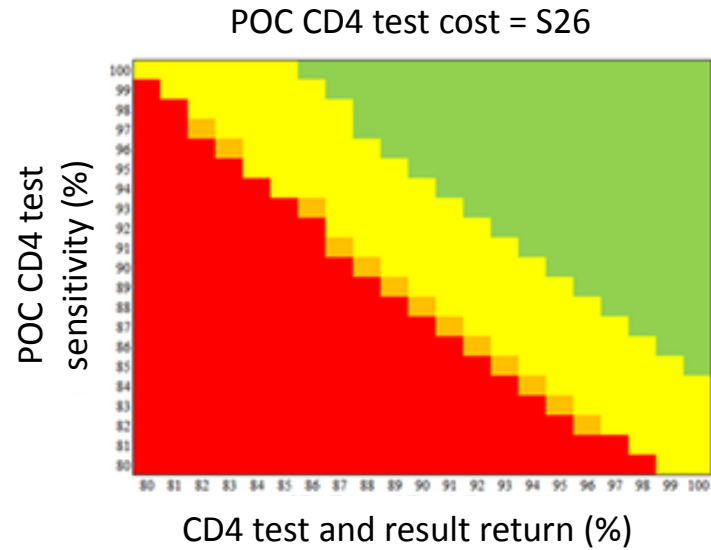
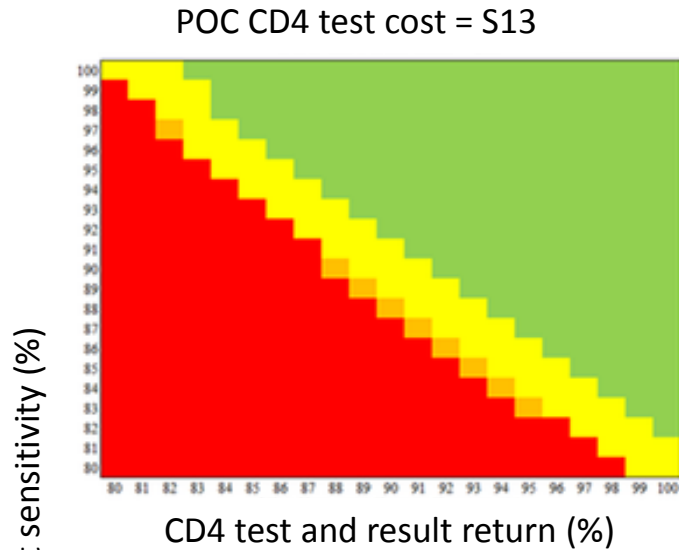
Specificity

Cost-effectiveness

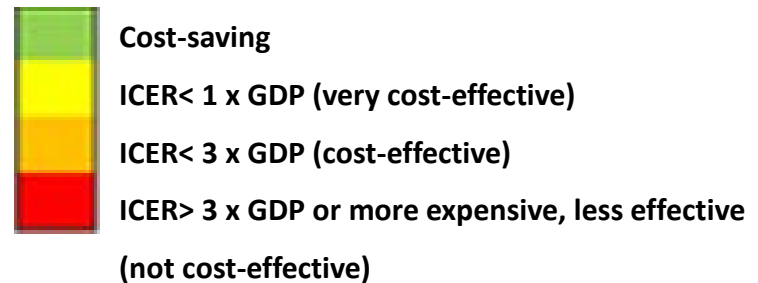
Negative predictive value

Positive predictive value

Multivariate sensitivity analyses: Cost-effectiveness of POC CD4 testing compared with laboratory testing



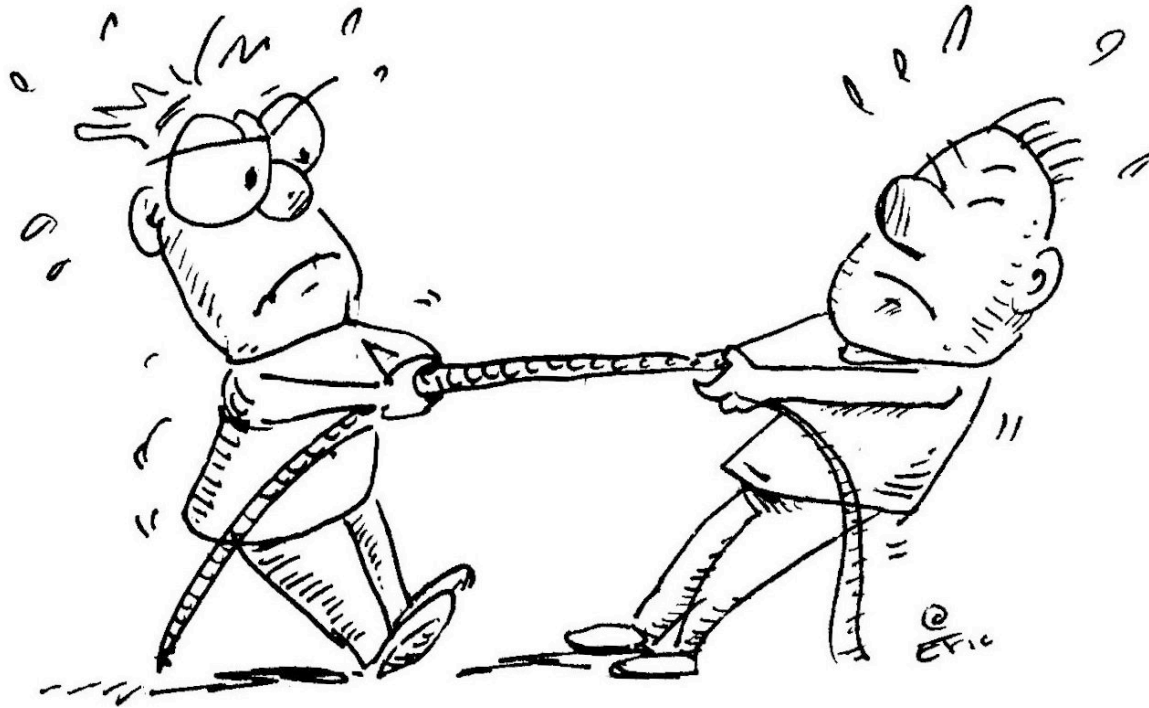
POC compared with laboratory



Ciaranello AL, Myer L, Kelly K, Christensen S, Daskilewicz K, et al. (2015) Point-of-Care CD4 Testing to Inform Selection of Antiretroviral Medications in South African Antenatal Clinics: A Cost-Effectiveness Analysis. PLoS ONE 10(3): e0117751. doi:10.1371/journal.pone.0117751 <http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0117751>

Potential of molecular tools for antibiotic stewardship

Surviving Sepsis Campaign



NATIONAL STRATEGY
FOR COMBATING ANTIBIOTIC-
RESISTANT
BACTERIA

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing

Ritu Banerjee,^{1,a} Christine B. Teng,^{2,a} Scott A. Cunningham,³ Sherry M. Ihde,³ James M. Steckelberg,⁴ James P. Moriarty,⁵ Nilay D. Shah,⁵ Jayawant N. Mandrekar,⁶ and Robin Patel^{3,4}

¹Division of Pediatric Infectious Diseases, Mayo Clinic, Rochester, Minnesota; ²Department of Pharmacy, National University of Singapore and Tan Tock Seng Hospital, Singapore; ³Division of Laboratory Medicine and Pathology, ⁴Division of Infectious Diseases, ⁵Division of Health Care Policy and Research, and ⁶Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

Effect of testing strategy/stewardship on time to organism id, phenotypic susceptibility results, & first appropriate modification of antimicrobial therapy

| Median time in hours (IQR) to: | control | rmPCR | rmPCR + stewardship |
|--------------------------------|--------------|----------------|---------------------|
| organism id | 22.3 (17–28) | 1.3 (0.9–1.6)* | 1.3 (0.9–1.6)* |
| de-escalation | 39 (19–56) | 36 (22–61) | 20 (6–36)** |
| escalation | 18 (2–63) | 4 (1.5–24)* | 4 (1.8–9)* |

Data for subset of subjects with organisms represented on rapid multiplex (rmPCR) panel (n = 481). Time 0 = positive Gram stain result reported. *P < .05 vs control; **P < .05 vs control & rmPCR groups.

Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study



Louise J Pankhurst*, Carlos del Ojo Elias*, Antonina A Votintseva*, Timothy M Walker*, Kevin Cole, Jim Davies, Jilles M Fermont, Deborah M Gascoyne-Binzi, Thomas A Kohl, Clare Kong, Nadine Lemaitre, Stefan Niemann, John Paul, Thomas R Rogers, Emma Roycroft, E Grace Smith, Philip Supply, Patrick Tang, Mark H Wilcox, Sarah Wordsworth, David Wyllie, Li Xu, Derrick W Crook, for the COMPASS-TB Study Group†

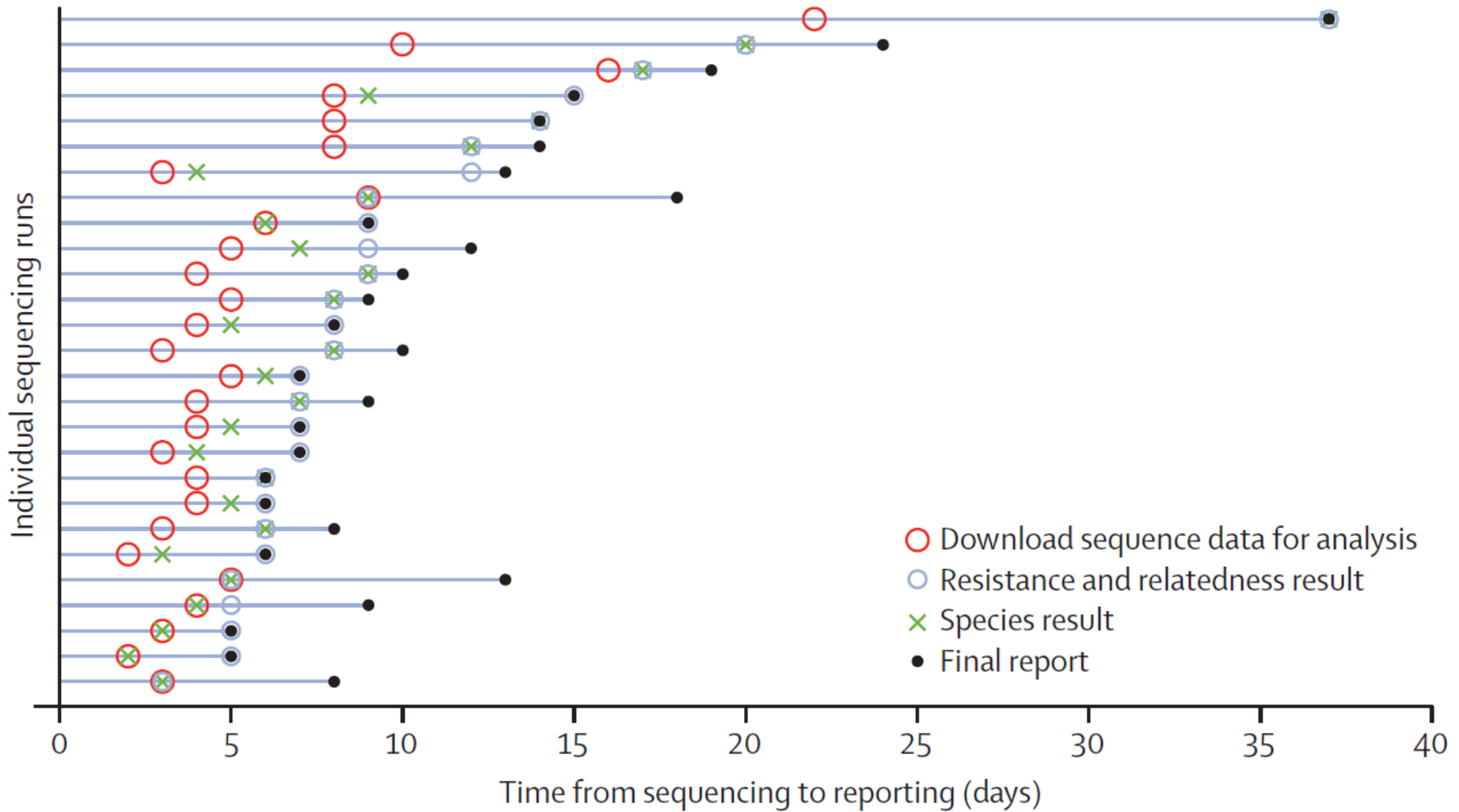


Summary

Background Slow and cumbersome laboratory diagnostics for *Mycobacterium tuberculosis* complex (MTBC) risk delayed treatment and poor patient outcomes. Whole-genome sequencing (WGS) could potentially provide a rapid and comprehensive diagnostic solution. In this prospective study, we compare real-time WGS with routine MTBC diagnostic workflows.

Lancet Respir Med 2016;
4: 49-58

Published Online
December 3, 2015
[http://dx.doi.org/10.1016/
S2213-2600\(15\)00466-X](http://dx.doi.org/10.1016/S2213-2600(15)00466-X)



- Full WGS diagnostics could be generated in a median of 9 days (IQR 6–10)
- Median 21 days (IQR 14–32) faster than final reference laboratory reports
- Cost of £481 per culture-positive specimen *versus* £518 for routine diagnosis

The number needed to test



THE GOOD THE BAD AND THE UGLY