The Clinical Need for Antibiotic Resistance Related Diagnostics

Professor Mark H. Wilcox

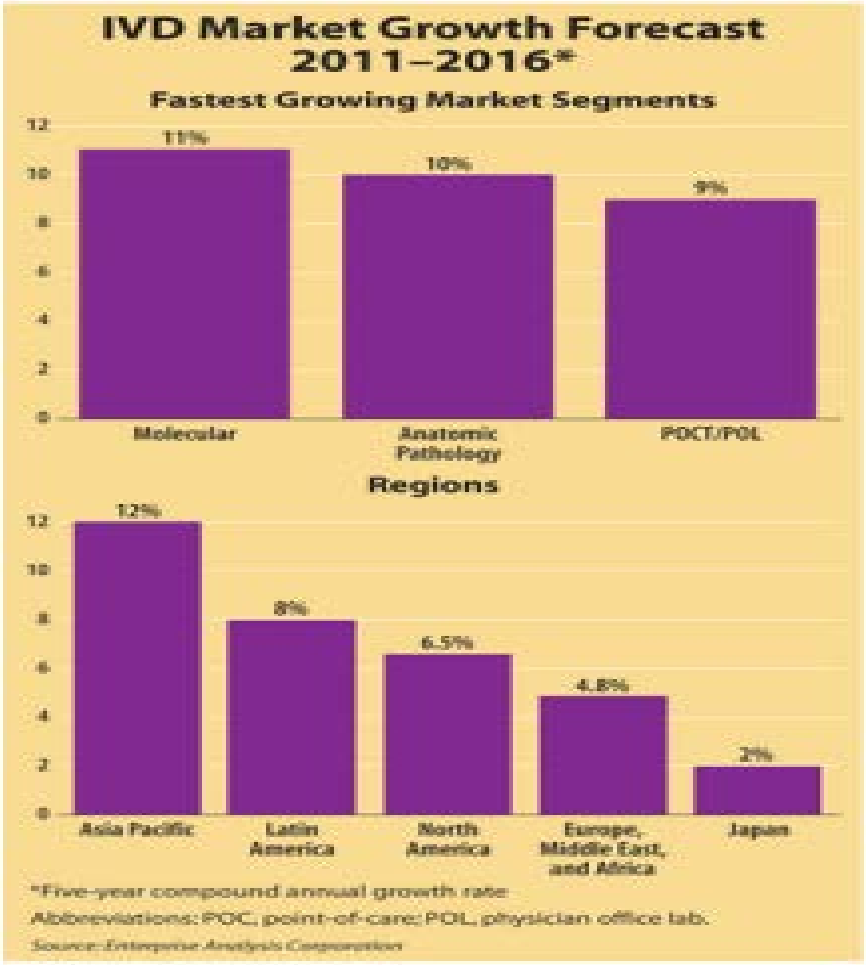
Leeds Teaching Hospitals, University of Leeds,
& Public Health England, UK

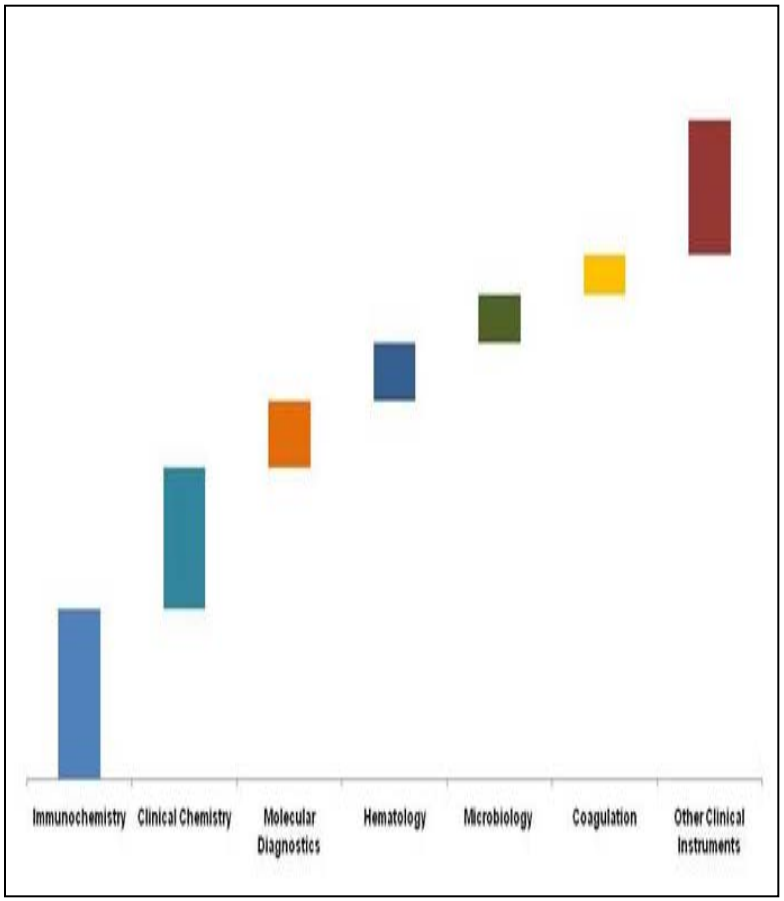
Facts (i)

- 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**

http://www.prnewswire.com/news-releases/medtech-market-to-achieve-global-sales-of-440-billion-by-2018-172274151.html

Facts (ii)





http://www.aacc.org/publications/cln/2012/ExpoIssue/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

THE WHITE HOUSE
WASHINGTON

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**

BMJ

BMJ 2013;346:f836 doi: 10.1136/bmj.f836 Page 1 of 2

EDITORIALS

Assuring the quality of diagnostic tests

How do we know that they do what we think they do?

Mark Wilcox *professor*

Microbiology Department, Old Medical School, Leeds General Infirmary, Leeds LS1 3EX, UK

BMJ 2013;346:f836 doi: 10.1136/bmj.f836

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

Public Health England

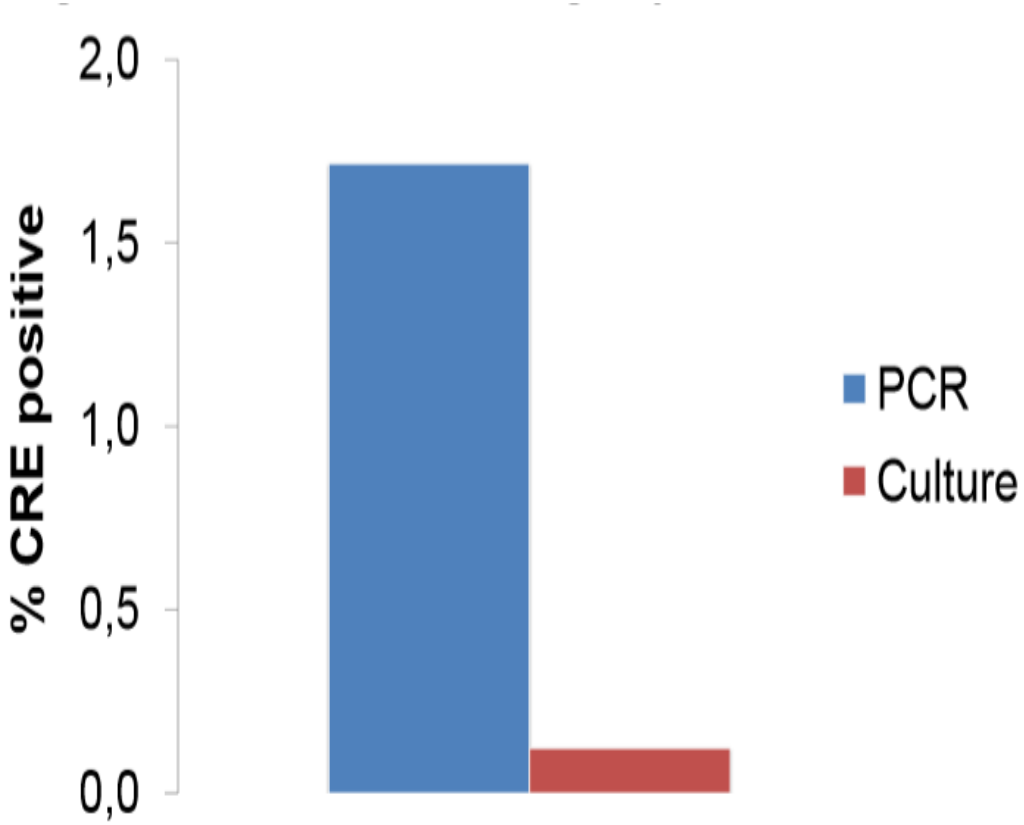
Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae

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

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)



Otter J et al. ECCMID 2015.

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

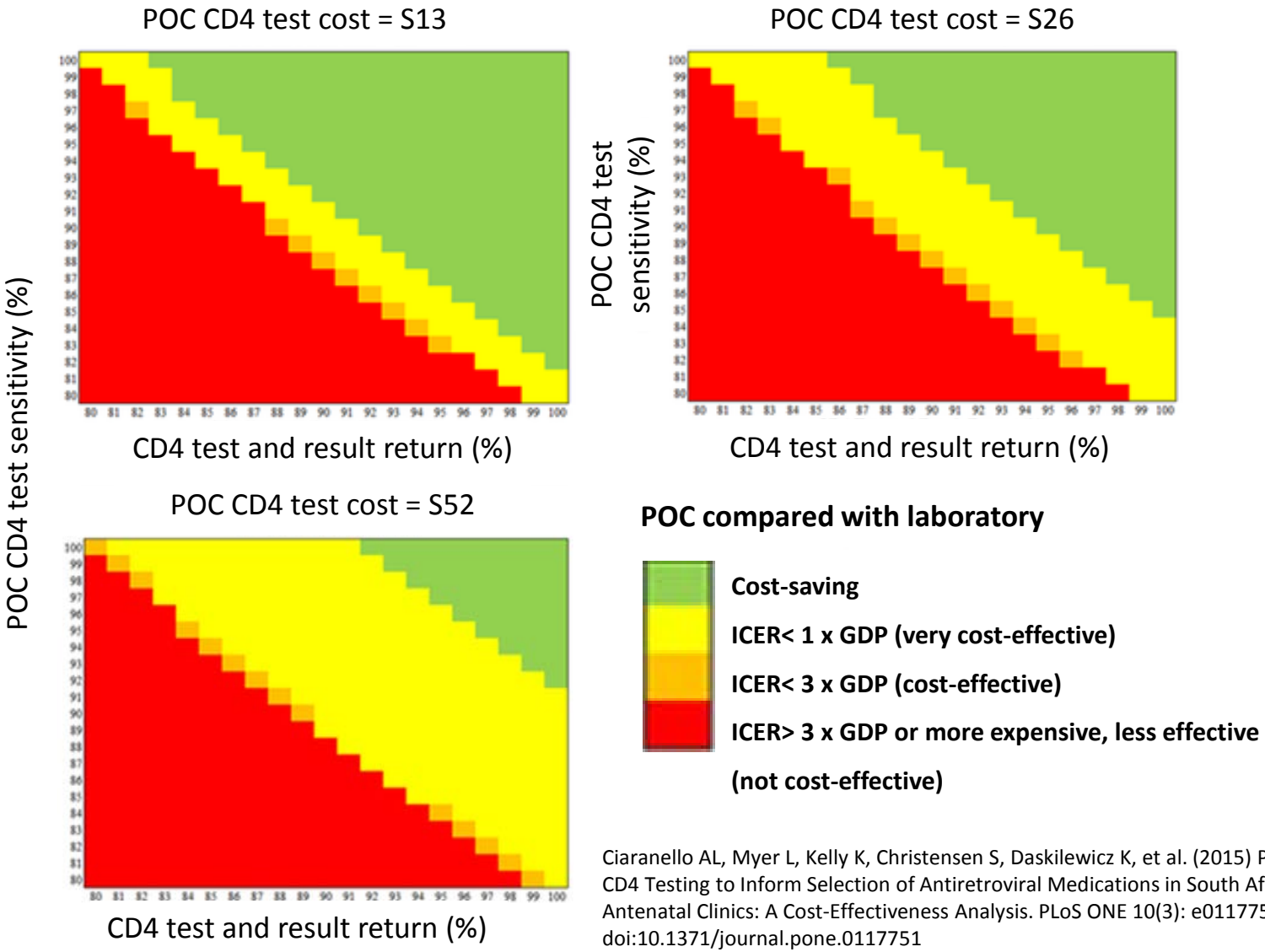
- There is a specific resistance profile
- There is not a specific resistance profile

Molecular diagnostics

Rapid
Sensitivity
Specificity
Cost-effectiveness

Negative predictive value
Positive predictive value

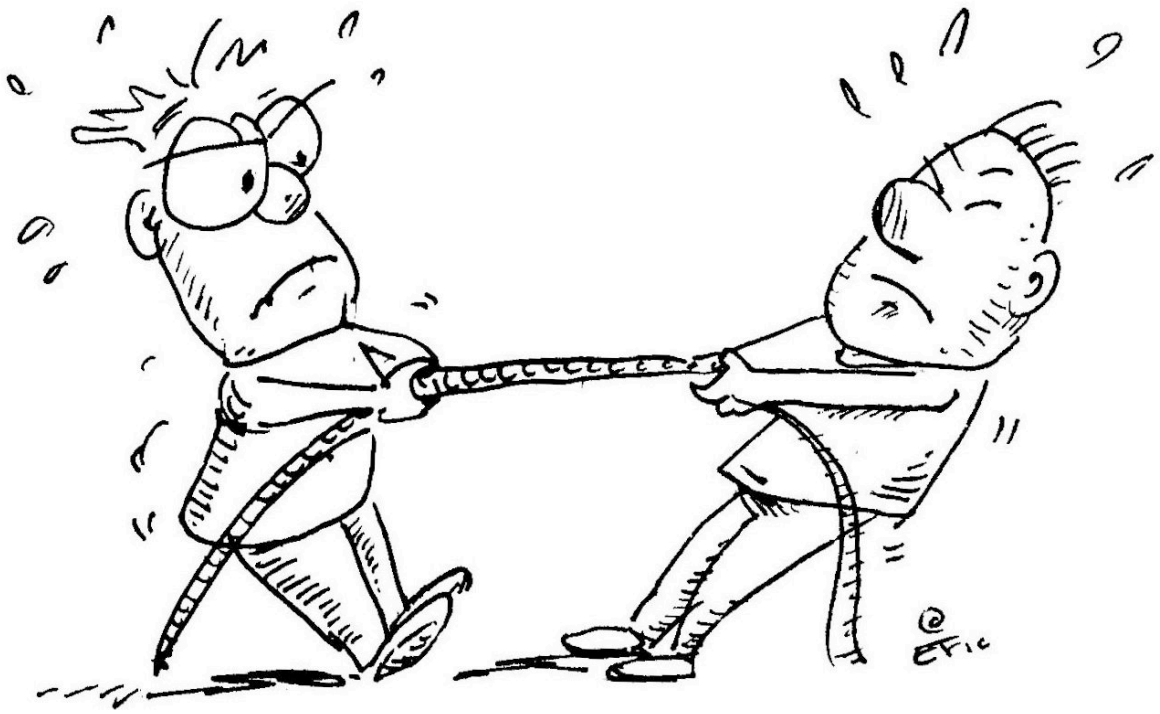
Multivariate sensitivity analyses:
Cost-effectiveness of POC CD4 testing compared with laboratory testing



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

MAJOR ARTICLE

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]

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

Banerjee R, et al. Clinical Infectious Diseases 2015;61:1071–80.

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†*

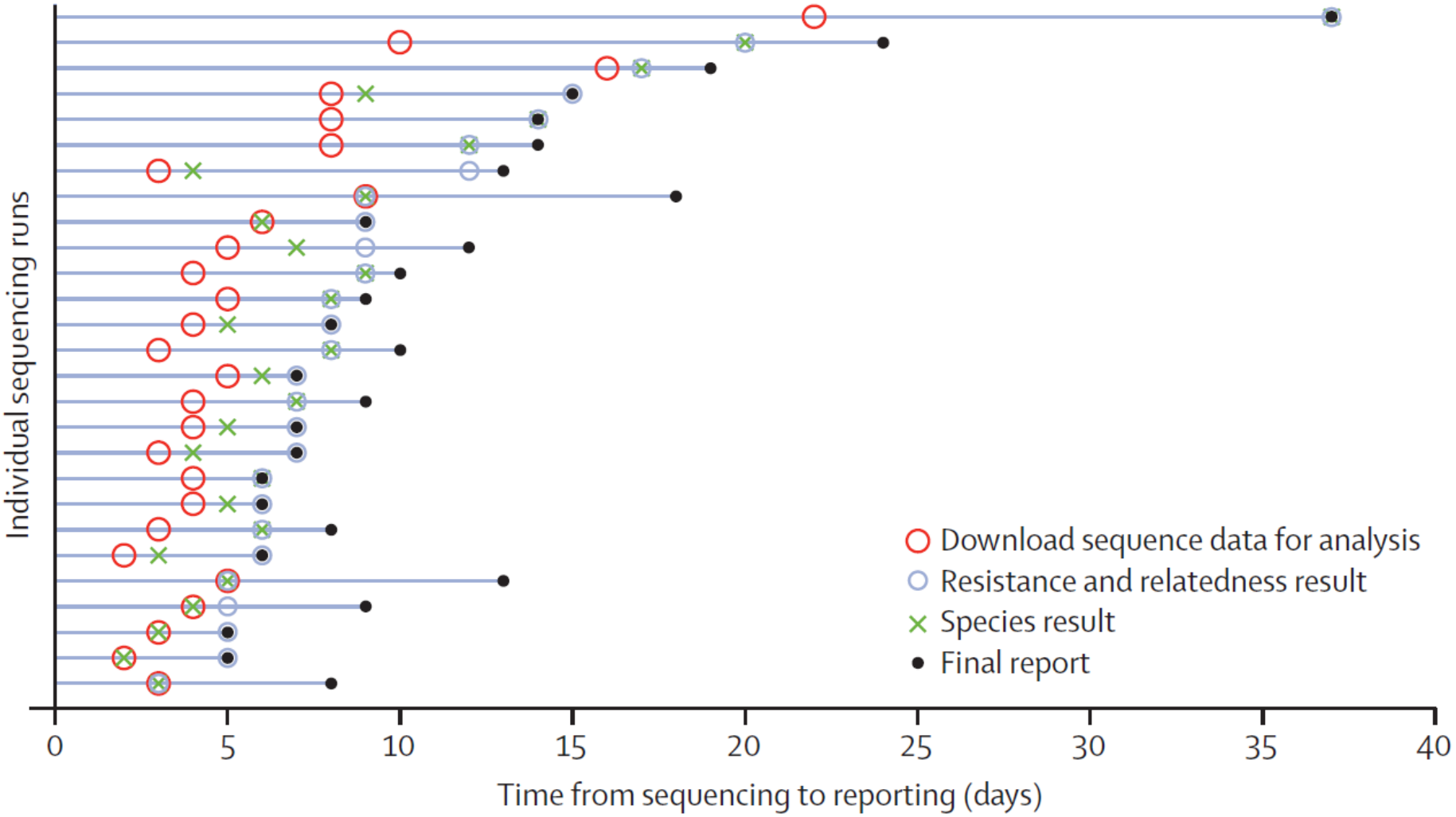
Summary

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



- **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