Waiting on the World to Change

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Disclaimer

- **The views expressed here are my own**.
- I am a consultant for Becton Dickinson, which involves a collaboration with Janssen and Thermo Fisher, the Foundation for Innovative New Diagnostics, the TB Alliance, and the WHO Global TB Programme.
- I am collaborating with PZA Innovation and am an unpaid advisor to GenoScreen.
- I worked as a consultant for QuantuMDx, the Stop TB Partnership, and the WHO Regional Office for Europe.
- I gave a paid educational talk for Oxford Immunotec.
- Hain Lifescience covered my travel and accommodation to present at a meeting.
- I was an unpaid advisor to BioVersys and Cepheid.

What will a mycobacterial lab look like in 10 years?

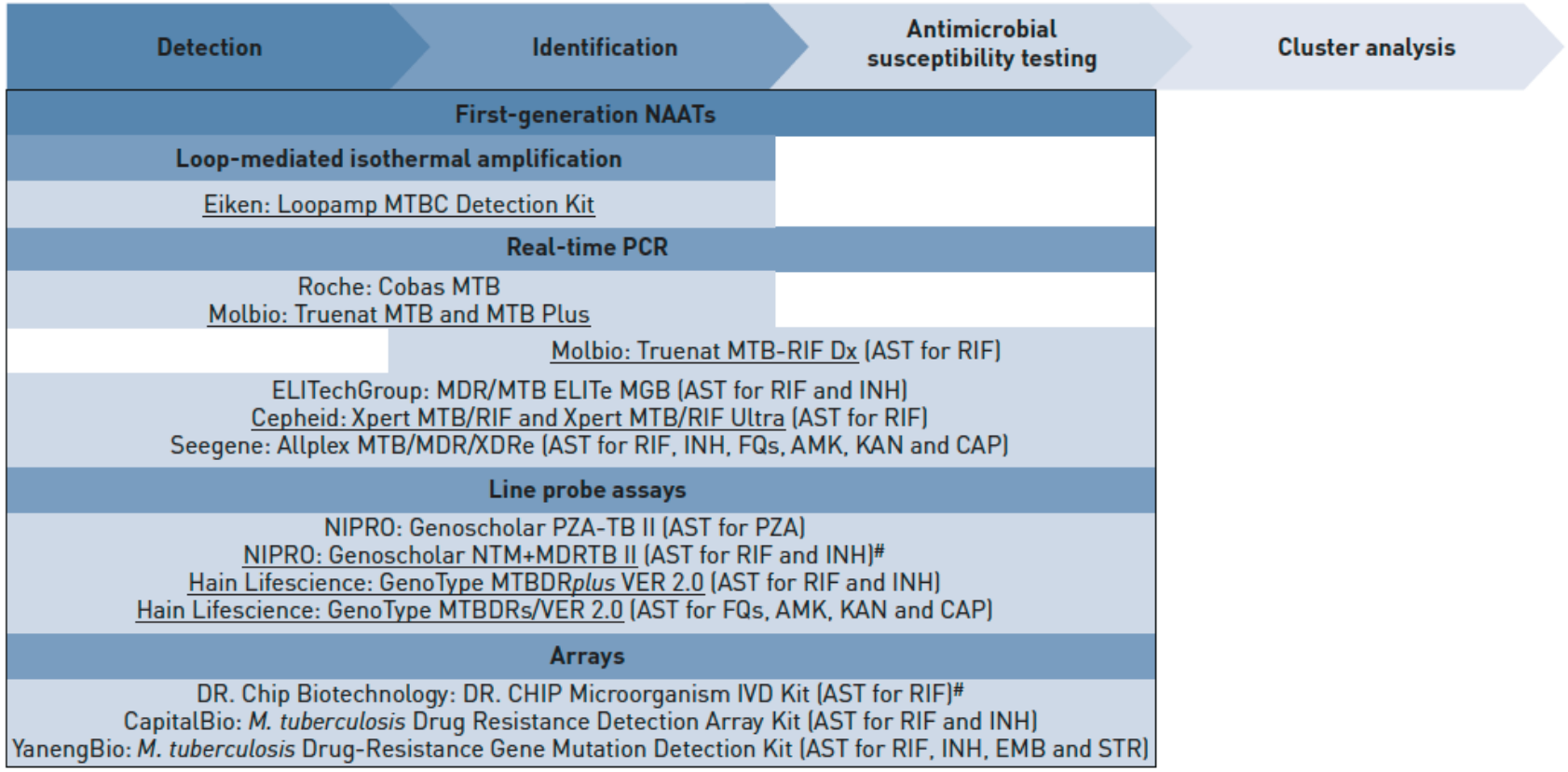
- Consequences of the dependencies on *de facto* monopoly providers:
  - Cost.
  - Supply disruptions.
  - Discontinuation of assays.
  - Information about known limitations of assays not collated and disseminated adequately.
- International collaborations:
  - Novel drugs and regimens.
  - Systematic reviews of different types of evidence.
- Novel diagnostic technologies.

Omar et al. Int J Tuberc Lung Dis. 2020 24:1307-11
Somoskovi & Bloemberg J Clin Microbiol. 2014 52:705
Ajileye et al. Antimicrob Agents Chemother. 2017 61:e02169-16

What will a mycobacterial lab look like in 10 years?

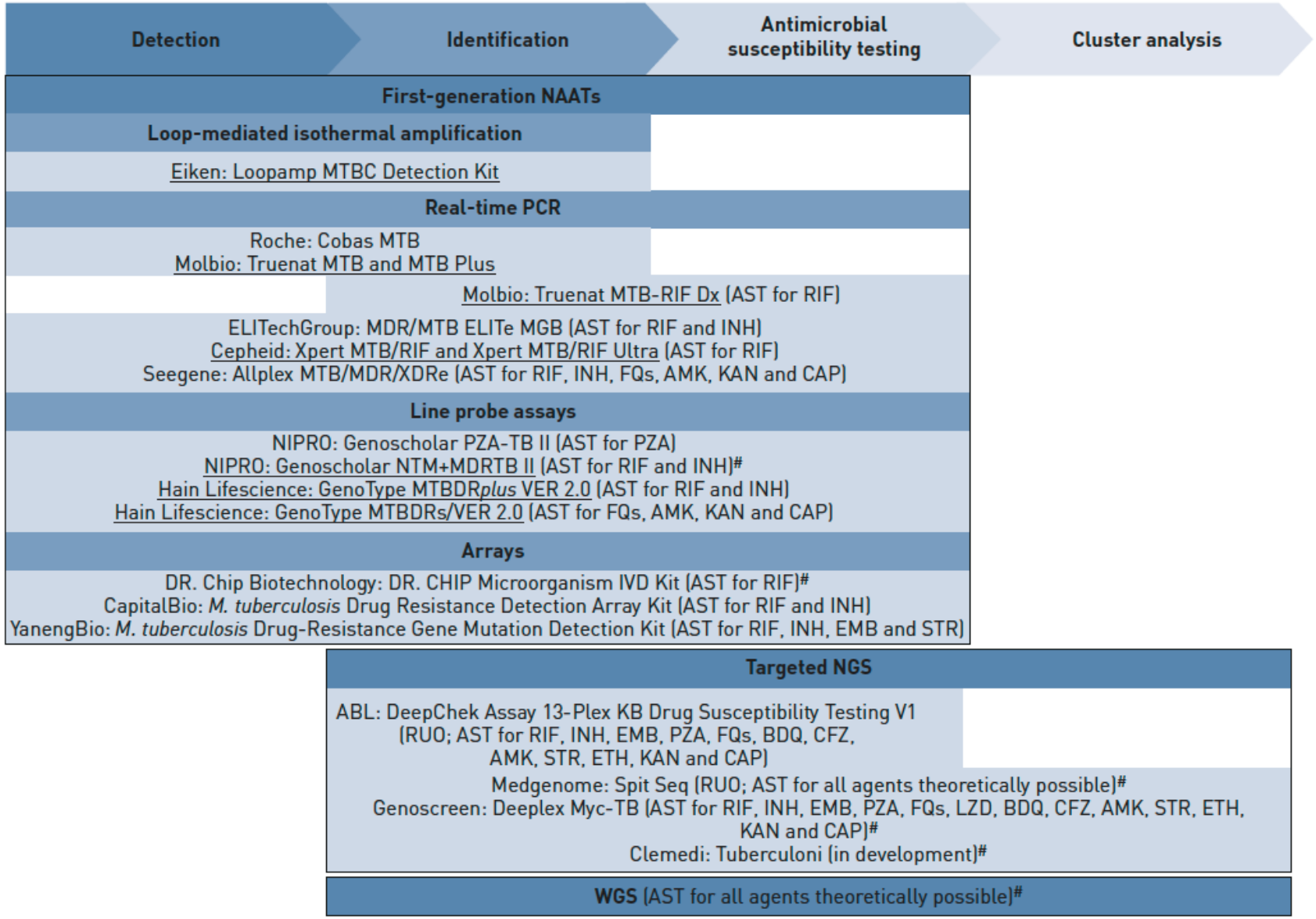
Mohamed et al. Eur Respir J. 2021 57:2004077

What will a mycobacterial lab look like in 10 years?



Mohamed et al. Eur Respir J. 2021 57:2004077

‘Should I Stay or Should I Go: Navigating the Landscape of tNGS for TB’



Mohamed et al. Eur Respir J. 2021 57:2004077

Antimicrobial susceptibility testing (AST)

- Genotypic AST (gAST) will not fully replace phenotypic AST (pAST).
- We cannot harness the full potential of gAST unless we modernise pAST:
  - AST needs to become more than an afterthought as it has fundamental implications for the intended use of regimens and long-term antibiotic sterwardship.
  - Adopt modern principles for setting breakpoints and abolish terminology specific to mycobacteria.
  - Provide clear guidance to mitigate random, cut-off and systematic errors, including discordances between gAST and pAST.
  - Scale up capacity for high-quality MIC testing.
  - Representative resistant control strains (panels for FQs, BDQ/CFZ, LZD, DLM/PMD and DCS will become available from BCCM/ITM and, likely, ATCC).

Köser et al. Int J Tuberc Lung Dis. 2021 Oct 1;25(10):791-4
Antimycobacterial Susceptibility Testing Group. Eur Respir J. 2022 59:2200166

J Antimicrob Chemother 2018; **73**: 564–568
doi:10.1093/jac/dkx427 Advance Access publication 5 December 2017

Journal of Antimicrobial Chemotherapy

MIC-based dose adjustment: facts and fables

Johan W. Mouton[1]*, Anouk E. Muller[1,2], Rafael Canton[3], Christian G. Giske[4], Gunnar Kahlmeter[5] and John Turnidge[6]

J Antimicrob Chemother 2018; **73**: 2374–2379
doi:10.1093/jac/dky232 Advance Access publication 21 June 2018

Journal of Antimicrobial Chemotherapy

Variation of MIC measurements: the contribution of strain and laboratory variability to measurement precision

Johan W. Mouton[1]*, Joseph Meletiadis[1,2], Andreas Voss[3,4] and John Turnidge[5]

J Antimicrob Chemother 2016; **71**: 141–151
doi:10.1093/jac/dkv309 Advance Access publication 12 October 2015

Journal of Antimicrobial Chemotherapy

Relative contribution of biological variation and technical variables to zone diameter variations of disc diffusion susceptibility testing

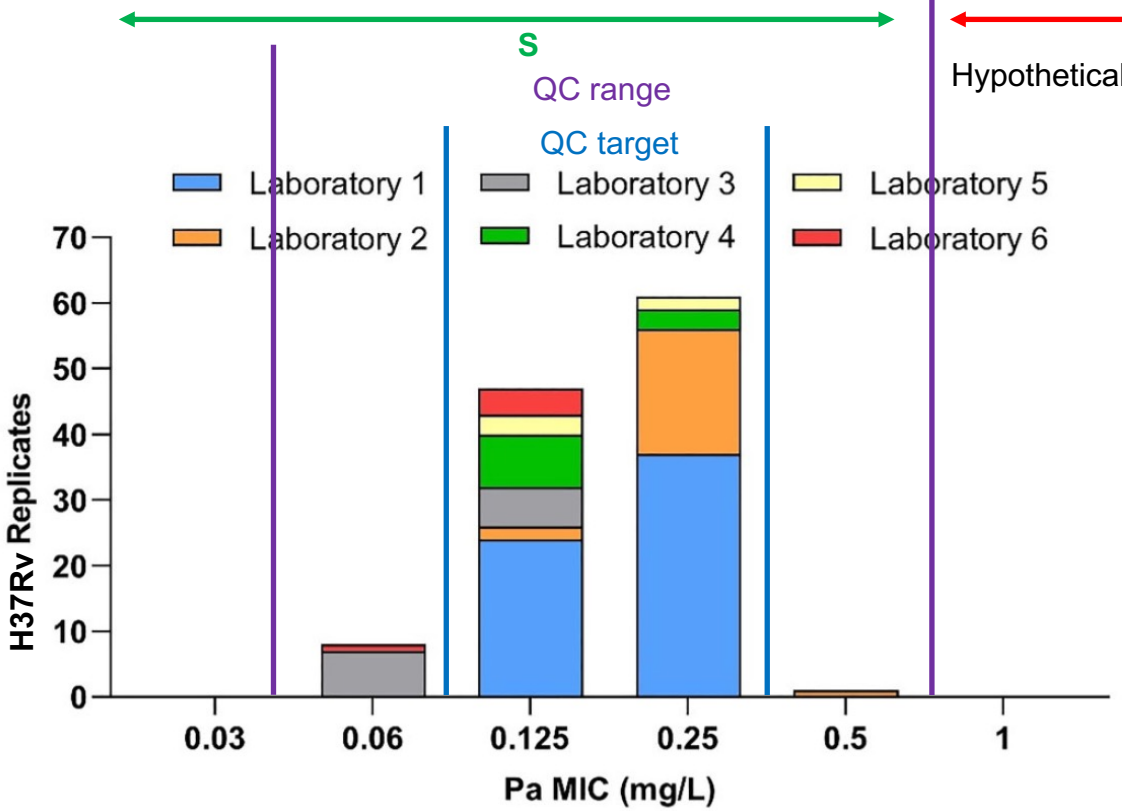
Michael Hombach[1]*, Carlos Ochoa[2], Florian P. Maurer[1], Tamara Pfiffner[1], Erik C. Böttger[1] and Reinhard Furrer[2]

Numerous factors influence MIC (i.e. there is no ‘true’ MIC)

- Composition of medium (e.g. pH for pyrazinamide or alanine for cycloserine).
- Use of CO_2.
- Incubation temperature.
- Incubation period.
- Inoculum.
- How end point is defined (1% growth control important as we usually set up pAST from a mixed culture, as opposed to 1-3 single colonies).

MIC testing is the best way to monitor the quality of pAST

- Even though there is no ‘true’ MIC, testing still has to be standardised once a protocol has been defined to minimise the technical variability.
- This is achieved by choosing a quality control (QC) strain that serves as a standard for all subsequent testing in clinical trials and routine pAST.
- The intra- and inter-laboratory reproducibilities of testing are measured to define the QC range, which should be between 3-5 doubling dilutions wide (i.e. larger than most PK/PD measurements) and optimally encompass ≥95% of the QC distribution, as well as a QC target, which corresponds to the mode of the distribution (unlike EUCAST, CLSI only sets QC ranges).

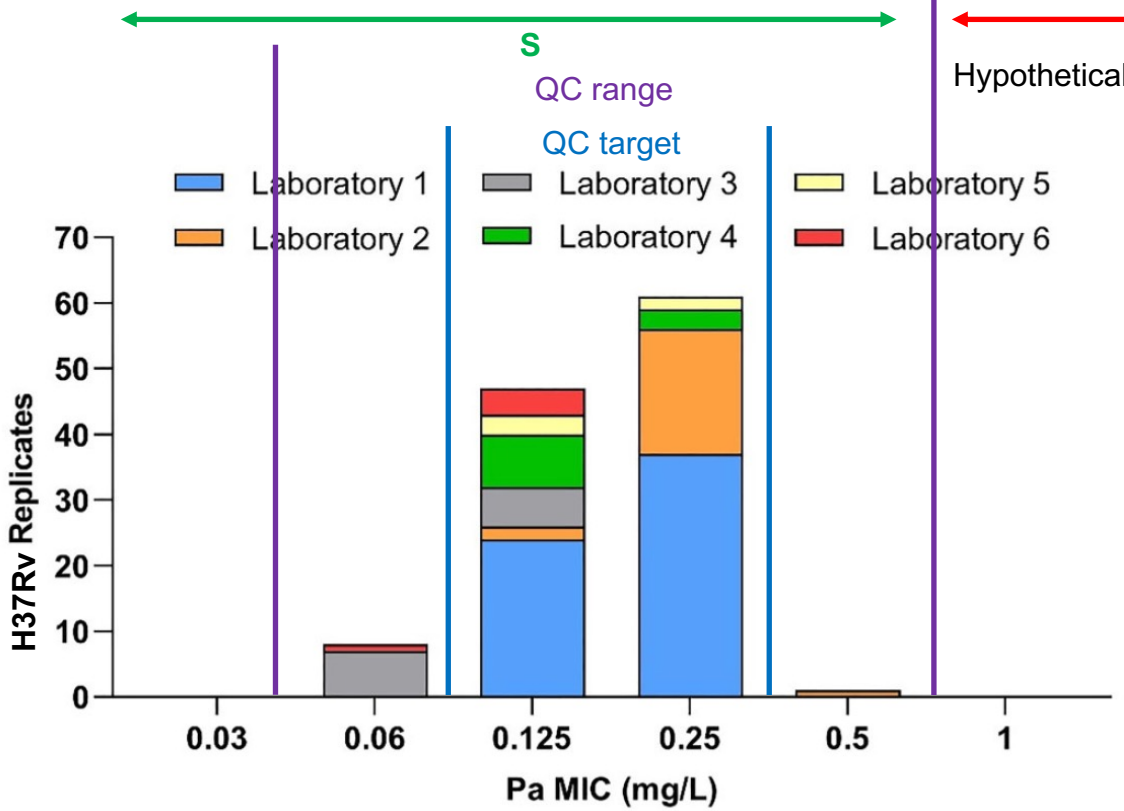


MGIT breakpoint for illustrative purposes only

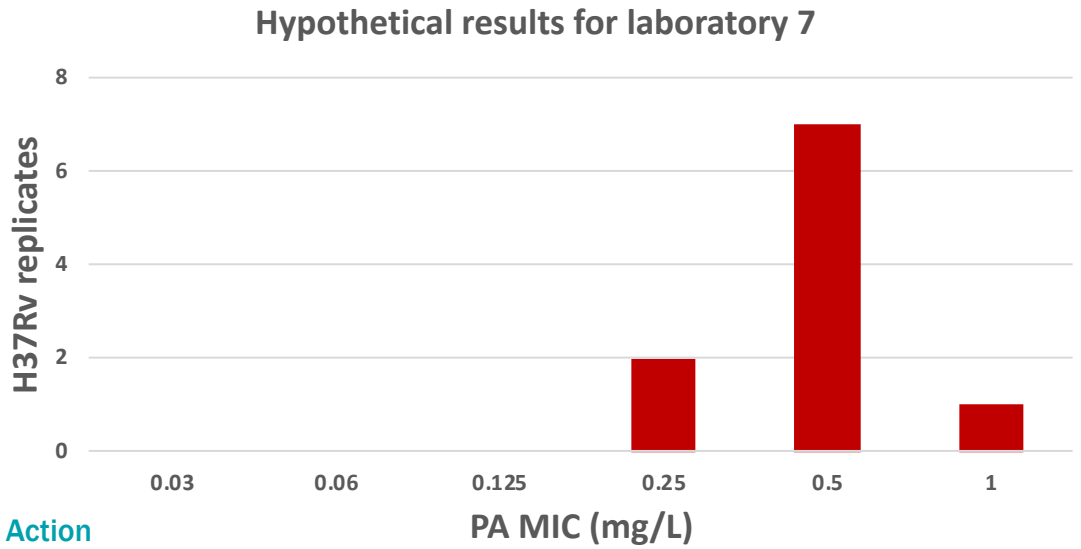
Think MIC distributions, not MICs!

Lowering the dose for supposedly ‘low MICs’ below the breakpoint is problematic!

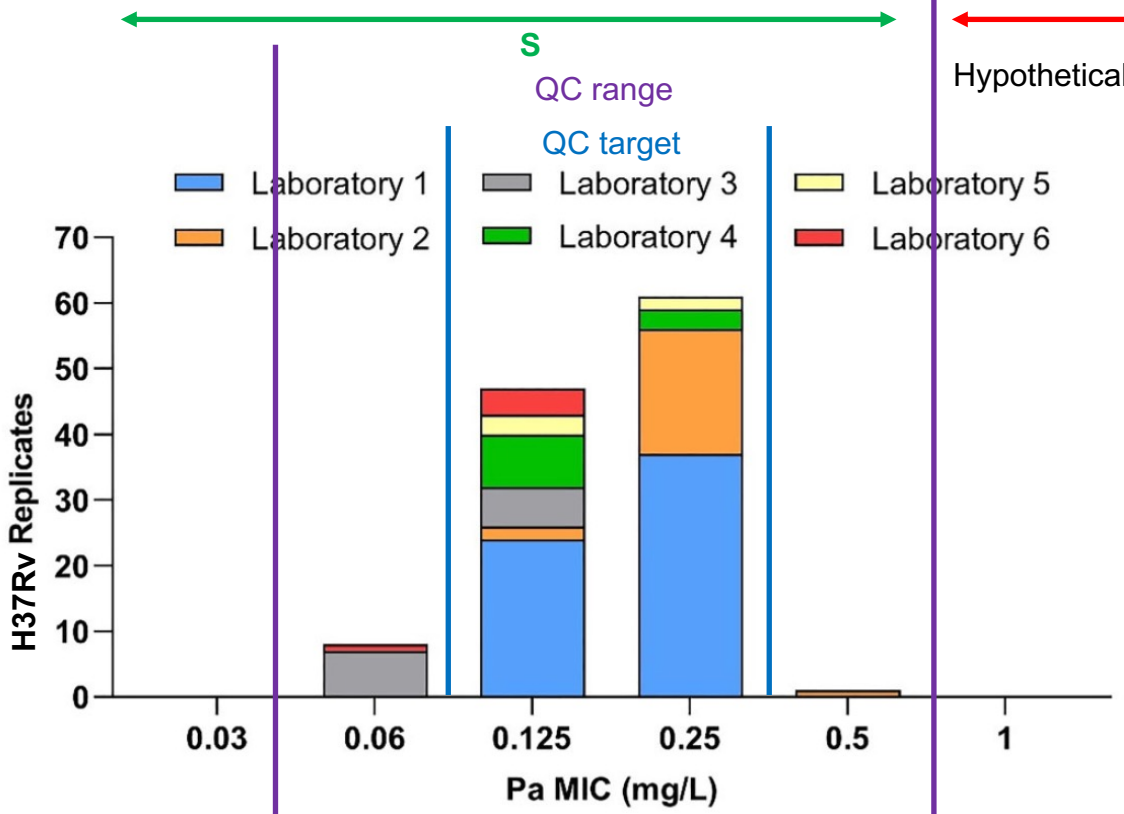
Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693



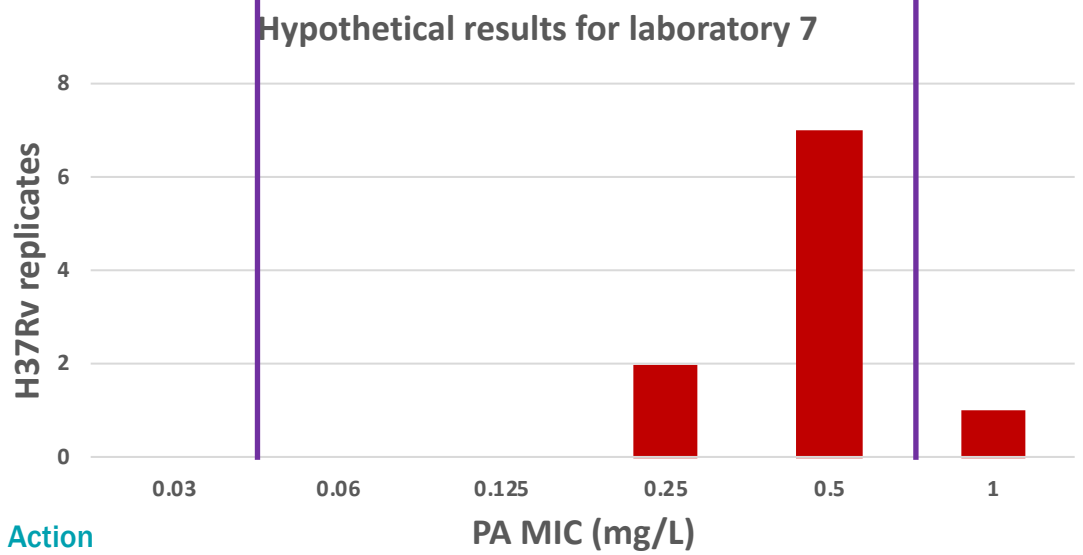
MGIT breakpoint for illustrative purposes only



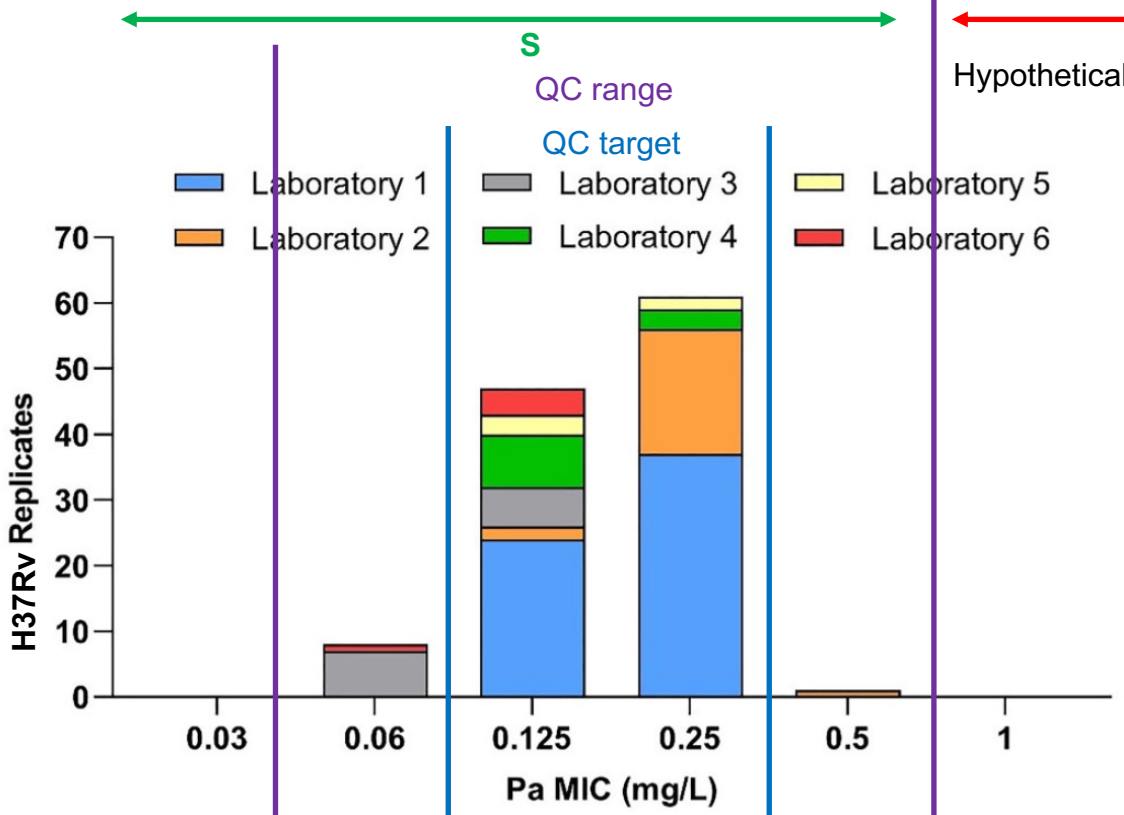
Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693



MGIT breakpoint for illustrative purposes only



Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693



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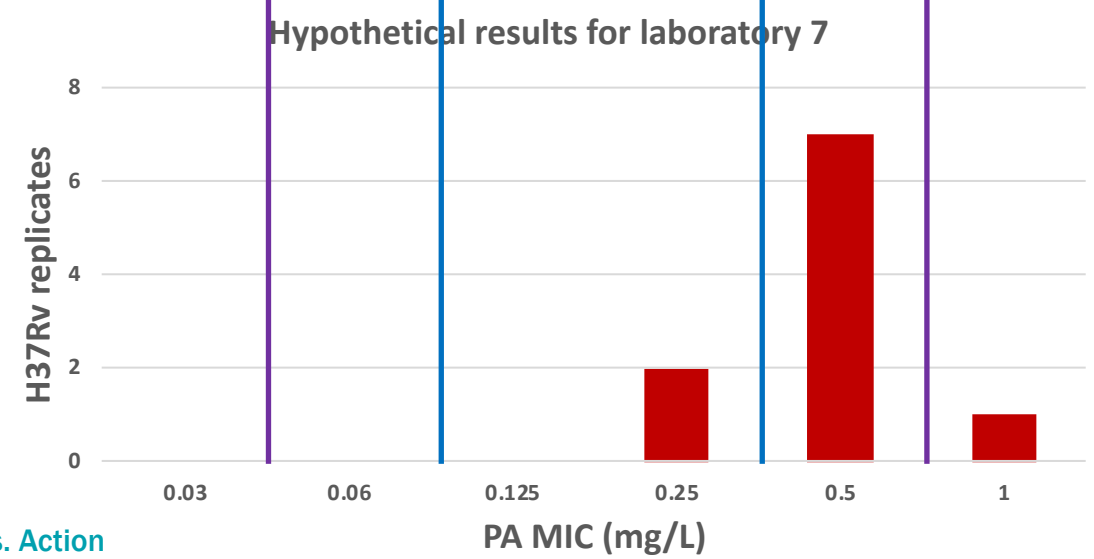
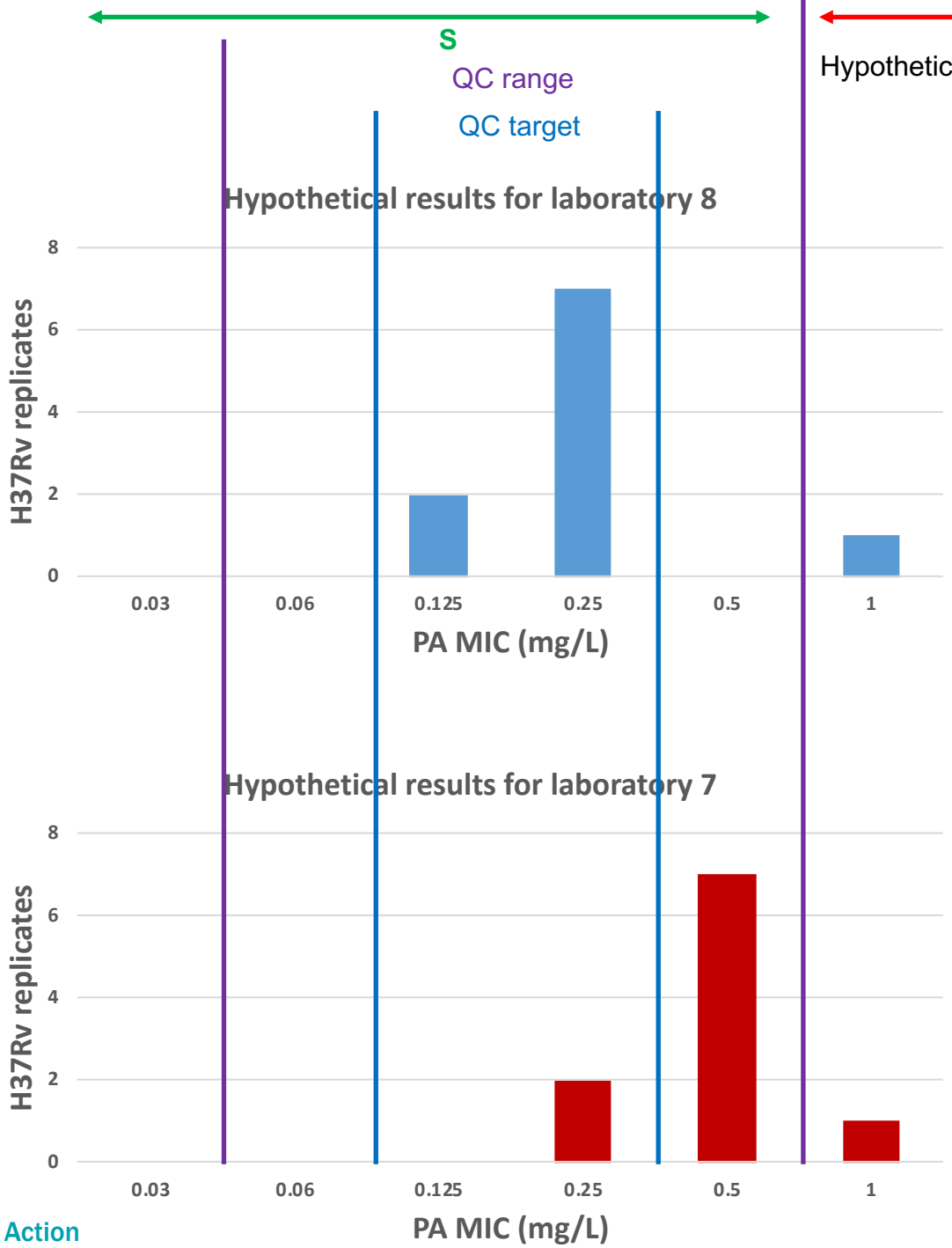


Systematic error

Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693



Random error
(or start of a systematic problem)

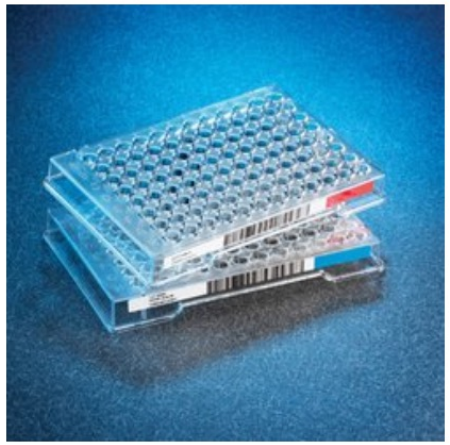
Systematic error

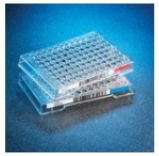
Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693

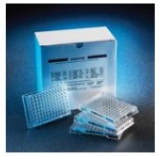
Limitations of MYCOTB(I) plate

Thermo Scientific™

Sensititre™ Mycobacterium tuberculosis MYCOTB AST Plate







Related applications: Clinical Microbiology

Obtain the minimum inhibitory concentration (MIC) results to first- and second-line anti-tuberculosis drugs for Mycobacterium tuberculosis isolates with Thermo Scientific™ Sensititre™ Mycobacterium tuberculosis MYCOTB AST Plate.

The convenient plate includes 12 antimicrobials on a single AST plate for cost-effective results and is intended for research use only. Easy set-up procedures and incubation requirements provide MIC results in 7 to 21 days, and inclusive on-scale QC ranges provide immediate quality assurance of testing methodology

Contact us for support ›

	Catalog number	Product Size	Description	Quantity	Price (GBP)
☆	MYCOTBI	-	Sensititre Mycobacterium tuberculosis MIC Plate	10/Pk.	Request A Quote

Full specifications ▶

Schön et al. Clin Microbiol Infect. 2019 25:403-405

https://www.thermofisher.com/order/catalog/product/MYCOTBI?SID=srch-hj-MYCOTBI, accessed 11 Feb 2023

Limitations of MYCOTB(I) plate

Table 1:

Tentative Quality Control Ranges[1] for *M.tuberculosis* QC strains

Drug	*M.tuberculosis* ATCC 27294
Amikacin	0.25-2
Cycloserine	4.0-16.0
Ethionamide	0.6 - 5
Ethambutol	≤2
Isoniazid	≤0.5
Kanamycin	0.6-5
Moxifloxacin	≤ 0.5
Ofloxacin	0.5 - 2
PAS	≤0.5
Rifampin	≤0.5
Rifabutin (Ansamycin)	≤ 0.12
Streptomycin	0.5-2

Note: [1] Ranges based on in-house testing

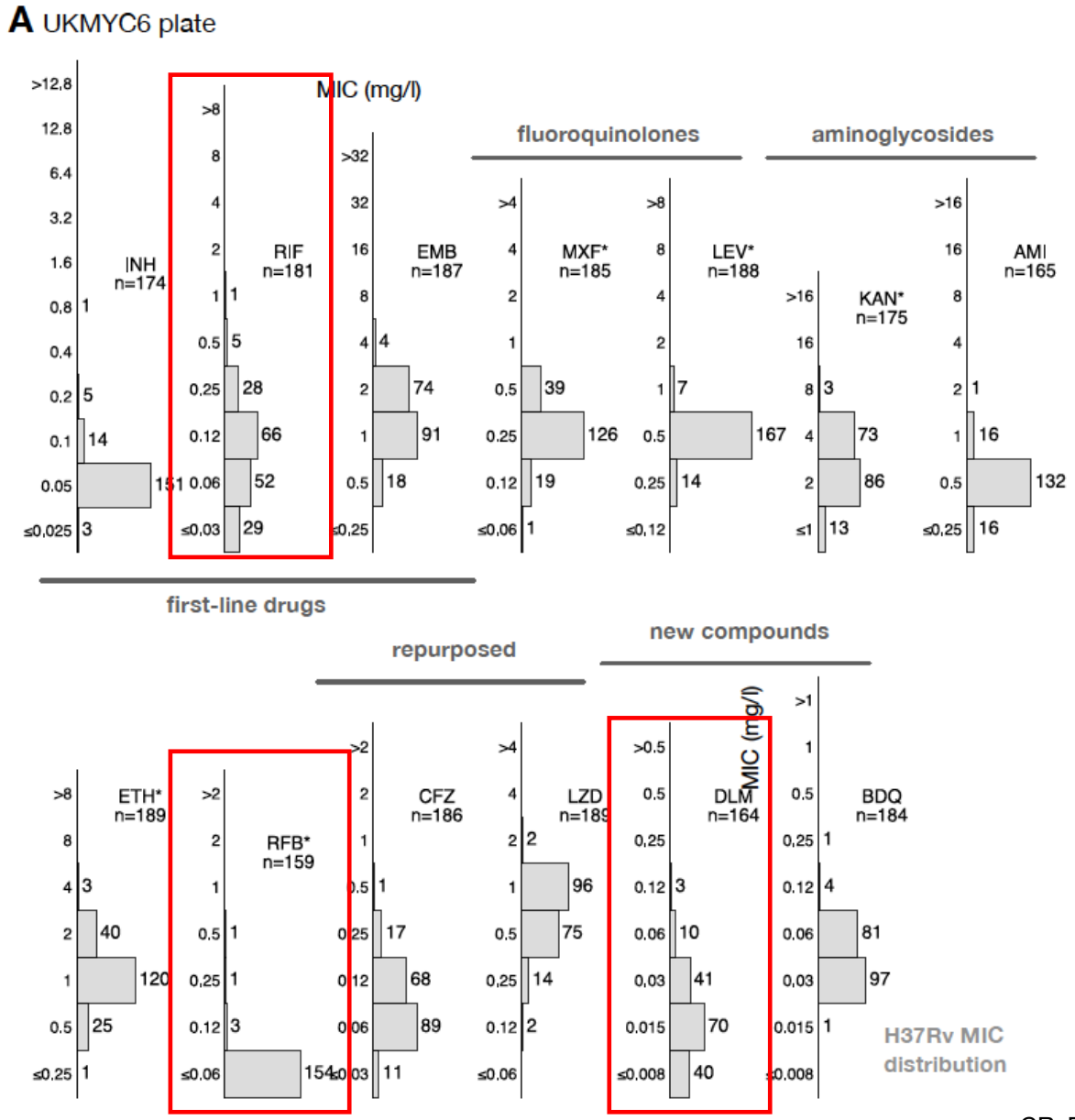
Contact Thermo Fisher Scientific Microbiology Technical Services for assistance in the event that quality control discrepancies cannot be resolved. . See final page for contact information

Plates are quality controlled to ensure that the correct activity of drug is present. Performance of the procedure has not been established at this point.

Schön et al. Clin Microbiol Infect. 2019 25:403-405

Instructions for Use Thermo Scientific™ Sensititre™ MIC Susceptibility Plates for Mycobacterium tuberculosis. 034-MYCOTB CID9556 Revision Date: November 9th, 2016.

Limitations of CRyPTIC study



Köser & Maurer. Eur Respir J. 2023 61:2202397
CRyPTIC Consortium. Eur Respir J. 2022 60:2200239

Epidemiological cut-off value (ECOFF or ECV) vs. clinical breakpoint (CB)

- **ECOFF**: Also known as microbiological breakpoint. It corresponds to the highest concentration/upper end of pWT MIC distribution (i.e. Gaussian distribution with organisms devoid of phenotypically detectable resistance).
- **CB**: MIC value that distinguishes organisms of the same species (or closely related species) that are likely to succeed therapy from those that are likely to fail (i.e. S/I/R system). CBs can differ between regulatory bodies.

S - Susceptible, standard dosing regimen: A microorganism is categorised as *Susceptible, standard dosing regimen,* when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
I – Susceptible, increased exposure: A microorganism is categorised as *Susceptible, Increased exposure** when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
R - Resistant: A microorganism is categorised as *Resistant* when there is a high likelihood of therapeutic failure even when there is increased exposure.
*Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

Kahlmeter. J Antimicrob Chemother. 2015 70:2427-39

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2018/Breakpoint_changes_with_introducing_new_definitions_of_SIR_4OCT2018_v2.pdf, accessed 7 Oct 2018

EUCAST 'I' differs from CLSI 'I'

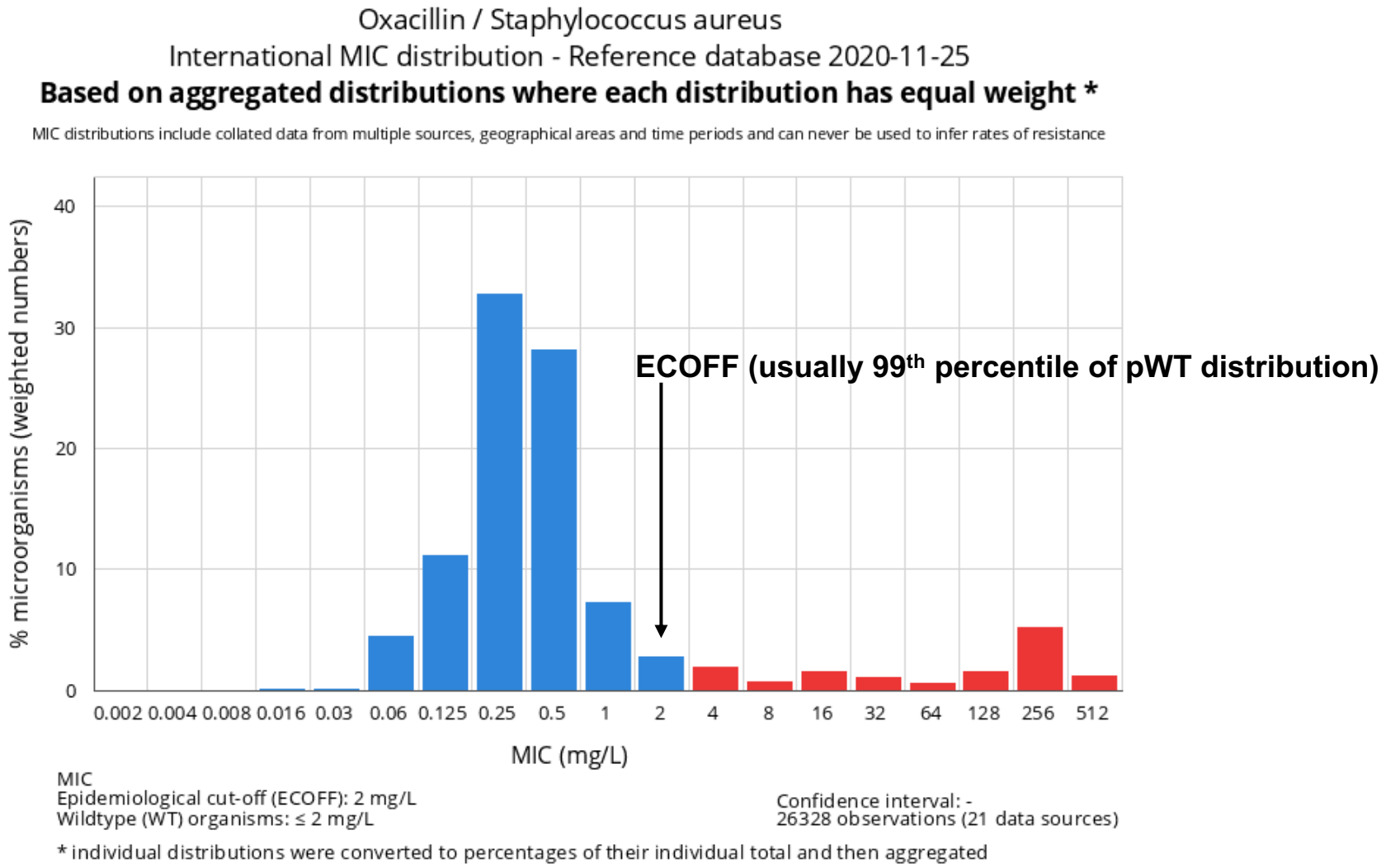
TABLE 2 Current interpretive categories, abbreviations, and definitions used in the CLSI M100 document

Interpretive category	Category abbreviation	Definition
Susceptible	S	A category defined by a breakpoint that implies that isolates for which the MIC is at or below the susceptible breakpoint or whose zone diameters are above those associated with the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.
Intermediate	I	A category defined by a breakpoint that includes isolates for which MICs or zone diameters are within the intermediate range; the drug approaches usually-attainable blood and tissue levels, and response rates may be lower than for susceptible isolates. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated. An I with a "^" in document M100 Table 2 is used to describe agents that have the potential to concentrate at an anatomical site. The I category also includes a buffer zone for inherent variability in test methods, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.
Susceptible, dose dependent	SDD	A category defined by a breakpoint that implies that the susceptibility of an isolate depends on the dosing regimen that is used in the patient. To achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosing regimen (i.e., higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum, literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of an SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function. The SDD category may be assigned when doses well above those used to calculate the susceptible breakpoint are supported by the literature, widely used clinically, and/or approved and for which sufficient data to justify the designation exist and have been reviewed. This category also includes a buffer zone for inherent variability in test methods, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.
Resistant	R	A category defined by a breakpoint that implies that isolates for which the MIC is at or above the resistant breakpoint or whose zone diameters are at or below those associated with the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that the MICs or zone diameters for the isolate fall in the range in which specific microbial resistance mechanisms are likely; also, the clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.
Nonsusceptible	NS	A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above the susceptible breakpoint or whose zone diameters are below those associated with the susceptible breakpoint should be reported as nonsusceptible. An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates for which MICs are above the susceptible breakpoint and that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time that the susceptible-only breakpoint was set. The term "nonsusceptible" should not be used when describing an organism/drug category with intermediate and resistant interpretive categories. Isolates that are in the categories of "intermediate" or "resistant" may be called "not susceptible" rather than "nonsusceptible."

Kahlmeter et al. J Clin Microbiol. 2019 57:e01129-19

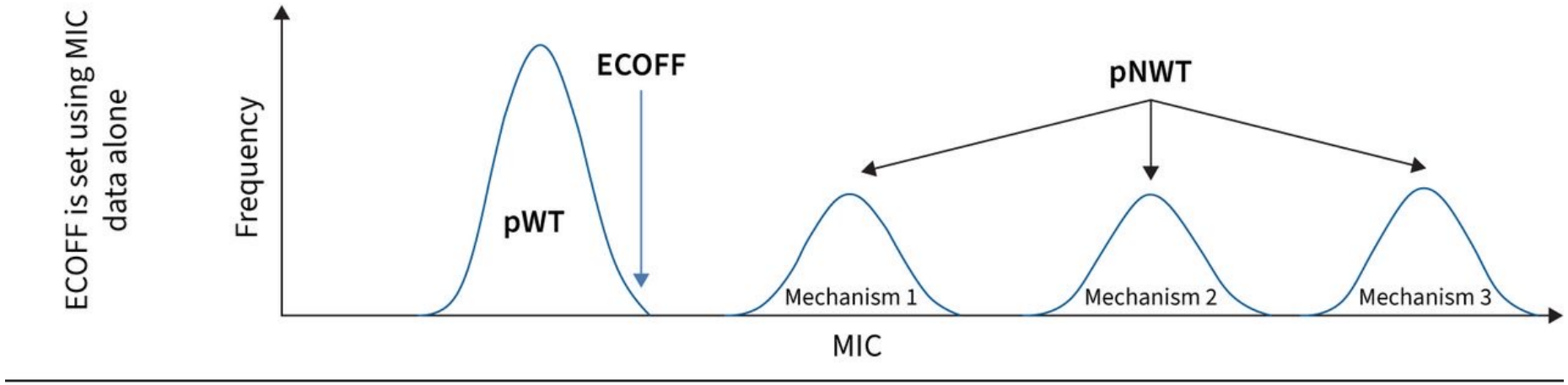
Kahlmeter et al. Clin Microbiol Infect 2020 26:1692-3

Epidemiological cut-off value (ECOFF or ECV)



https://mic.eucast.org/search/, accessed 25 Nov 2020

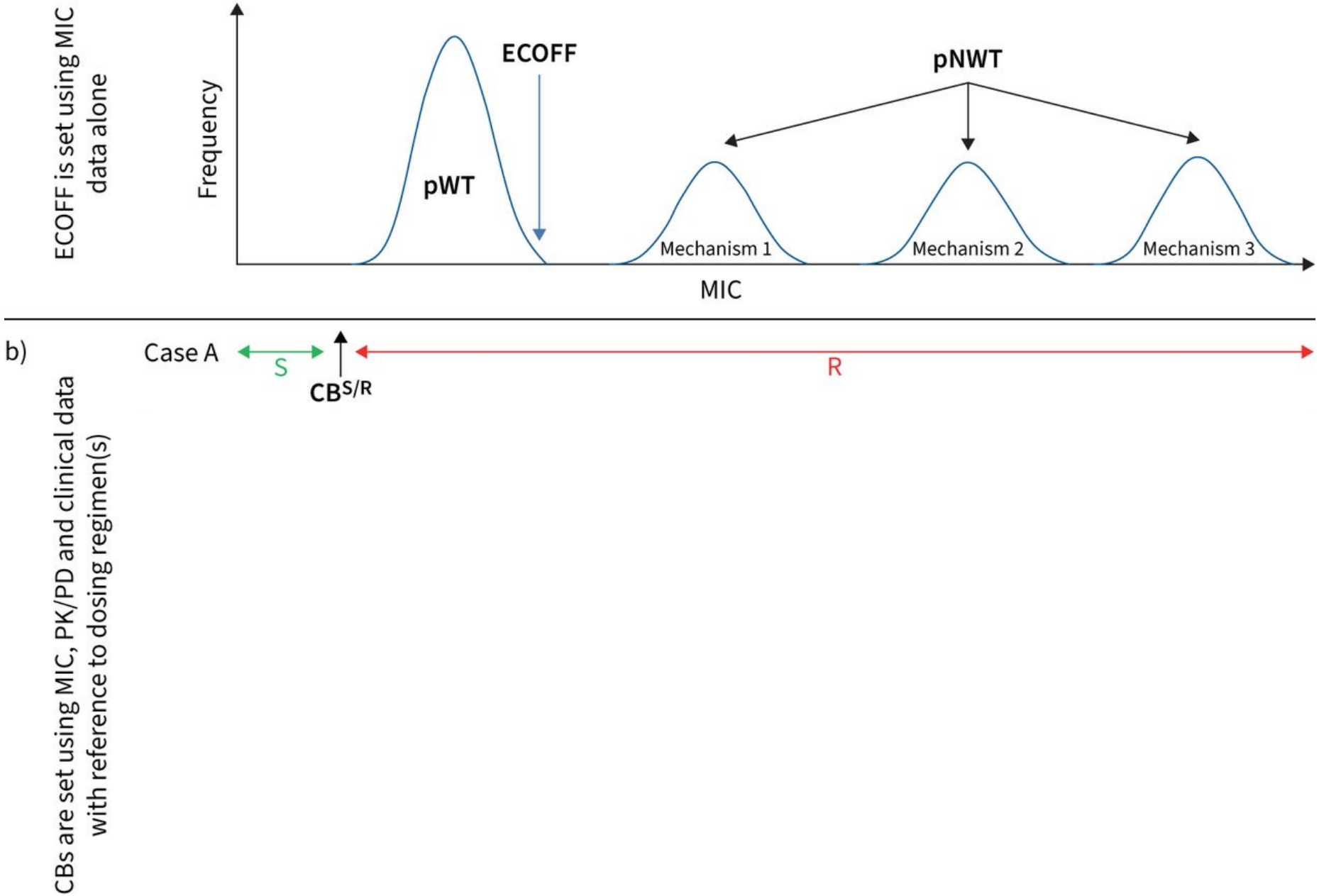
Kahlmeter. J Antimicrob Chemother. 2015 70:2427-39



b)

CBs are set using MIC, PK/PD and clinical data with reference to dosing regimen(s)

Antimycobacterial Susceptibility Testing Group. Eur Respir J. 2022 59:2200166



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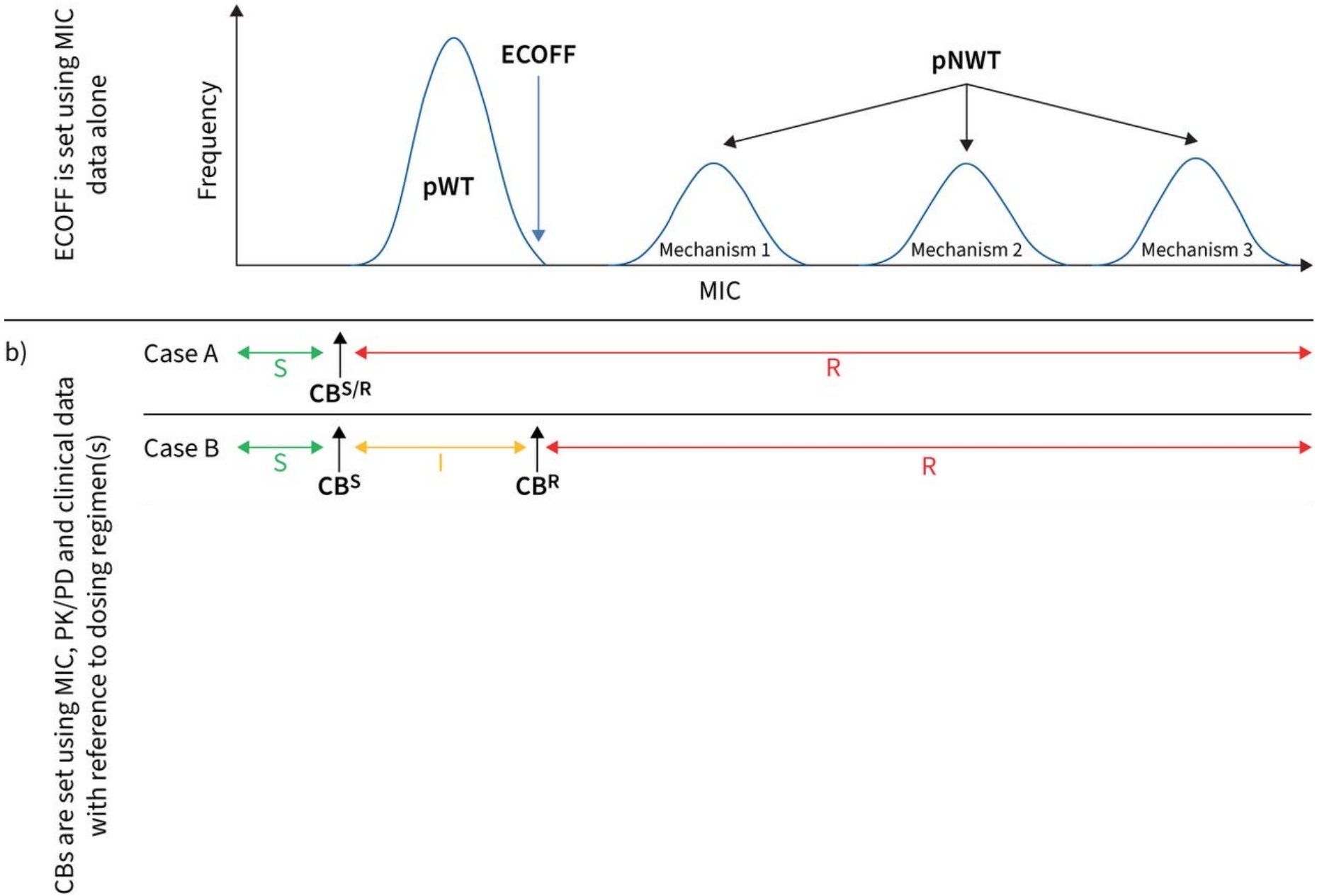

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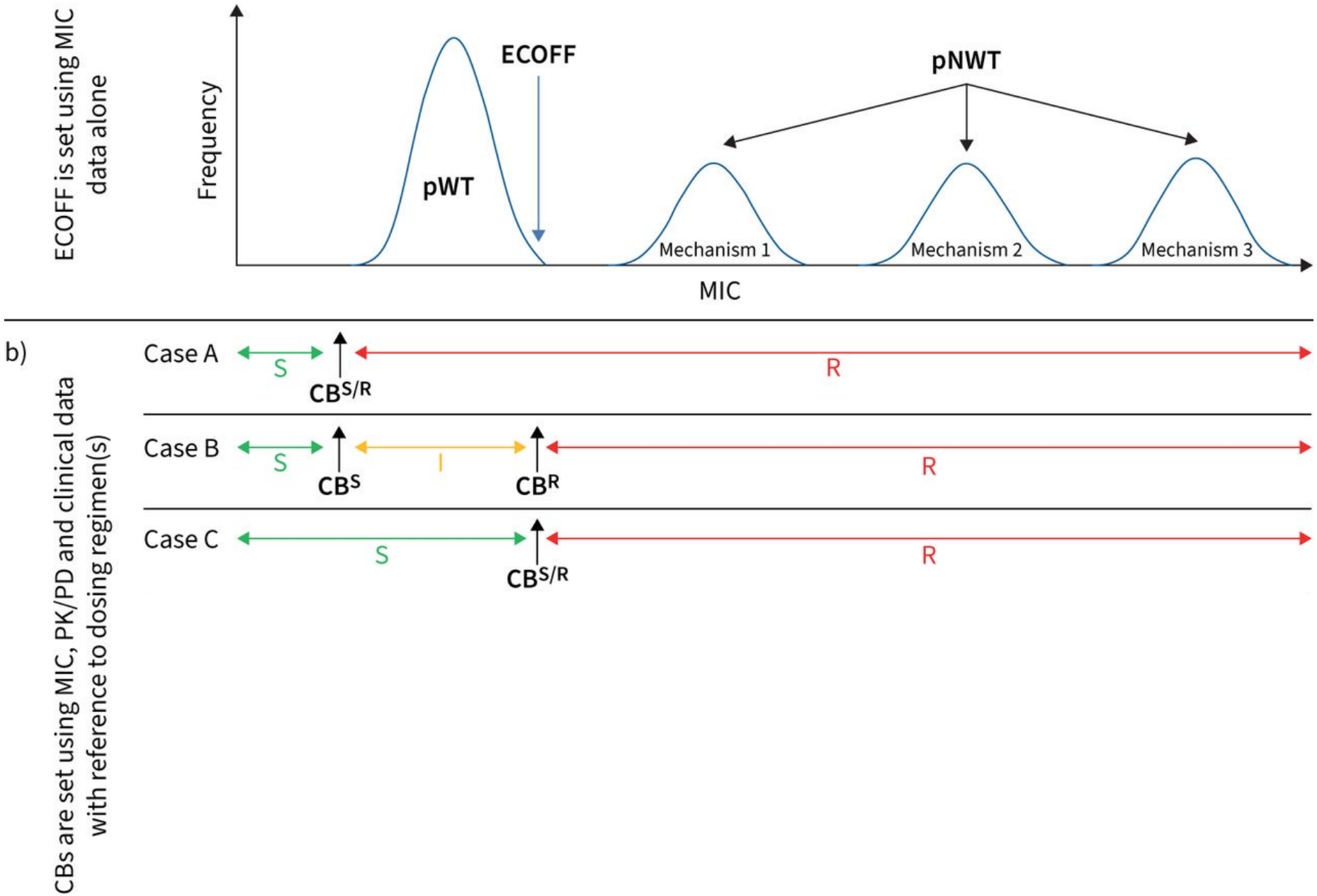

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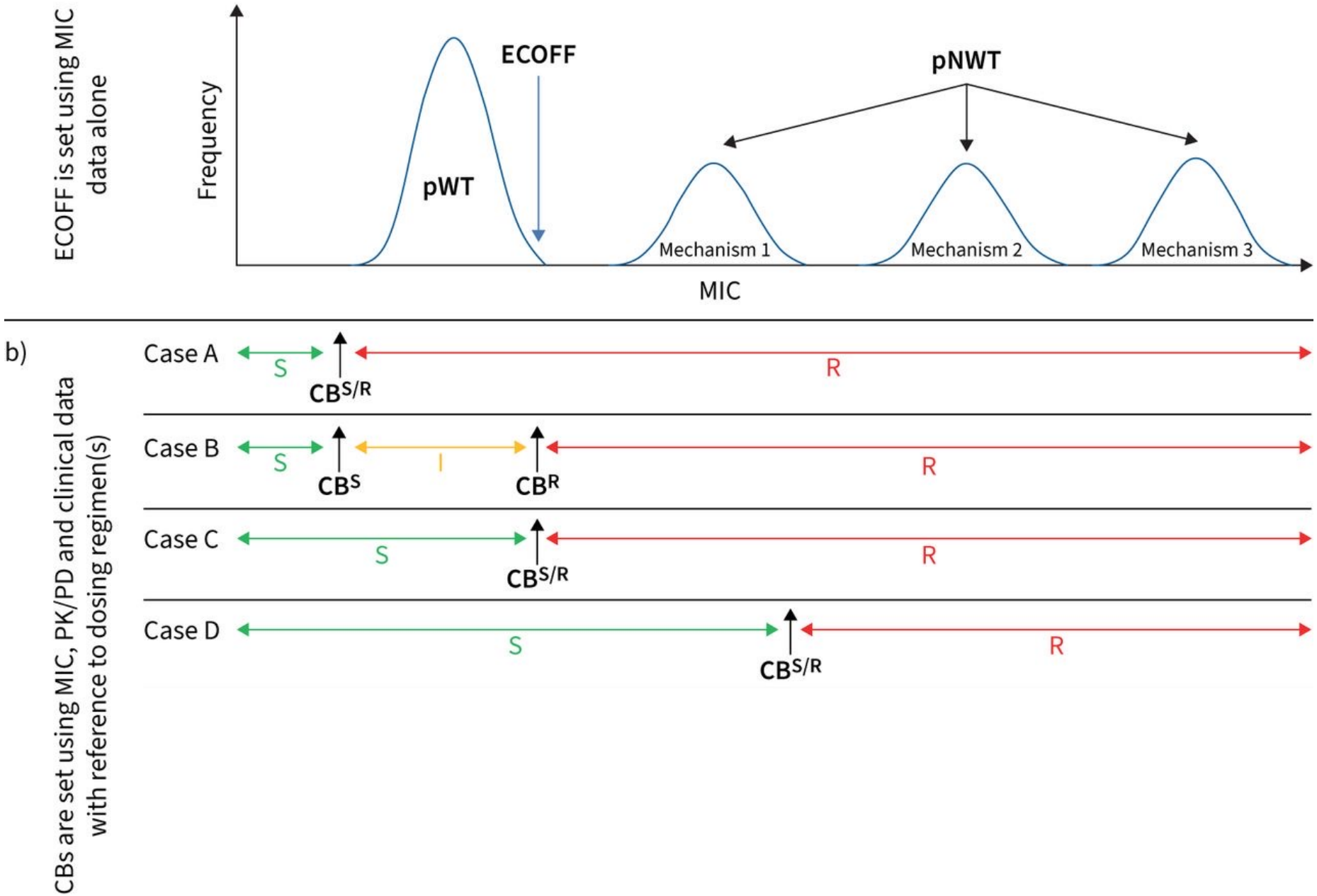
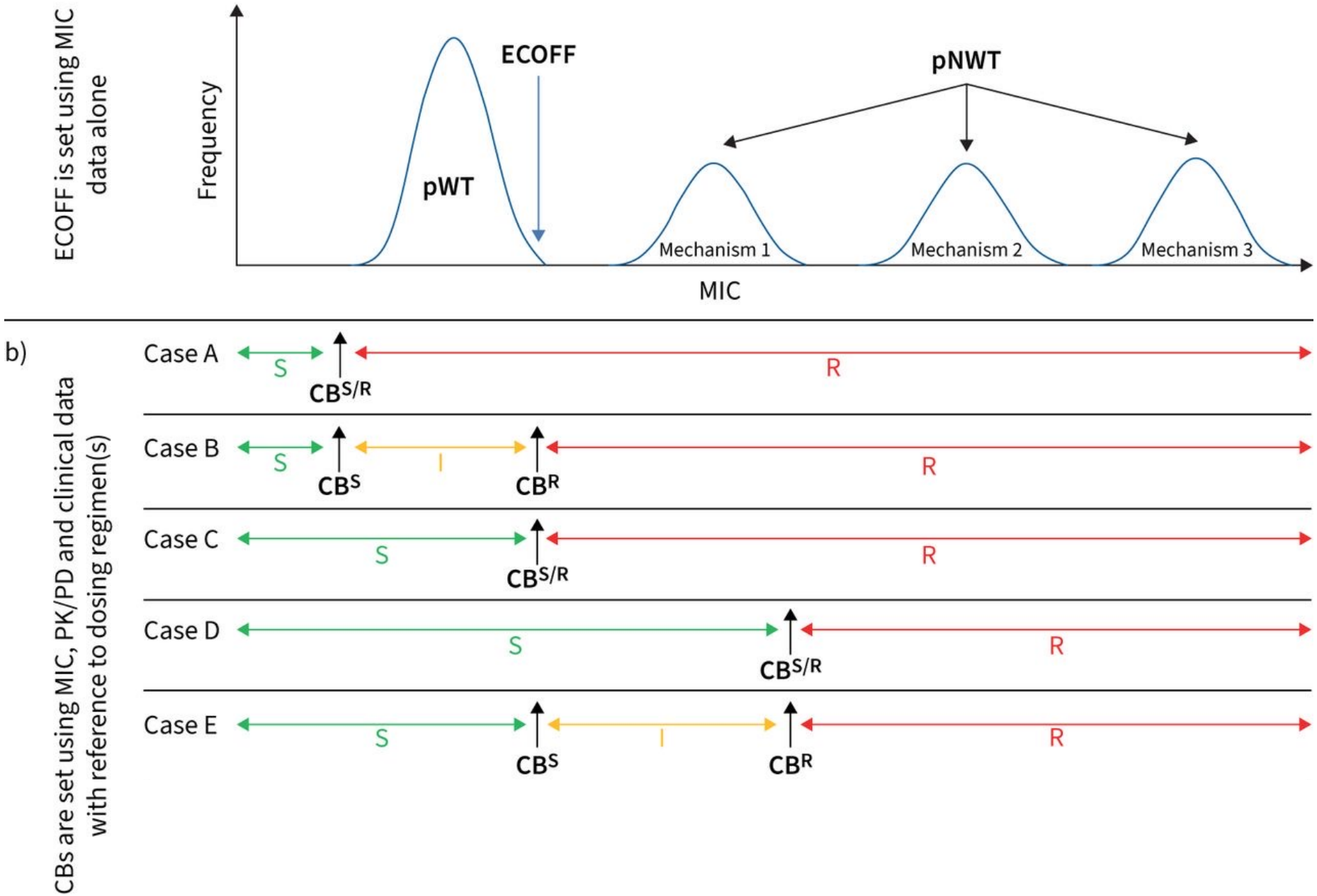


Antimycobacterial Susceptibility Testing Group. Eur Respir J. 2022 59:2200166



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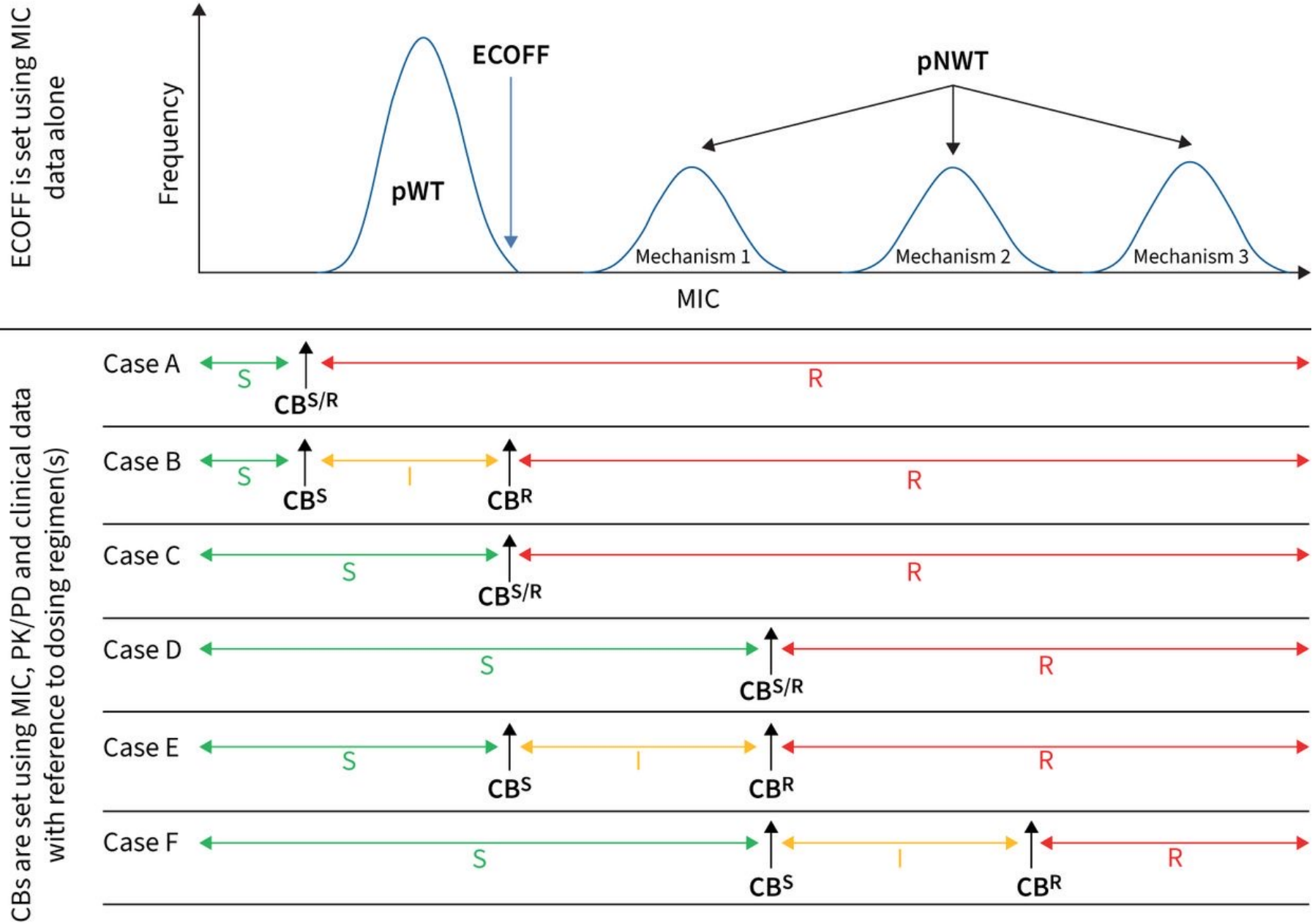
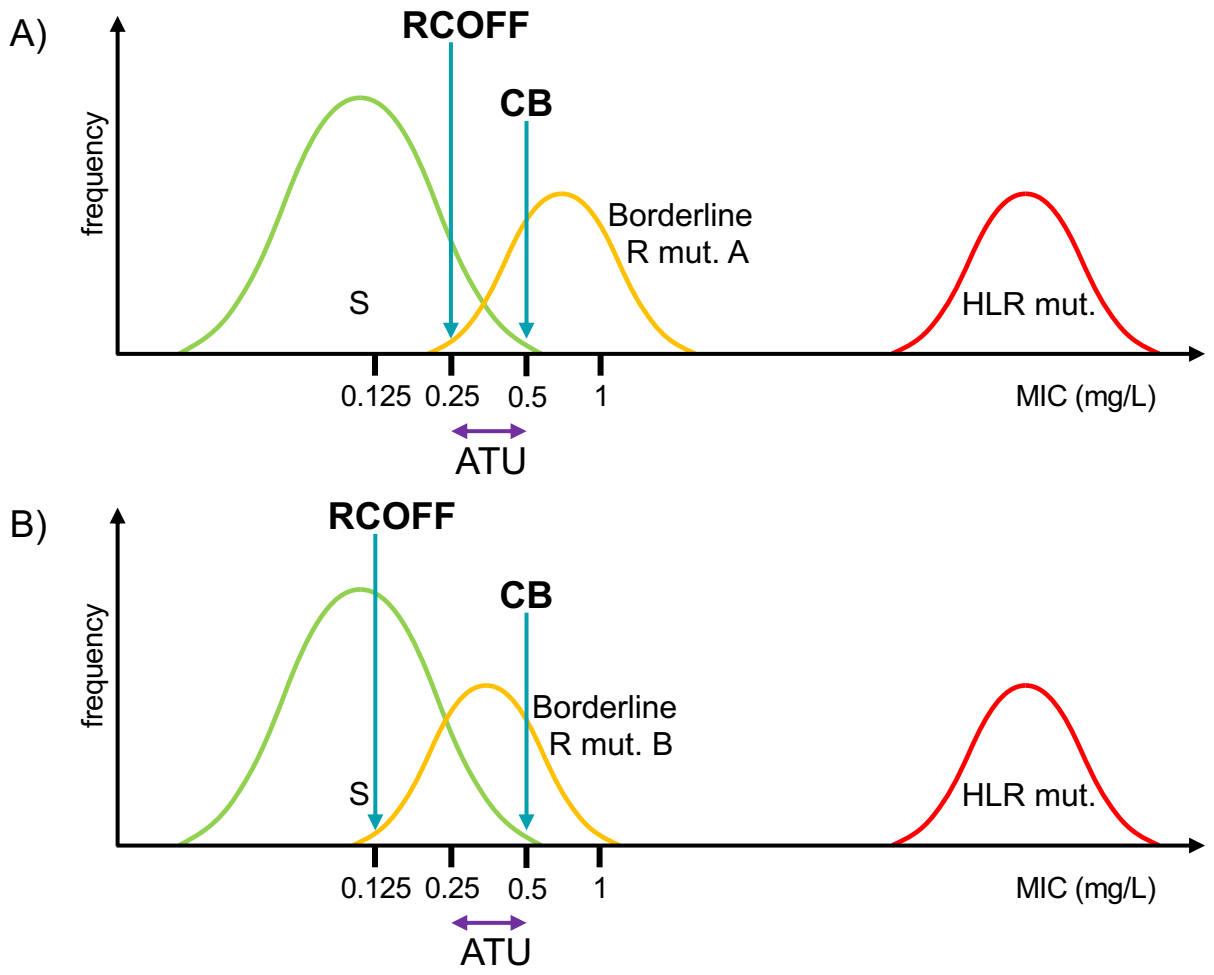


Antimycobacterial Susceptibility Testing Group. Eur Respir J. 2022 59:2200166

Area of technical uncertainty (ATU) to minimise effect of cut-off errors



Köser et al. J Clin Microbiol. 2021 59:e02328-20
Antimycobacterial Susceptibility Testing Group. Eur Respir J. 2022 59:2200166

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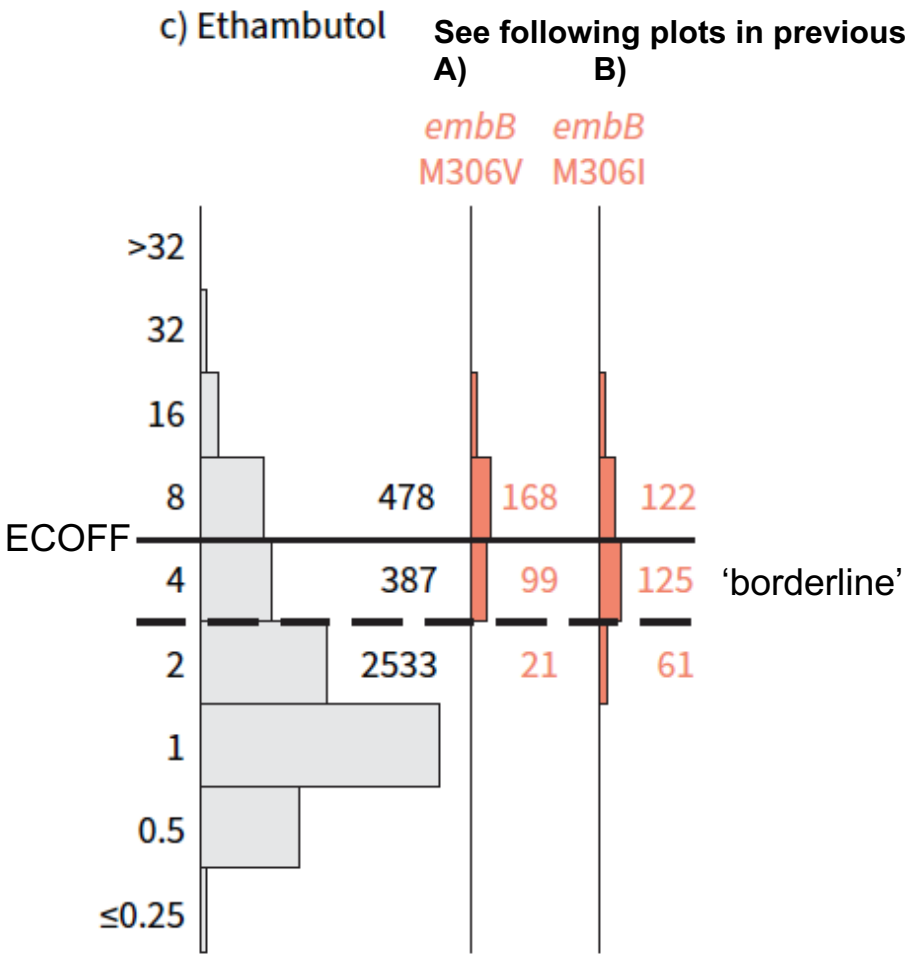
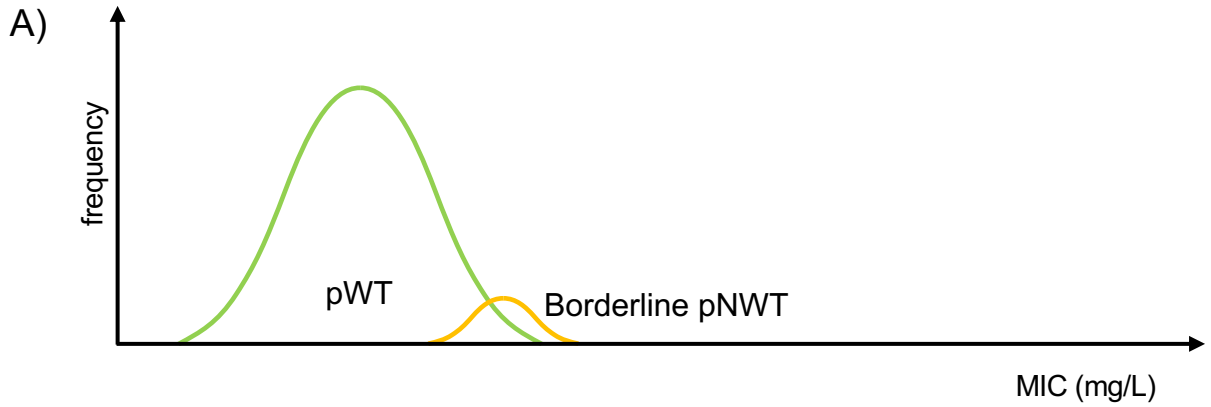


Antimicrobial Agent	MIC Breakpoints, µg/mL			Comments
	S	Inconclusive[3]	R	
Ethambutol	≤ 2	4	≥ 8	(5) Inconclusive MIC for ethambutol. An MIC of 4 µg/mL obtained by broth microdilution using **lyophilized panels** does not correlate with either a susceptible or resistant result in commercial automated, short-incubation broth systems, and there are no clinical data correlating such a result with ethambutol treatment response. **NOTE:** Repeat testing **using an alternative broth method (eg, critical concentration) or genotypic method** may determine whether the isolate in question is susceptible or resistant.

CLSI. M24S-Ed2

CRyPTIC Consortium. Eur Respir J. 2022 60:2200239

Setting ECOFFs



- If the ECOFF is used as the CB, the choice of the pWT percentile (95% vs. 97.5%, 99% or 99.9%) to set the ECOFF may have a major impact on positive predictive value (PPV) of pAST due to random errors.
- False resistant pAST results due to this error type are particularly relevant for novel drugs that often have a low true prevalence:
  - Sensitivity of resistance mechanisms is underestimated.
  - Confound association studies with outcomes.
- Rare borderline pNWT strains can result in an overestimation of the ECOFF if these are not removed when modelling the pWT distribution (to minimise this risk, genotypic and phenotypic data and, crucially, the lower end of the pWT distribution must be considered).

CLSI. M57S-Ed1
Köser & Maurer. Eur Respir J. 2023 61:2202397
CRyPTIC Consortium. Eur Respir J. 2022 60:2200239

Rifampicin

- WHO lowered RIF CCs for 7H10 and MGIT from 1 to 0.5 mg/L (concern raised about validity of 7H11 CC).
- MGIT ECOFF might be 0.25 mg/L, which has implications for borderline resistance mutations (*rpoB* L430P, D435Y, H445L, H445N, H445S, L452P, and I491F):

Mutation type	Percentage of mutants classified RIF-S with MGIT at			
	old CC 1 mg/L	CC+ATU 1 mg/L or new CC 0.5 mg/L	new CC+ATU 0.5 mg/L or CC 0.25 mg/L	CC+ATU 0.25 mg/L
S450 (S531)	0% (95% CI 0-1%)	0% (95% CI 0-1%)	0% (95% CI 0-1%)	0% (95% CI 0-1%)
other RRDR	3% (95% CI 2-5%)	1% (95% CI 0-3%)	1% (95% CI 0-2%)	1% (95% CI 0-2%)
V170F (V146F)	0% (95% CI 0-60%)			
borderline RRDR	74% (95% CI 67-81%)	53% (95% CI 45-61%)	35% (95% CI 28-43%)	11% (95% CI 6-17%)
borderline I491F (I572F)	100% (95% CI 69-100%)	80% (95% CI 44-97%)	70% (95% CI 35-93%)	7% (95% CI 0-34%)

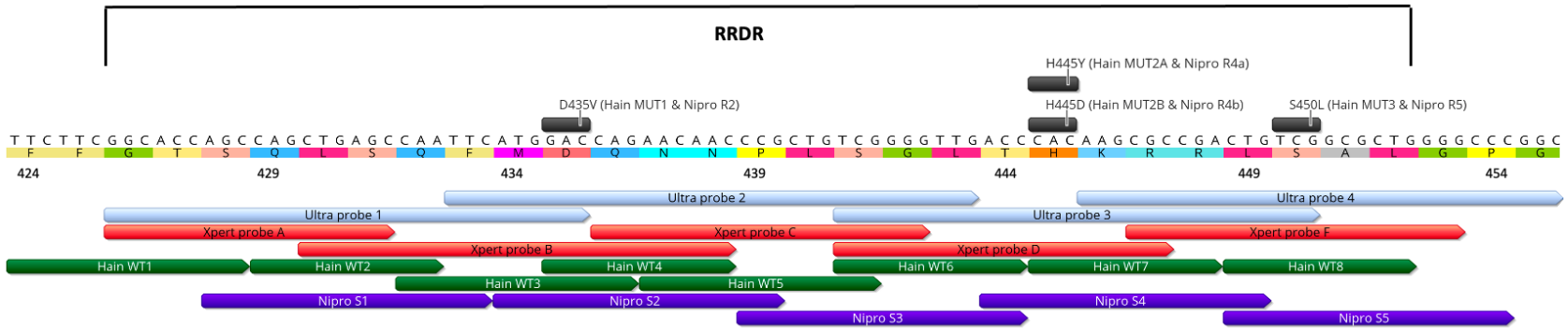
https://apps.who.int/iris/handle/10665/341981, accessed 26 Jun 2021

Rifampicin

Table 2. Sensitivity, specificity and PPV of the confidence-graded mutations as predictors of phenotypic drug susceptibility based on the ALL dataset

		1) Associated with R	2) Associated with R – Interim	3) Uncertain significance	4) NOT Associated with R – Interim	5) NOT Associated with R
RIF	# of variants identified	24	111	1550	0	28
	sens, spec, PPV (% 95% CI)	92.3 (91.8-92.8), 98.3 (98.1-98.5), 95.6 (95.2-96.0)	3.5 (3.2-3.9), 99.8 (99.8-99.9), 88.7 (85.2-91.7)			
	Combined Performance	**93.8 (93.3-94.2), 98.2 (98.0-98.3), 95.4 (94.9-95.8)**				

- 106 of 111 ‘associated with resistance – interim’ mutations classified based on RIF-resistance determining region (RRDR) expert rule.

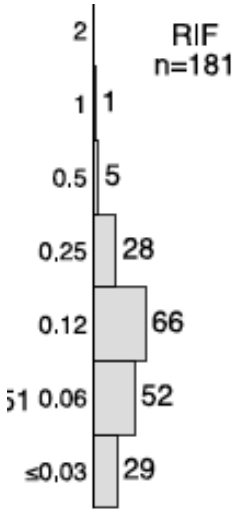


- High-quality MICs with definitive QC range/target and ECOFF/ATU are essential to identify potential exceptions to this rule (e.g. *rpoB* T427A).

https://apps.who.int/iris/handle/10665/341981, accessed 26 Jun 2021

‘Riffing on the Rifamycins’

- CLSI lowered RIF CC for BMD from 1 to 0.5 mg/L.
- Can the technical variability be reduced?



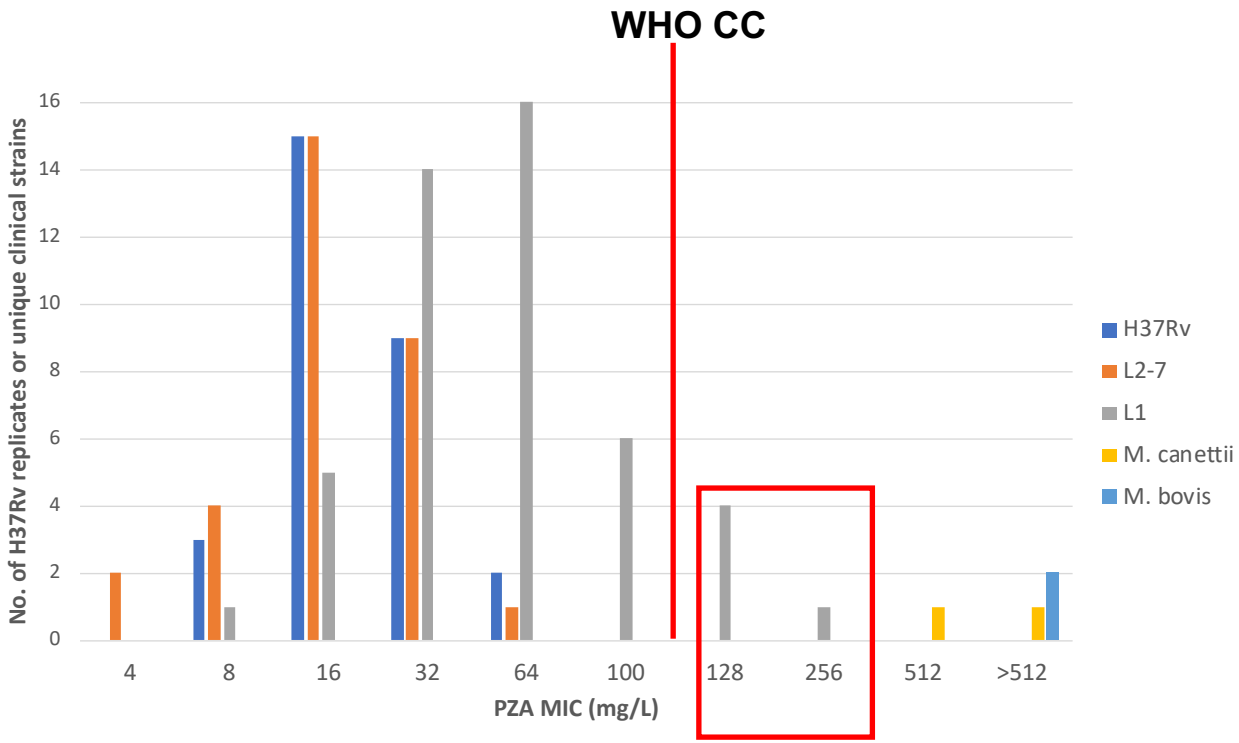
CRyPTIC H37Rv MICs

- Does RPT have a lower technical variability and/or provide a better resolution between wild-type strains and borderline resistance mutants? If so, should RPT be tested as a surrogate for RIF?
- Unlike for RIF and RPT, some *rpoB* mutations have little to no effect for RFB, but this does not explain why current CLSI CCs are several concentrations above ECOFFs.

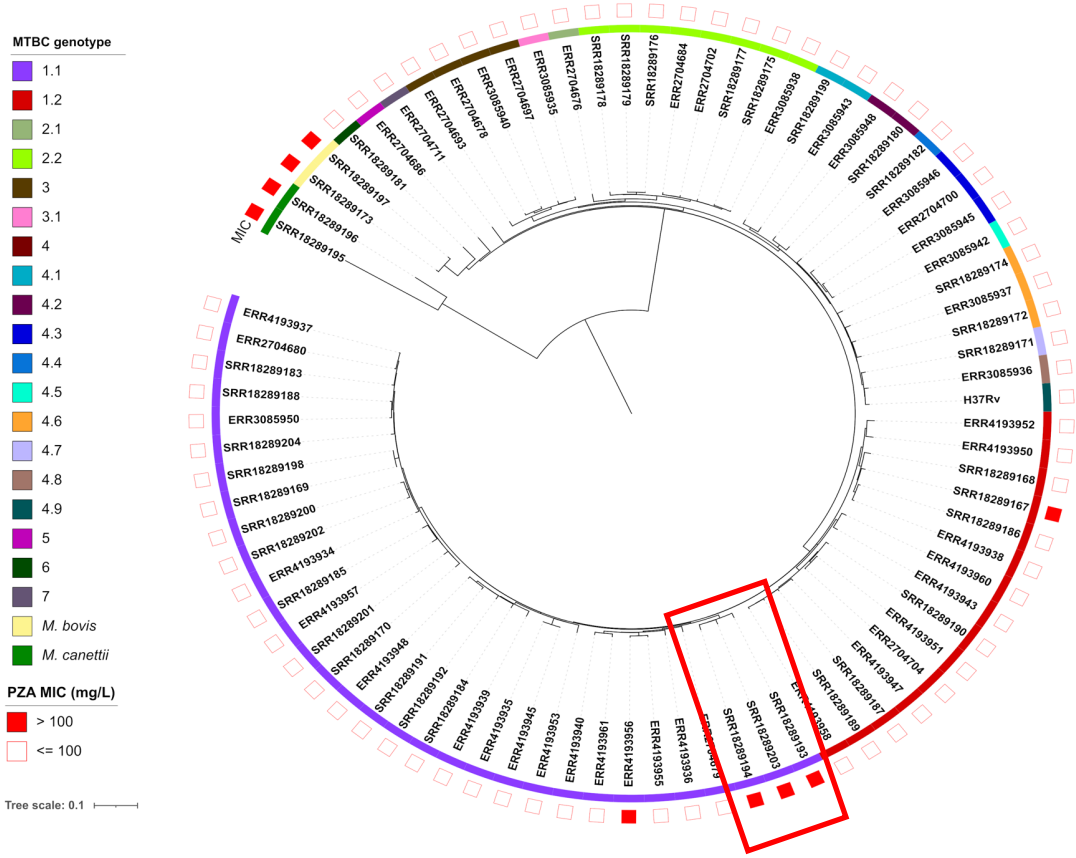
https://apps.who.int/iris/handle/10665/339275, accessed 13 Aug 2021

Pyrazinamide

- MGIT MICs from two laboratories:



5/47=11% (95% CI, 4-23%)
of L1s have MIC>100 mg/L



Köser et al. unpublished

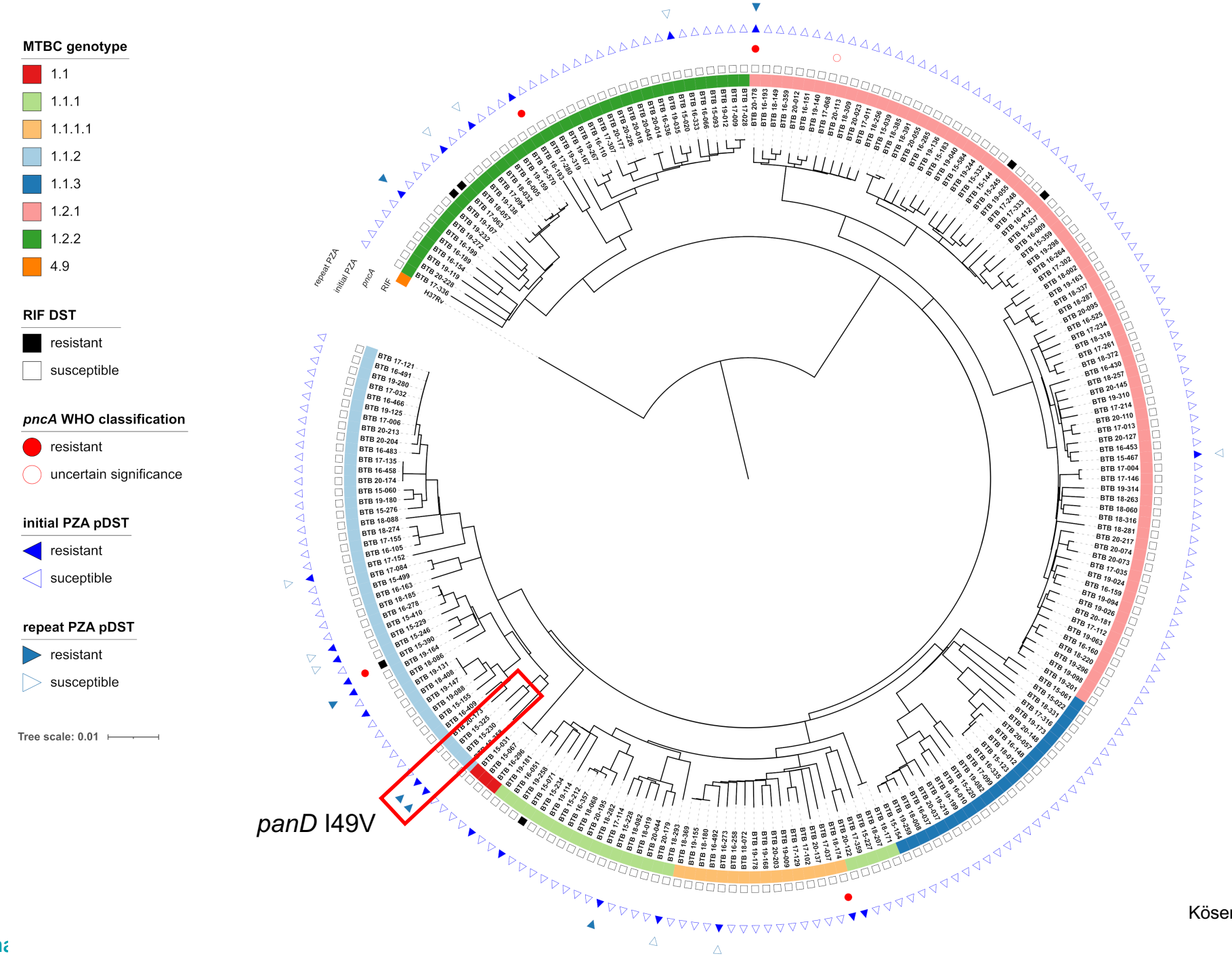
Pyrazinamide

- Swedish national surveillance data from 2015-2020:

Initial pAST as reference	S			R			Sensitivity (95% CI)[a]	Specificity (95% CI)[a]	PPV of *pncA* S (95% CI)
***pncA* WHO classification**	**R**	**U**	**S**	**R**	**U**	**S**			
Lineage 1	0	1	200	4	0	18	18% (5-40)	100% (98-100)	8% (5-13)
Lineage 2-4	4	4	1,742	75	0	3	96% (89-99)	100% (99-100)	0% (0-1)
Lineage 1-4	4	5	1,942	79	0	21	79% (70-87)	100% (99-100)	1% (0-2)

11% (95% CI, 4-23%) based on earlier MICs

Köser et al. unpublished



Köser et al. unpublished

Pyrazinamide

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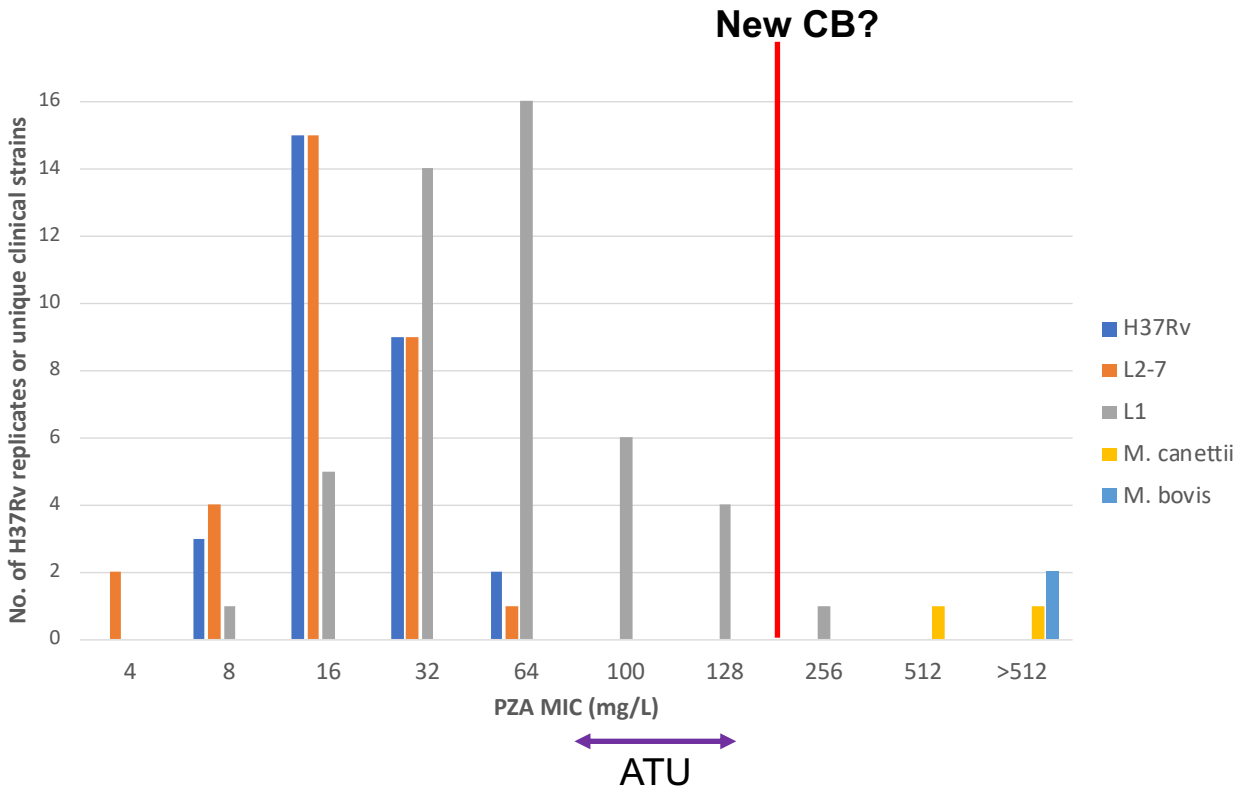

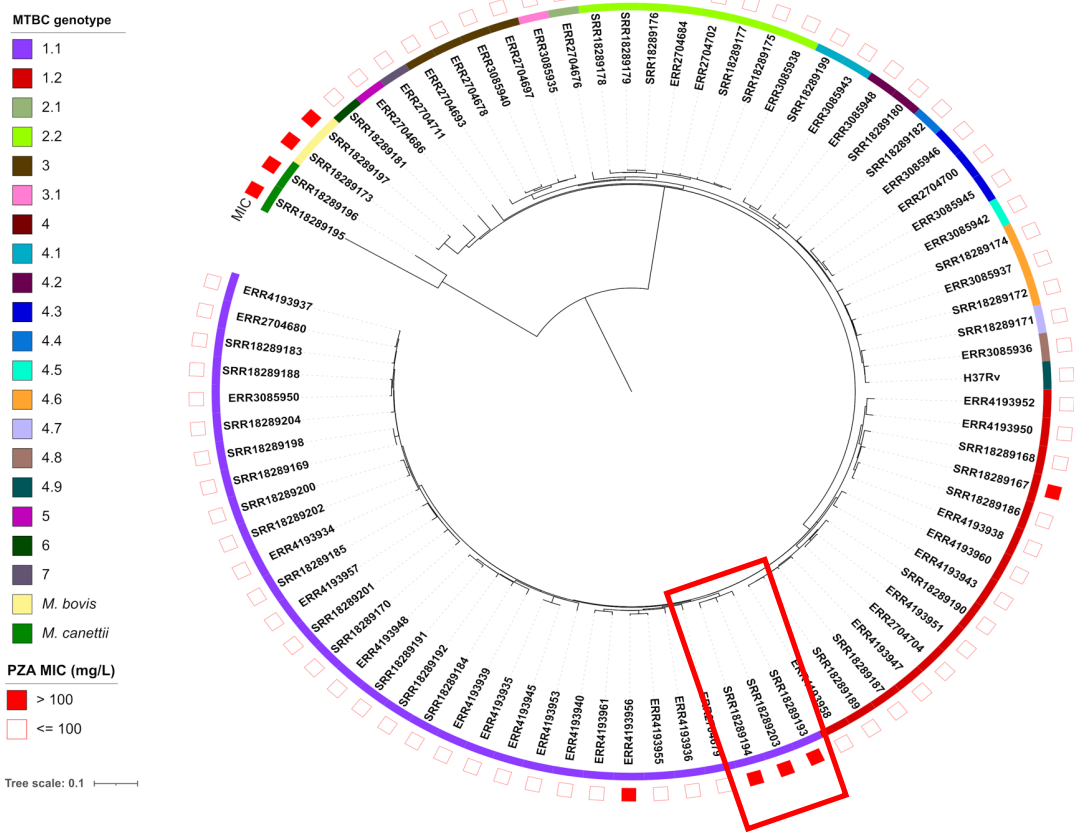

Köser et al. unpublished

Fluoroquinolones

- Between 2014-2018, 90% of MFX-resistant isolates could have been systematically misclassified as susceptible using MGIT because the WHO CC was eight times higher than the ECOFF (2 instead of 0.25 mg/L).
- WHO stratified resistance to MFX into low-level resistance (LLR) and high-level resistance (HLR).
- WHO recommended that the FQ that is used clinically should be used for pAST.

Antimycobacterial Susceptibility Testing Group. Eur Respir J. 2022 59:2200166

Fluoroquinolones

			UKMYC MIC (mg/L)																
			LFX								MFX								
			≤0.125	0.25	0.5	1	2	4	8	>8	≤0.06	0.125	0.25	0.5	1	2	4	>4	total
gWT	Lineage 3	count	8	**51**	26	3	0	2			57	26	3	3	1				90
		% sum (left to right)	8.9	65.6	94.4	97.8	97.8	100.0			63.3	92.2	95.6	98.9	100.0				
	Lineage 1, 2 & 4	count	4	144	**180**	14	2			1	15	117	**164**	46	2			1	345
		% sum (left to right)	1.2	42.9	95.1	99.1	99.7			100.0	4.3	38.3	85.8	99.1	99.7			100.0	

Concentrations in **bold** correspond to the modes of an MIC distribution, where these could be defined.
The green lines denote the pECOFFs.

https://apps.who.int/iris/handle/10665/353066, accessed 12 Apr 2022

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gyrA A90V	Lineage 3	count				2	**22**	14		1		1	2	**25**	10			1	39
		% sum (right to left)				5.1	61.5	97.4	97.4	100.0		2.6	7.7	71.8	97.4			100.0	
	Lineage 1, 2 & 4	count			1	2	**17**	**17**	3	2			1	8	**16**	11	6		42
		% sum (right to left)			2.4	7.1	47.6	88.1	95.2	100.0			2.4	21.4	59.5	85.7	100.0		

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Concentrations in **bold** correspond to the modes of an MIC distribution, where these could be defined.
The green lines denote the pECOFFs.

- Test LFX instead of MFX as it provides a better resolution between gWT and LLR strains.
- pAST not reliable to confirm LLR mutations.

https://apps.who.int/iris/handle/10665/353066, accessed 12 Apr 2022

Fluoroquinolones

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The red line denotes the pCB to stratify LLR and HLR for MFX.

- MFX 'CB' was meant to exclude HLR due to low-frequency HLR mutations if only a LLR mutation is found by gAST.

https://apps.who.int/iris/handle/10665/353066, accessed 12 Apr 2022

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- MFX 'CB' was meant to exclude HLR due to low-frequency HLR mutations if only a LLR mutation is found by gAST.
- Equivalent surrogate 'CB' for LFX is again superior to MFX but misses about 50% of HLR.

https://apps.who.int/iris/handle/10665/353066, accessed 12 Apr 2022

Fluoroquinolones

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Concentrations in **bold** correspond to the modes of an MIC distribution, where these could be defined.
The green lines denote the pECOFFs.
The red line denotes the pCB to stratify LLR and HLR for MFX.

- To minimise the chance of missing HLR, 2 mg/L LFX surrogate is likely the better option for strains that are susceptible by gAST or for which no gAST results are available.

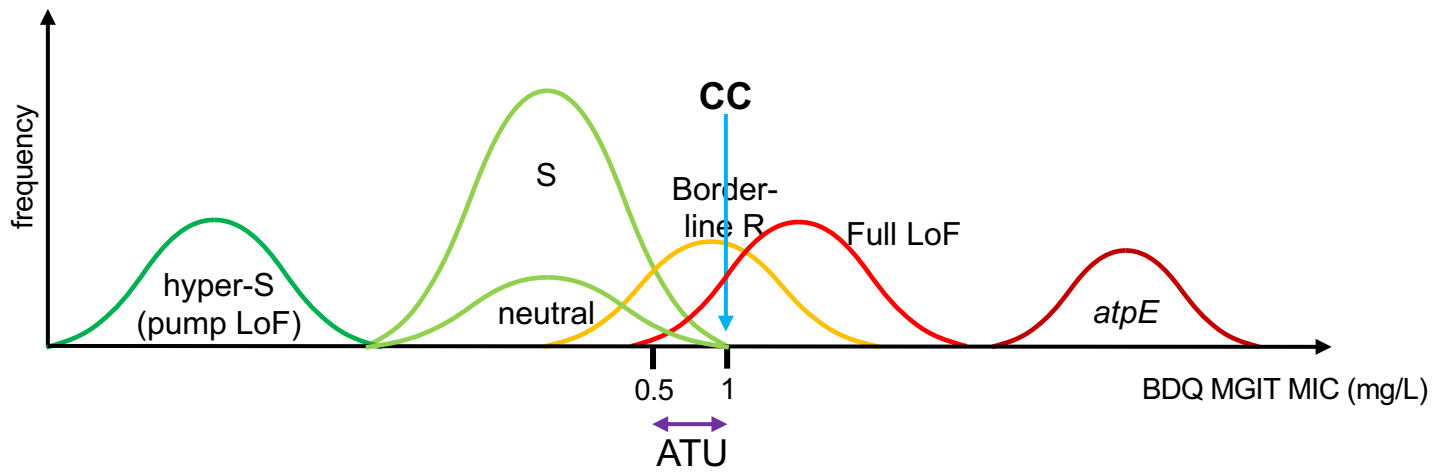
https://apps.who.int/iris/handle/10665/353066, accessed 12 Apr 2022

Bedaquiline

- I am the PI of a Janssen-sponsored study to calibrate MGIT and dry Thermo Fisher plate against the EUCAST reference method, which will yield QC range/targets and ECOFFs requested by European Medicines Agency (EMA).
- 0.25 mg/L proposed by CRyPTIC for dry BMD might be higher than ECOFF.
- Version 2 of WHO mutation catalogue will provide much more guidance for interpretation, taking clinical and *in vitro* selection data into account.

Köser & Maurer. Eur Respir J. 2023 61:2202397
CRyPTIC Consortium. Eur Respir J. 2022 60:2200239

Bedaquiline

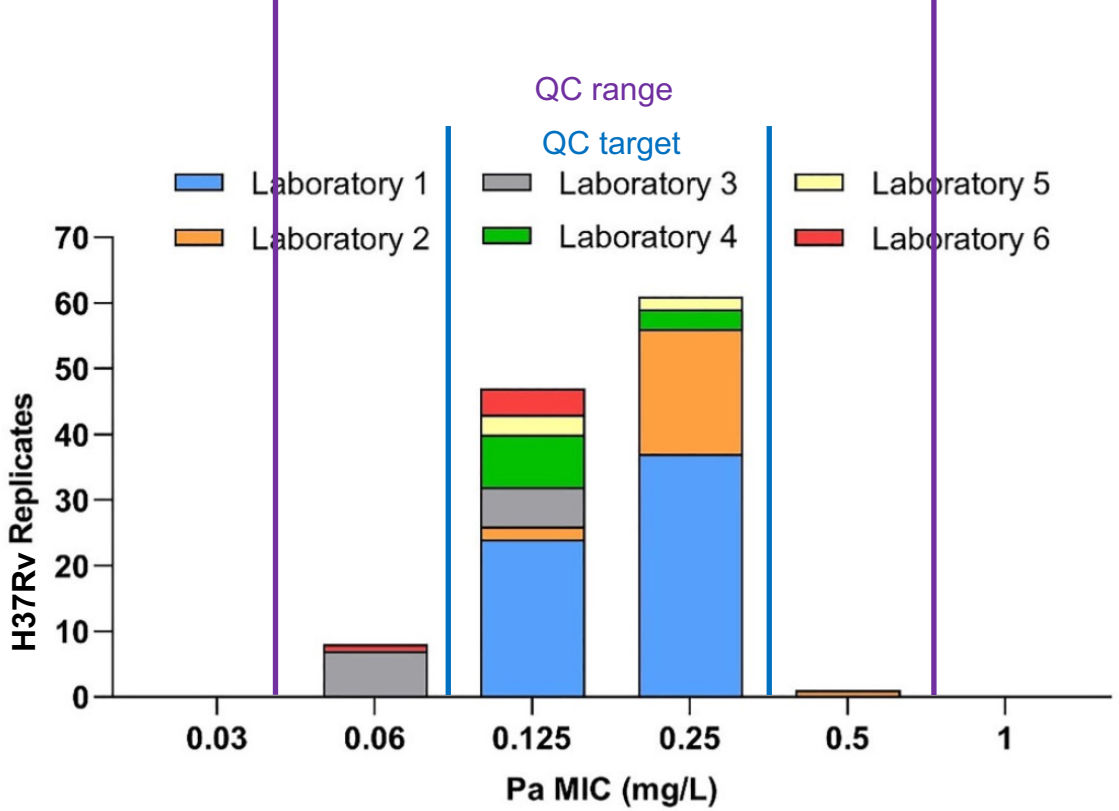


- Mutations in essential *atpE* target are easy to interpret and detect by pAST but are rare (NB: they are not always secondary resistance mutations).
- *Rv0678* is dominant resistance mechanism but:
  - Large spectrum of mutations, which can have no (neutral), modest (borderline R – e.g. M146T from Eswatini) or full loss-of-function (LoF) effect with maximal overexpression of *mmpS5-mmpL5* efflux pump.
  - Epistasis: *Rv0678* mutations cannot confer resistance in *mmpS5-mmpL5* LoF background (rare globally, but frequent in Lima, Peru, and some South-East Asian countries).
  - Hetereroresistance plays a major role as a greater proposition of resistance is selected vs. transmitted.
  - Low PPV of pAST as true prevalence of resistance is low in most settings.

Clofazimine

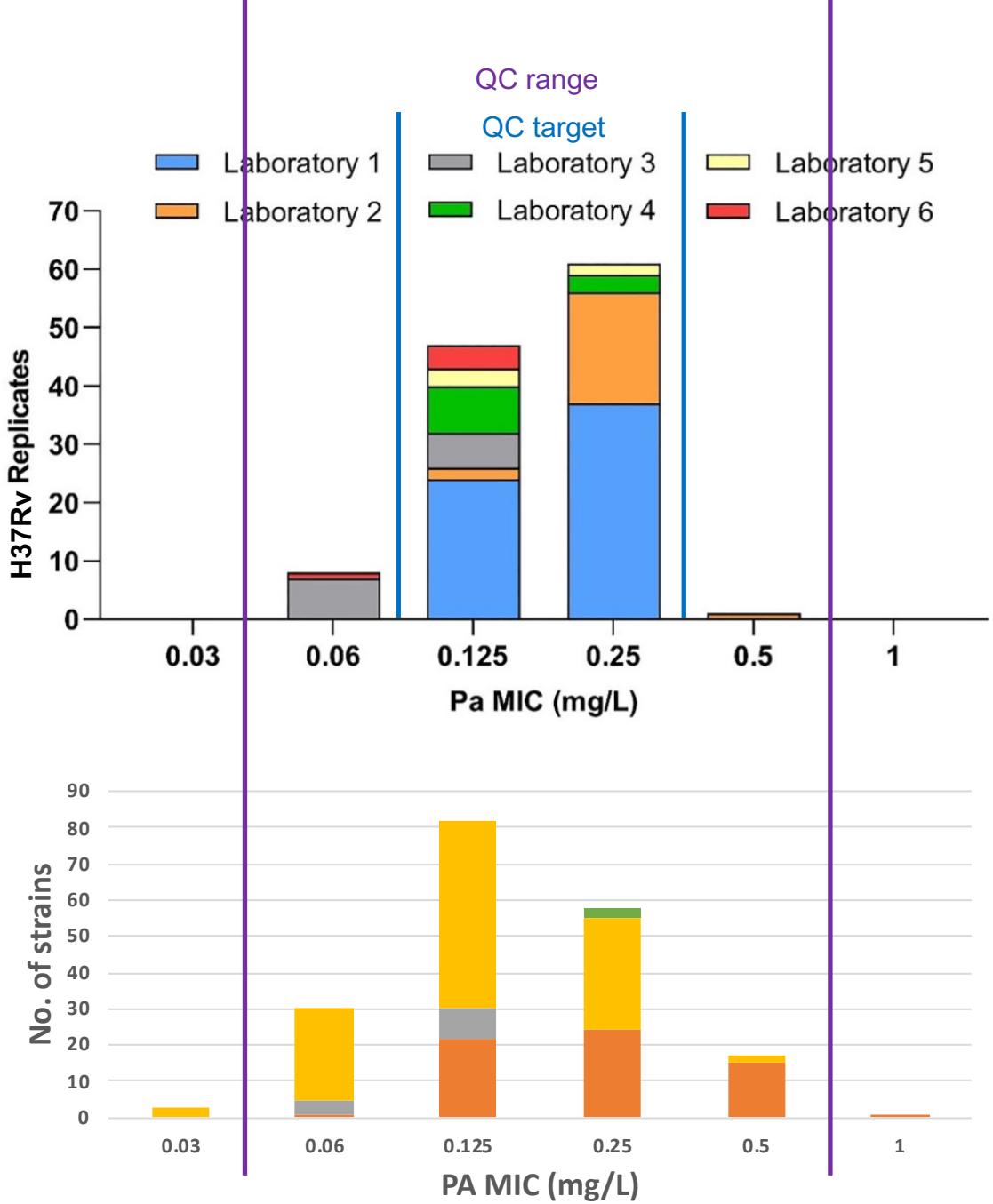
- Current WHO-endorsed and CRyPTIC CCs may be too high.
- MIC testing for CFZ appears to have greater technical variability than for BDQ, which likely means that there is a greater overlap between MIC distributions of susceptible strains and *Rv0678* mutants.
- WHO will provide guidance about cross-resistance for *Rv0678* and *pepQ* in version 2 catalogue.

Pretomanid



Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693

Pretomanid



Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693

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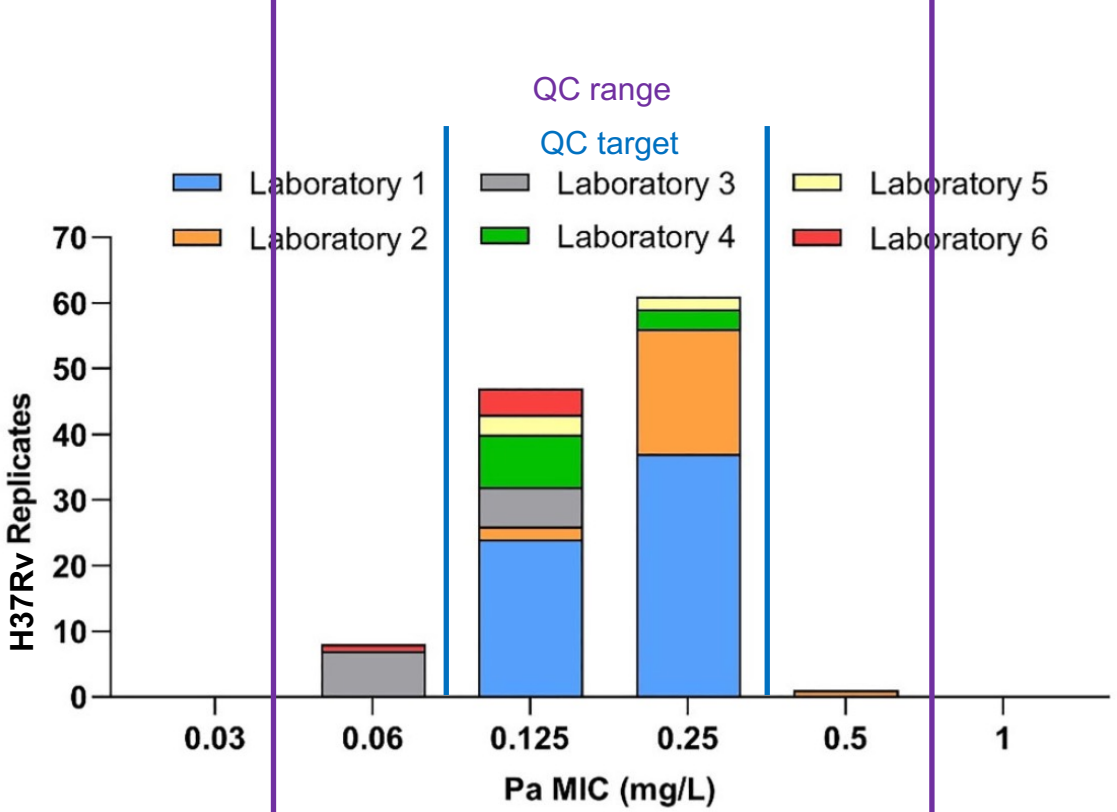
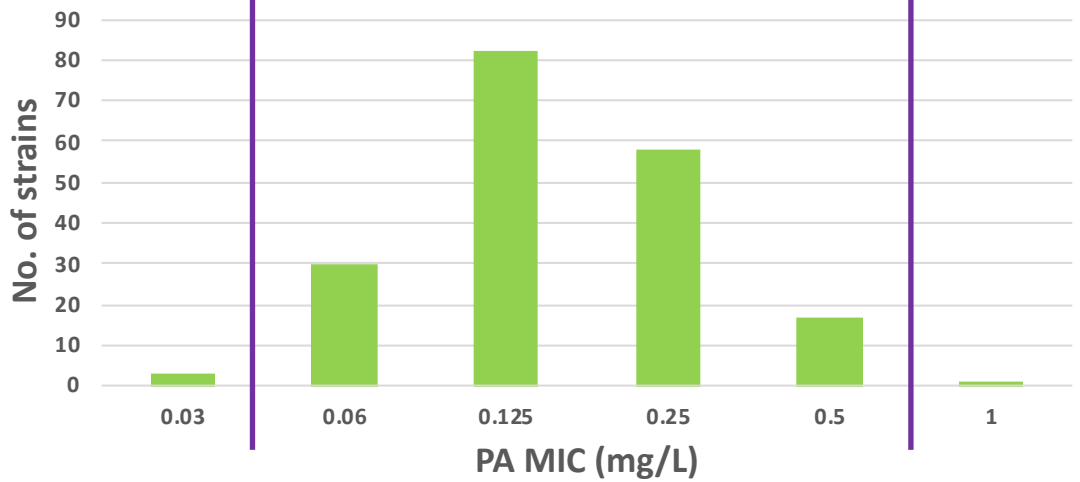
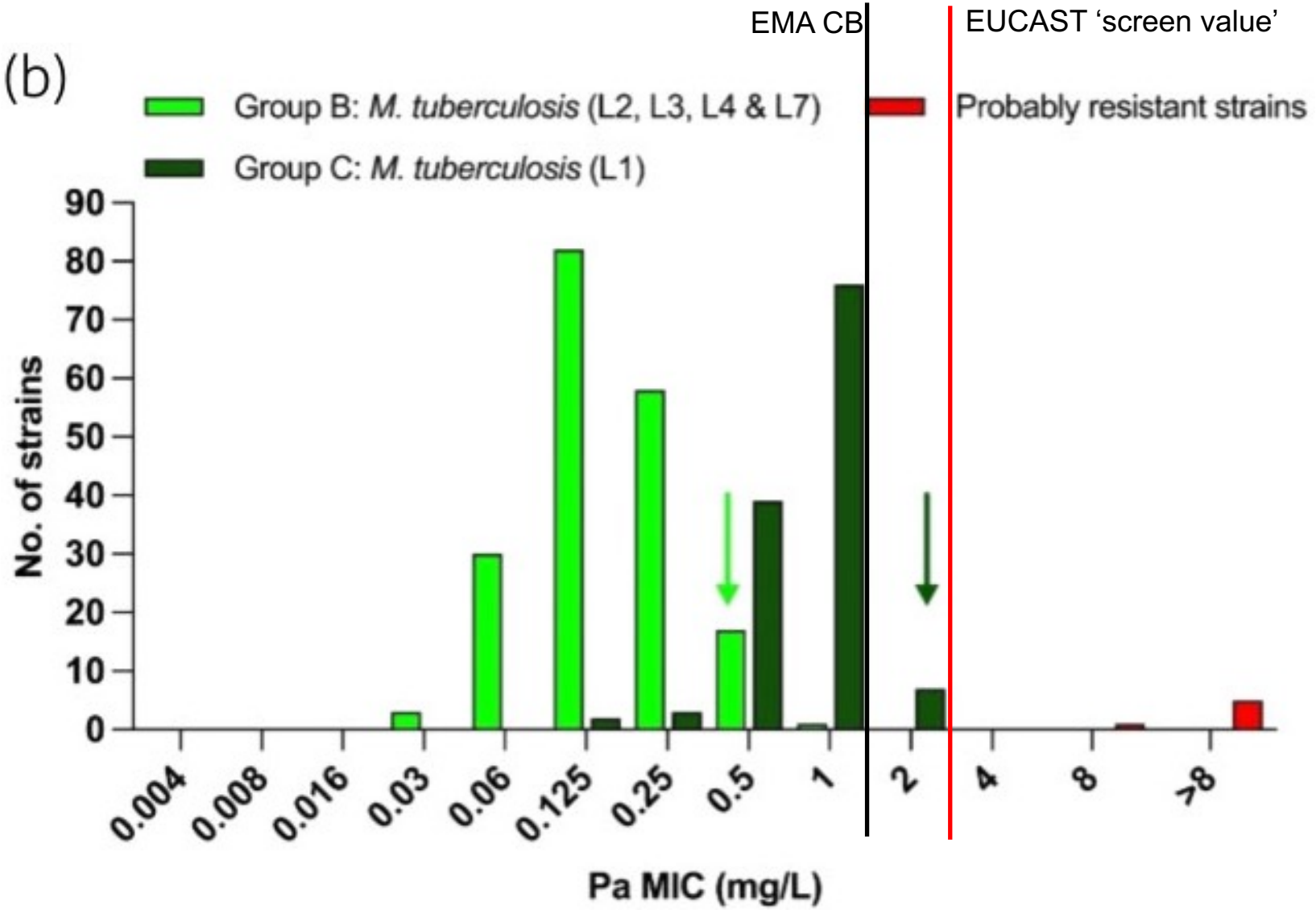


99th percentile for Group B



Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693

Pretomanid

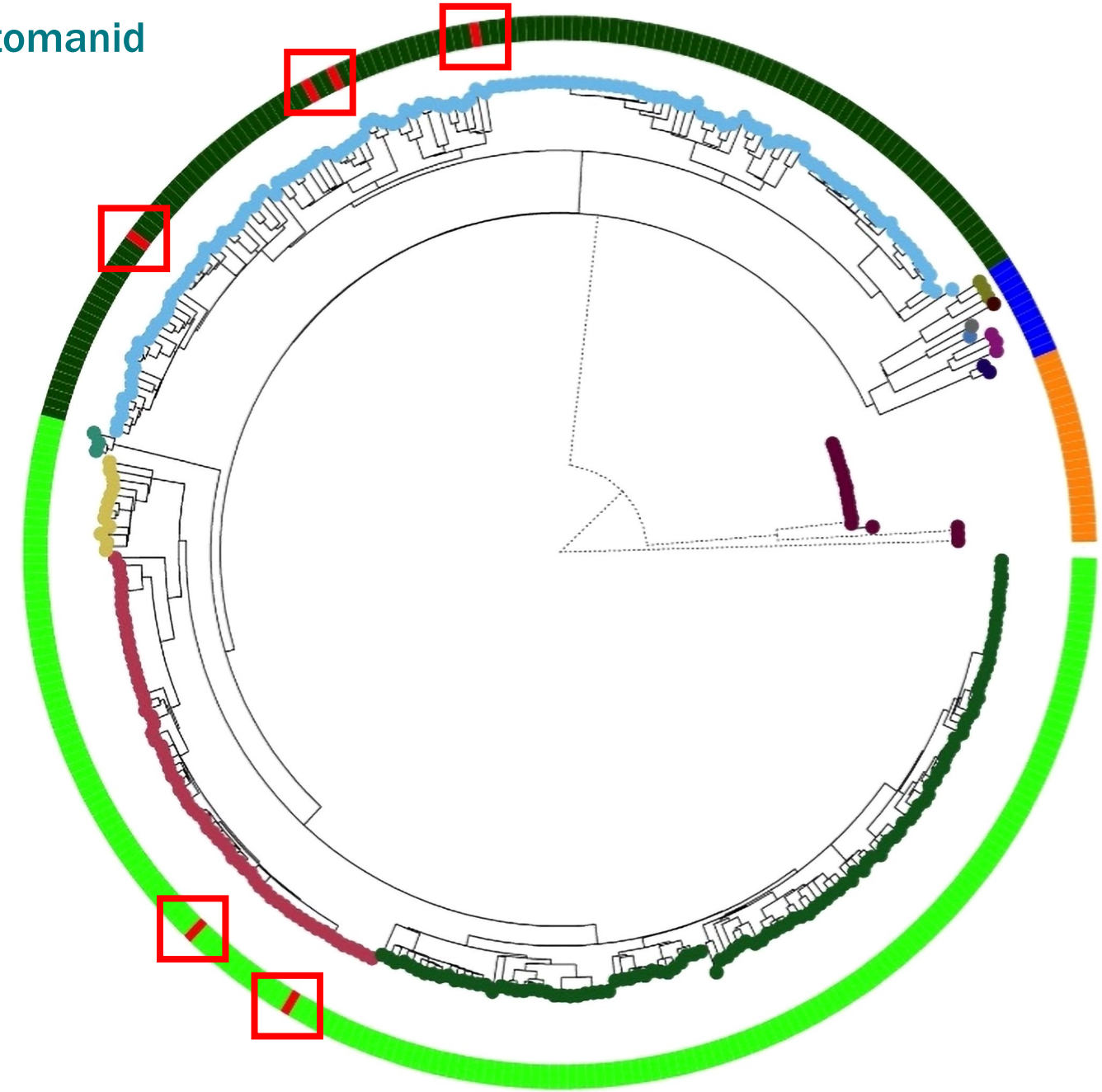


Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693

EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Version 13.0, valid from 2023-01-01

https://www.ema.europa.eu/en/documents/product-information/dovprela-epar-product-information_en.pdf, accessed 12 Feb 2023

Pretomanid



Pa MIC (mg/L): mode, 99th percentile

- Group A: 0.03, 0.125
- Group B: 0.125, 0.5
- Group C: 1, 2
- Group D: 2, 4
- Probably resistant strains: >8, n/a

MTBC member

- *M. tuberculosis* (L1)
- *M. tuberculosis* (L2)
- *M. tuberculosis* (L3)
- *M. tuberculosis* (L4)
- *M. africanum* (L5)
- *M. africanum* (L6)
- *M. tuberculosis* (L7)
- *M. bovis*
- *M. canettii*
- *M. caprae*
- *M. microti*
- *M. pinnipedii*

Bateson et al. J Antimicrob Chemother. 2022 77:1685-1693

Cycloserine

- No breakpoint by any regulator and false narrative that pAST is impossible because of stability of cycloserine.

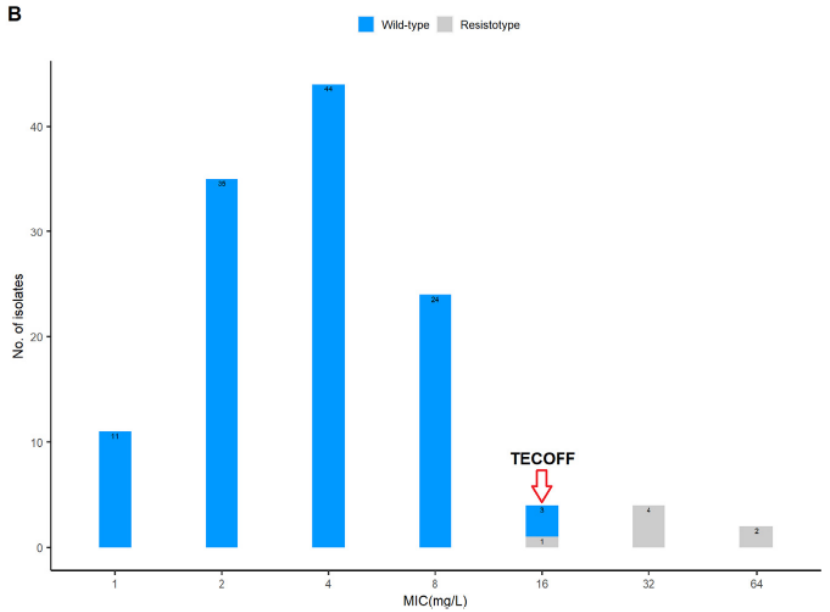


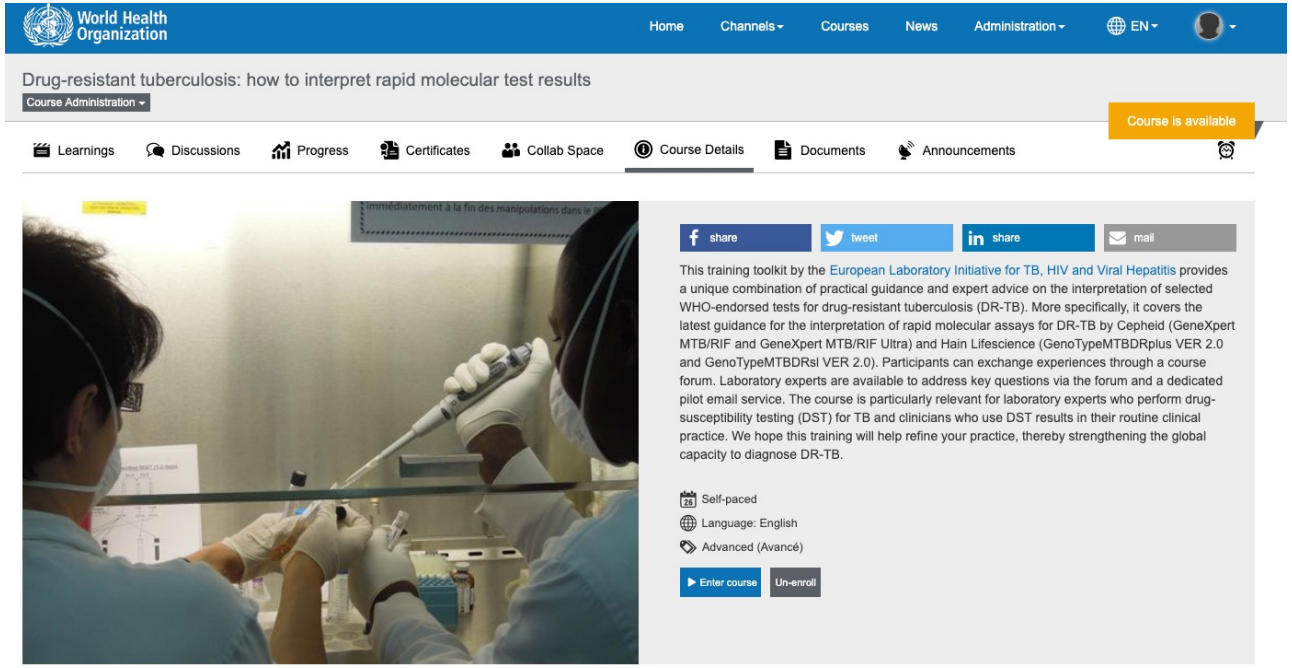
Figure 1. Distribution of cycloserine MICs (mg/L) in the MGIT for a panel of 124 MTB isolates. (A) Distribution of cycloserine MICs stratified to susceptibility patterns of MTB isolates. (B) Distribution of cycloserine MICs between wild-type and resistotype populations. MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MTB, *Mycobacterium tuberculosis*; TECOFF, tentative epidemiologic cutoff; XDR, extensively drug-resistant.

- WHO is carrying out an update to its 2018 systematic review to set breakpoints for this drug.
- Are animal-adapted MTBC strains intrinsically resistant as they have a frameshift in *ald*?

Wu et al. Int J Infect Dis. 2022 121:148-51
Wang et al. Infect Drug Resist. 2022 15:135-40
Zhu et al. Antimicrob Agents Chemother. 2023 67:e0170022

Concluding thoughts

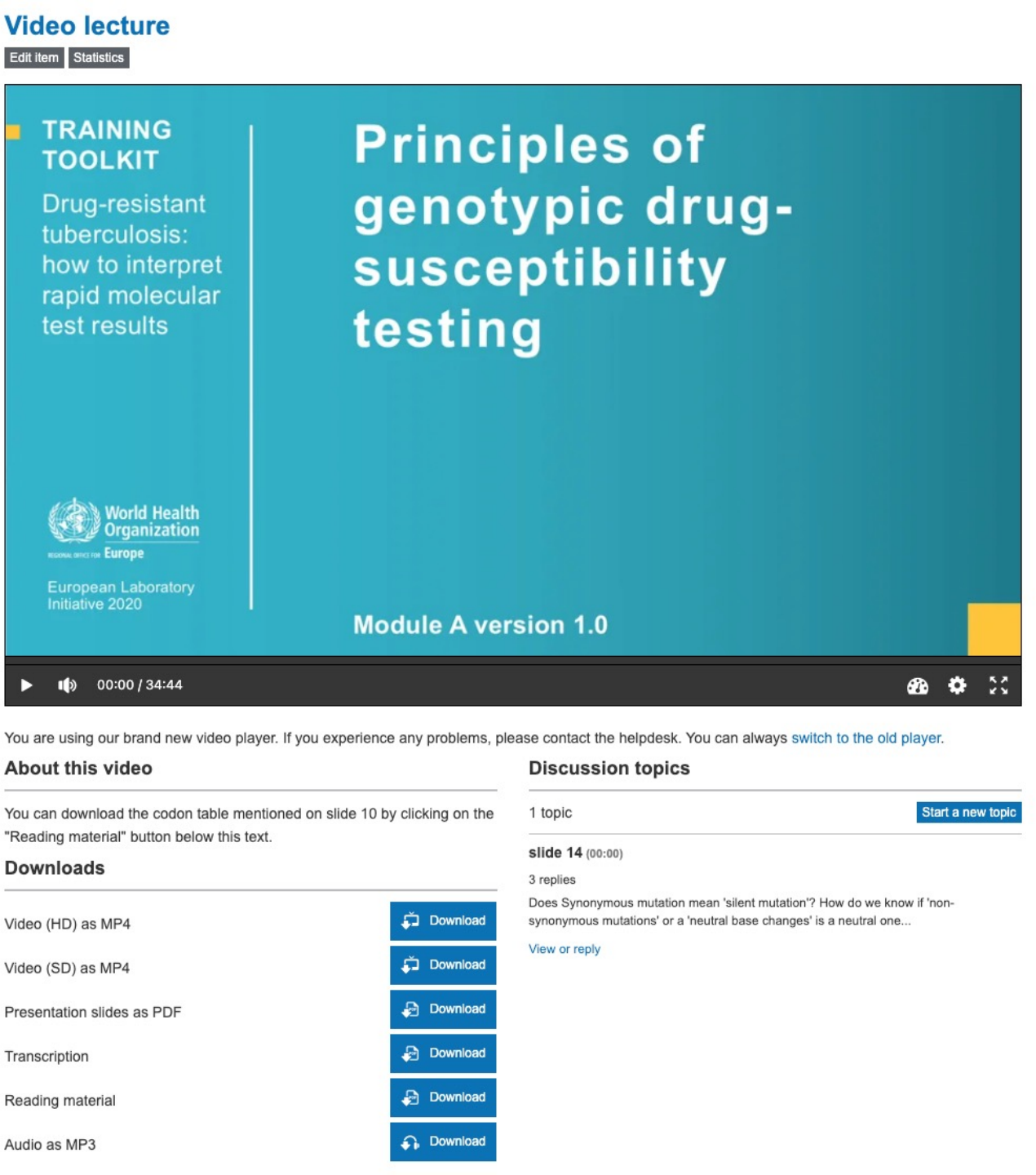
- Collaborate more widely as no single country has the necessary resources or expertise to address the ongoing challenges (‘Stop, Collaborate and Listen’).
- Greater alignment between key regulators.
- Exert greater pressure on commercial companies.
- Use online platforms to share relevant findings and scale up teaching.



https://openwho.org/courses/multi-drug-resistant-tb

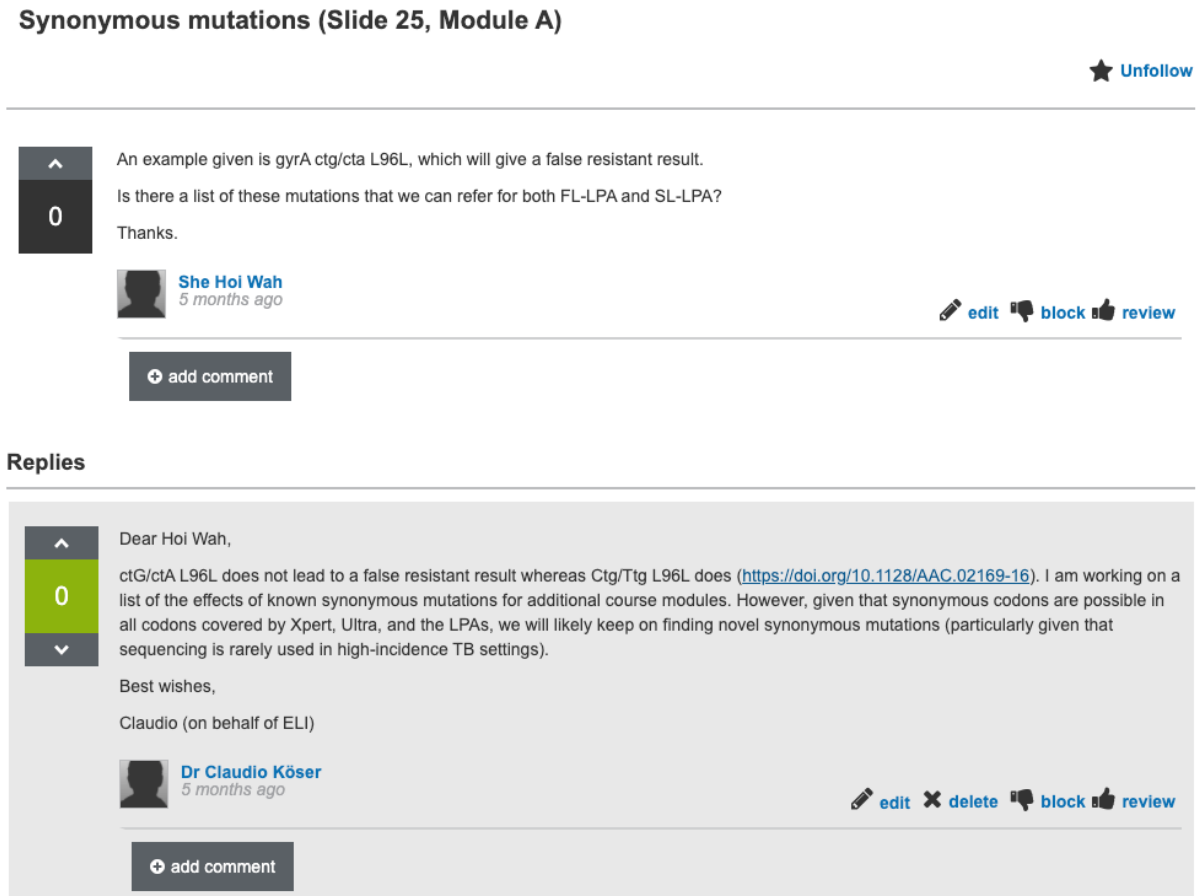
OpenWHO platform

- Video lectures with transcripts, links to relevant publications/guidelines, and quizzes.



OpenWHO platform as an example of online education

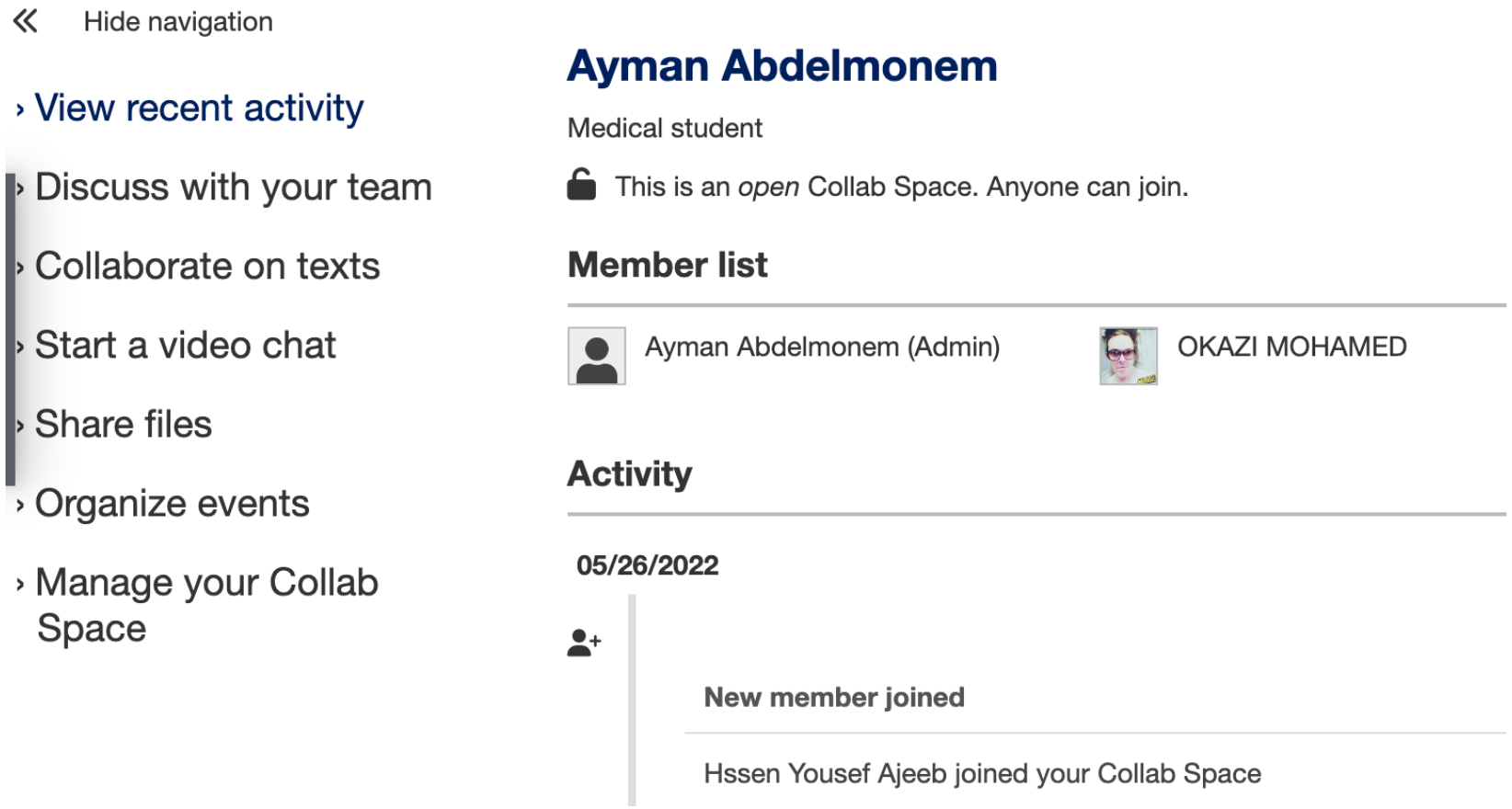
- Each module has a public forum.



https://openwho.org/courses/multi-drug-resistant-tb

OpenWHO platform as an example of online education

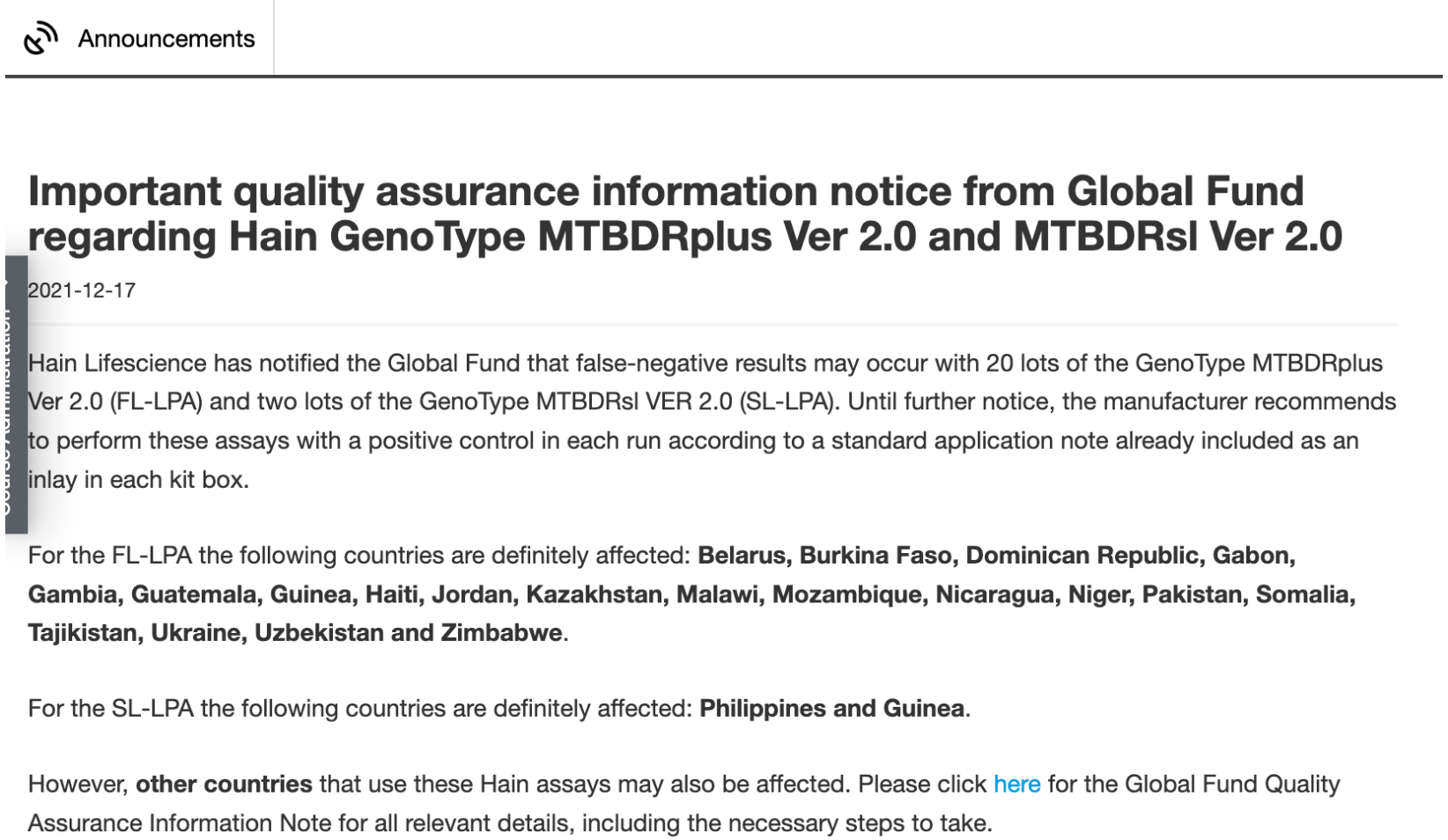
- Public or private collaboration spaces.



https://openwho.org/courses/multi-drug-resistant-tb

OpenWHO platform as an example of online education

- Announcement function to disseminate relevant information.



https://openwho.org/courses/multi-drug-resistant-tb

Thank you for your attention.