



Overview of SRLN efforts to date: rounds of DST proficiency testing

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Main SRLN achievement

- Standardised use of DST
 - annual rounds among SRL
 - first-line: INH, RMP, EMB, SM
 - since Rd 14 also Km, Ak, Cm and Ofx
 - initial discordances++
 - soon resolved through uniformisation of techniques
 - high agreement among established SRL
 - but less consistent for EMB, SM



Rounds organization

- Own preferred standard method
- Panels of 30 strains, from routine DRS
 - 10 in duplicate
 - variation of profiles; subset without MDR (no XDR)
- Pre-testing at coordinating SRL
 - since Rd 9
 - trying to exclude problematic strains

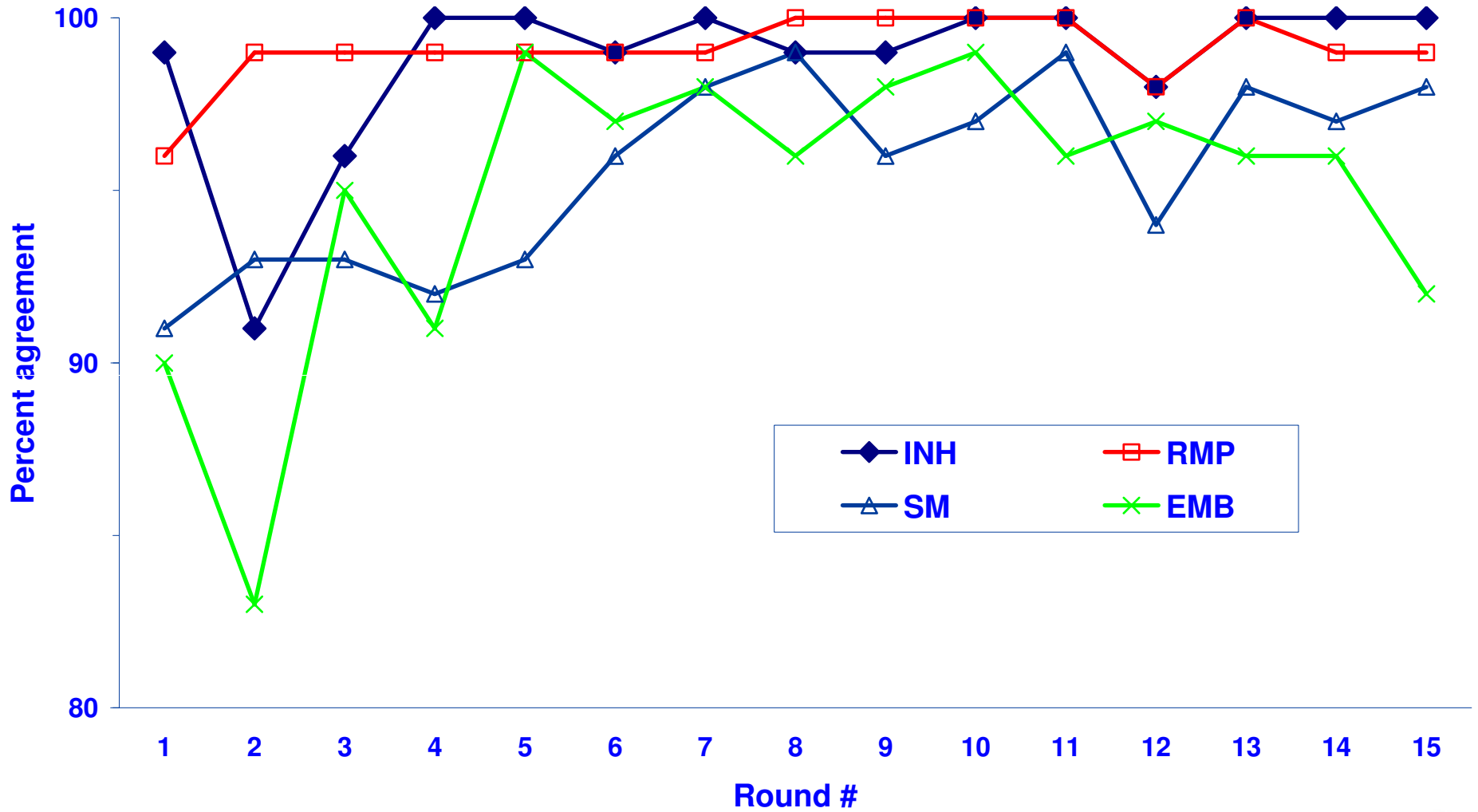


Rounds evaluation

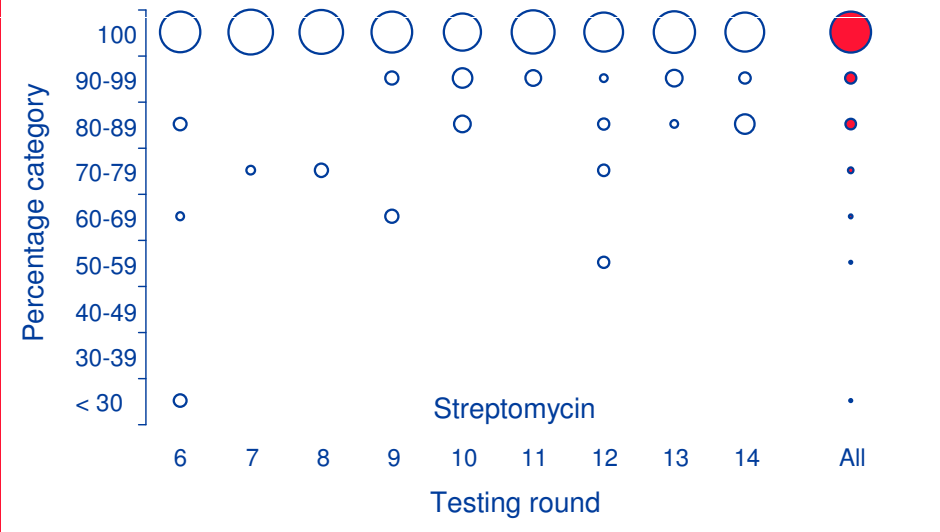
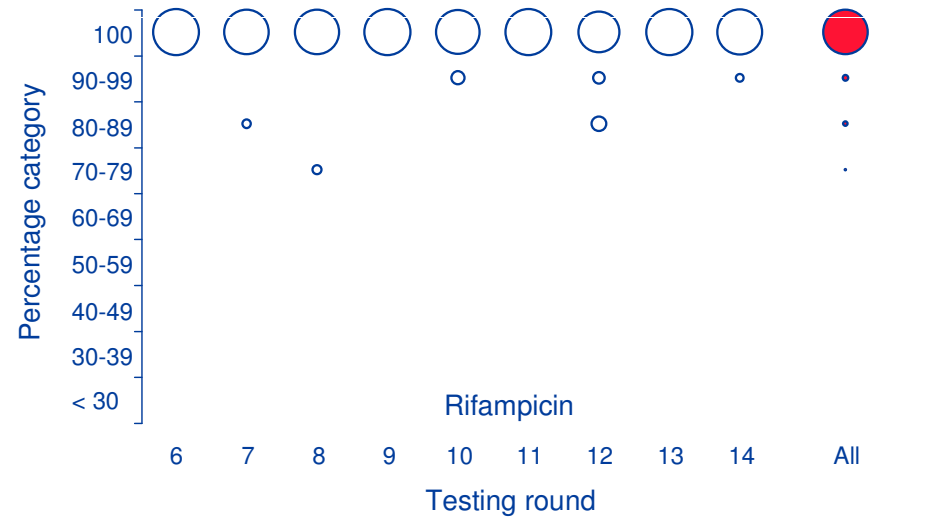
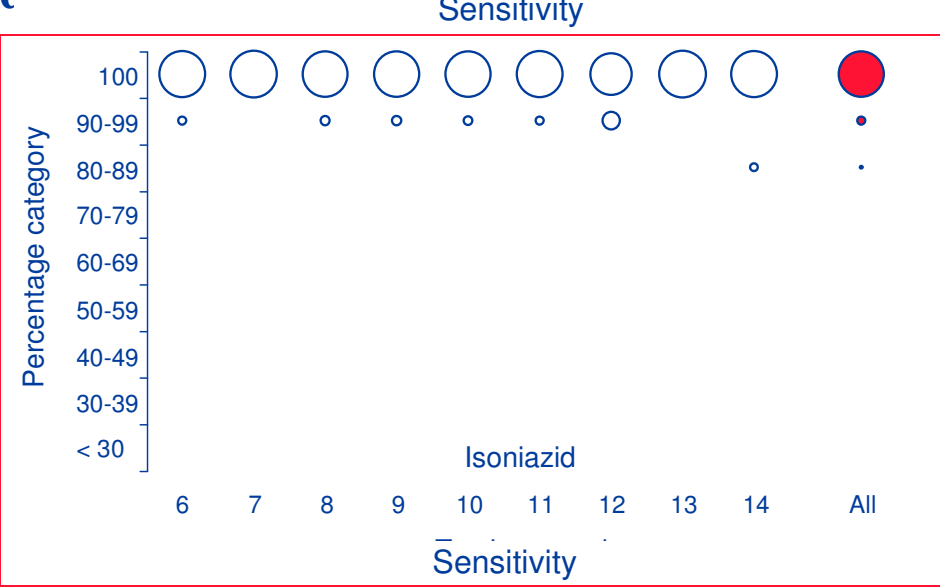
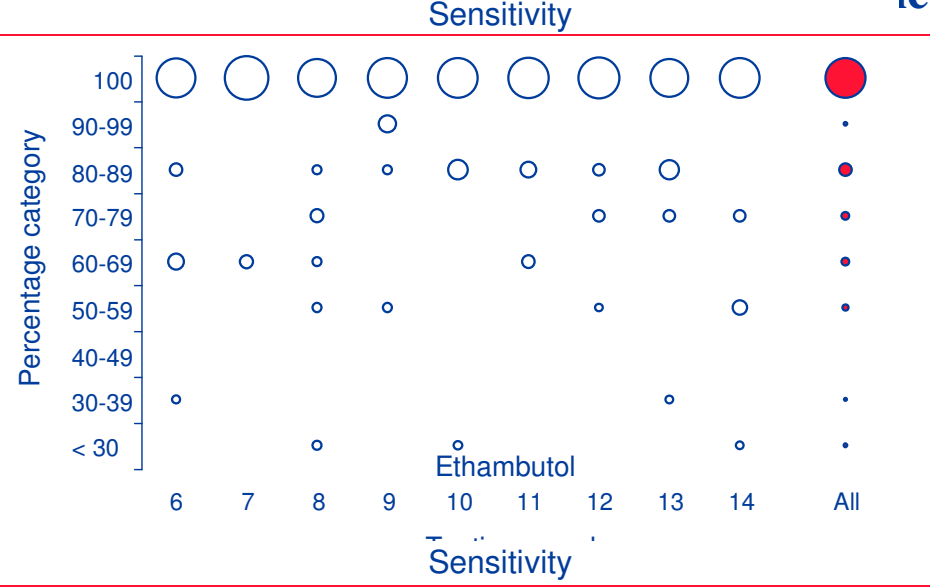
- Judicial result criterion
 - phenotypic DST only
 - majority susceptible / resistant
- <80% agreement excluded
 - overall 9% of strains/drugs (first-line)
 - Rd 6 to Rd 15, total 170 strains/drug
 - INH 6 strains = 4%
 - RMP 16 strains = 9%
 - SM 18 strains = 11%
 - EMB 24 strains = 14%

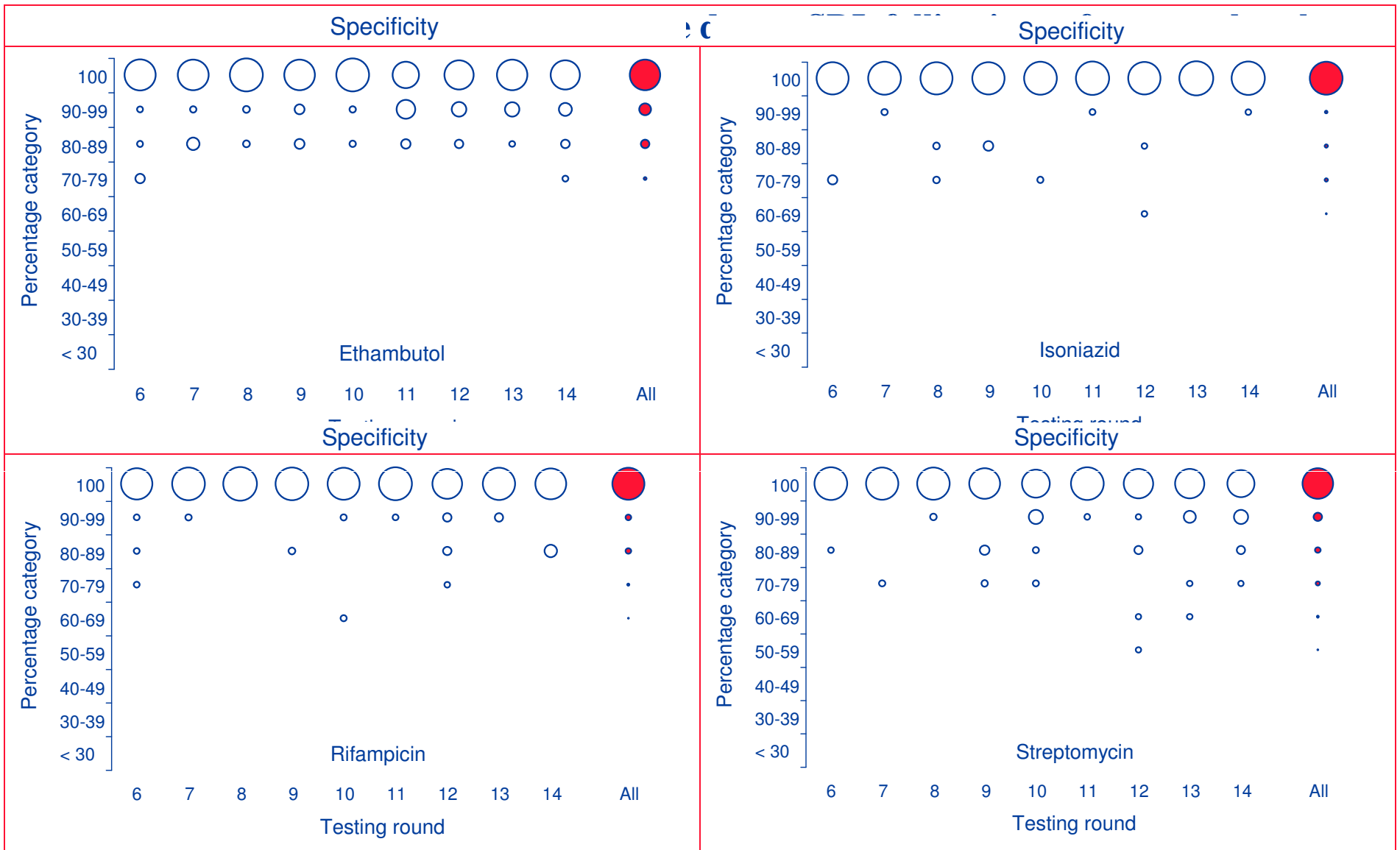


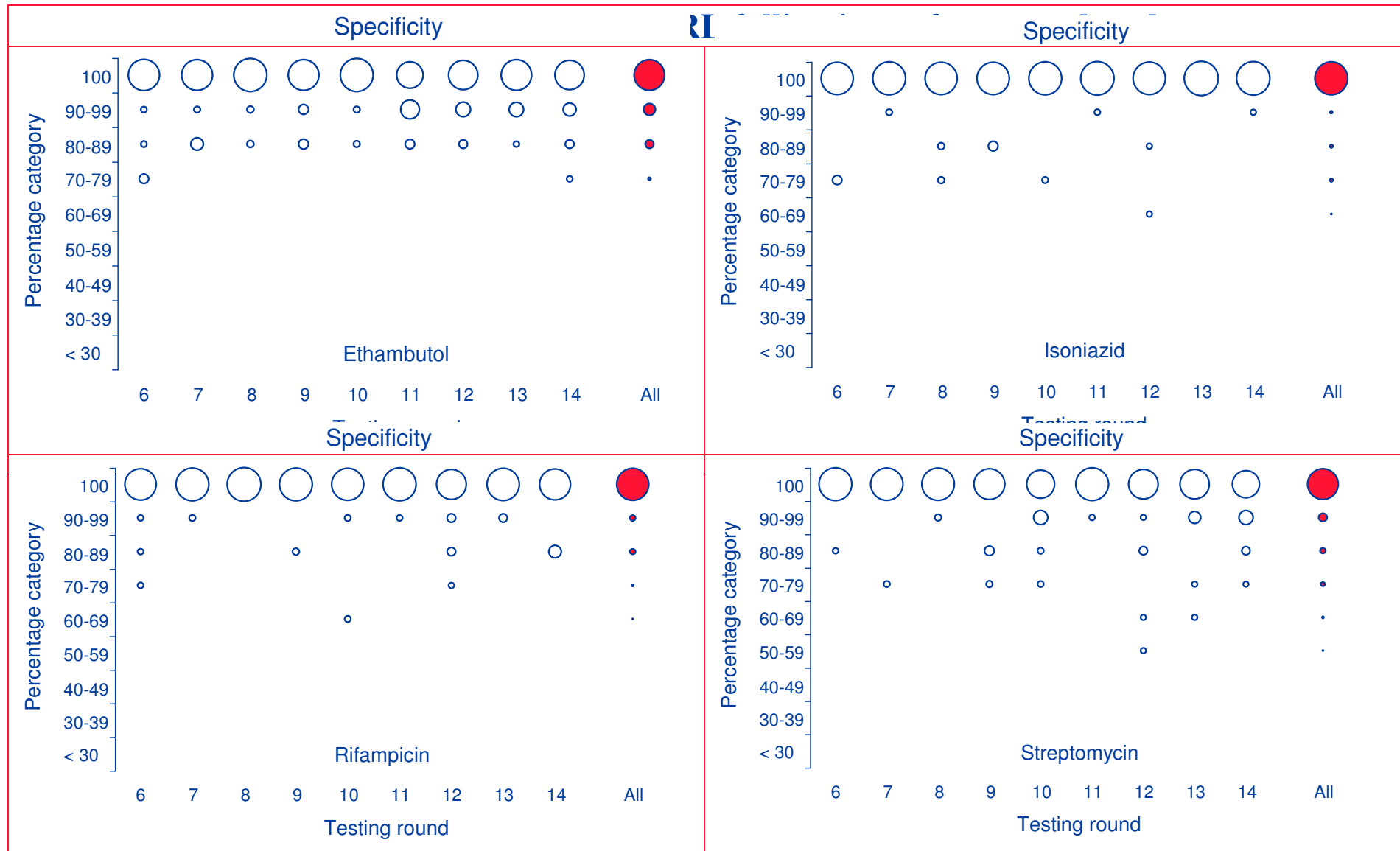
SRLN rounds: trends for agreement, round 1 - 15 (<80% concordant strains excluded)



Sensitivity in detecting resistance to first line drugs: SDI falling in performance brackets







Second-line proficiency testing

- Started recently, results of 2 rounds only
- Interim recommendations critical concentrations; drug powders provided
- Surprisingly good results
 - few exclusions: Km, Cm
 - Cm more problematic (some labs)
 - Km, Ak, Ofx: at par with FLD
 - but so far few resistant strains included



Results PT of SLD, rounds 14 / 15

Drug tested (no. resistant)		<u>Round 14 (22 SRL)</u>			<u>Round 15 (25 SRL)</u>		
		Average score	No. of SRL with		Average score	No. of SRL with	
			100%	<90%		100%	<90%
Kanamycin (6 & 5)	Sens.	97%	16	2	97%	18	6
	Spec.	97%	19	2	98%	19	1
Amikacin (3 & 4)	Sens.	99%	20	1	99%	20	2
	Spec.	96%	14	3	98%	16	1
Capreomycin (5 & 4)	Sens.	95%	17	3	87%	15	10
	Spec.	91%	16	5	97%	19	2
Ofloxacin (3 & 3)	Sens.	92%	17	5	100%	25	0
	Spec.	98%	17	3	98%	19	3



Methods used

- First-line: slow shift towards MGIT
 - early rounds:
 - 70% LJ proportion
 - 3-4 radiometric BACTEC
 - 1-2 agar / absolute concentration / resistance ratio
 - round 15:
 - 9/26 LJ proportion
 - 9/26 MGIT, no more radiometric BACTEC
- Second-line: slightly more agar proportion



Panels dissemination

- Insufficiently passed on to NRL
 - lack of resources
 - unclear links
 - particularly poor coverage: Africa



Problems encountered with rounds

1. No provision to support SRL with problems
2. Strains yielding highly discordant results
 - due to over-representation rare types / profiles
 - inadequacy of judicial result criterion → excluded
 - results shown not quite realistic
 - e.g. RMP: 90-98% correct rather than 97-100% ?
 - no provision for investigations
 - nobody interested to fund?
 - disbelief?

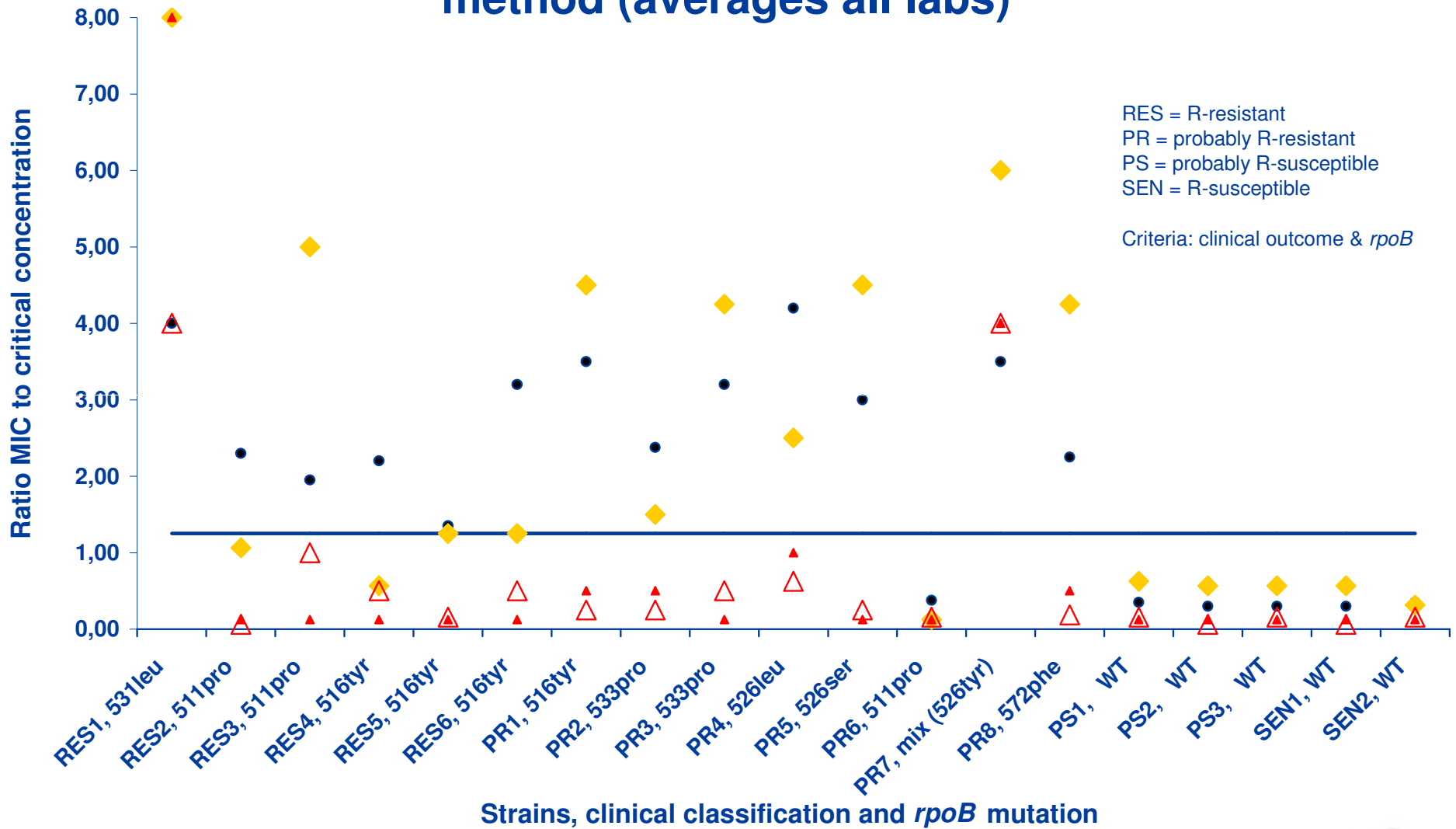


Are investigations needed?

- Partial evidence only
- RMP borderline strains study
 - 9 volunteer SRL; special panel of strains
 - particular mutations: MICs close to the breakpoint
 - systematically missed by BACTEC



Borderline R-resistant strains, variation of MIC by method (averages all labs)



— Resistance cut-off at 1.25X MIC • LJ 1%6W ◆ Agar1% △ BACTEC ▲ MGIT



Antwerp SRL collection

- Ongoing
 - strains with clinical information
 - specific rpoB mutations
 - MIC LJ vs. MGIT result
 - MGIT also at 0.5 $\mu\text{g/ml}$ critical conc.
 - other variations: no time
- Further studies: importance & frequency
 - need to adapt standard methods?



rpoB mutations: MIC on LJ vs. MGIT

LJ MIC	511Pro	513Pro	516Tyr/ Val	522Gln/ Leu	526Asp/ Leu/Tyr	531Leu/ Trp	533Pro	572Phe
20								
40	1							1
80	2							
160	1						1	
320	1		2		1		3	1
640	1			1	2	1		
>640		2		1	5	13		
LJ_MIC_R	5	2	2	2	8	14	4	1
MGIT_1.0_R	0	2	1	1	7	14	0	0
MGIT_0.5_R	1	2	1	2	8	14	0	0





Way Forward

Get more out of SRLN rounds

- Disseminate panels to all the NRL
 - links, regional networks
- TA for individual problems
 - NRL: from their SRL
 - SRL: on demand
- Solve systematic & recurrent problems
 - judicial result hampers further improvements



Improved gold standard ?

- Avoid exclusion of difficult strains
 - most sensitive indicator of quality
- SRL test two drug concentrations for rounds, any method
 - third possible result: “intermediate” (I)
- Judicial result reinforced by genotypic tests (coordinating SRL)
 - <80% concordance phenotypically: always I
 - ≥80%: presence of mutation overrides phenotypic susceptible → I
- Scoring system: takes into account clinical prognosis
 - RMP low-level: predictive of poor outcome
 - INH low-level: not so
 - SM, EMB, SLD: ??



Proposed RMP evaluation

Reported result	Judicial result	Score
S	S	correct
S	R	false
S	I	false
R	S	false
R	R	correct
R	I	correct
I	S	false
I	R	correct
I	I	correct



Proposed INH evaluation

Reported result	Judicial result	Score
S	S	correct
S	R	false
S	I	correct
R	S	false
R	R	correct
R	I	false
I	S	correct
I	R	false
I	I	correct

