An expanded WHO Control panel for surveillance of gonococcal antimicrobial resistance

Joan Knapp, Jo-Anne Dillon, Cathy Ison, Lai-King Ng and John Tapsall

For the International Collaboration on Gonococci

Background

- **1955** onwards: *in vivo* treatment failures were noted and associated with decreased penicillin sensitivity *in vitro*

- **1959** WHO Expert Committee recommended an ‘international reference method’ for *in vitro* testing

- **1965** WHO sponsored collaborative group: Reyn, Bentzon (Denmark), Wilkinson (UK) Thayer (USA)

First International Study

Reyn et al Bull WHO 1965; 32:477

- Quantitative estimates of sensitivity desirable *epidemiologically; for the individual case; treatment failures

- "If the same GC were tested in different laboratories (using different methods) one would expect…somewhat different values"

First International Study

Reyn et al Bull WHO 1965; 32:477

Examined 9 GC in 3 labs by 3 different methods (MICs)

- (a) for effect of method differences; and
- (b) possible use of a ‘corrective co-efficient’ to reconcile differences in MIC values

- Penicillin only (No PPNG)

First International Study Conclusions: Reyn et al

- Each laboratory accurately defined decreased sensitivity, using its own test
- Each laboratory used a different method that gave reproducible results in their own hands
- However, the IC (MIC) numeric values obtained by the three methods were quite different
- IC/MIC differences were non-uniform over the range tested
- Use of a ‘correction co-efficient’ was not possible

First International Study Recommendations: Reyn et al

(i) single reference method (techniques and media) was desirable but it was recognised that this was not possible at that time (*nor is it now*)

(ii) Pragmatic alternative

- Use of reference strains in testing procedures –
- III, V and VII from an earlier Scandinavian study were nominated, and distributed for use (penicillin only)

Increasing Resistance

- 1970's : More chromosomal penicillin resistance PPNG
- Spectinomycin (and other) resistance
- "Updated" set of control strains introduced – Inga Lind
    - WHO A – E
    - Very useful and extensively used

Still more resistance… 1990's

- Quinolones: use and resistance
- Urgent need for update of reference cultures
  - *Was a common method possible?*
  - *Can we make sense of each others data?*
  - **Second International Study – SIS**
- (Jo-Anne Dillon) by 6 reference labs
- Looked at 60 GC once only; 3 North American Labs; UK and Australia; Denmark

Second International Study

- *Consistency and reproducibility of results was high for labs using same or similar methods

  - *Different methods give the same ‘resistance phenotype”, but with different MIC numeric values

- Never published, but need for new reference set increased – azithromycin, quinolones, cephems

- Some GC from the SIS were extensively used as controls in some international and national programmes

Third International Study

- International Collaboration on Gonococci
- PI was Joan Knapp of CDC
- 5/6 labs from second study again participated
- Again compared some widely used methods to
  - *Compare interpretive criteria
- *Use resistance phenotype (R) NOT the numeric MIC value as the ultimate ‘evaluator’
- Develop, evaluate and distribute revised WHO reference panel

Surveillance of gonococcal AMR

- Resistant phenotype detection at 5% level
  - To optimise standardised treatment regimens
    - Criteria for a treatment regimen:

      cure of 95% of cases in a general population
- Conversely, need surveillance system to detect **resistance** at level of at least 5%

Surveillance for *5% resistance* level

- Resistant phenotype detection at 5% level or more is the primary aim

- The actual level of that resistance [numeric MIC] is inconsequential *for this purpose*

  - Can resistant phenotypes be reliably and reproducibly detected,
  - irrespective of the methods used or the (different) MIC values obtained by those methods?

Methods

- 24 ‘candidate’ GC tested in triplicate as unknowns in 5 labs
- Candidate GC nominated to accommodate range of susceptibilities including cefixime*, ciprofloxacin and azithromycin
- Many GC from SIS and were already used elsewhere (one recommended by CLSI), others discarded because of ‘fragility’ on transport

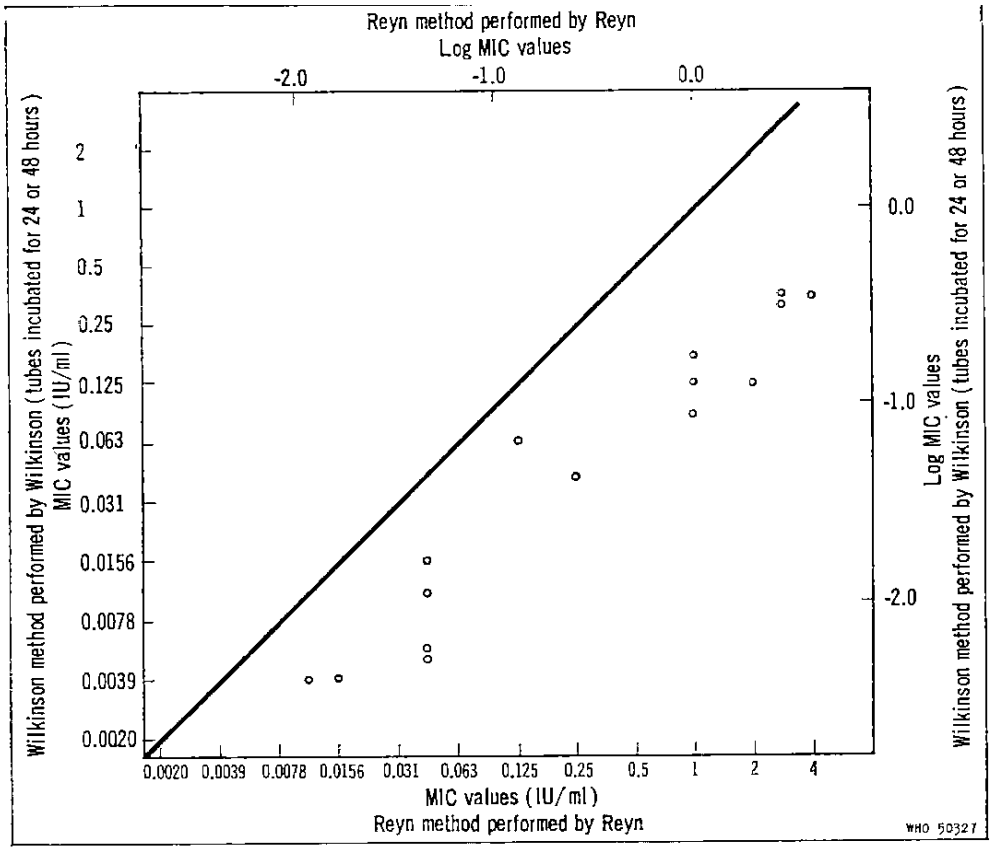
Methods cont

- North America – 3 labs used CLSI criteria and methods
- UK and Australia used similar methods and published criteria
- *Reproducibility* tested by examination in triplicate of unknowns
- *Comparability* by using CDC values as a baseline

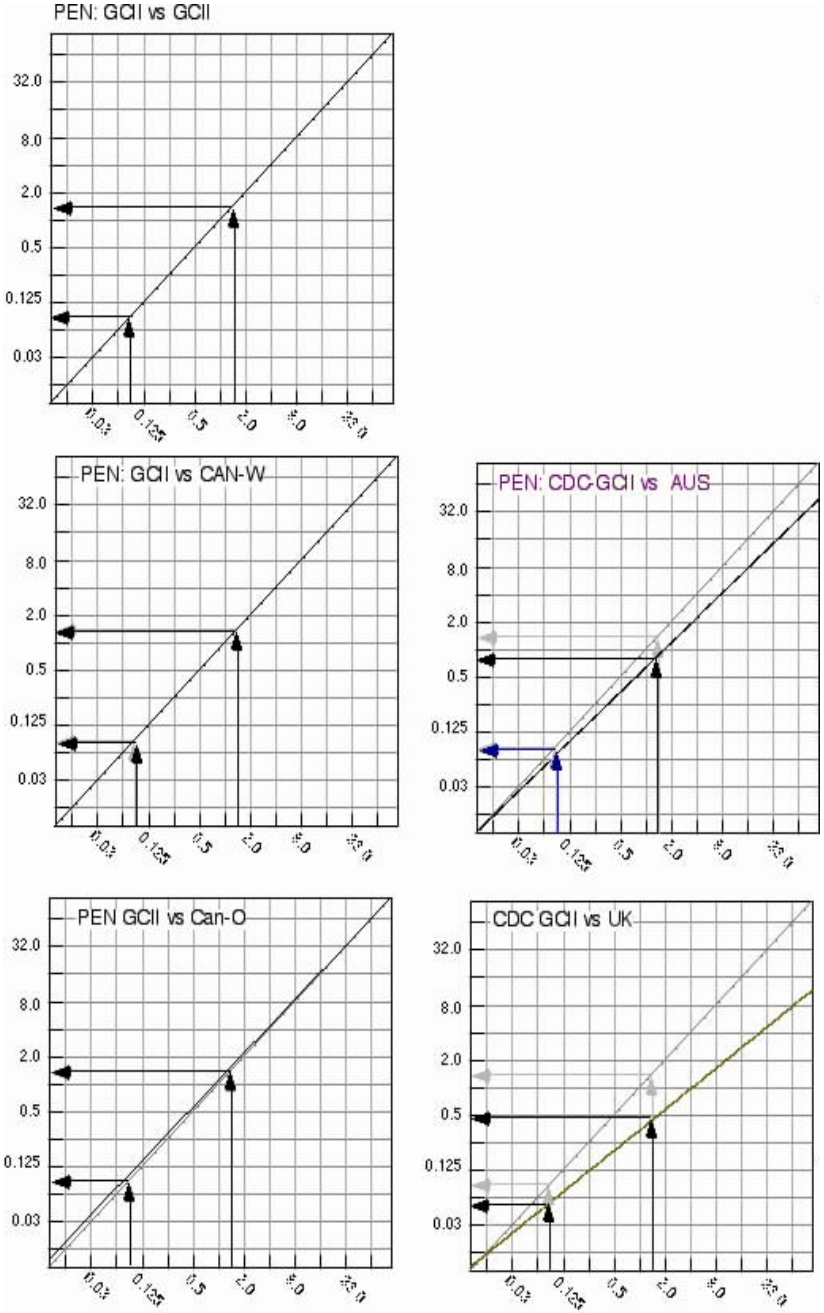
First IS – Reyn et al

FIG. 7

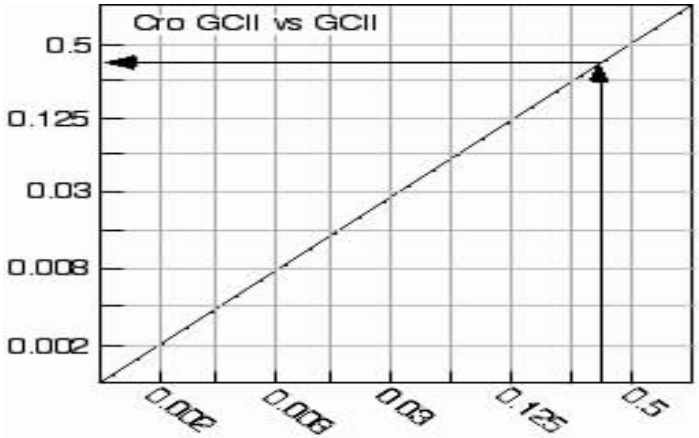
COMPARISON OF MIC VALUES OBTAINED BY THE PLATE DILUTION METHOD OF REYN PERFORMED BY REYN AND BY THE TUBE DILUTION METHOD OF WILKINSON PERFORMED BY WILKINSON

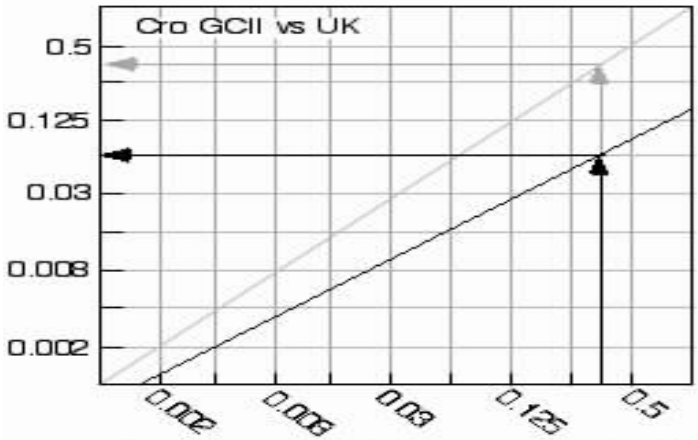


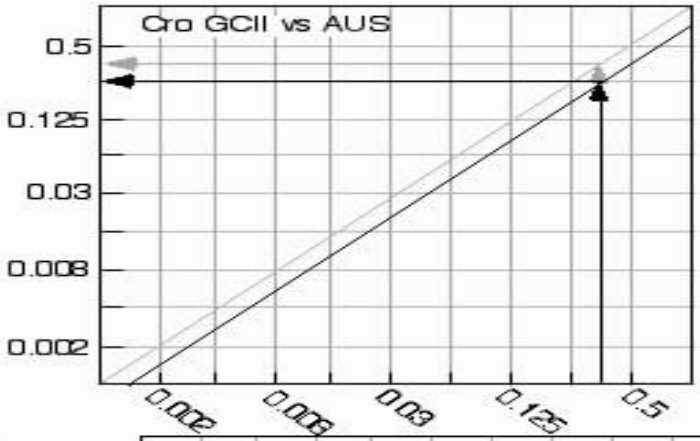
Penicillin

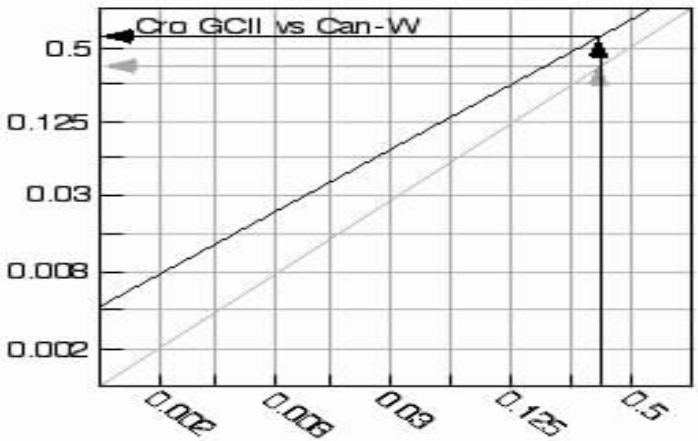

PEN: GCI vs GCII
PEN: GCI vs CAN-W
PEN: CDC-GCI vs AUS
PEN GCII vs Can-O
CDC GCI vs UK
32.0
8.0
2.0
0.5
0.125
0.03

Ceftriax


Cro GCII vs GCII
0.5
0.125
0.03
0.008
0.002
0.002
0.008
0.03
0.125
0.5


Cro GCII vs UK
0.5
0.125
0.03
0.008
0.002
0.002
0.008
0.03
0.125
0.5


Cro GCII vs AUS
0.5
0.125
0.03
0.008
0.002
0.002
0.008
0.03
0.125
0.5


Cro GCII vs Can-W
0.5
0.125
0.03
0.008
0.002
0.002
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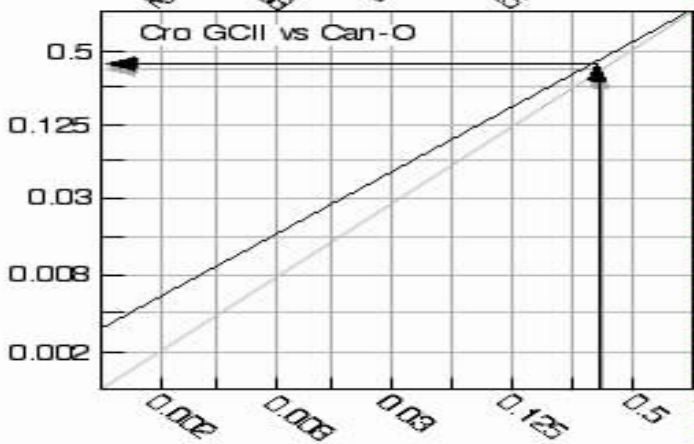
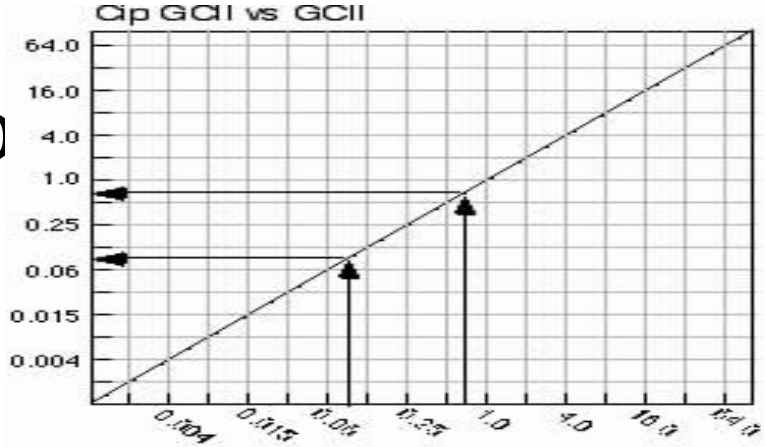
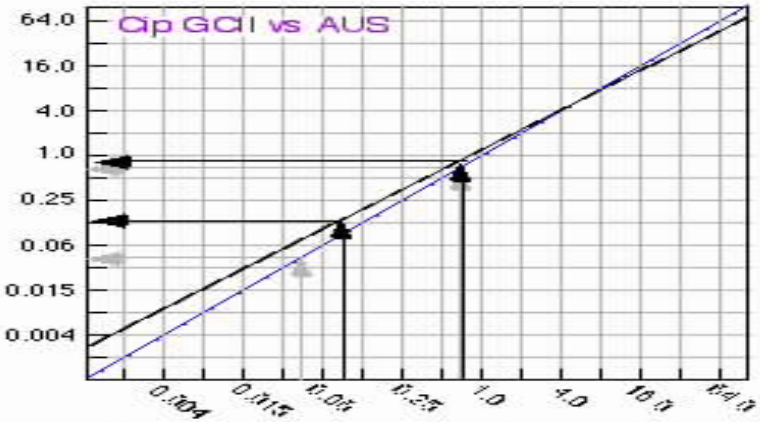
0.125
0.5


Cro GCII vs Can-O
0.5
0.125
0.03
0.008
0.002
0.002
0.008
0.03
0.125
0.5

	Ceftriaxone
	Sensitive
CDC-GCII	**≤=0.25**
Can-Winnipeg	**≤=0.5**
Can-Ontario	**≤=0.25**
Australia	**≤=0.25 [≤=0.03]***
United Kingdom	**≤=0.06**

Cipro


Cip GCI vs GCII
64.0
16.0
4.0
1.0
0.25
0.06
0.015
0.004


Cip GCI vs AUS
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16.0
4.0
1.0
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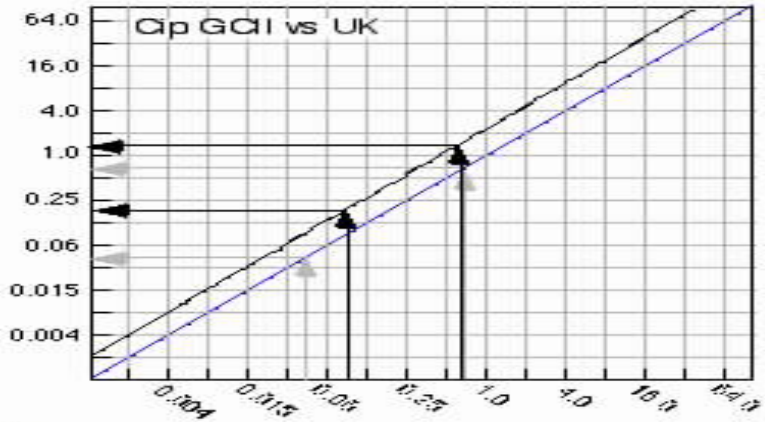
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16.0
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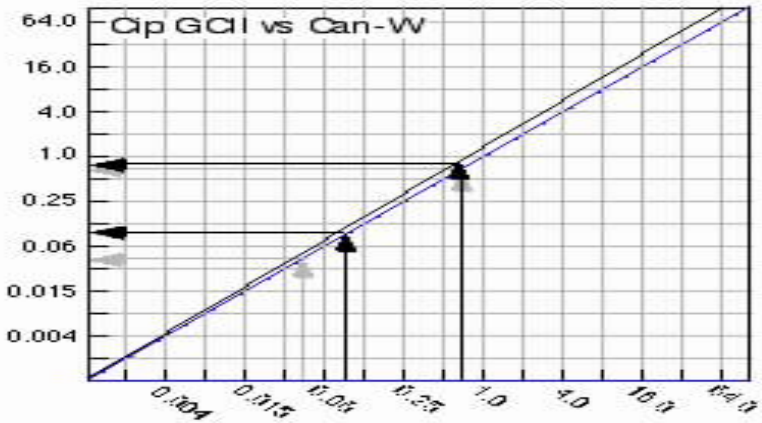
Cip GCI vs Can-W
64.0
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4.0
1.0
0.25
0.06
0.015
0.004

Third International Study Conclusions:

- Each laboratory accurately defined decreased sensitivity, using its own test
- Laboratories using a different methods had reproducible results in their own situation
- However, the MIC numeric values obtained by the different methods were sometimes disparate
- MIC differences were non-uniform over the range tested
- Use of a ‘correction co-efficient’ was not possible

Third International Study Conclusions:

- Resistance phenotype detection valid and comparable for each method
- Must use the nominated method (media, reagents, incubation, end point … *and method specific criteria*)

PRECISELY AND IN FULL

<u>Some further clarification needed regarding cephalosporins</u>

What GC comprise the new panel?

- Many GC were examined in the ICG process
- Provisional standard QC panel of 15 proposed in 2004
  - Trialled for the next 1 - 2 years
- Additional ‘candidate GC’ requested and evaluated in 2006 and also trialled later

- Final wider panel is the 15 GC selected via the ICG process
- Additionally, WHO A – E and CLSI ‘mandated’ strain are available as required

USE

- In internal Quality Control

for resistance screening in individual labs

- Many studies use no, or inappropriate, controls eg A – E for quinolone resistance

- Panel strains will be widely available from a number of sources globally: CDC, WHO

USE

- External Quality Assurance - EQA
- Distributed as ‘unknowns’ for testing
- Duplicates, at least, included for reproducibility
    - Not simply proficiency testing

Applicability

Tested by ICG in formal MIC systems only

- Scandinavian study tested WHO III, V, VII by disc and MIC – equivalent *for this purpose*
  - Disc screening procedures have been extensively evaluated with these strains and Etest procedures have also been investigated

Some of the ‘new’ panel strains

STRAIN ID	ORIGIN
WHO **F**	CANADA
WHO **G**	NSW/THAILAND
WHO **K**	JAPAN
WHO **L**	NSW /ASIA
WHO **M**	NSW/PHILIPPINES
WHO **N**	NSW
WHO **O**	CANADA
WHO **P**	CDC

	STRAIN ID	ANTIBIOGRAM PHENOTYPE	Pen categ	CEFT categ	CEFT MIC	CIP categ	SPEC categ	AZIT categ
1	WHO **F**	PEN S, CIPRO S	S	S		S	S	S
2	WHO **G**	PEN LS, **CIPRO LS,TRNG**	**LS**	S		**LS**	S	S
3	WHO **K**	CMRP,QRNG **CEFTRIAXONE LS**	**CMRP**	**LS***	0.06	**HLR**	S	S
4	WHO **L**	CMRP,QRNG **CEFTRIAXONE LS**	**CMRP**	**LS***	0.125	**HLR**	S	S
5	WHO **M**	**PPNG,QRNG;**	**PPNG**	S		**R**	S	S
6	WHO **N**	**PPNG,QRNG,TRNG;**	**PPNG**	S		**R**	S	S
7	WHO **O**	PPNG,**SpectR**	**PPNG**	S		S	**R**	S
8	WHO **P**	PenLS, **AZITH R;**	**LS**	S		S	S	**R**

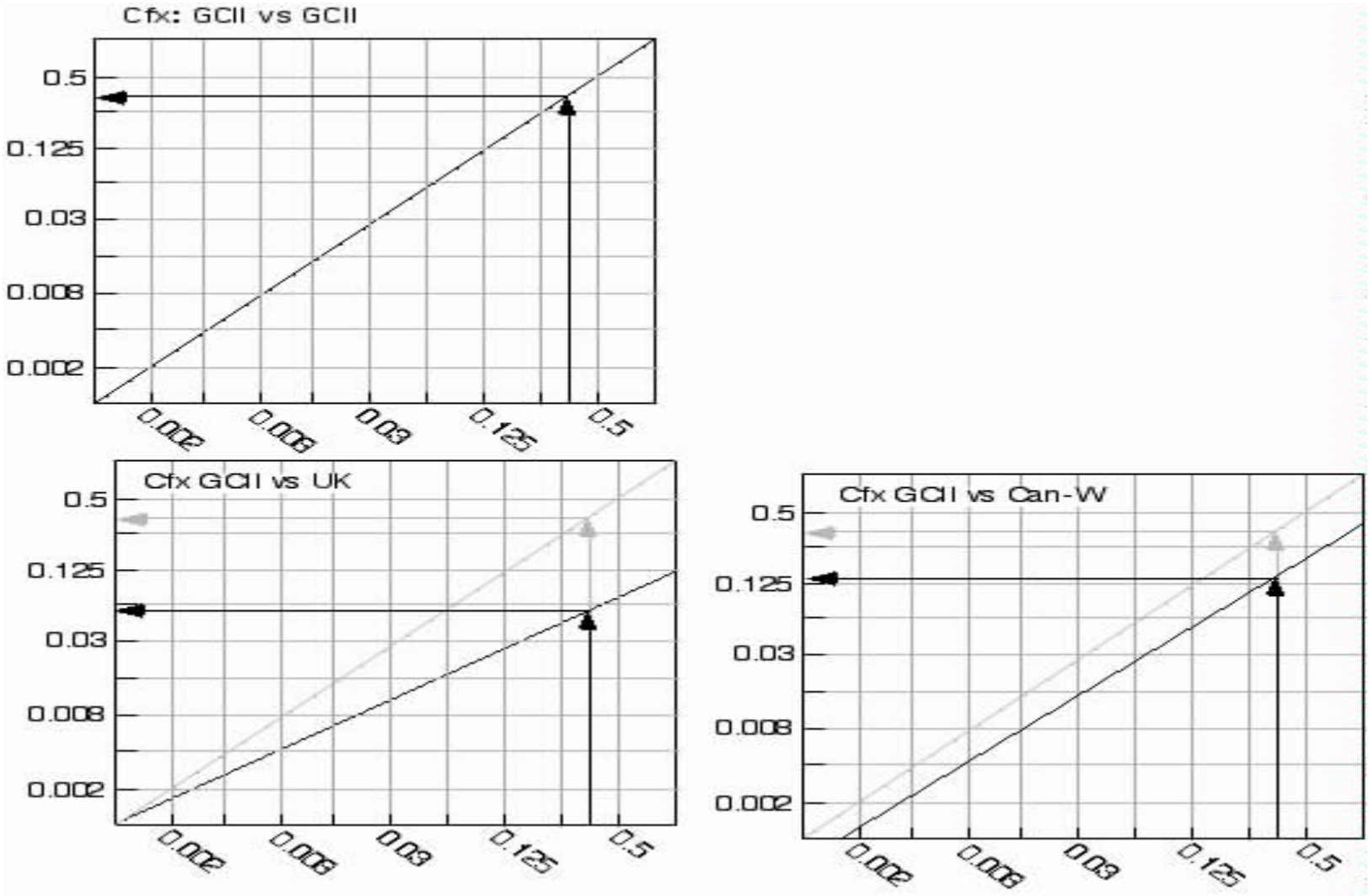
One example of a ‘useful’ panel

STRAIN ID	ANTIBIOGRAM PHENOTYPE
WHO **G**	PEN LS**, CIPRO LS ,TRNG**
*WHO **K**	CMRP, High level QRNG **NOT CEFTRIAXONE LS by CLSI; has mosaic PBP2; oral cephem?**
WHO **M**	**PPNG, Close to breakpoint QRNG;**
WHO **O**	PPNG,***Spectinomycin R**
WHO **P**	PenLS, ***Azithromycin R;**

Limitations

- Cephalosporins
  - *Ceftriaxone cannot be used as a surrogate marker for **oral** cephem resistance*
- Treatment failures increasing with oral cephems (cefixime), but current values defining 'resistance' are too high
- i.e. GC who may fail oral cephem treatment are now not detected – until that failure occurs
  - Insufficient data – more than just resistance screening needed?

Cefixime – only low MICs



Process

- ‘Candidate’ strains are distributed as unknowns
- These are tested in a number of labs
- “Breakpoints” for each method will apply but will also differ
- Consensus on resistance phenotype is obtained

- Strain ‘accepted’, designated, distributed

Summary

- Extensive, expensive and painstaking process required
- Accept that *for this purpose* resistance phenotype detection is the primary aim
- Standard method will not be achieved
- Can compare data from various sources if methods and controls conform
- Reliable and robust controls now available – *except for oral cephems*