Overcoming resistance: Trials, Tribulations & Treatments

Stephen Senn

crp SANTÉ
CENTRE DE RECHERCHE PUBLIC
MÉTHODOLOGY AND STATISTICS

Acknowledgements

Thank to STAT-net for the invitation

This work is partly supported by the European Union's 7th Framework Programme for research, technological development and demonstration under grant agreement no. 602552. "IDEAL"

Some of the work presented is that of a collaboration with my former PhD student Boikanyo Makubate

My basic problem

- Not only don't I have any answers
- I don't even have any sensible questions
- I am going to look at two other fields which *might* have some lessons for bacterial infection
  - HIV therapy
  - Infertility treatment
- However, I shall make some inexpert remarks on the basic problems

Issues/questions

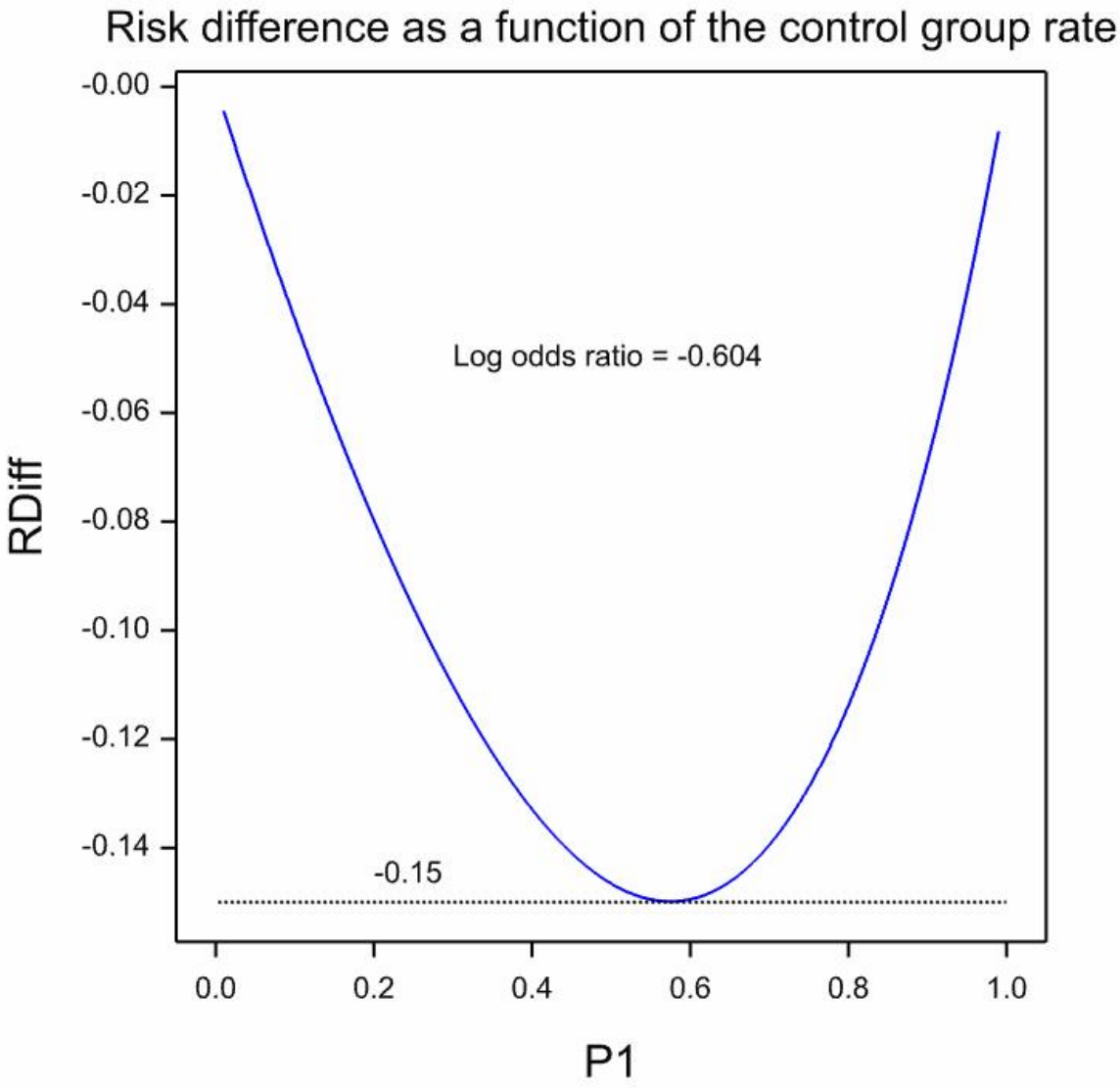
- What do we need to do?
- What do we need to prove/study?
- How are we going to study it?

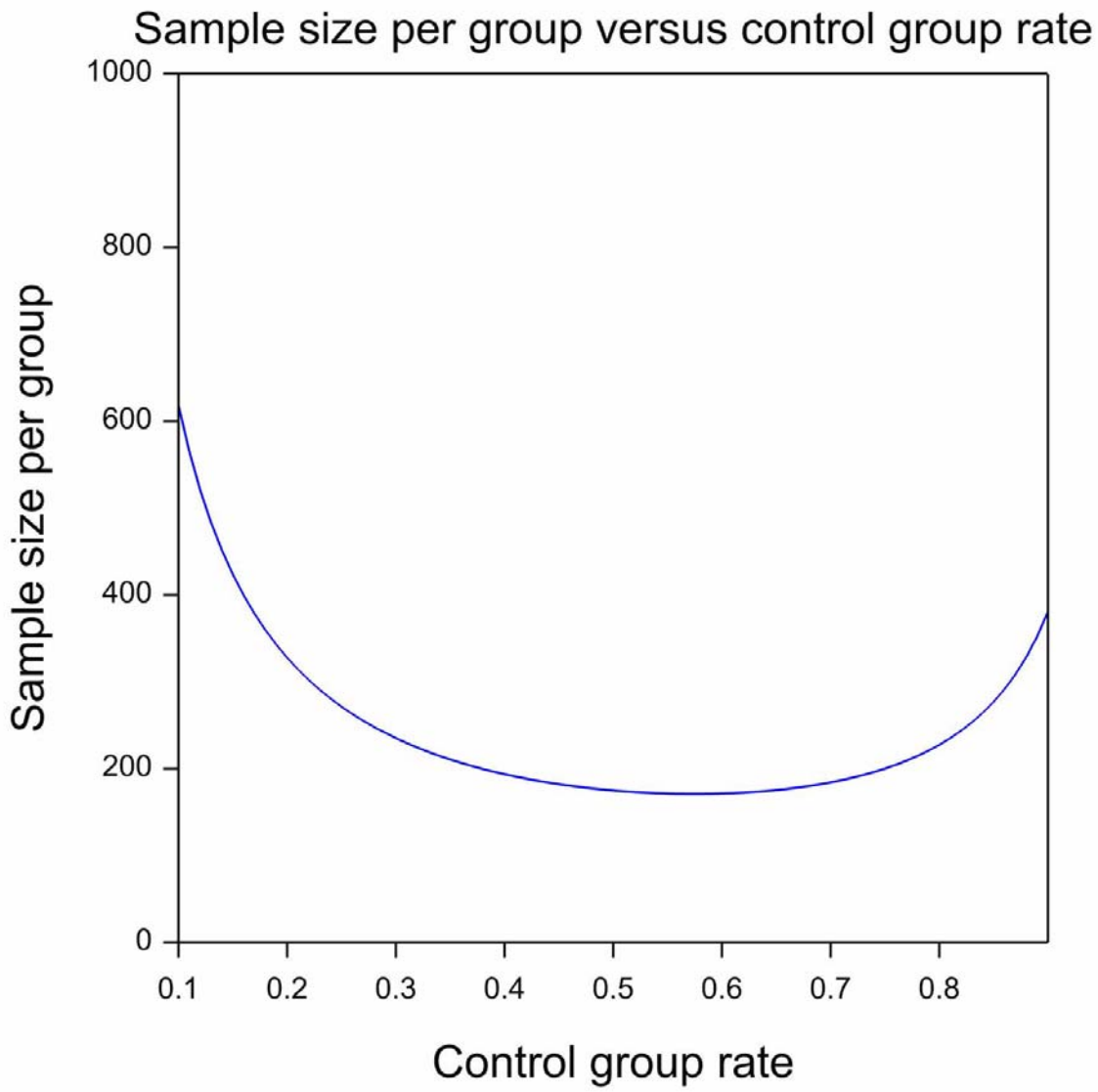
Possible uses of a new antibiotic
(Not necessarily mutually exclusive)

1. To replace existing antibiotics as a first line therapy
2. To treat cases that are resistant to existing antibiotics
3. To be given in combination to improve efficacy
4. To help control spread of resistance
5. To be available as an empirical back up

1. To replace existing antibiotics as a first line therapy

- Presumably requires non-inferiority trial against standard treatment
- Several technical issues and problems
  - Method of the putative placebo
    - Would require extensive data on active comparator compared to placebo
  - Non-inferiority boundary
    - Additive scale might be log-odds ratio but relevant scale could be risk difference
    - Usually large sample sizes required


Risk difference as a function of the control group rate
RDiff
-0.00
-0.02
-0.04
-0.06
-0.08
-0.10
-0.12
-0.14
Log odds ratio = -0.604
-0.15
0.0
0.2
0.4
0.6
0.8
1.0
P1


Sample size per group versus control group rate
Sample size per group
1000
800
600
400
200
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Control group rate

2. To treat cases that are resistant to existing antibiotics

- Should we only treat resistant cases in our trials?
  - If so, based on confirmation in-vitro of isolates?
    - Is this practical/ethical in terms of treatment?
  - Or empirically, using treatment failures ?
    - May work for some chronic infections (e.g. cephalosporin resistant gonorrhea?) but not for life-threatening ones
- Should we treat all cases but stratify post treatment by confirmed infection?

3. To be given in combination to improve efficacy

- Perhaps the control group should be a single standard antibiotic
  - With placebo to the new treatment to ensure blinding
- The combination is compared to this
- Superiority is the objective
- This approach has been a standard in the HIV community
  - To be discussed below
- Selection of cases?

An ethical issue

- Contrary to what many suppose, in serious diseases placebo-controlled trials are the only ethical solution
  - The placebo is given as an add-on
- Active controlled trials would be regarded as unethical
  - Because patients are denied a known effective treatment
- The approach of placebo (as add on) controlled trials with the new as combination has been used regularly among HIV researchers
- Is there a similar ethical imperative for some bacterial infections?

Placebo-controlled trials in AIDS

Author/ Trial	Journal	Year	Purpose	Background Therapy	Arms
Hammer et al	HIV Clinical Trials	2010	Treatment Intensif-ication	ZDV + 3TC+ IDV	Placebo ABC
AVANTI-2	AIDS	2000	Treatment of naïve patients	ZDV +3TC	Placebo IDV
PENTA-4	AIDS	1998	Treatment of children	Various forms of ZDV	Placebo 3TC
Merigan et al	Blood	1991	Treatment of haemophilia	?	Placebo ZDV

An ethical framework for treatment

- We first establish a patient's entitlement *outside the trial*
- Any treatment strategy is compared to this and involves elements of
  - M = maintenance
  - A = augmentation
  - E = elimination
  - S = substitution (which involves some combination of A,M and E)
- Placebos in themselves raise no ethical issues provided that informed consent is applied
- They only raise an issue to the extent that any element of A & E would raise an issue

4. To help control spread of resistance

- There may be a *prima facie* case for treating all infections with a standard and the new therapy in combination
- This seems to be very similar to the previous case
- However the objective is slightly different
- It is not just efficacy in treating current patients that is of interest but effect on the future on spread of disease
- This is clearly potentially very important but it is not obvious what to do

5 To be available as an empirical back up

- We may have no great ambitions for the new treatment, accepting that in many respects it is no better and possible worse than the standard
- However, it gives us another option if the standard fails
- The questions then is, what sort of trial would be appropriate for this?
- Recruit patients who have failed on existing therapy?
- Note, however, that this is precisely what happens in many trials in cancer
  - However, single arm studies are then often used

Could we use ‘cross-over’ trials?

- We compare two antibiotics
  - Only for diseases that are not life-threatening in the short run
- Patients are randomised to receive one or the other
- If they fail on treatment they are switched to the other
- Similar trials have been run in infertility treatment
  - Becoming pregnant is the analogy for being cured of infection

Two Views

CON	PRO
• The effect of treatment is not reversible • There will be missing data • This indication is inherently unsuitable for cross-over trials	• What we have is a parallel group trial with some extra data • How can more data be worse than fewer? • There must be a way of analysing this

The viewpoint of an ‘authority’

Cross-over trials are most suited to investigating treatments for ongoing or chronic diseases: for such conditions where there is no question of curing the underlying problem which has caused the illness but a hope of moderating its effects through treatment.

Who is this ‘authority’?

Stephen Senn

What do we observe?

Consider an AB/BA cross-over in infertility

We code the outcome as 0 for no pregnancy and 1 for pregnancy

We will then observe in each of the two sequences AB and BA the frequency of 00, 01 and 1

Note that 1 represents a marginal collapse of the possible sequence of results 10 and 11. The occurrence of 1 in the first period suppresses the result in the second.

Data from Gregoriou et al

Sequence	Period 1	Period 2	Number of couples
TI/IUI	0	0	20
	0	1	7
	1		4
			31
IUI/TI	0	0	22
	0	1	1
	1		8
			31

Data from Gregoriou et al

Sequence	Period 1	Period 2	Number of couples
TI/IUI	0	0	20
	0	1	7
	1		4
			31
IUI/TI	0	0	22
	0	1	1
	1		8
			31

21

Data from Gregoriou et al

Sequence	Period 1	Period 2	Number of couples
TI/IUI	0	0	20
	0	1	7
	1		4
			31
IUI/TI	0	0	22
	0	1	1
	1		8
			31

22

A Simple Analysis

- Treat the marginal table using the first period data and the conditional table using the second period data as two strata
- Because the second table is a conditional table it can be treated as if it were independent of the first
- Apply the Mantel-Haenszel procedure using period as a stratifying factor

23

Analysis

Alternative tabulation of data

Pregnancy		NO	YES
Period	Treatment		
Period1	IUI	23	8
	TI	27	4
Period2	IUI	20	7
	TI	22	1

Mantel-Haenszel test
Test statistic: 4.198 on 1 d.f. (with continuity)
Probability: 0.040
Common odds ratio: 0.2870
95% confidence interval for common odds ratio (0.09550, 0.8625)
Note: Continuity corrected

log-odds ratio	RBG Standard error
1.248	0.5614

24

A Random Effects Model (Ezzet and Whitehead, 1992)

$$P\left(Y_{ijk}=y_{ijk}\right)=\theta_{ijk}^{\,y_{ijk}}\left(1-\theta_{ijk}\right)^{1-y_{ijk}},\ y_{ijk}=0,1.$$

$$\eta_{ijk}=\log\left[\theta_{ijk}\Big/\left(1-\theta_{ijk}\right)\right]$$

$$\eta_{ijk}=\mu+\phi_{ik}+\pi_{j}+\tau_{[i,j]}$$

$$\phi\sim N\left(0,\sigma^{2}\right)$$

$i = sequence$
$j = period$
$k = couple$

This model has been analysed using maximum likelihood implemented in SAS® and R. However, it has also been used to simulate results when analysed using the MH approach.

25

Analysis of Gregoriou Example

	μ	τ	π
SAS®	-2.47 (0.95)	1.33 (0.64)	-0.18 (0.63)
R®	-2.47 (0.57)	1.33 (0.63)	-0.18 (0.57)
WinBugs®	-2.28 (0.53)	1.32 (0.58)	-0.31 (0.53)
GenStat®	-2.15 (0.51)	1.22 (0.56)	-0.25 (0.52)

26

Conclusions

- It’s all very difficult!
- We should consider purpose first
- Combination trials may be a possibility
  - May make superiority a feasible goal
- There can be ethical constraints for life-threatening infections
- For certain infectious organisms cross-over trials may be a possibility
- In the long term controlling the spread of resistance must become a goal

References

Bax, R., et al. (1999). "Antibiotic clinical trials–the Witley Park Symposium." Clinical Microbiology and Infection **5(12): 774-788.**

Bax, R., et al. (2001). "Surveillance of antimicrobial resistance - what, how and whither?" Clinical Microbiology and Infection **7(6): 316-325.**

Senn, S. J. (2000). "Consensus and controversy in pharmaceutical statistics (with discussion)." The Statistician **49: 135-176.**

Senn SJ. The Misunderstood Placebo. *Applied Clinical Trials 2001;* ***10: 40-46.***

Makubate, B. and S. Senn (2010). "Planning and analysis of cross-over trials in infertility." Stat Med **29(30): 3203-3210.**