Mastering variation: variance components and personalised medicine

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Acknowledgements

This is my 29th ISCB

– Thanks for having put up with me so long

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Basic thesis

- Both sides of the regulatory divide are convinced that there is a strong element of personal response to treatment
- The truth is that nobody knows
- This is because we statisticians have failed to teach others about components of variation
- And some of us have failed to learn about components of variation also

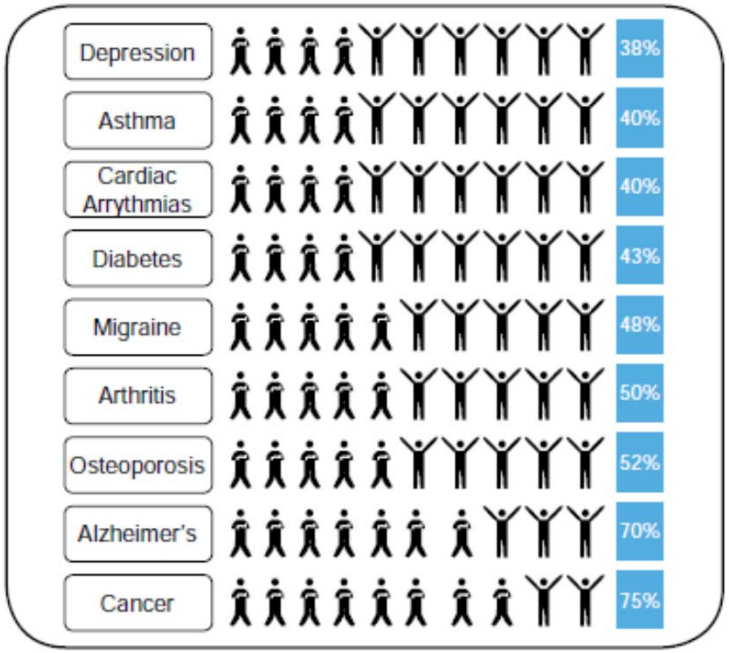
Seven key aspects

1. Better communication of the problems by statisticians to their colleagues
2. *Application of decision analysis to determine when personalisation is worth pursuing*
3. Appropriate design for teasing out components of variation
4. *Application of random effect methodology for improving estimates*
5. *Translating from additive to relevant scales.*
6. Application of Deming´s ideas to understanding the system
7. *Realistic monitoring and feedback*

Chinese whispers 1

Percentage of non-responders

What the FDA says



Paving the way for personalized medicine, FDA Oct2013

Where they got it

Table 1. Response rates of patients to a major drug for a selected group of therapeutic areas[1]

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Spear, Heath-Chiozzi & Huff, *Trends in Molecular Medicine*, May 2001

Chinese whispers 2

Where they got it

Where those who got it got it

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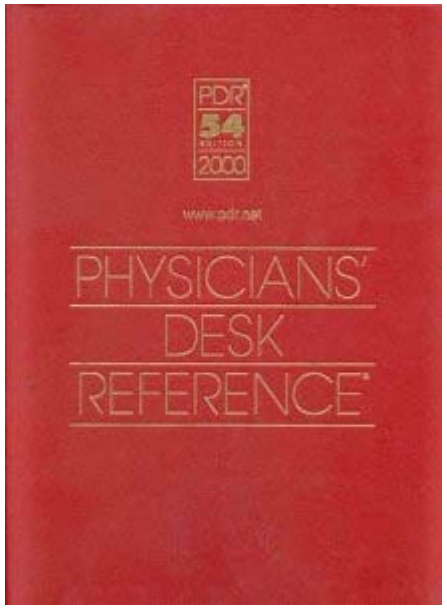


Spear, Heath-Chiozzi & Huff, *Trends in Molecular Medicine*, May 2001

1 Physicians' Desk Reference, 54th Edn., 2000

The Real Truth

- These are zombie statistics
- They refuse to die
- Not only is the FDA's claim not right, it's not even wrong
- It's impossible to establish what it might mean even if it were true

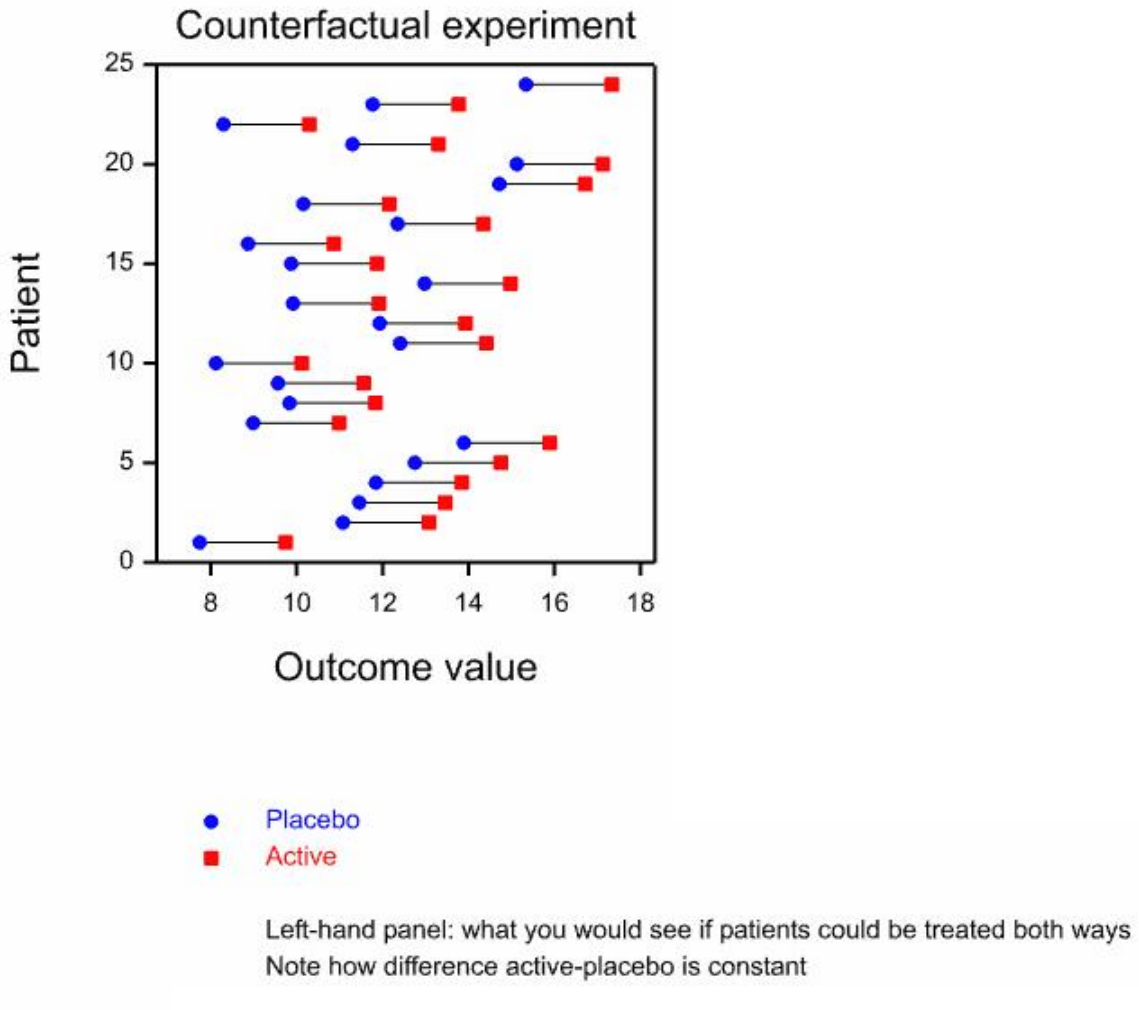
Sources of Variation in Clinical Trials

Label	Source	Description
A	Between treatments	The difference between treatments averaged over all patients
B	Between patients	The difference between patients given the same treatment
C	Patient-by-Treatment Interaction	The extent to which the effect of treatment varies from patient to patient
D	Within patients	The extent to which the results vary from occasion to occasion for patients given the same treatment

Senn SJ. Individual Therapy: New Dawn or False Dawn. *Drug Information Journal* 2001;35(4):1479-1494.

Identifiability and Clinical Trials

Type of Trial	Description	Identifiable Effects	Error Term
Parallel	Each patient is randomised to receive one treatment	A	B+C+D
Cross-over	Each patient receives each treatment in one period only	A and B	C+D
Repeated cross-overs	Each patient receives each treatment in at least two periods	A and B and C	D



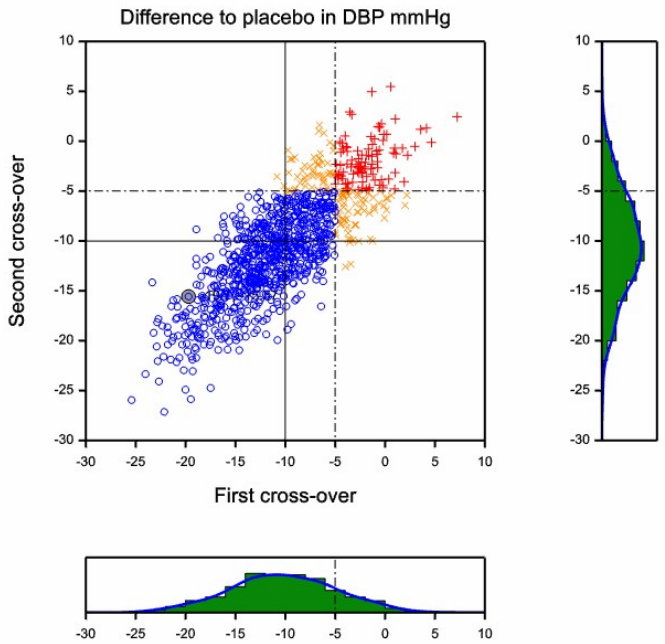
Left-hand panel: what you would see if patients could be treated both ways
Note how difference active-placebo is constant

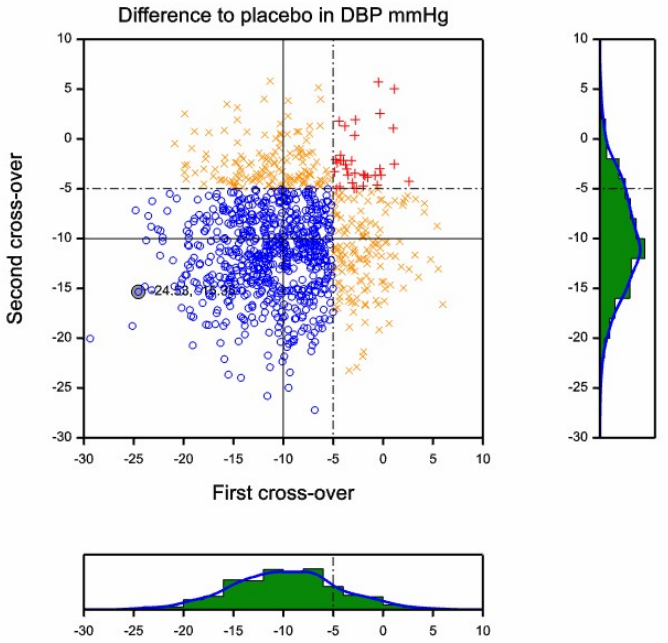
A Thought Experiment

- Imagine a cross-over trial in hypertension
- Patients randomised to receive ACE II inhibitor or placebo in random order
- Then we do it again
- Each patient does the cross-over twice
- We can compare each patient's response under ACE II to placebo twice

Design

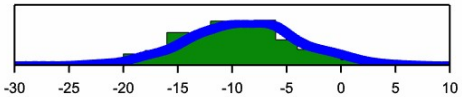
	First Cross-over		Second Cross-over	
	Period			
Sequence	1	2	3	4
I	A	B	A	B
II	B	A	B	A
III	A	B	B	A
IV	B	A	A	B





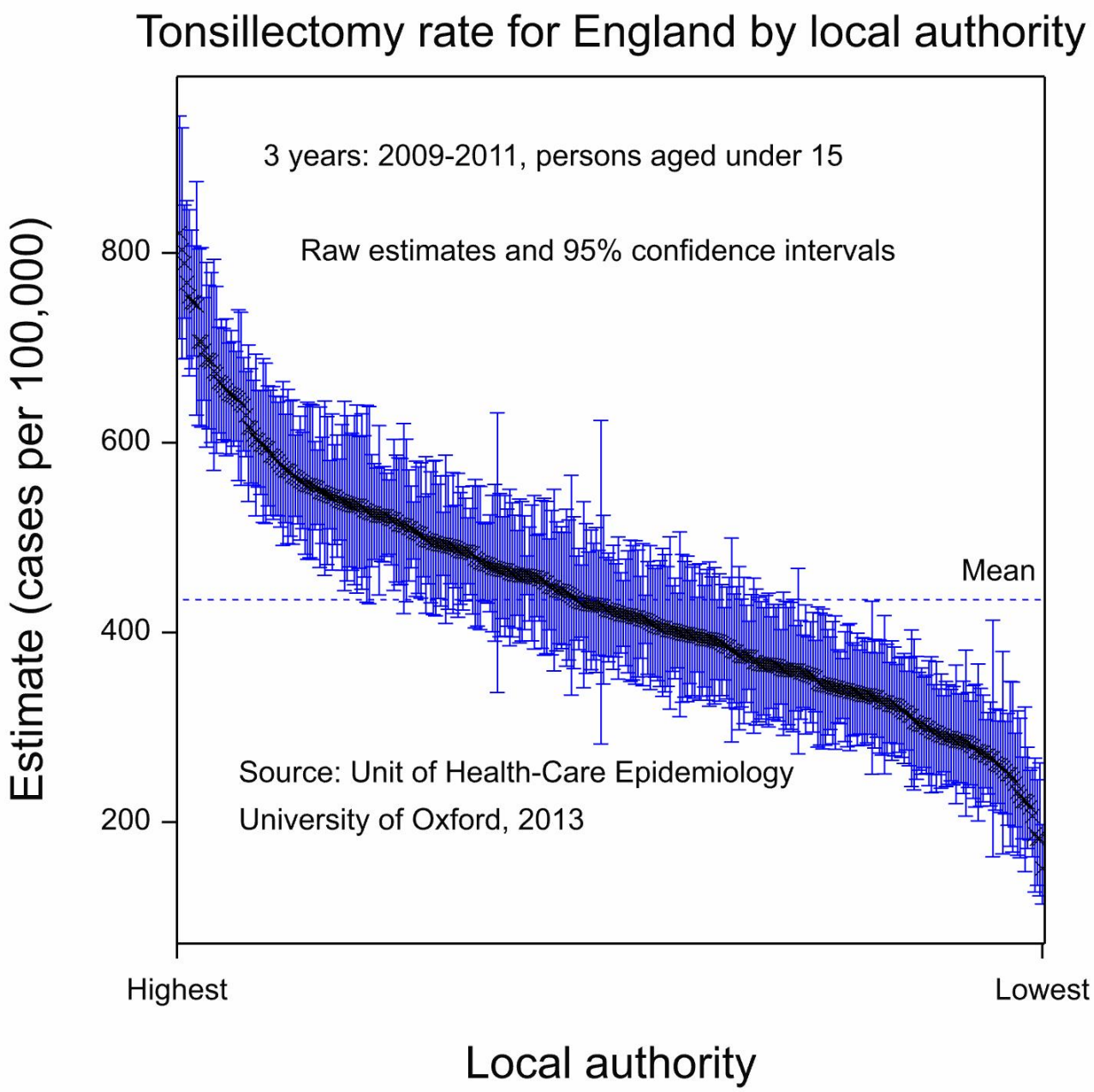
Patients are treated in two cross-over trials , thus permitting two estimates of the difference between active treatment and placebo. The difference on the second occasion is plotted against the first. Blue = response on both occasions, red = non-response on both occasions, orange = response on one occasion but not the other.

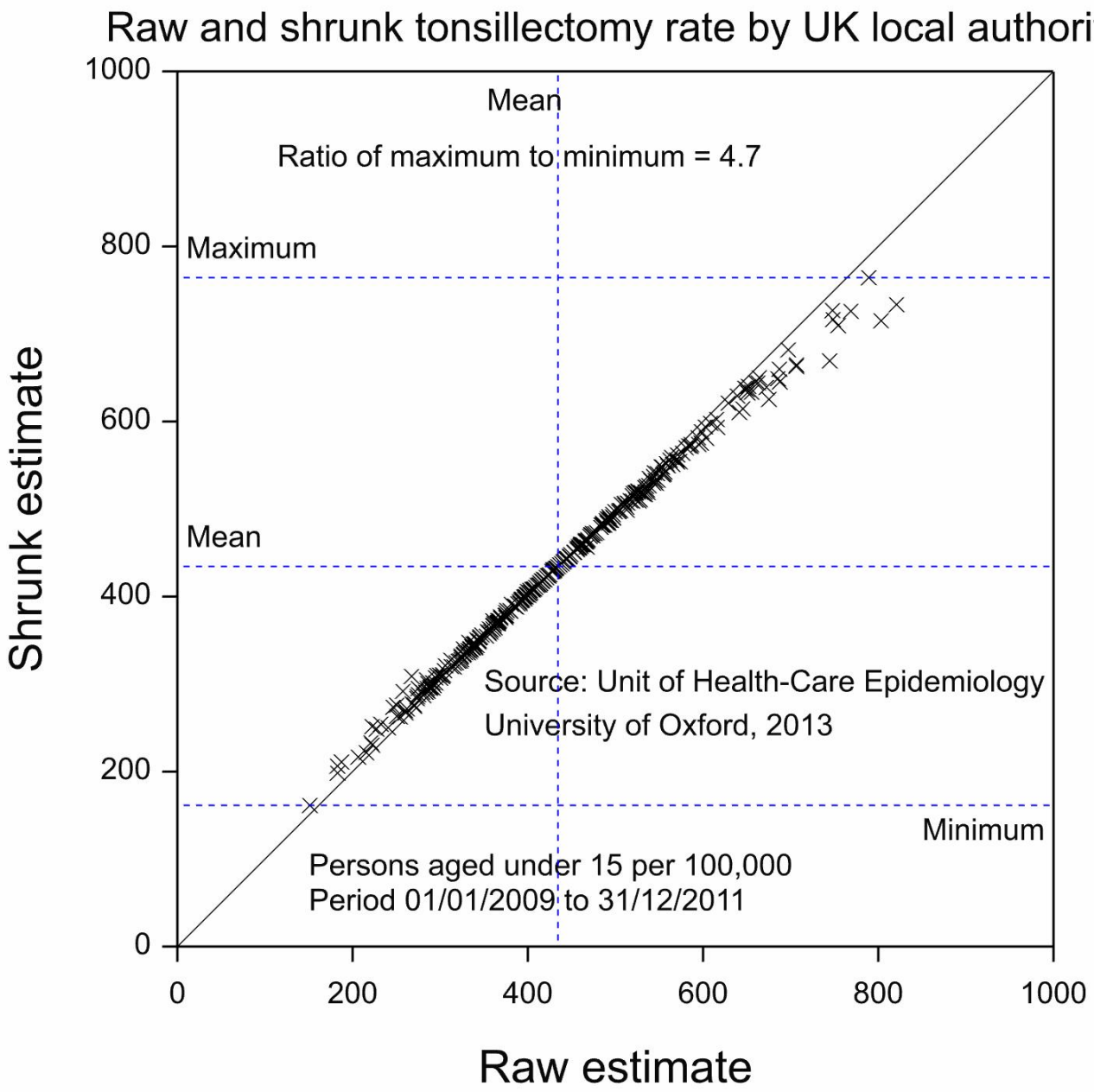
The marginal distributions are given as green histograms. LHS response on first occasion predicts response on second. RHS response on first occasion does **not** predict response on second. If you had only carried out one cross-over you would have the picture below. Which case does it apply to?



In the Meantime

- There is a massive source of unwanted variation
- Doctors
- Variation in practice is so large that it cannot be justified by variation in patients
- This is the basic idea behind the way that Intermountain Health under the leadership of Brent James has been applying Deming's principles to health care


Tonsillectomy rate for England by local authority
3 years: 2009-2011, persons aged under 15
Raw estimates and 95% confidence intervals
Estimate (cases per 100,000)
800
600
400
200
Mean
Source: Unit of Health-Care Epidemiology
University of Oxford, 2013
Highest
Lowest
Local authority


Raw and shrunk tonsillectomy rate by UK local authority
Mean
Ratio of maximum to minimum = 4.7
Maximum
Mean
Minimum
Source: Unit of Health-Care Epidemiology
University of Oxford, 2013
Persons aged under 15 per 100,000
Period 01/01/2009 to 31/12/2011
Shrunk estimate
Raw estimate
0
200
400
600
800
1000

“Guys, it’s more important that you do it the same way than what you think is the right way.”

Brent James, Advice to doctors

Giving this medicine to children:

It is important to know how much your child weighs to make sure you give them the correct amount of medicine. As a guide a child of 9 years of age will weigh about 30 kg (four and a half stone). If in doubt weigh your child, then follow the instructions in the table.

Do not give to children who weigh less than 30 kg.

Do not give to children under 2 years.

Age	How many to take	How often to take
Adults and children of 12 years and over	One tablet	Once a day
Children of 2 to 11 years who weigh **more than** 30 kg		
Children of 2 to 11 years who weigh **less than** 30 kg		

Who's to blame?

- You are
  - (And me)
- Our life scientist colleagues don't understand variation
- You do
- Tell them the truth

The supply of truth always greatly exceeds its demand

John F Moffitt