INTERVENTIONS TO REDUCE INAPPROPRIATE ANTIBIOTIC PRESCRIBING IN HOSPITALS (ANTIBIOTIC STEWARDSHIP)

Erwin M Brown

Frenchay Hospital

Bristol, UK

Reduce inappropriate antibiotic prescribing

- Report by the House of Lords Select Committee on Science and Technology: "Resistance to Antibiotics and other Antimicrobial Agents"
- Sub-Group on Antimicrobial Resistance of the Standing Medical Advisory Group: "The Path of Least Resistance"
- HSC 1999/049: "Resistance to Antibiotics and other Antimicrobial Agents"
- Invitational EU Conference on the Microbial Threat: "The Copenhagen Recommendations“
- Goldmann *et al*. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *JAMA* 1996; **275**: 234-40.

Response to challenges to reduce inappropriate antibiotic prescribing

Community

Antibiotic prescriptions in the UK fell by 25% between 1995 and 2000 (Wrigley & Majeed. *Health Stat Q* 2002; **14**:14-20)

47% reduction in prescribing to children, 1993-2002 (Kendall *et al. Arch Dis Child* 2004; **89**: A1)

Finkelstein *et al*. *Pediatrics* 2003; **112**: 620-7. Reduction in antibiotic use among US children, 1996-2000.

3 months - <3 years: 24%

3 years - <6 years: 25%

6 years - <18 years: 16%

(reduced numbers of prescriptions for OM accounted for 59% of total)

Hospitals

Muller-Pebody *et al*. *Journal of Antimicrobial Chemotherapy* 2004; **54**: 1122-6.

Hospital antimicrobial use in Denmark 1997-2001 increased by 18%

Stichting Werkgroep Antibioticabeleid (SWAB) [Online.]

Hospital antimicrobial use in The Netherlands 1997-2000 increased by 10.6%

Woodford *et al. J Antimicrob Chemother* 2004; **53**: 650-2.

of 253 UK hospitals surveyed:

formulary	76%
policy	56%
guidelines	87%

marginal changes compared with previous survey more than 1 decade previously (Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 1994; **34**: 21-42)

Lawton *et al. Infect Control Hosp Epidemiol* 2000; **21**: 256-9.

1998 survey of US hospitals: 70% provided guidelines for antibiotic usage

Diekema *et al. Clin Infect Dis* 2004; **38**: 78-85.

survey of 494 US hospitals:

antibiotic guidelines implemented	60%
appropriate resources to prevent antibiotic resistance	53%

Sunenshine *et al. Clin Infect Dis* 2004; **38**: 934-8.

of 502 IDSA respondents only 50% reported that restricted antibiotics were issued only after approval by an ID physician

Obstacles to reducing inappropriate antibiotic prescribing in hospitals

- failure of healthcare workers to accept ownership of ‘antibiotic resistance’
- difficulties in changing behaviour
- inadequate resourcing
- ‘process’ (optimal interventions) not defined

British Society for Antimicrobial Chemotherapy/Hospital Infection Society Joint Working Party on Optimising Antibiotic Prescribing in Hospitals (1999)

- membership: medical microbiologists (E. Brown, L. Fenelon, I. Gould, G. Hartman, M. Wilcox)

  infectious diseases physicians/clinical pharmacologist/epidemiologist (P. Davey, R. Finch, A. Holmes)

  surgeon (E. Taylor)

  pharmacist (P.Wiffen)

  statistician (C. Ramsay)

  international advisors (J.Garau, H. Goossens, P. Gross, E. Rubinstein)

Systematic Review

- *Objective*: to identify interventions designed to optimise antibiotic prescribing in hospitals

- *Literature search strategies (to November 2003)*

1. MEDLINE, Cochrane database and EMBASE searched from 1980 onwards (common search terms)
2. MEDLINE (1966-2000), using PubMed and OVID, and Cochrane database (different search terms)
3. Cochrane EPOC specialised register, compiled by searching MEDLINE (from 1966), Health STAR (back to 1975) and EMBASE (from 1980)
4. Manual search of References section of each paper

- **Yield**: 743 articles; 350 since 1980 contained original data about interventions in hospitals

- Criteria for inclusion in Cochrane Collaboration Effective Practice and Organization of Care Group (EPOC) review:

  Study design: Randomised controlled trials (RCT)

  Controlled clinical trials (CCT)

  Controlled before and after studies (CBA)

  Interrupted time series (ITS) (≥3 data points before and after intervention and a clearly defined point in time when the intervention was implemented)

- 350 studies

  invalid: 252 (72%) comprising:

  164 uncontrolled before and after studies (65%)

  79 inadequate ITS (31%)

  9 case-control studies (4%)

  leaving: 98 (28%)

- *Methodological inclusion criteria*

  (a) The study involved objective measurement of performance/provider behaviour of health/patient outcomes(s) in a clinical not test situation

  (b) Relevant and interpretable data presented or obtainable

- 98 studies

  excluded: 32 (9.1%) comprising:

  12 clinical trials (7 RCT, 5 CCT) with no relevant/interpretable data

  10 CBA with no relevant/interpretable data

  4 ITS with no relevant/interpretable data

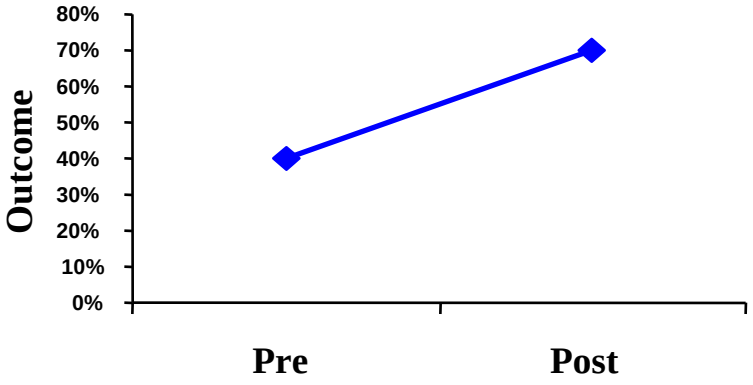
  3 secondary publications

  1 flawed CBA

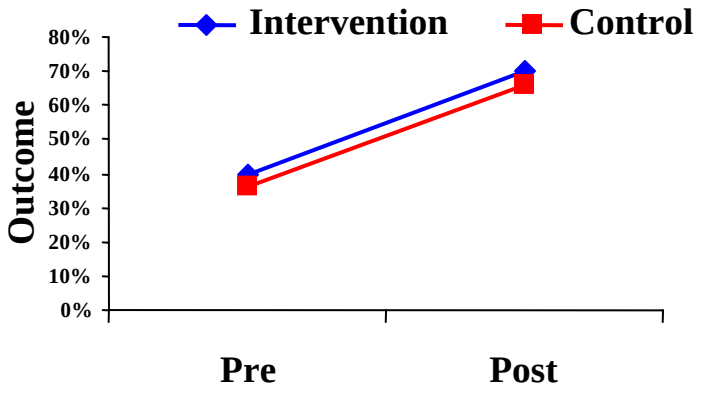
  2 flawed RCT

  included: 66 (18.9%): 43 ITS, 13 RCT, 6 CBA, 2 CCT, 1 cluster RCT, 1 cluster CCT

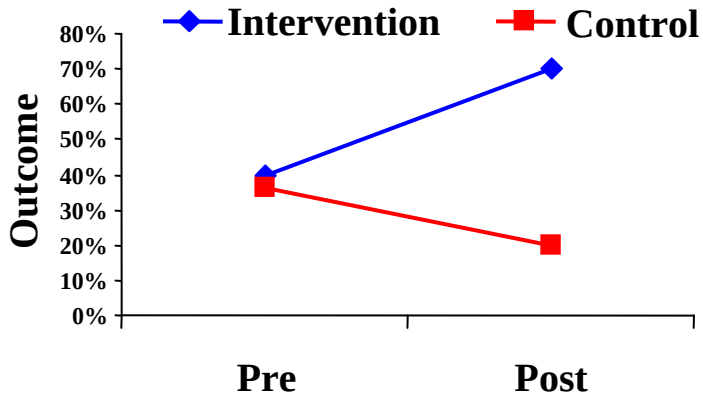
What is wrong with Uncontrolled Before & After Analysis?



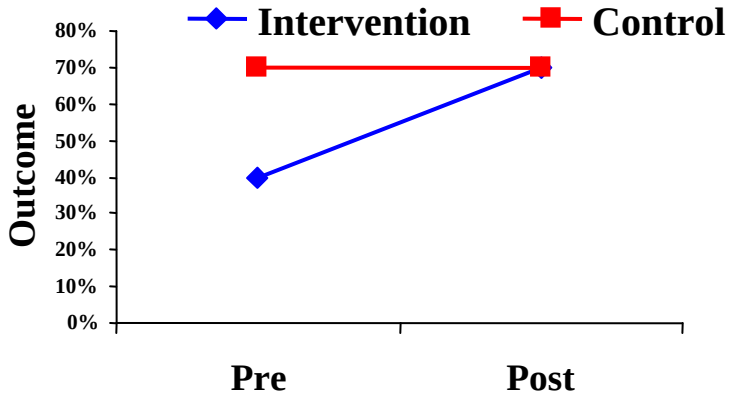
1: A similar change may have occurred anyway



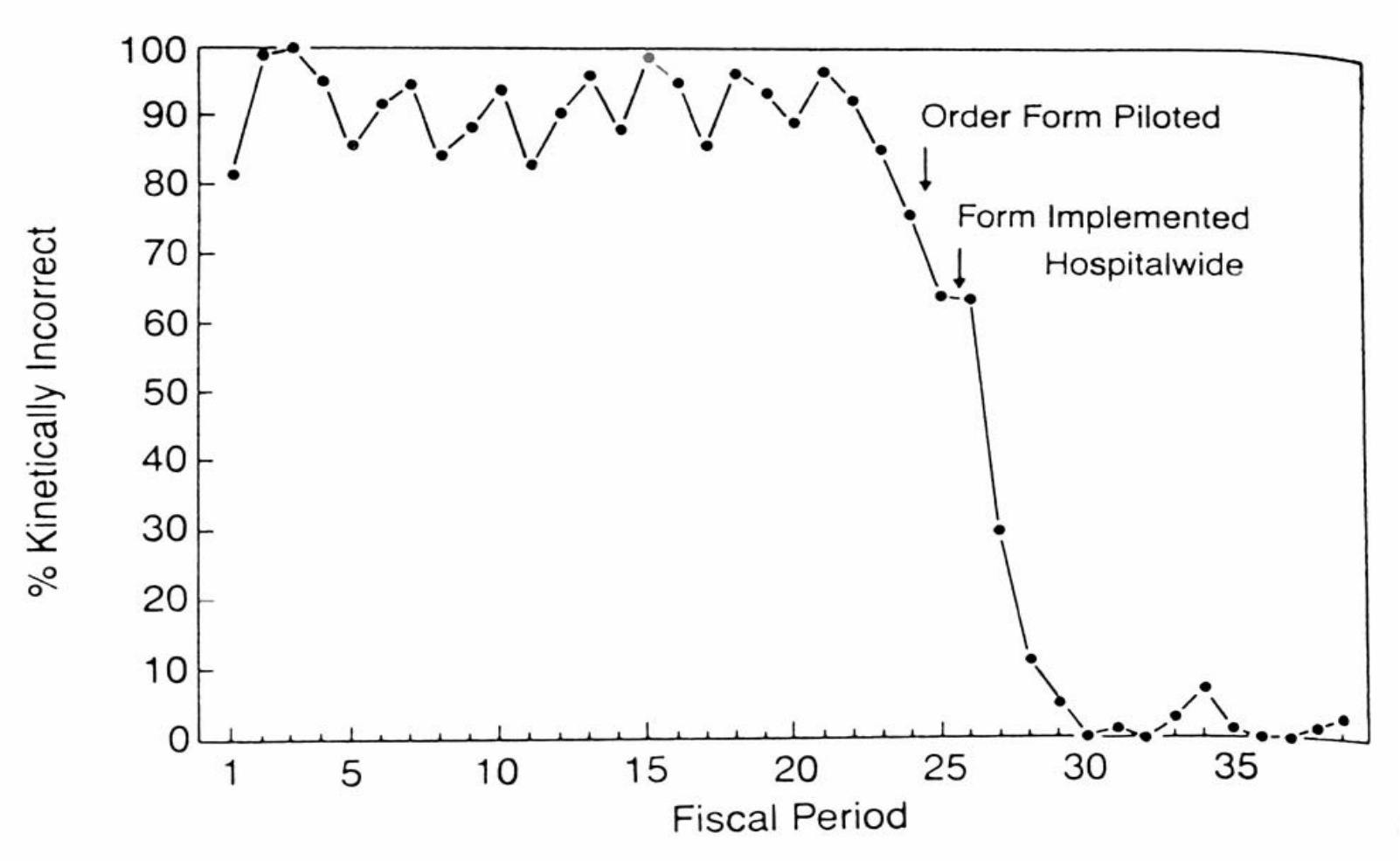
2: Or effect size may be under-estimated



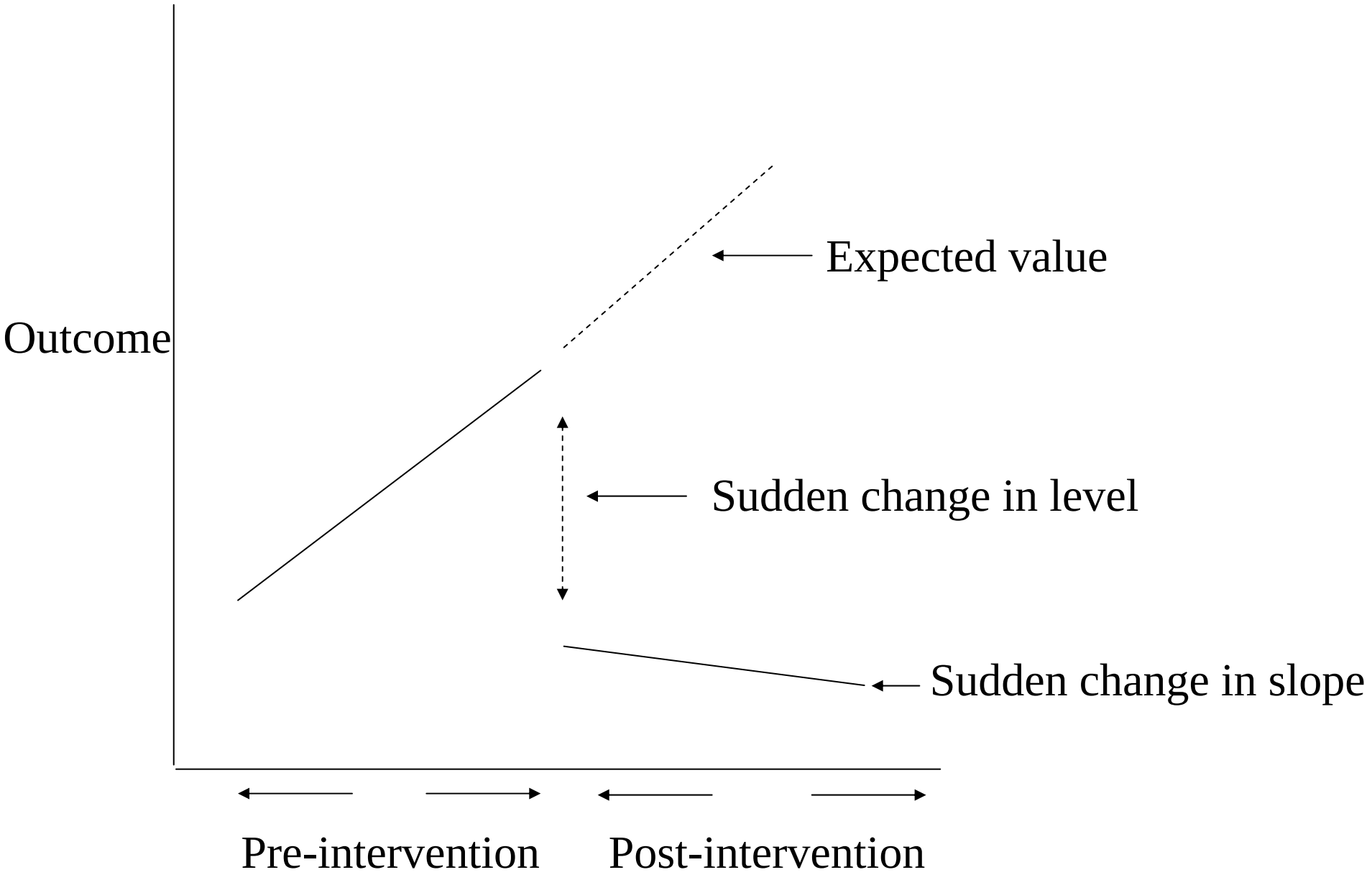
3: Or change in the intervention group may be just regression to the mean



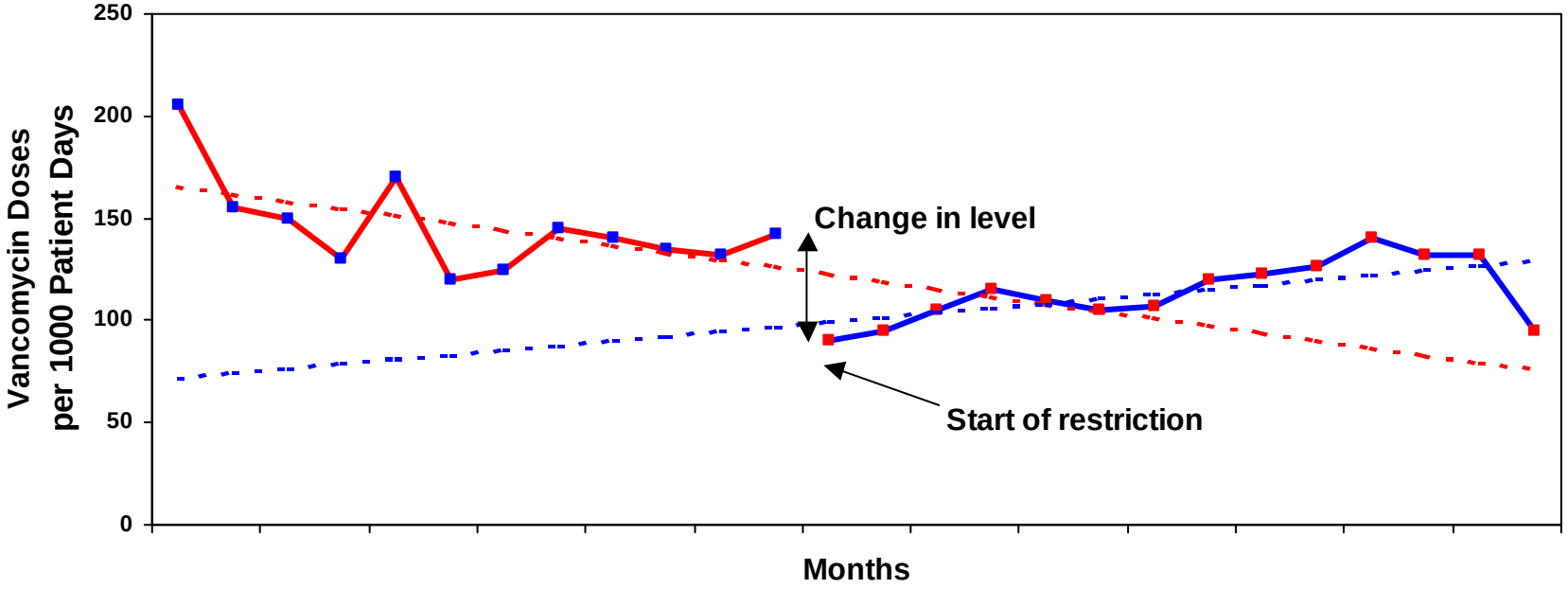
ITS study of clindamycin use patterns before and after introduction of form



Graphic illustration of segmented regression analysis of ITS data



Belliveau *et al*. Limiting vancomycin use to combat vancomycin-resistant *Enterococcus faecium*. *American Journal of Health-System Pharmacy* 1996; **53**: 1570-5.



Δ (post-intervention – pre-intervention)		***P***
Δ in mean	Decrease by 31 doses/1000 patient days	<0.001
Δ in level	Decrease by 23 doses/1000 patient days	0.05
Δ in slope	Increase by 6 doses/1000 patient days	<0.001

Types of interventions

1. Review/recommend changes to antibiotic therapy (*n*=16)
2. Expert approval of restricted drugs (*n*=14)
3. General education (academic detailing, lectures, posters, newsletters *etc*) (*n*=13)
4. Removal/restriction (*n*=9)
5. Reminders (*n*=8)
6. Antibiotic guidelines (*n*=5)
7. Antibiotic order form for restricted drugs (*n*=5)
8. Audit and feedback (*n*=4)

9. Cycling/rotation (*n*=4)
10. Clinical practice guideline/care pathway (*n*=3)
11. Therapeutic substitution (*n*=3)
12. Automatic antibiotic stop-order policy (*n*=2)
13. Rapid identification and susceptibility testing (*n*=2)
14. Opinion leaders (*n*=2)
15. Therapeutic drug monitoring (aminoglycoside dosing optimisation programme) (*n*=1)
16. Compulsory computer (*n*=1)

Efficacies of single *versus* multiple interventions

Intervention	No. (%) effective	
	Yes	No
Single (*n*=44)	35 (80)	9 (20)
Multiple (*n*=22)	16 (73)	6 (27)
All (*n*=66)	**51 (77)**	**15 (23)**

Educational *versus* restrictive interventions

Intervention	No. (%) effective
Educational single	6/17 (68)
Educational multi	9/12 (75)
Restrictive single	21/24 (87)
Restrictive multi	2/3 (67)
Combined multi	5/7 (71)

Educational *versus* restrictive interventions (meta-regression analysis)

- allows comparison of short-term effects only
- restrictive interventions have a greater (>3-fold) immediate impact than educational interventions

Efficacies of interventions

Intervention	*n*	Effective	
		Yes	No
Review/recommend changes	12	9	3
Expert approval	10	8	2

Microbiological outcomes

- 16 studies reported data on 20 microbiological outcomes (AGNB, 10; CDAD, 5; VRE, 3; MRSA, 2)
- 4 studies provided strong evidence of improvements in microbiological outcome secondary to changes in prescribing
- 8 studies provided less convincing evidence

    2 showed significant changes in prescribing associated with non-significant changes in the incidence of CDAD

    6 showed significant improvements in microbiological outcome, but provided no reliable data about effect on prescribing (potential alternative explanations for results)

- 4 studies yielded unequivocally negative results (1 showed a change in prescribing, 1 showed no change in prescribing and 2 provided no data on prescribing)

- The most consistent data concern CDAD: of 5 studies, 4 interventions were effective in terms of reducing incidence and 1 showed a trend toward reduced incidence [Caveat: there were potentially important differences in case definitions of CDAD]

Conclusions: The evidence supports the theory that limiting the use of specific agents will reduce the incidences of CDAD. For Gram negatives and -positives there is insufficient evidence to allow meaningful conclusions.

Clinical outcomes

- Insufficient data to allow reliable conclusions.

Cost of interventions

- may be substantial
- may not be offset by savings

Conclusions

Design issues

- The 66 studies included in the review represent <20% of the published literature which is still dominated by UBA and inadequate ITS.
- Even the 66 studies suffer from methodological flaws.
- Contamination from intervention to control arms was common owing to frequent use of single hospital sites.

- There is little evidence of external validity (only 5 studies evaluated interventions in ≥10 hospitals).
- The designs and outcome measures of studies involving the same type of intervention were not standardised.
- ITS is the most robust design for evaluating interventions in single hospitals. To protect against bias and confounding arising from changes over time and with season, 12 months of data before and after an intervention are needed (only 2 ITS fulfilled this criterion).

- Inappropriate statistical analysis of the results of ITSs overestimated the magnitude of the effect in some studies.
- The absence in most studies of standardised prescribing data confounds efforts to compare the efficacies of the same or different types of intervention.
- Many studies involved >1 intervention to reduce inappropriate prescribing.
- Many studies suffered from potential confounding (implementation or enhancement of infection control interventions) which hampers evaluation.
- Many studies which evaluated effects on microbiological outcome monitored incidences of infection rather than incidences of colonisation.

Intervention issues

- There are too few studies of the efficacies of individual interventions to allow reliable conclusions about the efficacy of each.
- As no study compared the efficacies of the different types of intervention it is not possible to reach conclusions regarding the most effective intervention(s) or combination(s) of interventions.
- Because pharmacists were the principal deliverers of interventions and they used prescribing data as the only outcome measure it is not possible to relate the effects of changes in prescribing data on clinical or microbiological outcomes.

- With the exception of a possible benefit in terms of reducing the incidence of *C. difficile*-associated diarrhoea it is not possible to draw meaningful conclusions about the effects of interventions on microbiological outcomes (resistance rates) (infection control interventions as confounding variables).
- There are only limited data for clinical outcome.
- There is inadequate information to enable conclusions to be reached about the safety of interventions to reduce inappropriate antibiotic prescribing.

Summary

- Absence of evidence is not the same as evidence of absence.
- Several interventions to optimise antibiotic prescribing can improve the therapy of hospital inpatients (with improvements in clinical or microbiological outcome).
- Which interventions?
- Superiority of multiple interventions over single interventions not confirmed, but it is likely that multiple interventions will be implemented.
- Restrictive interventions are more effective than educational interventions, at least in the short term.

Ideal study design

- ITS with at least 12 data points (months) before and after implementation of the intervention
- multicentre
- adequate power based on current time trends
- prescribing data and clinical and microbiological outcome measures
- minimise confounding
- published evidence and the need to measure prescribing, clinical and microbiological outcomes favour a multidisciplinary approach

Interventions to improve antibiotic prescribing practices for hospital inpatients

P Davey, E Brown, L Fenelon, R Finch, I Gould, G Hartman, A Holmes, C Ramsay, E Taylor, M Wilcox, P Wiffen

The Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003543. DOI: 10. 1002/14651858. CD003543. Pub2.

WHICH FACTORS INFLUENCE THE SUCCESS OF INTERVENTIONS TO REDUCE INAPPROPRIATE ANTIBIOTIC PRESCRIBING IN HOSPITALS?

Obstacles to reducing inappropriate antibiotic prescribing in hospitals

- failure of healthcare workers to accept ownership of 'antibiotic resistance'

education – undergraduate: *recognition/diagnosis of infection*

appropriate investigations

principles of prudent antibiotic prescribing

Davenport *et al. Journal of Antimicrobial Chemotherapy* 2005;**56**:196-203

influence of opinion leaders/consultants

- difficulties in changing behaviour

  Sbarbaro. Clin Infect Dis 2001; ***33*** *(Suppl 3): S240-4*

  "Changing physician behaviour is considered by many to be an exercise in futility - an unattainable goal intended only to produce premature ageing in those seeking the change. The more optimistic might describe the process as uniquely challenging."

  educational versus restrictive interventions

  educational interventions (passive activities, such as pharmacy bulletins and newsletters, lectures, conferences, handbooks) are of limited efficacies and effects are not sustained unless constantly reinforced

- inadequate resourcing

  adequate resourcing to enable implementation of interventions (including antibiotic pharmacists)

  Knox *et al. J Hosp Infect* 2003; **53**: 85-90.

  Weller & Jamieson. *J Antimicrob Chemother* 2004; **54**: 295-8.

  Wickens & Jacklin. *J Antimicrob Chemother* 2006; **58**: 1230-7.

- 'process' (optimal interventions) not defined

  *Dellit et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for developing an institutional program to enhance antimicrobial stewardship. Clinical Infectious Diseases 2007; **44**:159-77.*

  considered only small proportion of the published literature (n=174 versus 884)

  no critical evaluation of the literature

  no robust recommendations

Antimicrobial stewardship programme

- multidisciplinary team
- multifaceted interventions (consistently more effective than single interventions; Grindrod *et al*. *Ann Pharmacother* 2006; **40**: 1546-57)

Core interventions

- formulary + restrictions (expert approval)
- audit and feedback of antimicrobial use

Other interventions

- education

  Grindrod *et al*. What interventions should pharmacists employ to impact health practitioners' prescribing practices? *Ann Pharmacother* 2006; **40**: 1546-57. (systematic review)

  - consistently effective interventions: reminders (manual and computerised); audit and feedback; educational outreach visits; organisational strategies; patient-mediated interventions
  - inconsistently effective interventions: computer decision support systems; educational meetings
  - passive dissemination of information and didactic lectures should be abandoned as primary strategies for improving prescribing

- review and recommend changes (antibiotic pharmacist)
- antibiotic guidelines
  - development
  - dissemination
  - implementation
  - evaluation

Brown, E.M. *J Antimicrob Chemother* 2002; **49**: 587-92.

- antibiotic stop-order policy
- role of the clinical microbiology laboratory/clinical microbiologist

- **BUT NOT**

  antibiotic cycling/rotation

  combination therapy