



# **Interventions That Work in Hospitals**

**Peter Davey**

**Health Informatics Centre (HIC)**

# Agenda for Today

- Systematic Review of Interventions to Promote Prudent Antibiotic Prescribing
  - Education or Enforcement?
  - Clinical & microbiological outcomes
  - How far have we come with antibiotic stewardship?
- Implications for research
- Implications for practice

# Cochrane Effective Practice and Organisation of Care Group

- Acceptable study designs
  - Interrupted time series
  - Controlled before and after studies
  - Patient randomised controlled trials
  - Cluster randomised controlled trials

[www.epoc.uottawa.ca](http://www.epoc.uottawa.ca)

# Cochrane Hospital Antibiotic Review

- Joint Working Party of the British Society for Antimicrobial Chemotherapy and the Hospital Infection Society
- The primary aim was to systematically review the literature to identify interventions that alone, or in combination, are effective in promoting prudent antibiotic prescribing to hospital inpatients.

# Prudent Antibiotic Prescribing

- Use of antimicrobials in the most appropriate way for the treatment, or prevention, of human infectious diseases.
- Key elements in decision making:
  - Diagnosis (or presumed diagnosis)
  - Evidence of clinical effectiveness
  - Likely benefits
  - Safety
  - Cost (in comparison with relevant alternative choices)
  - Propensity for the emergence of resistance
- Key decisions:
  - Is an antibiotic needed?
  - If needed, choice of drug, route, dosage, frequency and duration of administration have been rigorously determined.

**743 Papers Since 1980**  
**393 Not eligible**

**350 Eligible**

**First Cut**

**N=107 (31%)**

**Invalid design**

**N=243 (69%)**

**Included**

**N=66(20%)**

**+2**

**secondary**

**Excluded**

**N=39(11%)**

**Inadequate Time Series**

**N=79 (22%)**

**Uncontrolled Before & After**

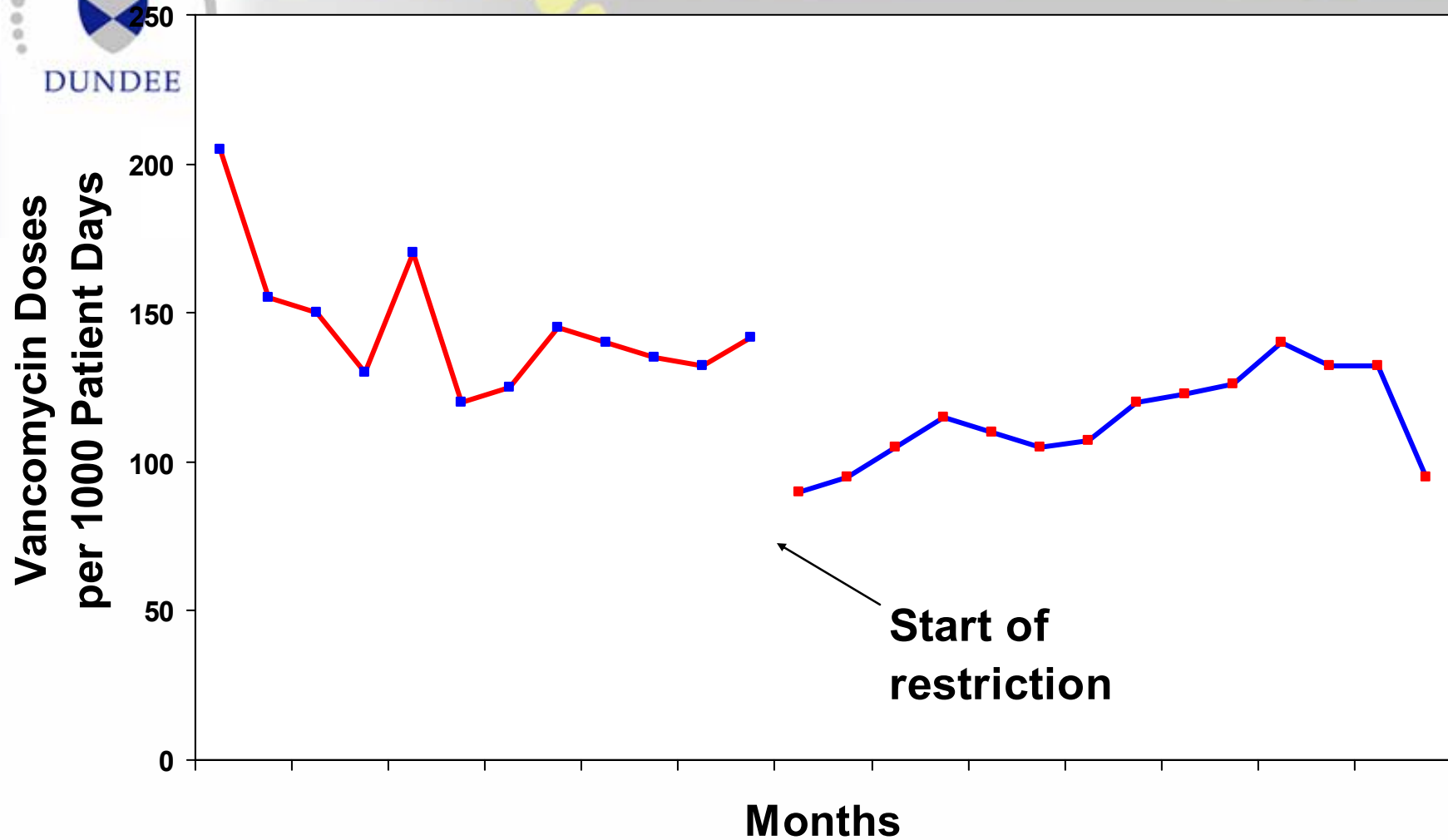
**N=164 (47%)**

# Evaluation Types

- **43 Interrupted Time Series**
- **13 Randomised Controlled Trials**
- **2 Controlled Clinical Trials**
- **1 cluster RCT**
- **1 cluster CCT**
- **6 Controlled Before & After**

# Interrupted time series (ITS) -minimum criteria

- **Clearly defined point in time when the intervention occurred.**
- **At least 3 data points before and after the intervention**
- **Both criteria must be met for a study to be included in a Cochrane review**



*Belliveau et al. American Journal of Health-System Pharmacy 1996; 53: 1570-5.*

## Conclusions: Methods

- Only 20% of published literature meets minimum standards
- 3 points is an absolute but very bare minimum for ITS
- Resist the temptation to reduce time series into averages

## Results 1: 66 Studies from Eleven Countries

- USA (42)
- UK (8)
- Canada (4)
- Australia (2)
- France (2)
- The Netherlands (2)
- Thailand (2)
- Brazil (1)
- Colombia (1)
- Norway (1)
- Spain (1)

## Number of hospitals in which interventions were implemented

- 57 in single hospitals
- 4 in 2-3 hospitals
- 5 in  $\geq 10$  hospitals (range 10-36)

## Objectives of interventions

1. Decrease antibiotic prescribing (n=57)
2. Increase antibiotic prescribing (n=6)
3. Decrease and increase antibiotic prescribing- rapid tests (n=3)

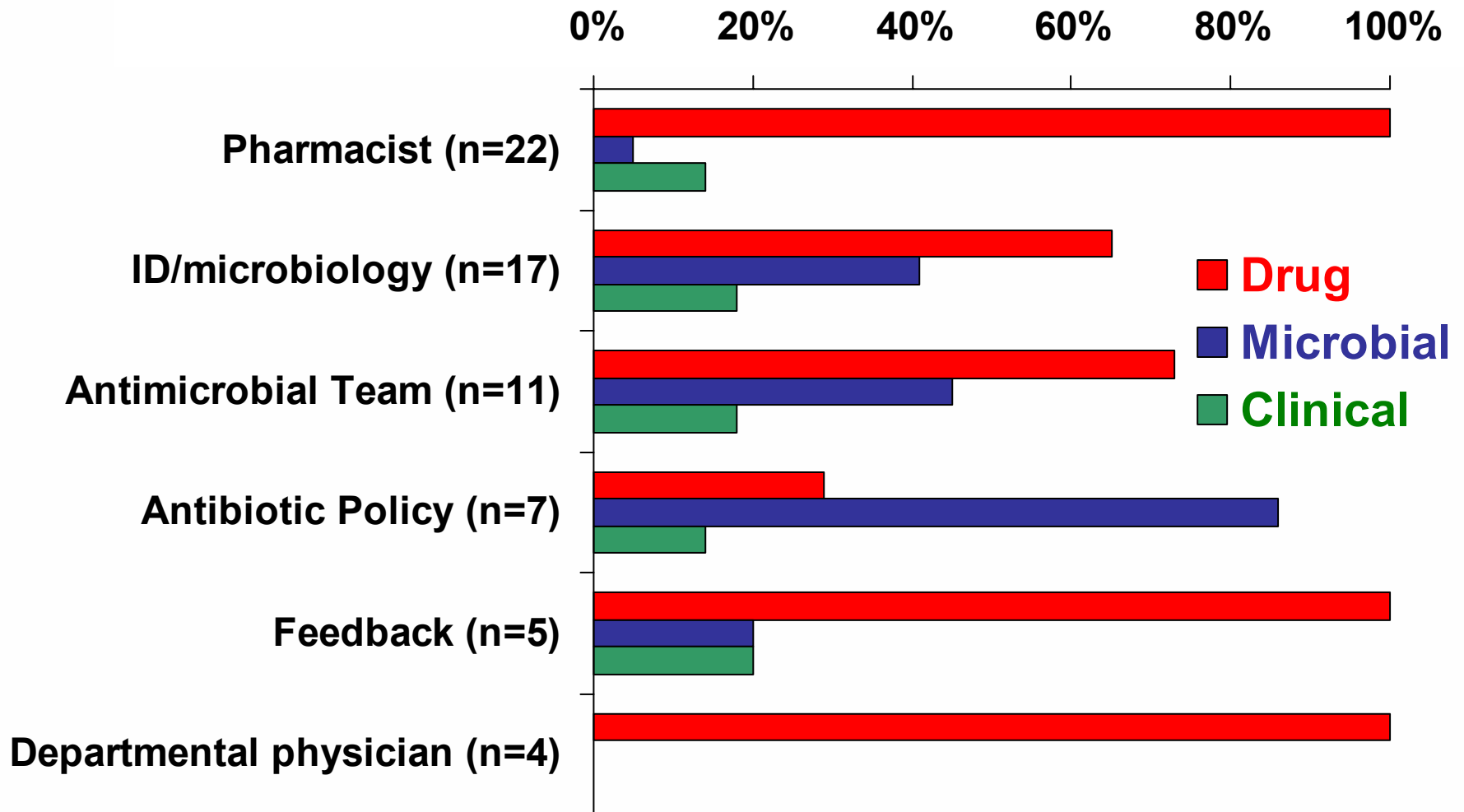
## Targets of interventions

1. Choice, dosage, route of administration (n=61)
2. Duration (n=3)
3. Timing (n=3)
4. Decision to give an antibiotic (n=1)

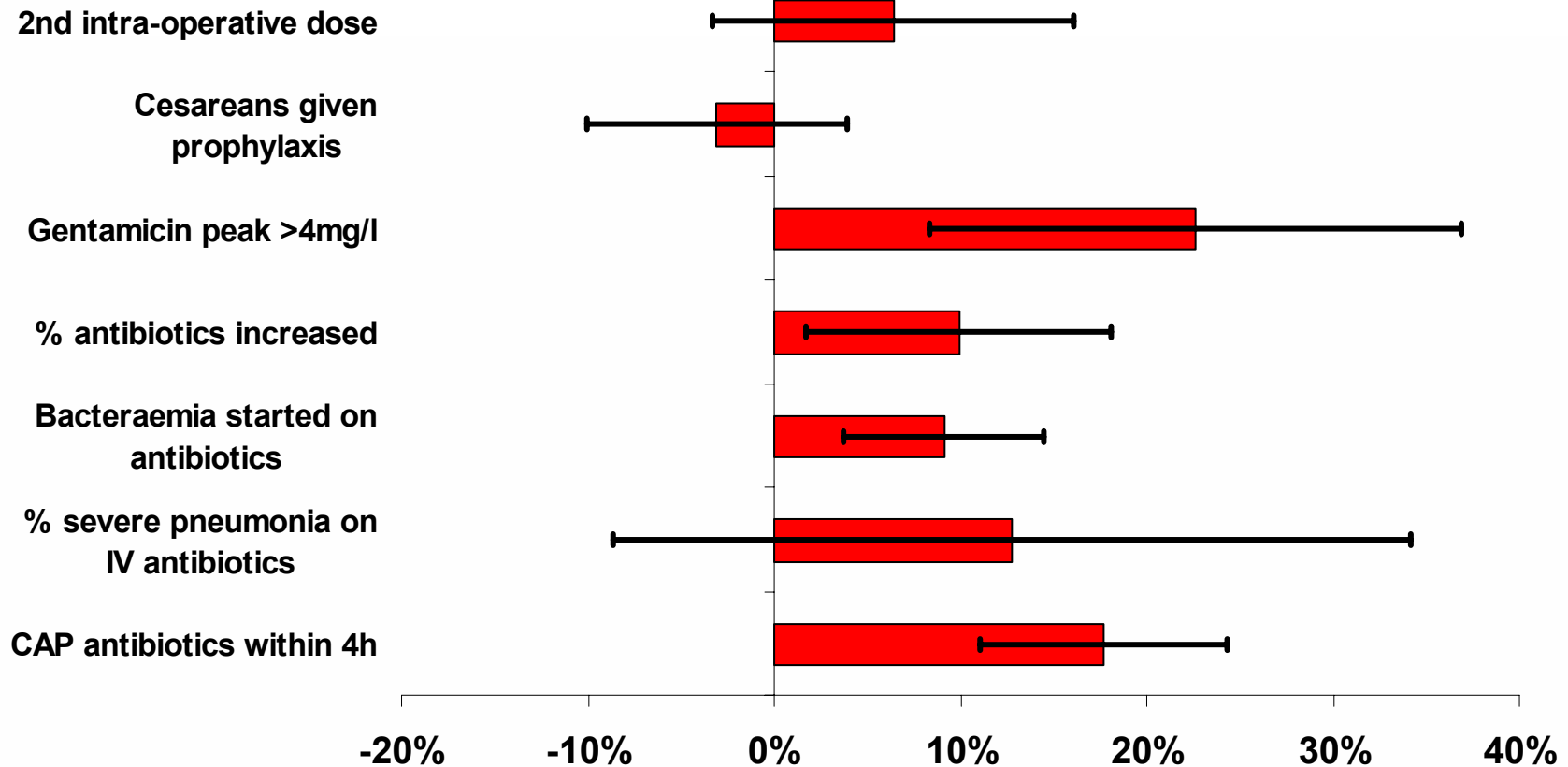
# Outcome Measures

1. Antibiotic prescribing, n=51
  - drug, dose, route, interval, duration
2. Clinical, n=14
  - LOS, response rate, mortality rate
3. Microbiological, n=16
  - *C. difficile*, colonisation/infection with antibiotic-resistant bacteria

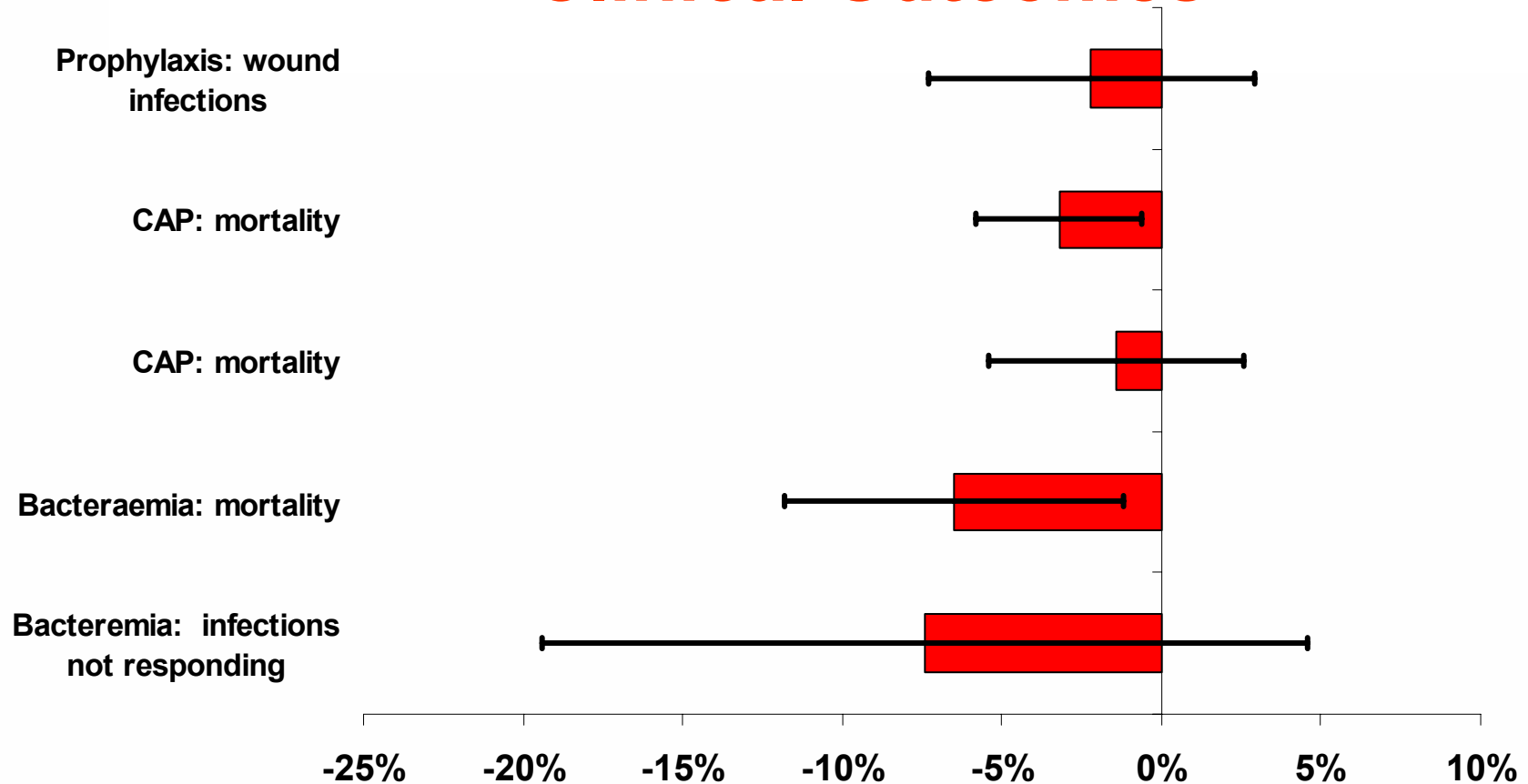
# Deliverer and Outcomes



# Increase Antibiotic Use: Drug Outcomes



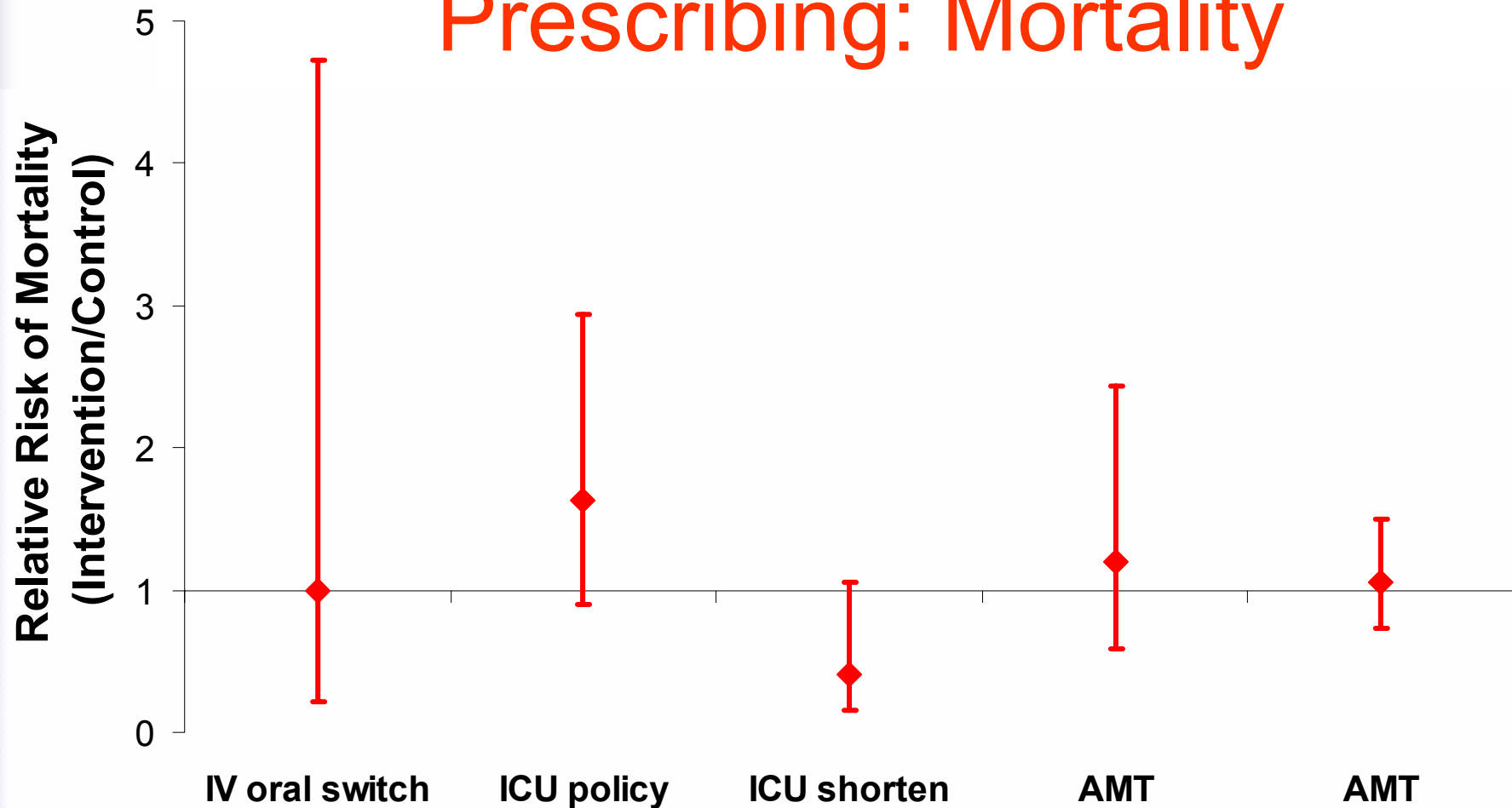
# Increase Antibiotic Use: Clinical Outcomes



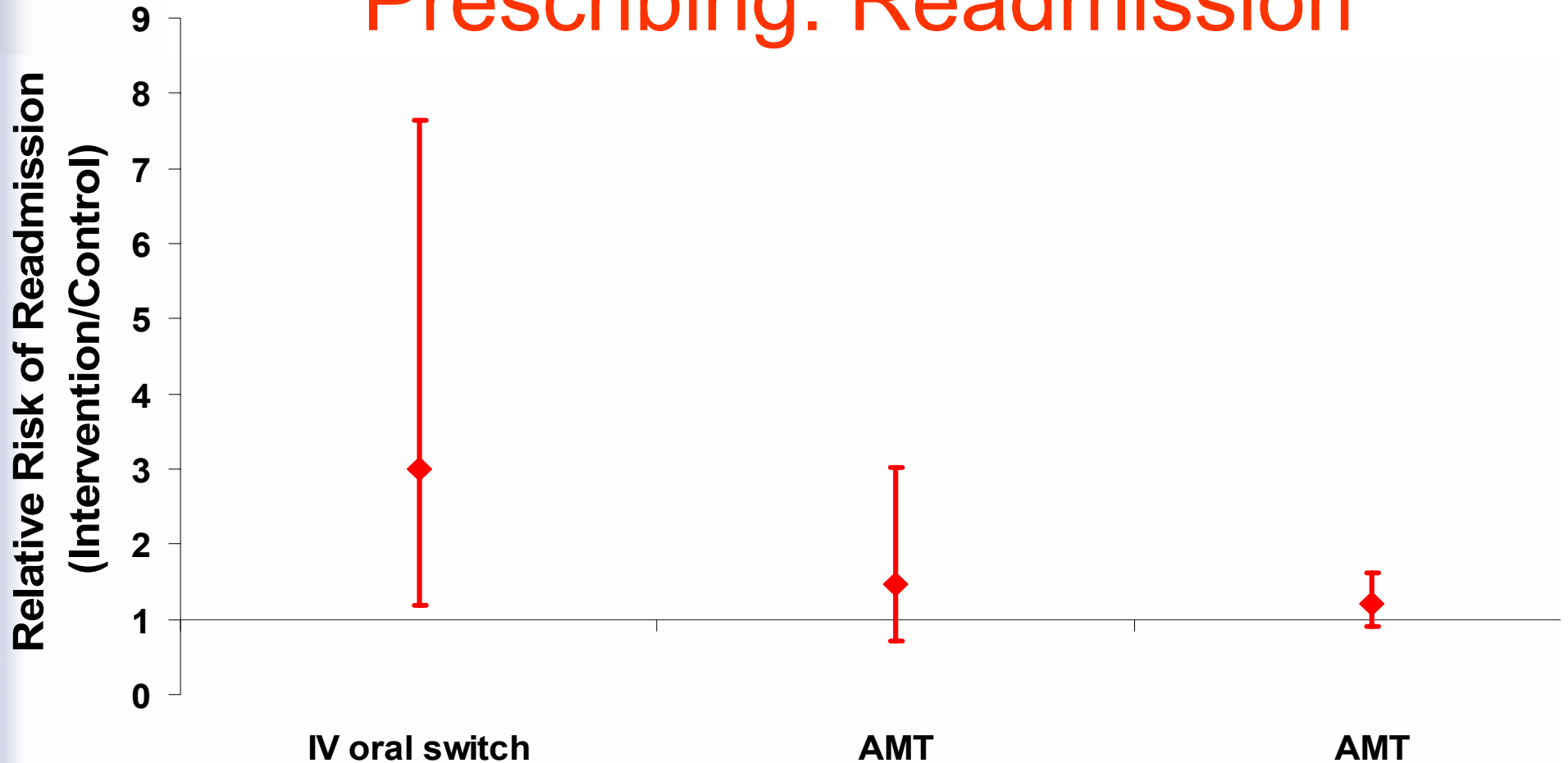
# Decrease Antibiotic Prescribing: Drug Outcomes

Design	N	Significant effect	Trend (p<0.1)
CBA, CCT, RCT	14	10 (71%)	3 (21%)
ITS	33	26 (79%)	2 ( 6%)
All	47	36 (77%)	5 (11%)

# Clinical Outcomes of Reduced Prescribing: Mortality



# Clinical Outcomes of Reduced Prescribing: Readmission



## **Educational**

## **Enforcement**

**Recommend change: 16**

**Expert approval: 14**

**General education: 13**

**Removal/restriction: 9**

**Reminders: 8**

**Compulsory order forms: 5**

**Guidelines: 5**

**Cycling/rotation: 4**

**Audit and feedback: 4**

**Therapeutic substitution: 3**

**Care pathway: 3**

**Automatic stop-order: 2**

**Opinion leaders: 2**

**Compulsory computer: 1**

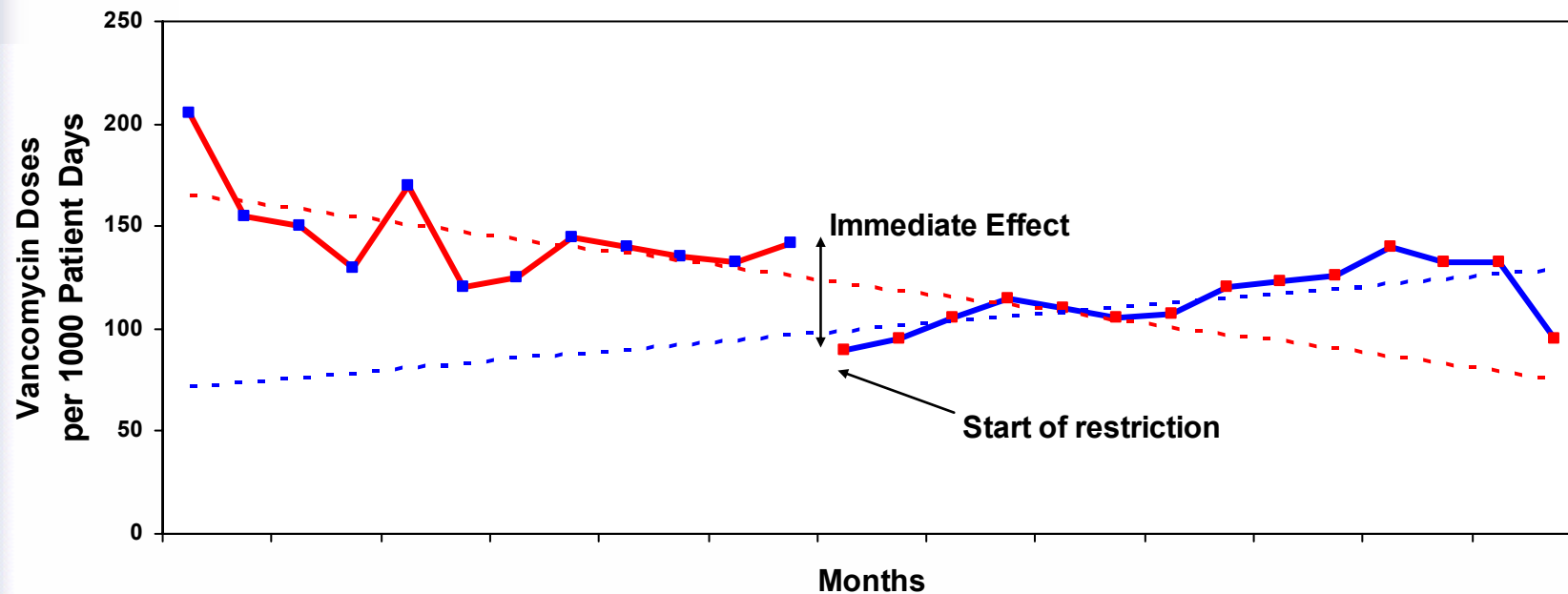
# ITS duration in months

	Pre intervention		Post intervention	
	Mean	Range	Mean	Range
<b>Education</b>	<b>20</b>	<b>3-36</b>	<b>33</b>	<b>5-84</b>
<b>Enforcement</b>	<b>18</b>	<b>1-48</b>	<b>23</b>	<b>2-84</b>
<b>Mixed</b>	<b>17</b>	<b>6-36</b>	<b>19</b>	<b>3-48</b>

# Meta regression 1

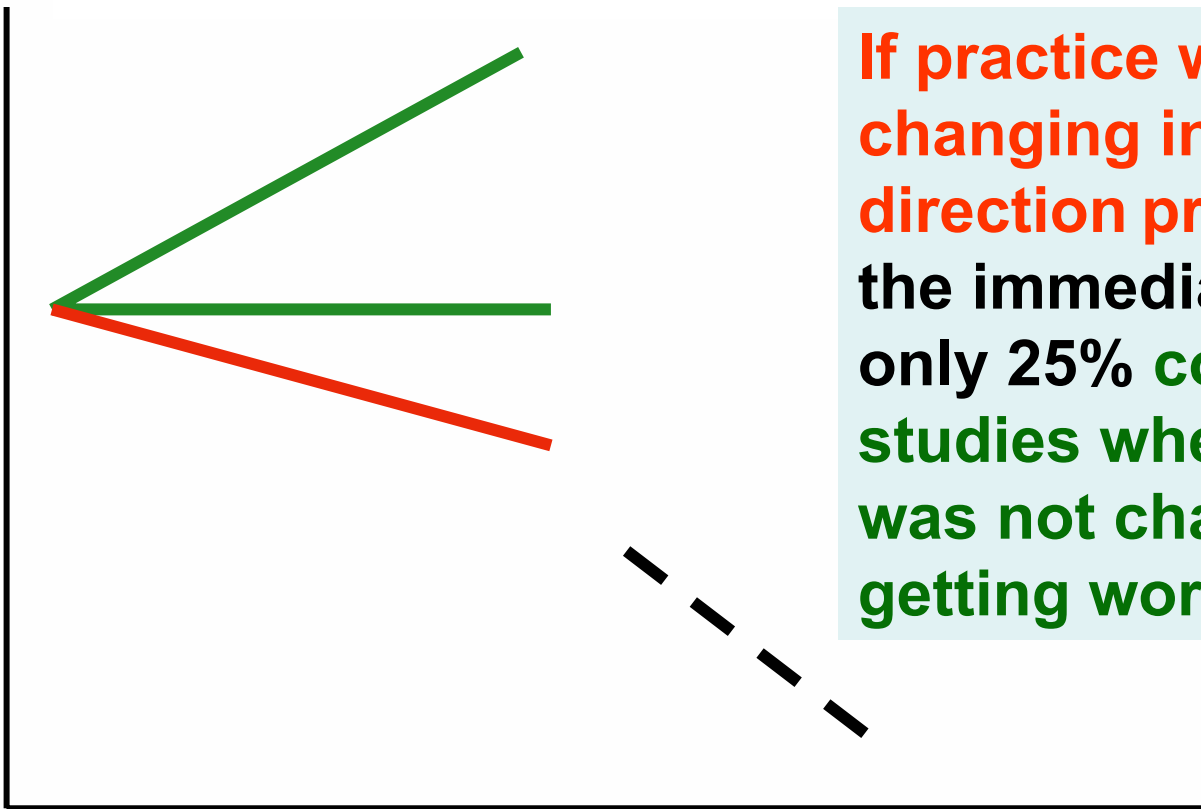
- **Drug outcomes, monthly intervals**
- **7 Educational vs 7 Enforcement**
- **Restrictive interventions 3.6-fold additional immediate effect (CI from 2.9- to 4.2-fold)**
- **Unable to compare sustained effects**

## Effect of Restriction Can Wear Off



$\Delta$ (post-intervention – pre-intervention)		<i>P</i>
Immediate	Decrease by 23 doses/1000 patient days	0.05
Sustained	Increase by 6 doses/1000 patient days	<0.001

# Meta-Regression 2

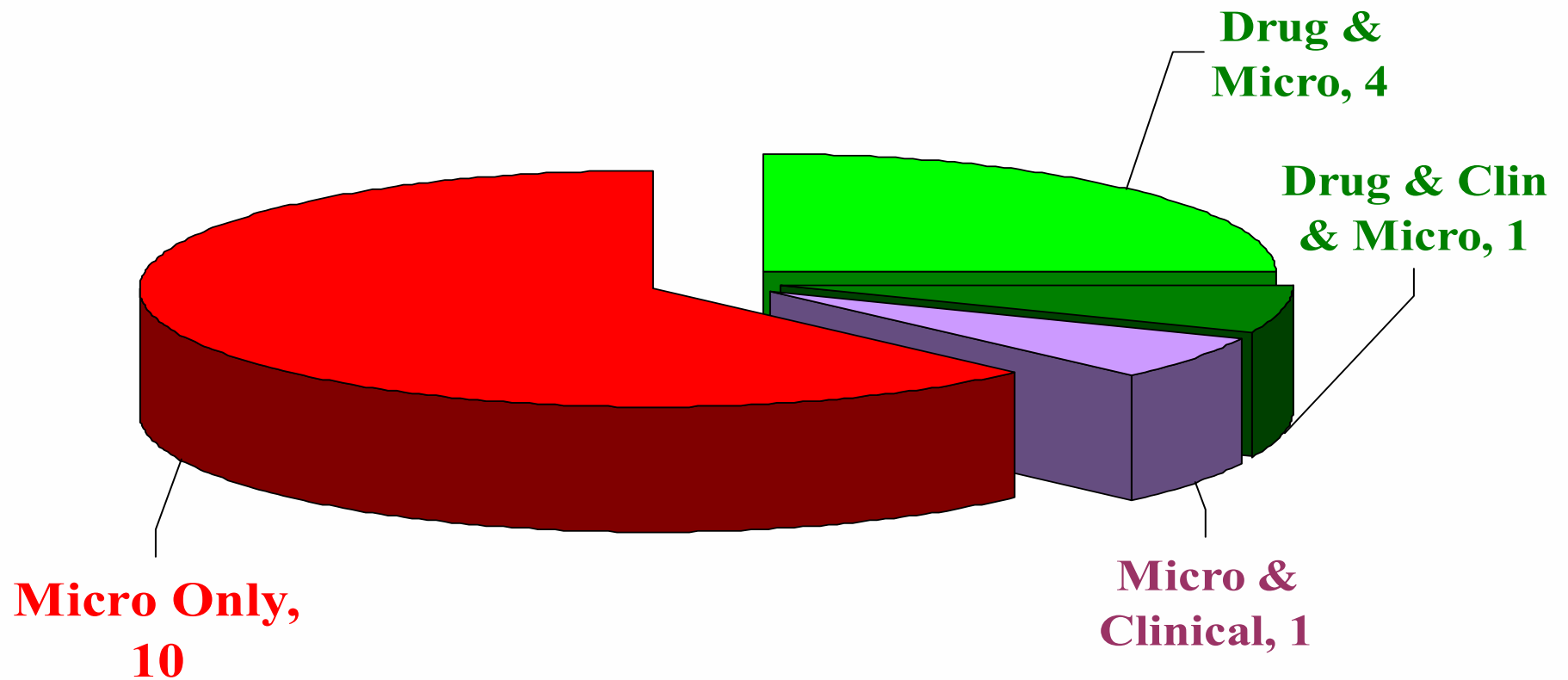


If practice was already changing in the intended direction pre-intervention the immediate effect was only 25% compared with studies where practice was not changing or getting worse

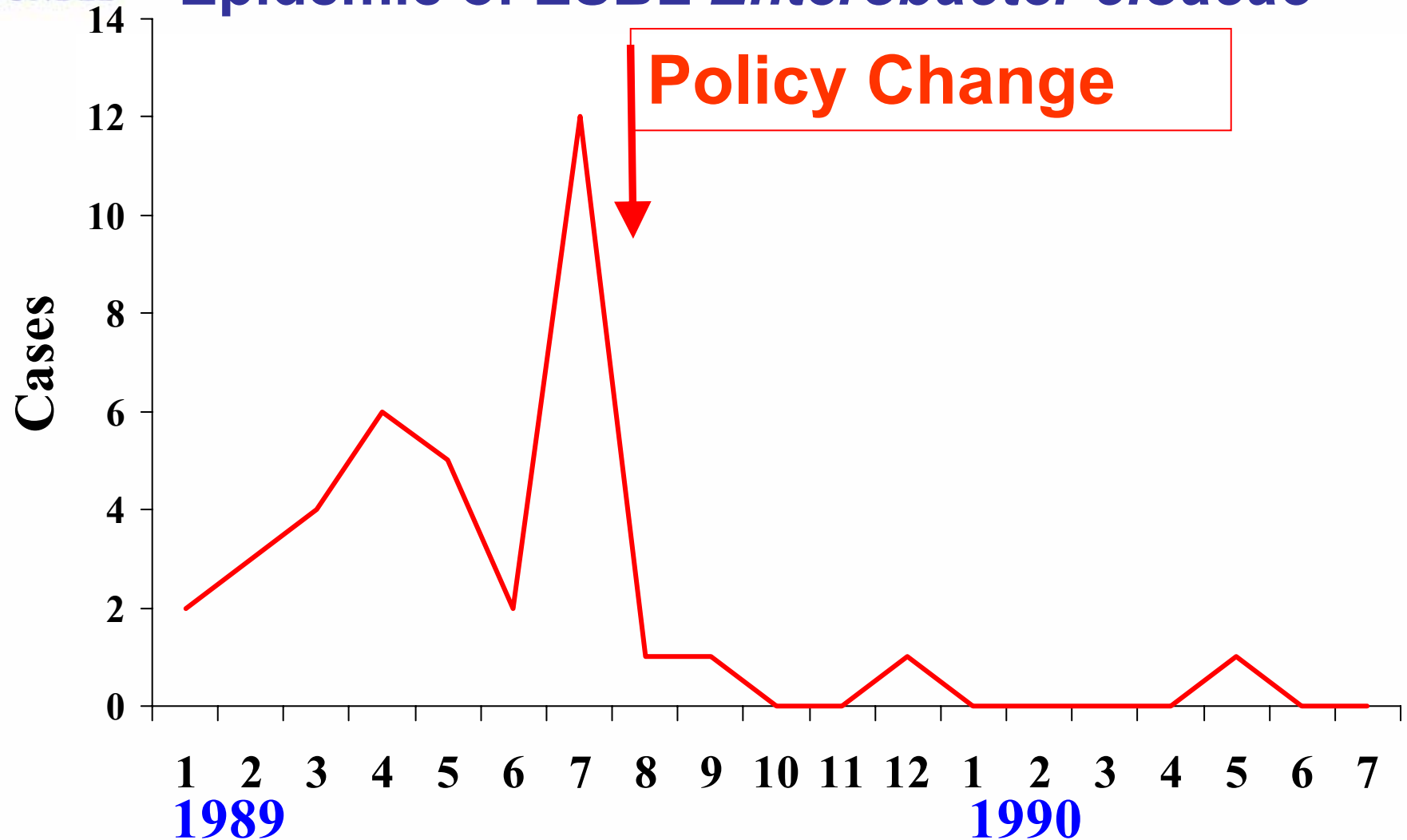
# Conclusions: Drug & Clinical

- Interventions to increase prescribing more likely to include clinical outcome
- Multidisciplinary teams choose multidisciplinary outcomes
- More interventions needed on duration of antibiotic treatment & decision to prescribe
- Enforcement interventions have a bigger short term impact *versus* Educational interventions  
BUT WHAT ABOUT LONG TERM?
- Standardised interval (months) and post-intervention (1 year?) would help comparison
- If it ain't broke don't fix it

# 16 Studies with Microbiological Data



## Epidemic of ESBL *Enterobacter cloacae*



de Champs et al, J Hosp Infect, 1994, 28: 219-229

# Common Threats to Validity = Plausible Alternative Explanations

- Unplanned intervention
- No reliable data about intervention effect on prescribing
- Imprecise case definition (colonization *versus* infection, reproducibility)
- Other infection control measures
- Changes in length of stay, bed occupancy, staffing levels

## Low Risk of Bias

Setting	Intervention	Outcome	Author
Haematology unit	Cephalosporin restriction	VRE	Bradley 1999
Whole hospital	Cephalosporin restriction	C difficile, gram-ves	Carling 2003
NICU	Pen + tobra vs Amox + cefotax	Multiresistant gram -ves	De Man 2001
ICU	Shorten duration	All resistant bacteria	Singh 2000
NICU	Antibiotic cyclilng	Multiresistant gram-ves	Toltzis 2002

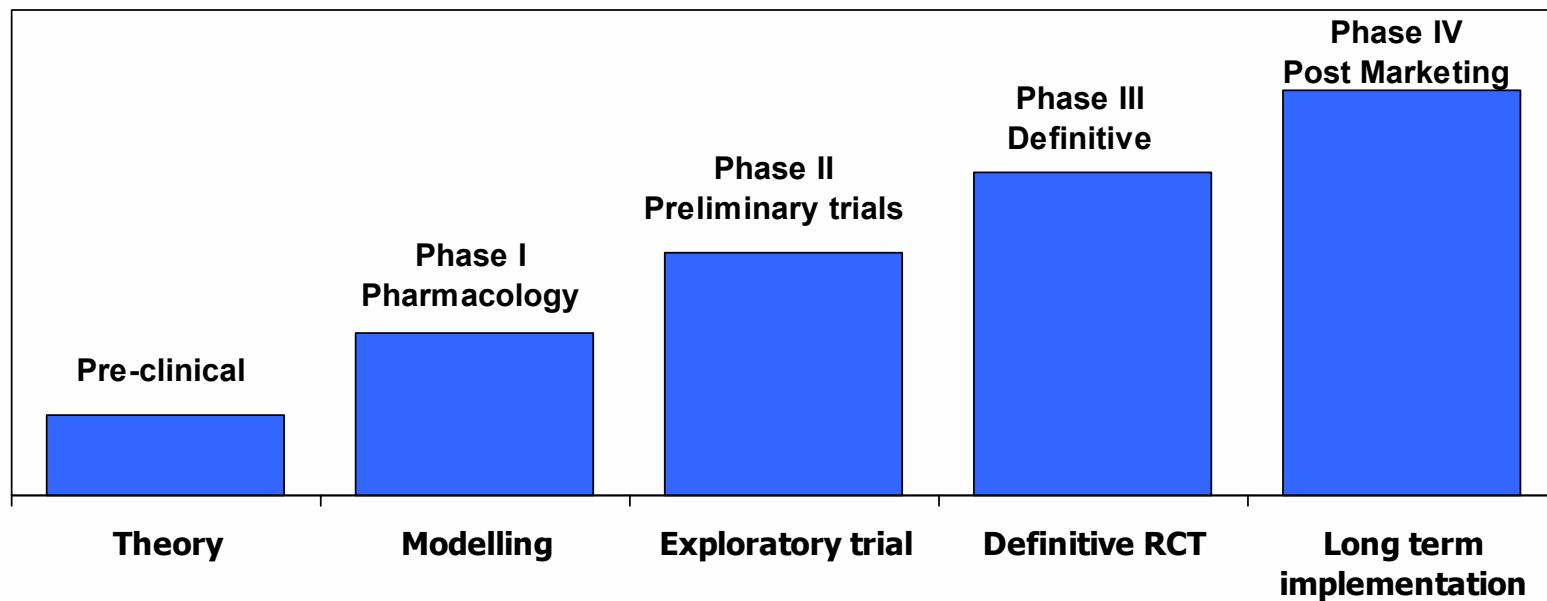
# Conclusions Microbiology

- 4 low bias studies provide good evidence that prescribing change can improve outcomes
- 11 studies had major threats to validity
- Need more planned interventions with pre-specified post-intervention duration (1 year?)
- Implementing checklist for reporting would help (ORION Sheldon Stone)

# Validity: How are we doing?

- Internal
  - Several interventions change prescribing
  - Increasing antibiotic prescribing improves clinical outcome
  - Decreasing antibiotic prescribing improves microbial outcome
- External
  - 4/6 ↑ interventions multi-centre vs 1/60 ↓ interventions
  - No really comparable single hospital studies
- Construct
  - Is increasing antibiotic prescribing harmful?
  - Is reducing antibiotic prescribing harmful?
  - Is choice of antibiotic the best target?

# UK MRC Framework for Evaluating Complex Interventions



**Continuum of increasing evidence**



[http://www.mrc.ac.uk/pdf-mrc\\_cpr.pdf](http://www.mrc.ac.uk/pdf-mrc_cpr.pdf)

# Implications

- Research
  - Multi-centre Cluster RCTs with embedded time series
  - Clinical and microbial outcomes rule not exception
  - Direct comparison of Education vs Enforcement
- Practice
  - Single hospitals can evaluate interventions with ITS
  - Primary aim is continuous quality improvement
  - Added value:
    - Laying the foundation for definitive research
    - If we all use the same methods we can learn from results in other hospitals
- Policy/ Government
  - No indicators allowed until you fund the necessary research!