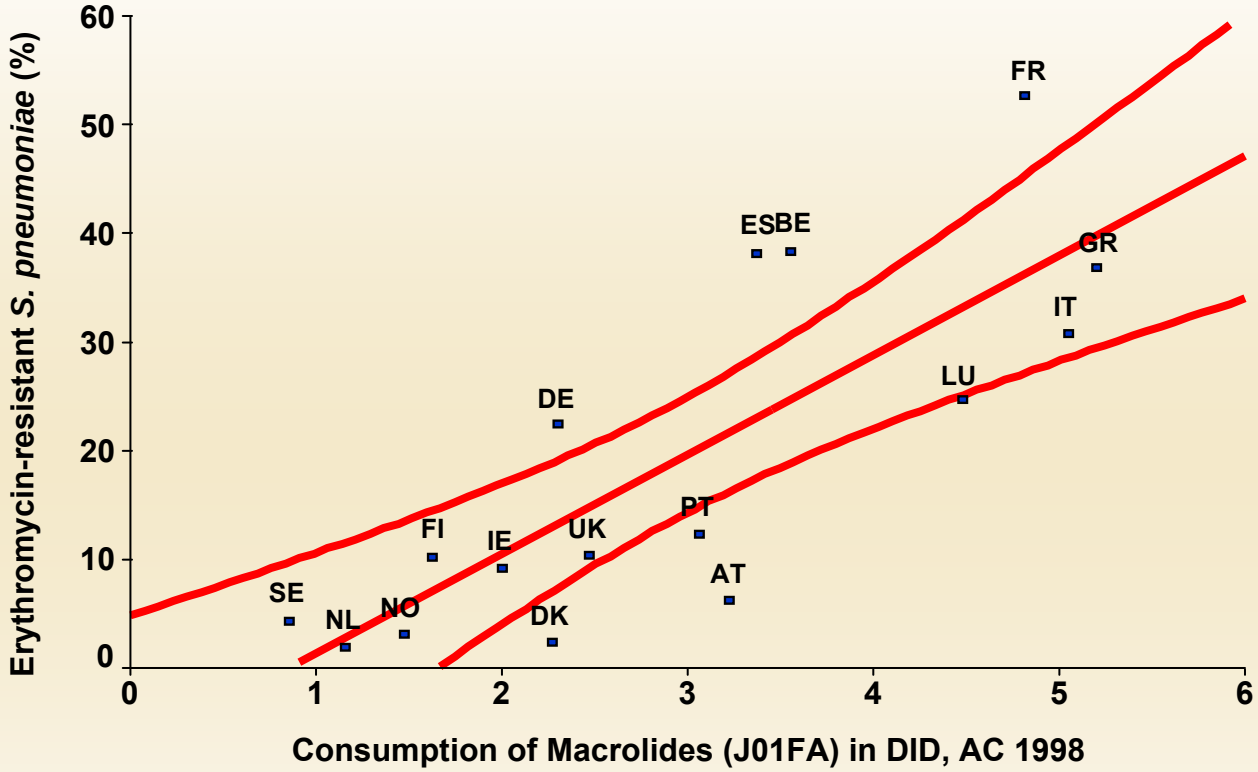
What is the link between Antibiotic Use and Resistance?

Herman Goossens

Universiteit Antwerpen

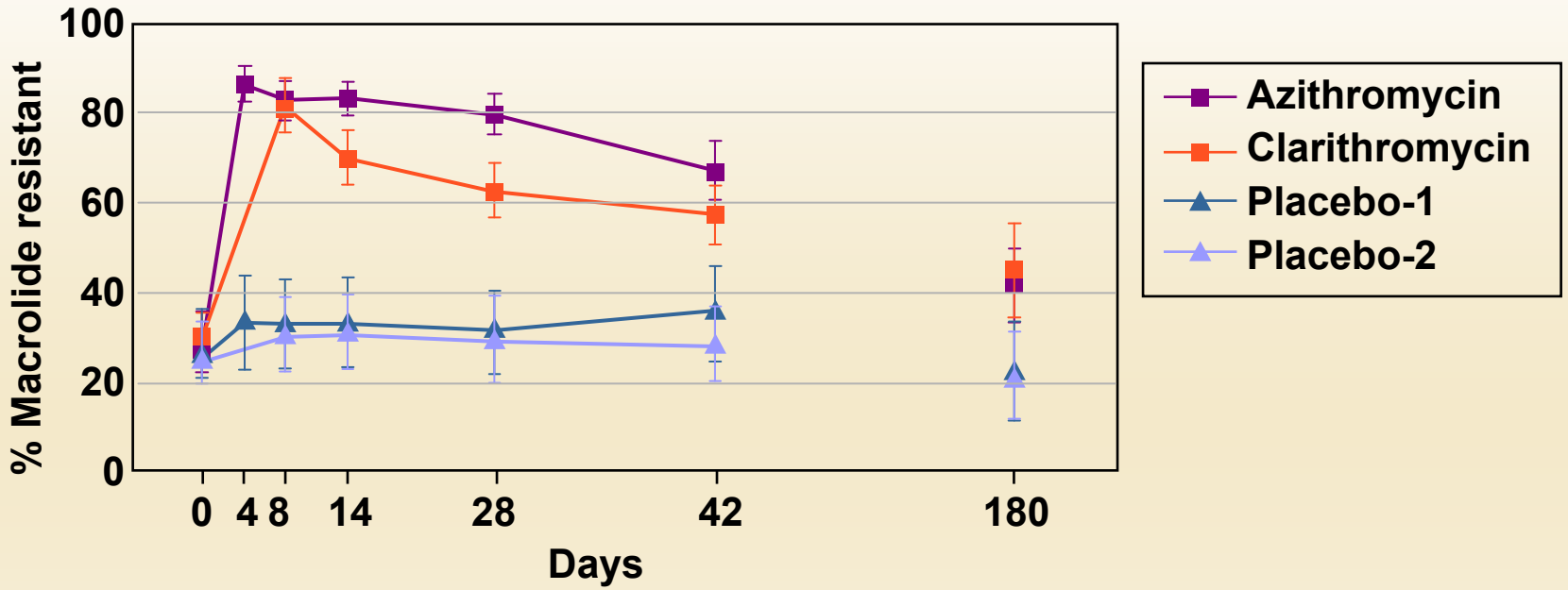
Correlation Between Macrolides Use and Prevalence of Erythromycin-resistant *S. pneumoniae*



Organism year of isolation *[source of information]*	Antibiotic resistance	Antibiotic use - ATC group (year of data)	No. of countries	Spearman correlation (r) (confidence interval)	*P*-value
S. pneumoniae 1999-2000 [8]	Erythromycin	Macrolides – J01FA (1998)	16	0.83 (0.67-0.94)	<0.001

Goossens H, et al. Lancet. 2005; 365: 579-587.

Temporal Changes in Proportion of Macrolide-resistant Oral Streptococci



MAIN FINDINGS

- **Mean pre-antibiotic (Day 0) carriage of macrolide-resistant streptococci was 28%**
- **Use of both macrolides resulted in a huge increase in resistant streptococci, which persisted for at least 6 months ($P \leq 0.01$)**
- **In the azithromycin group, resistance remained at a higher level than in the clarithromycin group during mid-time points ($P \leq 0.001$)**

Malhotra-Kumar S, et al. Lancet. 2007; 369: 482-490.

Why Proving the Obvious?

"As in all similar Darwinian selection systems, it is obvious that antibiotics generate resistance. It is also obvious to most that if more antibiotics are used, resistance will be more prevalent. So why prove the obvious? The answer is that the obvious correlation is not at all obvious when considered carefully."

Editorial: Antibiotic Use and Resistance - Proving the Obvious.

John Turnidge and Keryn Christiansen

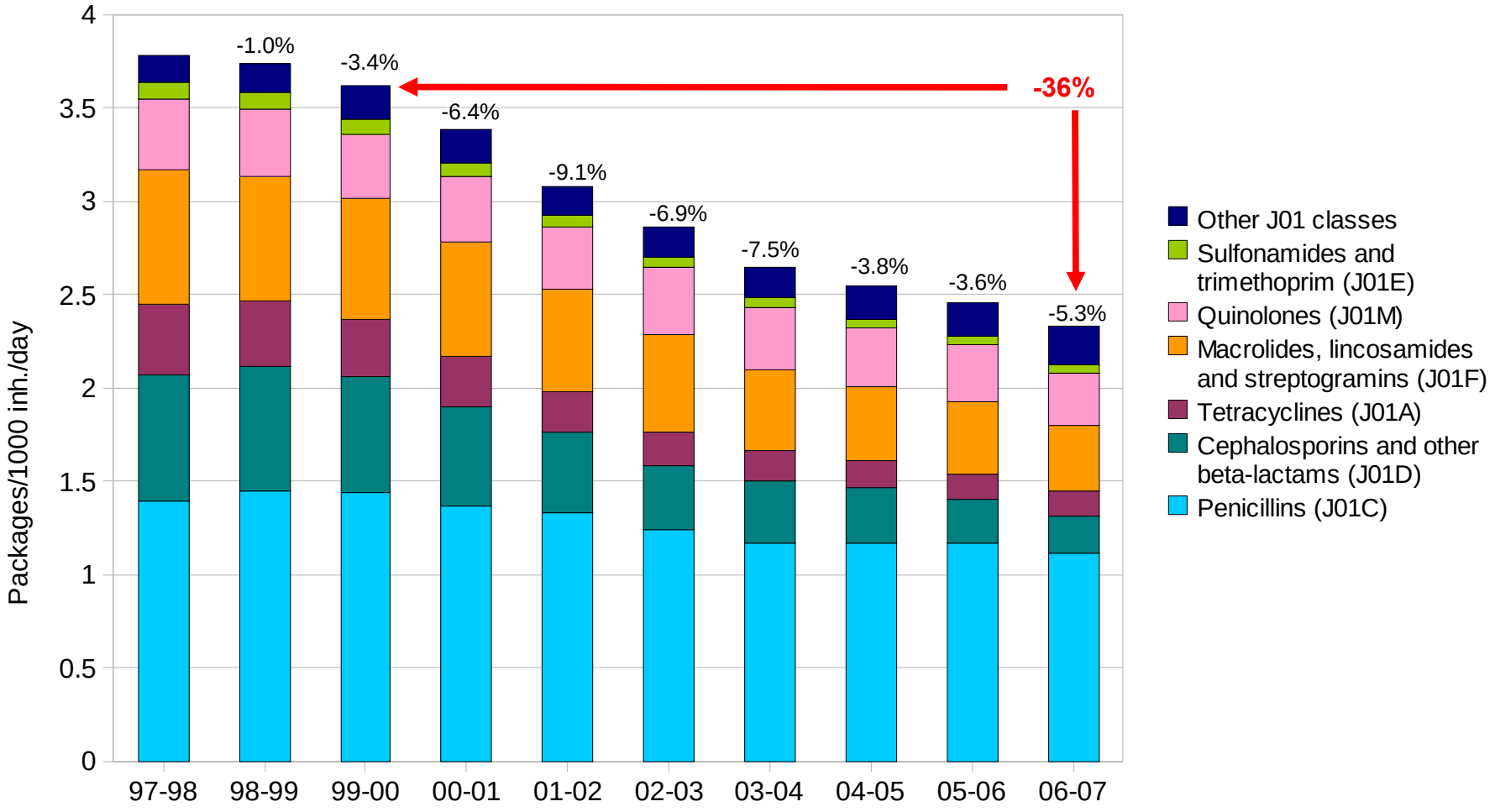
Lancet 2005, 365: 548-9

Many Confounders in Studying the Link between Antibiotic Use and Resistance

- How to measure antibiotic use (and link it with resistance)?
  - Which indicator?
  - How to correct for combination therapy?
  - How to assess dose-effect relationship?
- How to measure antibiotic resistance (and link it with use)?
  - Which indicator?
  - Colonization or positive clinical cultures?
- Which statistical methods to correlate use and resistance to address:
  - Selection bias (e.g. wrong control group)?
  - Insufficient power?
  - Violation of independence assumption (transmission!)?

Outpatient Antibiotic Use in Belgium

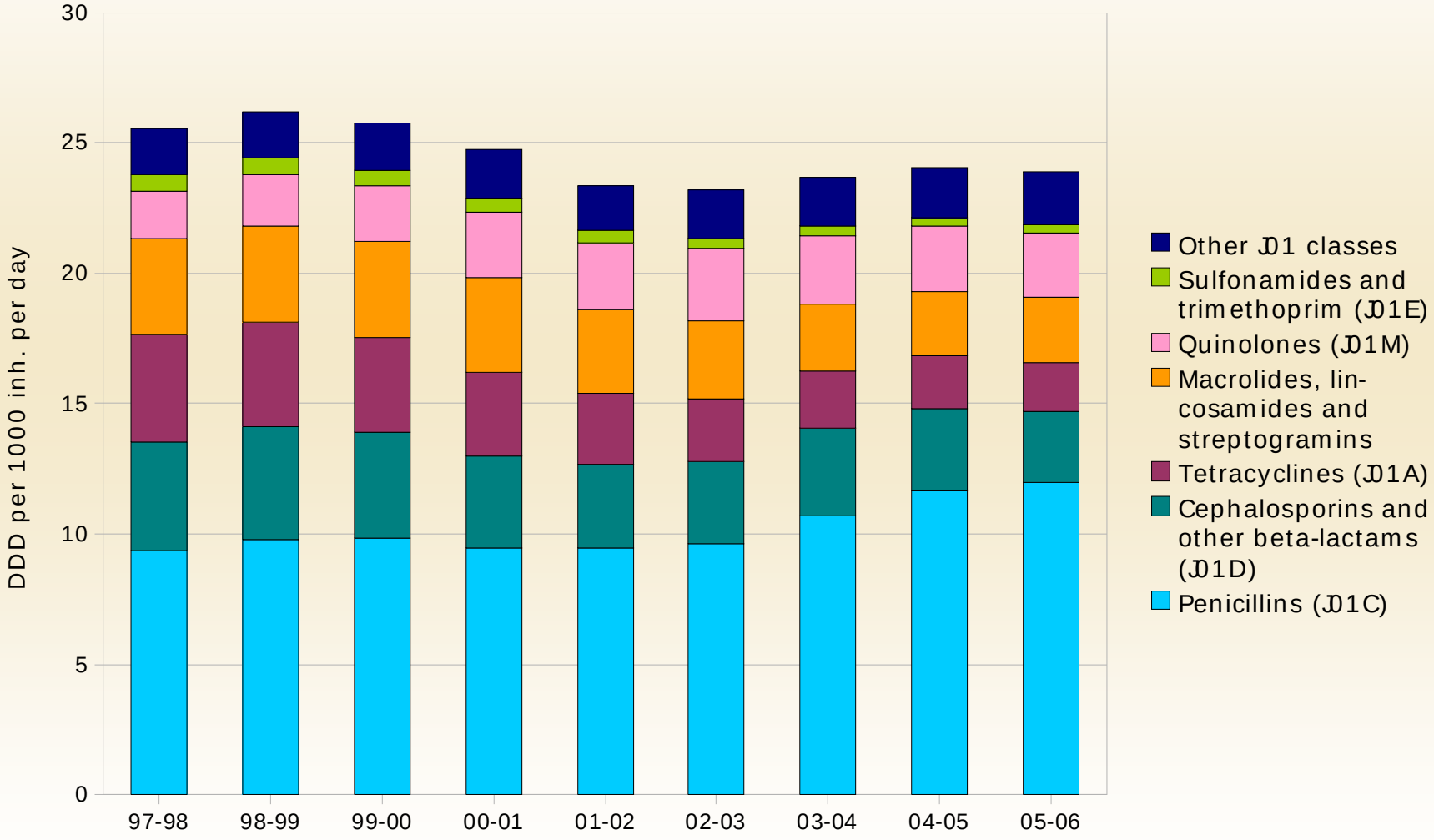
Packages per 1,000 inhabitants per day – 1997 – 2007, July to June



Goossens H. et al. Eurosurveillance 2008; 13:10 -13

Outpatient Antibiotic Use in Belgium

Defined Daily Doses per 1,000 Inhabitants per day – 1997 – 2006, July to June



Talk Outline

Not covered:

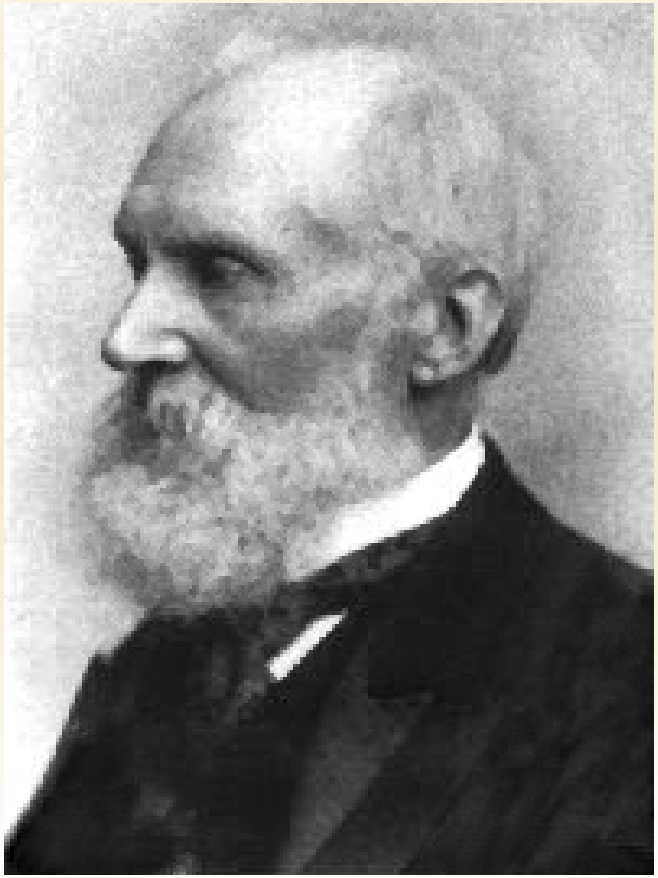
- Community
- Review on ecological studies linking antibiotic use and resistance

Covered:

- Why measure hospital antibiotic use and resistance
- How to measure antibiotic use in hospitals
- Evidence for cause-effect relationship
- A few confounders
- Conclusions and recommendations

Why Measure Hospital Antibiotic Use and Resistance?

- **Measurements for judgment:**
  - to provide league tables
- **Measurements for ecological purposes:**
  - to link antibiotic use and resistance
- **Measurements for targeting interventions:**
  - to show where problems are
- **Measurements for improvements:**
  - to show if improvements are being made



"If you cannot measure it, you cannot improve it"

Lord Kelvin, 1824-1907

Hospital Antibiotic Use Has Been Neglected

"Those responsible for the NHS Information Technology Strategy should consider the contrast between the excellent data on GP prescribing … and the lack of data on antimicrobial use in hospitals. All hospitals should install computer systems for patient-specific prescribing information at ward level"

House of Lords Science and Technology Committee Report, 1998.

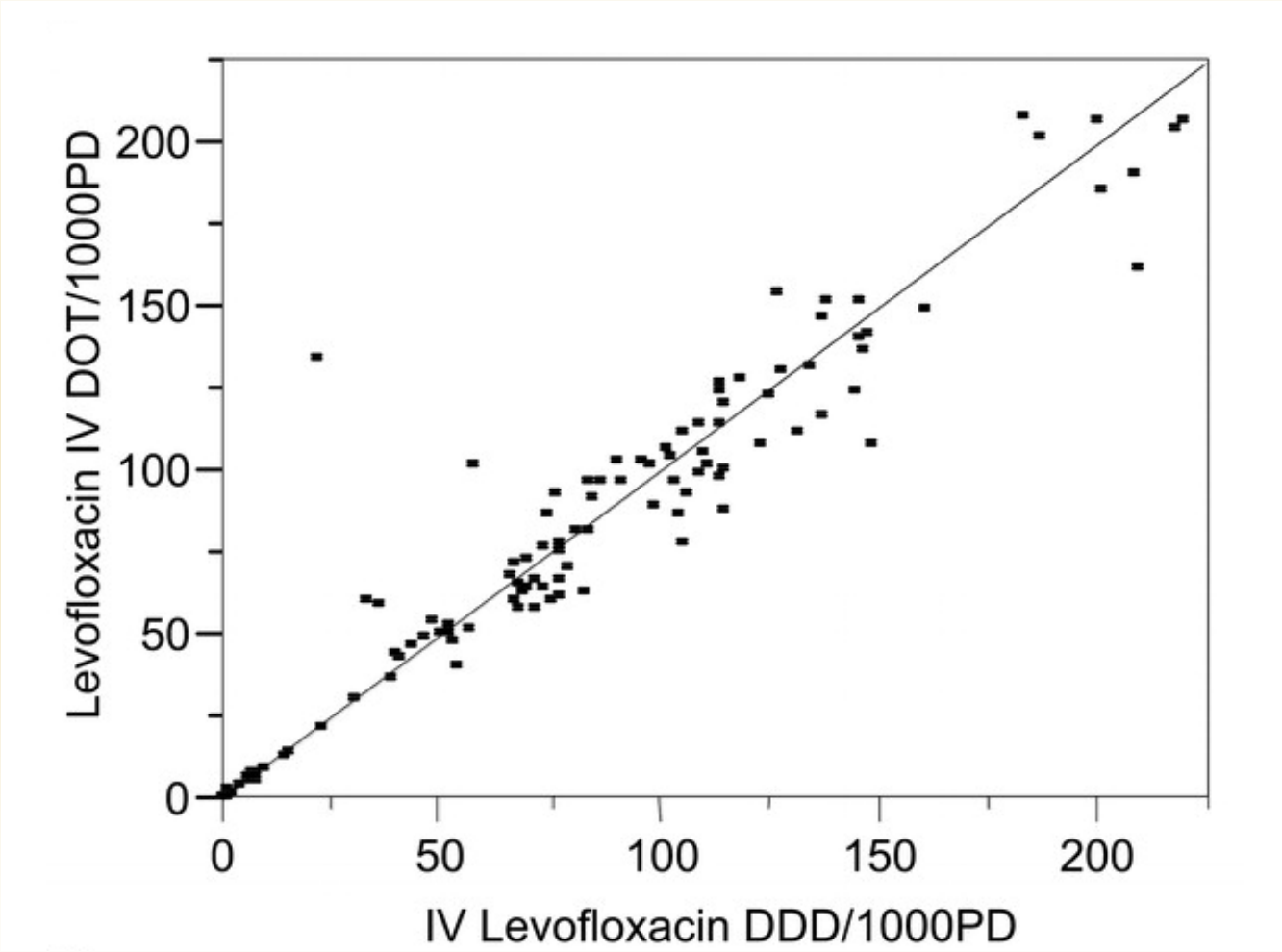
How to Measure Antibiotic Use in Hospitals: Which Indicators?

- DOT (Days of Treatment)
- Percentage of patients exposed to antimicrobials
- Weight (g or kg or units of treatment)/year)
- Grams/1,000 patient days
- Vials/month
- DDD or PDD/1000 inhabitants-days
- DDD or PDD/100 or 1,000 patient-days
- DDD or PDD/100 or 1,000 administrative bed-days
- DDD or PDD/100 or 1,000 occupied bed-days
- DDD or PDD/100 or 1,000 admissions
- DDD or PDD/100 or 1,000 discharges
- DDD or PDD/month/occupied bed

DDD, Defined Daily Dose; PDD, Prescribed Daily Dose

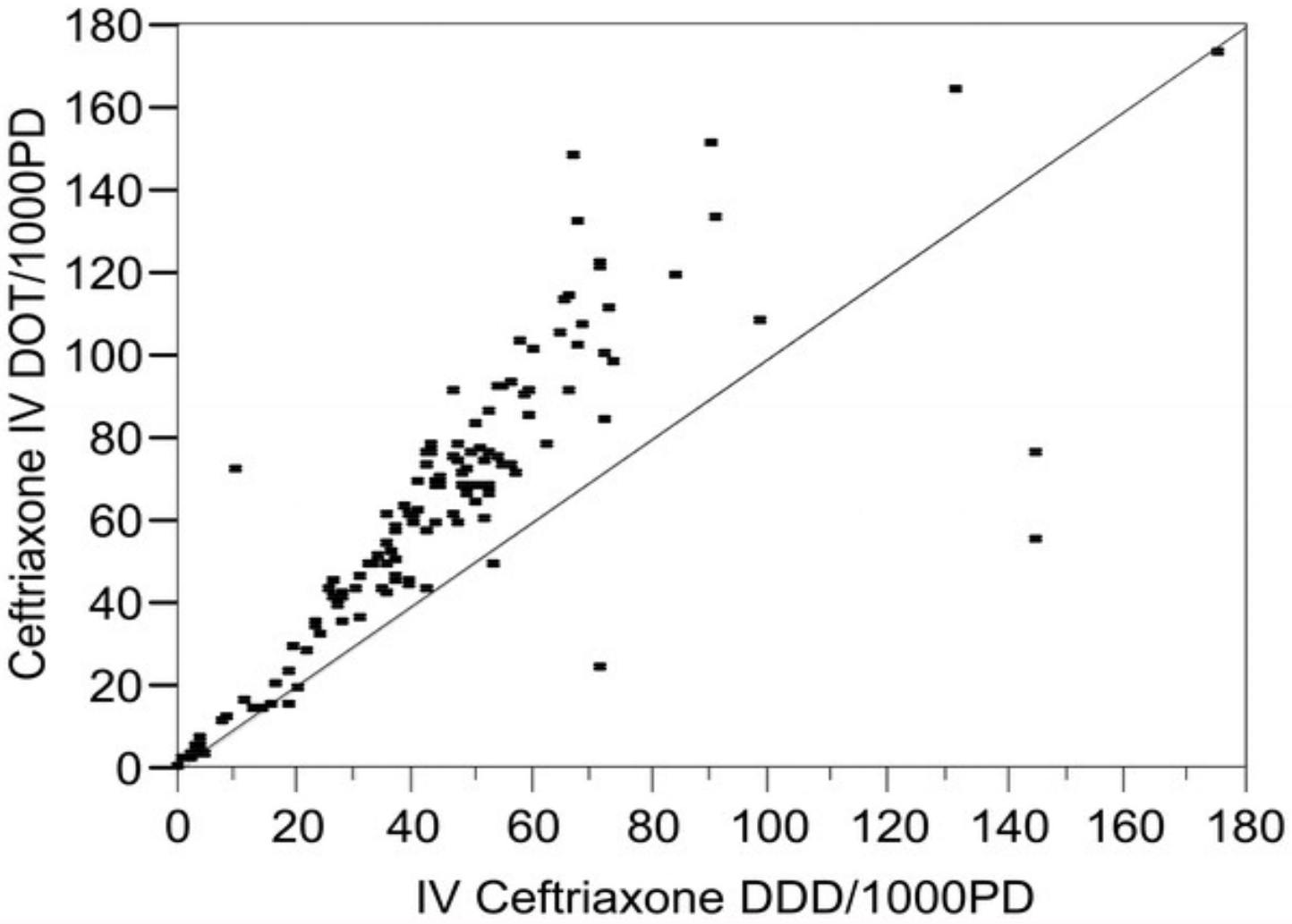
Which numerator to study ecological pressure?

Correlation of DDD to DOT per 1,000 Patient-days for Levofloxacin at Individual Hospitals: PDD = DDD



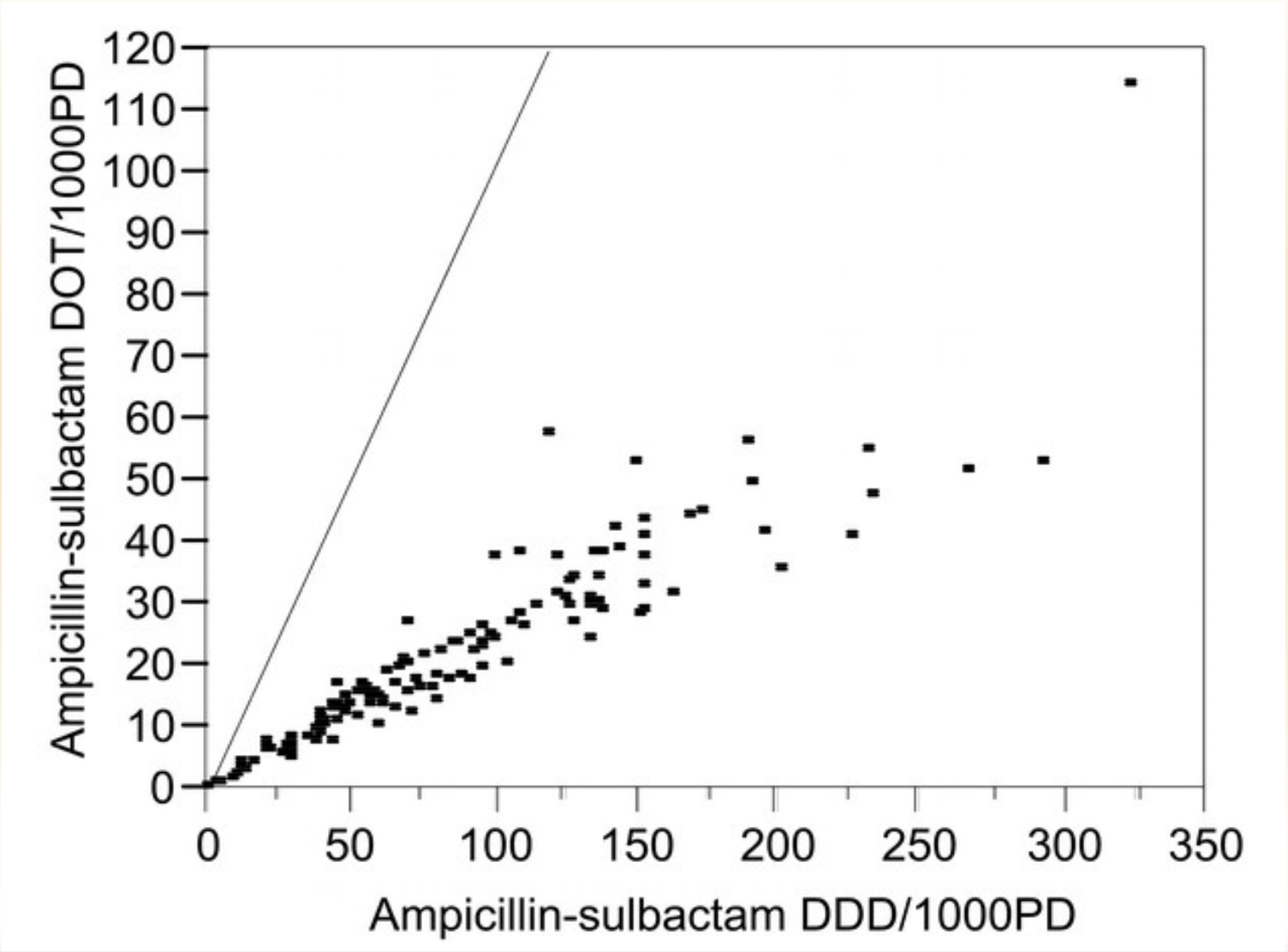
Polk R. et al., Clin Infect Dis, 2007; 44: 664-70

Correlation of DDD to DOT per 1,000 Patient-days for Ceftriaxone at Individual Hospitals: PDD < DDD



Polk R. et al., Clin Infect Dis, 2007; 44: 664-70

Correlation of DDD to DOT per 1,000 Patient-days for Ampicillin-Sulbactam at Individual Hospitals: PDD > DDD



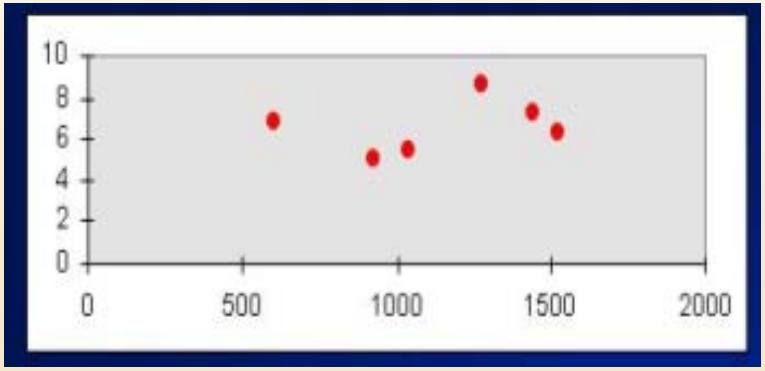
Polk R. et al., Clin Infect Dis, 2007; 44: 664-70

DDD versus DOT: Reflecting Different Ecological Pressure

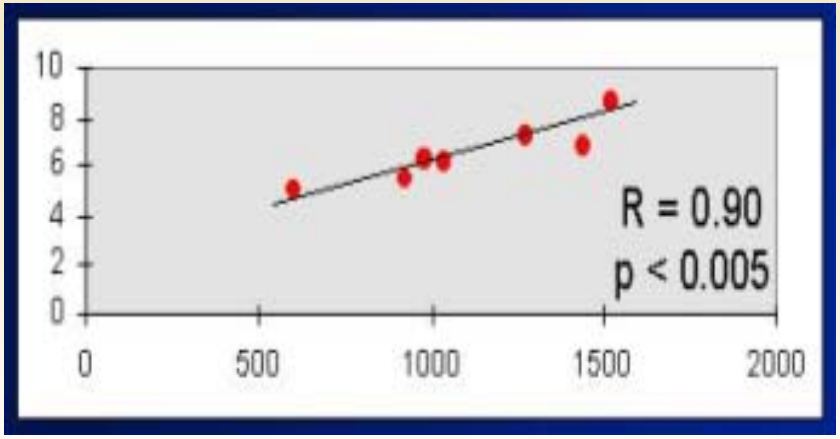
- **5 patients admitted to ward X**
- **Treated with antibiotic Y (DDD = 1 g)**
  - Situation A:
    - 1/5 patients treated with 3 g/daily/10 days
    - Aggregated number of DDD: 30
    - Aggregated number of DOT: 10
  - Situation B:
    - 3/5 patients treated with 1 g/daily/10 days
    - Aggregated number of DDD: 30
    - Aggregated number of DOT: 30

Correlation between Aggregate Gentamicin Use and Resistance among Gram-negatieve Bacilli Isolates, St Pieters Hospital, Brussels, 1979-1986

% Gentamicin-resistant Gram-negative Bacilli



Gentamicin use same year (g/year)



Gentamicin use previous year (g/year)

Goossens H, et al. Lancet 1986;2: 804.

Cause-effect Relationship: Beneath Superficiality there is Complexity

- **Cause:**
  - antibiotic use
  - infection control practises
- **Effect:**
  - prevalence of resistance
  - genodiversity of clones

CAUSE

- Modelling the impact of antibiotic use and infection control practices on the incidence of hospital-acquired methicillin-resistant *Staphylococcus aureus*: a time series analysis

Aldeyab et al , J Antimicrob Chemother 2008; 62: 593-600

Estimated Multivariate Time-Series Analysis Model for Monthly HA-MRSA Incidence ($R^2 = 0.784$)

Term	Time lag	Coefficient (SE)	*T* ratio	*P* value
Fluoroquinolone use (DDD/100 bed-days)	1	0.00481 (0.00098)	4.905	<0.0001
Third-generation cephalosporin use (DDD/100 bed-days)	2	0.0273 (0.00449)	6.080	<0.0001
Macrolide use (DDD/100 bed-days)	4	0.00212 (0.00099)	2.149	0.0376
Amoxicillin/clavulanic acid use (DDD/100 bed-days)	1	0.00349 (0.000651)	5.365	<0.001
Alcohol-based handrub bulk orders	3	-0.0390 (0.0149)	-2.619	0.0123
	4	-0.0755 (0.0153)	-4.932	<0.0001
Alhohol-impregnated wipes (no./100 bed-days)	2	-0.000345 (0.0000496)	-6.956	<0.0001
Patients actively screened for MRSA (no./100 bed-days)	3	-0.00721 (0.00306)	-2.357	0.0233
Patients admitted with MRSA (no./100 bed-days)	2	0.223 (0.0312	7.162	<0.0001
Autoregressive term (MRSA)	4	-0.552 (0.130)	-4.250	0.001
Moving average term (MRSA)	2	-0.980 (0.000709)	-1382.67	<0.0001

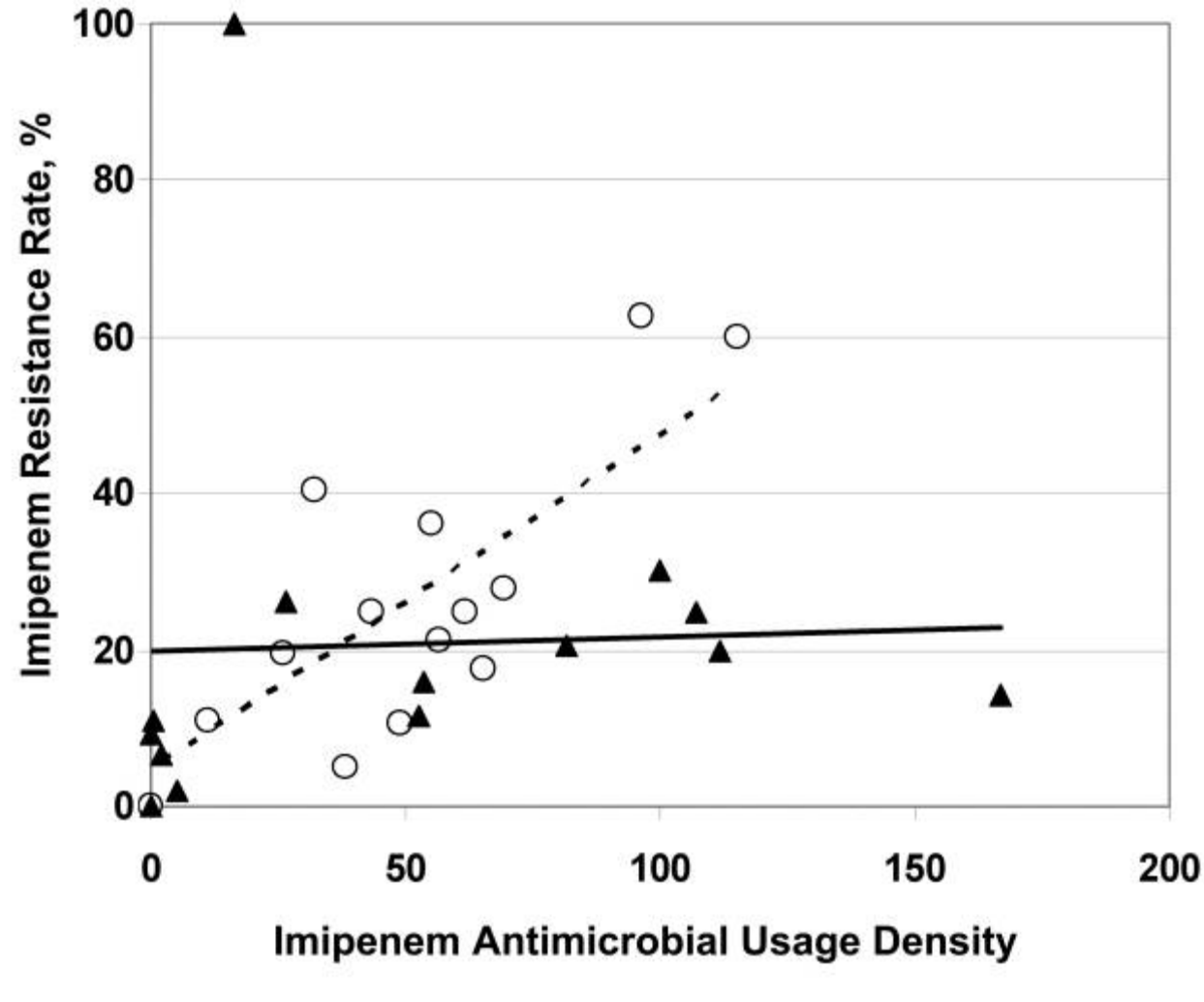
Aldeyab et al, J Antimicrob Chemother 2008; 62: 593-600

EFFECT

- Genodiversity of resistant *Pseudomonas aeruginosa* isolates in relation to antimicrobial usage density and resistance rates in intensive care units

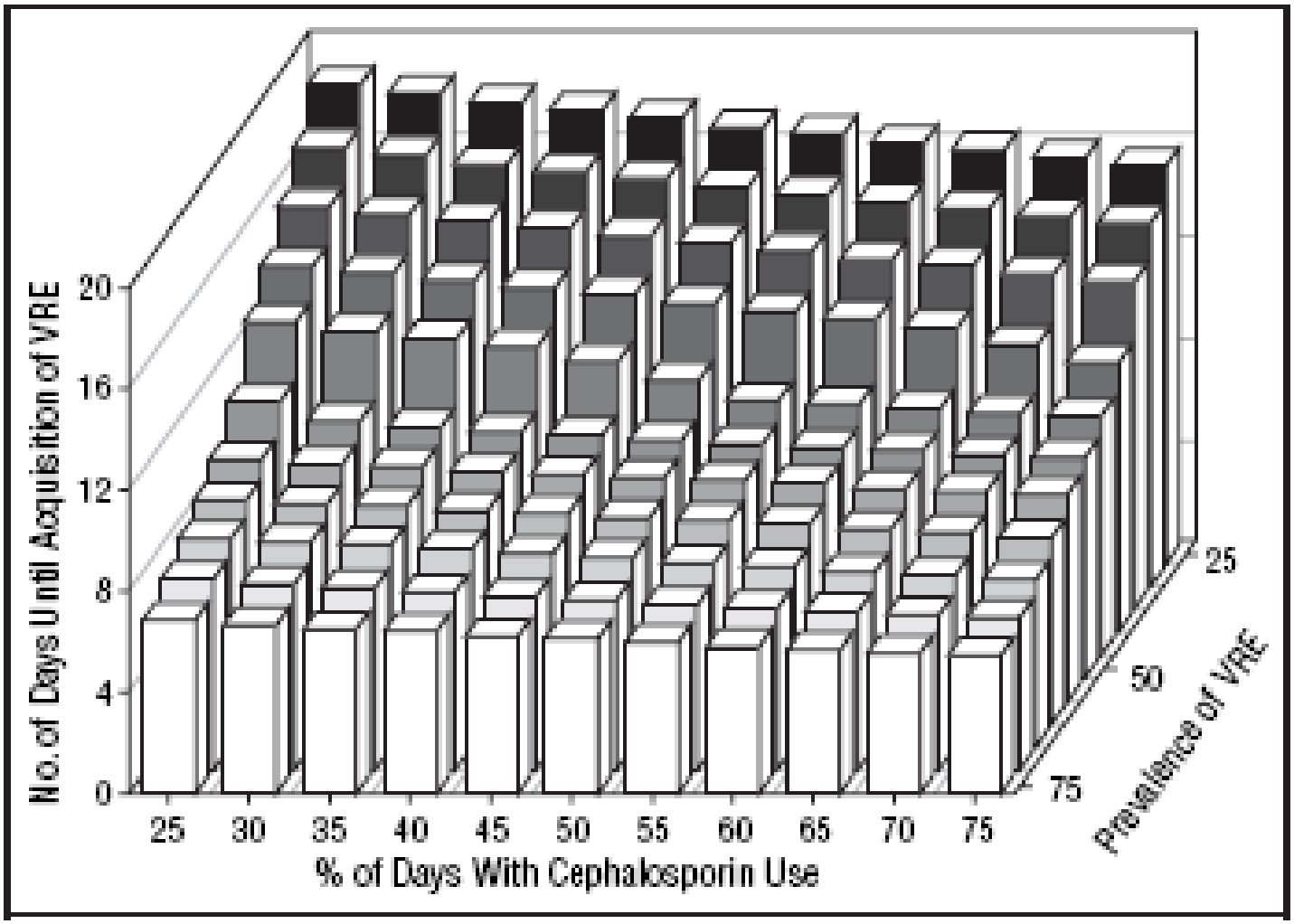
Jonas et al, Infect Control Hosp Epidemiol 2008; 29: 350 - 7

Imipenem Usage Density and Resistance Rate in ICUs with Low (circles) and High (triangles) Genodiversity of Resistant Strains



Jonas et al, Infect Control Hosp Epidemiol 2008; 29: 350 - 7

Confounder: Colonisation Pressure



Bonten et al. Arch Intern Med 2008; 158: 1127-1132

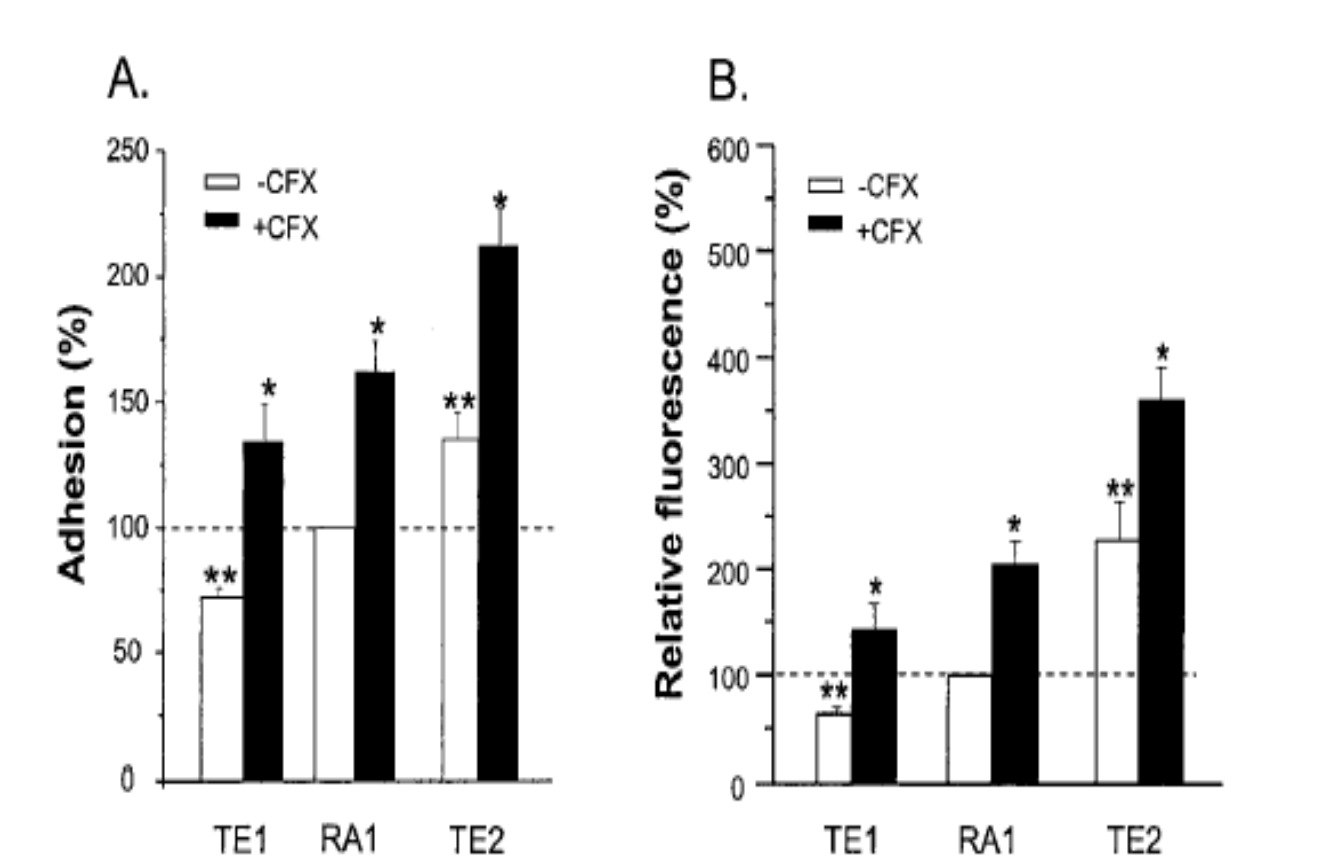
Confounder: Underlying Illness and Length of Stay

	MRSA cases		MSSA cases	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Primary covariates				
Levofloxacin	3.38 (1.94 to 5.90)	<0.001	0.69 (0.34 to 1.40)	0.30
Ciprofloxacin	2.48 (1.32 to 4.67)	0.005	0.47 (0.21 to 1.02)	0.06
Other covariates				
Lung disease	**3.94 (2.43 to 6.40)**	**<0.001**	**2.33 (1.43 to 3.81)**	**<0.001**
Renal disease	*		1.98 (1.03 to 3.80)	0.04
Penicillin	*		1.78 (0.93 to 3.39)	0.08
Metronidazole	1.92 (1.10 to 3.37)	0.02	1.29 (0.65 to 2.56)	0.46
ICU stay	**5.33 (3.28 to 8.68)**	**<0.001**	**4.60 (2.90 to 7.30)**	**<0.001**
Emergent admission	1.74 (1.09 to 2.78)	0.02	1.90 (1.17 to 3.08)	0.01

Weber et al., Emerg Infect Dis 2003; 9: 1415-22

Confounder: Virulence

Adhesion to fibronection *sigB* Null *S. aureus* grown in either the absene or presence of 4 µg of ciprofloxacin



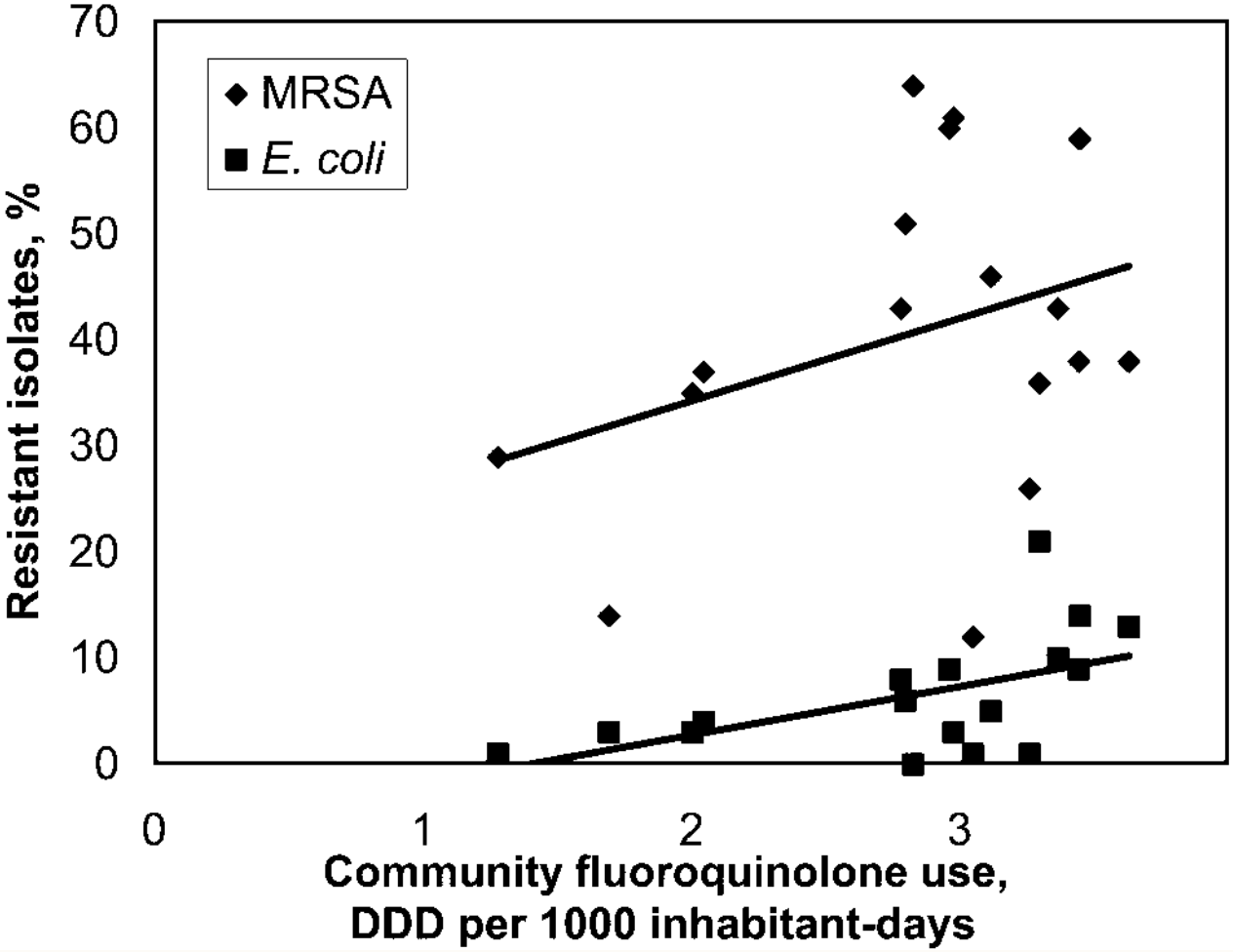
Li et al., Antimicrob Agents Chemother. 2005; 49: 916-24

Confounder: Duration of Treatment

- Objective:
  - Estimate the probability of carbapenem resistance among *P. aeruginosa* isolates
- Method:
  - Retrospective, cross-sectional study
  - Adult inpatients with respiratory tract infection
  - Log-binomial regression
- Results:
  - Independent predictors of carbapenem resistance were
    - prior receipt of mechanical ventilation for 11 days or more
    - prior exposure to fluoroquinolones and to carbapenems for 3 days or more

Lodisi et al., ICHE 2007; 28: 959 - 65

Confounder: Community Use



MacDougall et al. Clin Infect Dis 2005; 41: 435-440

CONCLUSIONS and RECOMMENDATIONS

- Both patient-level and ecological studies of antibiotic use and resistance confirm causal relationship
- No agreement on which methods of measurement of antibiotic use and resistance correlate best with selection of resistance
- Limited understanding of host and bacterial interaction to link antibiotic exposure with emergence of resistance (host factors, clonality, fitness, virulence, pathogenicity)
- Pk/Pd studies are needed to investigate association of antibiotic exposure with acquisition or progression from colonisation towards infection (resistance mechanism, interaction, duration of treatment, dose, time effect)
- Prospective human studies are needed to better define and quantify the risks associated with antibiotic exposure