Research needs and pitfalls in antimicrobial stewardship

Stephan Harbarth, MD MS
Infection Control Program
University of Geneva Hospitals, Switzerland

stephan.harbarth@hcuge.ch

Common goals of antibiotic stewardship programs

- To improve adequacy & efficacy of AB prophylaxis and therapy
- To minimize adverse events (eg. *C.difficile* colitis, mortality) and increase patient safety
- To decrease costs and waste
- To control AMR emergence & spread

Research needs and pitfalls in evaluating the impact of antimicrobial stewardship

Stephan Harbarth, MD MS
Infection Control Program
University of Geneva Hospitals, Switzerland

stephan.harbarth@hcuge.ch

Sources of inspiration (and slides) for this talk

- Matthew SAMORE, USA
- Nathalie VERNAZ, Switzerland
- Benedikt HUTTNER, Switzerland
- Peter DAVEY, Scotland
- Dominique MONNET, Sweden

Agenda

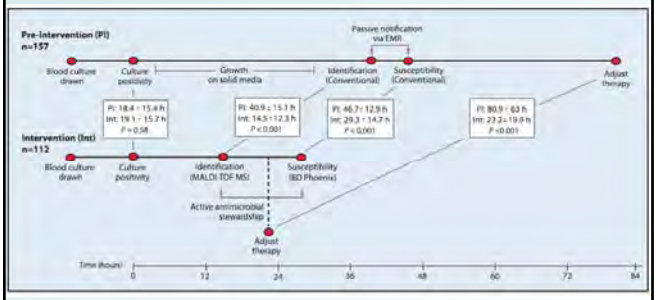
- Before-after studies
- ORION statement
- Segmented regression analysis
- Interrupted time-series analysis

- I will not cover randomised trials and meta-analyses

Before-after studies

Cohort Studies with Historical Controls

Stewardship improves patient outcomes



Timeline comparison of pre-intervention (PI) and intervention (Int) study periods. Adjusted therapy included de-escalation/escalation of antibiotic therapy, dosing/route modifications, and/or discontinuation of unnecessary Gram-positive coverage.

Perez KK et al. J Infect 2014; 69: 216-25

Stewardship improves patient outcomes

- Integrating rapid diagnostics with AMS improved time to optimal antibiotic therapy (80.9 h pre- vs 23 hours in the intervention period; P < .001)
- Mortality among patients during the intervention period was lower (21% vs 8.9%; P = .01)

Table 5 Length of stay and costs outcomes in hospital survivors.[a]

Outcome	Pre-intervention cohort (n = 128)	Intervention cohort (n = 103)	P value
Hospital length of stay	23.3 ± 21.6	15.3 ± 17.3	0.001
Hospital length of stay post-BSI onset	16.2 ± 17.7	10.8 ± 12.7	0.001
ICU length of stay	16 ± 19	10.7 ± 17.6	0.028
ICU length of stay post-BSI onset	12.5 ± 15.6	7.3 ± 9.4	0.004
Total hospital costs	$78,991 ± $90,106	$52,000 ± $83,526	0.002
MS DRG weight	3.6 ± 2.9	3.0 ± 3	0.1

Perez KK et al. J Infect 2014; 69: 216-25

Impact of an educational program on antibiotic use in a tertiary care hospital in Thailand

Appropriate antibiotic use (in-patients, %)

Variable	Preintervention period (n = 4305)	Postintervention period (n = 2930)	P
Inappropriate antibiotic use	1808 (42)	568 (20)	<.001
Reason for inappropriateness[a]			
Inappropriate surgical prophylaxis[b]	452 (25)	115 (20)	.02
Use of antibiotic without any evidence of infection	723 (40)	200 (35)	.04
Redundant spectrum	217 (12)	50 (9)	.03
Bacterial resistance[c]	235 (13)	91 (16)	.07
Narrow spectrum was available[d]	181 (10)	41 (7)	.04
Department[e]			
Surgery	633 (35)	170 (30)	.01
Obstetrics and gynecology	452 (25)	125 (22)	.12
Internal medicine	416 (23)	113 (20)	.14
Other[f]	307 (17)	118 (20)	.12

Apisarnthanarak et al. Clin Infect Dis 2006; 42: 768

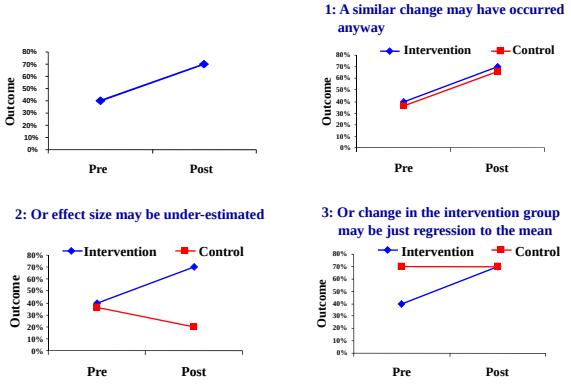
Impact of an educational program on antibiotic use in a tertiary care hospital in Thailand

Antibiotic resistance

Microorganism	Resistance rate, %[a] Preintervention period	Postintervention period
Methicillin-resistant *Staphylococcus aureus*	48	33.5
…	…	…
ESBL-producing *Escherichia coli*	33	21
ESBL-producing *Klebsiella pneumoniae*	30	20
Third-generation cephalosporin–resistant *Acinetobacter baumanii*	27	19
Imipenem-resistant *Pseudomonas aeruginosa*	5	4
Multidrug-resistant *Acinetobacter baumanii*	4	5

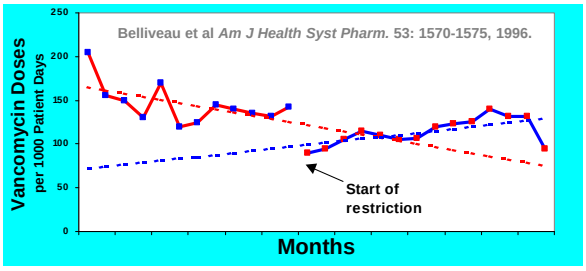
Apisarnthanarak et al. Clin Infect Dis 2006; 42: 768

What can be wrong with uncontrolled Before & After Studies?



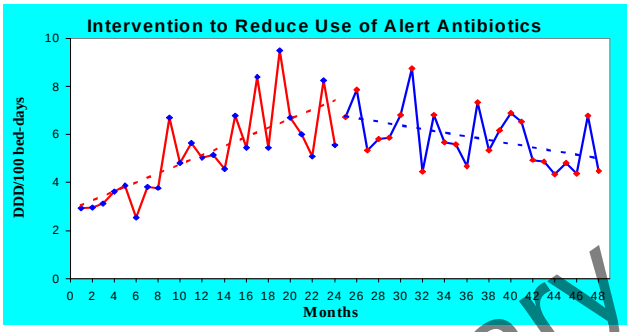
Limitations of Group Intervention Studies using a Before-After Comparison
(e.g., Cohort Studies with Historical Controls)

- Ecologic (aggregate-data) analyses



	Change (in Vancomycin doses)	P
t test	-31 per 1000 pd	<0.001
Slope	+ 6 per month	<0.001

Ramsay et al, J Antimicrob Chemother 2003; 52: 764-71
Courtesy: Peter Davey, Dundee (UK)



	Change: DDD/100 bdm	P
t test	+0.54	0.2
Slope	-0.266	<0.001

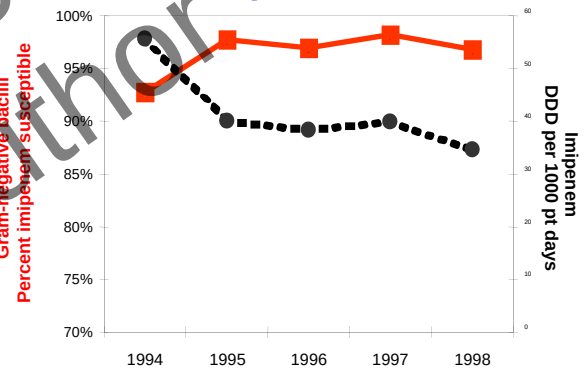
Ansari F et al, J Antimicrob Chemother 2003; 52: 842-848
Courtesy: Peter Davey, Dundee (UK)

Parallel Analysis of Individual and Aggregated Data on Antibiotic Exposure and Resistance in Gram-Negative Bacilli

Stephan Harbarth,[1] Anthony D. Harris,[2] Yehuda Carmeli,[3] and Matthew H. Samore[4]
[1]Harvard Medical School, Boston; [2]University of Maryland, Baltimore; [3]University Hospital of Utah, Salt Lake City; and [4]Sourasky Medical Center, Tel Aviv, Israel

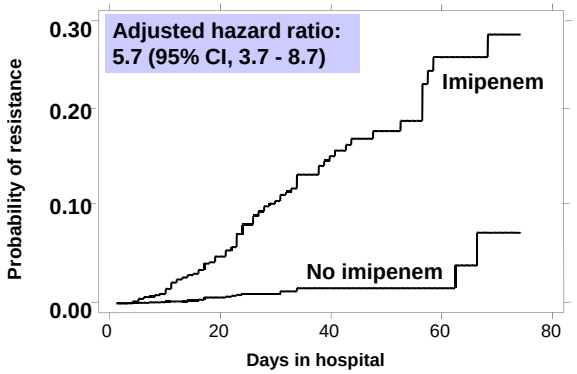
Clin Infect Dis 2001; 33: 1462-68

Group-level data



Clin Infect Dis 2001; 33: 1462-68

Individual-level data

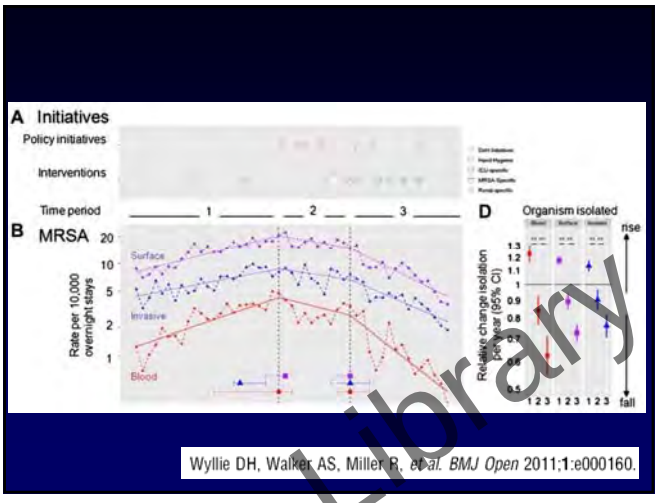


Clin Infect Dis 2001; 33: 1462-68

Limitations of Group Intervention Studies using a Before-After Comparison

(e.g., Cohort Studies with Historical Controls)

- Ecologic (aggregate-data) analyses
- Serial & simultaneous interventions



Limitations of Group Intervention Studies using a Before-After Comparison
(e.g., Cohort Studies with Historical Controls)

- Ecologic (aggregate-data) analyses
- Serial & simultaneous interventions
- Non-independent events

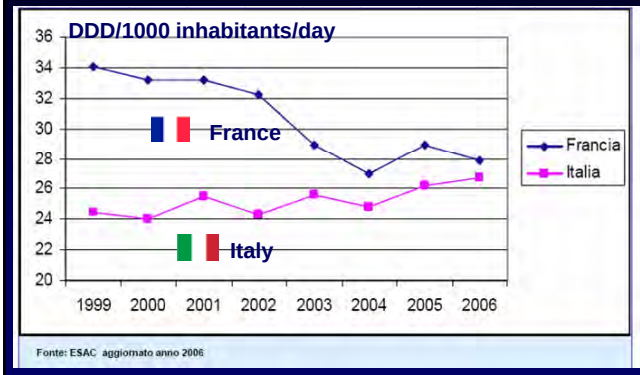
Intervention studies about infections – what have we been missing?

- Disease-causing agents are indirectly or directly transmitted between individuals
- In many analyses:
  - Independence assumption violated
  - Clustering effects ignored

Limitations of Group Intervention Studies using a Before-After Comparison
(e.g., Cohort Studies with Historical Controls)

- Ecologic (aggregate-data) analyses
- Serial & simultaneous interventions
- Non-independent events
- Lack of concurrent control group

Trends in antibiotic consumption France and Italy (1999-2006)



Control of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* using a computer-assisted management program to restrict third-generation cephalosporin use

Jeong Yeon Kim[1], Jang Wook Sohn[1,2], Dae Won Park[1,2], Young Kyung Yoon[1], Young Mi Kim[3] and Min Ja Kim[1,2]*

Phase I (pre-intervention)
Phase II (intensive-intervention)
Phase III (maintenance)

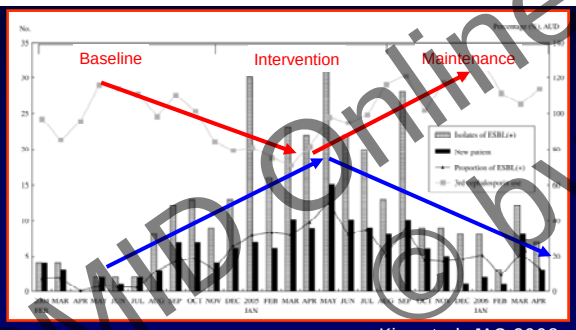
The proportion of ESBL-producing *K. pneumoniae* isolates increased significantly from 8.1% (47/578) in Phase I to 32.0% (188/587) in Phase II, and then decreased significantly to 20.6% (97/470) in Phase III (P < 0.05).

CONCLUSIONS:
The computerized antibiotic control program appears to be an effective tool for modifying antibiotic consumption, which may in turn prevent the spread of resistant pathogens.

Kim et al. JAC 2008

Control of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* using a computer-assisted management program to restrict third-generation cephalosporin use

Jeong Yeon Kim[1], Jang Wook Sohn[1,2], Dae Won Park[1,2], Young Kyung Yoon[1], Young Mi Kim[3] and Min Ja Kim[1,2]*



Kim et al. JAC 2008

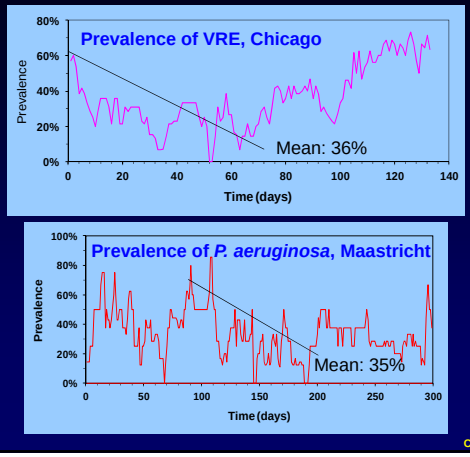
Limitations of Group Intervention Studies using a Before-After Comparison
(e.g., Cohort Studies with Historical Controls)

- Ecologic (aggregate-data) analyses
- Serial & simultaneous interventions
- Non-independent events
- Lack of concurrent control group
- Limited time period before intervention
- Baseline variability

Limitations of Group Intervention Studies using a Before-After Comparison
(e.g., Cohort Studies with Historical Controls)

- Ecologic (aggregate-data) analyses
- Serial & simultaneous interventions
- Non-independent events
- Lack of concurrent control group
- Limited time period before intervention
- Baseline variability
- Bias due to random time effects

Natural history of antibiotic resistance in ICUs



Courtesy: M Bonten

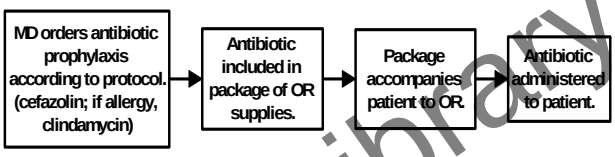
Reporting Data 1

- Time series/ run charts are much richer than point estimates and averages
- Graph the data
- Document ALL of the interventions

Courtesy: P Davey

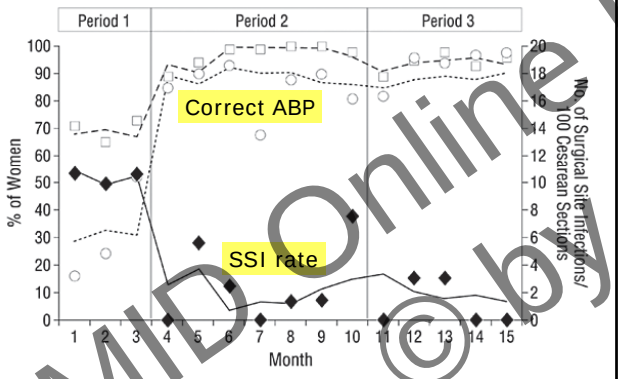
Prophylactic Antibiotics and Infections after Cesarean Section in Colombia

Antibiotic prophylaxis in C-section
- Appropriate indication
- Agent, dose, # of doses
- Timing of first dose



Weinberg et al. Arch Intern Med 2001; 161:2357-65

Use and timing of perioperative antibiotics and surgical site infection rates



Weinberg et al. Arch Intern Med 2001; 161:2357-65

Reporting Data 2

- Time series should be in months where possible
- 3 points before and after is the absolute minimum
- 24 points before and after is much better
- Fewer points seriously reduces ability to assess sustained effects and combine data
- ORION is a big step in the right direction

Courtesy: P Davey

The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection

Sheldon P Stone, Ben S Cooper, Chris C Kibbler, Barry D Cookson, Jenny A Roberts, Graham F Medley, Georgia Duckworth, Rosalind Lai, Shah Ebrahim, Erwin M Brown, Phil J Wiffen, Peter G Davey

Lancet Infect Dis 2007; 7: 282-88

Aims of ORION Statement

- Improve standards research & publication
- Increase transparency of reporting
- Framework for reviewers & editors
- Facilitate synthesis of evidence
- Decrease sources of bias, especially in before-after studies

Stone S et al. Lancet Infect Dis 2007; 7: 282-88

Key issues addressed by ORION

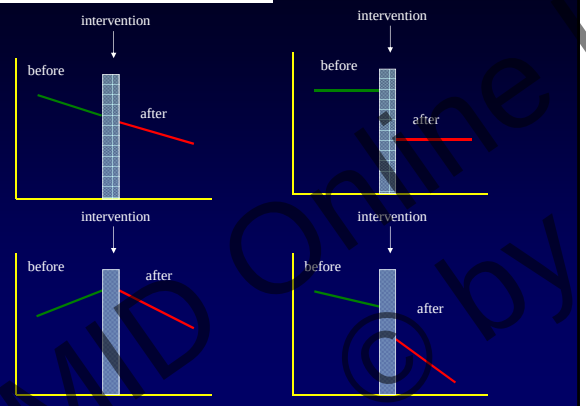
Transparency: Why was the study done? (hypothesis)
What sort of study? (design)
Exactly what was done, to whom, when?

Analysis: Disaggregated data
Account for dependencies
Confounders

Inference: How do findings relate to hypothesis?
What else influenced the findings?
Do findings generalise ?

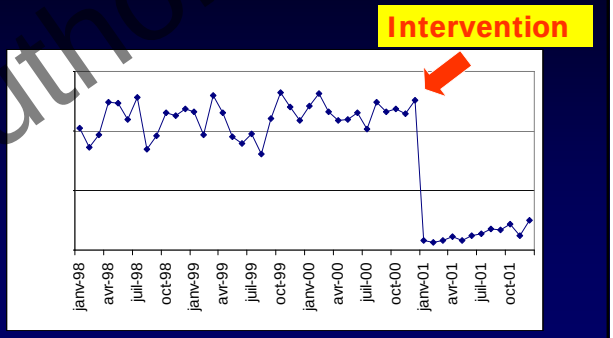
Segmented regression analysis

Intervention Effects

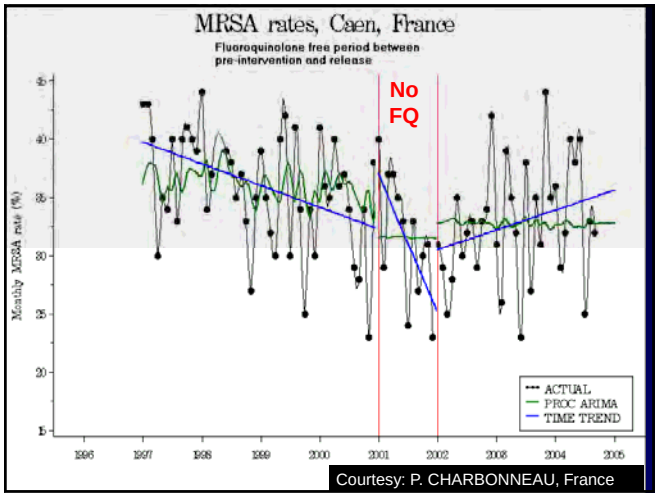


Effect of FQ restriction on MRSA

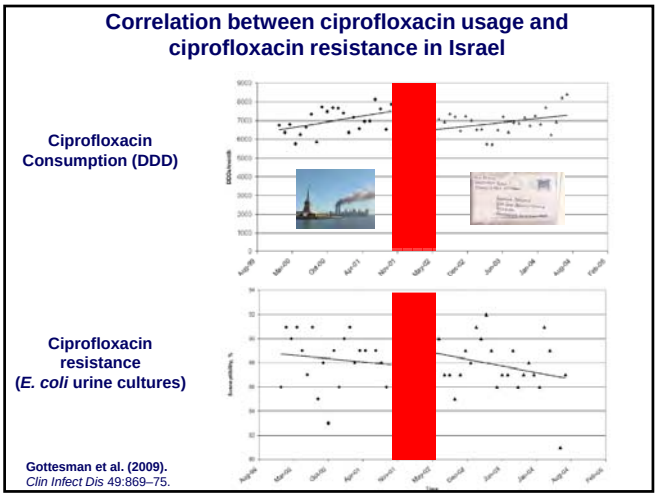
Caen Regional University hospital 1998-2001



Charbonneau P et al. Clin Infect Dis 2006

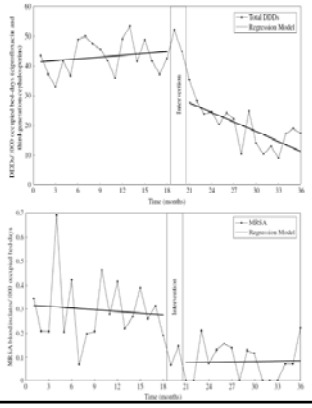


Correlation between ciprofloxacin usage and ciprofloxacin resistance in Israel



Gottesman et al. (2009). *Clin Infect Dis* 49:869–75.

Segmented Regression Analysis of Change in Ciprofloxacin and 3rd gen Cephalosporins and MRSA Bacteraemia

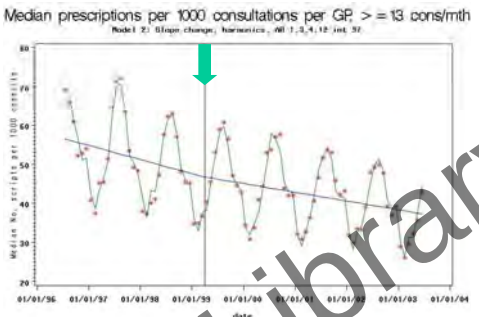


DDDs/1,000 bed-days for Ciprofloxacin and Third Generation Cephalosporins

MRSA Blood Isolates per 1,000 Bed-days

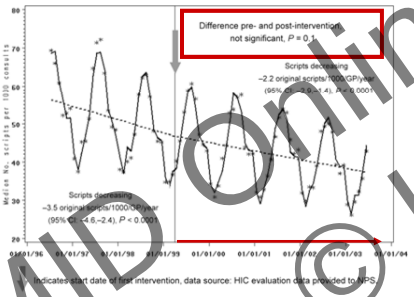
Liebowitz, J Hosp Infect 2008; 69: 328-36

GP prescriptions for URTI – continued decline, reduced peaks (Australia)



Australia - outcomes

- Prescription data from Medicare Australia



Wutzke et al. (2007). *Health Promot Int* **22**:53-64.

Time-Series Analyses

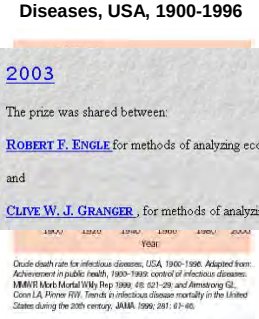
Courtesy: D. Monnet

What Is Time Series Analysis?

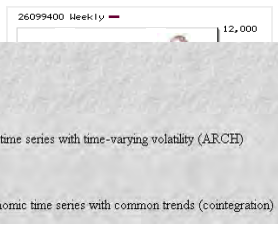
- **Time Series Analysis**: the analysis of time series, i.e. series of data collected over time at short intervals
- Ability to take auto-correlation into account
- In 1976, Box & Jenkins provided a practical method to build time series models

Examples of Time Series

Crude Death Rates for Infectious Diseases, USA, 1900-1996



Dow Jones Industrial Average



2003

The prize was shared between:

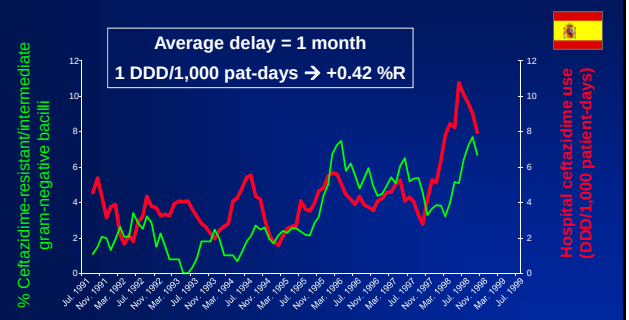
ROBERT F. ENGLE for methods of analyzing economic time series with time-varying volatility (ARCH)

and

CLIVE W. J. GRANGER, for methods of analyzing economic time series with common trends (cointegration)

Source: Aiello AE & Larson EL. Lancet Infect Dis 2002;2:103-10.

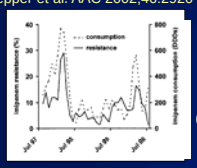
5-Month Moving Average Percent Ceftazidime-Resistant/Intermediate *P. aeruginosa* and Hospital Ceftazidime Use, Hospital Vega Baja, Spain, 1991-1999



Source: López-Lozano JM, et al. Int J Antimicrob Agents 2000;14:21-30.

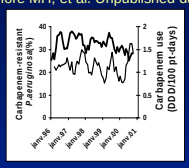
%Carbapenem-Resistant *Pseudomonas aeruginosa* and Carbapenem Use in 4 Hospitals, 1996-2003

Univ. Hospital, Ulm (D)
Lepper et al. AAC 2002;46:2920-5.



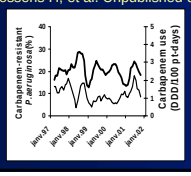
Average delay = 0-1 month

Univ. Hospital, Utah (USA)
Samore MH, et al. Unpublished data.



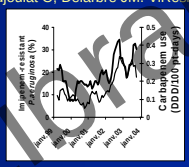
Average delay = 0-1 month

Univ. Hospital, Antwerp (B)
Goossens H, et al. Unpublished data.



Average delay = 0-2 months

Centre Hosp. Mulhouse (F)
Aujoulat O, Delarbre JM. ViReSiST.



Average delay = n.a.

Multivariate Time Series Analysis for Monthly MRSA (R^2 = 0.56) at University of Geneva Hospitals in Switzerland (02/2000 – 09/2006)

Variable	Lag (months)	Coefficient	*T* test	*P* value
Fluoroquinolone use (DDD/100 patient-days)	1	0.010	2.71	0.009
Third-generation cephalosporin use (DDD/100 patient-days)	4	0.014	2.15	0.035
Macrolide use (DDD/100 patient-days)	4	0.012	3.19	0.002
Cefepime use (DDD/100 bed-days)	3	0.014	2.56	0.013
Piperacillin/tazobactam use (DDD/100 patient-days)	3	0.041	2.97	0.004
Hand hygiene campaign	0	-0.032	-5.81	<0.0001
Autoregressive term	1	0.546	3.24	0.002
Moving average term	1	-0.732	-4.46	<0.0001

Vernaz et al, J Antimicrob Chemother 2008; 62:601-7.

Multivariate Time Series Analysis for Monthly HA-MRSA Infection (R^2 = 0.66) at Freiburg University Medical Center in Germany (01/2003 – 10/2007)

Variable	Lag (months)	Coefficient	*T* test	*P* value
Fluoroquinolone use (DDD/1000 patient-days)	4	1.12	2.73	0.01
Second-generation cephalosporin use (DDD/1000 patient-days)	1	1.41	2.39	0.023
Third-generation cephalosporin use (DDD/1000 patient-days)	3-4	1.03	2.03	0.05
Lincosamide use (DDD/1000 patient-days)	2	.42	2.04	0.05
Alcohol-based handrub	3-7	-5.37	-5.93	<0.001
Patients admitted with MRSA (no./1000 patient-days)	0	0.43	2.14	0.04
Autoregressive term (MRSA)	1	-0.33	-1.97	0.057

Kaier et al, Inf Control Hosp Epidemiol 2009; 30: 346-53

Multivariate Time Series Analysis for Monthly HA-MRSA (R^2 = 0.78) at Antrim Area Hospital in Nothern Ireland (01/2000 – 12/2004)

Variable	Lag (months)	Coefficient	*T* test	*P* value
Fluoroquinolone use (DDD/100 bed-days)	1	0.00481	4.905	<0.0001
Third-generation cephalosporin use (DDD/100 bed-days)	2	0.0273	6.080	<0.0001
Macrolide use (DDD/100 bed-days)	4	0.00212	2.149	0.0376
Amoxicillin/clavulanic acid use (DDD/100 bed-days)	1	0.00349	5.365	<0.001
Alcohol-based handrub bulk orders	3	-0.0390	-2.619	0.0123
	4	-0.0755	-4.932	<0.0001
Alhohol-impregnated wipes (no./100 bed-days)	2	-0.000345	-6.956	<0.0001
Patients actively screened for MRSA (no./100 bed-days)	3	-0.00721	-2.357	0.0233
Patients admitted with MRSA (no./100 bed-days)	2	0.223	7.162	<0.0001
Autoregressive term	4	-0.552	-4.250	0.0001
Moving average term	2	-0.980	-1382.67	<0.0001

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

Journal of Antimicrobial Chemotherapy Advance Access published June 12, 2008

JAC

Interventions to control MRSA: high time for time-series analysis?

S. Harbarth[1]* and M. H. Samore[2,3]

[1]Infection Control Program, University of Geneva Hospitals and Medical School, CH-1211 Geneva 14, Switzerland; [2]VA Salt Lake City Health Care System, Salt Lake City, UT 84148, USA; [3]Division of Epidemiology, University of Utah School of Medicine, Salt Lake City, UT 84108, USA

Time-series methods are useful in quasi-experimental study designs in which rates of antibiotic-resistant infections are ascertained before and after an intervention. However, uncertainties remain regarding the use of time-series analysis as an appropriate research methodology for analysing the effect of infection control interventions and antibiotic policies on the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA). In particular, there is still a substantial gap in our understanding of what actually happens to MRSA incidence when a planned intervention is made on use of one or more antibiotic drug classes.

Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis

Mark J Dayer, Simon Jones, Bernard Prendergast, Larry M Baddour, Peter B Lockhart, Martin H Thornhill

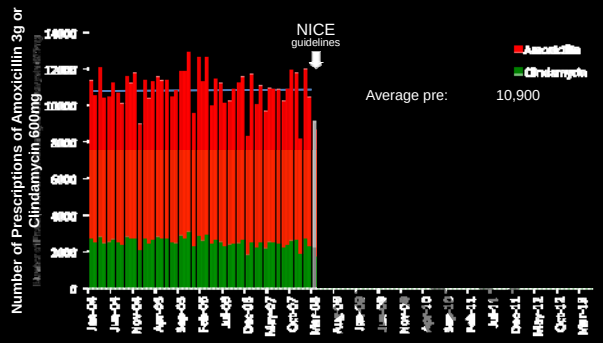
Summary

Background Antibiotic prophylaxis given before invasive dental procedures in patients at risk of developing infective endocarditis has historically been the focus of infective endocarditis prevention. Recent changes in antibiotic prophylaxis guidelines in the USA and Europe have substantially reduced the number of patients for whom antibiotic prophylaxis is recommended. In the UK, guidelines from the National Institute for Health and Clinical Excellence (NICE) recommended complete cessation of antibiotic prophylaxis for prevention of infective endocarditis in March, 2008. We aimed to investigate changes in the prescribing of antibiotic prophylaxis and the incidence of infective endocarditis since the introduction of these guidelines.

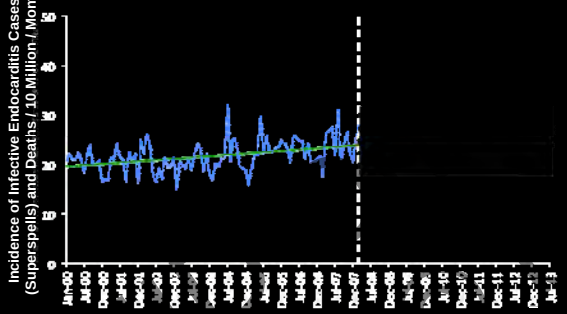
Lancet 2015; 385: 1219–28
Published Online November 12, 2014

Department of Cardiology, Taunton and Somerset NHS

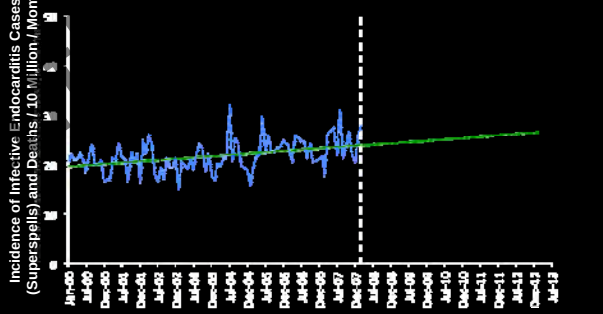
Antibiotic Prophylaxis Prescribing Data



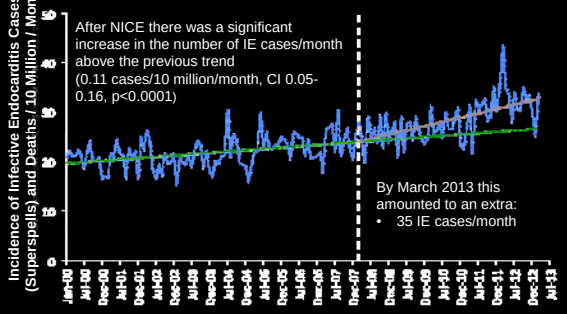
Incidence of IE



Incidence of IE



Incidence of IE



Limitations of this study

- UK hospital coding data
  - Diagnostic bias
- Ecologic bias
  - No individual patient analysis
- No data available on…
  - … improved diagnostic practices of endocarditis
  - … changes in pattern of dental care
  - … other potentially risk-prone procedures such as colonoscopy, renal dialysis, IV treatment
  - … organism-specific endocarditis

Summary

Important Limitations of Group Intervention Studies using a Before-after Comparison
(e.g., Cohort Studies with Historical Controls)

- Lack of concurrent control group and many unmeasured confounders may distort study results
- Limited time period before intervention insufficient to draw conclusions about baseline infection rates

Important Limitations of Group Intervention Studies using a Before-after Comparison
(e.g., Cohort Studies with Historical Controls)

- Bias due to the influence of random time effects
- Independence assumption of statistical tests may be violated

➔Study design providing the least amount of confidence that results of an intervention will reflect the true causal effect of the intervention

ORION statement

- Quality of infection control research must improve to provide robust evidence for policy & practice
- Doing it right is easy if you know what to do
- Designed especially for infection control interventions and outbreak reports
  - Checklist for consistent reporting of key data items
  - Plot the dots, infection is a time dependent variable

Strengths and limitations of time series analysis

- Appropriate

&

- Robust

- Time & effort
- Careful evaluation
- Learn methodology & software
- Aggregate analysis, without control for covariates at individual level

Statistical Analysis and Application of Quasi Experiments to Antimicrobial Resistance Intervention Studies

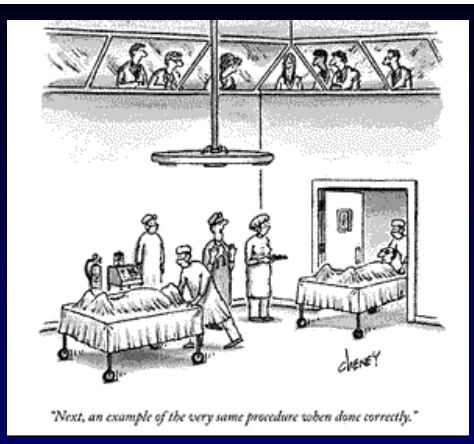
Michelle Shardell,[1] Anthony D. Harris,[1] Samer S. El-Kamary,[1] Jon P. Furuno,[1] Ram R. Miller,[1] and Eli N. Perencevich[1,2]
[1]Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, and [2]Veterans Affairs Maryland Health Care System, Baltimore

Table 2. Characteristics of each statistical method.

Characteristic	Statistical method: Two-group tests	Regression analysis: Standard model	Regression analysis: Segmented model	Time-series analysis: Standard model	Time-series analysis: Segmented model
Data requirements, no. of observations	≥2 (1 before, 1 after)	≥10 per parameter	≥10 per parameter	≥50 overall and ≥10 per parameter	≥50 overall and ≥10 per parameter
Can control for confounders and time trends	No	Yes	Yes	Yes	Yes
Can estimate changes in time trends	No	No	Yes	No	Yes
Can account for autocorrelation	No	No	No	Yes	Yes

902 • CID 2007:45 (1 October) • ANTIMICROBIAL RESISTANCE

Clin Infect Dis 2007; 45: 901-7



"Next, an example of the very same procedure when done correctly"