23rd ECCMID Berlin, Germany 27 – 30 April 2013
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

From data to words: writing up your work for publication
Educational Workshop, 30 April 2013

Epidemiological study

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UNIVERSITÄTS KLINIKUM TÜBINGEN

LONG PERIODS OF THINKING
SHORT PERIODS OF WRITING

Hemingway

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Why do we publish?

- To obtain tenure
- To get money
- **To communicate results to as great an audience as possible and advance our understanding of infectious diseases and clinical microbiology in order to improve patients' outcome**

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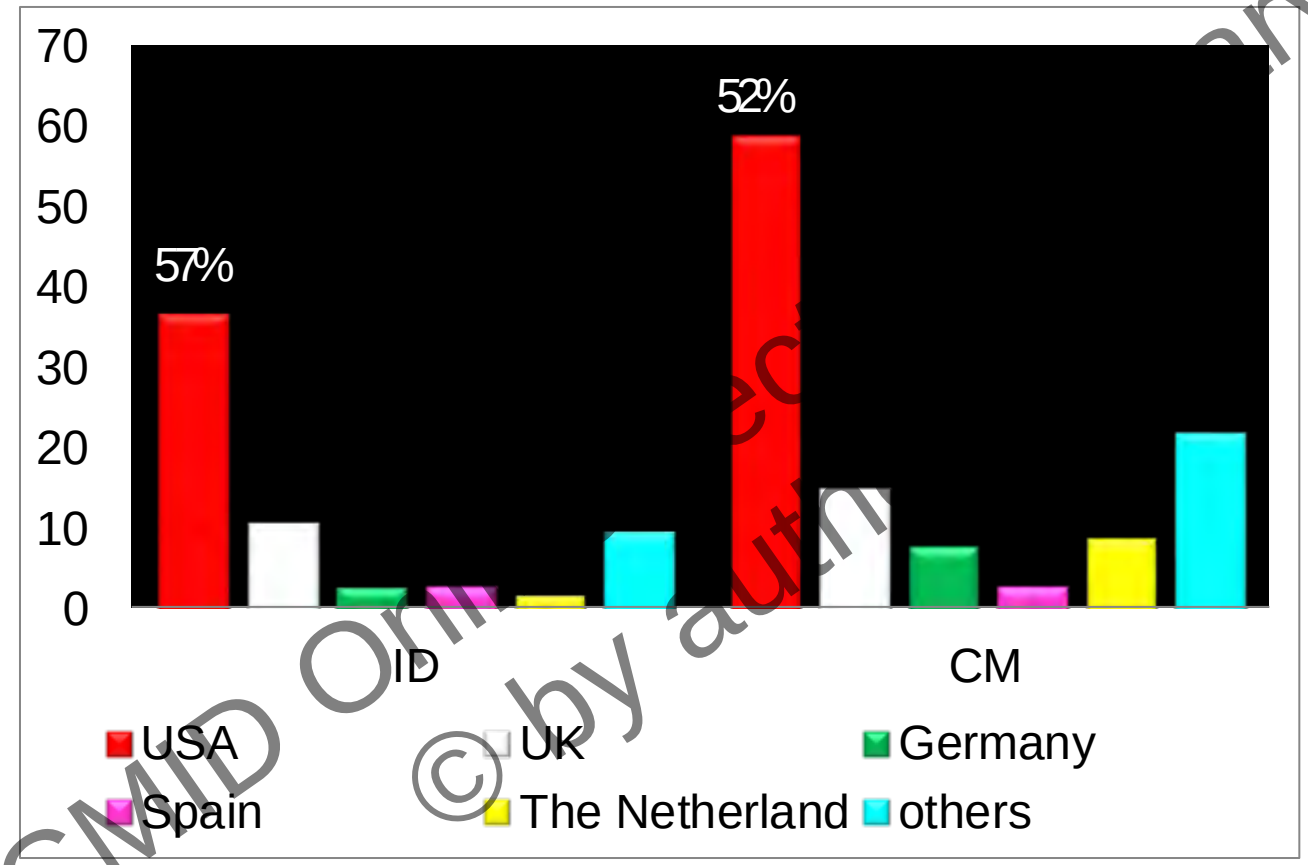
65 Journals in Infectious Diseases and 13 in Microbiology



Where do we publish?

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STROBE Statement

Strengthening the reporting of observational studies in epidemiology

STROBE checklists

Version 4 as published in Oct / Nov 2007!

- STROBE checklist for **cohort, case-control, and cross-sectional studies** (combined)
  download PDF / Word
- Checklist for **cohort studies**
  download PDF / Word
- Checklist for **case-control studies**
  download PDF / Word
- Checklist for **cross-sectional studies**
  download PDF / Word
- Draft STROBE checklist for **conference abstracts**
  download PDF

How do we publish?

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Level of satisfaction	Statement	Section
< 25% of studies	3. State specific objectives, including any pre-specified hypotheses	Introduction
	Description of intervention and whether triggered by outcome data	
	Formally implemented with protocol and endpoints?	Methods
	9. Describe any efforts to address potential sources of bias	Methods
	10. Explain how the study size was arrived at	Methods
	11. Explain how quantitative variables were handled	Results
	17. Report other analyses done – e.g., analyses of subgroups	
> 25 < 50% of studies	1a. Indicate the study design with a commonly used term in the title or the abstract	Title and abstract
	Pro /Retro-spective	Title and abstract
	1b. Provide in the abstract an informative and balanced summary	
	19. Discuss limitations of the study, taking into account sources of potential bias or imprecision	Discussion
	21. Discuss the generalisability	
	22. Give the source of funding	Discussion
		Funding

STROBE application in 154 epidemiological studies on MRSA and MDR-Acinetobacter

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> 50 < 75% of studies	2. Explain the scientific background and rationale for the investigation	Introduction
	Organism endemic epidemic sporadic	
	Outbreak or and an intervention	Methods
	4. Present key elements of study design early in the paper	Methods
	7. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers (incl fidelity to intervention)	
	8. For each variable of interest, give sources of data and details of methods of assessment	Methods
	13. Report the numbers of individuals at each stage	
	Dynamics eg admissions transfers lengths of stay	Results
	16. Give unadjusted estimates and, if applicable, confounder-adjusted estimates	Results
> 75% of studies		Methods
	5. Describe the setting, locations, and relevant dates	Methods
	6. Description of participants - eligibility criteria, sources and methods -	
	12. Describe all statistical methods, including those used to control for confounding	Methods
	14. Give characteristics of study participants	
	15. Report outcome data	Results
	18. Summarise key results with reference to study objectives	Results
	20. Give a cautious overall interpretation of results	Discussion
		Discussion

STROBE application in 154 epidemiological studies on MRSA and MDR-Acinetobacter

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Study subgroups	No. of studies	No. of patients	No. of cases	Summary risk ratio (95% CI)	Q test of heterogeneity
Study design					
retrospective	20	2344	902	1.9 (1.7–2)	<0.001
prospective	50	20 734	2974	1.8 (1.7–1.8)	<0.001
case–control	31	6145	1806	1.9 (1.7–2)	<0.001
cohort	33	12 496	1942	1.7 (1.6–1.8)	<0.001
prevalence surveys	6	4437	128	1.7 (1.3–2.2)	0.3
Definition of controls					
MSSA-positive	32	5652	2156	1.9 (1.8–2)	<0.001
S. aureus-negative	10	3111	300	1.6 (1.5–1.8)	0.002
mixed population	28	14 315	1420	1.7 (1.6–1.8)	<0.001
Definition of cases					
colonized	27	14 145	1048	1.6 (1.5–1.7)	<0.001
infected	35	6490	2140	1.9 (1.8–2)	<0.001
Sampling frame for inclusion					
nosocomial/HCA-based	30	9544	1490	1.7 (1.6–1.9)	<0.001
community-based	26	8924	1274	1.6 (1.5–1.7)	<0.001
Performed in ICU					
yes	9	4139	452	1.4 (1.3–1.5)	<0.001
no	61	18 939	3424	1.9 (1.8–2)	<0.001
Adjusted for covariates					
yes	10	1643	379	2 (1.8–2.3)	0.001
no	60	21 435	3497	1.8 (1.7–1.8)	<0.001
Adjusted for hospital stay[a]	4	332	109	1.8 (1.4–2.2)	0.07
Performed during MRSA outbreak					
yes	7	899	344	1.9 (1.7–2.1)	<0.001
no	63	22 179	3532	1.8 (1.7–1.9)	<0.001

Table 1
Examples of meta-analyses on risk factors for infections

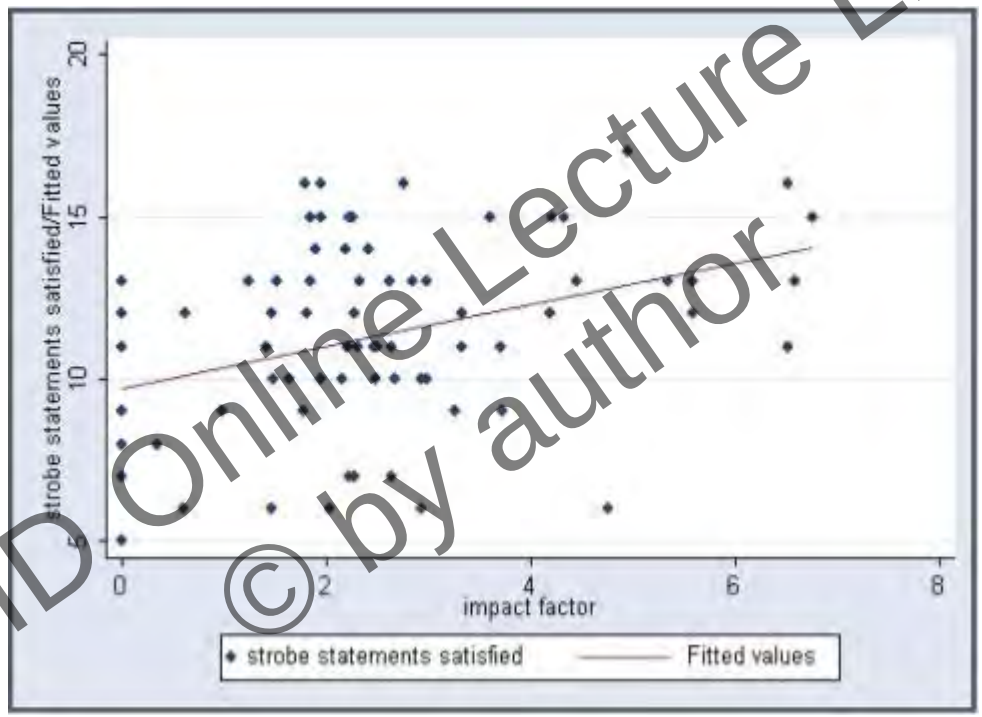
First Author, Year of Publication [ref.]	Risk Factor(s)/ Infection (Setting)	Included Studies, n	Study Design	Main Results	Major Limits
Safdar 2008[42]	MRSA colonization/ MRSA infection	10	Clinical trial, case-control, cohort	MRSA colonization increases the risk for MRSA infection	Significant between studies heterogeneity; differences in severity of illness, frequency of sampling to detect colonization, choice of patients population
Tacconelli 2008[13]	Antimicrobial therapy/ MRSA acquisition	76	Case-control, cohort, cross-sectional	Antimicrobial exposure increases the risk for MRSA acquisition	Significant between studies heterogeneity; case definition bias; control selection bias
Baral 2007[27]	MSM/HIV infection (low- and middle-income countries)	83	Convenience samples, cross-sectional	MSM have a greater risk for being infected with HIV	Study design; control selection bias
Chen 2007[28]	Sexual behaviors/HIV infection (Africa)	68	Cross-sectional, case-control, longitudinal	Number of partners, paid sex, HSV-2 infection increase the risk for HIV transmission	Significant heterogeneity of risks; misclassification of exposures; limited choice of risk factors
Weiss 2006[34]	Male circumcision/genital herpes, syphilis, and chancroid	26	Cross-sectional, case-control, cohort	Circumcision decreases the risk for chancroid and syphilis; less association with genital herpes	Significant heterogeneity between studies; misclassification of serologic status and of circumcision status

Meta-analyses on epidemiological studies on risk factors for infections (I)

Vamvakas 2002[38]	Allogeneic and autologous blood transfusion/ postoperative infections	5	RCTs	No difference in risk for infection	Case definition bias
Thomas 2003[40]	Antimicrobial therapy/ *C difficile* acquisition	48	Cross-sectional, case-control, cohort	Antibiotic exposure increases the risk for *C difficile* acquisition	Control group selection bias; lack of precision in the effect estimates
Bignardi 1998[39]	Risk factors/ *C difficile* acquisition	30	Clinical trial, case-control, cohort	Increasing age, underlying diseases, nonsurgical gastrointestinal procedures, nasogastric tube, antiulcer medications, stay on ICU, duration of hospital stay and antibiotic course, administration of multiple antibiotics increases the risk for *C difficile* acquisition	Control group selection bias; study design; inadequate sample size; inadequate control of confounders; diagnostic bias
Carmeli 1999[43]	Vancomycin use/VRE acquisition	20	Case-control	Vancomycin use increases the risk for VRE acquisition	Significant between studies heterogeneity; control group selection bias

Meta-analyses on epidemiological studies on risk factors for infections (II)

Linear regression showing correlation between rate of satisfaction of STROBE statement and journals' impact factors (2010)



Can we trust the IF?

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Type of epidemiological studies

1. Clinical observations (case series)
2. Cross-sectional studies
3. Case-control studies
4. Cohort studies

„Why to me?“

CASE-CONTROL STUDY

„Am I like my neighbours?“

CROSS-SECTIONAL STUDY

„What happen to me?“

COHORT STUDY

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- Investigates prior exposure of individuals with a particular health condition and those without
- Great potential for bias
- Rare condition (<5% of population)
- Major disadvantages:
  - Select cases and controls after both the outcome and the assumption of risk have occurred

Case-control study

- If strict criteria are not employed to define precisely what constitutes a case, the case group may be diluted with non-cases resulting in spurious associations

- Including cases of a different disease with a different etiology in the case group can increase the probability of a type II error (finding no association when one really exists)

- It can require multiple level of evidence (clinical, diagnostic, and microbiological)

- It can be multi-classified (i.e. suspect, probable, and definite)

Case-control definition

- Cases and control may be selected retrospectively or prospectively but always during the same respective time periods
- One advantage to selecting cases and controls retrospectively is that the investigator can go back as far as needed to get a sufficient number of subjects to maintain a desired level of power in the study
- Disadvantages: exposure data on intake forms may be incomplete or unreliable; change in diagnostic methods or disease classifications

Case-control definition

TABLE 3. Differences in Independent Risk Factors Between Patients Harboring Ciprofloxacin-Resistant *Pseudomonas aeruginosa* (CRPA) and Those Harboring Multidrug-Resistant *P. aeruginosa* (MDR-PA)

Patient group	Adjusted OR (95% CI)	*P*
CRPA group		
Nonambulatory status	5.6 (1.4-23)	.02
Quinolones[a]	5.0 (1.2-21)	.03
MDR-PA group		
Charlson score of >2	3.3 (1.8-6.0)	<.001
Quinolones[a]	2.8 (1.2-5.0)	.001
Cephalosporins[a,b]	3.5 (1.7-7.1)	<.001
Carbapenems[a]	3.8 (1.2-12.1)	.02
Gentamicin[a]	2.3 (1.04-5.1)	.04

Definition of case

Table 4
Multivariate analyses using 'class' and 'spectrum' categorisations

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value
Final multivariate model: antibiotic class categorisation			
Use of third-generation cephalosporin	16.0 (2.00–127.92)	1.35 (0.10–17.73)	0.82
Use of vancomycin	7.15 (2.36–21.63)	8.74 (2.09–36.46)	0.003
Duration of hospitalisation prior to ESBL-EK infection	1.03 (1.01–1.05)	1.03 (1.01–1.05)	0.03
Renal insufficiency	11.56 (2.59–51.67)	3.94 (1.00–15.60)	0.05
Final multivariate model: antibiotic spectrum categorisation			
Use of antimicrobial agent active against *Pseudomonas aeruginosa*	14.82 (3.40–64.66)	3.70 (0.49–27.79)	0.20
Use of antibiotic active against Gram-negative organisms	27.90 (3.72–209.24)	10.27 (1.21–86.47)	0.03
Duration of hospitalisation prior to ESBL-EK infection	1.03 (1.01–1.05)	1.01 (0.98–1.03)	0.31
Central venous catheter	11.56 (2.59–51.67)	5.48 (0.63–48.08)	0.12

OR, odds ratio; 95% CI, 95% confidence interval; ESBL-EK, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp.

ESBL+E. coli and Klebsiella spp
Antibiotic classification

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- Studies that select cases from clinical facilities are commonly referred to as hospital-based case-control studies
- These cases are usually not representative of all possible cases in the general population because of differences in disease severity or socioeconomic factors related to hospitalization
- This can affect external validity, but it will not affect internal validity if the controls are similar to the cases
- Restriction, when properly applied, does not invalidate case-control studies as long as it is applied equally to the controls

Hospital-based case-control studies

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Control selection

- To achieve comparability between cases and controls, the controls should come from the same population that generated the cases.
- Risks: selection bias or confounding
- Most frequent matching criteria: race, sex, age-group, comorbid, from the same hospital, and during the same time period
- Depending on the specific hypothesis being tested, there may be other factors that need to be controlled to minimize potential confounding or selection bias

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Table 2. Multivariable analyses of risk factors for the isolation of vancomycin-resistant enterococci.

Control group, risk factor	OR (95% CI)
2a[a]	
Use of vancomycin	4.38 (3.24–5.93)
Use of aminoglycosides	1.99 (1.45–2.74)
Use of piperacillin-tazobactam	2.10 (1.56–2.84)
Use of first-generation cephalosporin	0.52 (0.35–0.77)
Use of second-generation cephalosporin	0.41 (0.22–0.78)
Use of quinolones	1.66 (1.26–2.19)

Table 1. Assessment of 3 methodological principles of case-control studies among 37 studies that analyzed risk factors for antibiotic resistance.

Methodological recommendation	Adherence with recommendation, no. (%)			
	Yes	No	Uncertain	Not applicable
Control group selected from study base	13 (35%)	24 (65%)	0	0
Time at risk assessed	11 (30%)	22 (60%)	0	4 (11%)
Comorbid illnesses assessed	27 (73%)	8 (22%)	0	2 (5%)
Intensive care unit stay				

[a] Patients with vancomycin-susceptible enterococci.
[b] Randomly selected patients.

Control selection

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Table 1. Multivariable analyses of risk factors for the isolation of imipenem-resistant *Pseudomonas aeruginosa*.

Control group, risk factor	OR (95% CI)
1a[a]	
Use of imipenem	27.12 (13.91–52.90)
Use of aminoglycosides	2.38 (1.40–4.05)
Use of quinolones	3.25 (1.92–5.49)
Surgery	0.42 (0.21–0.85)
1b[b]	
Use of imipenem	6.34 (3.66–11.00)
Use of aminoglycosides	3.28 (1.98–5.42)
Time at risk, days	1.03 (1.01–1.04)
Intensive care unit stay	3.85 (2.16–6.86)

[a] Patients with imipenem-susceptible *P. aeruginosa*.
[b] Randomly selected patients.

Control selection

Table 3. Multivariable analyses of risk factors for the isolation of ampicillin-sulbactam–resistant *Escherichia coli*.

Control group, risk factor	OR (95% CI)
3a[a]	
Use of ampicillin-sulbactam	2.71 (1.64–4.46)
Use of quinolones	2.72 (1.16–6.37)
3b[b]	
Age	1.01 (1.00–1.03)
Use of ampicillin	2.69 (1.08–6.69)
Use of ampicillin-sulbactam	1.68 (1.02–2.77)
Use of first-generation cephalosporins	0.31 (0.18–0.53)
Male sex	0.33 (0.23–0.48)
Hepatic disease	1.89 (1.08–3.32)
Intensive care unit stay	2.42 (1.62–3.63)
Surgery	2.07 (1.36–3.17)
Transfer from a different hospital	1.41 (0.96–2.07)

[a] Patients with ampicillin-sulbactam–susceptible *E. coli*.
[b] Randomly selected patients.

Control selection

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- Cases and controls are based on a total or representative sample of a defined population
- Less common than hospital-based studies because of the time and expense involved in identifying eligible subjects and obtaining the required data
- Cases obtained from these studies, however, should be representative of those in the target population
- One way of identifying incident cases for population-based studies is to utilize a population-based disease registry

Population-based case-control studies

- Controls from population-based case-control studies are usually selected randomly from the source populations. These controls should represent the actual exposure rate of subjects without the study disease in the source population
- Potential selection bias due to low rates of participation and possible measurement bias due to poor recall
- Neighbours, family members, friends, of coworkers from the source population. These types of controls may improve participation and reduce recall bias, but they may also introduce a negative bias in the study results because the controls may be too similar to the cases with regard to exposure status

Population-based case-control studies

Power is related to sample size.

- There are some Internet sites with applets that will calculate required sample size or power based on study parameters that you provide
- **Example**: Epi Info requires:
- The confidence level desired (usually 95% corresponding to a p-value of 0.05)
- The level of power desired (usually between 80 and 95%)
- The ratio of controls to cases (may be 1:1, 2:1, 3:1, etc.)
- The expected frequency of the exposure in the control group (usually estimated from previous surveys in the source population; 50% can be used if there is no estimate available, since it will maximize the sample size required)

- Exposure precedes the health outcome
- Expensive, time consuming and most ligistically difficult of all studies
- Useful for relatively common diseases

Cohort study

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- They clearly demonstrate an appropriate temporal sequence between exposure and outcome
- They permit the direct calculation of incidence rates in both the exposed and unexposed groups
- Easy to calculate risk or rate ratios as needed
- Permit multiple outcomes to be assessed
- They can be used to study exposures that are relatively uncommon

Advantages

Disadvantages

- Potential large sample size requirements
- Long follow-up periods
- Need to reassess exposure on a frequent basis
- Outcomes must be determined as they develop
- Potential losses to follow-up
- Potential exposure misclassification
- Possible outcome misclassification

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Table 2| Frequency of cardiovascular events in patient cohorts. Values are numbers (percentages)

Events	COPD cohort		CAP cohort	
	Clarithromycin user (n=281)	Non-clarithromycin user (n=1062)	Clarithromycin user (n=980)	Non-clarithromycin user (n=651)
Patients with ≥1 cardiovascular event	73 (26.0)	195 (18.4)	123 (12.6)	48 (7.4)
Myocardial infarction	12 (4.3)	29 (2.7)	25 (2.6)	9 (1.4)
NSTEMI or acute coronary syndrome	14 (5.0)	40 (3.8)	29 (3.0)	11 (1.7)
Congestive cardiac failure or left ventricular failure	32 (11.4)	56 (5.3)	32 (3.3)	21 (3.2)
Arrhythmia	47 (16.7)	108 (10.2)	64 (6.5)	23 (3.5)
Cardiac arrest/sudden cardiac death	2 (0.7)	3 (0.3)	14 (1.4)	6 (0.9)

Sum total of events may be greater than number of patients with events, as some patients had more than one cardiovascular event.

CAP=community acquired pneumonia; COPD=chronic obstructive pulmonary disease; NSTEMI=non-ST elevation myocardial infarction.

Cardiovascular events after clarithromycin use

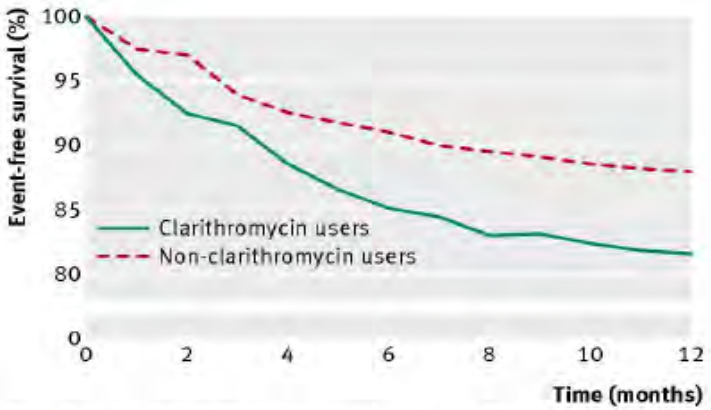

Fig 1 Cox adjusted survival curves for cardiovascular events in acute exacerbations of chronic obstructive pulmonary disease cohort

- ✓ Hospital based cohort
- ✓ Different period of time
- ✓ Heterogeneity of diagnosis (12 hospitals)

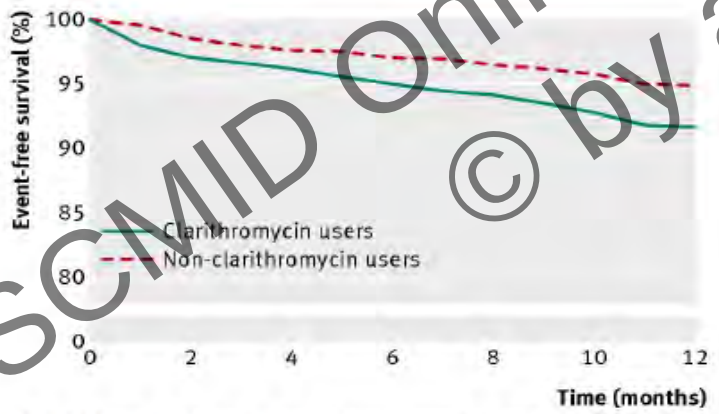

Fig 2 Cox adjusted survival curves for cardiovascular events in community acquired pneumonia cohort

Cardiovascular events after clarithromycin use

- A sufficient number of the individuals in the cohort must have been exposed to high enough levels of the factor that an adequate number of outcomes are likely to have occurred
- Must be a sufficiently accurate source of existing data on exposure levels
- It must be possible to identify an appropriate comparison group
- The comparison group is usually an external comparison group
- It is important to have available sources from which to identify potentially confounding factors in the study and comparison groups

Retrospective cohort studies

Table 4. Severe Adverse Events Per 100,000 Visits by Antibiotic Class

Grouped Visits
All antibiotic use vs none
Specific antibiotic class vs none
β-Lactams
Macrolides
Flouroquinolones

- ✓ Inaccuracy of the system
- ✓ Information about real use of ATB missing
- ✓ ATB prescription is not randomised

Retrospective cohort adult patients with ARI visits from a UK primary care database.
Exposure: antibiotic prescribed with the visit.
Primary outcomes were hospitalization within 15 days for
(1) severe adverse drug events or (2) CAP

- Compares groups in terms of their current health and exposure status and assess their similarities
- Easy to conduct
- Disadvantage: a cause cannot be inferred because only current health and exposure are being studied

Cross-sectional studies

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- ✓ Heterogeneity in case distribution
- ✓ Parents' self-report about their knowledge
- ✓ Language and medical terms used

Background. Upper respiratory trac
viral, but parents' attitudes often co
resistance. The objective of this stu
Greece, a country with high levels of antibiotic use and antibiotic resistance. *Methods*. A knowledge-attitude-practice (KAP) questionnaire was developed and distributed to Greek parents caring for children who were 5-6 years old, between January and July of the same school year. *Results*. The sample of the study contained 5312 parents from all geographic areas of Greece. The risk factors of being a father, having low education, having immigrant status, being a single parent, having low income, having <2 or >3 children, living in the islands, and being without experience in recurrent URTIs were significantly associated to inadequate knowledge, inappropriate attitudes, and wrong practices. *Conclusions*. This study has identified the main groups of parents that should be targeted in future intervention programs.

Antibiotic Misuse for Upper Respiratory Tract Infections

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- Erroneous selection of the control group, matching criteria
- Lack or erroneous definitions
- Lack of definition of exposure
- Lack of adjustment
- Subgroup analysis missing
- Different length of follow up

Most frequent mistakes in epidemiological studies in ID and CM

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Limited controlling for confounding

- Comorbidity
- Context where data are gathered (outbreak or endemic)
- Patients population
- Infection versus colonisation
- Length of hospitalization
- Site of acquisition

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What to do

- Exactly what information do I wish to present in this paper?
- For what specific group or readers am I writing?
- Make a detailed outline of your data according to the STROBE list
- Plan tables and figures
- Be clear
- Be concise
- Be complete

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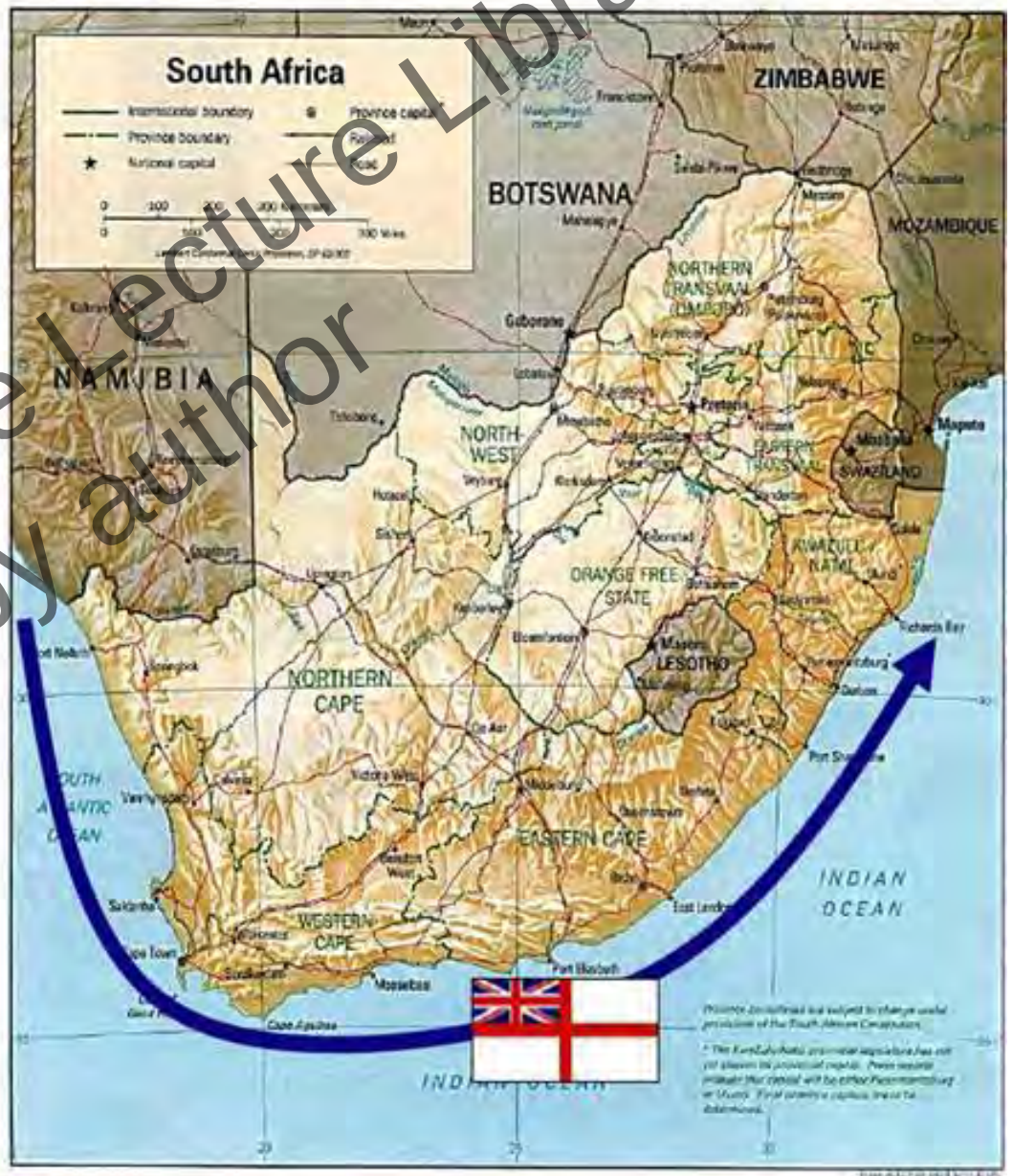
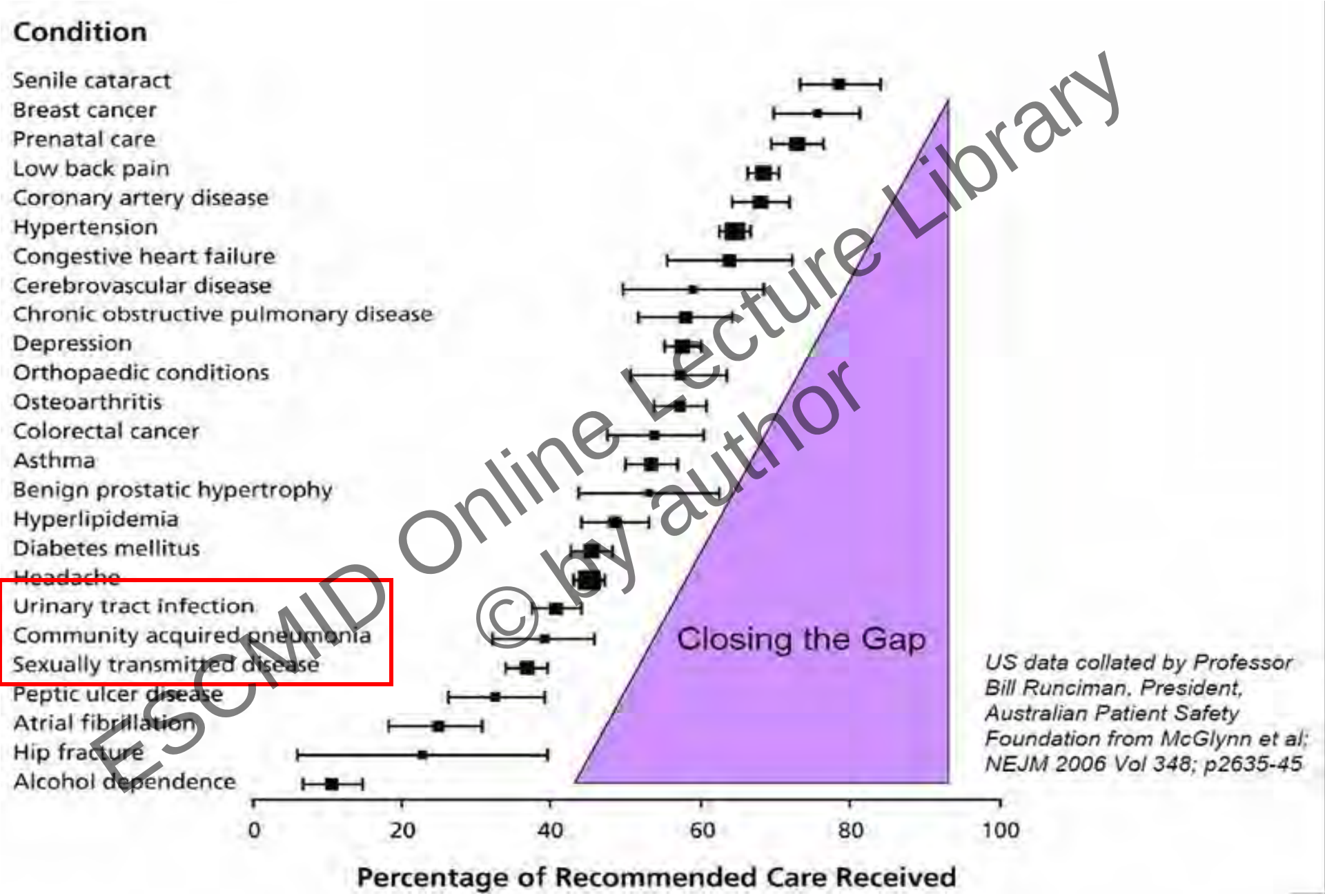
Translating Evidence into Practice: A Long and Tough Journey

Captain James Lancaster, 1601

The medical evidence was compelling, and the British Navy would put it to good use, making sure that all sailors on long voyages received sufficient vitamin C beginning in 1795

194 YEARS
AFTER LANCASTER'S VOYAGE





From: http://www.healthbeatblog.org/2008/04/the-difficulty.html

"You can't fix by analysis what you bungled by design"

Light, Singer and Willett