

# Designing before-after studies to build evidence

Mical Paul

Rambam Health Care Campus, Haifa, Israel  
Associate Professor, Technion - Israel Institute of  
Technology

# Disclosures

- No conflicts of interests

ESCMIID eLibrary  
© by author

# Background

- Our hospital is endemic for carbapenem-resistant enterobacteriaceae (CRE)
- The infection control unit issues a daily report on the prevalence and incidence of patients with CRE in the hospital. Among the 850 adult beds in our hospital the daily prevalence typically ranged between 20-30 patients with CRE
- Around 2016 we observed that the numbers finally went down and celebrated the day with five carriers in the hospital. The number of patients with CRE bacteremia dropped from 2-3 per month to 0-1 per month

# Objective

- We wanted to prove that patient cohorting was responsible for the control of CRE in our hospital
- We designed a study based on the prospective surveillance of CRE at our hospital
- We compared the time-period before and after patient cohorting



# Methods

- Study design: prospective before-after study
- Intervention: patient cohorting. All patients in medical wards were cohorted in a rotating medical ward, cared for by dedicated nurses 24/7. Surgical and ICU patients were similarly cohorted in their department
- Time-periods: The year before full cohorting implementation (2015) and the year after (2016)

# Outcome

- Primary: CRE incidence defined as patients newly-acquiring CRE per 100,000 hospital days. Acquisition was detected through a hospital protocol for CRE surveillance (by rectal swabs) or clinical samples
- Secondary: CRE prevalence (carrier days in-hospital) and incidence of CRE bacteremia, all per 100,000 hospital days

# Analysis

- Risk factors and confounders: Age, Charlson score, admission from nursing home, duration of hospital stay, new decubitus ulcers
- Analysis: Before-after comparison unadjusted (chi-square) and adjusted through logistic regression using the outcome as the dependent variable, the exposure (intervention) and confounders as independent variables
- Ethical aspects: Study approved by our ethics committee, using anonymous data

# Results

		Before 2015 (272684 HD)	After 2016 (315940 HD)	P	Adjusted OR
CRE incidence	New acquisitions	142	76	<0.001	0.46 (95% CI 0.35-0.61)
CRE prevalence	Carrier days	6856	3736	<0.001	
CRE bacteremia	Patients	12	5	0.04	

Cohorting





## Confidence in the effect of cohorting on CRE incidence

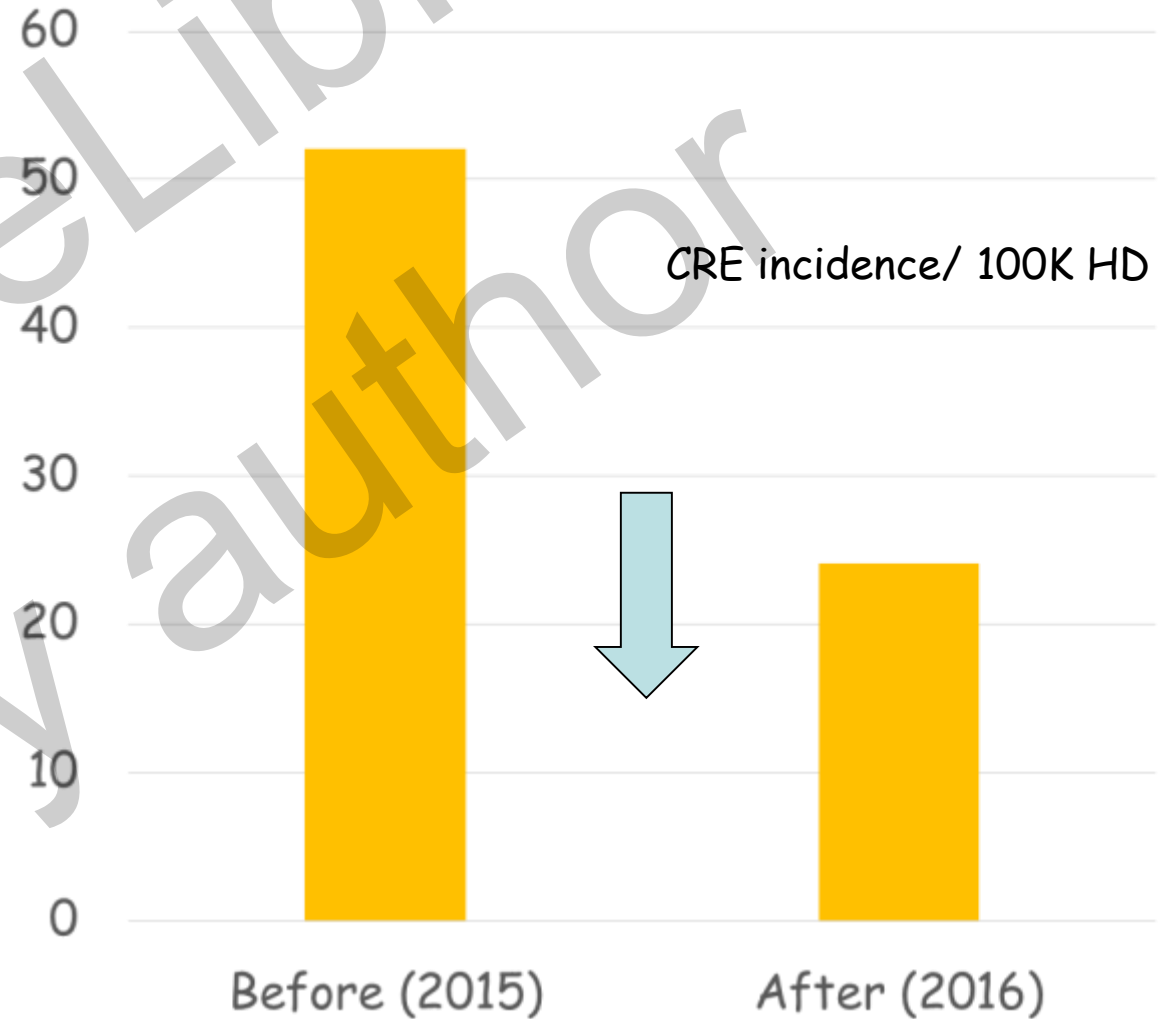
1. High
2. Moderate, effect exaggerated
3. Moderate, effect under-estimated
4. Low
5. Very low
6. No confidence what so ever, ignore

# Problems with the study



# Study started from the outcome

- Not prospective
- Result determined in advance of the study
- Any intervention could have been "retro-implemented"



# Co-interventions missing

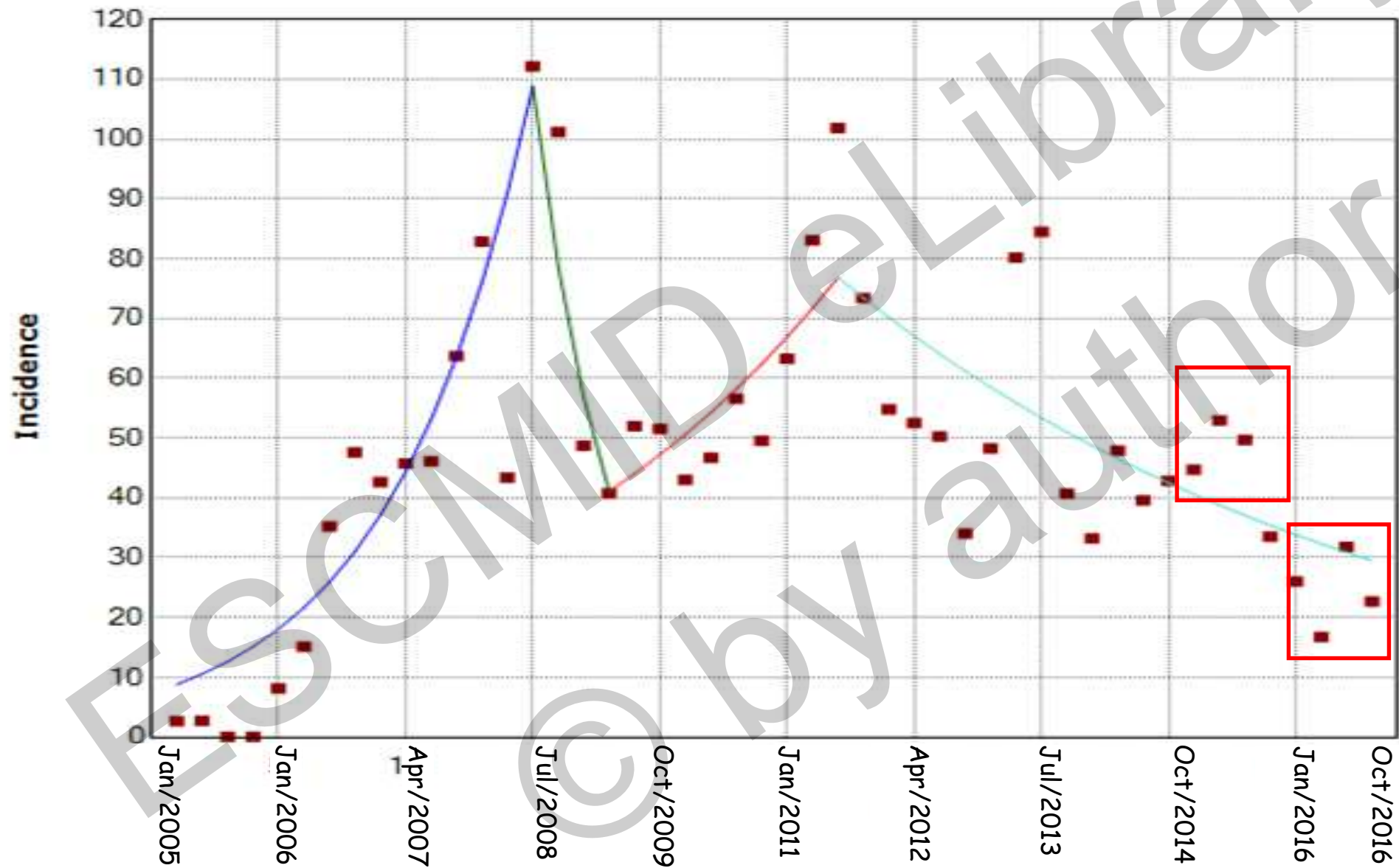
- Hand hygiene campaigns
- Hand hygiene compliance
- Contact isolation compliance
- Colonization surveillance methods
- Antibiotic stewardship campaign
- Administration involvement
- Infection control staffing
- Nurse/ patient ratio
- Laboratory hours
- Infection control trustees program

# Statistical concerns

- Aggregate data ignore fluctuations within the time periods analysed
- Statistical tests (chi-square) assume independence between patients, when by definition the risk to one patient depends on colonization status other patients



# Discrete time periods along a timeline



- Observed
- 1-15 APC = 19.65^
- 15-18 APC = -27.72
- 18-27 APC = 7.20
- 27-48 APC = -4.45^

Time periods reported, chance or selection?

# Could have helped our before-after study

1. An adequate control (all identical) without the intervention showing no CRE decline
2. Description of the epidemiology of other MDR bacteria showing no decline of non-targeted MDR



Requirements from a before-after study

ESCMID © by author



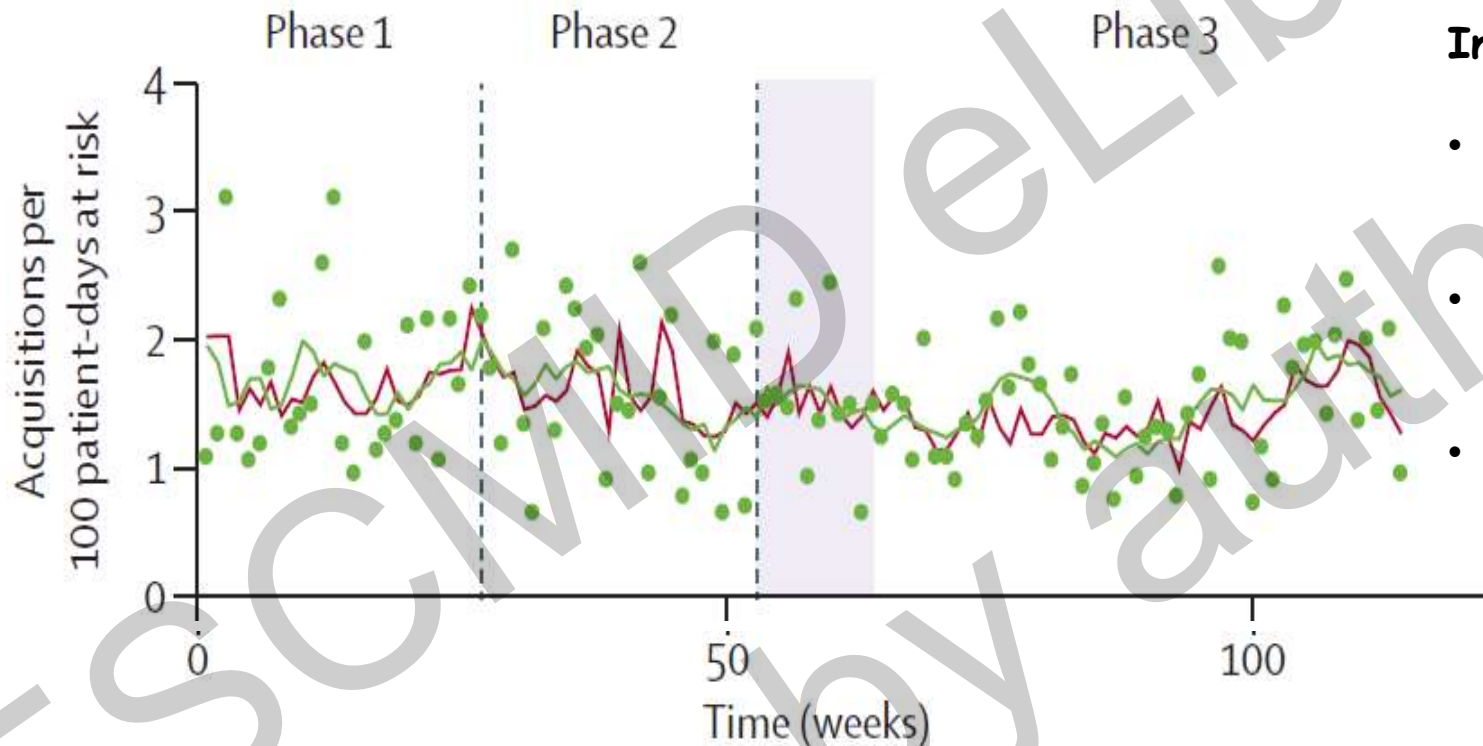
# Prospective planning defined by the intervention

- Study starts from planning an intervention, not from the outcome
- Differentiate an outbreak report from an intervention study
  - Interventions aimed at outbreak control are successful by definition of the term outbreak
- Control all other co-interventions while assessing the planned intervention
- Collect data on all co-interventions

# Time series rather than before-after analysis

- "The absolute minimum number of data points is three before and three after the intervention. Uncontrolled before and after studies with fewer data points than this are unacceptable. A general pragmatic recommendation is for at least 12 monthly data points before and 12 monthly points after the intervention, although more data points and longer study periods provide even stronger evidence because trends, seasonal effects and natural stochastic variability can be better identified" (A)
- "To enhance discrimination of intervention effects and other secular trends (including seasonality), at least 12 monthly data points before and after the intervention should be recorded. And, at each time point, at least 100 observations (prescriptions, patients, isolates) should be included to keep random variation at a minimum. In this way, the power to detect true intervention effects on the outcome of preference is optimized" (1)

# Interrupted time series statistical analysis



## Incidence rate ratios

- Phase 1 trend: 1.014  
(0.996-1.031;  $p=0.12$ )
- Phase 2 change in trend: 0.976  
(0.954-0.999;  $p=0.04$ )
- Phase 3 change in trend: 1.015  
(0.998-1.032;  $p=0.09$ )

Derde, LPG et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis.* 2014 Jan;14(1):31-39.

# Points increasing the quality of evidence

- Performing the time series analysis in a control without the intervention
- Reporting of other MDR epidemiology

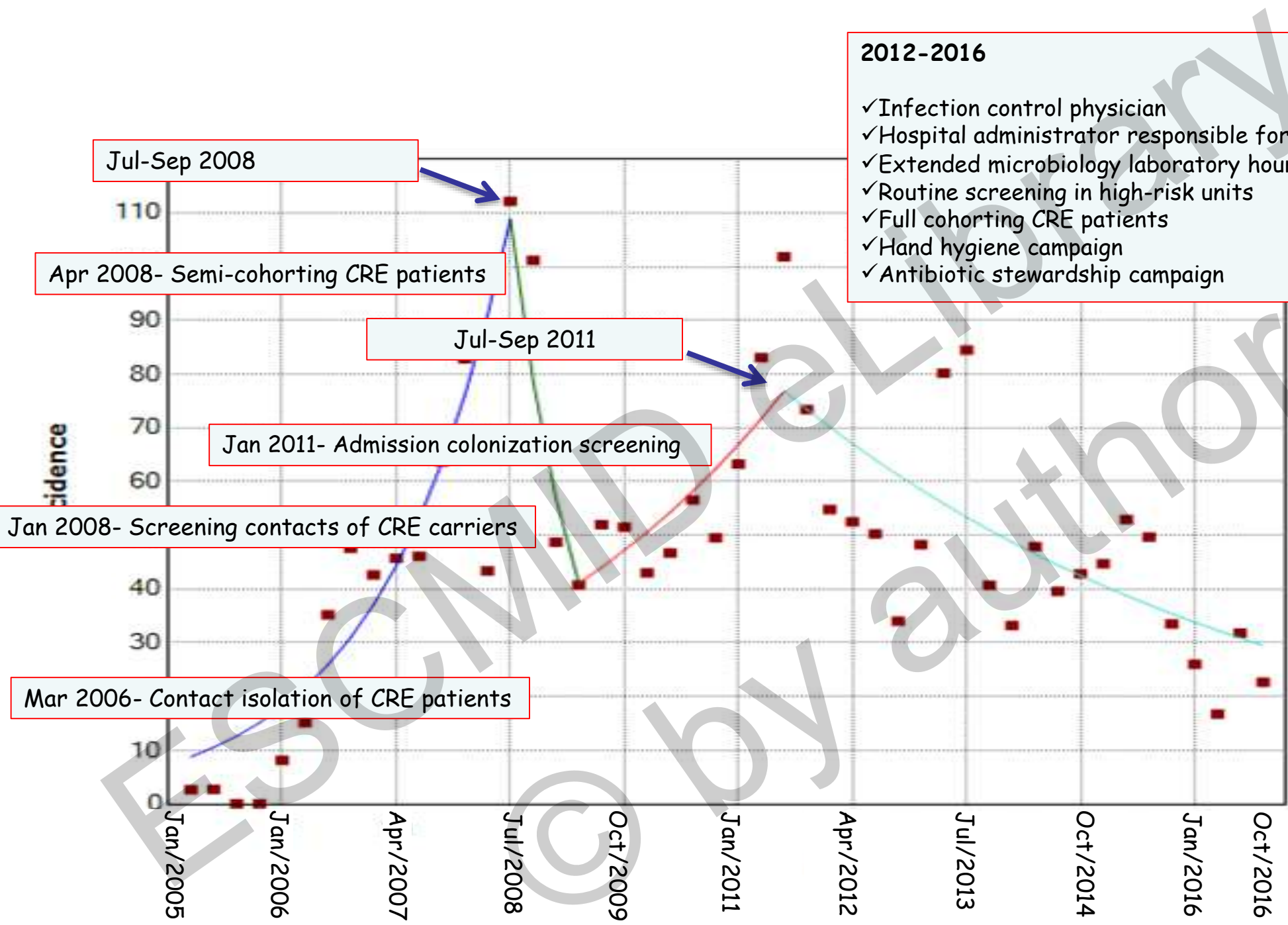
GRADEpro GDT						
Certainty assessment						
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
New outcome						

What is the most significant single factor lending credibility to a "before after" study?

1. Prospective planning of the intervention
2. Reporting all co-interventions
3. Appropriate statistical analysis
4. Showing the trend graph
5. Reporting of multiple MDR
6. Analyzing a concurrent control

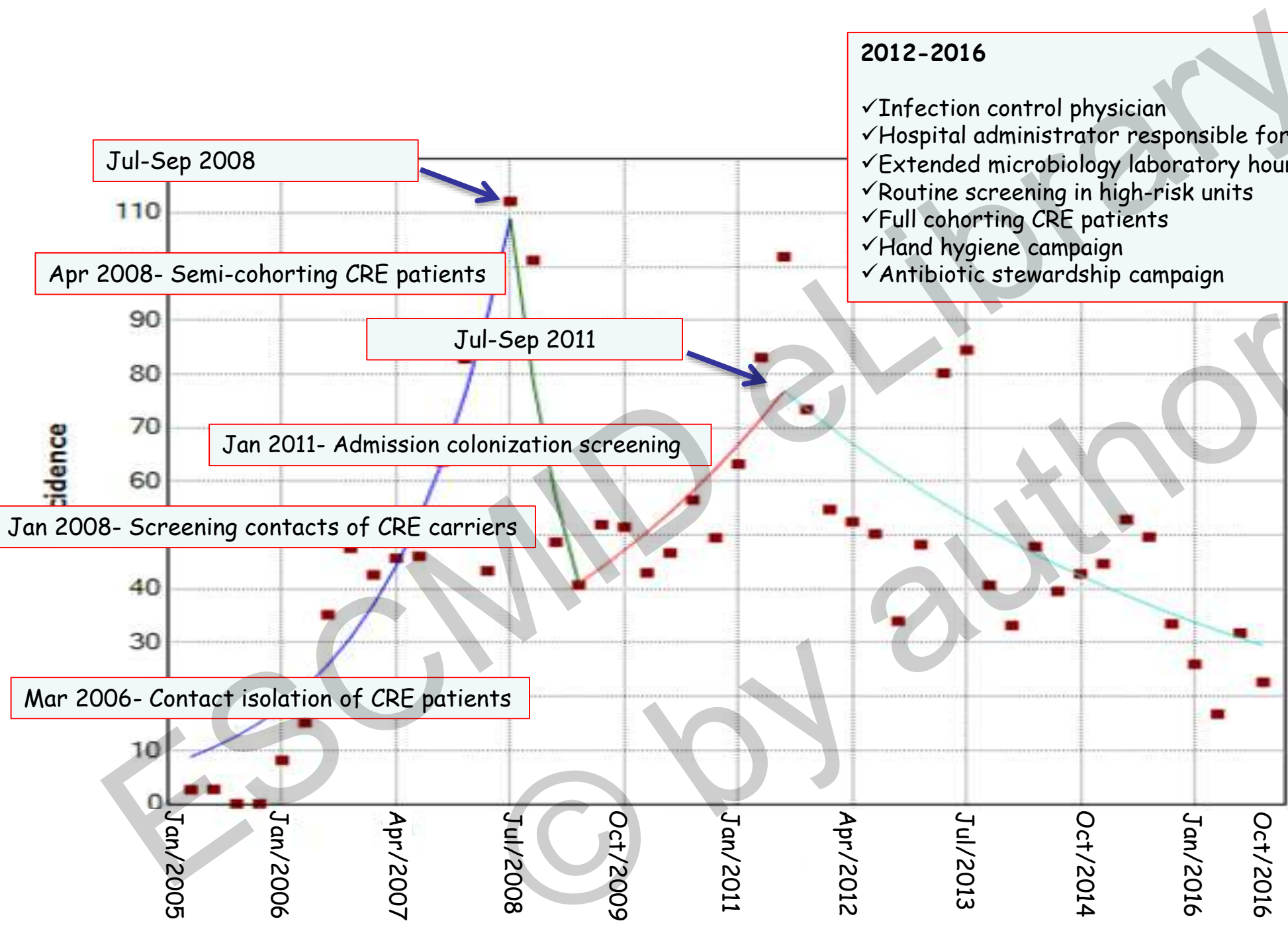
## Take home messages

- Do not waste time on retrospective before-after studies



**2012-2016**

- ✓ Infection control physician
- ✓ Hospital administrator responsible for infection control
- ✓ Extended microbiology laboratory hours
- ✓ Routine screening in high-risk units
- ✓ Full cohorting CRE patients
- ✓ Hand hygiene campaign
- ✓ Antibiotic stewardship campaign

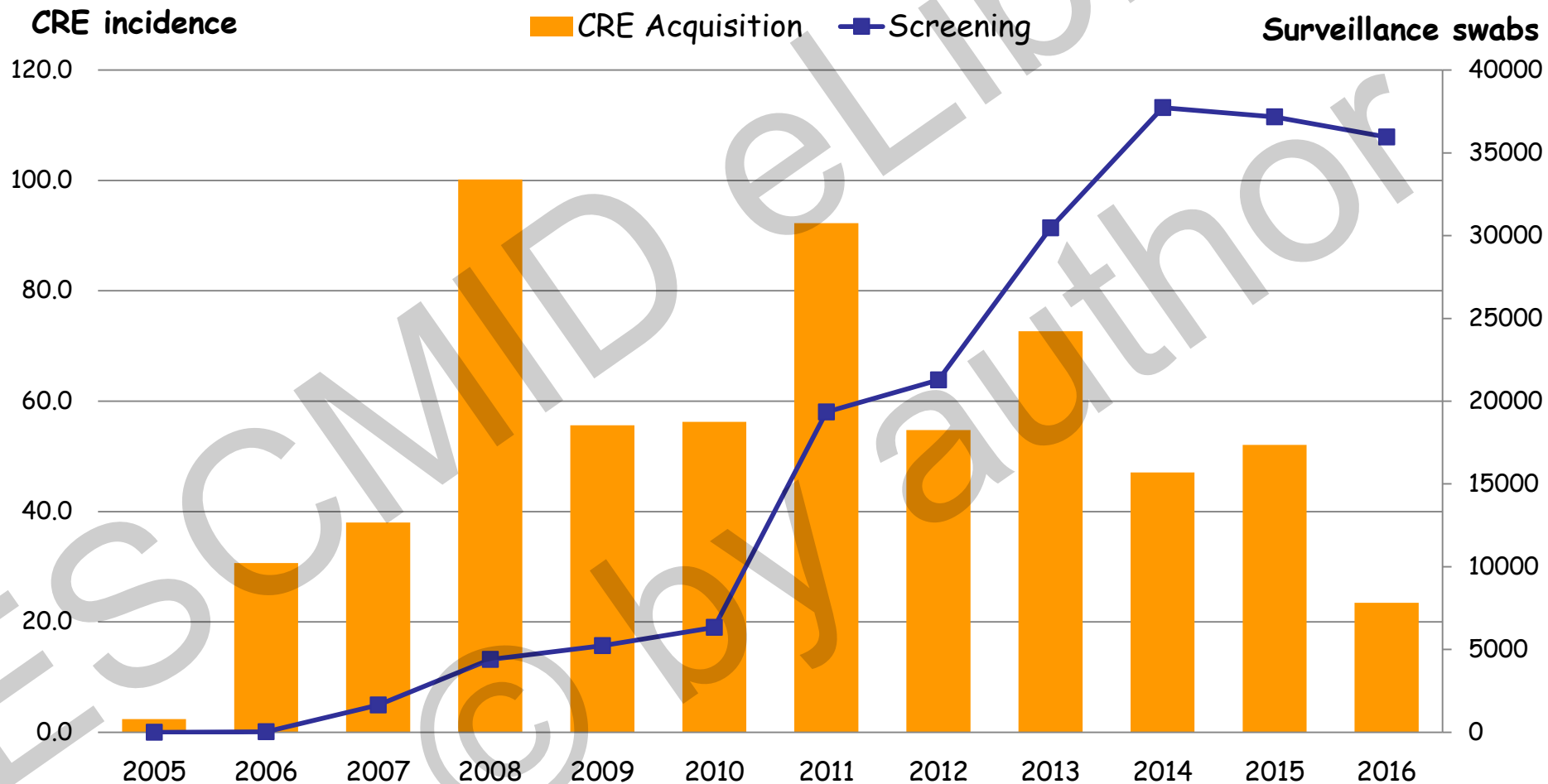


**2012-2016**

- ✓ Infection control physician
- ✓ Hospital administrator responsible for infection control
- ✓ Extended microbiology laboratory hours
- ✓ Routine screening in high-risk units
- ✓ Full cohorting CRE patients
- ✓ Hand hygiene campaign
- ✓ Antibiotic stewardship campaign



# CRE incidence and yearly number of rectal surveillance swabs



# Take home messages

- Do not waste time on retrospective before-after studies
- Do not believe in studies where the outcome was already known before designing the study
- Appropriately conducted interrupted time series analyses may be the optimal study design to assess infection control and antibiotic stewardship interventions

# Interrupted time series methods sources

1. de Kraker MEA, Abbas M, Huttner B, Harbarth S. Good epidemiological practice: a narrative review of appropriate scientific methods to evaluate the impact of antimicrobial stewardship interventions. Clin Microbiol Infect 2017
2. Cochrane Effective Practice and Organisation of Care (EPOC). Interrupted time series (ITS) analyses. EPOC Resources for review authors, 2017
3. <https://surveillance.cancer.gov/joinpoint/>

# Reporting recommendations

- A. The ORION statement: guidelines for transparent reporting of Outbreak Reports and Intervention studies Of Nosocomial infection
- B. SQUIRE 2.0: Standards for QUality Improvement Reporting Excellence
- C. All reporting recommendations to be found in <https://www.equator-network.org/>

# Better methods for clinical studies in infectious diseases and clinical microbiology: a hands-on workshop

## Faculty

- Marc Bonten
- Saskia le Cessie
- Belén Gutiérrez-Gutiérrez
- Benedikt Huttner
- Mariska Leeflang
- Leonard Leibovici
- Pontus Naucler
- Mette Nørgaard
- Mical Paul
- Zaira Palacios-Baena
- Celine Pulcini
- Jesús Rodríguez-Baño
- Evelina Tacconelli
- Martin Wolkewitz



MANAGING INFECTIONS  
PROMOTING SCIENCE

ESCMID Postgraduate  
Technical Workshop

**Better Methods for  
Clinical Studies in  
Infectious Diseases and  
Clinical Microbiology:  
a Hands-on Workshop**

Seville, Spain  
7 – 9 November 2018



Thank you

ESCMID © by author Library