Mercoledì 30 novembre 2022

Ore 10:00 - 14:00

CORSI PRE-CONGRESSUALI

Corso: LA TERAPIA ANTIBIOTICA NELL'ANZIANO

Fattori di rischio di multi-antibiotico resistenza nell'anziano

Nicola Petrosillo

Infettivologo, Fondazione Policlinico Universitario Campus Bio-Medico, Roma

DISCLOSURE

In qualità di RELATORE, ai sensi dell'art.76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Pfizer, MSD, Roche, ImmuneMed, Tillots, Ferring, Becton & Dickinson

Dichiaro, inoltre, che i contenuti formativi esposti sono indipendenti da interessi commerciali.

Carbapenem Resistance and Mortality in Institutionalized Elderly With Urinary Infection

- ✓ This cohort study of 196 patients with UTI confirmed by a positive urine culture was conducted in a nursing home in Italy. Data on 6-month mortality was obtained by nursing home records and confirmed by death certificates

- ✓ Carbapenem resistance was found in 39/196 (20%) patients. After adjusting for potential confounders, carbapenem resistance was associated in Cox regression modeling with 6-month mortality (relative risk = 2.79; 95% confidence interval = 1.17-6.70; P = .021).

Marinosci F et al. J Am Med Dir Assoc 2013;14(7):513-7.

Risk factors for resistance to ciprofloxacin in community-acquired urinary tract infections due to *Escherichia coli* in an elderly population

Urinary cultures of UTIs caused by E. coli were collected from participants in the Rotterdam Study, a prospective cohort study in an elderly population, and analysed for susceptibility to ciprofloxacin.

- ✓ **Ciprofloxacin resistance in 1080 E. coli isolates was 10.2%.**
- ✓ **Multivariate analysis showed that higher age (OR 1.03; 95% CI 1.00–1.05) and use of two (OR 5.89; 95% CI 3.45–10.03) and three or more (OR 3.38; 95% CI 1.92–5.97) prescriptions of fluoroquinolones were associated with ciprofloxacin resistance, while no association between fluoroquinolone use more than 1 year before culture and ciprofloxacin resistance could be demonstrated.**
- ✓ **Furthermore, a high intake of pork (OR 3.68; 95% CI 1.36–9.99) and chicken (OR 2.72; 95% CI 1.08–6.85) and concomitant prescription of calcium supplements (OR 2.51; 95% CI 1.20–5.22) and proton pump inhibitors (OR 2.04; 95% CI 1.18–3.51) were associated with ciprofloxacin resistance**

Mulder M et al. J Antimicrob Chemother 2017; 72: 281–289

Antibiotic Exposure during the Preceding Six Months Is Related to Intestinal ESBL-Producing Enterobacteriaceae Carriage in the Elderly

- ✓ **An observational study of a 921-elderly cohort was examined at health checkup for intestinal ESBL-PE carriage at a tertiary medical center.**

- ✓ **The prevalence and risk factors of intestinal ESBL-PE carriage, especially antimicrobial use in the preceding 9 months, were studied.**

- ✓ **The prevalence of intestinal ESBL-PE carriage was 53.3% (491/921) in community-dwelling elderly people. A total of 542 ESBL-producing isolates, including E. coli (n = 484) and K. pneumoniae (n = 58), were obtained**

Zhang M et al. Antibiotics (Basel) 2022;11(7):953.

Antibiotic Exposure during the Preceding Six Months Is Related to Intestinal ESBL-Producing Enterobacteriaceae Carriage in the Elderly

Zhang M et al. Antibiotics (Basel) 2022;11(7):953.

Table 2. Univariate and multivariate analyses of the risk factors for intestinal carriage of ESBL-producing *Enterobacteriaceae* in the elderly.

Risk Factor	Carriers (n = 491) no. (%)	Noncarriers (n = 430) no. (%)	Univariate Analysis		Multivariate Analysis	
			p Value	OR (95% CI)	p Value	OR (95% CI)
Age, years						
61–70	100 (20.4)	41 (9.5)		1		
71–80	190 (38.7)	158 (36.7)	0.001	0.493 (0.324, 0.751)	0.001	0.419 (0.249, 0.706)
≥81	201 (40.9)	231 (53.7)	<0.001	0.357 (0.237, 0.537)	<0.001	0.312 (0.186, 0.522)
Sex (male/female)	431/60	387/43	0.001	0.427 (0.259, 0.704)	0.533	0.847 (0.503, 1.427)
Hypertension	308 (62.7)	275 (64.0)	0.701	0.949 (0.725, 1.241)		
Coronary artery disease	101 (20.6)	98 (22.8)	0.414	0.877 (0.640, 1.201)		
Respiratory tract diseases [a]	90 (18.3)	85 (19.8)	0.579	0.911 (0.655, 1.267)		
Diabetes mellitus	136 (27.7)	95 (22.1)	0.050	1.351 (0.999, 1.827)	0.116	1.348 (0.929, 1.956)
Benign prostatic hyperplasia	55 (11.2)	48 (11.2)	0.985	1.004 (0.666, 1.514)		
Constipation	27 (5.5)	19 (4.4)	0.453	1.259 (0.690, 2.298)		
Prior surgery	95 (19.4)	81 (18.8)	0.844	1.034 (0.743, 1.437)		
Tumor	31 (6.3)	22 (5.1)	0.436	1.250 (0.712, 2.193)		
Thyroid disease	7 (1.4)	16 (3.7)	0.026	0.374 (0.152, 0.918)	0.28	0.604 (0.242, 1.506)
Prostate disease	80 (16.3)	80 (18.6)	0.356	0.852 (0.605, 1.198)		
Peptic ulcer	29 (5.9)	35 (8.1)	0.184	0.708 (0.425, 1.180)		
Liver disease	29 (5.9)	26 (6.1)	0.929	0.975 (0.565, 1.684)		
Use of gastric mucosal protective agent	104 (21.2)	85 (19.8)	0.596	1.091 (0.791, 1.504)		
Oral probiotics	62 (12.6)	60 (14.0)	0.554	0.891 (0.609, 1.305)		
Laxatives	85 (17.3)	83 (19.3)	0.435	0.875 (0.626, 1.223)		
Oral digestive enzymes	48 (9.8)	59 (13.7)	0.062	0.681 (0.454, 1.022)		
Long-term steroid use	7 (1.4)	9 (2.1)	0.439	0.677 (0.250, 1.832)		
Self-care deficit	13 (2.7)	10 (2.3)	0.755	1.142 (0.496, 2.632)		
Nursing home residence	166 (33.8)	32 (7.4)	<0.001	6.353 (4.234, 9.532)	<0.001	9.13 (5.526, 15.085)
International travel	67 (13.7)	8 (1.9)	<0.001	8.335 (3.955, 17.566)	0.088	2.112 (0.896, 4.982)
Antibiotic exposure	415 (84.5)	157 (36.5)	<0.001	9.495 (6.939, 12.992)	<0.001	11.12 (7.734, 15.989)
Hospital admission	40 (8.2)	29 (6.7)	0.420	1.226 (0.746, 2.015)		

Antibiotic Exposure during the Preceding Six Months Is Related to Intestinal ESBL-Producing Enterobacteriaceae Carriage in the Elderly

Zhang M et al. Antibiotics (Basel) 2022;11(7):953.

- ✓ **Prior use of second generation cephalosporins (p = 0.001), third generation cephalosporins (p < 0.001), fluoroquinolones (p < 0.001), and macrolides (p = 0.013) increased the risk of intestinal ESBL-PE carriage.**

- ✓ **Treatment with third generation cephalosporins had the most prominent effect (RR = 2.557).**

Table 5. Correlation between intestinal ESBL-PE carriage and antimicrobial exposure during the 9 months prior to sample collection.

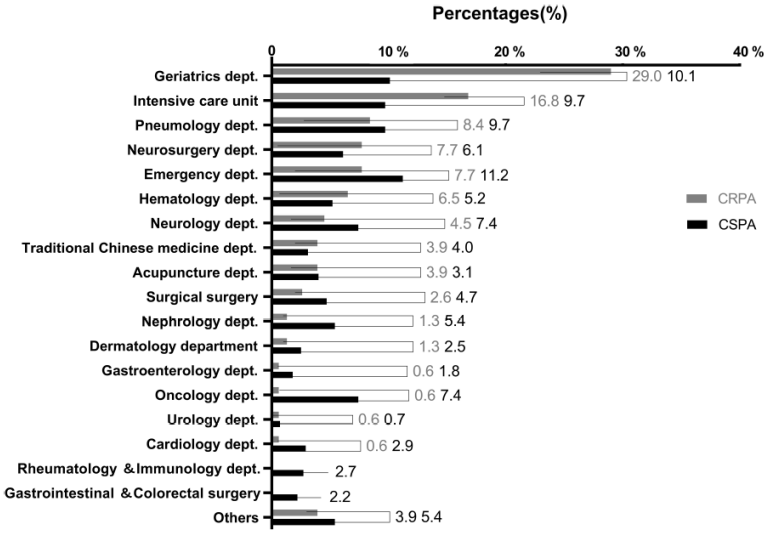
Antimicrobials	Antimicrobials Exposure			
	ESBL-PE Carriers (n = 780) n (%)	ESBL-PE Noncarriers (n = 492) n (%)	p Value	RR (95%CI)
No exposure	76 (9.7)	273 (55.5)	<0.001	0.176 (0.140, 0.221)
1st generation cephalosporins	37 (4.7)	24 (4.9)	0.913	1.822 (1.269, 2.617)
2nd generation cephalosporins	104 (13.3)	36 (7.3)	0.001	2.048 (1.662, 2.525)
3rd generation cephalosporins	289 (37.1)	89 (18.1)	<0.001	2.557 (1.947, 3.359)
Fluoroquinolones	223 (28.6)	55 (11.2)	<0.001	2.334 (1.171, 4.650)
Macrolides	37 (4.7)	10 (2.0)	0.013	1.766 (0.640, 4.873)
Others	14 (1.8)	5 (1.0)	0.265	1.822 (1.269, 2.617)

ESBL-PE = ESBL-producing *Enterobacteriaceae*; n = sum of antimicrobial exposures during the 9 months prior to sampling; RR = relative risk.

Carbapenem Resistant *Pseudomonas aeruginosa* Infections in Elderly Patients: Antimicrobial Resistance Profiles, Risk Factors and Impact on Clinical Outcomes

- ✓ **A retrospective study of 600 elderly inpatients infected with *P. aeruginosa* was conducted at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine from January 1st 2018 to December 31st 2020.**

- ✓ **All 155 patients with CRPA infection were designated as a case group. Patients with carbapenem-susceptible *Pseudomonas aeruginosa* (CSPA) were randomly selected from remaining 445 cases in a 1:1 ratio to case group as a control group.**



e 1 Department distribution of *P. aeruginosa* isolates.

Table 1 Susceptibility of *P. aeruginosa* to Antimicrobial Agents During the Period from 2018 Through 2020

Antimicrobial Agents	CRPA (N= 155)			CSPA (N= 445)			Overall (N= 600)		
	Resistance n (%)	Intermediate n (%)	Susceptibility n (%)	Resistance n (%)	Intermediate n (%)	Susceptibility n (%)	Resistance n (%)	Intermediate n (%)	Susceptibility n (%)
Ciprofloxacin	79 (51.0)	15 (9.7)	61 (39.4)	87 (19.6)	23 (5.2)	335 (75.3)	166 (27.7)	38 (6.3)	396 (66.0)
Levofloxacin	75 (48.4)	10 (6.5)	70 (45.2)	74 (16.6)	27 (6.1)	344 (77.3)	149 (24.8)	37 (6.2)	414 (69.0)
Aztreonam	56 (36.1)	58 (37.4)	41 (26.5)	56 (12.6)	177 (39.8)	212 (47.6)	112 (18.7)	235 (39.2)	253 (42.2)
Cefoperazone	67 (43.2)	43 (27.7)	45 (29.0)	50 (11.2)	99 (22.3)	296 (66.5)	117 (19.5)	142 (23.7)	341 (56.8)
Gentamicin	44 (28.4)	8 (5.2)	103 (66.5)	43 (9.7)	21 (4.7)	381 (85.6)	87 (14.5)	29 (4.8)	484 (80.7)
Piperacillin	45 (29.0)	53 (34.2)	57 (36.8)	41 (6.8)	82 (18.4)	322 (72.4)	86 (14.3)	135 (22.5)	379 (63.2)
Ceftazidime	43 (27.7)	25 (16.1)	87 (56.1)	37 (8.3)	19 (4.3)	389 (87.4)	80 (13.3)	44 (7.3)	476 (79.3)
Tobramycin	42 (27.1)	12 (7.7)	101 (65.2)	31 (7.0)	7 (1.6)	407 (91.5)	73 (12.2)	19 (3.2)	508 (84.7)
Cefepime	36 (23.2)	15 (9.7)	104 (67.1)	21 (4.7)	34 (7.6)	390 (87.6)	57 (9.5)	49 (8.2)	494 (82.3)
Cefoperazone-sulbactam	34 (21.9)	40 (25.8)	81 (52.3)	15 (3.4)	45 (10.1)	385 (86.5)	49 (8.2)	85 (14.2)	466 (77.7)
Piperacillin-tazobactam	31 (20.0)	40 (25.8)	84 (54.2)	13 (2.9)	37 (8.3)	395 (88.8)	44 (7.3)	77 (12.8)	479 (79.8)
Amikacin	27 (17.4)	4 (2.6)	124 (80.0)	10 (2.3)	5 (1.1)	430 (96.6)	37 (6.2)	9 (1.5)	554 (92.3)
Meropenem	109 (70.3)	19 (12.3)	27 (17.4)	0 (0.0)	0 (0.0)	445 (100.0)	109 (18.2)	19 (3.2)	472 (78.7)
Imipenem	136 (87.7)	19 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	455 (100.0)	136 (22.7)	19 (3.2)	445 (74.2)

Abbreviations: CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-susceptible *Pseudomonas aeruginosa*.

Qin J et al. Infect Drug Resist 2022;15:2301-2314.

Carbapenem Resistant *Pseudomonas aeruginosa* Infections in Elderly Patients: Antimicrobial Resistance Profiles, Risk Factors and Impact on Clinical Outcomes

In a multivariate conditional logistic regression analysis, significant risk factors related to CRPA infection included:

- ✓ **age 75–84 years (odds ratio [OR]=0.458, 95% CI: 0.263–0.800, *P*=0.006),**
- ✓ **cerebrovascular disease (OR=3.517, 95% CI: 2.054–6.021, *P*<0.001),**
- ✓ **foley catheter (OR=2.073, 95% CI: 1.135–3.784, *P*=0.018),**
- ✓ **length of hospital stay ≥ 14 days (OR=1.980, 95% CI: 1.154–3.399, *P*=0.013),**
- ✓ **Albumin < 35 g/L (OR=2.049, 95% CI: 1.121–3.746, *P*=0.020),**
- ✓ **previous antibiotic exposure to carbapenems (OR=7.022, 95% CI:1.861–26.493, *P*=0.004),**
- ✓ **previous antibiotic exposure to third- or fourth-generation cephalosporins (OR=12.649; 95% CI: 2.473–64.690, *P*=0.002)**

Qin J et al. Infect Drug Resist 2022;15:2301-2314.

Carbapenem Resistant *Pseudomonas aeruginosa* Infections in Elderly Patients: Antimicrobial Resistance Profiles, Risk Factors and Impact on Clinical Outcomes

Clinical Outcomes and Risk Factors for Mortality Among Patients with CRPA Infection

Of the 155 patients with CRPA infections, 26 (16.8%) patients were no-survived.

Multivariate logistic regression analysis showed that patients

- ✓ **with receiving mechanical ventilation (OR=3.671, 95% CI: 1.424–9.467, *P*=0.007) and**
- ✓ **neutrophil percentage > 80% (OR=2.908, 95% CI: 1.151–7.343, *P*=0.024)**

remained independent risk factors which associated with worse clinical outcomes

Qin J et al. Infect Drug Resist 2022;15:2301-2314.

Risk factors and mortality for elderly patients with bloodstream infection of carbapenem resistance *Klebsiella pneumoniae*: a 10-year longitudinal study

Retrospective cohort study, enrolling 252 inpatients aged ≥ 65 years with BSI caused by KP from January 2011 to December 2020 in China

- ✓ **Among the 252 BSI patients, there were 29 patients (11.5%) caused by CRKP and 223 patients (88.5%) by carbapenem-susceptible KP (CSKP).**

- ✓ **The overall 28-day mortality rate of elderly patients with a KP BSI episode was 10.7% (27/252), of which CRKP BSI patients (14 / 29, 48.3%) were significantly higher than CSKP patients (13 / 223, 5.83%) ($P < 0.001$).**

Chen Y et al. BMC Geriatr 2022;22(1):573.

Risk factors and mortality for elderly patients with bloodstream infection of carbapenem resistance *Klebsiella pneumoniae*: a 10-year longitudinal study

- ✓ **Hypertension (OR: 13.789, [95% CI: 3.883–48.969], *P* < 0.001), exposure to carbapenems (OR: 8.073, [95% CI:2.066–31.537], *P* = 0.003), and ICU stay (OR: 11.180, [95% CI: 2.663–46.933], *P* = 0.001) were found to be associated with the development of CRKP BSI in elderly patients.**

- ✓ **A multivariate analysis showed that isolation of CRKP (OR 2.881, 95% CI 1.228–6.756, *P* = 0.015) and KP isolated in ICU (OR 11.731, 95% CI 4.226–32.563, *P* < 0.001) were independent risk factors for 28-day mortality of KP BSI.**

Chen Y et al. BMC Geriatr 2022;22(1):573.

An International Prospective Cohort Study To Validate 2 Prediction Rules for Infections Caused by Third-generation Cephalosporin-resistant Enterobacterales

In 33 hospitals in 13 countries we prospectively enrolled 200 patients per hospital in whom blood cultures were obtained and intravenous antibiotics with coverage for Enterobacterales were empirically started.

Deelen JWT et al. Clin Infect Dis 2021;73(11):e4475-e4483.

Community onset rule	Hospital onset rule
Age (number of years)	Prior identification of 3GC-R EB in the last year (Y/N)
Prior identification of 3GC-R EB in the last year (Y/N)	Prior cephalosporin use in the last two months (Y/N)
Prior antibiotic use in the last two months (Y/N)	Surgery in the last 30 days (Y/N)
Immunocompromised patient (Y/N)	Suspected respiratory tract infection (Y/N)
Suspected infection source: urinary tract (Y/N)	Solid malignancy (Y/N)
Suspected infection source: respiratory tract (Y/N)	Renal disease (Y/N)
	Signs of hypoperfusion (Y/N)
	Length of stay prior to infection onset (number of days)

Prediction Rules

An International Prospective Cohort Study To Validate 2 Prediction Rules for Infections Caused by Third-generation Cephalosporin-resistant Enterobacterales

- ✓ **4650 CO infection episodes were included and the prevalence of 3GC-R-BSI was 2.1% (n = 97).**
- ✓ **IAT occurred in 69 of 97 (71.1%) 3GC-R-BSI and UCU in 398 of 4553 non–3GC-R-BSI patients (8.7%).**
- ✓ **The prediction rule potentially reduced IAT to 62% (60/97) while keeping UCU comparable at 8.4% or could reduce UCU to 6.3% (287/4553) while keeping IAT equal.**

Deelen JWT et al. Clin Infect Dis 2021;73(11):e4475-e4483.

Impact of a Mortality Prediction Rule for Organizing and Guiding Antimicrobial Stewardship Program Activities

- ✓ **Antimicrobial stewardship program surveillance at their hospital is supplemented by an internally developed surveillance database.**
- ✓ **In 2013, the database incorporated a validated, internally developed, prediction rule for patient mortality within 30 days of hospital admission.**
- ✓ **This study describes the impact of an expanded ASP review in patients at the highest risk for mortality.**

Collins CD et al. Open Forum Infect Dis 2021;8(3):ofab056.

Impact of a Mortality Prediction Rule for Organizing and Guiding Antimicrobial Stewardship Program Activities

Appendix Table 2. Mortality Prediction Rule Risk Variables [7]

Demographics and diagnoses
Age
Female sex
Previous hospitalization within the past 365 days
Emergent admission
Admitted to a medicine service
Current or past atrial fibrillation
Current or past cancer without metastases, excluding leukemia or lymphoma
Current or past history of leukemia or lymphoma
Current or past metastatic cancer
Current or past cognitive deficiency
Current or past history of other neurological conditions (eg, Parkinson's disease, multiple sclerosis, epilepsy, coma, stupor, brain damage)
Injury such as fractures or trauma at the time of admission
Sepsis at the time of admission
Heart failure at the time of admission
Respiratory failure on admission

Clinical laboratory values within preceding 30 days
Maximum serum blood urea nitrogen (mg/dL)
Minimum hemoglobin, g/dL
Minimum platelet count, 1,000/UL
Maximum white blood count, 1,000/UL
Maximum serum lactate, mEq/L)
Minimum serum albumin
Minimum arterial pH
Minimum arterial pO2
Maximum serum troponin

Collins CD et al. Open Forum Infect Dis 2021;8(3):ofab056.

Impact of a Mortality Prediction Rule for Organizing and Guiding Antimicrobial Stewardship Program Activities

A total of 3282 and 5456 patients were included in the historical and intervention groups, respectively.

There were significant reductions in

- **median antimicrobial duration (5 vs 4 days; *P* < .001),**
- **antimicrobial days of therapy (8 vs 7; *P* < .001),**
- **antimicrobial cost ($96 vs $85; *P* = .003),**
- **length of stay (LOS) (6 vs 5 days; *P* < .001),**
- **intensive care unit (ICU) LOS (3 vs 2 days; *P* < .001),**
- **total hospital cost ($10 946 vs $9119; *P* < .001),**
- **healthcare facility-onset vancomycin-resistant *Enterococcus* (HO-VRE) incidence (1.3% vs 0.3%; *P* ≤ .001), and**
- **HO-VRE infections (0.6% vs 0.2%; *P* = .018)**

in the intervention cohort.

Collins CD et al. Open Forum Infect Dis 2021;8(3):ofab056.

Impact of a Mortality Prediction Rule for Organizing and Guiding Antimicrobial Stewardship Program Activities

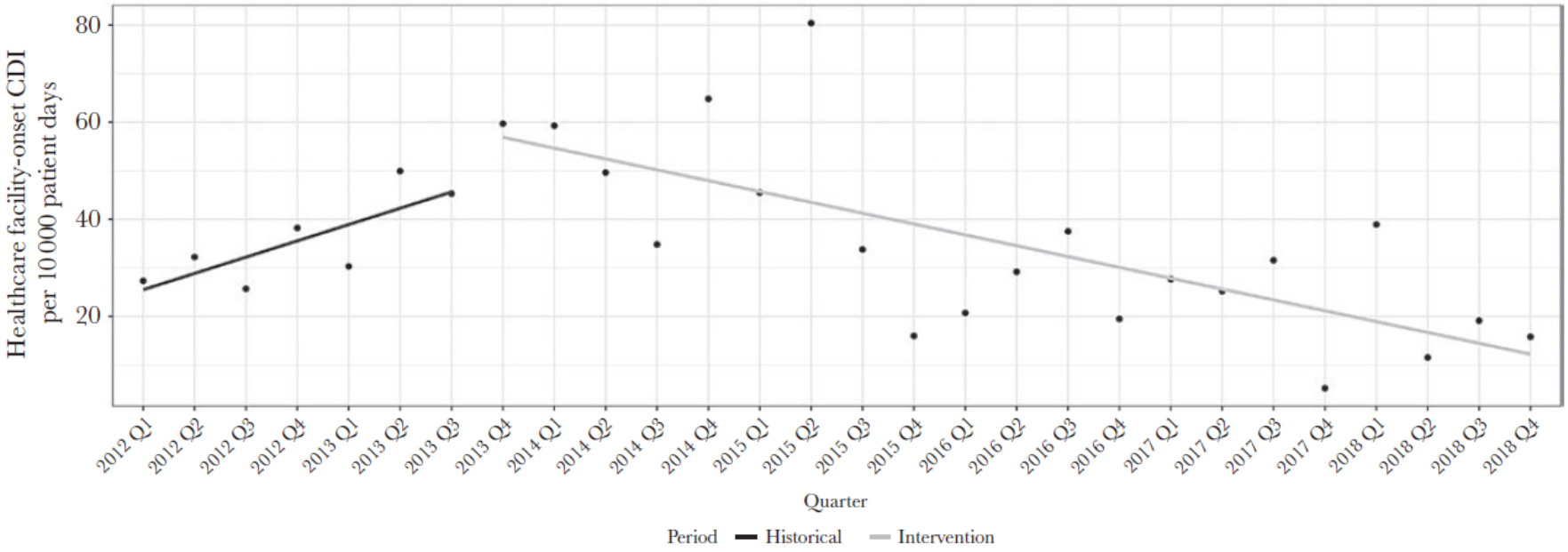


Figure 1. Interrupted time-series analysis on healthcare facility-onset *Clostridioides difficile* infection per 10 000 patient days by calendar year quarter.

Collins CD et al. Open Forum Infect Dis 2021;8(3):ofab056.

Impact of a Mortality Prediction Rule for Organizing and Guiding Antimicrobial Stewardship Program Activities

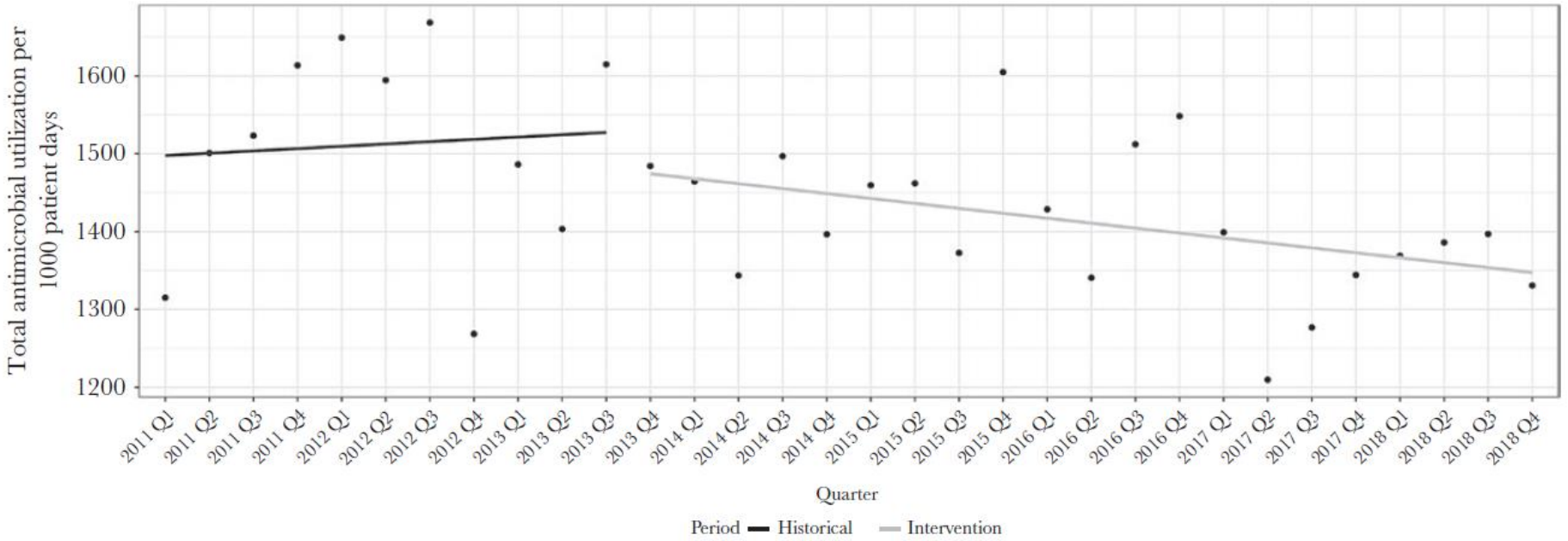


Figure 2. Interrupted time-series analysis on total antimicrobial utilization defined as days of therapy per 1000 patient days by calendar year quarter.

Collins CD et al. Open Forum Infect Dis 2021;8(3):ofab056.

Quality indicators (QIs) for evaluation of appropriate antibiotic treatment in hospitalized patients, adapted from van den Bosch *et al.* [7]

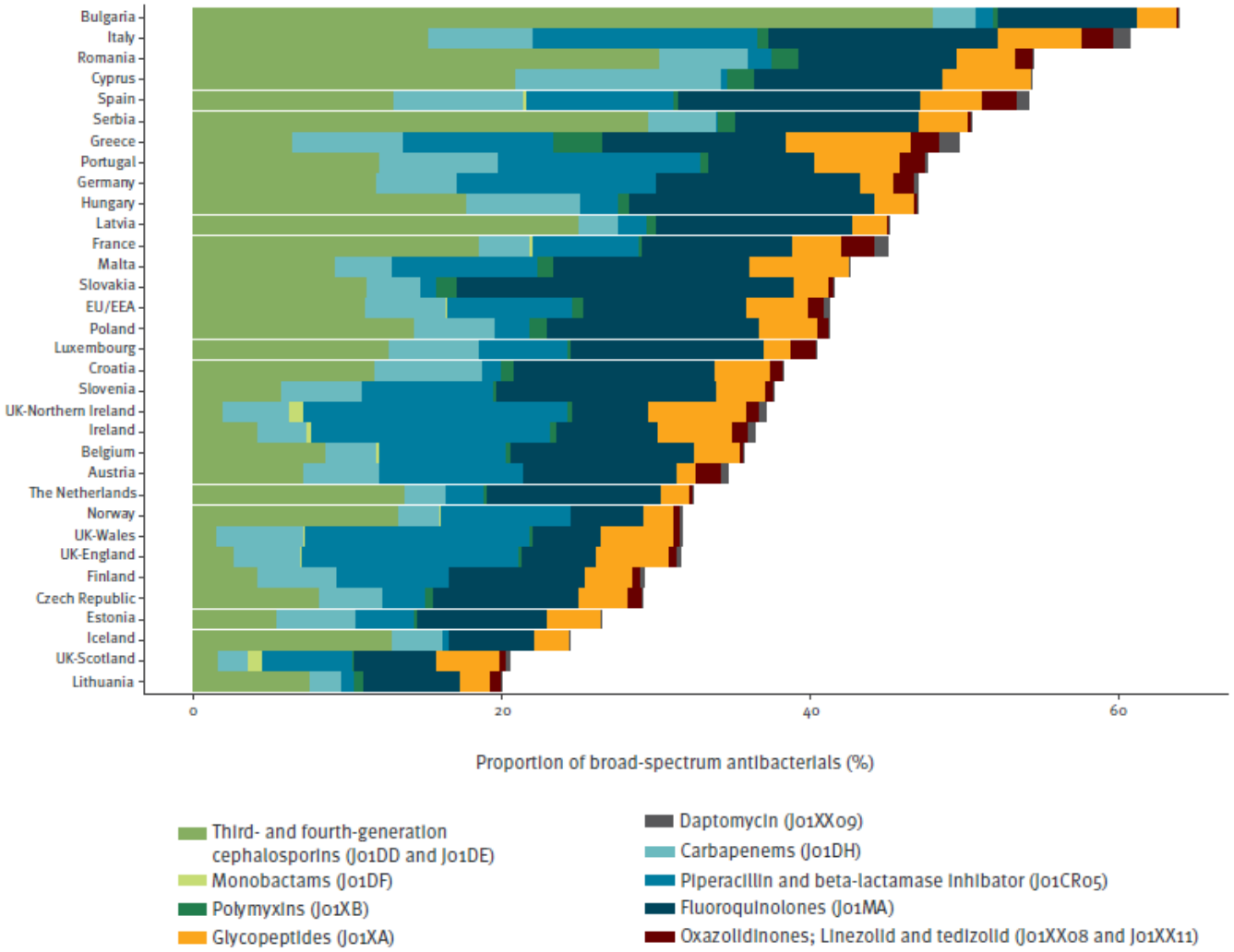
1. Before starting systemic antibiotic therapy, at least two sets of blood cultures should be taken.
2. When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started (cultures should be taken until a maximum of 24 h after antibiotics are started).
3. Empirical systemic antibiotic therapy should be prescribed according to the local guidelines.
4. A current local antibiotic guideline should be present in the hospital and an evaluation whether an update should be considered should be done every three years.
5. Local antibiotic guidelines should correspond to the national antibiotic guidelines, but should deviate based on local resistance patterns.
6. Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available.
7. Dose and dosing intervals of systemic antibiotics should be adapted to renal function.
8. Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate.
9. An antibiotic plan should be documented on the case notes at the start of systemic antibiotic treatment.
10. Therapeutic drug monitoring should be performed when the treatment duration is more than three days for aminoglycosides and more than five days for vancomycin.
11. Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be seven days.

Van de Bosch CM et al. Clin Microbiol Infect 2016; 22:888.e1– 888.e9

Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017

Plachouras D et al. Euro Surveill. 2018 Nov;23(46)

Proportion of broad-spectrum antibacterials[a] among all antibacterials for systemic use (J01), 28 European Union/European Economic Area countries[b] and Serbia, 2016–2017



What is antimicrobial stewardship?

- **A strategy, a coherent set of actions designed to use antimicrobial responsibly.**

- **Responsible use: it should be defined and translated into context- and time-specific actions**

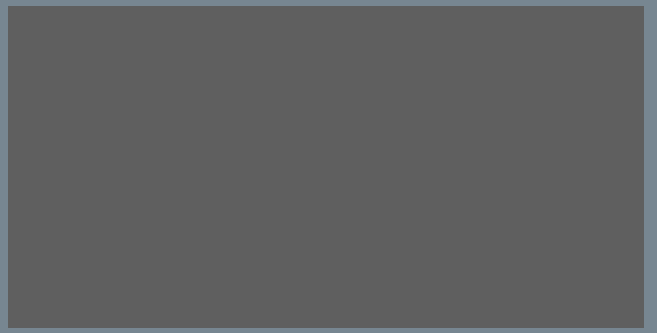
Dyar OJ et al. *Clin Microb Infection 2017*

ANTIBIOTIC STEWARDSHIP

IN YOUR FACILITY WILL

DECREASE

- ☐ ANTIBIOTIC RESISTANCE
- ☐ C. DIFFICILE INFECTIONS
- ☐ COSTS



ANTIBIOTIC STEWARDSHIP

IN YOUR FACILITY WILL

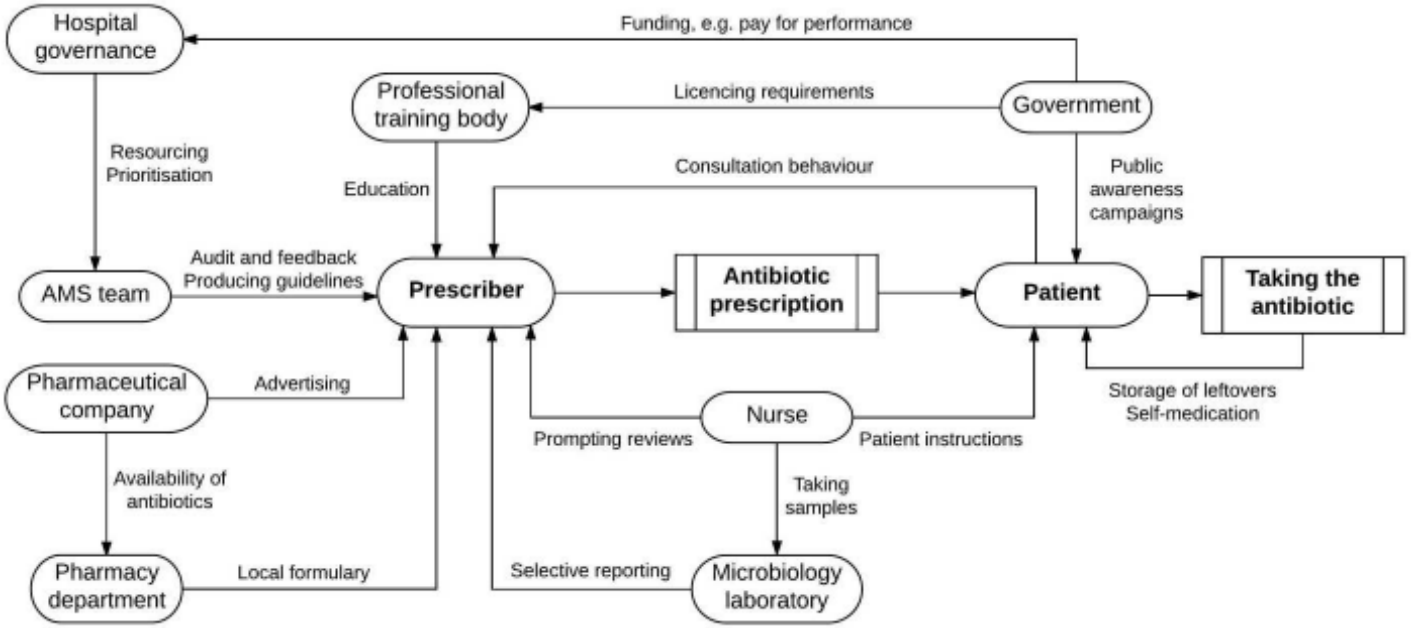
DECREASE

- ANTIBIOTIC RESISTANCE
- C. DIFFICILE INFECTIONS
- COSTS

INCREASE

- GOOD PATIENT OUTCOMES

Figure 2. Examples of actors and actions within antimicrobial stewardship



Dyar OJ et al. *Clin Microb Infection 2017*

Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

Lancet Infect Dis 2017;17(9):990-1001.

David Baur*, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli

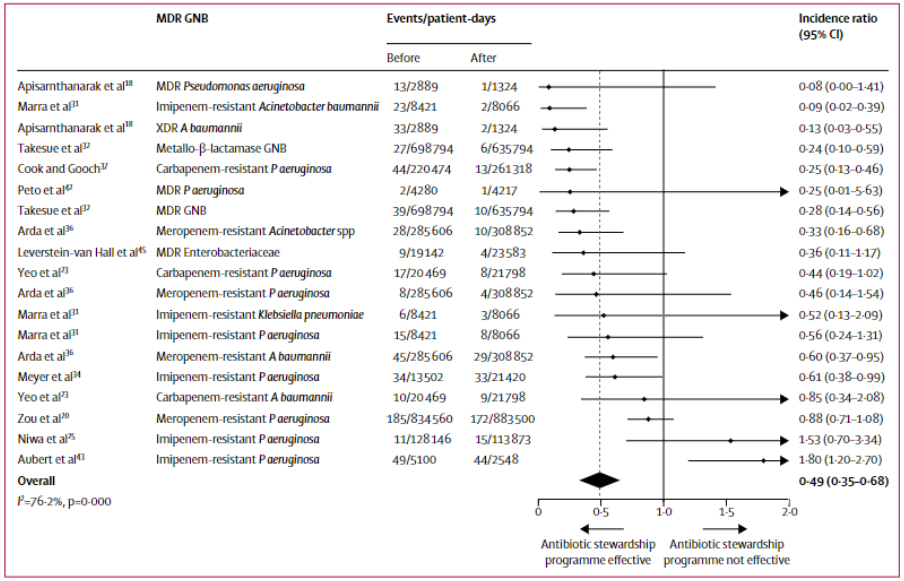


Figure 2: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB
GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

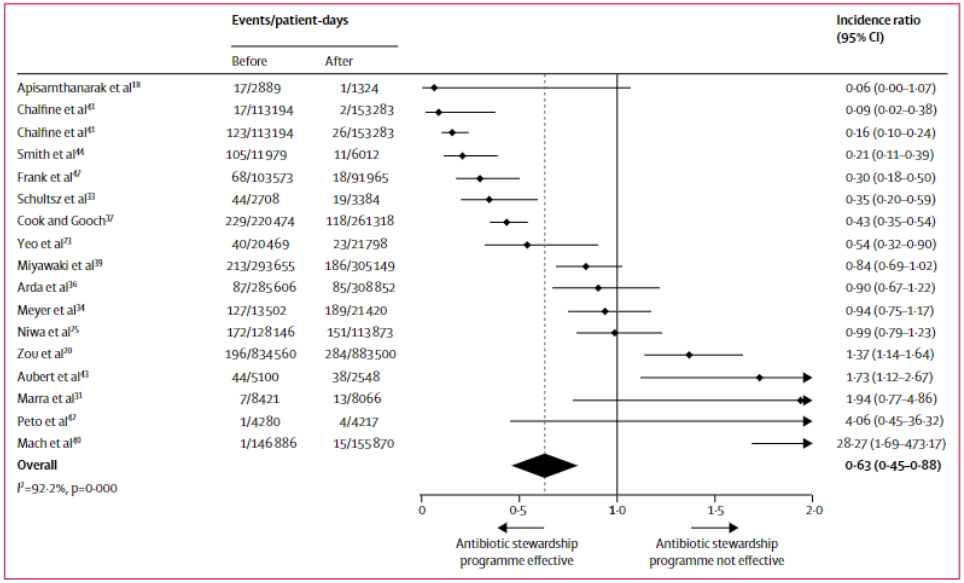


Figure 3: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of meticillin-resistant *Staphylococcus aureus*

Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

Lancet Infect Dis 2017;17(9):990-1001.

David Baur, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli*

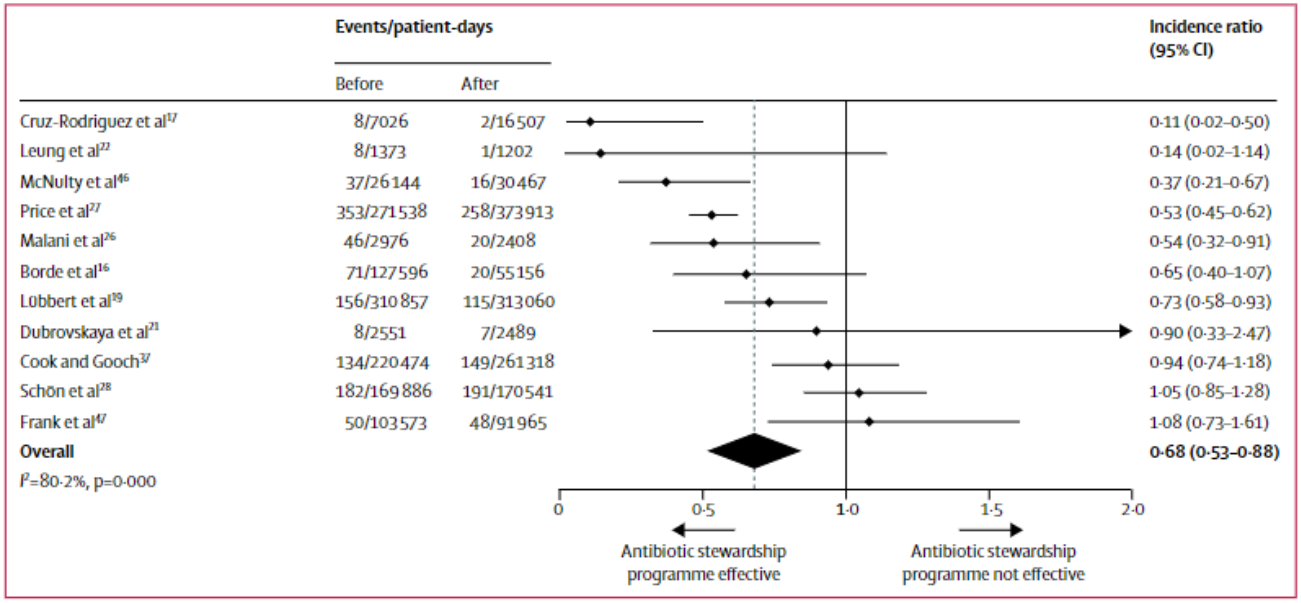


Figure 4: **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections**