SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

MEETING MULTIDISCIPLINARE
SUI MICRORGANISMI MULTIDRUG RESISTANT
E LE RELATIVE PROBLEMATICHE MICROBIOLOGICHE,
EPIDEMIOLOGICHE, DIAGNOSTICHE E CLINICHE

CEUB | BERTINORO- 27 NOVEMBRE 2019

Le infezioni da germi MDR in chirurgia

Giorgio Ercolani, PhD
Dir.: U.O. Chirurgia Generale e Oncologica
Presidio Ospedaliero di Forlì
Professore Associato – Università di Bologna

CIAO Study

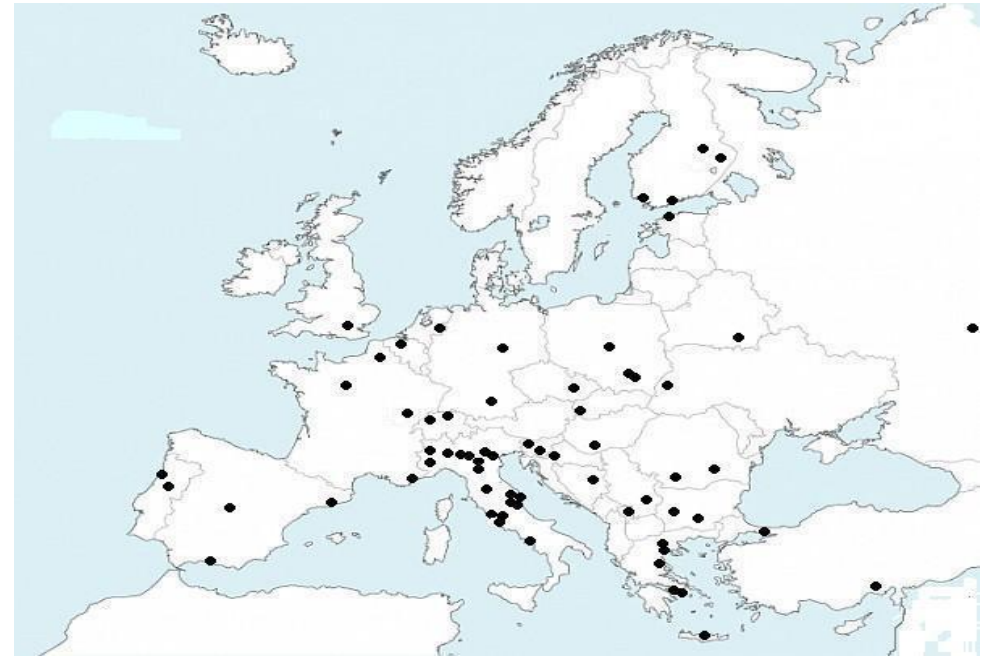
Sartelli *et al. World Journal of Emergency Surgery* 2012, 7:36
http://www.wjes.org/content/7/1/36

WORLD JOURNAL OF EMERGENCY SURGERY

RESEARCH ARTICLE Open Access

Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study

Massimo Sartelli[1*], Fausto Catena[2], Luca Ansaloni[3], Ari Leppaniemi[4], Korhan Taviloglu[5], Harry van Goor[6], Pierluigi Viale[7], Daniel Vasco Lazzareschi[1], Federico Coccolini[3], Davide Corbella[8], Carlo de Werra[9], Daniele Marrelli[10], Sergio Colizza[11], Rodolfo Scibè[1], Halil Alis[12], Nurkan Torer[13], Salvador Navarro[14], Boris Sakakushev[15], Damien Massalou[16], Goran Augustin[17], Marco Catani[18], Saila Kauhanen[19], Pieter Pletinckx[20], Jakub Kenig[21], Salomone Di Saverio[22], Elio Jovine[22], Gianluca Guercioni[23], Matej Skrovina[24], Rafael Diaz-Nieto[25], Alessandro Ferrero[26], Stefano Rausei[27], Samipetteri Laine[28], Piotr Major[29], Eliane Angst[30], Olivier Pittet[31], Ihor Herych[32], Ferdinando Agresta[33], Nereo Vettoretto[34], Elia Poiasina[3], Jaan Tepp[35], Gunter Weiss[36], Giorgio Vasquez[37], Nikola Vladov[38], Cristian Tranà[39], Samir Delibegovic[40], Adam Dziki[41], Giorgio Giraudo[42], Jorge Pereira[43], Helen Tzerbinis[44], David van Dellen[45], Martin Hutan[46], Andras Vereczkei[47], Avdyl Krasniqi[48], Charalampos Seretis[49], Cristian Mesina[50], Miran Rems[51], Fabio Cesare Campanile[52], Pietro Coletta[53], Mirjami Uotila-Nieminen[54], Mario Dente[55], Konstantinos Bouliaris[56], Konstantinos Lasithiotakis[57], Vladimir Khokha[58], Dragoljub Zivanovic[59], Dmitry Smirnov[60], Athanasios Marinis[61], Ionut Negoi[62], Ludwig Ney[63], Roberto Bini[64], Miguel Leon[65], Sergio Aloia[9], Cyrille Huchon[66], Radu Moldovanu[67], Renato Bessa de Melo[68], Dimitrios Giakoustidis[69], Orestis Ioannidis[70], Michele Cucchi[2], Tadeja Pintar[71], Zoran Krivokapic[72] and Jelena Petrovic[72]



The CIAO Study ("Complicated Intra-Abdominal infections Observational" Study) is a multicenter study performed throughout Europe over the course of a 6-month observational period (January - June 2012).

Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. ***Sartelli M et al, World J Emerg Surg 2012;7:36*.**

Source of infection in 4553 patients from 132 hospitals worldwide
(15 Oct 2014– 15 Feb 2015)

Source of infection	Number (%)
Appendicitis	1553 (34.2)
Cholecystitis	837 (18.5)
Post-operative	387 (8.5)
Colonic non-diverticular perforation	269 (5.9)
Gastro-duodenal perforations	498 (11)
Diverticulitis	234 (5.2)
Small bowel perforation	243 (5.4)
Others	348 (7.7)
PID	50 (1.1)
Post traumatic perforation	114 (2.5)
Total	4553 (100)

CIAO Study

Multivariate analysis: risk factors for occurrence of death during hospitalization

Risk factors	Odds Ratio	95%CI	p
Age	3.3	2.2-5	<0.0001
Severe sepsis in the immediate post-operative course	27.6	15.9-47.8	<0.0001
Septic shock in the immediate post-operative course	14.6	8.7-24.4	<0.0001
Colonic non diverticular perforation	4.7	2.5-8	<0.0001
Complicated diverticulitis	2.3	1.5-3.7	<0.0001
Small bowel perforation	21.4	8-57.4	<0.0001
Delayed initial intervention	2.4	1.5-3.7	0.0001

Stepwise multivariate analysis, PR=0.005 E PE=0.001 (Hosmer-Lemeshow chi 2(8)=1.68, area under ROC curve=0.9465)

CIAO Study

Aerobic bacteria from intra-operative peritoneal fluid

Total	**1,525 (100%)**
Aerobic Gram-negative bacteria	**1,041 (69.2%)**
Escherichia coli	632 (41.4%)
(Escherichia coli resistant to third generation cephalosporins)	64 (4.2%)
Klebsiella pneuumoniae	109 (7.1%)
(Klebsiella pneumoniae resistant to third generation cephalosporins)	37 (2.4%)
Enterobacter	63 (4.1%)
Proteus	33 (2.1 %)
Pseudomonas	80 (5.2%)
Others	124 (8.1%)
Aerobic Gram-positive bacteria	**484 (31.7%)**
Enterococcus faecalis	169 (11%)
Enterococcus faecium	72 (4.7%)
Staphylococcus Aureus	56 (3.7%)
Streptococcus spp.	100 (6,6%)
Others	87 (5.7%)

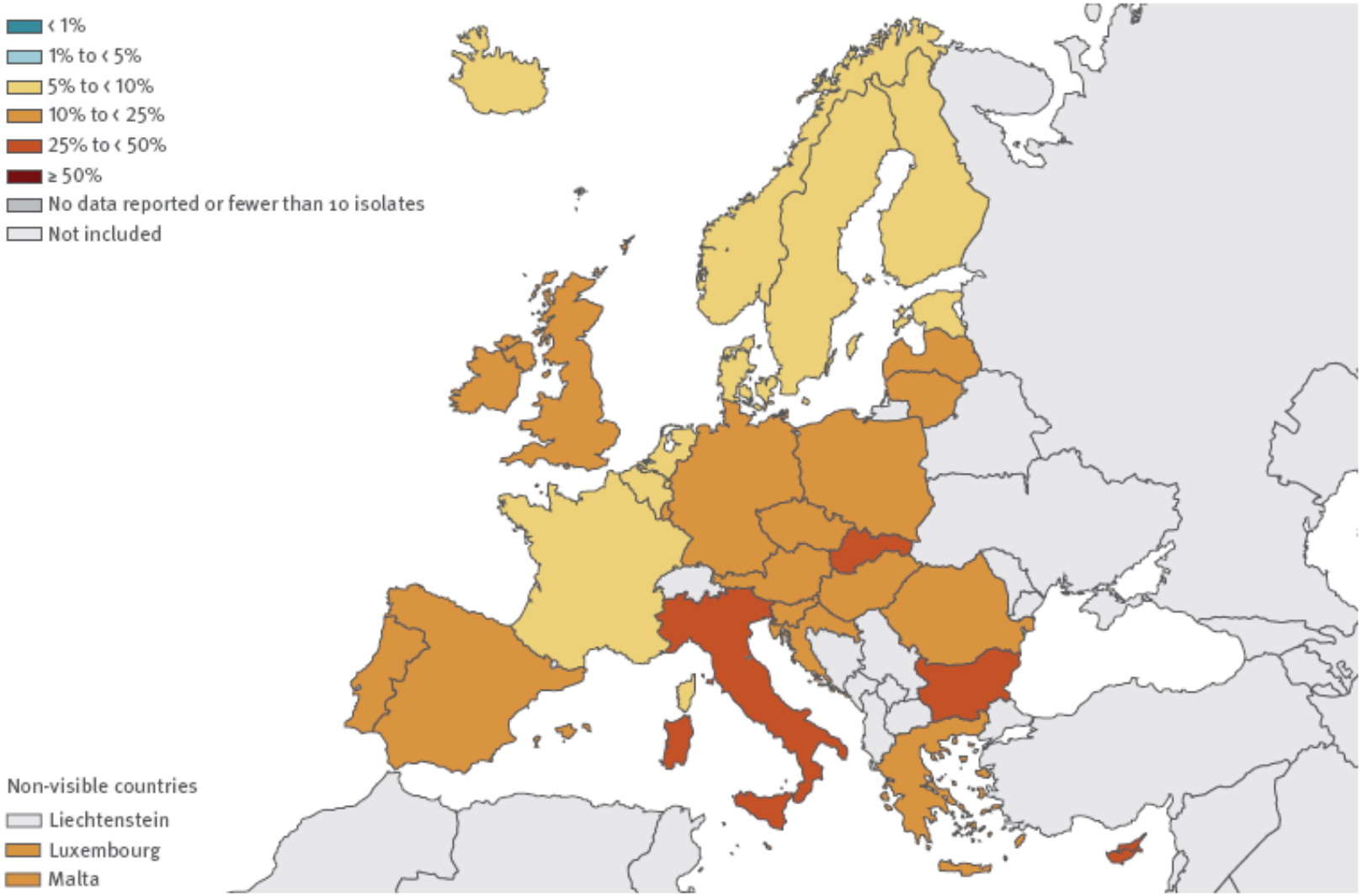
Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. ***Sartelli M et al, World J Emerg Surg 2012;7:36*.**

2,152 patients
1,701 (79%) affected by CA-IAIs
451 (21%) affected by HA-IAIs

	Community-acquired IAIs	Healthcare-associated (nosocomial) IAIs
	Isolates n°	Isolates n°
Aerobic bacteria	988 (100%)	567 (100%)
Escherichia coli	480 (48.6%)	152 (26.8%)
(Escherichia coli resistant to third generation cephalosporins)	30 (3%)	34 (6%)
Klebsiella pneumoniae	52 (5.2%)	57 (10%)
(Klebsiella pneumoniae resistant to third generation cephalosporins)	11 (1,7%)	22 (6.7%)
Pseudomonas	42 (4.2%)	38 (6.7%)
Enterococcus faecalis	78 (7.9%)	91 (16%)
Enterococcus faecium	39 (3.9%)	43 (7.6%)

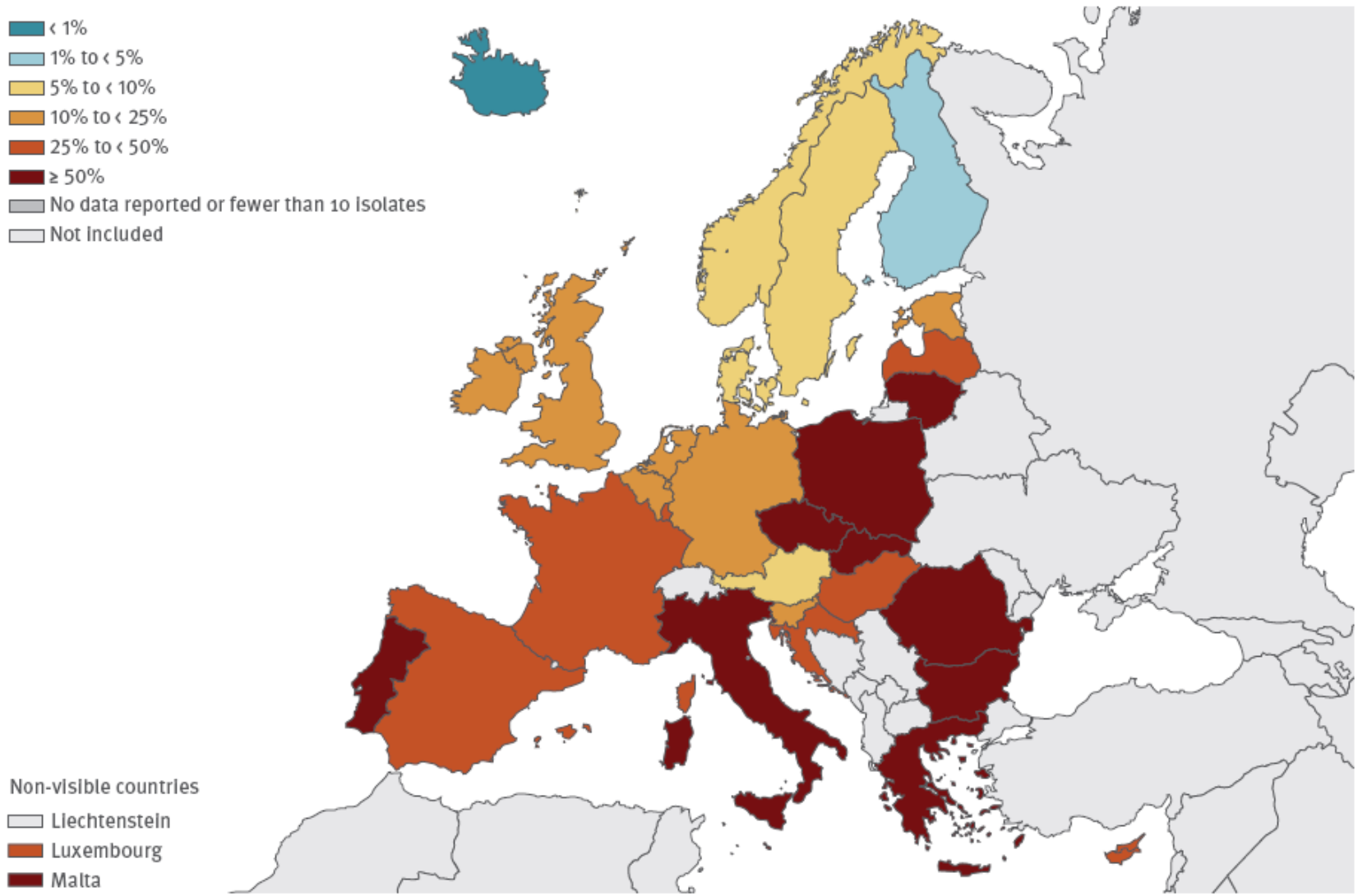
Surveillance of antimicrobial resistance in Europe
2018

Figure 3.3. ***Escherichia coli*****. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2018**



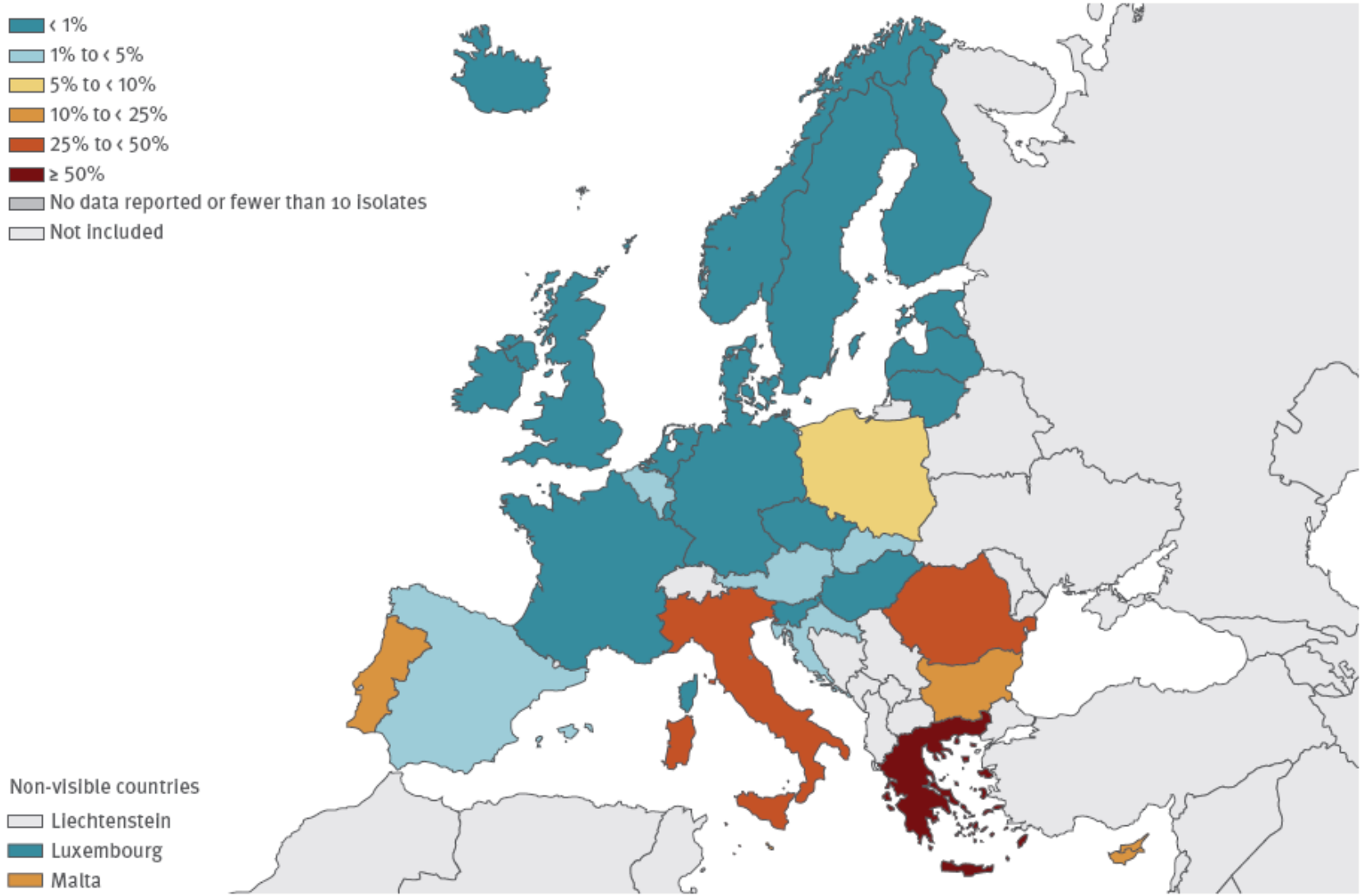
Surveillance of antimicrobial resistance in Europe
2018

Figure 3.9. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2018



Surveillance of antimicrobial resistance in Europe
2018

Figure 3.11. ***Klebsiella pneumoniae*****. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2018**



Current status of post-operative infections due to antimicrobial-resistant bacteria after digestive tract surgery in Japan: Japan Postoperative Infectious Complications Survey in 2015 (JPICS'15)

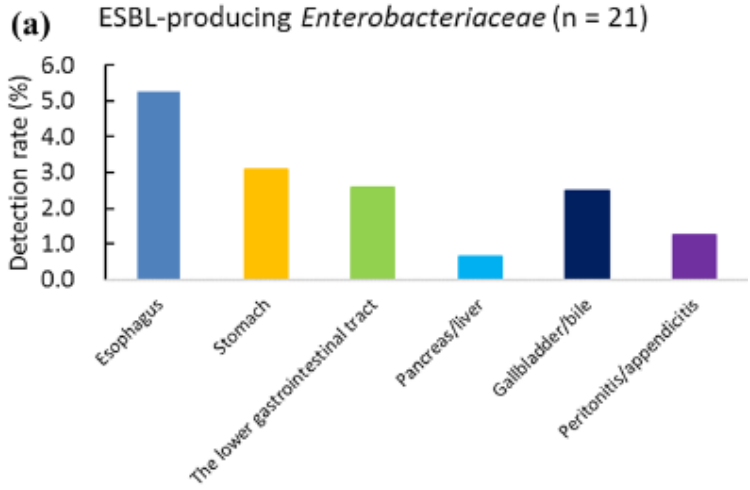
Surgery Today

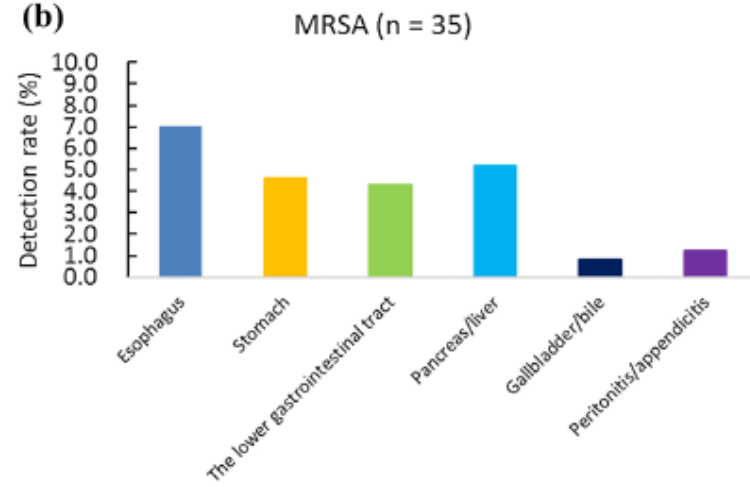
Mao Hagihara[1] · Shinya Kusachi[2] · Yukiko Kato[1] · Yuka Yamagishi[1] · Toru Niitsuma[2] · Hiroshige Mikamo[1] · Yoshio Takesue[3] · Yoshinobu Sumiyama[4]

7516 surgeries

7.5%

	Cases (*n*)						
	Total	ESBL	MRSA	VRE	MDRP	MDR-GN	IPM-RP
Cases (total)	905[a]	21	35	0	0	6	4
Number of centers	28	14	17	0	0	4	4





Mortality:6.7%

Current status of post-operative infections due to antimicrobial-resistant bacteria after digestive tract surgery in Japan: Japan Postoperative Infectious Complications Survey in 2015 (JPICS'15)

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Table 4 AMR bacteria detected after digestive surgeries for each open surgery type

Surgical procedure[a]	Cases (*n*)				
	Total[a]	ESBL	MRSA	MDR-GN	IPM-RP
Cases (total)	723[b]	16	31	4	3
Esophageal malignant tumor surgery (combined digestive tract reconstructive surgery)	47	2	2	0	0
Secondary reconstruction after esophagectomy	4	1	1	0	0
Reconstruction of the esophagus	2	0	1	0	0
Stomach incision	2	0	1	0	0
Stomach local excision	3	1	0	0	0
Gastrectomy	27	1	1	0	0
Cardia side gastrectomy	4	0	1	0	0
Gastrointestinal anastomosis (including Brown anastomosis)	9	0	1	0	0
Gastrostomy additional surgery (including percutaneous endoscopic gastrostomy)	3	0	1	0	0
Hepatectomy (expansion lobectomy)	14	0	1	0	0
Hepatectomy (Lobectomy)	7	0	1	0	0
Hepatectomy (expansion lobectomy with revascularization)	2	0	0	1	0
Acute disseminated peritonitis surgery	43	1	1	0	1
Colectomy (colon half-side resection)	19	2	0	0	1
Colectomy (small-range resection)	28	1	1	0	0
Colectomy (all resection, subtotal resection or malignant tumor surgery)	29	1	5	0	0
Small bowel resection	27	0	2	0	0
Colostomy closure (with intestinal resection)	19	1	0	1	0
Colostomy closure (without intestinal resection)	10	1	1	0	0
Colostomy additional surgery	25	0	2	1	0
Common bile duct stomach (intestine) anastomosis	9	1	0	0	1
Cholecystectomy	14	1	0	0	0
Bowel obstruction surgery	15	0	1	0	0
Rectal resection–amputation (amputation)	24	1	0	0	0
Rectal resection–amputation (low anterior resection surgery)	14	0	1	0	0
Pancreatic head tumor resection (lymph node dissection)	45	1	2	1	0
Pancreatic head tumor resection (combined resection of peripheral organs)	10	0	1	0	0
Pancreatic head tumor resection (amputation)	1	0	1	0	0
Head of the pancreas tail tumor resection (lymph node dissection)	13	0	1	0	0
Head of the pancreas tail tumor resection (combined resection of peripheral organs)	6	0	1	0	0

Surgical procedure [a]	Cases (*n*)				
	Total	ESBL	MRSA	MDR-GN	IPM-RP
Total	182[b]	5	4	2	1
Laparoscopic gastrectomy	29	1	1	0	0
Laparoscopic total gastrectomy	9	1	0	0	0
Laparoscopic small bowel resection	5	0	1	0	0
Laparoscopic colectomy (small-range resection,·colon half-side resection)	33	1	0	2	0
Laparoscopic colectomy (all resection,·subtotal resection)	3	1	0	0	0
Laparoscopic rectal resection–amputation (amputation)	15	0	1	0	0
Laparoscopic cholecystectomy	84	1	1	0	0
Laparoscopic biliary incision stones, hysterectomy	4	0	0	0	1

Sartelli et al. World Journal of Emergency Surgery (2017) 12:22
DOI 10.1186/s13017-017-0132-7

World Journal of Emergency Surgery

REVIEW Open Access

Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference

Massimo Sartelli[1*], Fausto Catena[2], Fikri M. Abu-Zidan[3], Luca Ansaloni[4], Walter L. Biffl[5], Marja A. Boermeester[6], Marco Ceresoli[3], Osvaldo Chiara[7], Federico Coccolini[3], Jan J. De Waele[8], Salomone Di Saverio[9], Christian Eckmann[10], Gustavo P. Fraga[11], Maddalena Giannella[12], Massimo Girardis[13], Ewen A. Griffiths[14], Jeffry Kashuk[15], Andrew W. Kirkpatrick[16], Vladimir Khokha[17], Yoram Kluger[18], Francesco M. Labricciosa[19], Ari Leppaniemi[20], Ronald V. Maier[21], Addison K. May[22], Mark Malangoni[23], Ignacio Martin-Loeches[24], John Mazuski[25], Philippe Montravers[26], Andrew Peitzman[27], Bruno M. Pereira[11], Tarcisio Reis[28], Boris Sakakushev[29], Gabriele Sganga[30], Kjetil Soreide[31], Michael Sugrue[32], Jan Ulrych[33], Jean-Louis Vincent[34], Pierluigi Viale[12] and Ernest E. Moore[35]

Classification

Diagnosis

Source control

Antimicrobial therapy

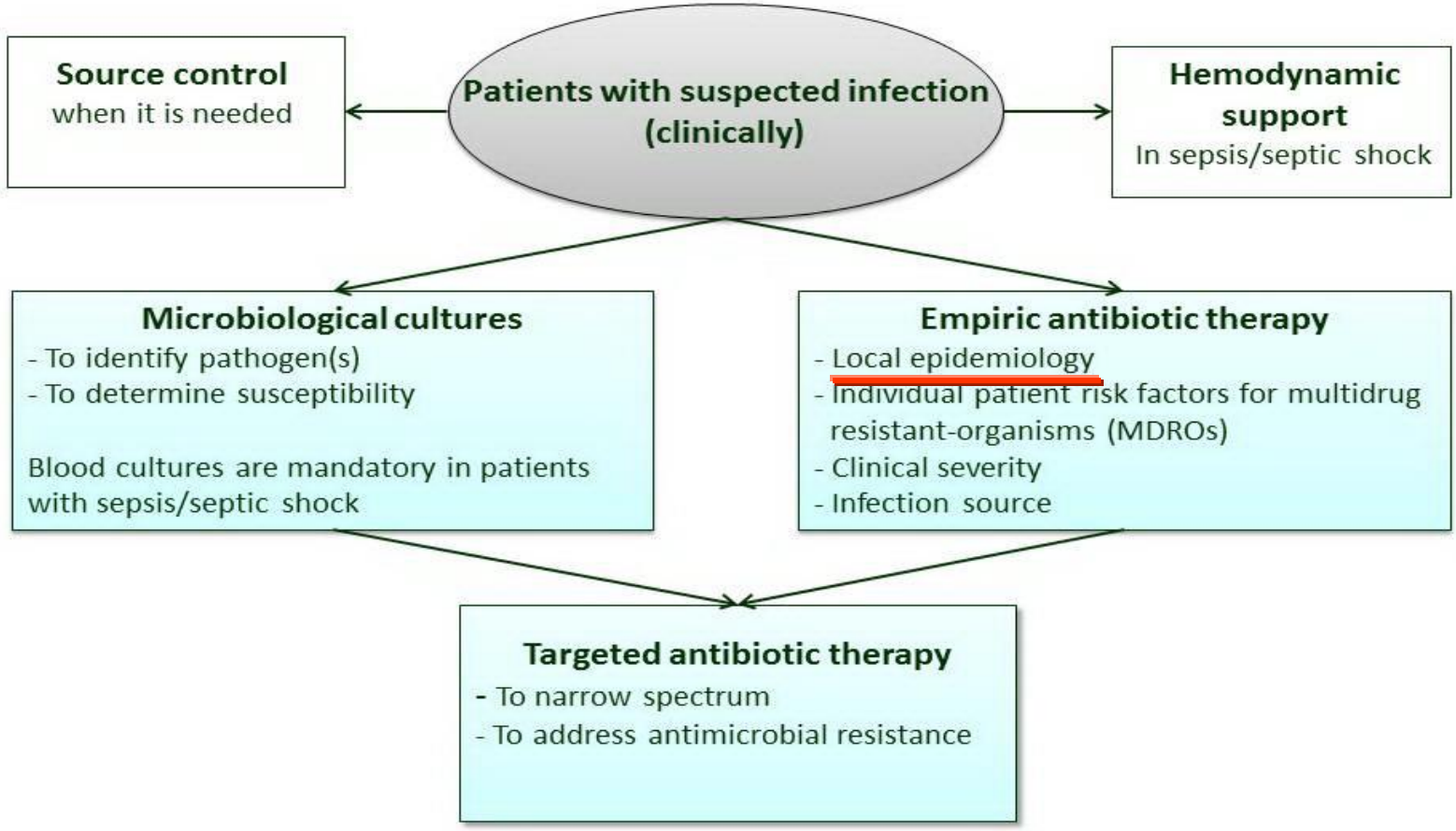
Sepsis control

Antimicrobial therapy

The treatment of patients with complicated IAI involves both timely source control and antimicrobial therapy.

Empiric antimicrobial therapy is important in the management of intra-abdominal infections and must be broad enough to cover all likely organisms. Adequate source control is mandatory in the management of complicated IAIs.

Rational use of antibiotics in surgery



WHICH ARE THE PRINCIPLES OF ANTIBIOTIC THERAPY?

It is important to know the **local epidemiological context** to define therapeutic protocols / guidelines for surgical infections treatment.

It is important to frame **clinical conditions**, in particular to differentiate between critical and non-critical patients.

It is important to pursue as much as possible **targeted therapy or in any case a de-escalation** in order to preserve some molecules: eg. Carbapenems.

It is important to assess properly the **duration of therapy** based on **source control**.

Community-acquired IAIs

The major pathogens involved in community-acquired intra-abdominal infections are Enterobacteriaceae (especially *E. coli, K pneumoniae*, *Enterobacter*) Streptococcus species, and anaerobes (especially *B. fragilis*).

Community-acquired IAIs and ESBL

However, if CA-IAI patients have prior exposure to antibiotics or serious comorbidities requiring concurrent antibioitic therapy, anti-ESBL-producer coverage may be warranted.

Ben-Ami R, Rodriguez-Bano J, Arsian H, Pitout JD, Quentin C, Calbo ES, Azap OK, Arpin C, Pascual A, Livermore DM, Garau J, Carmeli Y: A multinational survey of risk factors for infection with extended-spectrum β-lactamaseproducing Enterobacteriaceae in nonhospitalized patients. Clin Infect Dis 2009, 49:682–690.

In the past 20 years, the incidence of healthcare-associated infections caused by drug-resistant microorganisms has risen dramatically, probably in correlation with escalating levels of antibiotic exposure and increasing frequency of patients with one or more predisposing conditions, including elevated severity of illness, advanced age, degree of organ dysfunction, low albumin levels, poor nutritional status, immunodepression, presence of malignancy, and other comorbidities.

“ESKAPE” pathogens

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumanii*
- *Pseudomonas aeruginosa*
- *Enterobacteriaceae* species

WHICH ARE THE PRINCIPLES OF ANTIBIOTIC THERAPY?

It is important to know the **local epidemiological context** to define therapeutic protocols / guidelines for surgical infections treatment.

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It is important to assess properly the **duration of therapy** based on **source control**.

SURGEONS IN MANY WAYS ARE ON THE FRONTLINE OF THE FIGHT AGAINST RESISTANCE.

This begins with appropriate use of **antimicrobial prophylaxis**. The elements of this are:

- correct selection of patients known to benefit from prophylaxis
- proper choice of antibiotics at the right dose
- timing (administration with 60 minutes of incision)
- intra-operative redosing for procedures lasting more than two half-lives of the antibiotic and **no** post-operative administration

Therapeutic use of antibiotics for soft tissue, intra-abdominal, and other infections should be guided by microbiology results and attention paid to when therapy should be terminated.

"Calendar-based prescribing" (one week, two weeks, etc.) should be replaced by monitoring of progress.

Diagnostic tool in certain situations…

Role of the biomarkers in surgery

C-reactive protein (CRP) and procalcitonin (PCT) can help clinicians to **diagnose** surgical infections.

PCT can help clinicians in **early discontinuation of antibiotics** in critically ill patients and in patients undergoing intervention for acute peritonitis.

Biomarkers as an antimicrobial stewardship instrument !

A procalcitonin based algorithm to guide antibiotic therapy in secondary peritonitis following emergency surgery: A prospective study with propensity score matching analysis. ***Huang TS, et al. PLoS One 2014;9:e90539*.**

patients diagnosed at the emergency department with secondary peritonitis and underwent emergency surgery were enrolled. PCT concentrations were obtained preoperatively, on post-operative days 1, 3, 5, and 7, and on subsequent days if needed. Antibiotics were discontinued if PCT was <1.0 ng/mL or decreased by 80% versus day 1, with resolution of clinical signs.

	PCT group	*Control*	*p*
median duration of antibiotics (days)	**3.4**	**6.1**	**< 0.001**

the PCT-based algorithm was substantially associated with a 87% reduction in hazard of antibiotic exposure within 7 d (HR) 0.13, 95% CI 0.07–0.21, and a 68% reduction in hazard after 7 d (adjusted HR 0.32, 95% CI 0.11-0.99)

Procalcitonin-guided therapy may reduce length of antibiotic treatment in intensive care unit patients with secondary peritonitis: A multicenter retrospective study.
Maseda E, et al. J Crit Care 2015;30:537–542

A total of 121 patients (52 PCT-guided, 69 non-PCT-guided) were enrolled

	PCT	*control*	*p*
Median length of intra-SICU (days)	5	5	NS
Median LOS	20	17	NS
In-H Mortality (%)	9.6	13	NS
28 day mortality	19.2	29	NS
ATB duration (days)	5.1	10.2	<.001

Trial of Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Sawyer RG et al N Engl J Med 2015; 372:1996-2005

518 patients with complicated intraabdominal infection and adequate source control were randomly assigned to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4±1 calendar days. The primary outcome was a composite of surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure, according to treatment group. Secondary outcomes included the duration of therapy and rates of subsequent infections.

Characteristics of index infection		
APACHE II score‡	9.9±0.4	10.3±0.4
Maximum white-cell count — per mm^3	15,600±0.4	17,100±0.7
Maximum body temperature — °C	37.8±0.1	37.7±0.1
Organ of origin — no. (%)		
Colon or rectum	80 (30.8)	97 (37.6)
Appendix	34 (13.1)	39 (15.1)
Small bowel	31 (11.9)	42 (16.3)
Source-control procedure — no. (%)		
Percutaneous drainage	86 (33.1)	86 (33.3)
Resection and anastomosis or closure	69 (26.5)	64 (24.8)
Surgical drainage only	55 (21.2)	54 (20.9)
Resection and proximal diversion	27 (10.4)	37 (14.3)
Simple closure	20 (7.7)	12 (4.7)
Surgical drainage and diversion	3 (1.2)	4 (1.6)

Trial of Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Sawyer RG et al N Engl J Med 2015; 372:1996-2005

	Control Group (N=260)	Experimental Group (N=257)	P Value
Duration of outcome — days			
Antimicrobial therapy for index infection			<0.001
Median	8	4	
Interquartile range	5–10	4–5	
Antimicrobial-free days at 30 days			<0.001
Median	21	25	
Interquartile range	18–25	21–26	
Hospitalization after index procedure			0.48
Median	7	7	
Interquartile range	4–11	4–11	
Hospital-free days at 30 days			0.22
Median	23	22	
Interquartile range	18–26	16–26	

Trial of Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Sawyer RG et al N Engl J Med 2015; 372:1996-2005

Variable	Control Group (N=260)	Experimental Group (N=257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Surgical-site infection	23 (8.8)	17 (6.6)	0.43
Recurrent intraabdominal infection	36 (13.8)	40 (15.6)	0.67
Death	2 (0.8)	3 (1.2)	0.99
Time to event — no. of days after index source-control procedure			
Diagnosis of surgical-site infection	15.1±0.6	8.8±0.4	<0.001
Diagnosis of recurrent intraabdominal infection	15.1±0.5	10.8±0.4	<0.001
Death	19.0±1.0	18.5±0.5	0.66

Protocol violation **18%** **27%**

Longer-duration antimicrobial therapy does not prevent treatment failure in high-risk patients with complicated intra-abdominal infections

Hassinger TE et al, Surgical Infect 2017; 18

Patients enrolled in the Study to Optimize Peritoneal Infection Therapy trial were evaluated retrospectively to identify risk factors associated with treatment failure, which was defined as the composite outcome of recurrent IAI, surgical site infection, or death.

The STOP-IT trial included 517 patients enrolled The overall rate of treatment failure was 22.1%.

Four variables showed significant association with failure

- **steroid use,**
- **hospital acquired infection,**
- **APACHE II score >15,**
- **colonic source of infection**

Both the presence and the number of risk factors were associated independently with treatment failure, but treatment duration WAS NOT !

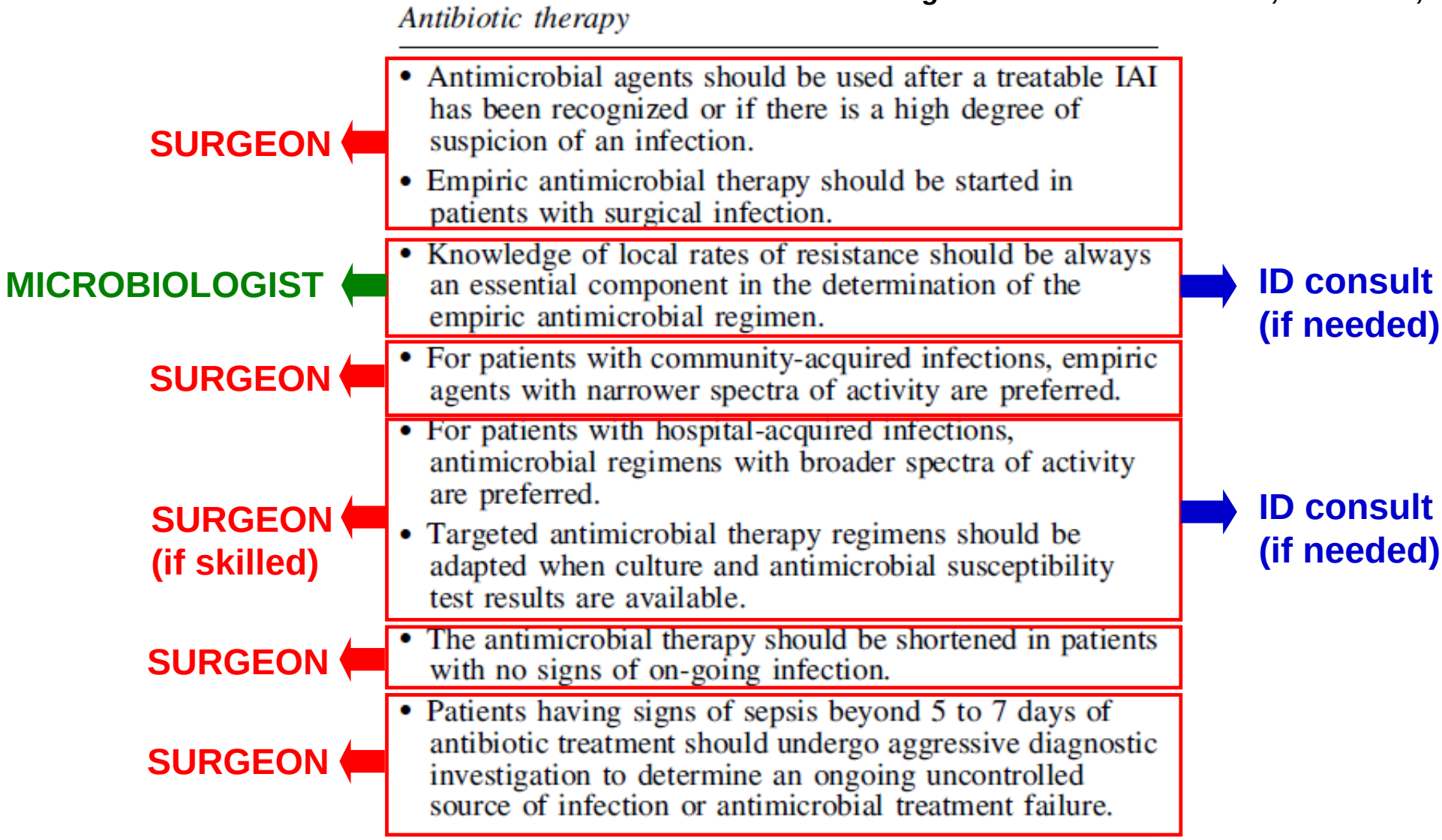
OPPORTUNITA’ DI STEWARDSHIP ANTIMICROBICA IN CHIRURGIA

GLI ATTORI PRINCIPALI:

HIERACHICAL PATTERN OF PRESCRIPTIONS

Antimicrobial Stewardship: A Call to Action for Surgeons

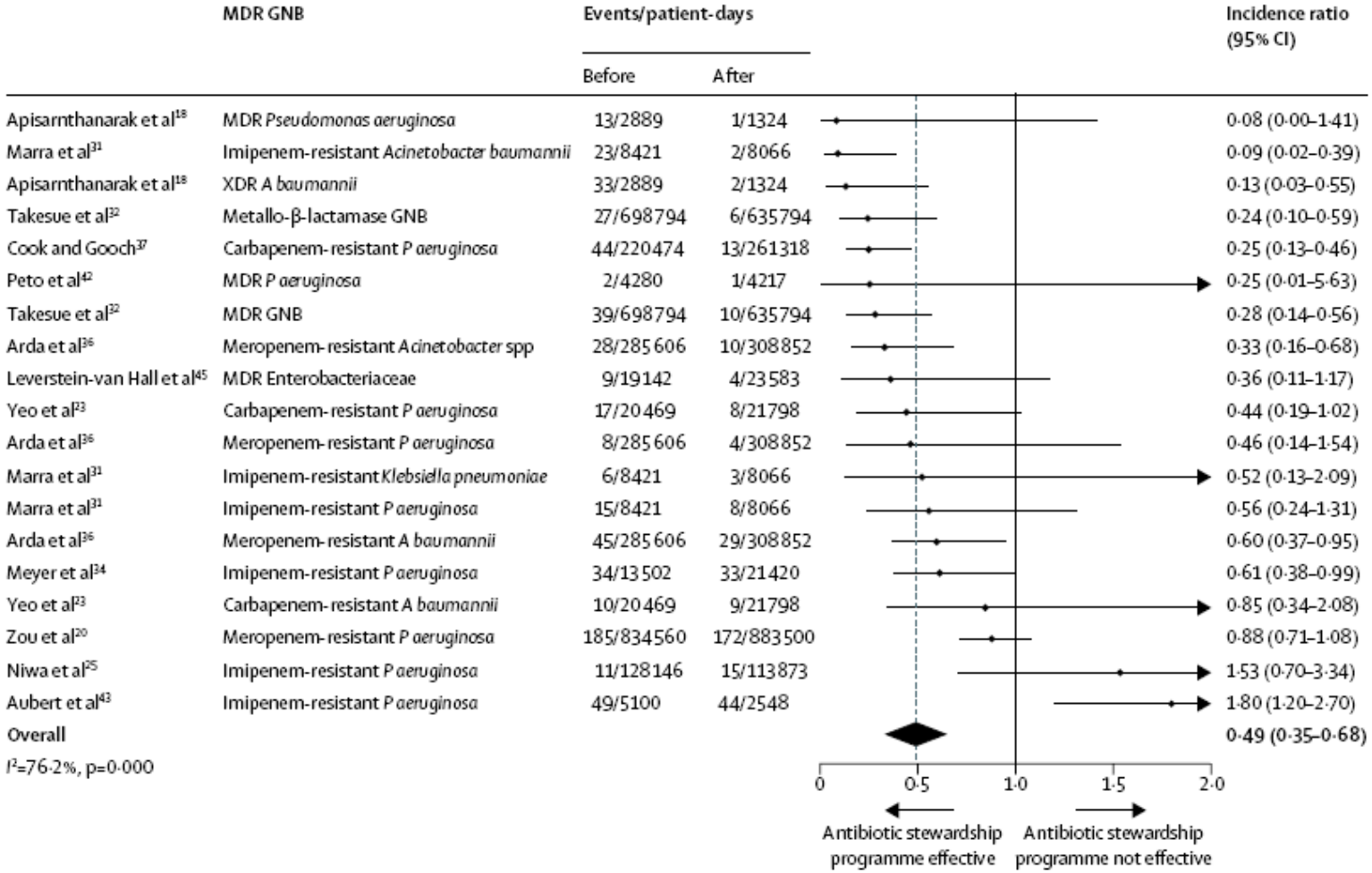
Sartelli M et al - Surgical Infections Volume 17, Number 6, 2016



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

David Baur et al - Lancet Infect Dis 2017; 17: 990–1001

Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB



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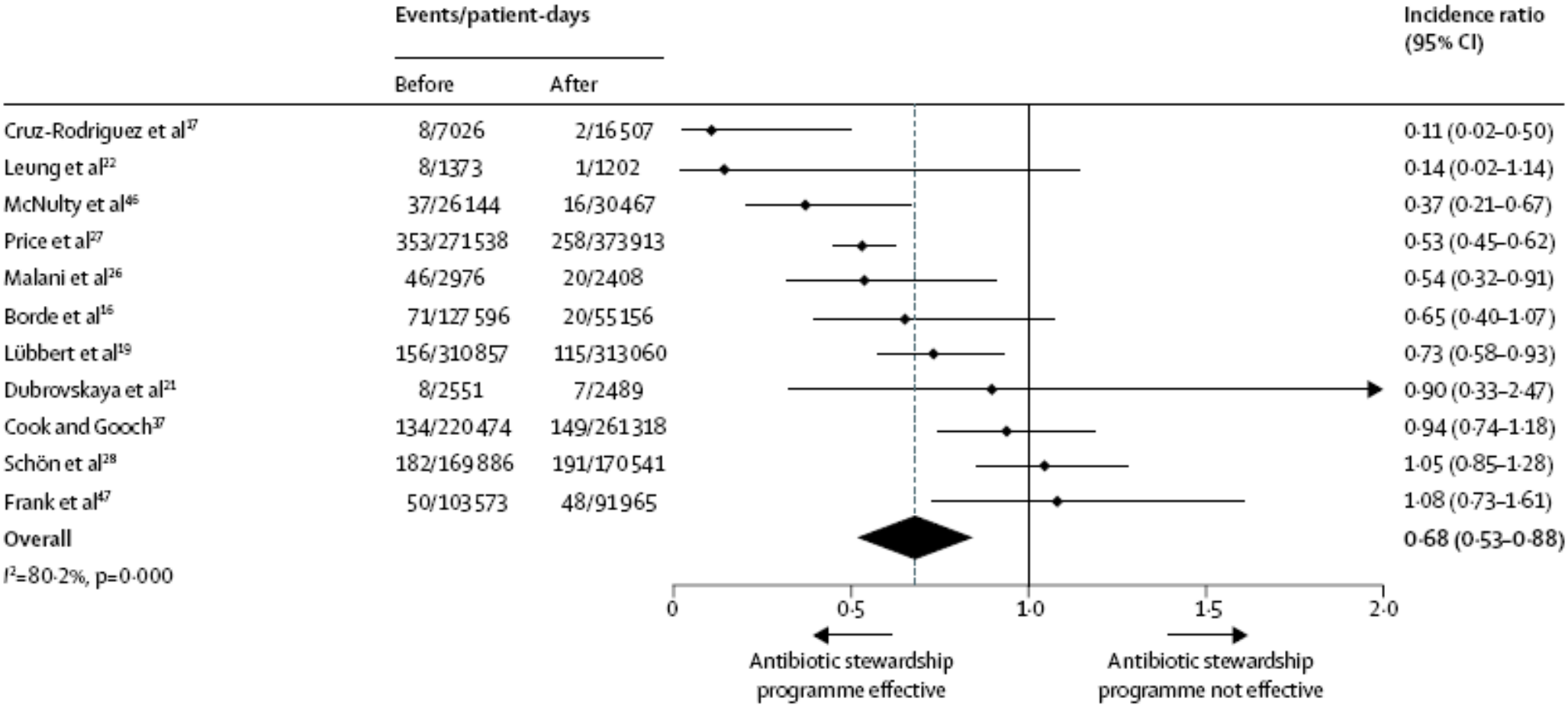

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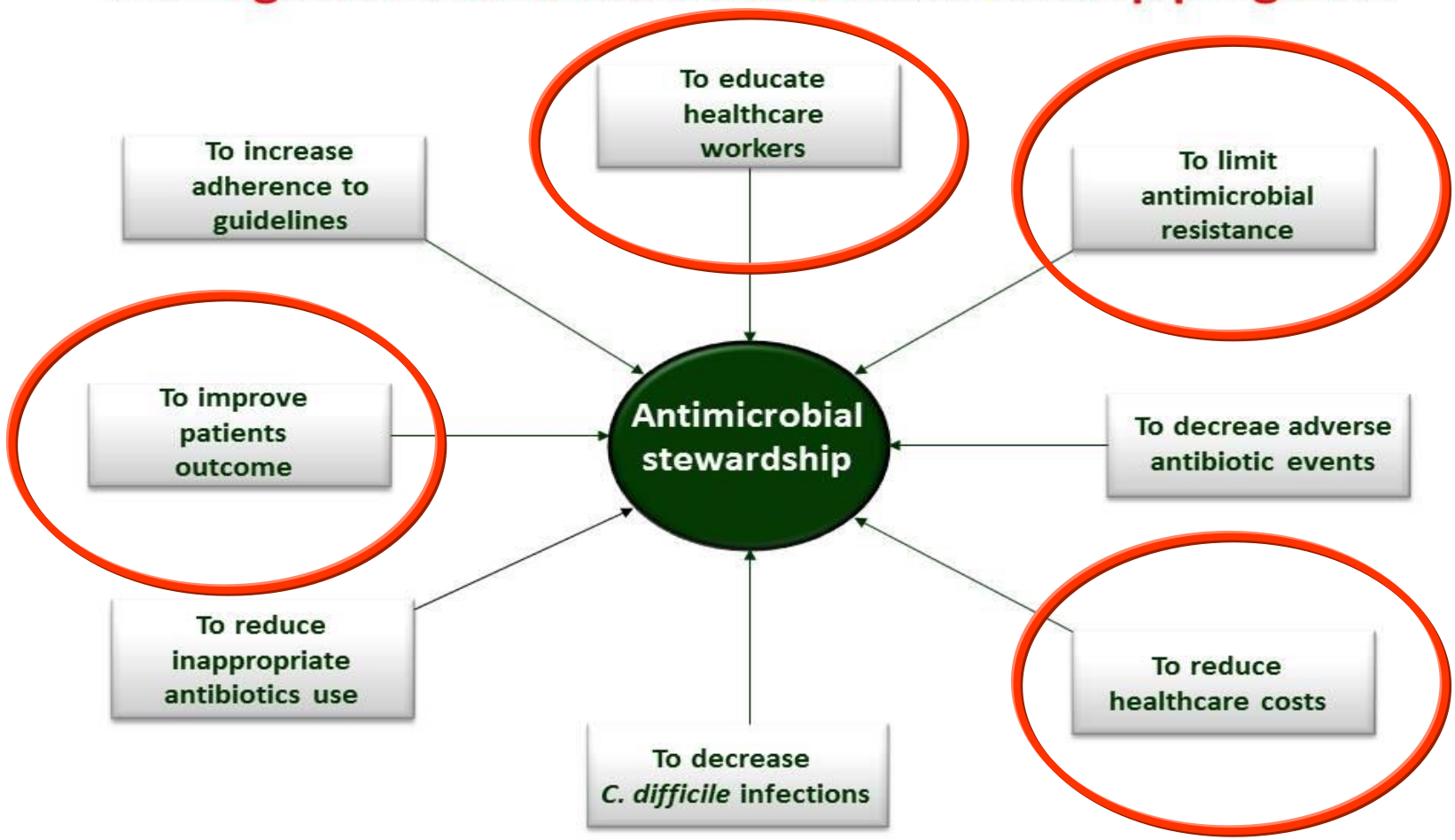
David Baur et al - Lancet Infect Dis 2017; 17: 990–1001

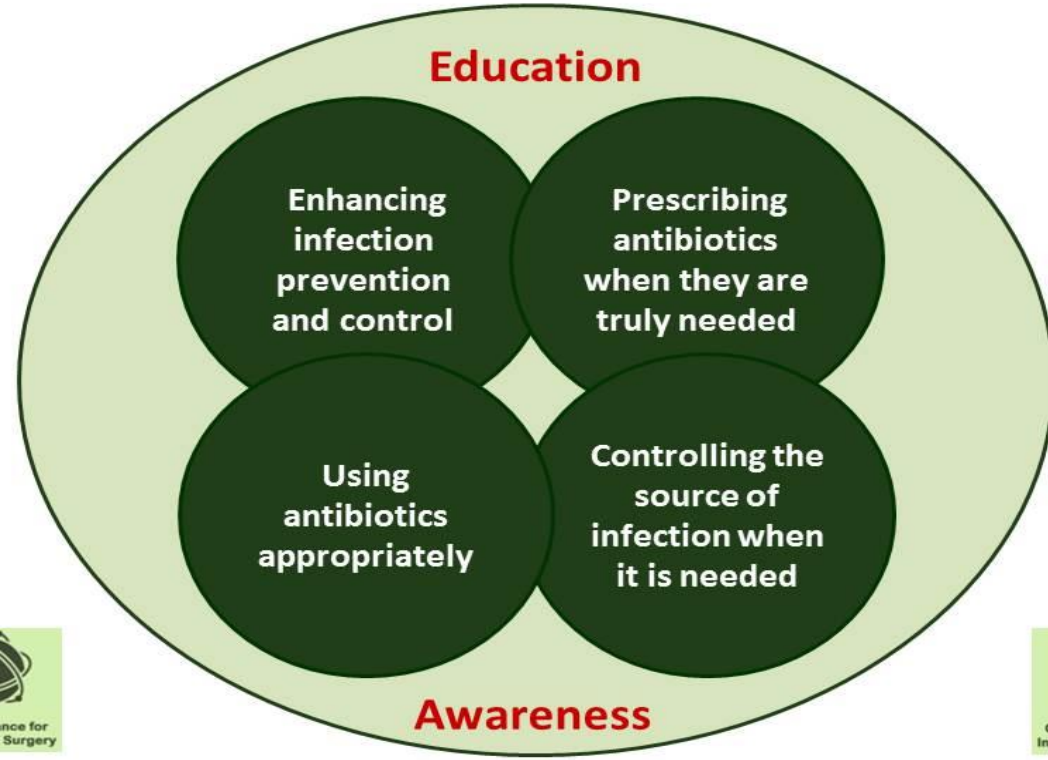
Added value of this study

This systematic review and meta-analysis showed, for the first time, the effectiveness of antibiotic stewardship programmes in reducing the incidence of infections and colonisation due to multidrug-resistant Gram-negative bacteria, extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, meticillin-resistant *Staphylococcus aureus*, and *C difficile*.

The 8 goals of the antimicrobial stewardship programs



Let's combat antimicrobial resistance in our hospitals



Global Alliance for Infections in Surgery

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