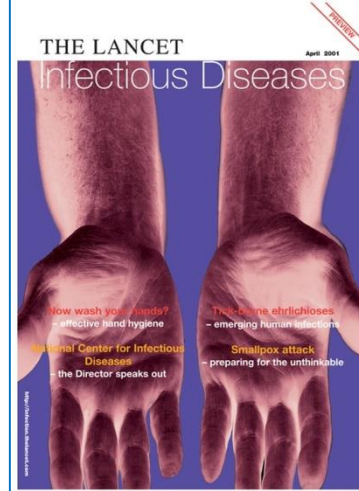


Governance e sostenibilità nell'antibioticoterapia

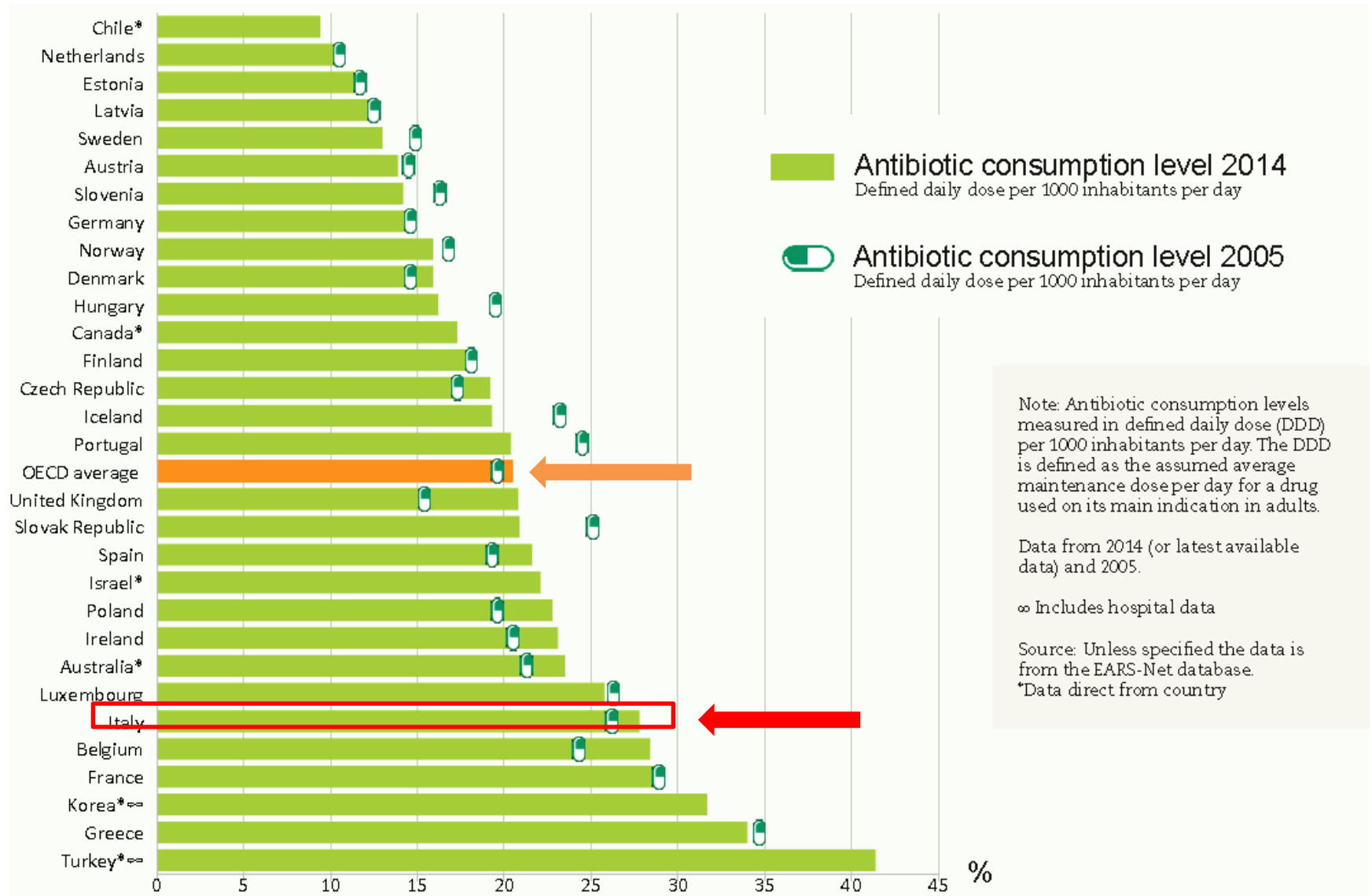
Anna Maria Cattelan
UOC Malattie Infettive
Azienda Ospedaliera Universitaria Padova



*16 years ago, in an editorial in the first issue of
The Lancet Infectious Diseases,
antimicrobials were described as*

“A gift to be used sparingly”

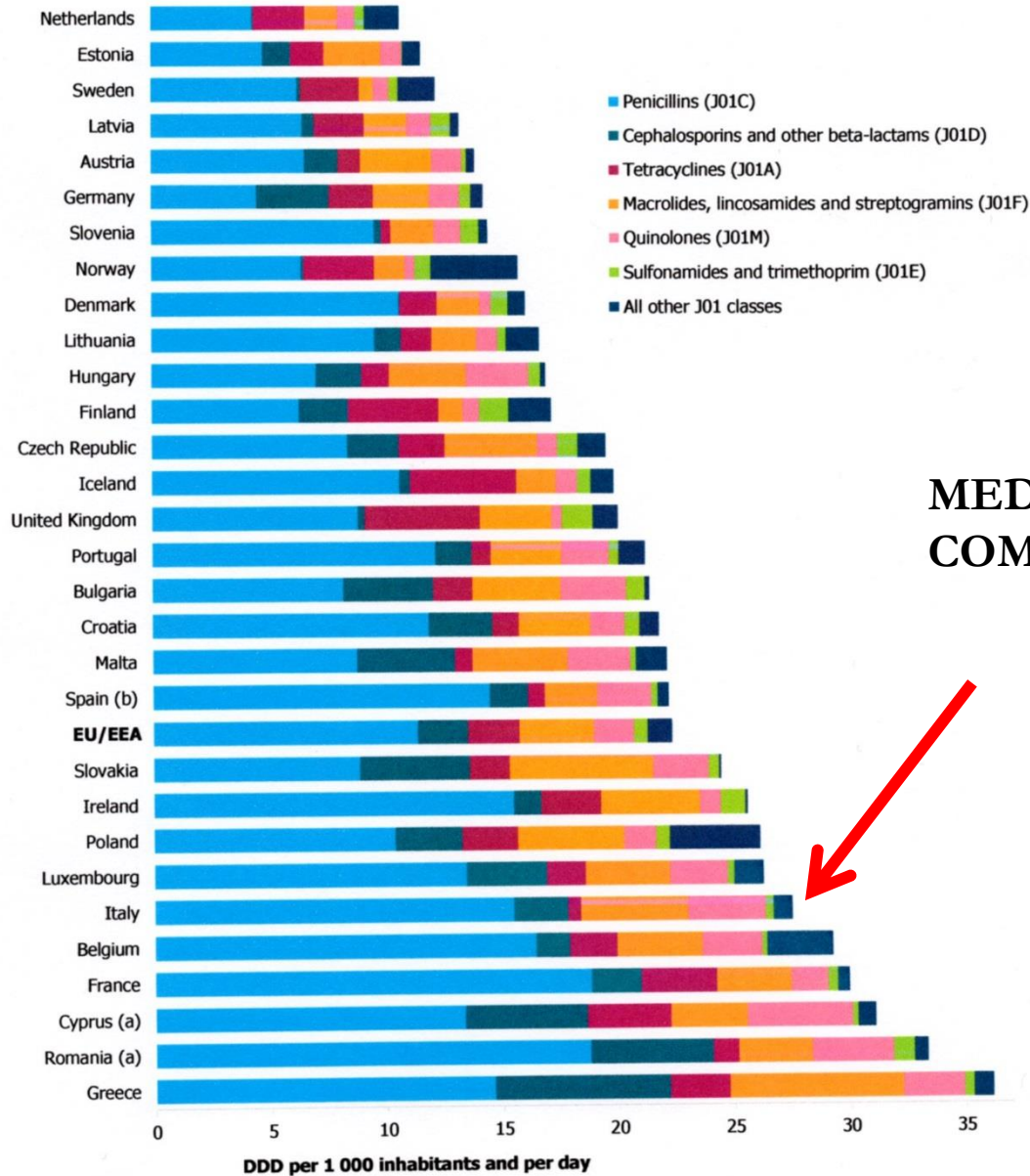
Human consumption of antibiotics



Source: ESAC-Net Database and CDDEP,OECD, November 2016

Figure 1. Consumption of antibiotics for systemic use in the community by antibiotic group, EU/EEA countries, 2015 (expressed in DDD per 1 000 inhabitants and per day)

2015



MEDICINA DI
COMUNITA'



	Uso di antibiotici		Uso di MAC, FLU, CEF		Uso di CEF-I e FLU		Uso di FLU	
	Influenza, raffreddore, laringotracheite acuta [N=46.019]		Faringite e Tonsillite acuta [N=28.227]		Bronchite acuta° [N=11.310]		Cistite semplice* [N=6.973]	
	%	Δ % 11-10	%	Δ % 11-10	%	Δ % 11-10	%	Δ % 11-10

ANALISI GEOGRAFICA

Piemonte/Val d'Aosta	34,9	-1,3	24,0	-3,4	28,2	-4,5	40,1	-4,3
Lombardia	37,5	-2,1	24,2	+0,1	22,1	-1,6	41,2	-3,8
Liguria	38,7	-2,5	33,6	+1,5	32,2	-8,2	38,5	-4,3
Bolzano/Trento/ Friuli VG	26,7	-0,9	26,0	+2,2	17,6	-1,4	29,4	-7,8
Veneto	29,1	-7,0	27,8	+3,3	22,7	0,6	50,9	-7,7
E. Romagna	29,8	-3,4	21,0	-2,0	18,4	-0,5	41,6	-2,6
NORD	32,5	-3,2	25,1	+0,3	22,1	-1,5	41,6	-2,8
Toscana	52,7	-1,2	23,7	-1,1	24,2	-3,7	45,5	-1,6
Marche/Umbria	40,5	-9,2	22,8	-1,4	25,4	-2,9	42,1	-6,9
Lazio	41,0	-5,4	23,7	-2,2	42,2	0,7	40,4	-2,3
CENTRO	44,6	-5,3	23,4	-1,6	31,7	-1,0	41,7	-2,6
Abruzzo/Molise	54,6	-1,6	22,9	-2,2	37,9	-1,8	39,8	+1,5
Puglia	52,3	-7,4	24,0	-1,2	49,0	-2,2	47,7	-0,1
Campania	53,5	-3,0	29,0	+0,2	50,8	-3,5	40,1	-3,9
Basilicata/Calabria	42,7	-9,4	24,6	-2,6	41,0	-3,9	48,3	-2,9
Sicilia/Sardegna	42,0	-0,5	24,7	-0,9	43,8	-2,6	36,4	-2,7
SUD E ISOLE	48,9	-3,5	25,6	-1,1	46,4	-2,7	40,6	+0,1

ANALISI PER GENERE

Maschi	38,3	-3,4	23,9	-0,7	32,0	-1,7	-	-
Femmine	41,5	-4,0	25,9	-0,4	32,6	-1,3	41,1	-1,3

ANALISI PER ETÀ

≤45	35,5	-4,2	25,4	-0,2	23,3	-0,8	40,6	-1,5
46-65	40,7	-4,5	24,5	-1,4	33,6	-0,7	44,0	-0,6
66-75	53,1	+1,6	24,8	-0,4	38,8	-3,3	-	-
>75	54,6	+1,6	24,7	+0,8	44,2	-2,9	-	-
ITALIA	40,1	-3,8	25,1	-0,5	32,4	-1,5	41,1	-1,3

L'uso degli antibiotici nei reparti di Medicina Interna risultati
preliminari di uno studio multicentrico nel Lazio

M. Galie' - FADOI

NOVEMBRE 2014 – DICEMBRE 2015



PAZIENTI TRATTATI CON ANTIBIOTICI: 61,1 %

Antibiotic Use / Overuse in LTCF

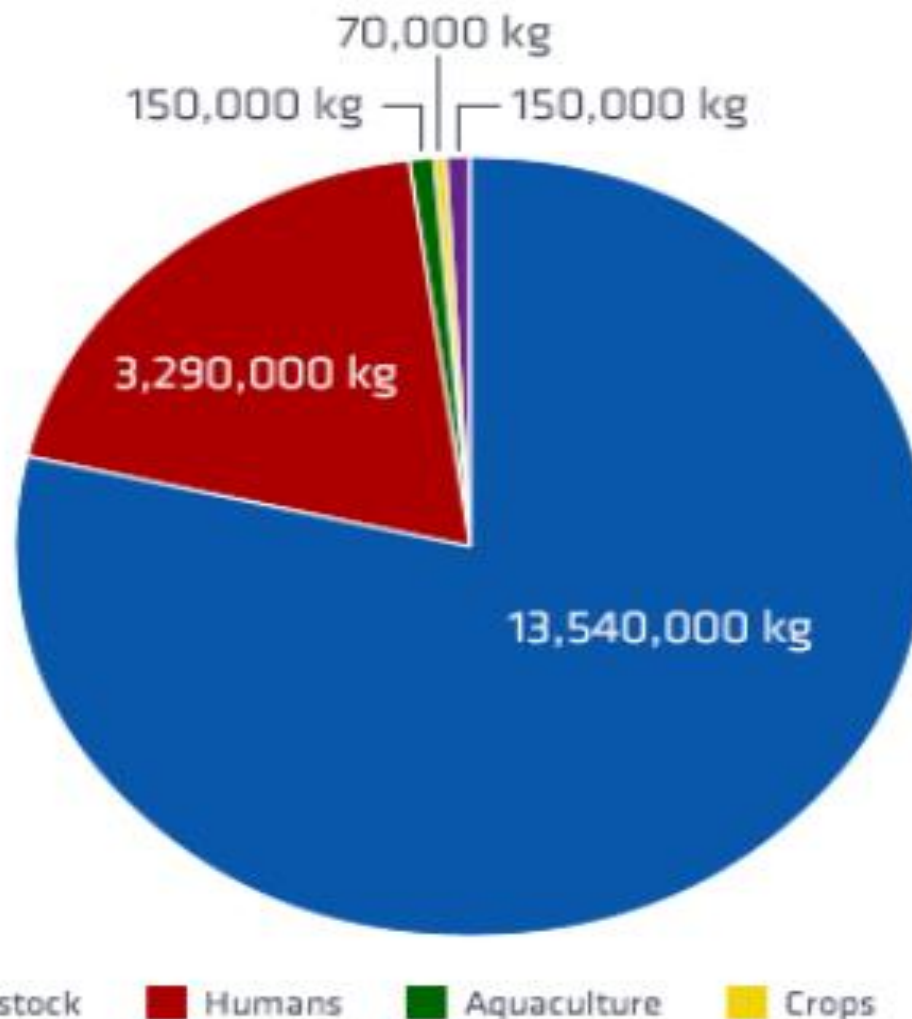
- **50-80% of LTCF residents** receive an antibiotic every year
- **25% - 75%** of antimicrobials prescribed in nursing homes are considered **inappropriate**

USE OF ANTIBIOTICS

Where antibiotics Are used	Types of use	Questionable use
Human use (50%)	<u>20% Hospital</u> 80% Community	20-50% Unnecessary
Agricultural use (50%)	<u>20% Therapeutic</u> 80% Prophylactic /growth promotion	40-80% Highly questionable

P.F Harrison 1998

Estimated Annual Antibiotic Use in the United States



Data are shown as approximate numbers of kilograms of antibiotics used per year.

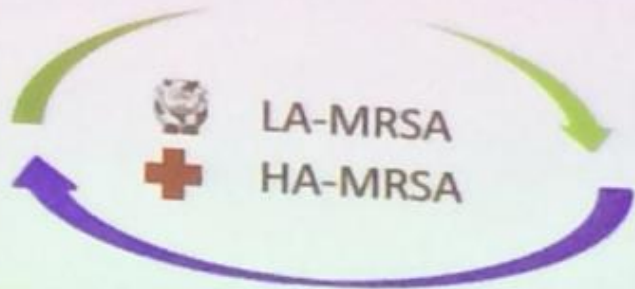
Source: Food and Drug Administration

Percentuali di resistenza riscontrate nei **POLLI**

AMPICILLINA	73
CEFOTAXIME	19
GENTAMICINA	62
STREPTOMICINA	65
TETRACICLINE	62
TRIMETOPRIM	65
CIPROFLOXACINA	58
CLORAMFENICOLO	25
COLISTINA	0

Study of MRSA in milk farms in North-East Italy

Comparison of genotypes of MRSA from cow milk and MRSA from nasal carriage of farmers



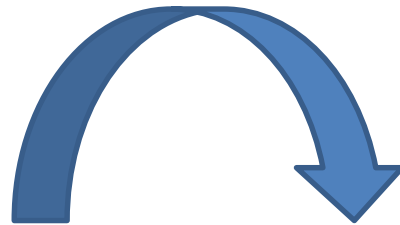
A	t4208/ ST398		t899/ ST398	
C	t032/ ST22		t032/ ST22	
E	t899/ ST398		t899/ ST398	
G	t127/ST1		t127/ ST1	
I	t899/ ST398		t899/ ST398	
S	t127/ ST1		t127/ ST1	
T	t127/ ST1		t852/ST22	
Z	t899/ ST398		t899/ ST398	

INFECTIOUS RISK CONTROL

PREVENTION OF INFECTIONS

MANAGEMENT OF INFECTIONS

PREVENTION OF RESISTANCES



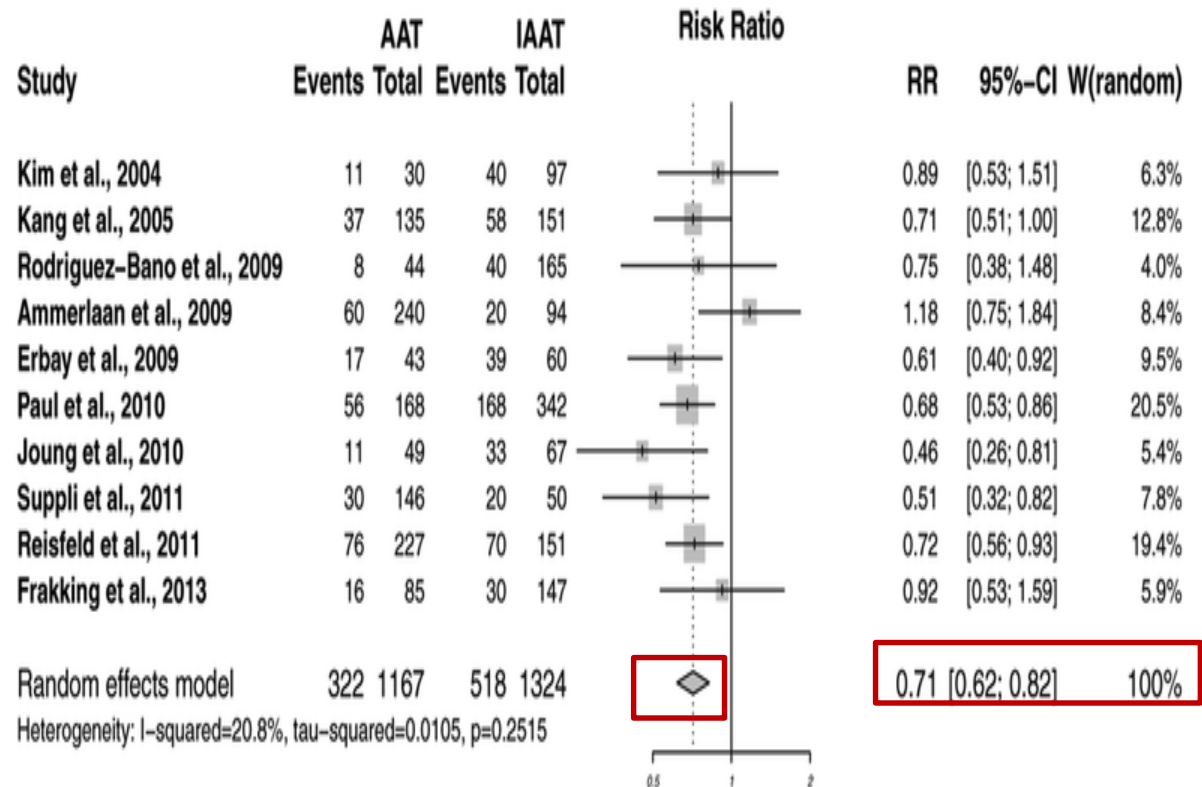
**The GOAL IS THE APPROPRIATENESS
OF THE PRESCRIPTIONS**

The MULTIFACETED concept of APPROPRIATENESS

- RIGHT INDICATION (epidemiologically, microbiologically and PK/PD driven)
- RIGHT DAILY DOSE
- RIGHT MODALITY OF ADMINISTRATION
- RIGHT PRESCRIBER
- SHARED CRITERIA FOR DE-ESCALATION / INTERRUPTION
- IMPROVEMENT OF MICROBIOLOGICAL WORK UP

Effect of inappropriate antibiotic therapy against severe infections

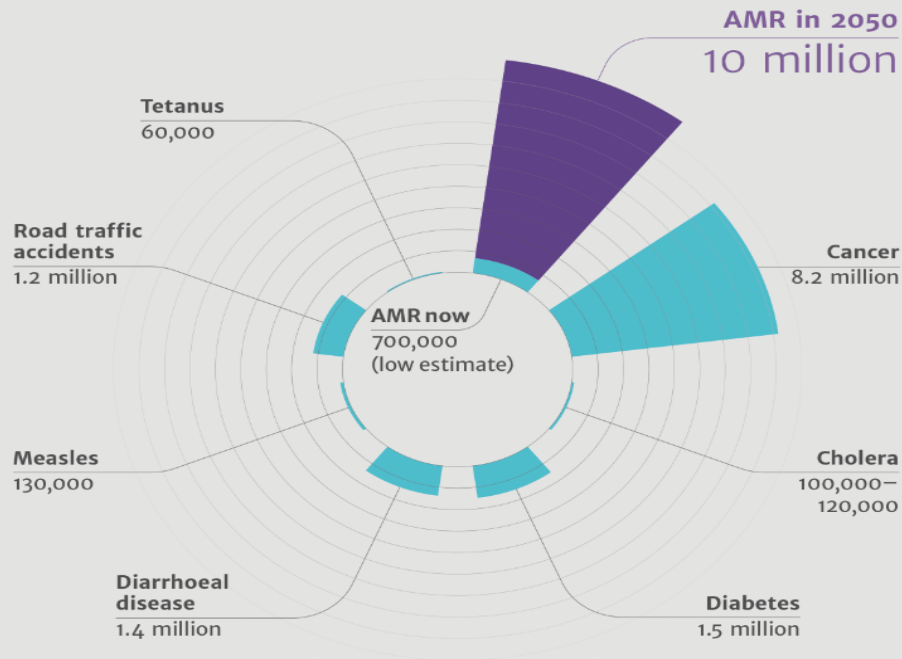
The percentage of inappropriate empiric antibiotic use ranged from 14% to 79%; 13 of 27 studies (48%) described an incidence of 50% or more



29% increase in mortality in patients receiving inappropriate therapy

Antimicrobial Resistance (AMR) scenario

Deaths attributable to AMR every year compared to other major causes of death



10 million extra deaths
Per year by 2050



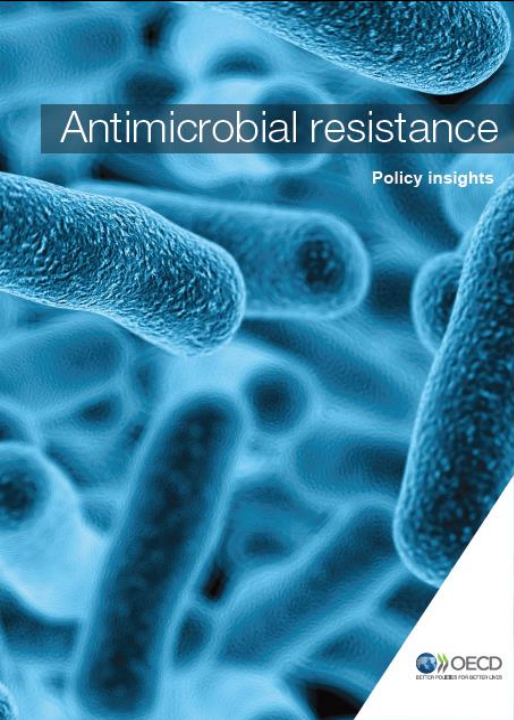
Macroeconomic loss

8 trillions \$ loss per year

100 trillions \$ by 2050

Sources

Diabetes www.who.int/mediacentre/factsheets/fs312/en/
Cancer www.who.int/mediacentre/factsheets/fs297/en/
Cholera www.who.int/mediacentre/factsheets/fs107/en/
Diarrhoeal disease www.sciencedirect.com/science/article/pii/S0140673612617280
Measles www.sciencedirect.com/science/article/pii/S0140673612617280
Road traffic accidents www.who.int/mediacentre/factsheets/fs358/en/
Tetanus www.sciencedirect.com/science/article/pii/S0140673612617280



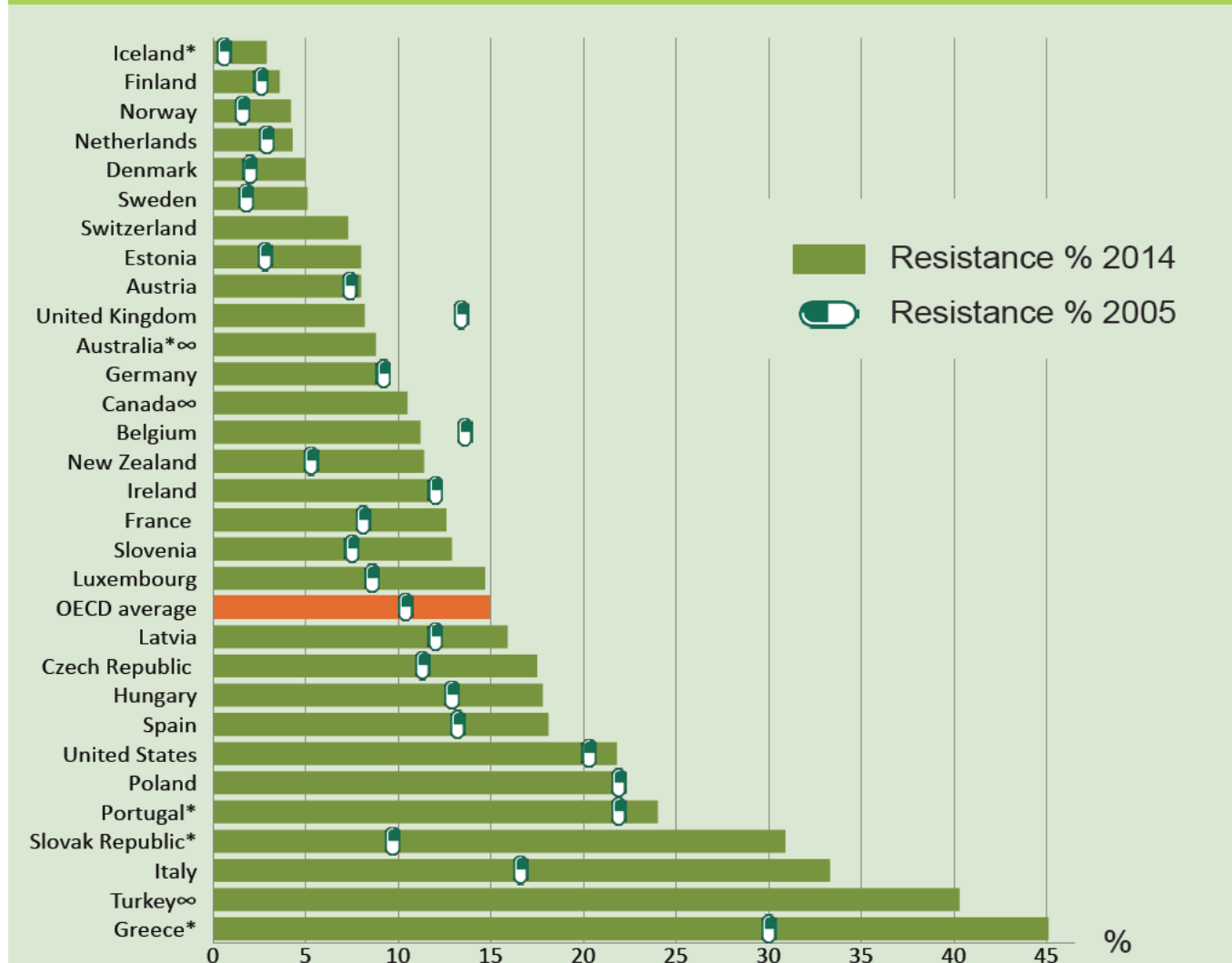
Antimicrobial resistance

Policy insights



Trends across OECD countries

Antibiotic resistance is growing



In Italia l'antibioticoresistenza è raddoppiata tra il 2005 e il 2014

Antibiotic resistance in Italy in 2015: comparison with the European mean and 4-year trends

	Italy 2015 %RES	EU/EAA 2015 (mean)	Trend 2012-2015
<i>Klebsiella pneumoniae</i>			
3rd gen cephalosporins	55.9	30.3	↑
aminoglycosides	34.0	22.5	
carbapenems	33.5	18.6	
<i>Escherichia coli</i>			
3rd gen cephalosporin	30.1	13.1	↑
aminoglycosides	20.2	10.4	
Fluoroquinolones	44.4	22.8	↑
<i>Pseudomonas aeruginosa</i>			
piperacillin-tazobactam	29.5	18.1	
Ceftazidime	21.7	13.3	
Aminoglycosides	17.2	13.3	↓
carbapenems	23.0	17.8	
<i>Acinetobacter spp.</i>			
carbapenems	78.3	NA	
<i>Staphylococcus aureus</i>			
oxacillin (MRSA)	34.1	16.8	
<i>Streptococcus pneumoniae</i>			
penicillin (NS)	12.3		
macrolides	24.5		↓
<i>Enterococcus faecium</i>			
vancomycin (VRE)	11.2	8.3	↑

Klebsiella

ECDC REPORT SUMMARY

Summary of latest data on antibiotic resistance in the EU, November 2016

Figure 1. *Klebsiella pneumoniae*: percentage of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, EU/EEA, 2012 (left), 2015 (right)

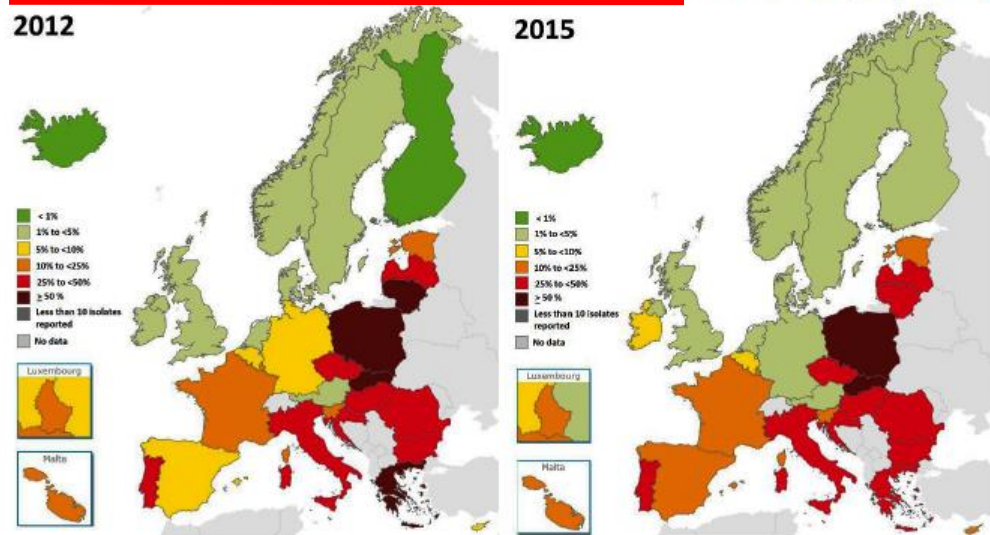
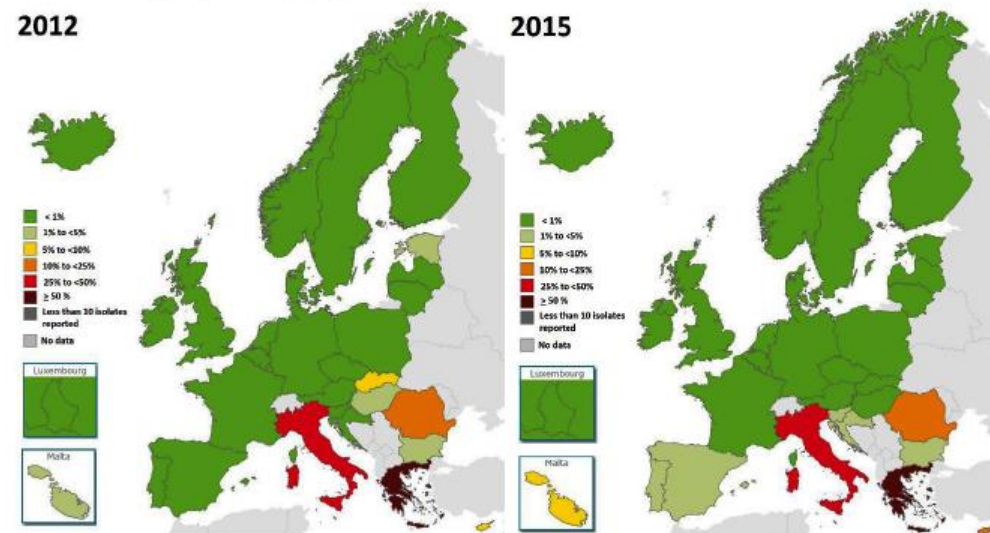


Figure 2. *Klebsiella pneumoniae*: percentage of invasive isolates with resistance to carbapenems, EU/EEA, 2012 (left), 2015 (right)



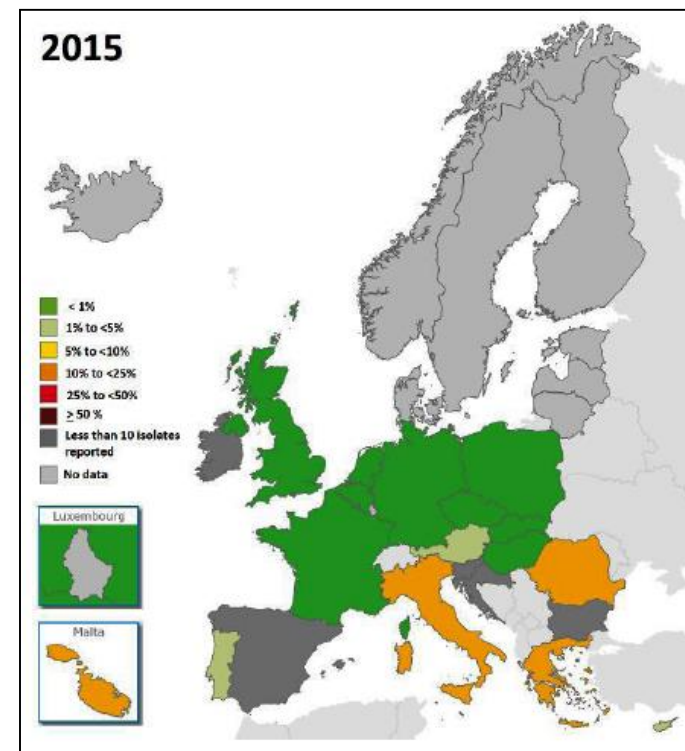
EUROPEAN ANTIBIOTIC AWARENESS DAY

A European Health Initiative

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Summary of the latest data on antibiotic resistance in the European Union
EARS-Net surveillance data
November 2016

***Klebsiella pneumoniae*: percentage of invasive isolates with combined resistance to carbapenems and colistin*, EU/EEA, 2015**



* Only isolates that were tested for both carbapenem resistance and colistin resistance were included in the analysis.

Cost of care and antibiotic prescribing attitudes for community-acquired complicated intra-abdominal infections in Italy: a retrospective study

Lidia Dalfino^{1*}, Francesco Bruno¹, Sergio Colizza², Ercole Concia³, Andrea Novelli⁴, Fabrizio Rebecchi⁵, Federico Spandonaro⁶ and Cristina Alato⁶

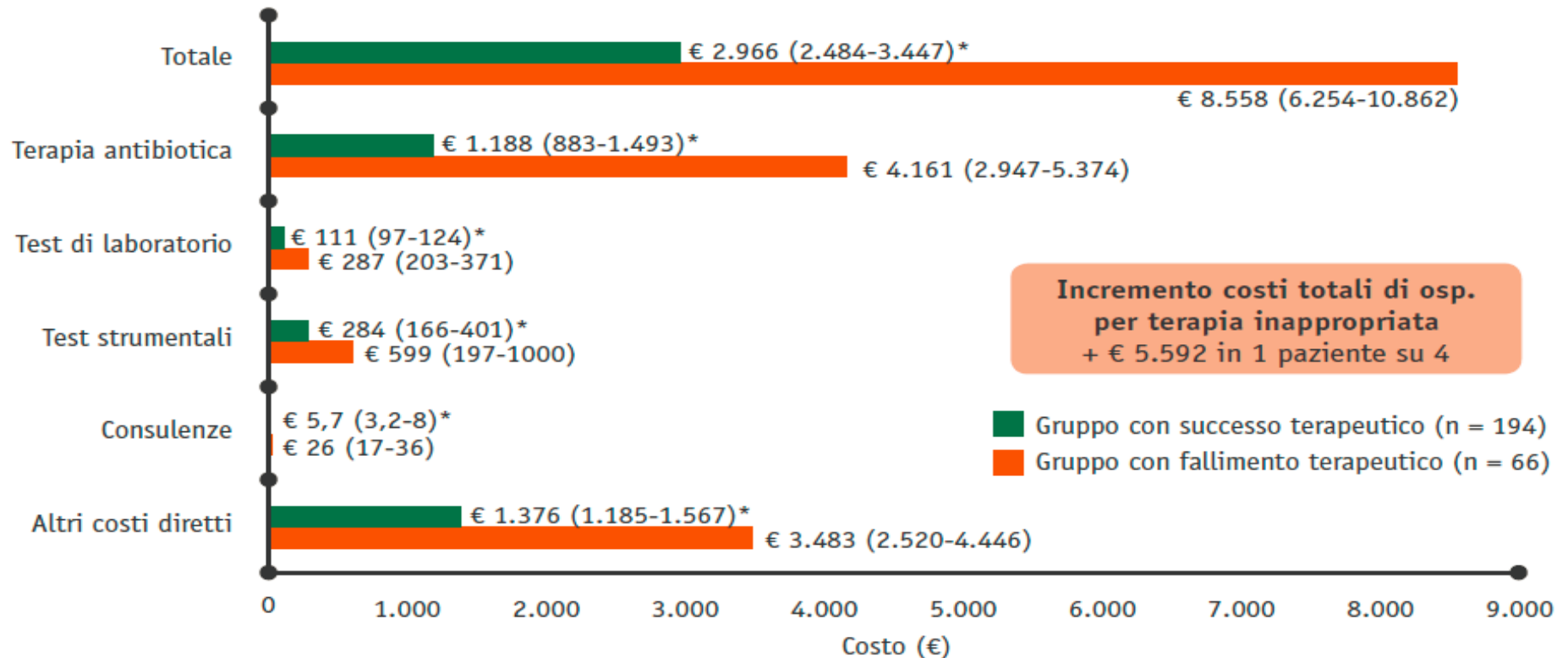
Abstract

Introduction: Complicated intra-abdominal infections (cIAls) are a common cause of morbidity worldwide, and in spite of improvements in patient care, therapeutic failure still occurs, impacting in-hospital resource consumption. This study aimed to assess the costs associated with the treatment of community-acquired cIAls, from the Italian National Health Service perspective.

Methods: This retrospective study analyzed the charts of patients who were discharged from four Italian university hospitals between January 1 and December 31, 2009 with a primary diagnosis of community-acquired cIAls. Patient characteristics, diagnosis, surgical procedure, antibiotic therapy, and length of hospital stay were all recorded and the cost of total hospital care was estimated. Costs were calculated in Euros at 2009 values.

Results: The records of 260 patients (mean age 48.9 years; 57% males) were analyzed. The average cost of care

In caso di fallimento si ha una spesa aggiuntiva per antibiotici di circa 3.000 € rispetto ai casi di successo¹



La voce "altri costi diretti" include il personale, ordinaria manutenzione e costi di degenza o ricovero.

* p<0,05 vs. clinical failure group.

- incremento dei giorni di terapia antibiotica (+8,2 gg)
- incremento della durata di degenza ospedaliera (+11 giorni)
- incremento dei costi totali di ospedalizzazione di circa 3 volte (+€ 5.592)

Antimicrobial Stewardship: DEFINITIONS

A marriage of infection control (Epidemiologist), and antimicrobial management (Infectious Diseases specialist) finalized to share the principles of the optimized treatment **between the bench to bed side point of view and the hospital-wide vision**

GOAL: An activity that **optimizes antimicrobial management** and includes microbiological work out, drugs selection, dosing, route and duration of antimicrobial therapy.

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Dellit TH, et al. Clin Infect Dis 2007; 44:159–177*

Antibiotic Stewardship in Europe

- **57% European hospitals have a written antibiotic policy**
 - 20% teaching hospitals do not
- **Hospitals in Northern and Western Europe are most likely to have antibiotic committees**
- **Policies and practices relating to antibiotic stewardship vary considerably across Europe**

Comparison of Antibiotic Stewardship Situation in 3 Countries

	UK	France	US
No. of hospitals	2412	Appr. 2500	Appr. 5723
Main driver	↓ Resistance	↓ HAIs	Improve patient outcomes
Legislation	2008 law mandates AS practices	ASP since 2002 Performance indicators 2007 Financial penalty	Only in California since 2008. VA hospitals since 2014
Infrastructure	IDs manage	Antibiotic advisor w/wo ID training	IDs and ID pharmacists
Local strategies	Start Smart-Then Focus program	National guidance and local implement.	Varies to local facilities
Outcomes	Hospitals monitor outcomes	Annual public reports, R rates are monitored	Mixed data monitored. Most Ab expenditures

Effect of antimicrobial stewardship on hospitalized patients

145 studies / 14 objectives

	Definitions
Empirical therapy according to the guidelines	Empirical systemic antibiotic therapy prescribed according to local guide or national guidelines*
Blood cultures	Take at least two sets of blood cultures before starting systemic antibiotic therapy
Cultures from the site of infection	Take cultures from suspected sites of infection, preferably before starting systemic antibiotic therapy
De-escalation of therapy	Change to narrow-spectrum antibiotic or stop antibiotics as soon as culture results are available ²⁰⁻²³
Adjustment of therapy to renal function	Adjustment of dose and dosing interval of systemic antibiotics
Switch from intravenous to oral therapy	Switch after 48-72 h, when the clinical condition of the patient is stable, oral intake and gastrointestinal absorption are adequate, and when sufficiently high concentrations in blood with a suitable oral antibiotic can be achieved ^{20,24,25}
Documented antibiotic plan	Documented anti-indication, drug name and dose, and administration route and doses at the start of systemic antibiotic treatment interval, and should be reported in the literature Lancet Infect Dis 2016; 16: 847-56
Therapeutic drug monitoring	NA
Discontinuation of antibiotic therapy if infection is not confirmed	Discontinuation of empirical treatment based on lack of clinical or microbiological evidence of infection†
Presence of a local antibiotic guide	Local antibiotic guide present in the hospital and assessed for update every 3 years
Local antibiotic guide in agreement with national antibiotic guidelines	Corresponds for all features but can deviate on the basis of local resistance patterns
List of restricted antibiotics	Removal of specific antibiotics from the formulary or restriction of use by requiring preauthorisation by a specialist (infectious diseases or medical microbiology) or allowing use for only 72 h with mandatory approval for further use; studies in outbreak settings excluded
Bedside consultation	Formal consultation by an infectious disease specialist leading to written comments and advice on treatment based on physical examination and review of medical records (informal consultation, for example by telephone, does not count as bedside consultation)
Assessment of patients' adherence	NA

NA=not applicable. *All results extracted if both reported. †Studies only reporting on differences between discontinuing and continuing treatment were included, whereas those including more general reports on de-escalation of therapy (broad to narrower spectrum or stopping treatment based on culture results) were included in the review of de-escalation of therapy.

Effect of antimicrobial stewardship on hospitalized patients

Guideline-adherent empirical therapy was associated with a Risk Reduction for mortality of 35% and the escalation therapy with a RR of 56%

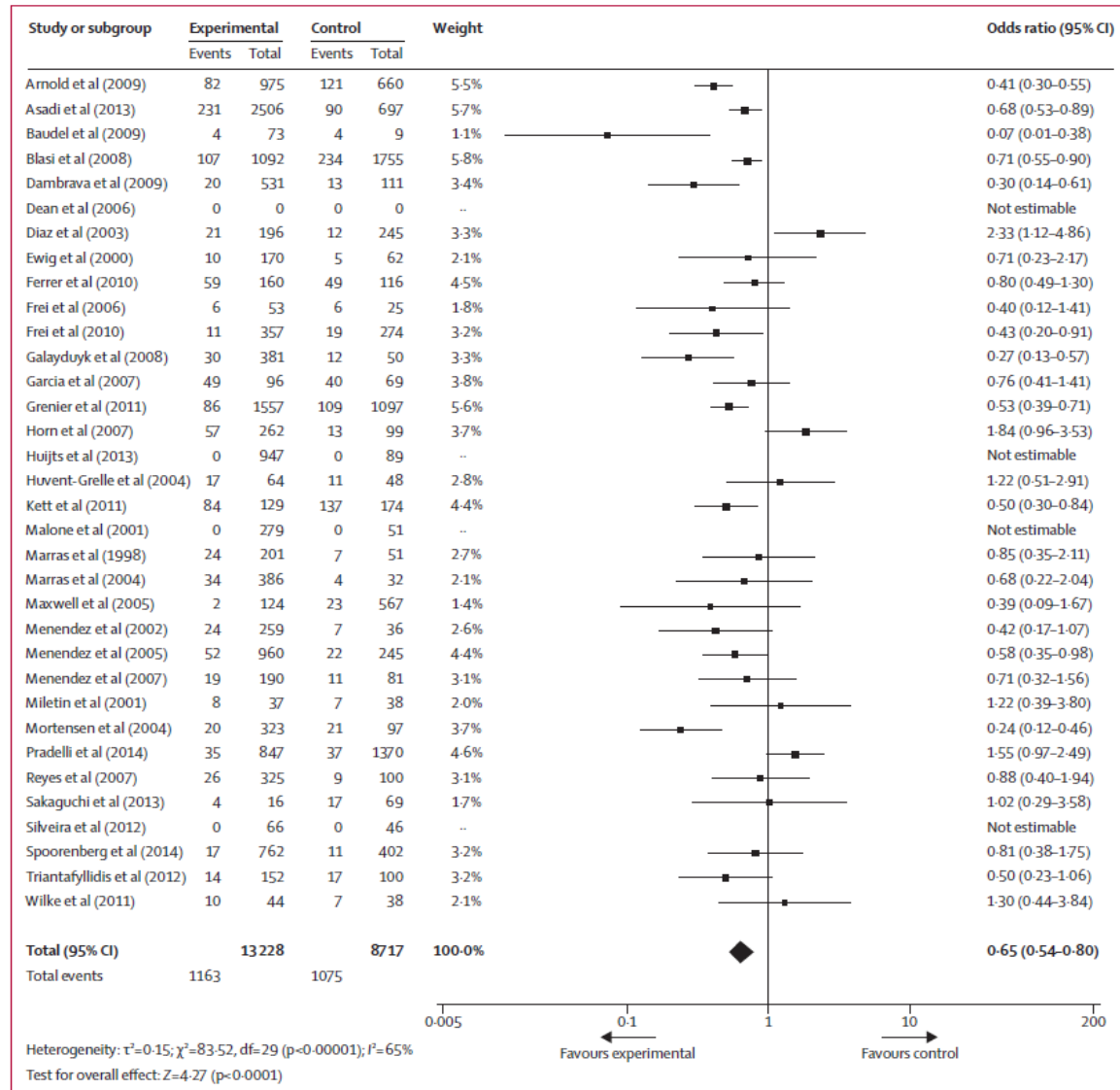


Figure 2: Effect on mortality of prescribing empirical antimicrobial therapy according to guidelines

Roma, **15 Aprile 2016**
Istituto Superiore di Sanità
Riunione con **“Stakeholders”** e **Commissione Europea** su :
“Non prudent use of antibiotics”

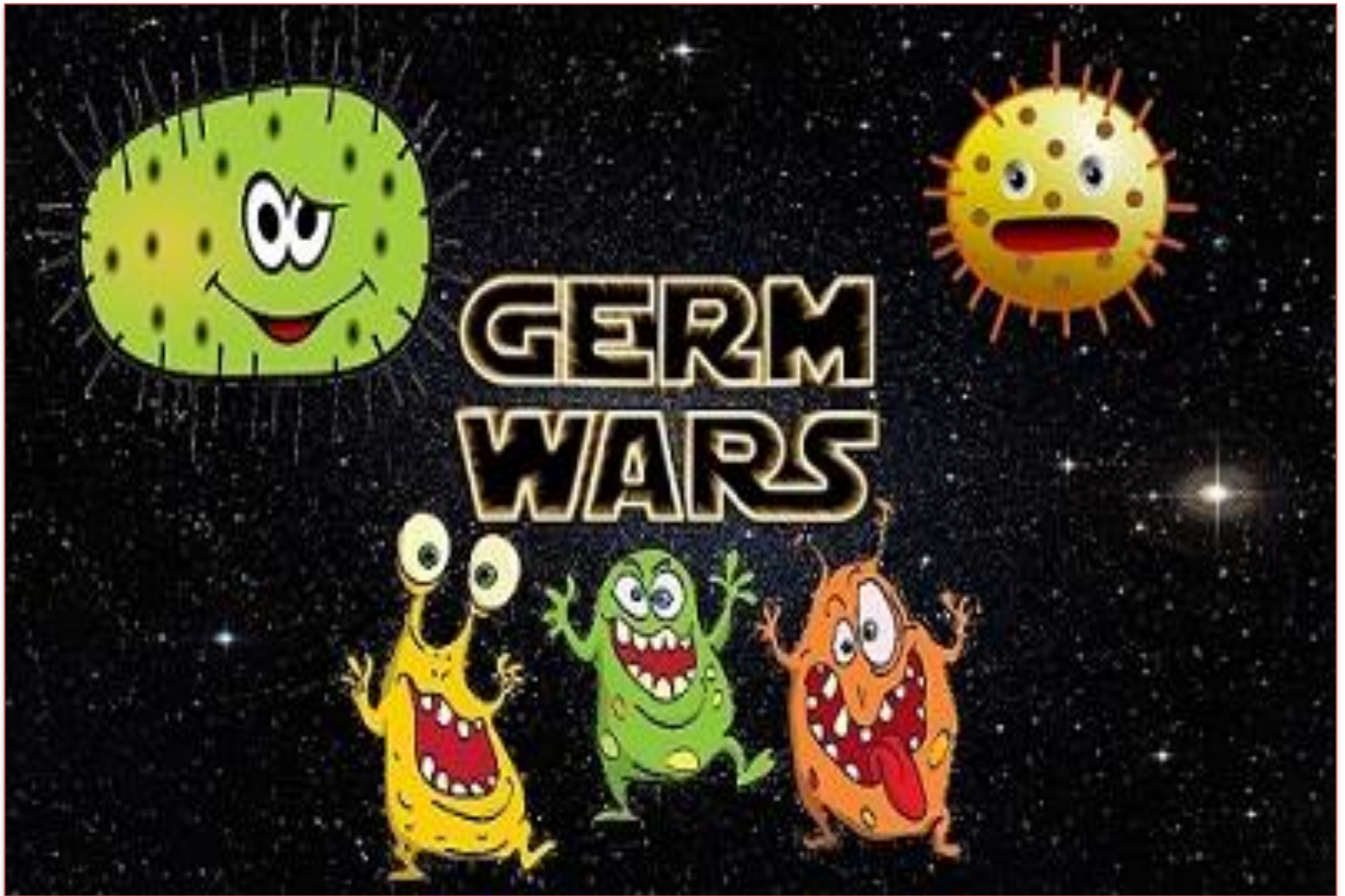
Amsterdam, **18 aprile 2016**
Riunione informale dei **Ministri della Salute**
dei 31 paesi europei ha come obiettivo prioritario:
**“La prevenzione della resistenza agli antibiotici, attraverso la
cooperazione tra i ministri della salute e dell'agricoltura in
un "One Health " come approccio, con tempi e metodi
comuni su obiettivi e risultati.”**

Roma, **21 Aprile 2016**
Ministero della Salute
Riunione con **“Stakeholders”** su :
“Piano Nazionale Antibiotico Resistenza”

Roma, **3 Maggio 2016**
Ministero Salute
Riunione con **Regioni Italiane** su:
“Piano Nazionale Antibiotico Resistenza”

Keys actions

1. Antibiotic resistance is an adverse effect of antibiotic therapy.
2. Antibiotic prescription and stewardship must be pillars of the medical education.
3. Surveillance systems must be representative and connected among countries and with animal / food surveillance.
4. Significant improvements cannot be achieved without political and cultural changes.



Grazie per l'attenzione