



UNIVERSITÀ
di VERONA

ZIONE E
LA PRATICA CLINICA

XII Workshop Nazionale

**TERAPIA
E PREVENZIONE
DELL'INFEZIONE
DA HIV
E MICRORGANISMI
EMERGENTI**

**09-10
GIUGNO
2021**



MDR e immunodepressione

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Declaration of
interest (DOI)

2016-2021

- Innovative Medicine Initiative (IMI)
- European Commission
- Joint Antimicrobial Initiatives
- Horizon 2020
- WHO
- ESCMID
- German Center Infectious Diseases Research (DZIF)
- GARDP

AIDS: IN MEMORIAM

SETH ALLEN
actor-director, 45MARIO AMAYA
art critic, 52ED ARMOUR
painter, 42WAY BANDY
makeup artist, 45LAUGHLIN BARKER
Perry Ellis
fashion executive, 37ROBERT DRIVAS
actor-director, 50KENN DUNCAN
dance photographer, 56PERRY ELLIS
fashion designer, 46ALLAN ESTES
artistic director, 29MICHEL POUCAULT
philosopher, 57ROBERT HAYES
Interview
magazine editor, 33DAVID HICKS
New York City Opera
director, 48LYN HILTON
record producer, 41ROCK HUDSON
actor, 59PAUL JACOBS
pianist, 53JOE MACDONALD
model, 37KENNETH MCGOWAN
photographer, 45ED MOCK
dancer, 48ROBERT MOORE
actor-director, 56NICOLAS MOUFARREGE
writer-artist, 36RONALD BENTLEY
New York City Opera
director, 48ED BRINKLEY
Hirsch & Adler
gallery manager, 37MARTIN BURGOYNE
artist, 24LINO CORREIA
interior designer, 45ANGELO DONGHIA
interior designer, 50ROBERT FRASER
art dealer, 43EDMUND GAULTNEY
art dealer, 39ROBERT GORDY
painter, 52JACK HABER
GQ magazine editor, 45ESME HAMMOND
jazz supporter
and friend, 66ROBIN JACOBSEN
interior designer, 45ROBERT LA TOURNEAUX
actor, 39THIERRY LE LURON
French comedian, 34PETER LESTER
Interview
magazine editor, 34BARRY LOWEN
TV executive, 50KLAUS NOMI
singer, 39STEPHEN PENDER
actor, 35HENRY POST
New York
magazine writer, 34CHARLES ROBERTS JR.
newspaper publisher, 30JAY ROGERS
art dealer, 30s

List of priorities of antimicrobial resistant bacteria



Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*²⁵

Other priority bacteria

Priority 1: critical

- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high

- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

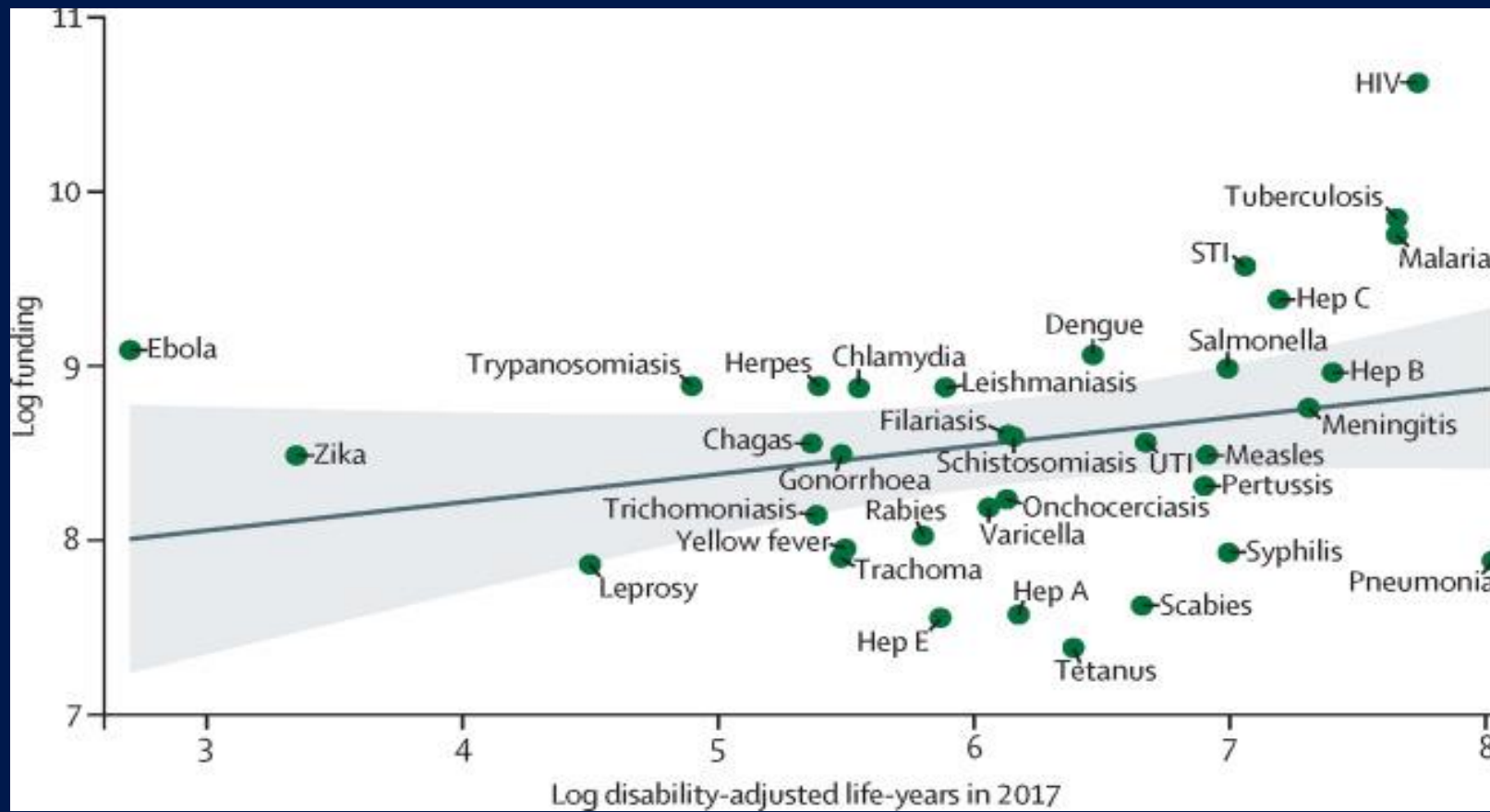
Priority 3: medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant

FIGURE 1

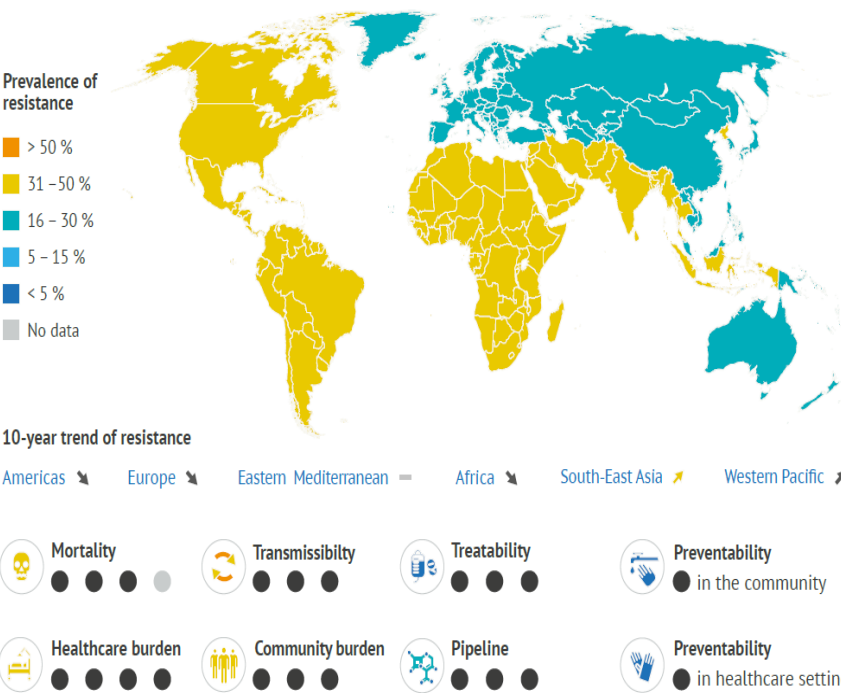


The allocation of US\$105 billion in global funding from G20 countries for infectious disease research 2000 - 2017

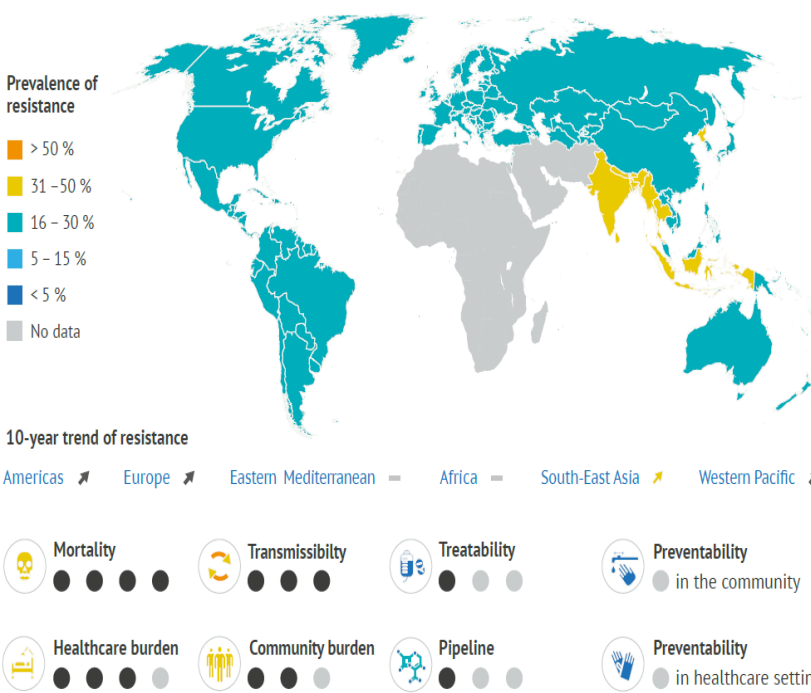


Knowledge of AMR pattern at global level

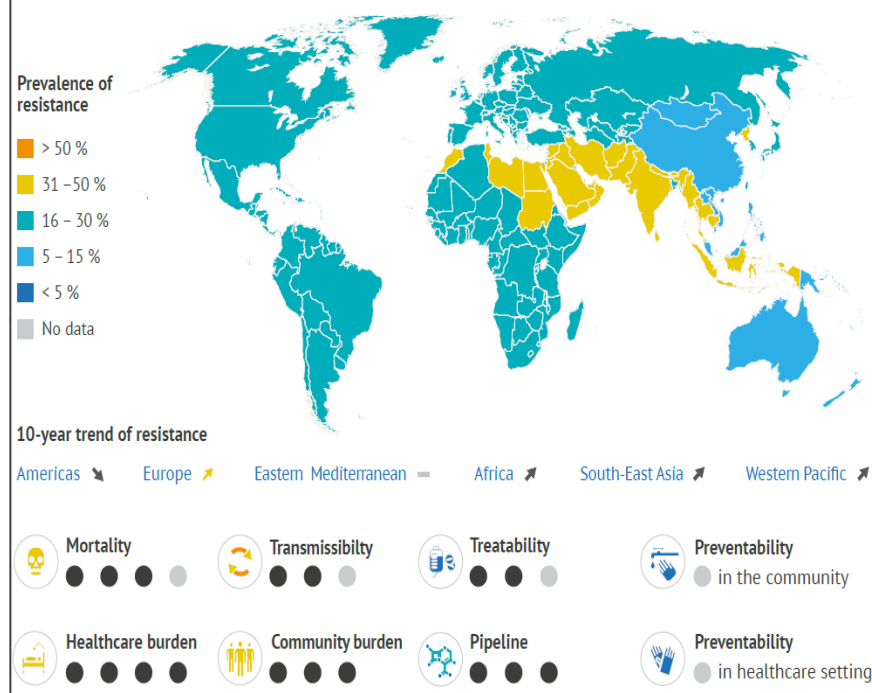
Staphylococcus aureus, methicillin-resistant (MR)



Pseudomonas aeruginosa, carbapenem-resistant (CR)



Klebsiella spp., third generation cephalosporin-resistant (3GCR)



AMR Worldwide

14,000 Patients Die

of *C.difficile* infection annually in the **USA**.⁽¹⁾ The use of antibiotics was a major contributing factor in up to 85% of cases.⁽²⁾



23,000 Patients Die Each Year as a result of **antibiotic-resistant infections** in the **USA**.⁽¹⁾



2,000,000 Infections per year contain bacteria that are resistant to one or more antibiotics in the **USA**.⁽¹⁾



11,000 Estimated Deaths caused by methicillin-resistant *Staphylococcus aureus* (**MRSA**) each year in the **USA**.⁽³⁾



25,000 Patients Die Each Year as a result of antibiotic-resistant infections in **Europe**.⁽⁵⁾



400,000 Infections per year with the 6 most frequent multi-drug resistant (MDR) bacteria, in 4 types of infection, in **Europe**.⁽⁶⁾



480,000 People Infected by drug-resistant TB strains in 2013 **Worldwide**.⁽⁴⁾



1 Child Dies Every 9 Minutes

from an infection caused by antibiotic-resistant bacteria in **India**.⁽⁷⁾



ANTIBIOTIC RESISTANCE THE GLOBAL THREAT

Antibiotic resistance – when bacteria change and cause antibiotics to fail – is happening **RIGHT NOW**, across the world

The full impact is unknown. There is no system in place to track antibiotic resistance globally



Without urgent action, many modern medicines could become obsolete, turning even common infections into deadly threats.



A GROWING CRISIS WORLDWIDE

In the **EUROPEAN UNION**, antibiotic resistance causes 25,000 deaths per year and 2.5m extra hospital days¹



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Obama administration proposes increased funding for antibiotic resistance, sustained investments for HIV

“There are only two infectious disease situations that can be considered inevitable, serious pandemic threats: influenza and antimicrobial resistance”

Mark Olshaker & Michael T. Osterholm, 2017

DEADLIEST ENEMY

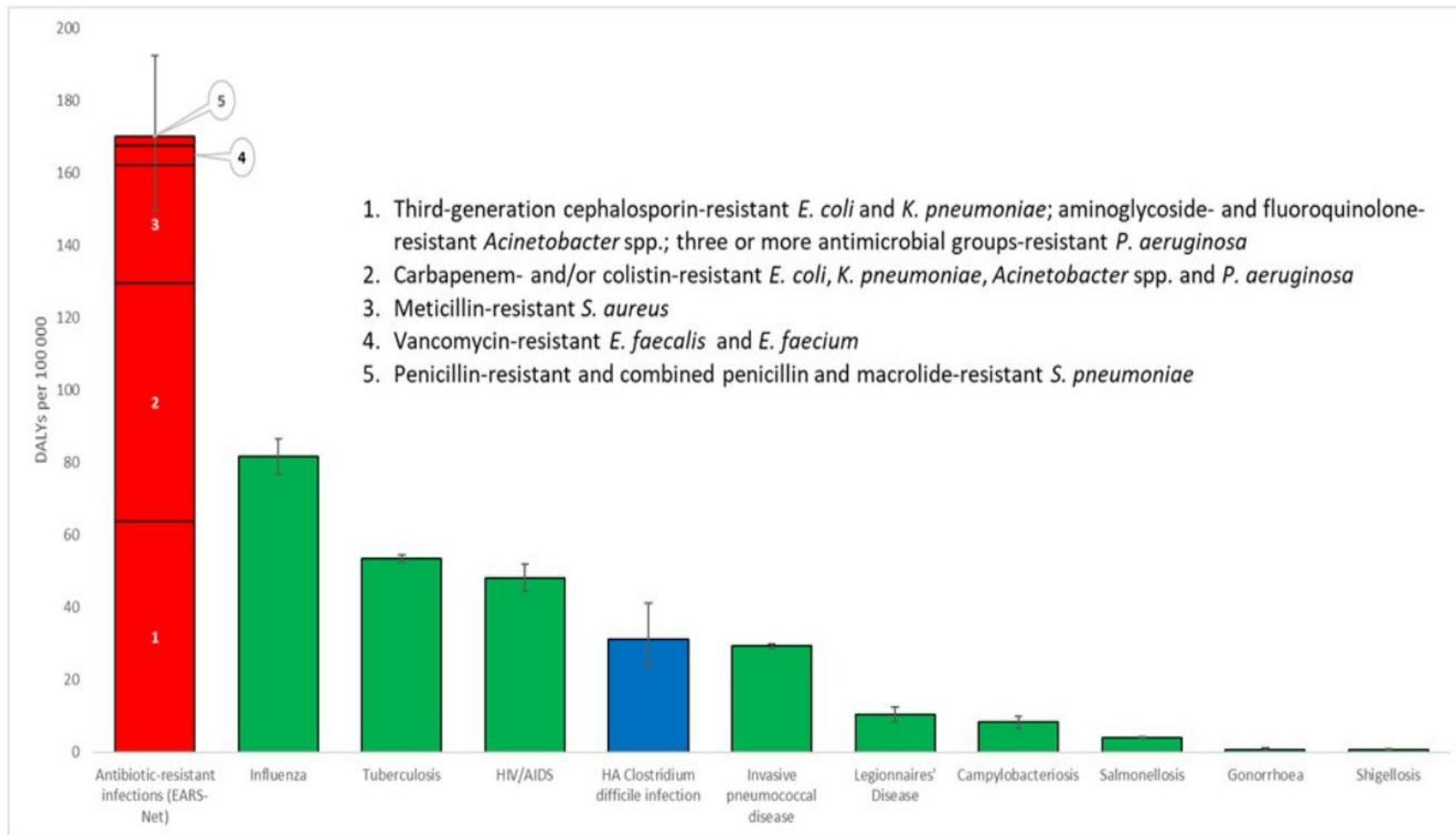
Michael T. Osterholm, PhD, MPH,
and Mark Olshaker



OUR WAR AGAINST KILLER GERMS



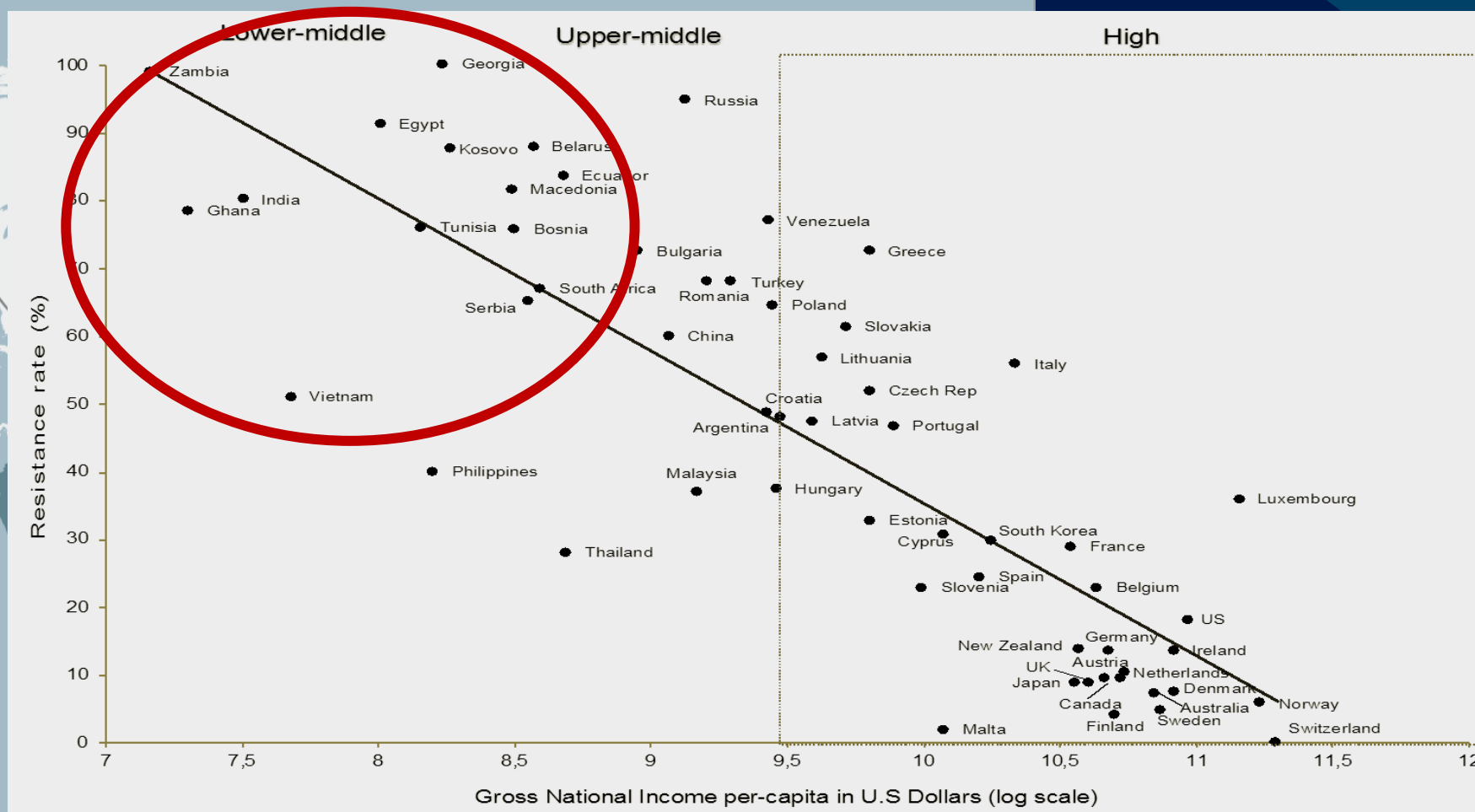
Burden is comparable to the combined burden of influenza, TB & HIV/AIDS



Adapted from: Cassini A, et al. Eurosurveillance 2018;23(16):pii=17-00454
Cassini A, et al. The Lancet Infectious Diseases. 5 November 2018

Impatto sui pazienti HIV?

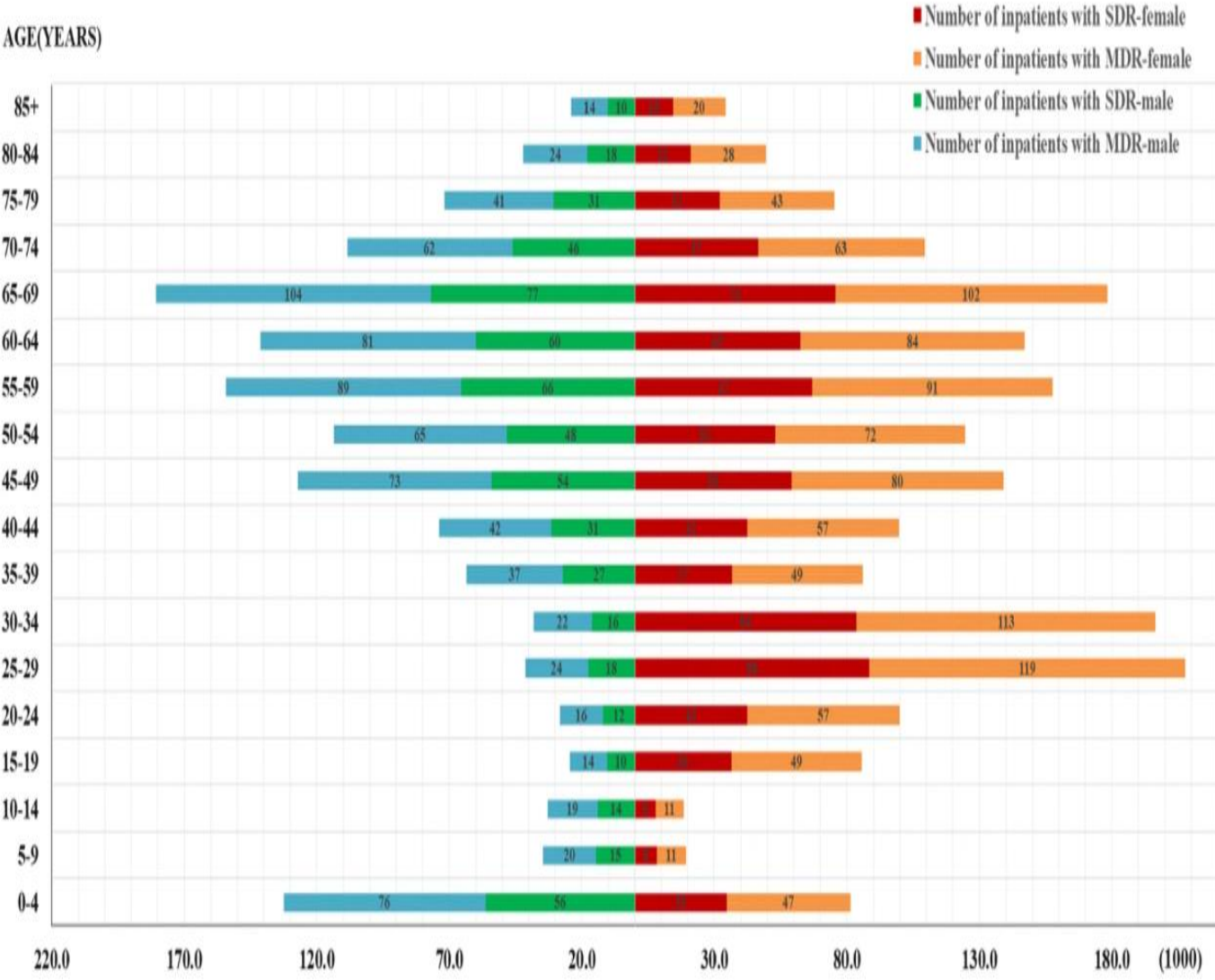
Deaths Attributable to Antimicrobial Resistance Every Year by 2050



Source: Review on Antimicrobial Resistance. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*. 2014.

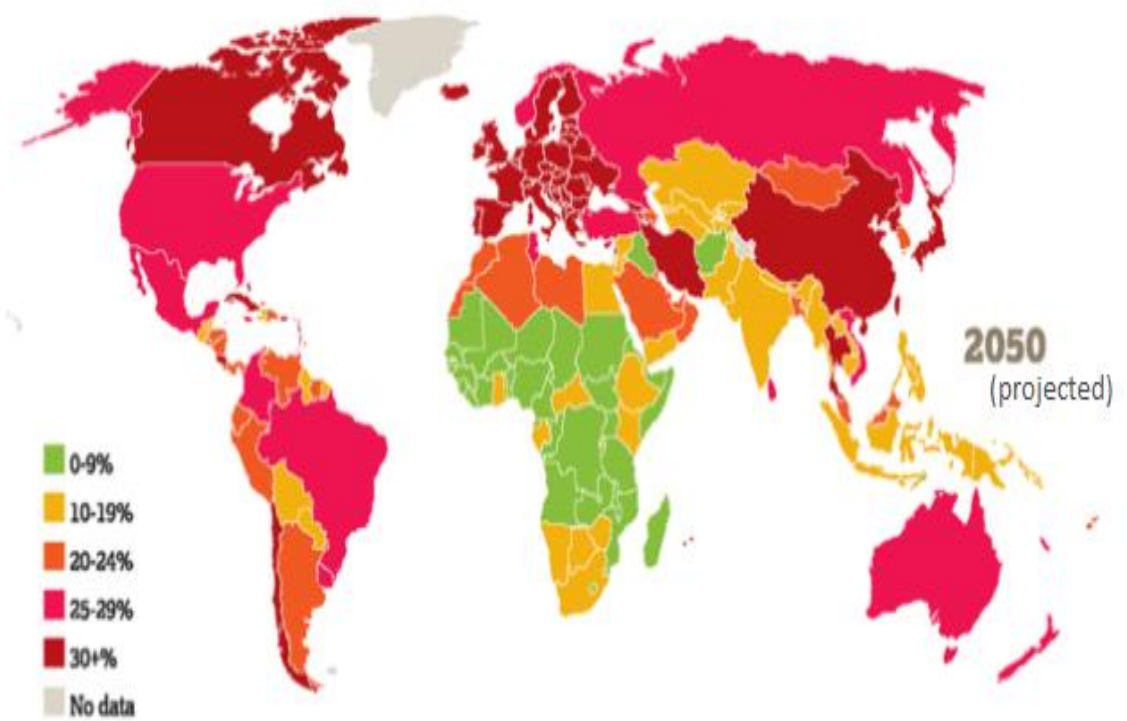
Savoldi & Tacconelli JAC 2019

From: [Economic burden of antibiotic resistance in China: a national level estimate for inpatients](#)



The estimated number of inpatients with antibiotic resistance in China. *SDR* single-drug resistance, *MDR* multiple-drug resistance

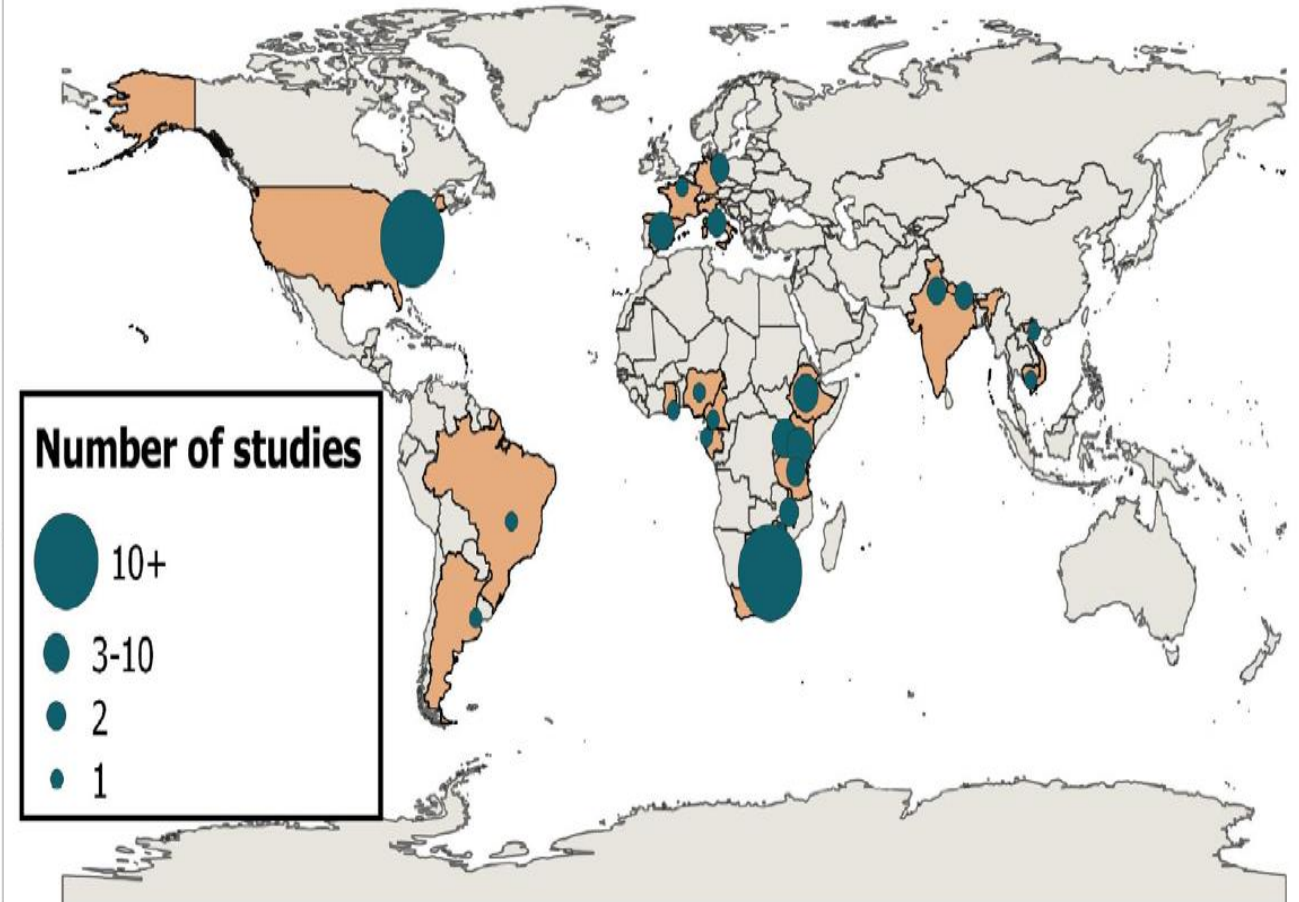
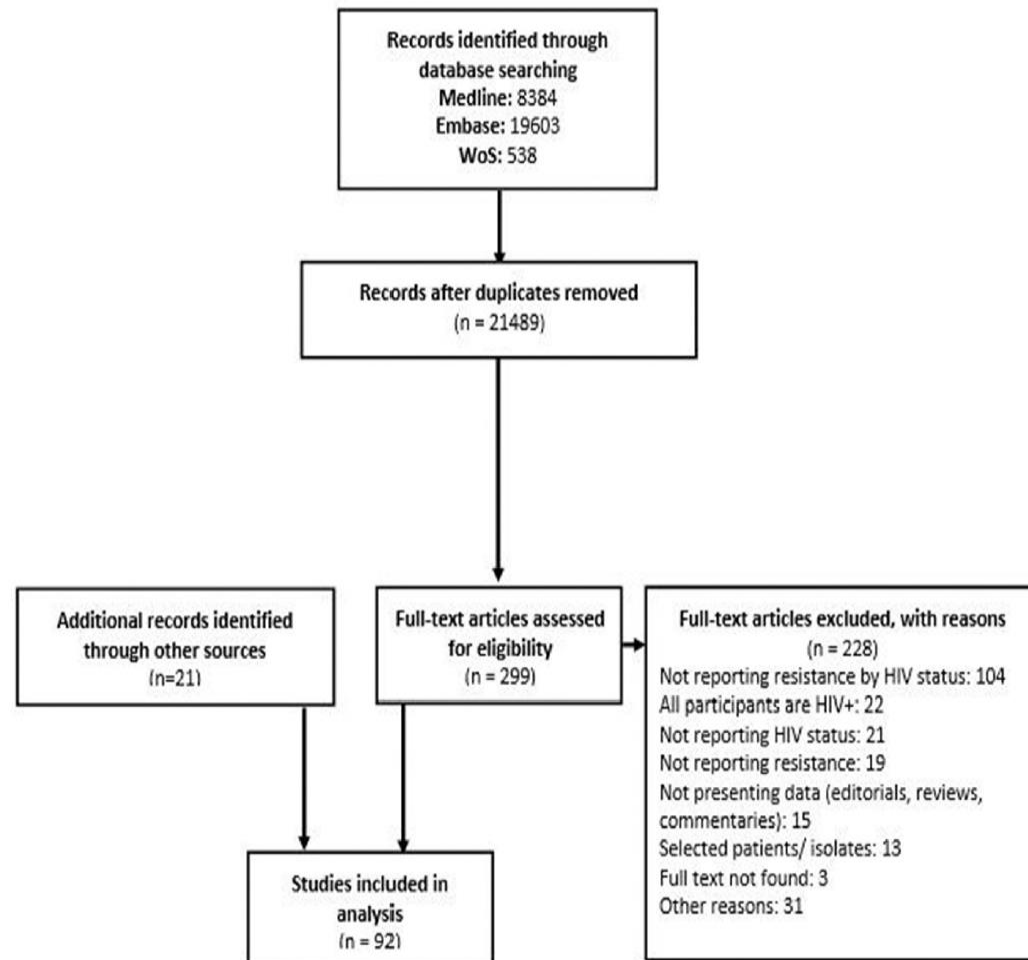
Zhen, ARIC 2021

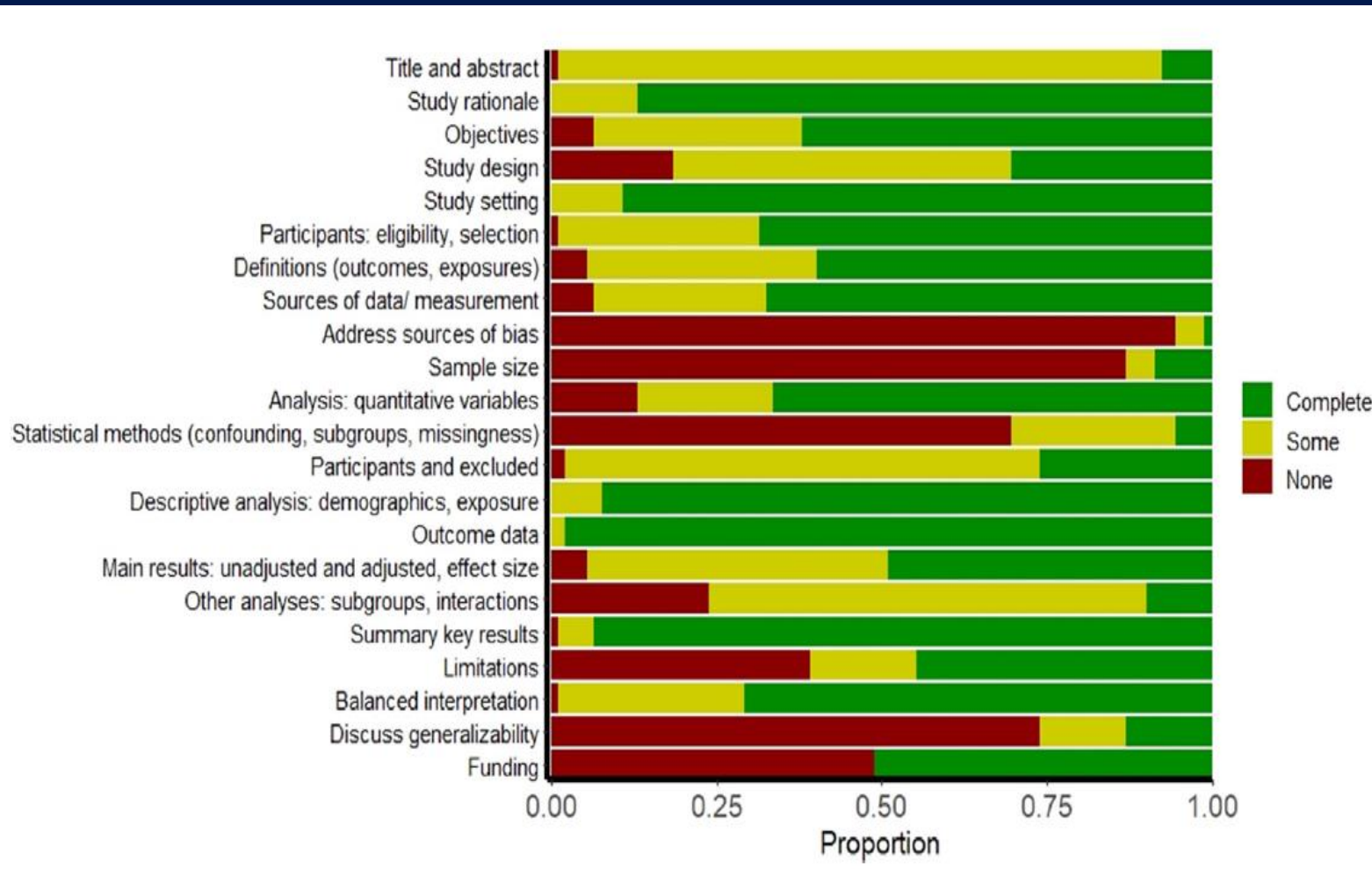


Popolazione > 60 anni

Evidenze su MDR e HIV

92 studies: 1995-2020





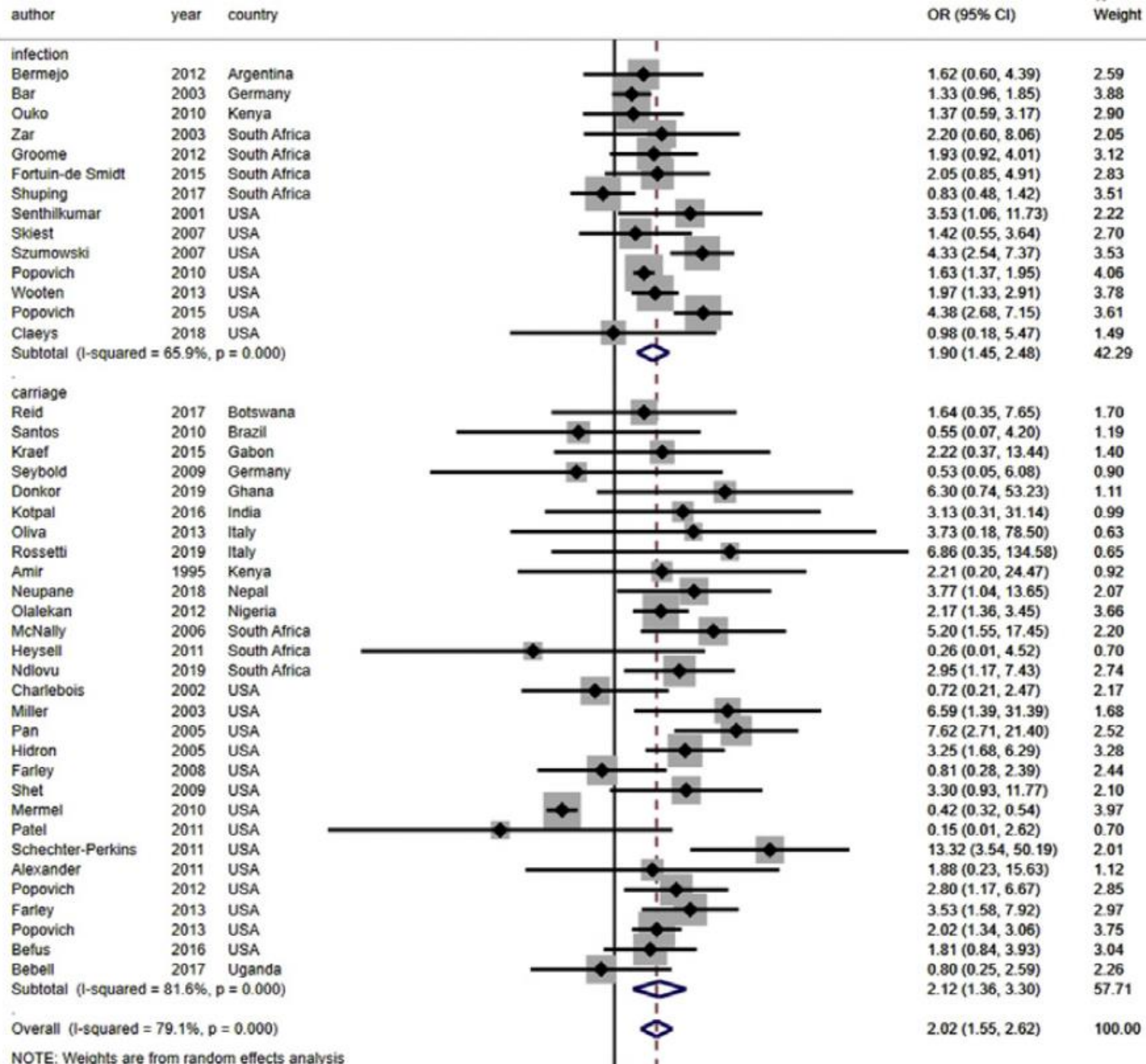
- Completeness of reporting (STROBE): moderate
- Modified Newcastle Ottawa Scale: moderate /low quality
7 studies high quality

Resistenza nei Gram-positivi

Antimicrobial resistance to selected drugs

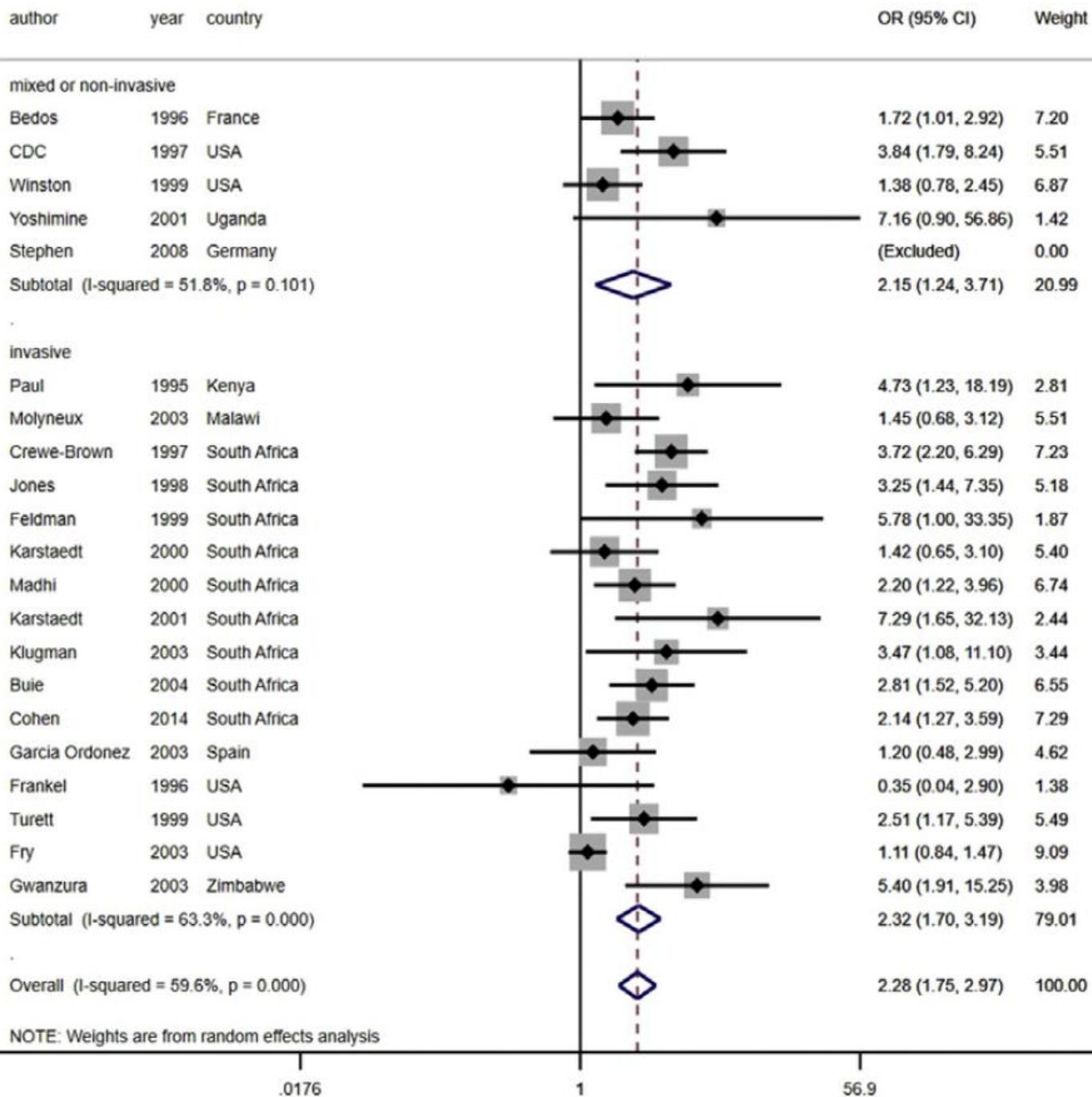
Organism	Antimicrobial	Number of studies reporting resistance by HIV status	Pooled prevalence of resistance (95%CI)	
			HIV+	HIV–
<i>Staphylococcus aureus</i> (infection)	MRSA	14	49% (32–65)	35% (25–44)
<i>S. aureus</i> (colonization)	MRSA	29	9% (7–11)	6% (4–8)
	Co-trimoxazole	5	65% (44–86)	55% (46–64)
<i>Streptococcus pneumoniae</i> (infection)	Penicillin	20	29% (23–36)	15% (11–19)
	Co-trimoxazole	7	38% (30–47)	20% (13–28)
	Tetracyclines	6	14% (8–20)	19% (12–26)
	Macrolides	6	8% (4–12)	8% (5–12)

Data were not pooled if there were three or fewer studies reporting prevalence by organism and drug class, or if the number of studies was small and estimates were highly heterogeneous. Studies where prevalence could not be calculated for both HIV-infected and non-infected individuals were also excluded. MRSA, methicillin-resistant *S. aureus*.



47 studies
1.90 (95%CI 1.45-2.48)
higher odds for infection
with methicillin-resistant
S. aureus

Ia S. pneumoniae non-susceptibility



28 studies

2.28 (95%CI 1.75-2.97) higher odds of infection with S. pneumoniae with decreased penicillin susceptibility

Resistance/ organism	Category	Type	Studies	OR (95% CI)
Methicillin resistant <i>S. aureus</i>	All studies	Carriage	29	2.12 (1.36-3.30)
		Infection	14	1.90 (1.45-2.48)
	Pre-ART	Carriage	2	4.37 (1.48-12.90)
		Infection	2	2.84 (1.18-6.85)
	ART	Carriage	27	2.04 (1.29-3.22)
		Infection	11	1.88 (1.40-2.53)
	Published since 2015	Carriage	9	2.17 (1.41-3.33)
		Infection	4	1.75 (0.65-4.69)
	LMIC	Carriage	12	2.21 (1.60-3.05)
		Infection	6	1.39 (0.98-1.96)
	HIC	Carriage	17	2.14 (1.15-4.00)
		Infection	8	2.19 (1.54-3.12)
	CD4 <200	Carriage	2	1.02 (0.13-7.76)
		Infection	3	1.67 (1.41-1.99)
	CD4 ≥200	Carriage	11	2.42 (1.78-3.28)
		Infection	3	3.67 (2.31-5.85)
	ART <50%	Carriage	4	3.33 (1.67-6.67)
		Infection	1	3.53 (1.06-11.73)
	ART ≥50%	Carriage	6	2.99 (1.65-5.43)
		Infection	2	3.24 (1.58-6.62)
Penicillin non- susceptible <i>S. pneumoniae</i>	All studies	Infection	20	2.28 (1.75-2.97)
	Pre-ART	Infection	18	2.39 (1.78-3.22)
	ART	Infection	2	1.82 (1.09-3.03)
	Published after 2010	Infection	1	2.14 (1.27-3.59)
	LMIC	Infection	13	2.74 (2.14-3.49)

MDR – Gram negative

resistance to third-generation cephalosporins and co-trimoxazole

- 7 studies
- *E. coli* / *K. pneumoniae*
 - 849 HIV-infected and 12 573 non-HIV-infected individuals
 - +++ BSI /UTI
- *E. coli* infections: OR 1.59 (95%CI 0.83-3.05)
- *K. pneumoniae*: OR 2.43 (95%CI 1.36-4.32)

E' piu' facile oggi prescrivere una terapia per un paziente con HIV naive o per una UTI recidivante in una donna di 50 anni?

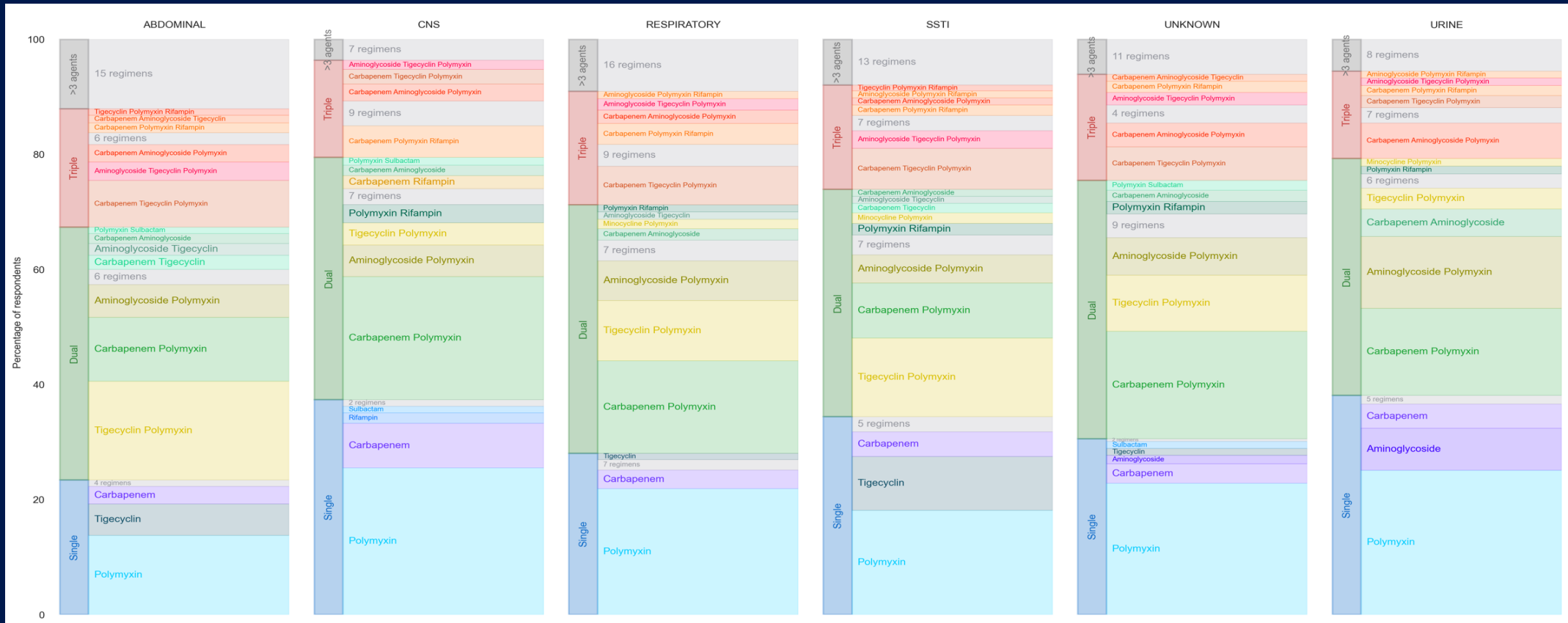
E' piu' facile oggi prescrivere una terapia in un paziente con AIDS, diagnosi tardiva e resistenze multiple o in un paziente in TI con sospetta infezione da KPC?

Clinical management of sepsis caused by CR-GN In real life

36-item survey, 1012 respondents, 95 countries, 687 hospitals, worldwide

40 regimens in *Acinetobacter* spp.

100 regimens in Enterobacterales



Retrospective cohort study 2016 - 2018, 46 hospitals in the Michigan Hospital Medicine Safety Consortium.

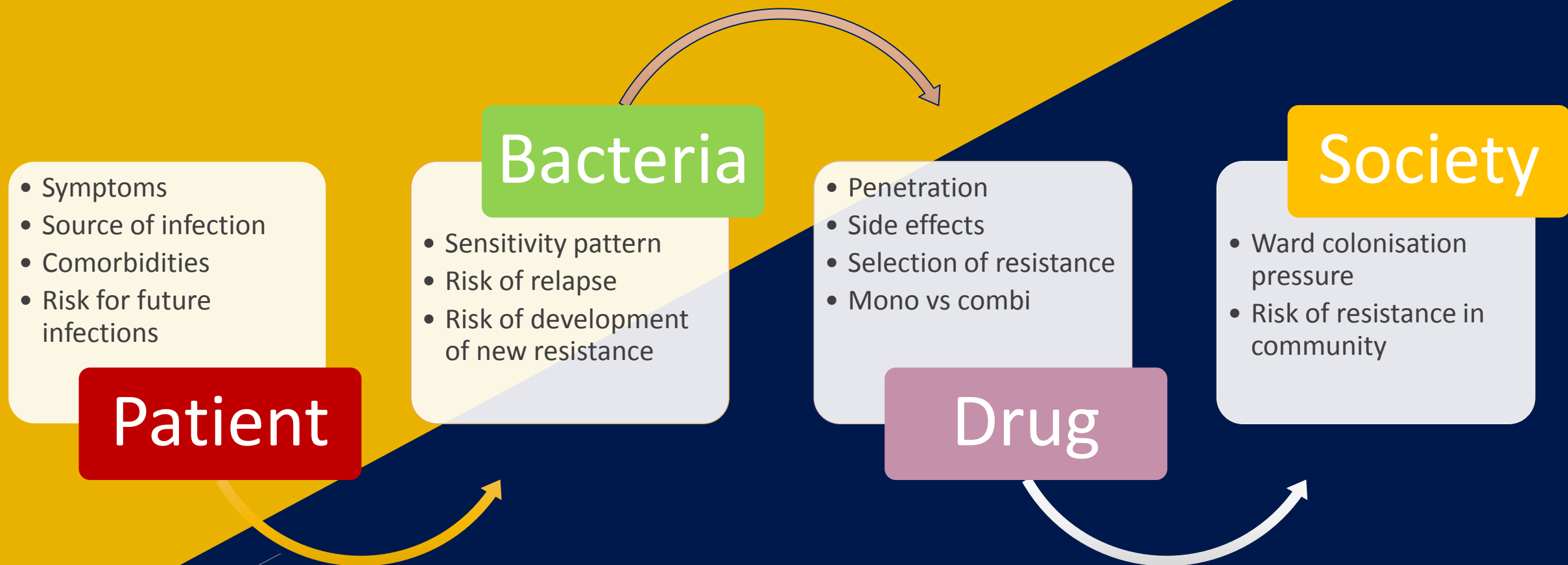
A total of 2733 hospitalized medical patients with ASB, defined as a positive urine culture without any documented signs or symptoms attributable to urinary tract infection.

A total of 2259 patients (82.7%) were treated with antibiotics for a median of 7 days (IQR, 4-9 days).

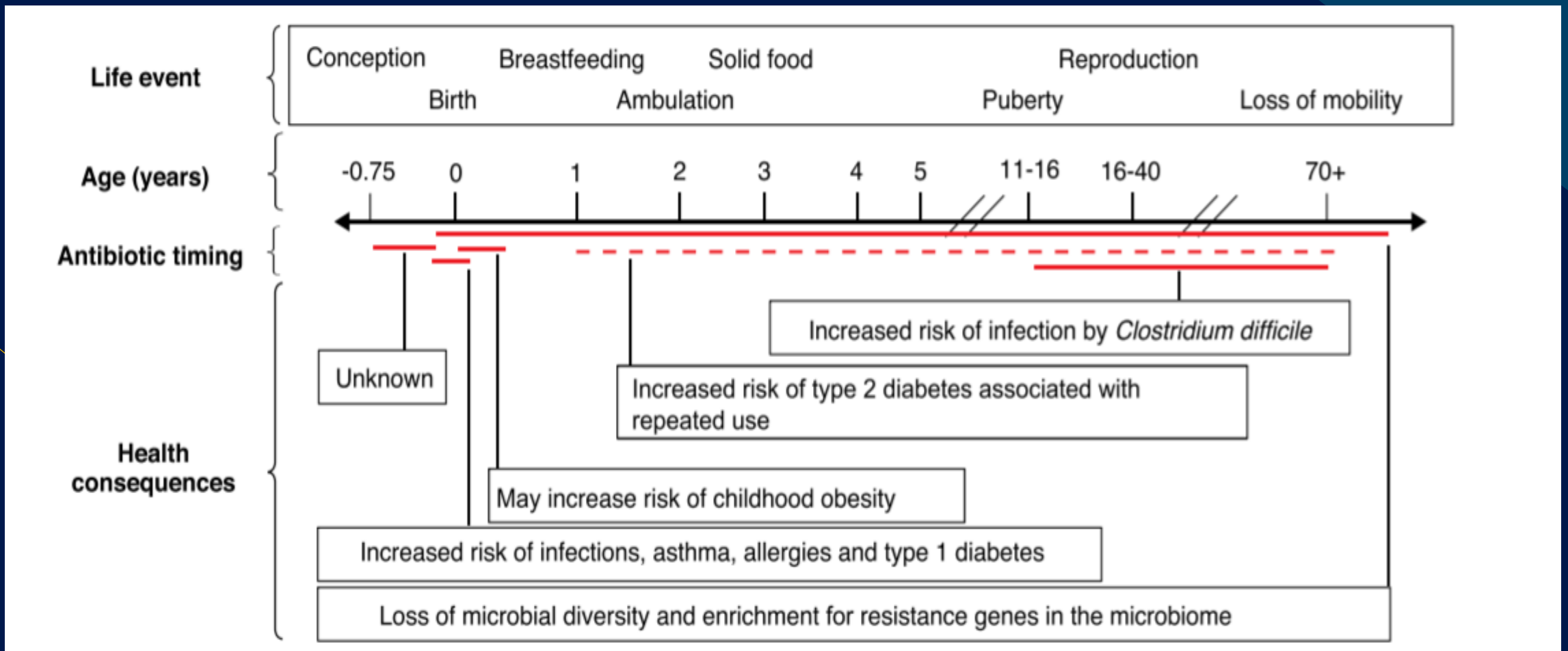
Treatment of ASB was associated with longer duration of hospitalization after urine testing

Table 4. Outcomes for Treatment vs No Treatment for Asymptomatic Bacteriuria (N = 2733)

Outcome ^a	No. (%)		Unadjusted Odds Ratio (95% CI)	Unadjusted P Value	Adjusted Odds Ratio (95% CI)	Adjusted P Value
	Antibiotics (n = 2259)	No Antibiotics (n = 474)				
30-d Postdischarge mortality ^b	63 (2.8)	11 (2.3)	1.22 (0.66-2.26)	.53	1.34 (0.72-2.49)	.35
30-d Postdischarge readmission ^b	362 (16.0)	66 (13.9)	1.16 (0.87-1.56)	.31	1.29 (0.92-1.81)	.14
30-d Postdischarge ED visit ^b	272 (12.0)	62 (13.1)	0.91 (0.70-1.18)	.48	0.90 (0.66-1.24)	.52
Discharge to post-acute care facility ^{b,c}	811 (35.9)	102 (21.5)	1.98 (1.58-2.48)	<.001	1.19 (0.90-1.57)	.22
<i>Clostridioides difficile</i> infection ^d	14 (0.6)	2 (0.4)	1.39 (0.41-4.68)	.59	0.88 (0.20-3.86)	.86
Duration of hospitalization, median (IQR), d ^e	4 (3-6)	3 (2-5)	1.37 (1.28-1.47) ^f	<.001	1.37 (1.28-1.47) ^f	<.001



Health consequences linked to the disruption of human-associated microbiota involving antibiotic use during development and adulthood



Evidenza Stewardship

Guideline-adherent empirical therapy was associated with a RR for mortality of **35%**

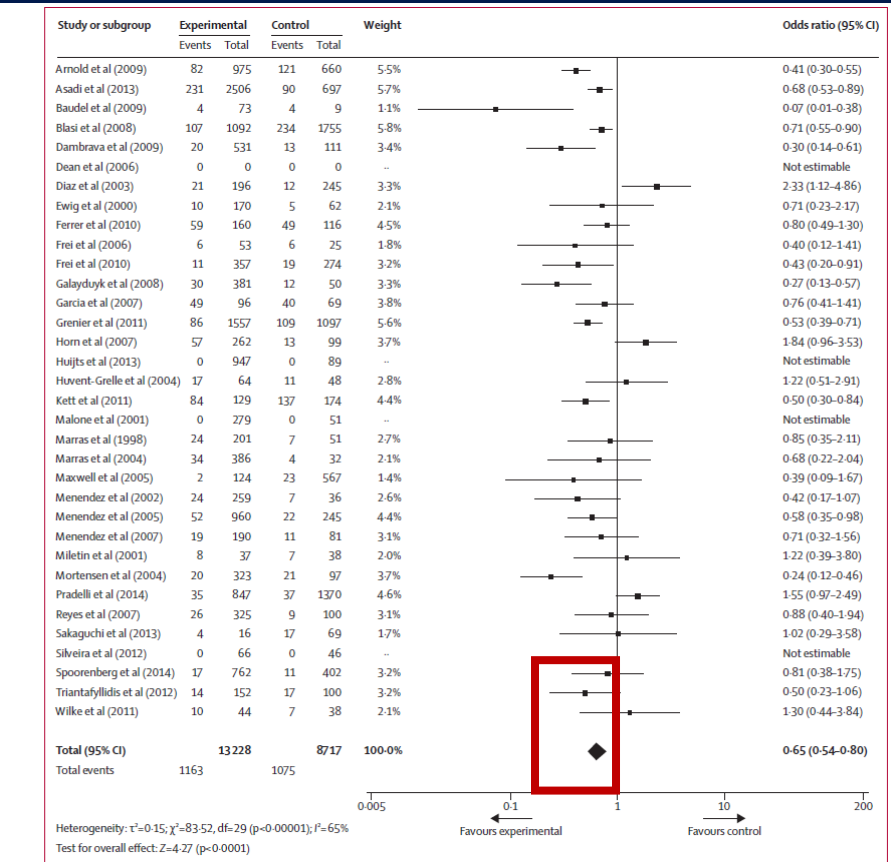


Figure 2: Effect on mortality of prescribing empirical antimicrobial therapy according to guidelines

Schuts, Lancet Infect Dis 2016

Antibiotic stewardship interventions was associated with a reduction of incidence of MDR-GNB by **48%**

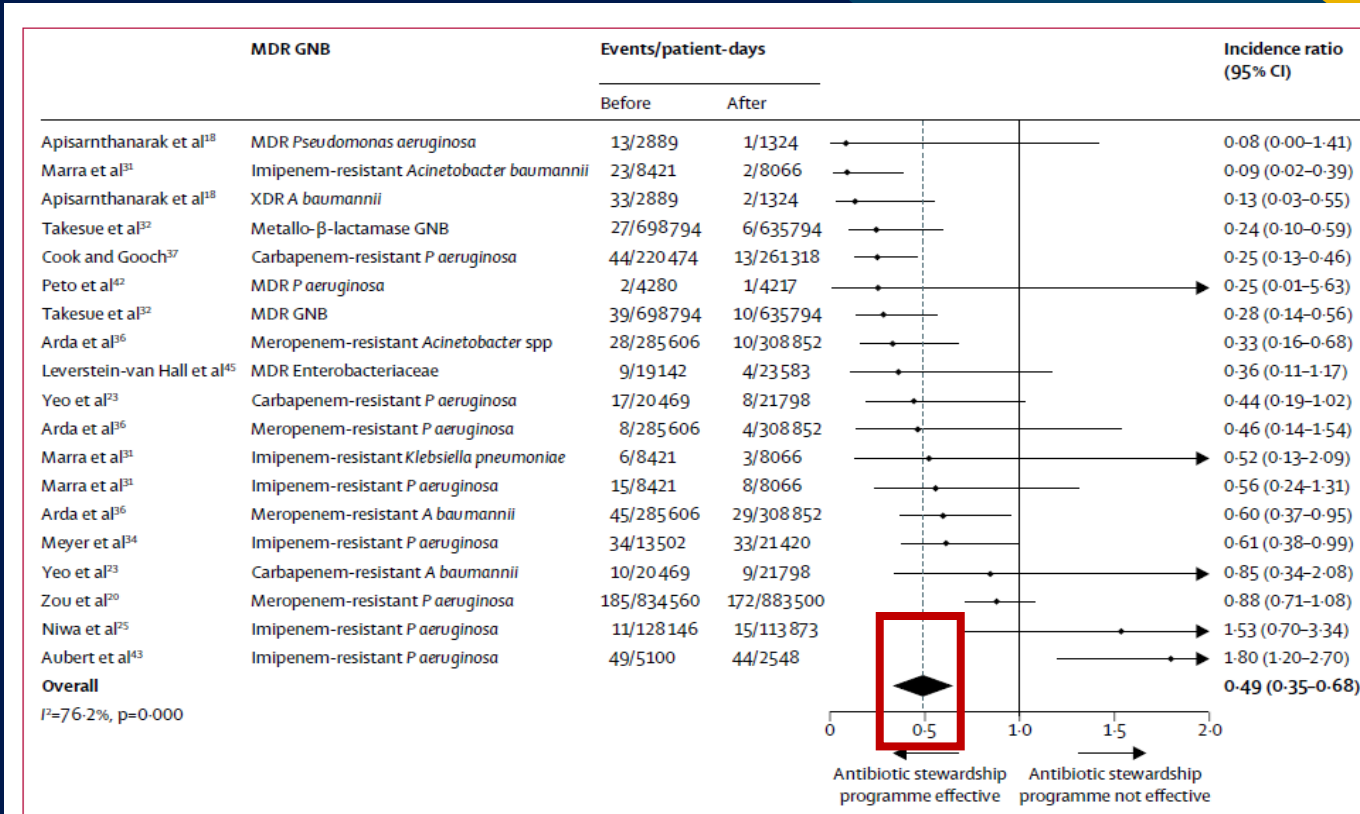


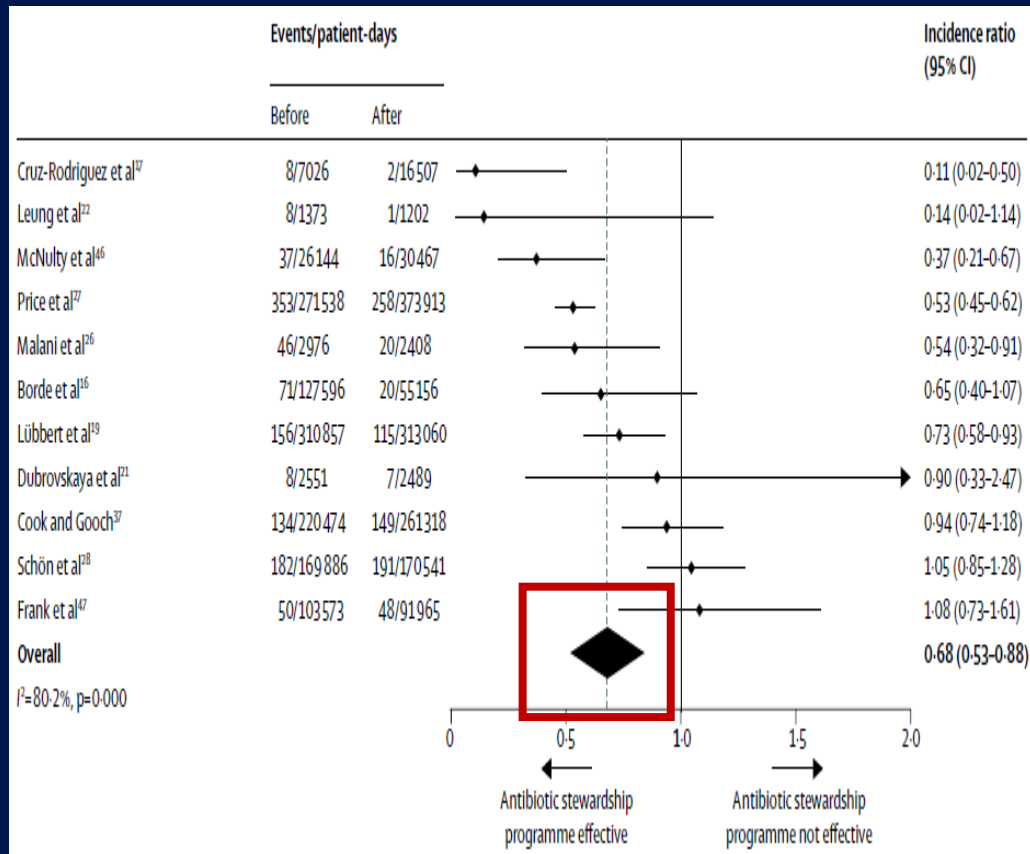
Figure 2: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB
GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

Tacconelli, Lancet Infect Dis 2017

Evidence

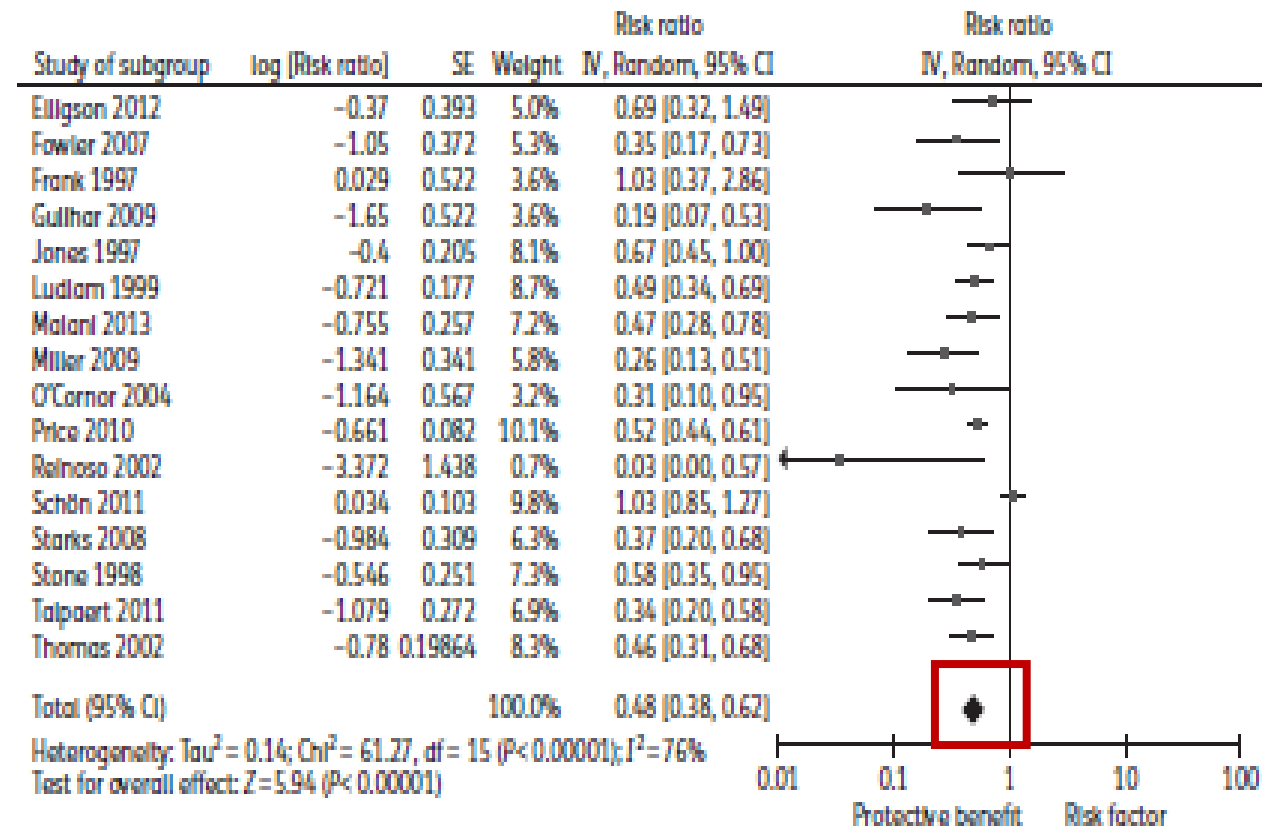
Antibiotic Stewardship

ATBS intervention was associated with a reduction of incidence of CDI by **32% (IR 0.68, 0.53–0.88; p=0.0029)**



Tacconelli Lancet Infect Dis 2017

Restrictive ATBS were particularly effective in geriatric settings



Feazel JAC 2014

Pooled RR 0.48, 95%CI 0.38 – 0.62

ATBS plus IC and CDI

4-year, non-restrictive, multi-faceted intervention
Intervention: ATBS plus ICPM (education)

ITS study design
42886 patients evaluated in ED
receiving an antibiotic treatment

NOT **antibiOTika**
RETTE LEBEN

1. **Übermäßiger Einsatz und unsachgemäßer Gebrauch von Antibiotika ist ein Hauptgrund für Antibiotika-Resistenz**
2. **Antibiotika-Resistenz und damit verbundene Mortalität steigen weltweit**
3. **Die Antibiotika-"Pipeline" ist derzeit leer**



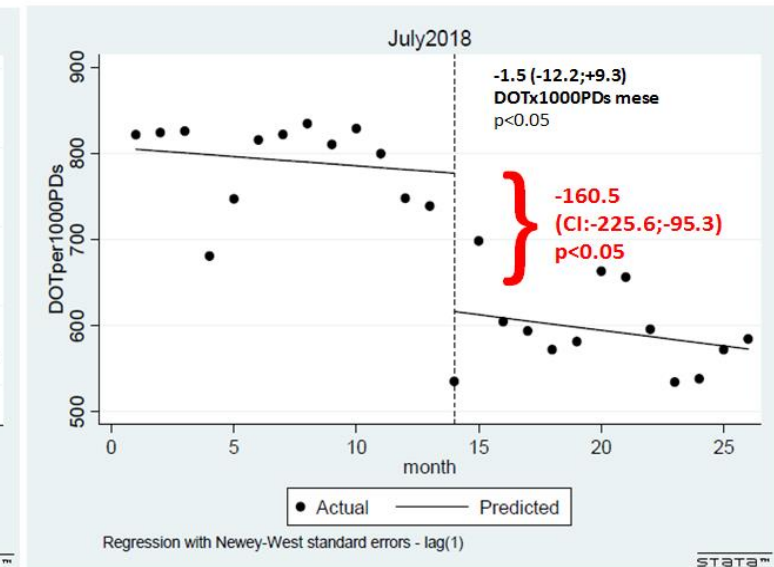
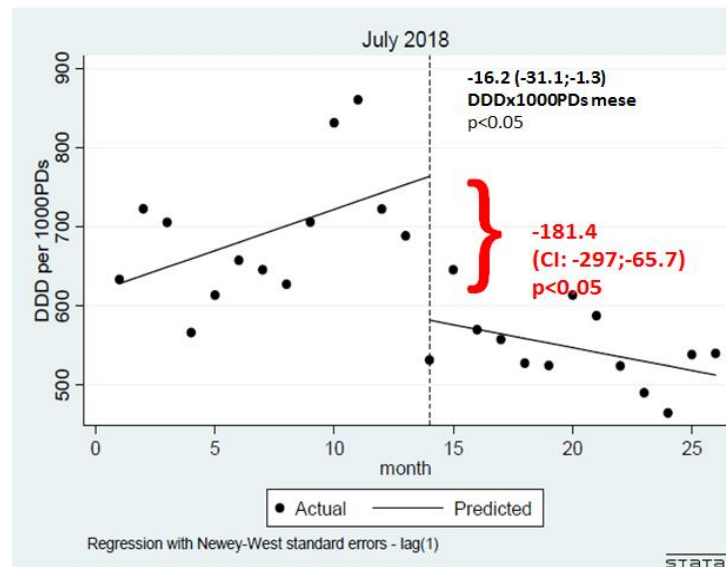
**Kein Patient sollte
unnötig Antibiotika
bekommen**

NOT ist ein Projekt der UKT
gegen übermäßigen Gebrauch von Antibiotika

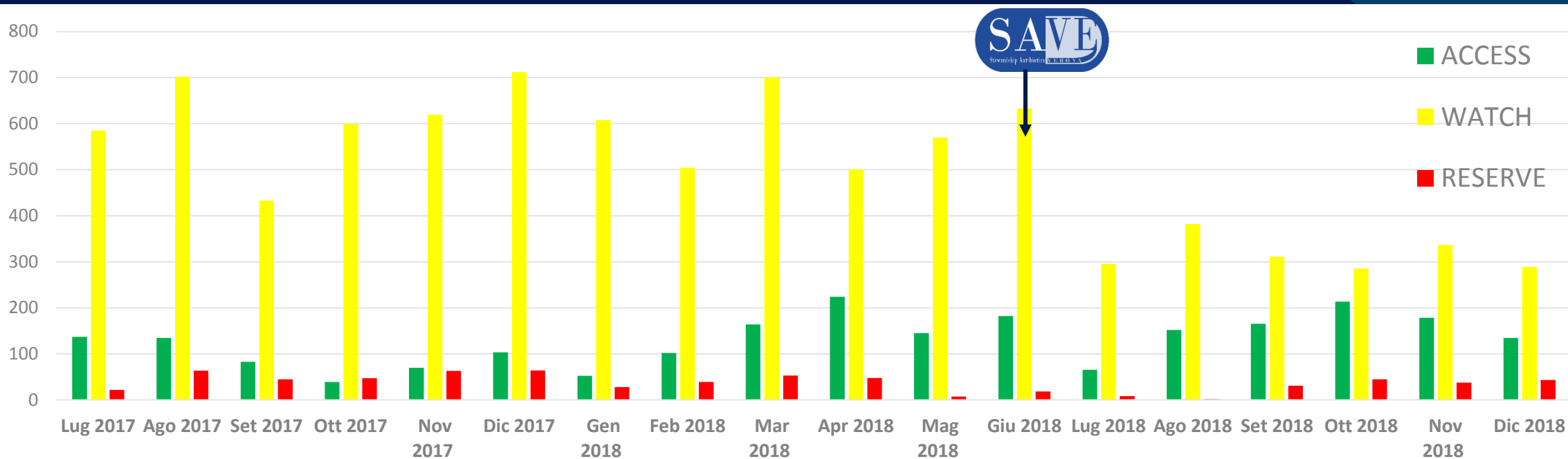
	140	Phase I	Phase II	Phase III	Phase IV	
INCIDENCE RATE OF <i>C. DIFFICILE</i> INFECTIONS per 100 patient days						
Study phase	Baseline level (β ₀)	Baseline slope	Change in level (CI 95%)	P value	Change in slope (CI 95%)	P value
Phase I	0.80	0.12	—	—	—	—
Phase II	—	—	−0.45 (−0.52 to 0.43)	0.847	0.04 (−0.01 to 0.09)	0.133
Phase III	—	—	−0.23 (−0.75 to −0.29)	0.381	−0.06 (−0.10 to −0.01)	0.014
Phase IV	—	—	0.11 (−0.31 to 0.54)	0.588	0.002 (−0.05 to 0.05)	0.946

- ANTIBIOTICI + EDUCAZIONE = SALUTE

AREA MEDICO-GERIATRICA consumo antibiotici DDD e DOT



ANTIMICROBIAL CONSUMPTION: DOT CLASSIFICAZIONE AWARE OMS

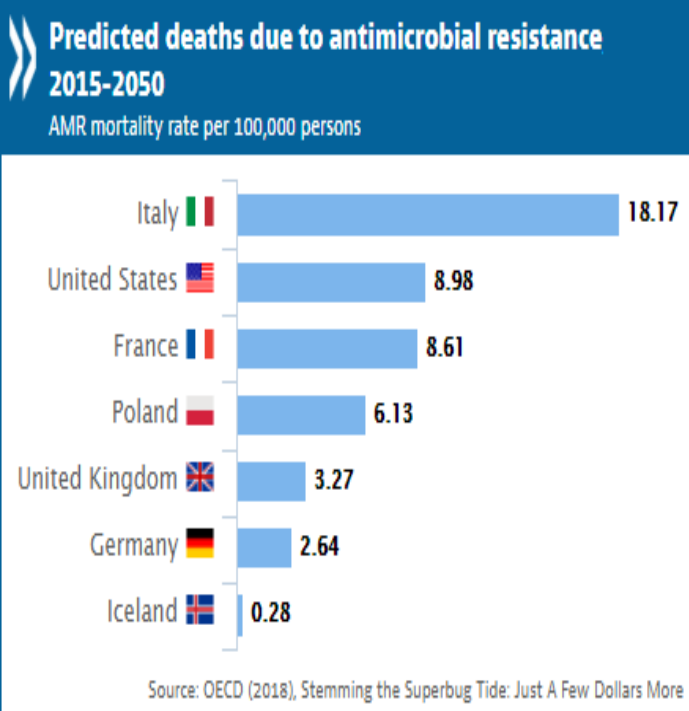


DOT/1000gg	before						after						media before	media after	p ≤ 0,05
ACCESS	135,8	134,6	72,2	43,8	81,8	82,6	65,5	166,4	161,9	213,5	171,6	133,1	92	152	0,0376
WATCH	585,1	701,9	433,1	599,8	620,4	712,8	295,7	381,9	310,8	285,6	340,5	288,7	609	317	0,0001
RESERVE	26,0	65,1	55,6	54,2	65,2	89,2	8,4	1,6	34,4	44,7	40,5	44,8	59	29	0,0252

QUADRO 1: TERAPIA EMPIRICA DELLE INFEZIONI DELLE VIE URINARIE

 minore impatto ecologico  consulenza per prosecuzione terapia  consulenza obbligatoria entro 48h

TIPO DI INFEZIONE	QUADRO	ALTERNATIVE	DURATA
Infezione delle vie urinarie (in assenza di segni e sintomi sistemici)	QUADRO 2: BATTERIURIA ASINTOMATICA*		
	Definizione: presenza di una o più urino-colture positive ad una carica di almeno 10 ⁵ CFU/ml in assenza di segni o sintomi di infezione		
	QUANDO TRATTARE	QUANDO NON TRATTARE	
	- prima di procedure urologiche: post-nefrostomia/ - procedure endourologiche - un'interruzione di gravidanza	- diabete mellito - trapianto di rene oltre il 1° mese - presenza di catetere urinario, <i>stent</i> ureterale o derivazioni urinarie - neutropenia - uropatia ostruttiva o anomalia funzionale del tratto urinario	
	NOTA: la sola positività all'urino-coltura o allo <i>stick</i> -urine non costituisce indicazione ad inviare urino-coltura. Per le indicazioni all'esecuzione di urino-coltura in paziente portatore di catetere vescicale vedere Figura 1.		
	Complicazione	Se anamnesi di IVU da germi MDR nei 12 mesi precedenti	Se necessario iniziare una terapia empirica
		Preferibile attendere l'antibiogramma	fosfomicina trometamolo 3 g q48h (proseguire con 3 dosi totali se sensibile)
			7 gg 



Cosa fare?

1. La **prescrizione corretta dell'antibiotico** è un **diritto** del paziente ed un **dovere** dell'operatore sanitario
1. È necessario sviluppare momenti educazionali indipendenti e corsi di studio dedicati nel corso di Medicina
2. La discussione con esperti senza conflitti di interesse sul posizionamento delle ultime molecole riveste un ruolo importante
3. Definire indicazioni di terapia locale:
 - Selezione delle molecole a basso impatto ecologico (vedi classificazione AWARE di OMS)
 - Definire la durata della terapia
 - Definire le indicazioni per l'associazione degli antibiotici
 - Attenzione massima alla prescrizione empirica e alla de-escalation dopo 48-72 ore
5. **AUDIT interni periodici !!!!!**
6. Definire protocolli di terapia antibiotica nei pazienti con infezione da SARS-CoV-2 (solo se co-infezione...!)



1. Define leadership, budget, personnel
2. Invite for dinner your microbiologist
3. Define your targets
4. Define the settings
5. Choose your indicators (including for side effects)
6. Share a bottle of Italian wine with your infection control practitioner
7. Revise careful national or regional guidelines and stay update with new studies on stewardship
8. Go multidisciplinary
9. Get married with IT expert
10. Let's do it together

<https://epi-net.eu/publications/>

About Activities Network News & Events Newsletter Resources

**Bridging the gap between
human and animal AMR
surveillance and antibiotic policy
and stewardship**



ARCH NET

excellence in AMR research - May 18, 2020 Progress against project objectives II - April 29, 2020 COVID-19: how antimicrobial stewardship programmes can assist - March 30, 2020 ARCH at ECCMID 2020, Paris - January 28, 2020

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Which resistant pathogens should be targeted

3.1) Essential

Monitor methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, carbapenem-resistant Gram-negatives, ESBL-producing bacteria and colistin resistant Gram-negative bacteria in all blood cultures and *Clostridioides difficile*.

3.2) Essential

In highly endemic settings for tuberculosis, check availability of local data on resistance in tuberculosis and consider having a section of the periodic report summarising most important information

3.3) Essential

Before starting a surveillance program, ensure minimum infrastructural requirements and alignment with quality control programs to support AMR surveillance.

3.4) Essential

Monitor antibiotic resistance to new antibiotics in settings highly endemic for multidrug resistant Gram negatives.

3.5) Desirable

Monitor resistance in *Candida* spp. if the stewardship intervention is targeting institutions/wards with high rates of invasive fungal infections (i.e. haematology, transplant centre, ward with high consumption of broad spectrum antibiotics).

How should resistance be monitored

3.6) Desirable

Monitor MICs (or inhibition zones) of resistant bacteria of primary clinical importance at the local/unit level.

3.7) Desirable

Where resources allow, monitor molecular mechanisms of resistance in clinically-relevant strains according to the antimicrobial stewardship team.

Should non-clinical samples (screening and colonisation status) be monitored

3.8) Desirable

Monitor resistance in screening samples in settings with infection control measures applied to colonised patients (e.g. targeting screening and contact precautions, preventive isolation).

Which time interval for reporting

JAC Dec 2020

Downloadable checklists from the website

Numerose posizioni disponibili per ricerca

Specializzandi per stage on stewardship
nel progetto SAVE (da 4 a 12 mesi)



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