# Θεραπεία Λοιμώξεων από Πολυανθεκτικά Gram-αρνητικά Βακτήρια

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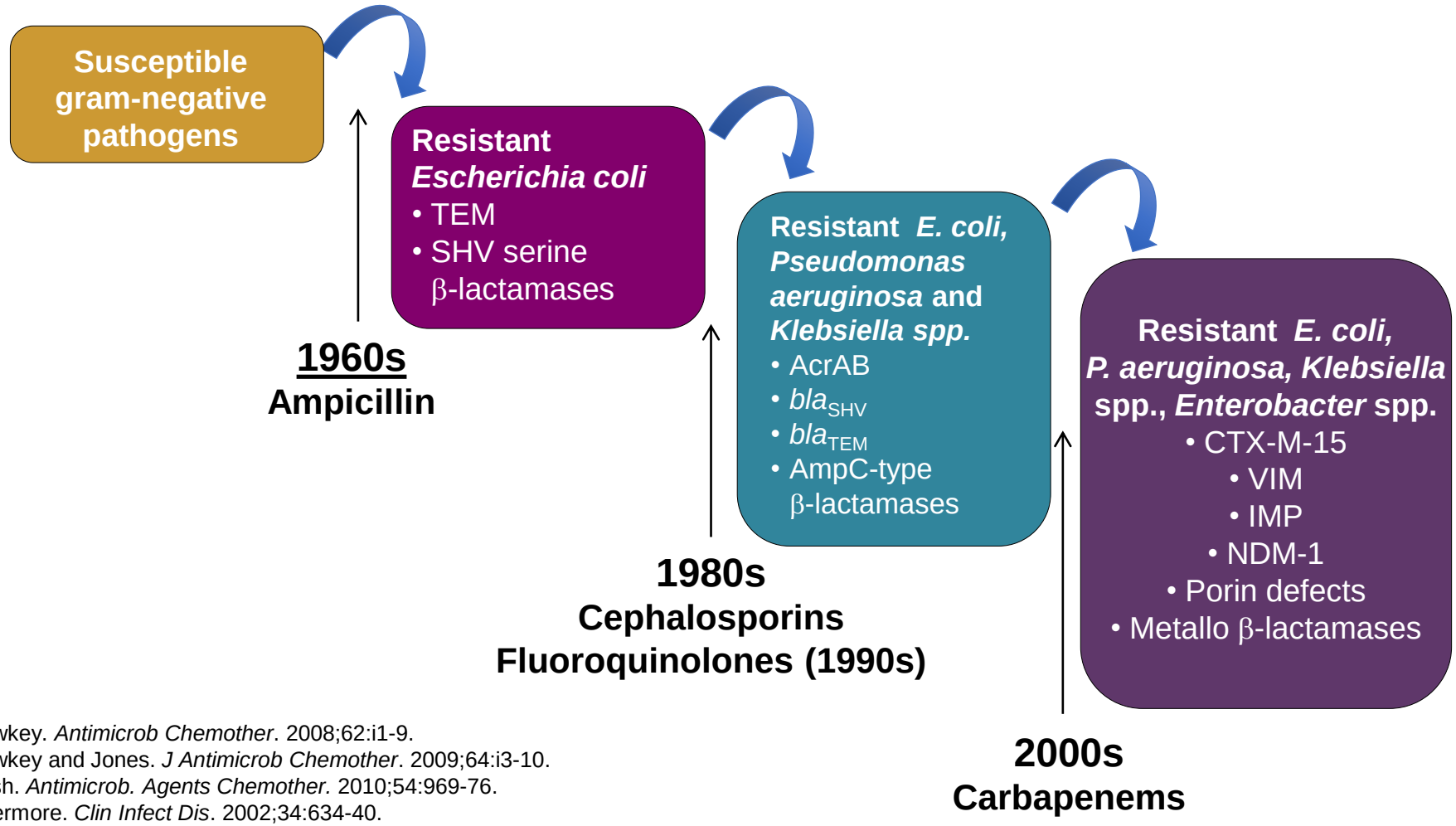
1η Νοεμβρίου 2020

- Το Μάρτιο του 1942 η κ Anne Miller από το New Haven ήτο ετοιμοθάνατη λόγω βακτηριαιμίας.

- Ο γιατρός της απελπισμένος της χορήγησε ένα πειραματικό φάρμακο «πενικιλλίνη»

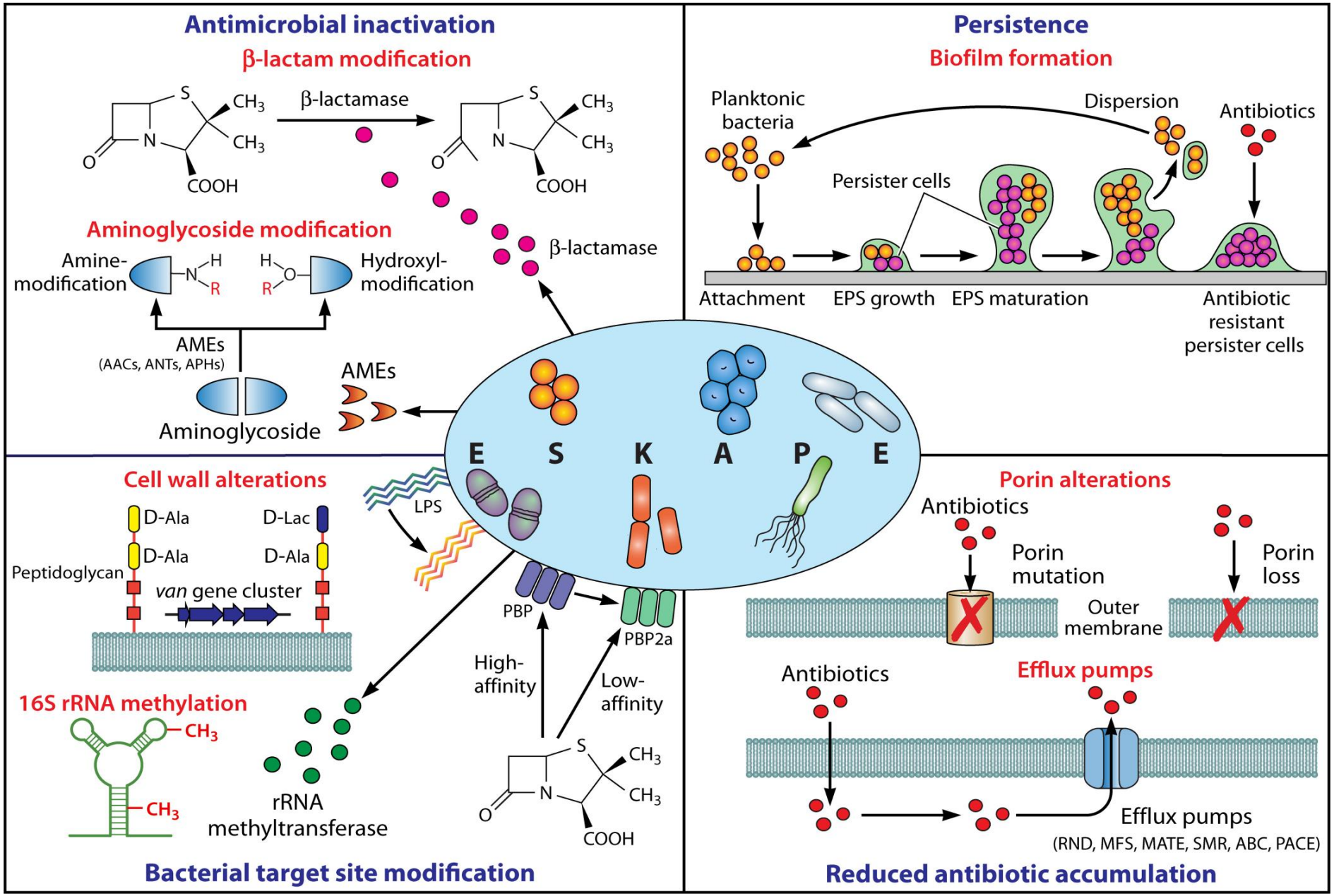
- Σε λίγες ημέρες ανέρρωσε και ήταν ο πρώτος άνθρωπος που διεσώθη από χορήγηση αντιβιοτικού

# Evolution of Gram-negative Pathogens Has Caused Widespread Drug Resistance





1. Hawkey. *Antimicrob Chemother*. 2008;62:i1-9.
2. Hawkey and Jones. *J Antimicrob Chemother*. 2009;64:i3-10.
3. Bush. *Antimicrob. Agents Chemother.* 2010;54:969-76.
4. Livermore. *Clin Infect Dis*. 2002;34:634-40.
5. Olivares et al. *Front Microbiol*. 2013;4:103.




De Oliveira et al. CMR July 2020

## Αντοχή στα β-λακταμικά αντιβιοτικά

-β-Λακταμάσες
-μειωμένη διαπερατότητα
-αλλαγές στις PBPs

Κυρίαρχος μηχανισμός στα Gram-αρνητικά είναι η παραγωγή β-λακταμασών ενώ στα Gram-θετικά οι αλλαγές στις PBPs.

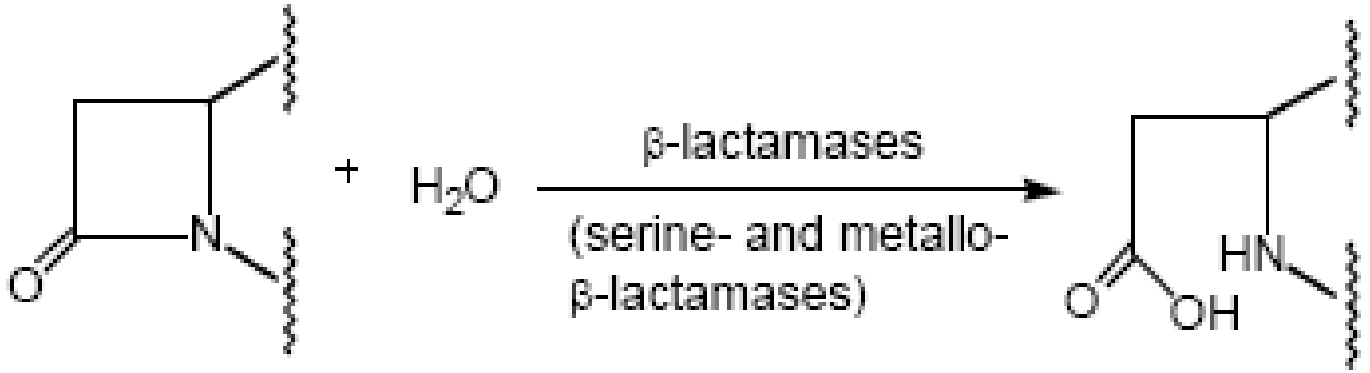
# MDR, XDR

- MDR: Αντοχή σε τουλάχιστον ένα αντιβιοτικό από τουλάχιστον 3 διαφορετικές ομάδες
- XDR: Αντοχή σε τουλάχιστον ένα αντιβιοτικό από όλες τις ομάδες εκτός από 2

- Αυξημένη θνητότητα
- Παρατεταμένη νοσηλεία
- Αύξηση κόστους νοσηλείας

# ΑΝΤΟΧΗ ΣΤΑ β-ΛΑΚΤΑΜΙΚΑ

## β-ΛΑΚΤΑΜΑΣΕΣ




-Είναι υδρολάσες. Δηλαδή χρησιμοποιούν νερό για να διασπάσουν το β-λακταμικό δακτύλιο. Τα προϊόντα υδρόλυσης είναι αδρανή.

# Ambler Classification of β-lactamases

| Ambler Class | A | B | C | D |
|---|---|---|---|---|
| Active Site | Serine | Metallo (zinc-binding thiol) | Serine | Serine |
| Enzyme Type | TEM, SHV, CTX-M, KPC | NMD-1, IMP, VIM | AmpC, CMY | OXA |
| Host Organisms | Enterobacteriaceae and Non-fermenters | Enterobacteriaceae and Non-fermenters | *Enterobacter* spp. *Citrobater* spp. | Enterobacteriaceae and Non-fermenters |
| Substrates | Ampicillin; cephalotin; penicillins; 3rd gen cephalosporins; Extended-spectrum cephalosporins; carbapenems | All β-lactams | Cephamycins; 3rd-generation cephalosporins | Cloxacillin; Extended-spectrum cephalosporins; carbapenems |

**KPC-2 is the most prevalent class A carbapenemase in the world and can hydrolyze the β-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam.**

# Εξέλιξη της Επιδημιολογίας των ESBLs

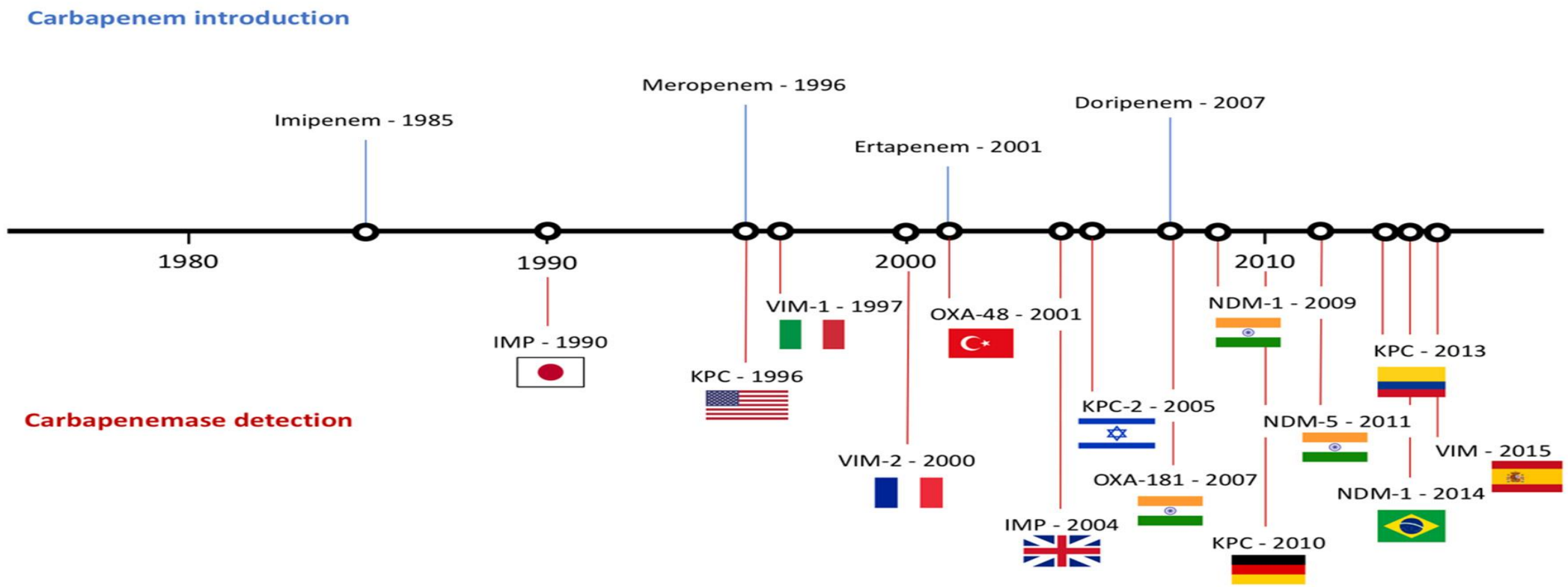
**1990s**

- **Επικρατούντα ένζυμα: SHV and TEM types**
- **Κυρίως νοσοκομειακά στελέχη**
- ***Klebsiella > E. coli***

**2000s**

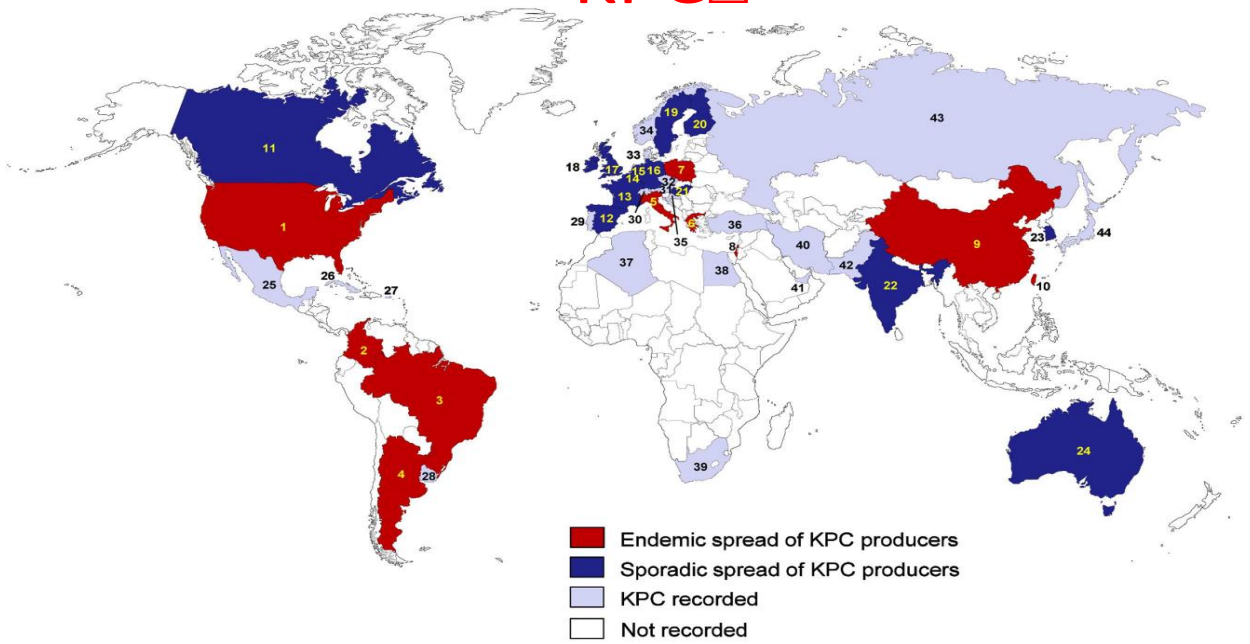
- **Επικρατούντα ένζυμα: CTX-M types**
- **Κυρίως λοιμώξεις εκ της κοινότητας/UTIs**
- ***E. coli > Klebsiella***

# Timeline of introduction of carbapenems and appearance of carbapenemases

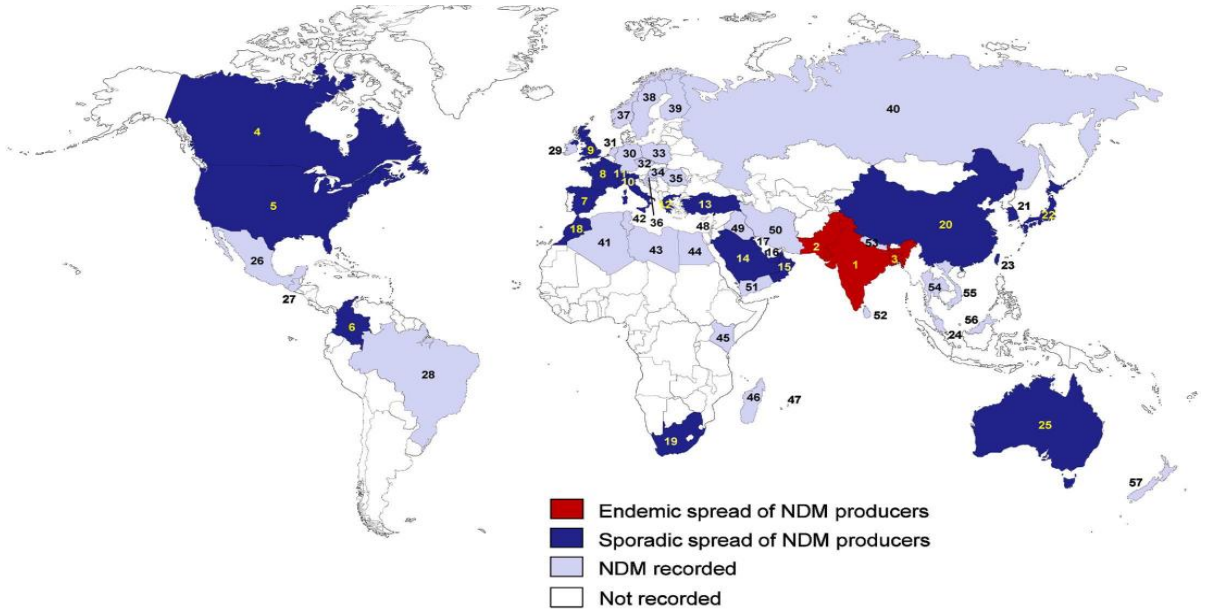



KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase;
VIM, Verona Integron-encoded-β- lactamase.
Suay-García B, et al. *Antibiotics* 2019;8:122. doi:10.3390/antibiotics8030122.

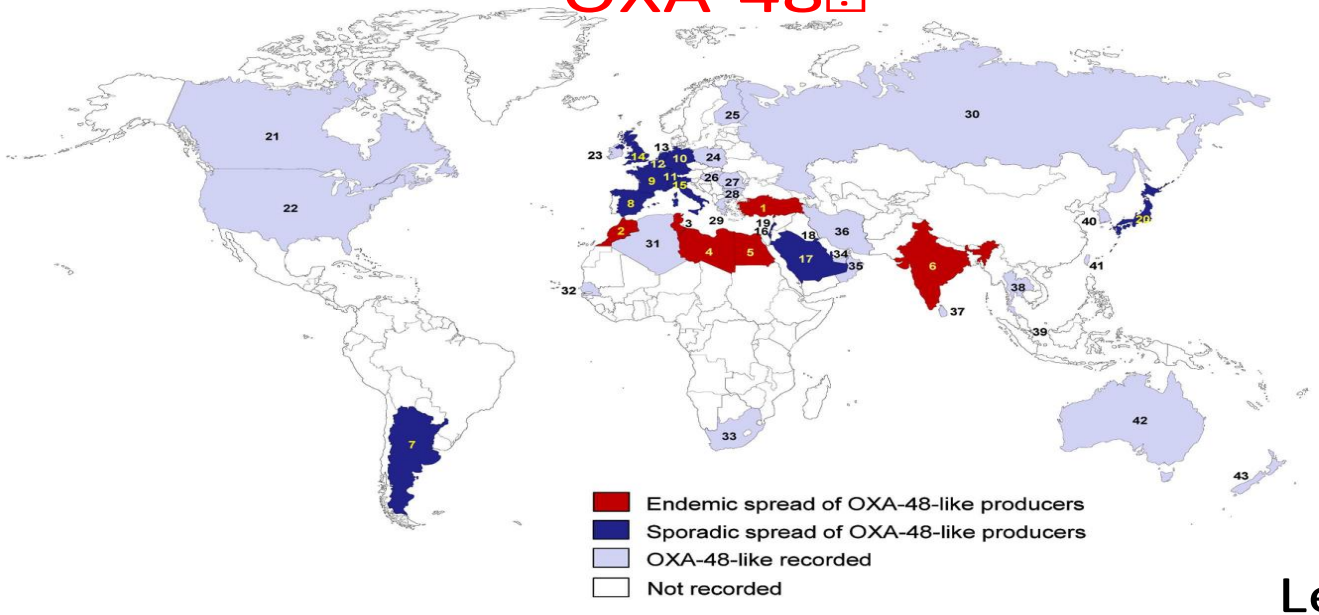
## KPC




## NDM

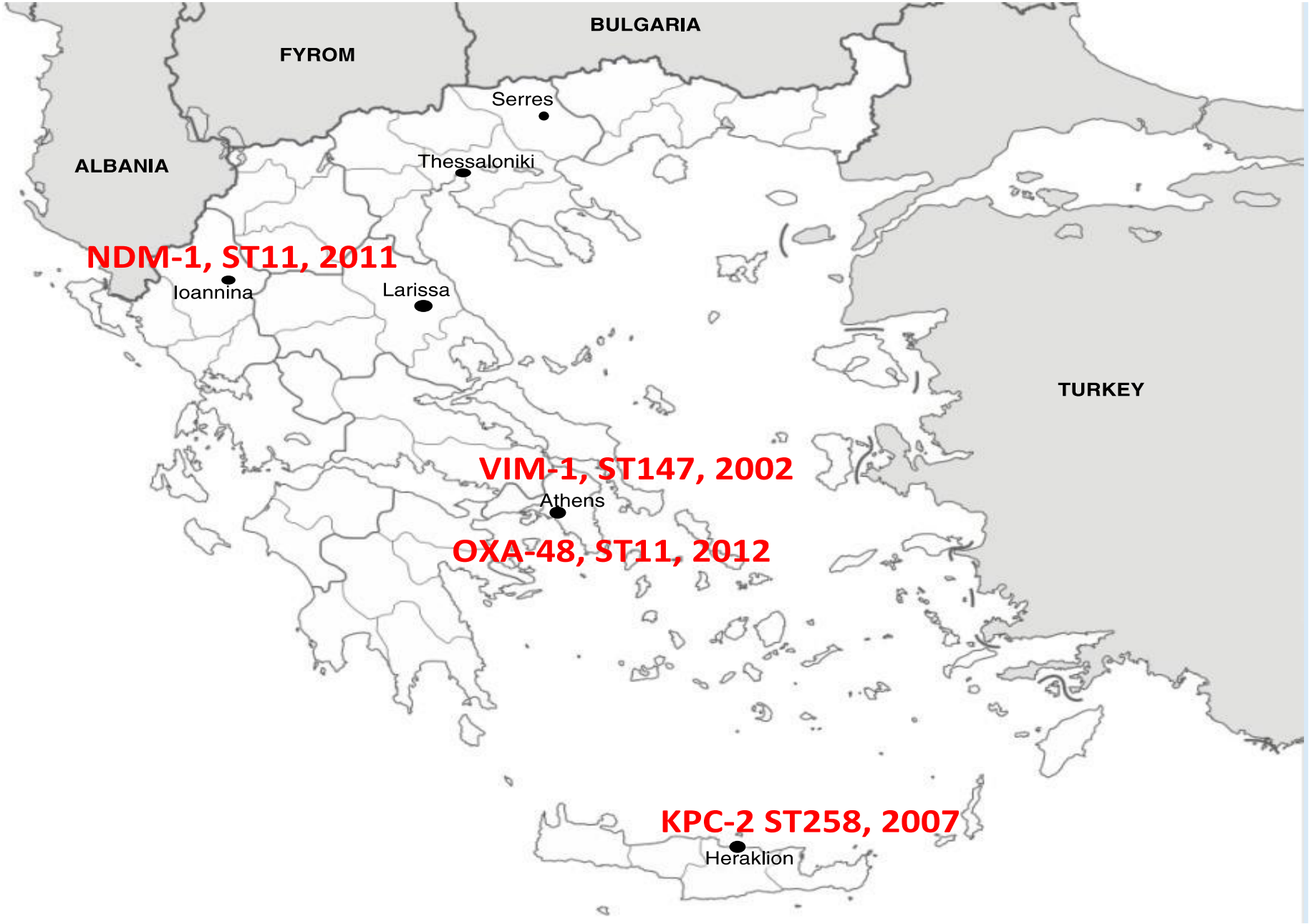



## OXA-48



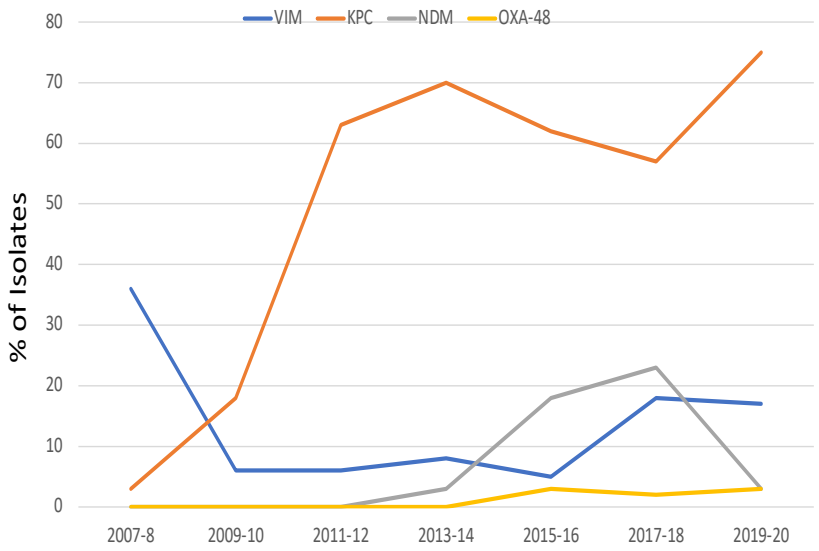

The VIM and IMP producing strains are largely confined to their original foci i.e. the Mediterranean countries (VIM) and the Far East (IMP)

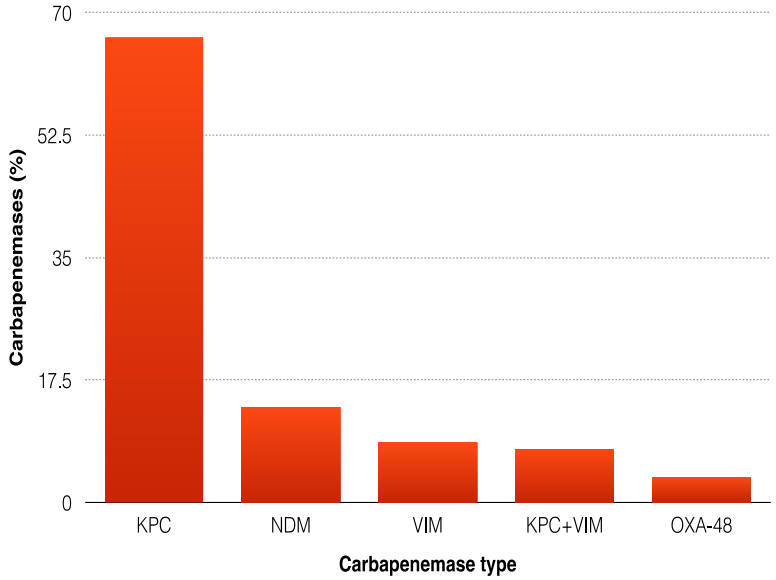
Lee CR Fron J ers In Microbiol 2016; 7: 895




Karampatakis et Future Microbiol 2016

# Carbapenemase-producing-KP by Type of Carbapenemase, Greece



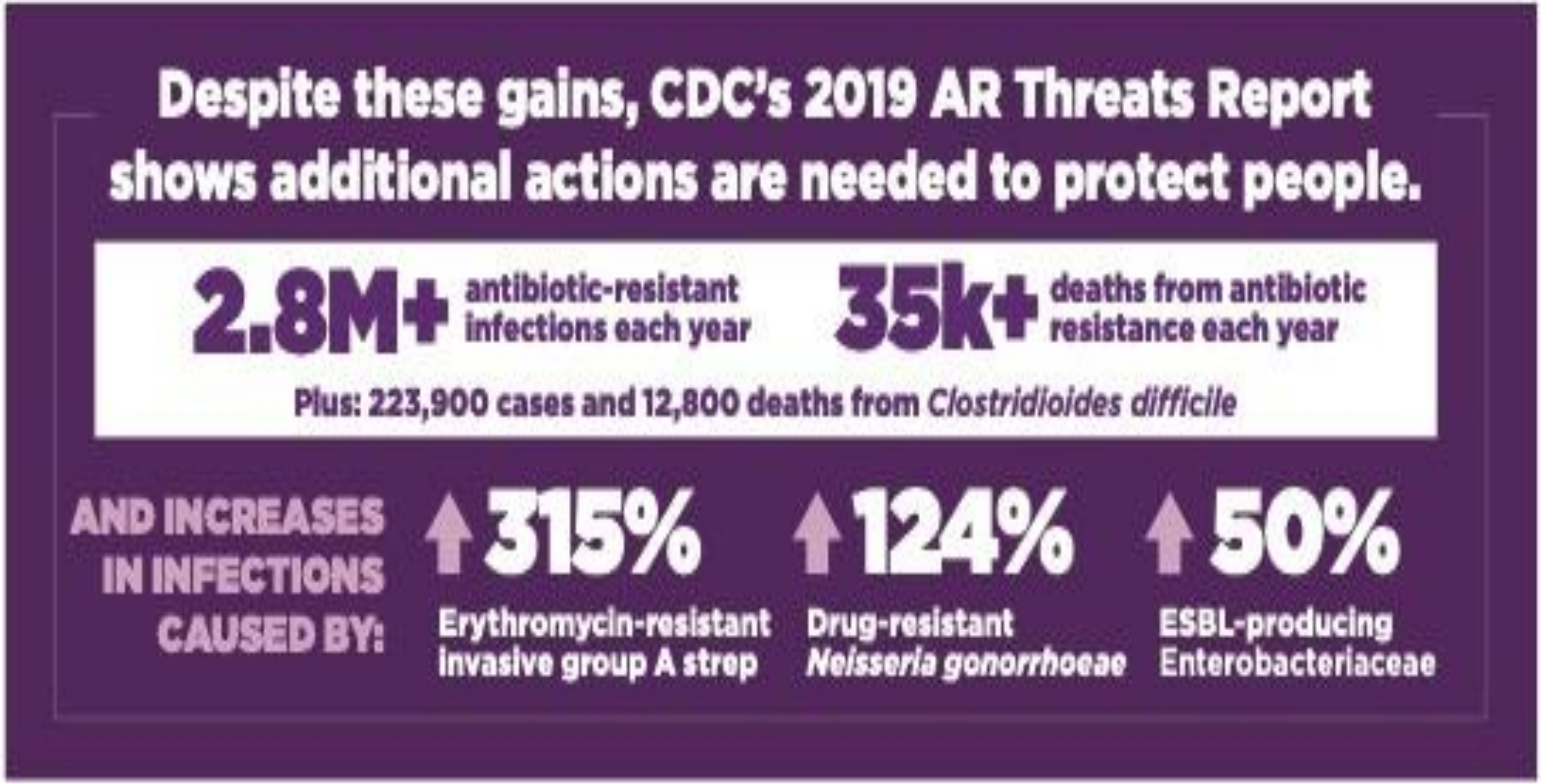

Laiko General Hospital, 2007-2020

Galani I et al DOI: 10.2807/1560-7917.ES.2018.23.30.1700775

# HIGH RISK MDR CLONES WITH GLOBAL SPREAD

| High-risk clone | Geographic distribution | Predominant resistance mechanism[a] | Extent of resistance[b] |
|---|---|---|---|
| *Escherichia coli* | | | |
| ST131 | Global | CTX-M-15 | MDR |
| *Klebseilla pneumoniae* | | | |
| ST258 | Global | KPC-2, KPC-3 | XDR, PDR |
| ST11 | South America, East Asia, South Asia, Europe | KPC-2, NDM-1, VIM, OXA-48 | XDR, PDR |
| ST340 | West Asia, North America, Europe | NDM, KPC, KPC-2, NDM-1 | XDR, PDR |
| ST512 | Europe, West Asia | KPC-3 | XDR, PDR |
| ST147 | North America, Europe, East Asia, West Asia, South Asia | KPC, KPC-2, NDM-1, OXA-48, OXA-48-like, VIM | XDR, PDR |
| ST15 | North America, Europe | OXA-48 | XDR, PDR |
| *Acinetobacter baumannii* | | | |
| ICLI | Global | NDM, OXA-23, OXA-58, VIM | XDR, PDR |
| CC1/CC109 | | | |
| ICLII | Global | NDM, OXA-23, OXA-24/40, OXA-58, VIM | XDR, PDR |
| CC2/CC92 | | | |
| *Pseudomanas aeruginosa* | | | |
| ST235 | Europe, Asia, South America, Africa | IMP, VIM | XDR, PDR |
| ST111 | Europe | IMP, VIM, | XDR, PDR |

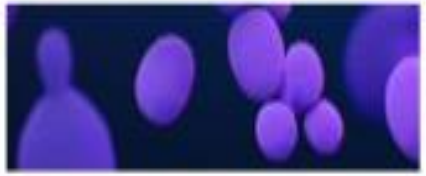
Data extracted from Diene and Rolain CMI 2014; 20: 831


Despite these gains, CDC's 2019 AR Threats Report shows additional actions are needed to protect people.
2.8M+ antibiotic-resistant infections each year
35k+ deaths from antibiotic resistance each year
Plus: 223,900 cases and 12,800 deaths from Clostridioides difficile
AND INCREASES IN INFECTIONS CAUSED BY:
↑315% Erythromycin-resistant invasive group A strep
↑124% Drug-resistant Neisseria gonorrhoeae
↑50% ESBL-producing Enterobacteriaceae

## Urgent Threats

These germs are public health threats that require urgent and aggressive action:

CARBAPENEM-RESISTANT
***ACINETOBACTER***



***CANDIDA AURIS***

***CLOSTRIDIOIDES DIFFICILE***

CARBAPENEM-RESISTANT
**ENTEROBACTERIACEAE**

DRUG-RESISTANT
***NEISSERIA GONORRHOEAE***

## Serious Threats

These germs are public health threats that require prompt and sustained action:

DRUG-RESISTANT
***CAMPYLOBACTER***

DRUG-RESISTANT
***CANDIDA***

ESBL-PRODUCING
**ENTEROBACTERIACEAE**

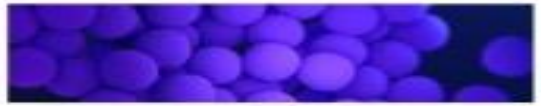
VANCOMYCIN-RESISTANT
***ENTEROCOCCI***

MULTIDRUG-RESISTANT
***PSEUDOMONAS AERUGINOSA***

DRUG-RESISTANT
**NONTYPHOIDAL *SALMONELLA***

DRUG-RESISTANT
***SALMONELLA* SEROTYPE TYPHI**

DRUG-RESISTANT
***SHIGELLA***



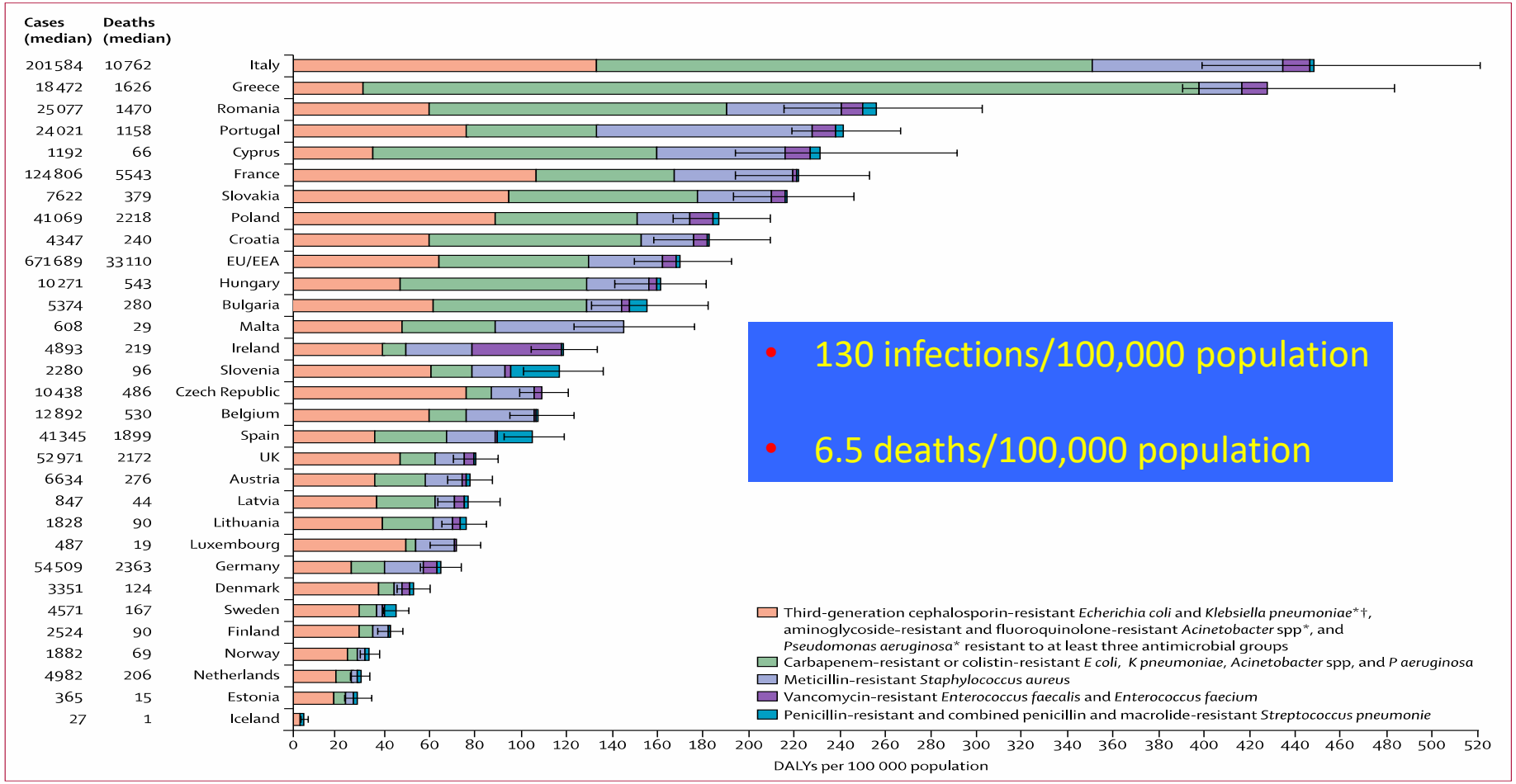
METHICILLIN-RESISTANT
***STAPHYLOCOCCUS AUREUS***

DRUG-RESISTANT
***STREPTOCOCCUS PNEUMONIAE***

DRUG-RESISTANT
**TUBERCULOSIS**

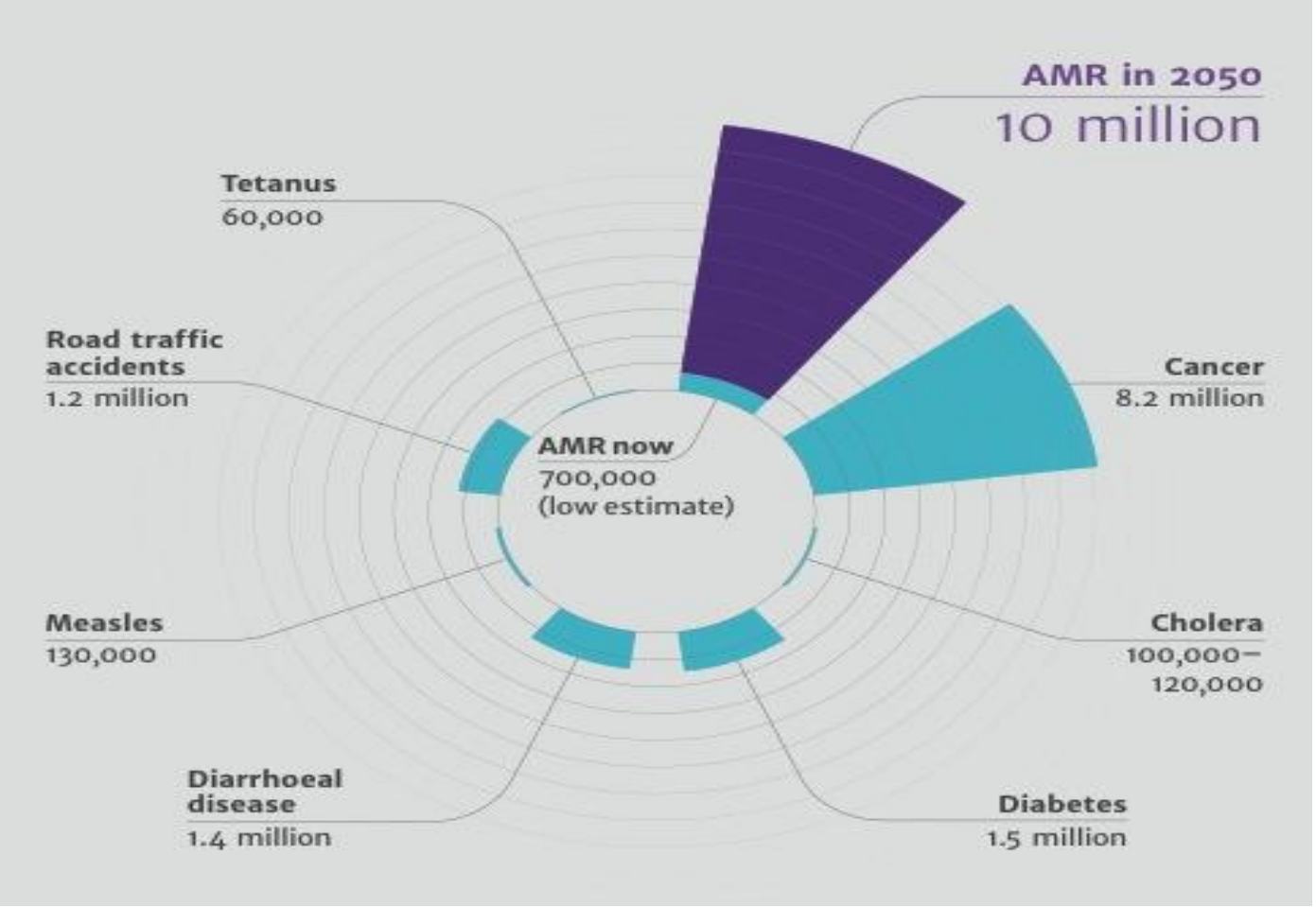
# Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira,*




Cassini A, et al. *Lancet Infect Dis* 2019;19:56–6.

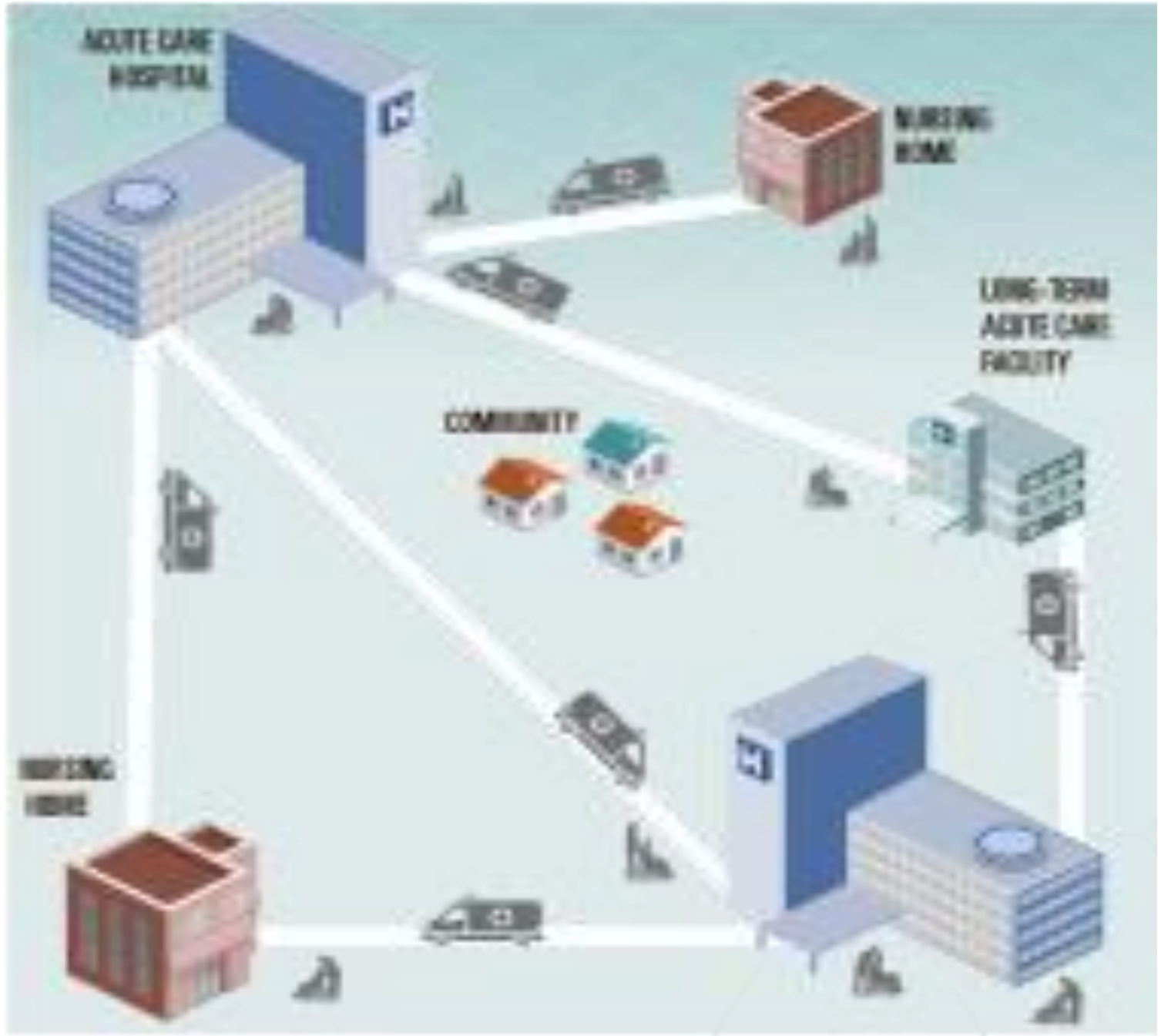
# Predicted Deaths by Infections Caused by Antimicrobial Resistant Organisms




**Jim O Neill**

# Antibiotic Resistance Spreads Easily Across the Globe

**Resistant bacteria and fungi can spread across countries and continents through people, animals, and goods.**


ACUTE CARE
HOSPITAL
NURSING
HOME
LONG-TERM
ACUTE CARE
FACILITY
COMMUNITY
NURSING
HOME

A ONE HEALTH CHALLENGE

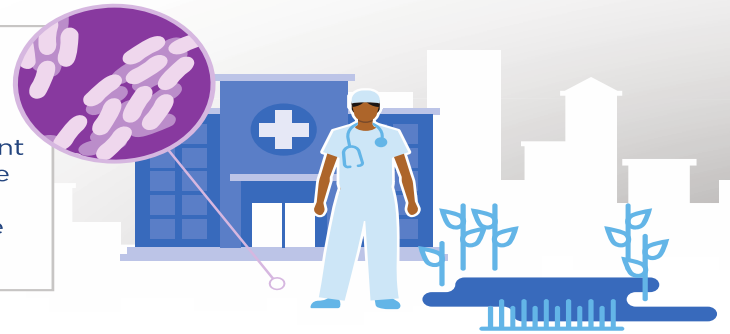
# The Interconnected Threat of Antibiotic Resistance

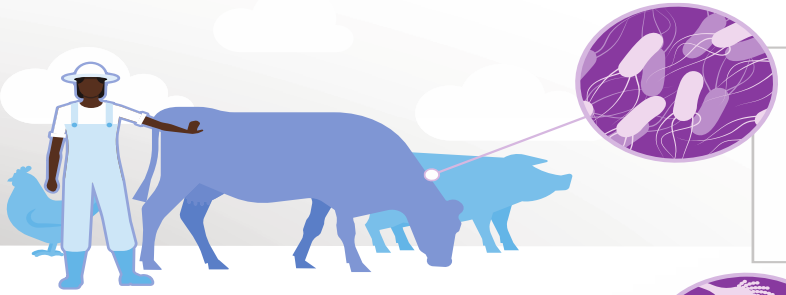
Resistance happens when germs (bacteria and fungi) defeat the drugs designed to kill them. Any antibiotic use—in people, animals, or crops—can lead to resistance. Resistant germs are a One Health problem—they can spread between people, animals, and the environment (e.g., water, soil).

## Examples of How Antibiotic Resistance Affects Humans, Animals & the Environment

### People

Some types of antibiotic-resistant germs can spread person to person. "Nightmare bacteria" carbapenem-resistant Enterobacteriaceae (CRE) can also survive and grow in sink drains at healthcare facilities and spread to patients and to the environment through the wastewater.





### Animals

Resistant germs can spread between animals and people through food or contact with animals. For example, *Salmonella* Heidelberg bacteria can make both cattle and people sick.

### Environment

Antibiotic-resistant germs can spread in the environment. *Aspergillus fumigatus*, a common mold, can make people with weak immune systems sick. In 2018, resistant *A. fumigatus* was reported in three patients. It was also found in U.S. crop fields treated with fungicides that are similar to antifungals used in human medicine.

# Θεραπεία Λοιμώξεων από Βακτήρια που Παράγουν ESBL (IDSA 2020)

| **Source of Infection** | **Preferred Treatment** | **Alternative Treatment** (first-line options not available or tolerated) |
|---|---|---|
| Cystitis | Nitrofurantoin, trimethoprim-sulfamethoxazole | Amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin (*E. coli* only)<br><br>Ciprofloxacin, levofloxacin, ertapenem, meropenem, imipenem-cilastatin |
| Pyelonephritis or cUTI[1] | Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole | |
| Infections outside of the urinary tract | Meropenem, imipenem-cilastatin, ertapenem<br><br>Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole can be considered[2]. | |

# Carbapenem Resistant  Gram negative Organisms (WHONET, Greece 2020)

| Pathogen | Medical Wards | Surgical Wards | ICU |
|---|---|---|---|
| Acinetobacter | 90% | 95% | 97% |
| Pseudomonas | 34% | 32% | 39% |
| Klebsiella | 46% | 61% | 87% |

# 7477 Episodes of Infections Caused by Carbapenem Resistant Gram-negative Bacteria

**Department**

- ICU 51.7%
- Medicine 31.7%
- Surgery 16.6%

**Source of Infection**

- Pneumonia 34.0%
- Bacteremia 31.3%
- UTIs 22.8%
- SSI 11.9%

Hellenic Center for Disease Control and Prevention (KEELPNO)

# Therapeutic Options for CR-GNB Infections

## Pseudomonas

- Colistin
- Fosfomycin
- Aztreonam
- Ceftolozane/tazobactam
- Ceftazidime/ avibactam
- Cefiderocol

## Klebsiella

- Colistin
- Aminoglycosides
- Tigecycline
- Fosfomycin
- Ceftazidime/avibactam
- Meropenem/vaborbactam
- Imipenem/relebactam
- Aztreonam/avibactam
- Eravacycline

## Acinetobacter

- Colistin
- Tigecycline
- Sulbactam
- TMP/SMX
- Minocycline
- Cefiderocol
- Eravacycline

# The 10 × ‘20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020

**Infectious Diseases Society of America**[a]

Infectious Diseases Society of America, Arlington, Virginia

# Spectrum of activity of new antibiotics

| | ESBL | CRE-KPC | CRE-OXA48 | CRE-MBL | DTR *P. Aeruginosa* | DTR *Acinetobacter* |
|---|---|---|---|---|---|---|
| **BL/BLI Combination** | | | | | | |
| • Ceftolozane/Tazobactam | 🟢 | 🔴 | 🔴 | 🔴 | 1 🟢 | 🔴 |
| • Ceftazidime-Avibactam | 🟢 | 🟢 | 🟢 | 🔴 | 🟢 | 🔴 |
| • Imipenem-Relebactam | 🟢 | 🟢 | 2 🔴 | 🔴 | 3 🟢 | 🔴 |
| • Meropenem-Vaborbactam | 🟢 | 🟢 | 🔴 | 🔴 | 🔴 | 🔴 |
| • Aztreonam-Avibactam | 🟢 | 🟢 | 🟢 | 4 🟢 | 5 🔴 | 🔴 |
| • Cefepime/Zidebactam | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| • Meropenem/Nacubactam | 🟢 | 🟢 | 🟢 | 🔴 | 🔴 | 🔴 |
| • Ceftaroline/Avibactam | 🟢 | 🟢 | 🟢 | 🔴 | 🔴 | 🔴 |
| **Novel Cephalosporine** | | | | | | |
| • Cefiderocol | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| **Novel Amynoglicoside** | | | | | | |
| • Plazomicin | 🟢 | 🟢 | 6 🟢 | 7 🟢 | 8 🔴 | 8 🔴 |
| **Novel Tetracycline** | | | | | | |
| • Eravacyclin | 🟢 | 🟢 | 🟢 | 🟢 | 🔴 | 🟢 |
| • Murepavadin | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 | 🔴 |

BL/BLI, β-lactam/β-lactamase inhibitor; CRE, carbapenem resistant Enterobacteriaceae; DTR, difficult-to-treat resistance; ESBL, extended-spectrum beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBLs, metallo-β-lactamases.

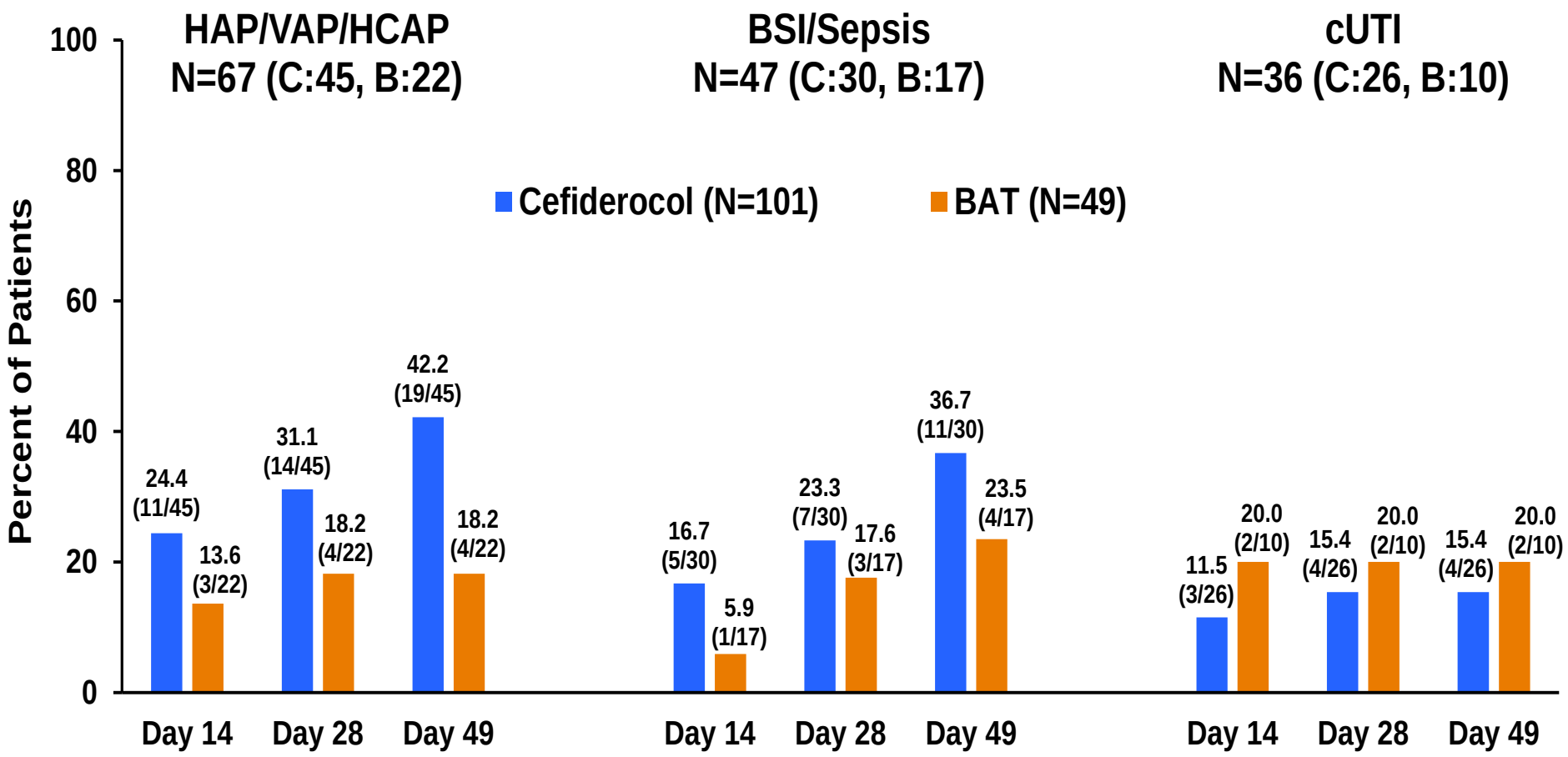
Bassetti M, et al. *Antibiotics* 2020;9:632. https://doi.org/10.3390/antibiotics9090632.

# Νεότερο ή Παλαιό Αντιβιοτικό?

# RCTs in the Treatment of CRE Infections

- McKinnell JA DOI: 10.1056/NEJMc1807634
  - Plazomicin based regimen vs Colistin based regimen for HAP/VAP and BSI
- Wunderink R Infect Dis Ther 2018; 7: 439
  - Meropenem-vaborbactam vs Best available therapy for HAP/VAP and BSIs
- RESTORE IMI 1 CID 2019
  - Imipenem-relebactam vs Imipenem plus colistin for imipenem nonsusceptible bacterial infections

# Cefiderocol vs BAT

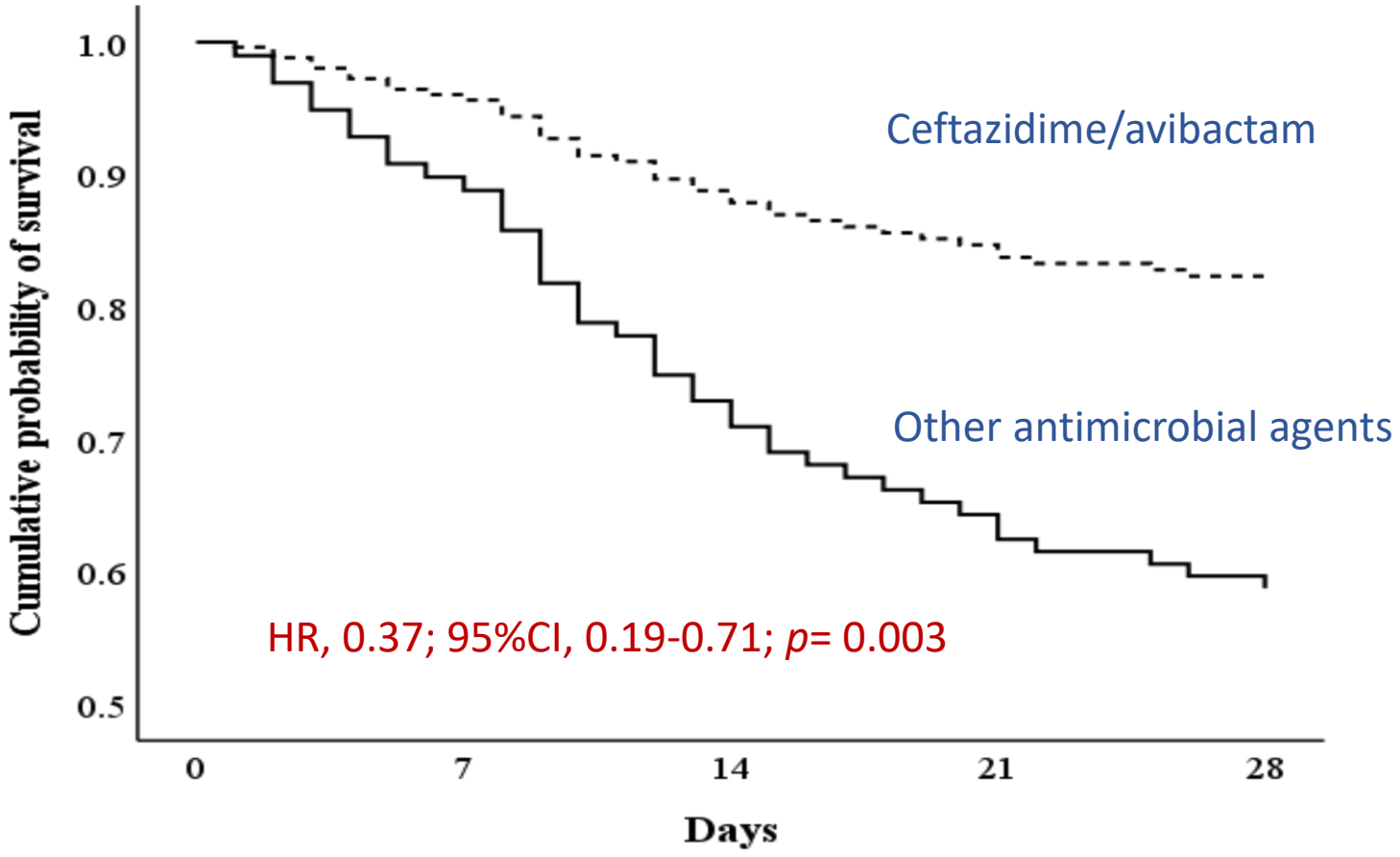


# Ceftazidime–avibactam vs other regimens in the treatment of CRE

- Observational studies
  - **Van Duin D, et al. *Clin Infect Dis* 2018;66(6):163–71.**
    CAZ–AVI based (n=38) vs colistin based (n=99) therapy. IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was 9% (C–A) versus 32% (CS)
  - **Tumbarello M, et al. *Clin Infect Dis* 2019;68(3):355–64.**
    For KPC BSIs treatment with CAZ–AVI was independent predictor for 30-day survival
  - **Ackley R, et al. *OFID* 2019;6(Suppl 2):S303.**
    CAZ–AVI (n=105, the majority in combination with another agent) vs meropenem–vaborbactam (n=26, 3 received combination). Composite end point, no difference in clinical success, 3 isolates in CAZ–AVI group developed resistance, none in the meropenem–vaborbactam group

BSI, bloodstream infections; CAZ–AVI, ceftazidime–avibactam; CRE, carbapenem resistant Enterobacteriaceae; IPTW, inverse probability of treatment weighting; KPC, *Klebsiella pneumoniae* carbapenemase.
Van Duin D, et al. *Clin Infect Dis* 2018;66:163–71; Tumbarello M, et al. *Clin Infect Dis* 2019;68:355–64; Ackley R, et al. *OFID* 2019;6(Suppl 2):S303.

# Cumulative probability of survival of 142 patients with KPC-producing *K. pneumoniae* BSIs according to treatment regimen



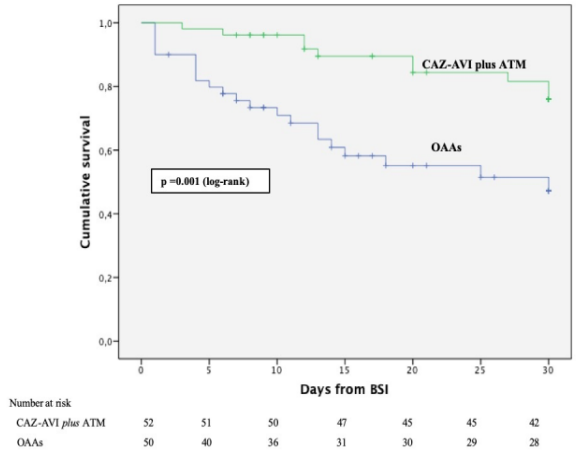

Karaiskos I et al J Antimicrob Chemotherapy in press

# Efficacy of ceftazidime–avibactam plus aztreonam in patients with bloodstream infections caused by MBL-producing Enterobacterales*

**Cox regression analysis of factors independently associated with 30-day mortality**

| Variable | HR (95% CI) |
|---|---|
| Cardiovascular dis | 6.6 (2.8-15.8) |
| Transplanta9on | 3.5 (1.4-8.7) |
| SOFA | 1.2 (1.1-1.3) |
| CAZAVI + ATM | 0.17 (0.07-0.4) |

**Kaplan Meier survival curves according to treatment regimens (CAZ-AVI plus ATM versus OAAs).**




*Based on Prof Daikos' personal experience.
ATM, aztreonam; BSI, bloodstream infection; CAZ–AVI, ceftazidime–avibactam; CI, confidence interval; HR, hazard ratio; MBL, metallo-β-lactamase; OAA, other active antibiotics; SOFA, sequential organ failure assessment score.
Falcone M, et al. *Clin Infect Dis* 2020; ciaa586. doi: 10.1093/cid/ciaa586 (Epub ahead of print).

| Εστία Λοίμωξης | Πρώτη επιλογή | Δεύτερη επιλογή |
|---|---|---|
| **Κυστίτιδα** | Αμινογλυκοσίδη | Φωσφομυκίνη ή κολιστίνη ή Κεφταζιδίμη/αβιμπμακτάμη |
| **Πυελονεφρίτιδα ή cUTIs**<br>**KPC ή OXA-48** | Κεφταζιδίμη/αβιμπμακτάμη | **Αμινογλυκοσίδη ή κολιστίνη**<br>**±**<br>**Φωσφομυκίνη ή μεροπενέμη εάν MIC ≤8 mg/L** |
| **VIM ή NDM** | Κεφταζιδίμη/αβιμπμακτάμη + αζτρεονάμη | |
| **VIM ή NDM σε συνδυασμό με KPC ή OXA-48** | Κεφταζιδίμη/αβιμπμακτάμη + αζτρεονάμη | |
| **Λοιμώξεις εκτός ουροποιητικού**<br>**KPC ή OXA-48** | Κεφταζιδίμη/αβιμπμακτάμη ± αμινογλυκοσίδη ή κολιστίνη | Συνδυασμός δύο εκ των κάτωθι αντιμικροβιακών παραγόντων ανάλογα με το είδος της λοίμωξης |
| **VIM ή NDM** | Κεφταζιδίμη/αβιμπμακτάμη + αζτρεονάμη ± αμινογλυκοσίδη ή κολιστίνη | Φωσφομυκίνη, αμινογλυκοσίδη, κολιστίνη, τιγκεκυκλίνη ή μεροπενέμη εάν MIC ≤8 mg/L |
| **VIM ή NDM σε συνδυασμό με KPC ή OXA-48** | Κεφταζιδίμη/αβιμπμακτάμη + αζτρεονάμη ± αμινογλυκοσίδη ή κολιστίνη | Η τιγκεκυκλίνη προτιμάται σε ενδοκοιλιακές λοιμώξεις και λοιμώξεις δέρματος και μαλακών μορίων |

# Μη Έγκαιρη Έναρξη Δραστικής Αντιμικροβιακής Αγωγής

- 40% των ασθενών με λοίμωξη από CR-Gram αρνητικό βακτήριο λαμβάνει μη δραστική εμπειρική αντιμικροβιακή αγωγή

- Καθυστέρηση έναρξης δραστικής αντιμικροβιακής αγωγής κατά 30 ώρες

- Κάθε ώρα καθυστέρησης στην έναρξη δραστικής αντιμικροβιακής αγωγής στο σηπτικό ασθενή αυξάνει τη θνητότητα κατά 7%

# Clinical prediction tools

- Local epidemiology
- Individual patient risk factors
  - Comorbid conditions
  - Cumulative exposure to antibiotics
  - Prior hospitalisation
  - Surgery or other interventions
- Infection-related factors
  - ICU, non-ICU
  - Source of infection
  - Severity of infection

ICU, intensive care unit.
Speaker's personal opinion.

# Συστάσεις για τη χορήγηση του συνδυασμού Κεφταζιντίμη-Αβιμπακτάμη

(Οδηγίες της Εθνικής Επιτροπής Αντιβιογράμματος)

**Εμπειρική Θεραπεία**

- Μπορεί να χορηγηθεί **επί κλινικής υποψίας λοίμωξης**, σε ασθενείς με παράγοντες κινδύνου για λοίμωξη από CPE, όπως:
- Α. Προηγούμενη λοίμωξη ή αποικισμό από CPE που παράγει KPC ή OXA-48.
- Β. Νοσηλεία σε ΜΕΘ το τελευταίο εξάμηνο.
- Γ. Νοσηλεία στον ίδιο θάλαμο με γνωστούς φορείς των μικροβίων αυτών.

**Και έχοντες τουλάχιστον ένα από τα παρακάτω:**

- 1. **Κατάσταση του ξενιστή:** Βαρέως πάσχοντες, ασθενείς ΜΕΘ, ανοσοκατεσταλμένοι ασθενείς.
- 2. **Βαρύτητα της λοίμωξης:** Ασθενείς με σοβαρή σήψη, σηπτική καταπληξία.

# Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study

M. Giannella[1], E. M. Trecarichi[2], F. G. De Rosa[3], V. Del Bono[4], M. Bassetti[5], R. E. Lewis[1], A. R. Losito[2], S. Corcione[3], C. Saffioti[4], M. Bartoletti[1], G. Maiuro[2], C. S. Cardellino[3], S. Tedeschi[1], R. Cauda[2], C. Viscoli[4], P. Viale[1] and M. Tumbarello[2]

**TABLE 2.** Logistic regression analysis of risk factors for CR-KP BSI development in rectal carriers

| | OR (95% CI) | P-value | Risk score point |
|---|---|---|---|
| Admission to ICU | 1.65 (1.05–2.59) | 0.03 | 2 |
| Invasive abdominal procedures | 1.87 (1.16–3.04) | 0.01 | 3 |
| Chemotherapy/radiation therapy | 3.07 (1.78–5.29) | <0.0001 | 4 |
| Colonization at site besides stool (risk per each additional site) | 3.37 (2.56–4.43) | <0.0001 | 5 per site |

ICU, intensive care unit; OR, odds ratio.

## Validation of the score

- Score <7: infection 6.3%
- Score ≥7: infection 84.8%
- Sensitivity: 92.9%
- Specificity: 85%

Giannella M, et al. *Clin Microbiol Infect* 2014;20:1357–62; Cano A. *Clin Infect Dis* 2018;66:1204.

# Ταχεία Διάγνωση με Μοριακές Μεθόδους ή Άλλες Μεθόδους

- Ελάττωση θνητότητας
- Ελάττωση του χρόνου έναρξης δραστικής αντιμικροβιακής αγωγής
- Ελάττωση χρόνου παραμονής στο νοσοκομείο

# Ταχεία Διάγνωση

- Συνδρομική διερεύνηση (π.χ FilmArray)
- T2 (Candida, Bacteria, μηχανισμοί αντοχής)
- MALDI-TOF MS
- Next generation sequence
- Accelerate Pheno Test (17 παθογόνα σε 90 λεπτά, MIC σε 7 ώρες)
- CRISPR

RAPID COMMUNICATION

# Detection in two hospitals of transferable ceftazidime-avibactam resistance in *Klebsiella pneumoniae* due to a novel VEB β-lactamase variant with a Lys234Arg substitution, Greece, 2019

**E. Voulgari[1], S.D. Kotsakis[1], P. Giannopoulou[2], E. Perivolioti[3], L.S. Tzouvelekis[1,4], V. Miriagou[1]**
1. Laboratory of Bacteriology, Hellenic Pasteur Institute, Athens, Greece
2. Department of Clinical Microbiology, Thriassio General Hospital, Elefsina, Greece
3. Department of Clinical Microbiology, Evangelismos General Hospital, Athens, Greece
4. Department of Microbiology, Medical School, University of Athens, Athens, Greece

**Correspondence: Vivi Miriagou (miriagou@pasteur.gr)**

RAPID COMMUNICATIONS

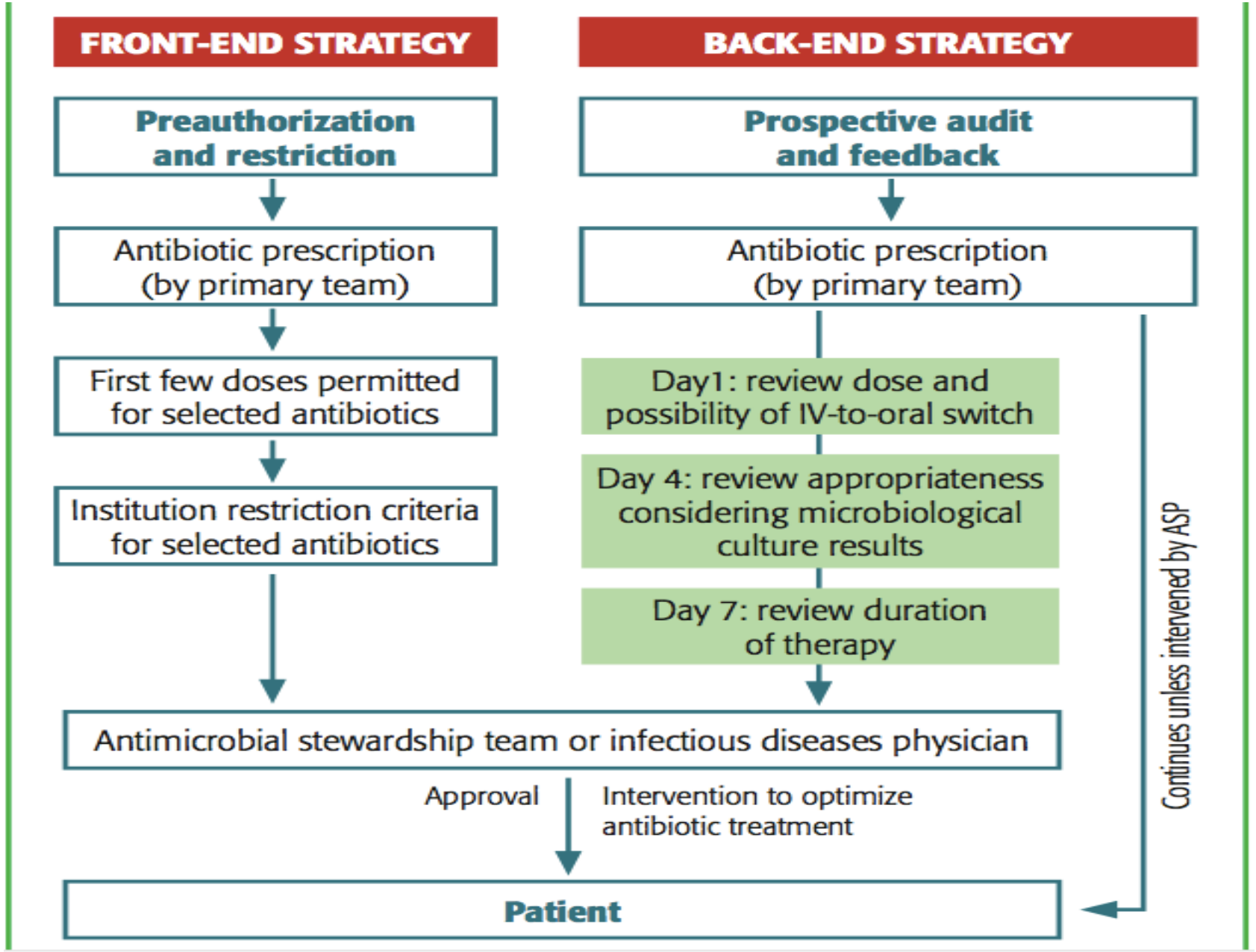
# Outbreak of KPC-2-producing *Klebsiella pneumoniae* endowed with ceftazidime-avibactam resistance mediated through a VEB-1-mutant (VEB-25), Greece, September to October 2019

**Irene Galani[1], Ilias Karaiskos[2], Maria Souli[1], Vassiliki Papoutsaki[3], Lamprini Galani[2], Aikaterini Gkoufa[2], Anastasia Antoniadou[1], Helen Giamarellou[2]**
1. Infectious Diseases Laboratory, 4th Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece
2. 1st Internal Medicine & Infectious Diseases Department, Hygeia General Hospital, Athens, Greece
3. Infectious Diseases Laboratory, Hygeia General Hospital, Athens, Greece

**Correspondence: Irene Galani (egalani@med.uoa.gr)**

KPC, *Klebsiella pneumoniae* carbapenemase.

Voulgari E, et al. *Euro Surveill* 2020;25. doi 10.2807/1560-7917.ES.2020.25.2.1900766; Galani I, et al. *Euro Surveill* 2020;25. doi: 10.2807/1560-7917.ES.2020.25.3.2000028.

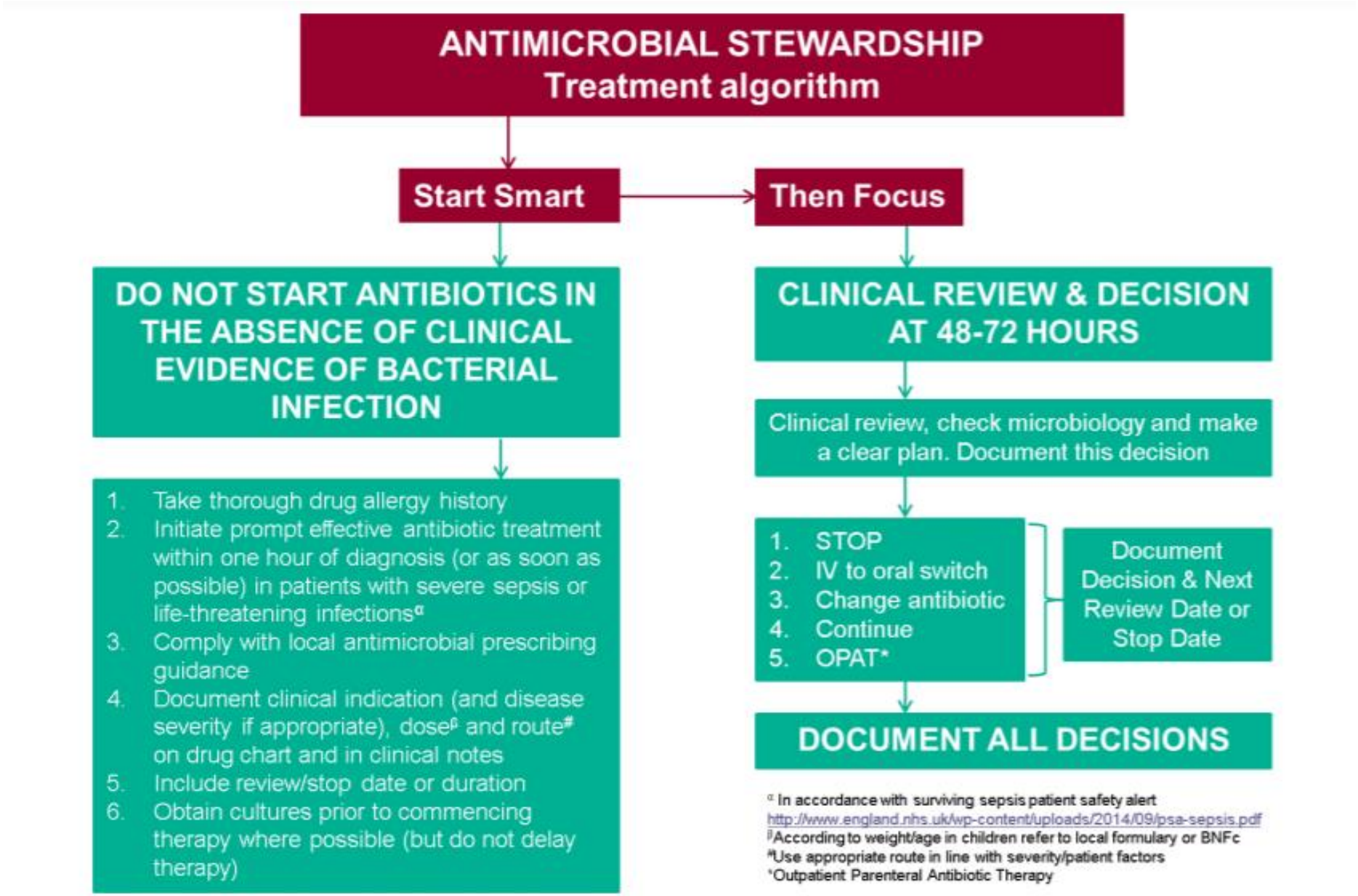



ASP, antimicrobial stewardship programme; IV, intravenous.
Chung GW, et al. *Virulence* 2013;4:1–7.

# Common strategies used among institutions

- Restricted formulary: 80%
- Education: 77%
- Prospective audit and feedback: 66%
- Prior approval: 38%

Pop SD, et al. *Infect Control Hosp Epidemiol* 2009;30:97–8.




IV, intravenous; OPAT, outpatient parenteral antibiotic therapy.
Antimicrobial Stewardship Toolkit for English Hospitals, Public Health England. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF. Accessed October 2020.

# Impact of antimicrobial stewardship programmes

## Intervention for a More Successful Outcome

- Interventions to improve antibiotic prescribing in hospitals:
  - 89 Studies until 2009
    - 55 from North America
    - 37 from Europe
    - 3 from Far East
    - 3 from South America
    - 2 from Australia
- Persuasive and restrictive interventions

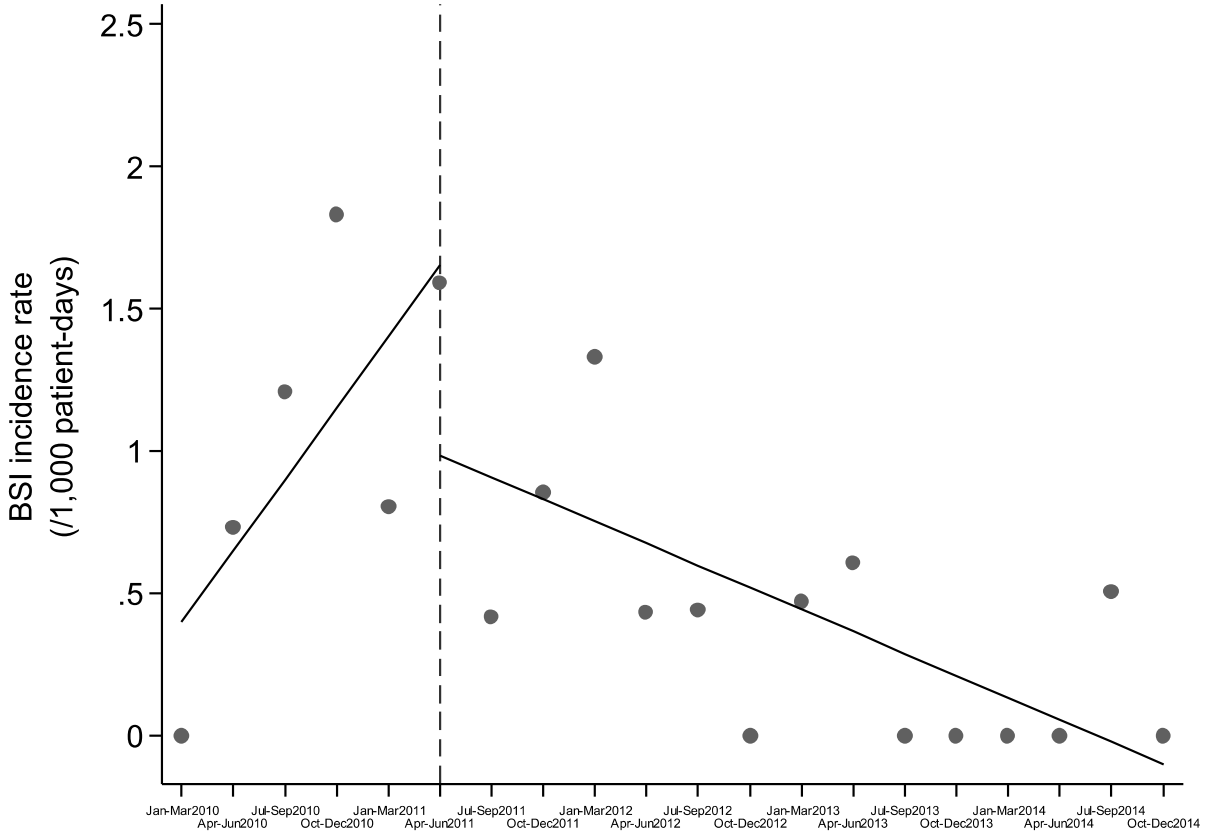
- Evidence to support beneficial impact on:
  - Decrease in antibiotic use does not increase mortality and can improve clinical outcomes
  - Better use of antibiotics will reduce SSI's
  - Decrease and better use of antibiotics reduces/stabilizes resistance and *C. difficile*
  - Emerging data on cost-reduction

SSI, surgical site infections.

Davey P, et al. *Cochrane Database of Systematic Reviews* 2013: CD003543.

# Containing Carbapenemase-producing Klebsiella pneumoniae in an endemic setting

| | |
|---|---|
| **Pre-intervention period**<br>**January 2010-May 2011** | • BSIs data |
| **First intervention period**<br>**June 2011-December 2012** | • Active surveillance on admission and weekly<br>• Hand hygiene<br>• Separation of carriers or infected patients<br>• Staff cohorting<br>• Contact precautions<br>• Environmental cleaning<br>• BSIs data |
| **Second intervention period**<br>**January 2013-June 2013** | • Active surveillance on admission<br>• Hand hygiene<br>• Separation of carriers or infected patients<br>• Staff cohorting<br>• Contact precautions<br>• Environmental cleaning<br>• BSIs data |
| **Third intervention period**<br>**July 2013-December 2014** | • Hand hygiene<br>• Separation of known carriers or infected patients<br>• Staff cohorting<br>• Contact precautions<br>• Environmental cleaning<br>• BSIs data |




Spyridopoulou et al. doi.org/10.1186/s13756-020-00766-x

Microbiology and Diagnostic Stewardship (MDS) Programme

Infection Prevention & Control (IPC) Programme

Antibiotic Stewardship (ABS) Programme

**Integrated, evidence-based, modular strategy** with complementary intervention programmes for reducing the clinical burden of infections caused by multidrug resistant (MDR) bacteria in high endemic settings.