

# Access, Watch, Reserve pentru salvarea antibioticelor...



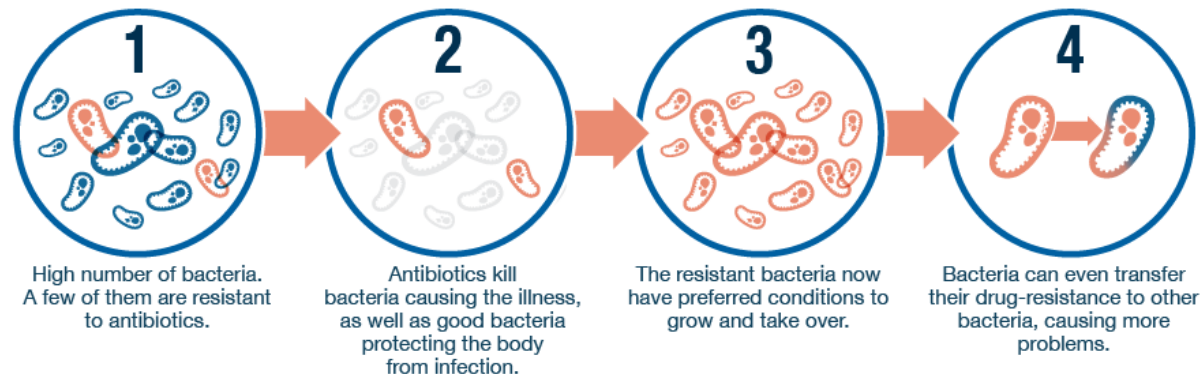
Prof.univ.dr. Irina Magdalena Dumitru

- ❖ Dupa **descoperirea penicilinei** si introducerea antibioticelor in practica medicala curenta, principalele cauze mondiale de deces – **bolile infectioase – au fost reduse semnificativ, si tinute sub control mai multe decenii.**
- ❖ Infectiile sunt in prezent una din primele trei cauze de deces pe plan mondial (chiar in tarile dezvoltate).

# Care au fost cauzele de aparitie a rezistentei?

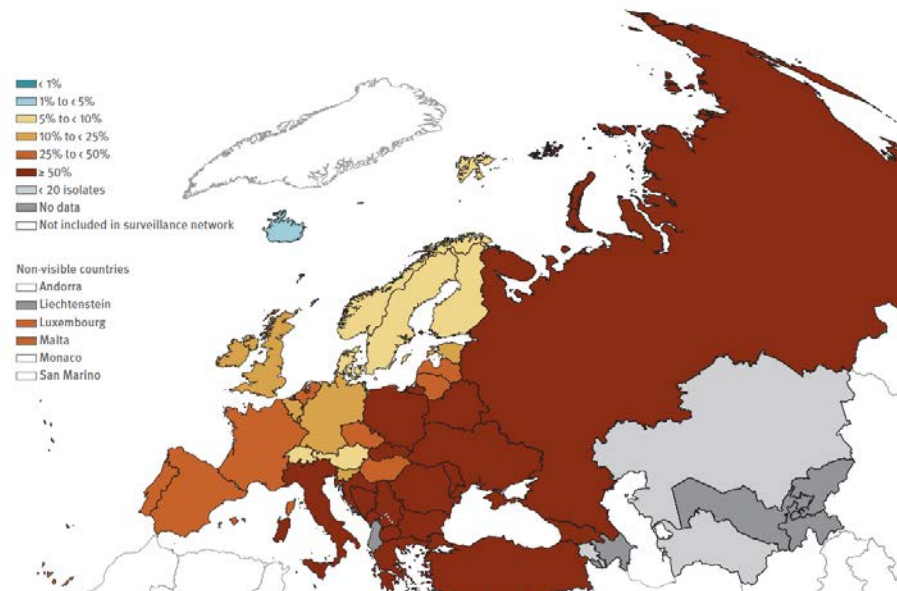
- Utilizarea in exces (**infectii virale, colonizari**)
- Profilaxia antibiotica perioperatorie in exces
- Antibiotice cu spectru larg
- Subdozarea antibioticelor
- Tratamentele prelungite, mult dupa disparitia simptomatologiei

## How does antibiotic resistance occur?

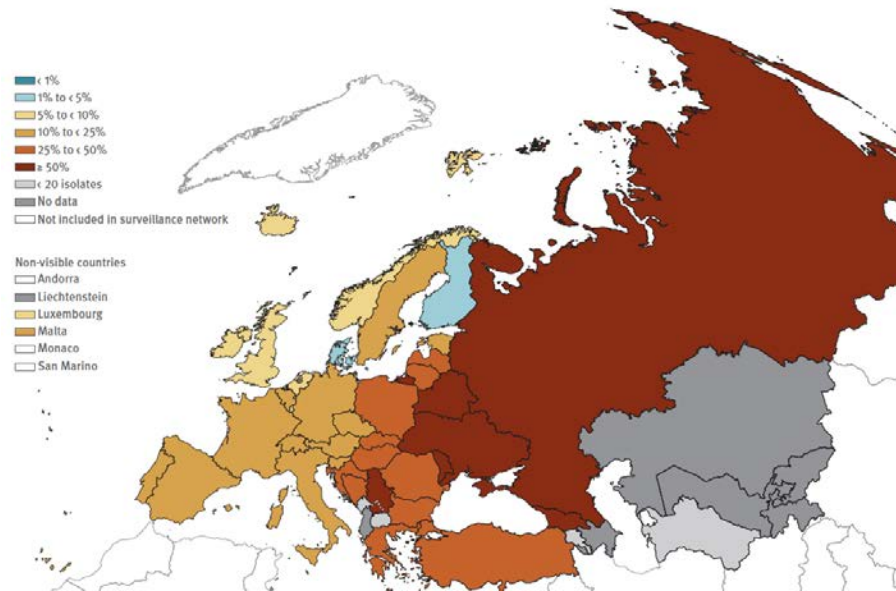


# WHO European Surveillance of Antimicrobial Resistance -2023

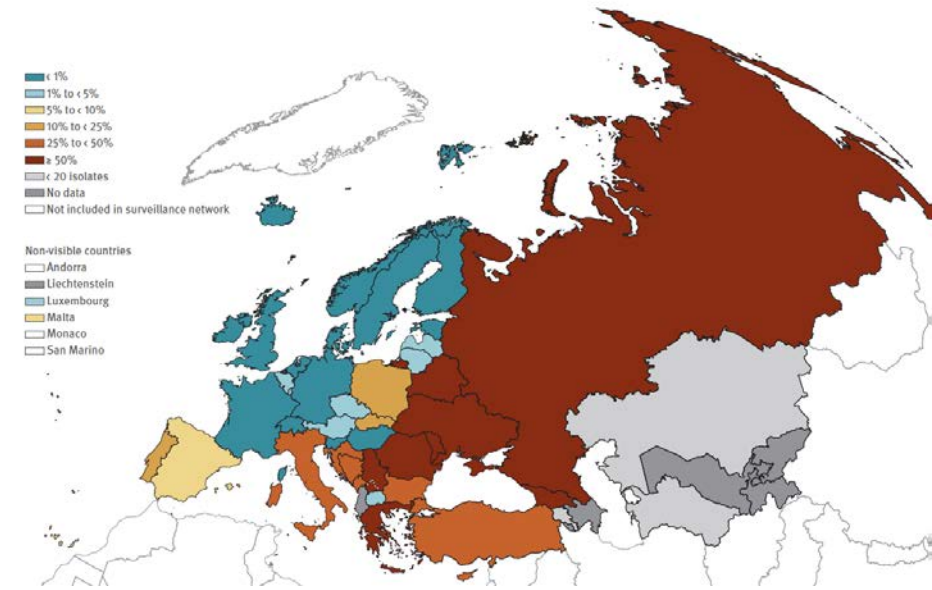
**Fig. 4** *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021



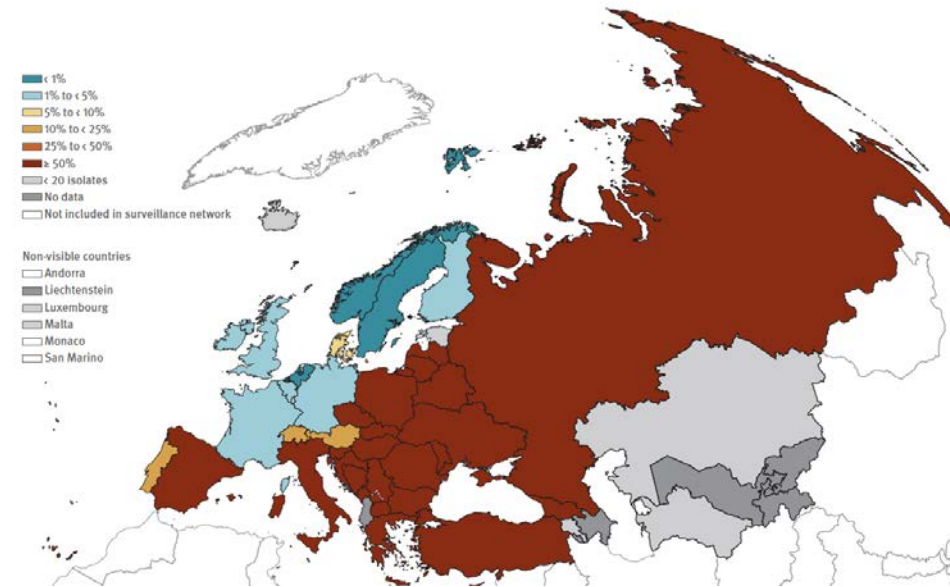
**Fig. 6** *Pseudomonas aeruginosa*. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021



**Fig. 5** *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021



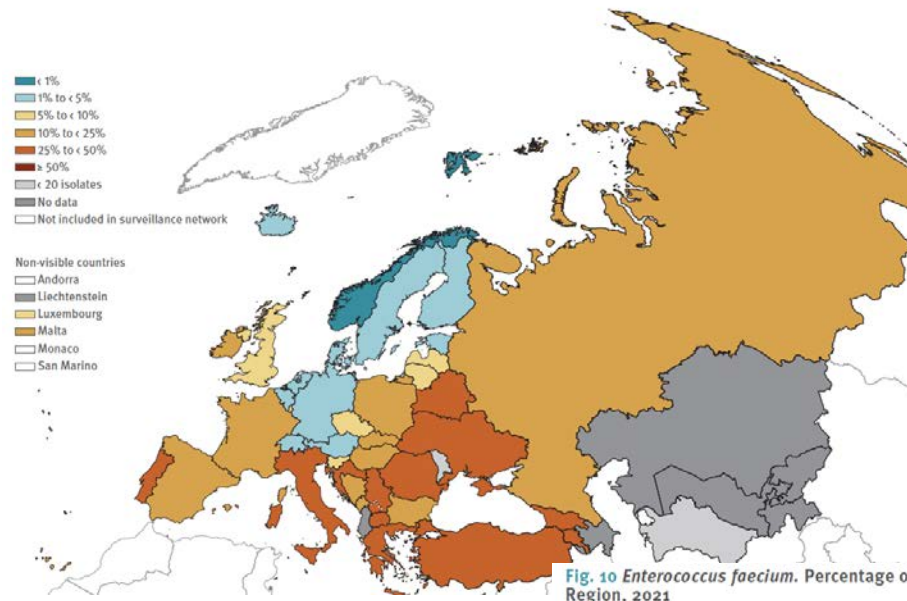
**Fig. 7** *Acinetobacter* species. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021



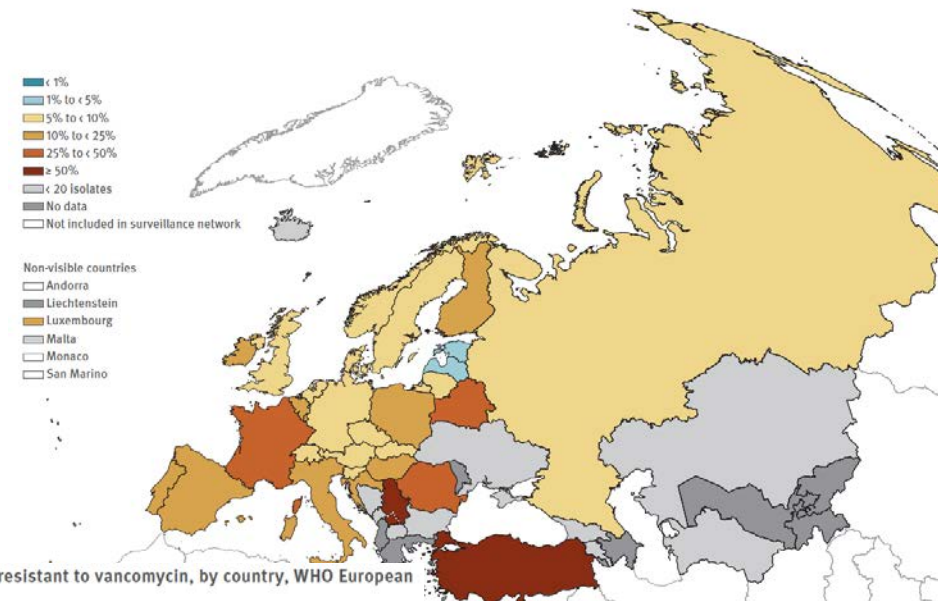


# WHO European Surveillance of Antimicrobial Resistance -2023

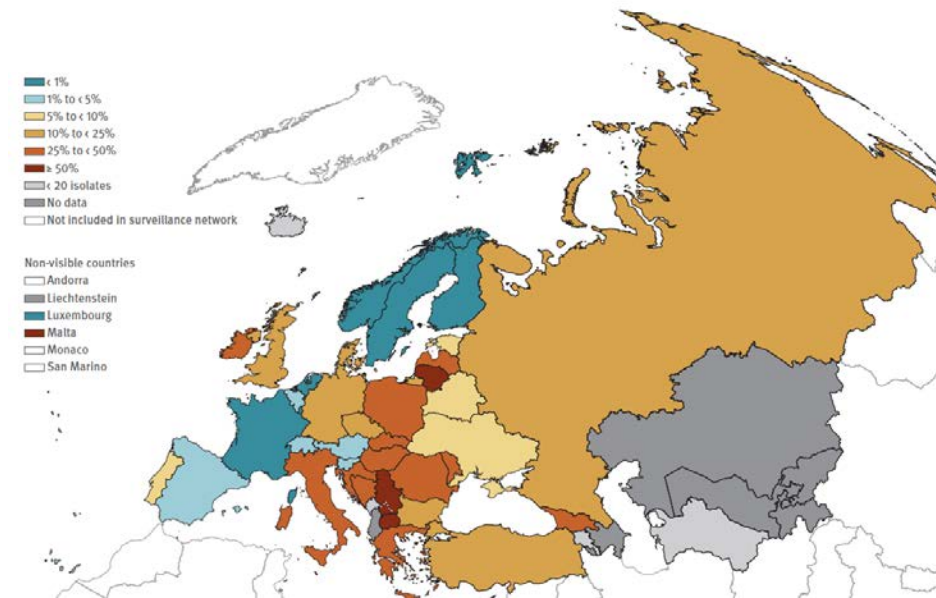
**Fig. 8** *Staphylococcus aureus*. Percentage of invasive isolates resistant to meticillin (MRSA),<sup>a</sup> by country, WHO European Region, 2021



**Fig. 9** *Streptococcus pneumoniae*. Percentage of penicillin<sup>a</sup> non-wild-type<sup>b</sup> invasive isolates, by country, WHO European Region, 2021



**Fig. 10** *Enterococcus faecium*. Percentage of invasive isolates resistant to vancomycin, by country, WHO European Region, 2021



# Clasificarea AWaRe a antibioticelor

- Clasificarea AWaRe a antibioticelor
  - dezvoltată în 2017
  - este o inițiativă a Organizației Mondiale a Sănătății (OMS)
  - își propune să îmbunătățească utilizarea antibioticelor și să combată rezistența la antibiotice.
- Antibioticele sunt clasificate în trei grupuri, **Access, Watch și Reserve**, ținând cont de impactul diferitelor antibiotice și clase de antibiotice asupra rezistenței antimicrobiene,

- **Categoria Access (Acces):**

- antibiotice care au activitate împotriva unei game largi de patogeni susceptibili întâlniți frecvent,
- prezintă și un **potențial mai scăzut de rezistență** decât antibioticele din celelalte grupuri.
- opțiuni esențiale de tratament empiric de primă sau a doua alegere

- **Categoria Watch (Supraveghere):**

- antibioticele din această categorie prezintă un **risc mai mare de rezistență** la utilizarea lor frecventă.
- acestea trebuie supravegheate cu atenție și utilizate cu precauție pentru a evita creșterea rezistenței la antibiotice.

- **Categoria Reserve (Rezervă):**

- include antibioticele considerate **ultima opțiune de tratament**,
- rezervate pentru situații foarte severe și cazuri în care alte antibiotice nu au fost eficiente.

- Prin implementarea acestei clasificări, OMS își propune
  - să promoveze accesul la antibioticele esențiale,
  - să reducă utilizarea inadecvată a antibioticelor din categoria Watch
  - să mențină eficacitatea antibioticelor din categoria Reserve.
- Scopul final este prevenirea și controlul rezistenței la antibiotice, pentru a asigura tratamentul eficient al infecțiilor bacteriene în viitor.



# ACCESS GROUP

- first or second choice antibiotics
- offer the best therapeutic value, while minimizing the potential for resistance

# WATCH GROUP

- first or second choice antibiotics
- only indicated for specific, limited number of infective syndromes
- more prone to be a target of antibiotic resistance and thus prioritized as targets of stewardship programs and monitoring

# RESERVE GROUP

- “last resort”
- highly selected patients (life-threatening infections due to multi-drug resistant bacteria)
- closely monitored and prioritized as targets of stewardship programs to ensure their continued effectiveness

# Access

## Antibiotic Class

Antibiotic	Class
Amikacin	Aminoglycosides
Amoxicillin	Penicillins
Amoxicillin/clavulanic-acid	Beta-lactam/beta-lactamase-inhibitor
Ampicillin	Penicillins
Ampicillin/sulbactam	Beta-lactam/beta-lactamase-inhibitor
Azidocillin	Penicillins
Bacampicillin	Penicillins
Benzathine-benzylpenicillin	Penicillins
Benzylpenicillin	Penicillins
Brodimoprim	Trimethoprim-derivatives
Cefacetrile	First-generation-cephalosporins
Cefadroxil	First-generation-cephalosporins
Cefalexin	First-generation-cephalosporins
Cefaloridine	First-generation-cephalosporins
Cefalotin	First-generation-cephalosporins
Cefapirin	First-generation-cephalosporins
Cefatrizine	First-generation-cephalosporins
Cefazedone	First-generation-cephalosporins
Cefazolin	First-generation-cephalosporins
Cefradine	First-generation-cephalosporins
Cefroxadine	First-generation-cephalosporins
Ceftazidime	First-generation-cephalosporins
Chloramphenicol	Amphenicols
Clindamycin	Lincosamides
Clometocillin	Penicillins
Cloxacillin	Penicillins
Dicloxacillin	Penicillins
Doxycycline	Tetracyclines
Epicillin	Penicillins
Flucloxacillin	Penicillins
Furazidin	Nitrofurans derivatives
Gentamicin	Aminoglycosides
Hetacillin	Penicillins
Mecillinam	Penicillins
Metampicillin	Penicillins

Metronidazole_IV	Imidazoles
Metronidazole_oral	Imidazoles
Nafcillin	Penicillins
Nifurtoinol	Nitrofurans derivatives
Nitrofurantoin	Nitrofurans-derivatives
Ornidazole_IV	Imidazoles
Ornidazole_oral	Imidazoles
Oxacillin	Penicillins
Penamecillin	Penicillins
Phenoxymethylpenicillin	Penicillins
Pivampicillin	Penicillins
Pivmecillinam	Penicillins
Procaine-benzylpenicillin	Penicillins
Propicillin	Penicillins
Secnidazole	Imidazoles
Spectinomycin	Aminocyclitols
Sulbactam	Beta-lactamase-inhibitors
Sulfadiazine	Sulfonamides
Sulfadiazine/tetroxoprim	Sulfonamide-trimethoprim-combinations
Sulfadiazine/trimethoprim	Sulfonamide-trimethoprim-combinations
Sulfadimethoxine	Sulfonamides
Sulfadimidine	Sulfonamides
Sulfadimidine/trimethoprim	Sulfonamide-trimethoprim-combinations
Sulfafurazole	Sulfonamides
Sulfaisodimidine	Sulfonamides
Sulfalene	Sulfonamides
Sulfamazone	Sulfonamides
Sulfamerazine	Sulfonamides
Sulfamerazine/trimethoprim	Sulfonamide-trimethoprim-combinations
Sulfamethizole	Sulfonamides
Sulfamethoxazole	Sulfonamides
Sulfamethoxazole/trimethoprim	Sulfonamide-trimethoprim-combinations
Sulfamethoxyypyridazine	Sulfonamides
Sulfametomidine	Sulfonamides
Sulfametoxydiazine	Sulfonamides

# Access

Sulfametrole/trimethoprim	Sulfonamide-trimethoprim-combinations
Sulfamoxole	Sulfonamides
Sulfamoxole/trimethoprim	Sulfonamide-trimethoprim-combinations
Sulfanilamide	Sulfonamides
Sulfaperin	Sulfonamides
Sulfaphenazole	Sulfonamides
Sulfapyridine	Sulfonamides
Sulfathiazole	Sulfonamides
Sulfathiourea	Sulfonamides
Sultamicillin	Beta-lactam/beta-lactamase-inhibitor
Talampicillin	Penicillins
Tetracycline	Tetracyclines
Thiamphenicol	Amphenicols
Tinidazole_IV	Imidazoles
Tinidazole oral	Imidazoles
Trimethoprim	Trimethoprim-derivatives

## *Bioavailability of Oral Antimicrobials*

Antimicrobial agents with a high oral bioavailability will usually afford excellent penetration of drug into the systemic circulation. In most cases, intravenous administration of such agents offers little to no significant advantage over oral administration. The table below provides bioavailability information of agents for which oral administration is usually sufficient.

<b>Antimicrobial</b>	<b>Oral Bioavailability<sup>2,3,4</sup></b>
Clindamycin	90%
Fluconazole	>90%
Metronidazole	100%
Ciprofloxacin	70-80%
Trimethoprim + Sulfamethoxazole	>85%

# Watch

- 1. Cefalosporine de a treia și a patra generație:** Exemple includ cefotaxim, ceftriaxon, ceftazidim.
- 2. Fluoroquinolone:** Exemple includ ciprofloxacin, levofloxacin. Sunt utilizate pentru tratamentul infecțiilor respiratorii, urinare și ale altor organe.
- 3. Carbapeneme:** Exemple includ meropenem, imipenem. Aceste antibiotice sunt rezervate pentru tratamentul unor infecții severe rezistente la alte clase de antibiotice.
- 4. Aminoglicozide:** Exemple includ gentamicin, amikacin. Sunt utilizate în special pentru infecții grave, dar pot avea efecte secundare și pot contribui la dezvoltarea rezistenței.



Antibiotic	Class
Arbekacin	Aminoglycosides
Aspoxicillin	Penicillins
Azithromycin	Macrolides
Azlocillin	Penicillins
Bekanamycin	Aminoglycosides
Biapenem	Carbapenems
Carbenicillin	Penicillins
Carindacillin	Penicillins
Cefaclor	Second-generation-cephalosporins
Cefamandole	Second-generation-cephalosporins
Cefbuperazone	Second-generation-cephalosporins
Cefcapene-pivoxil	Third-generation-cephalosporins
Cefdinir	Third-generation-cephalosporins
Cefditoren-pivoxil	Third-generation-cephalosporins
Cefepime	Fourth-generation-cephalosporins
Cefetamet-pivoxil	Third-generation-cephalosporins
Cefixime	Third-generation-cephalosporins
Cefmenoxime	Third-generation-cephalosporins
Cefmetazole	Second-generation-cephalosporins
Cefminox	Second-generation-cephalosporins
Cefodizime	Third-generation-cephalosporins
Cefonicid	Second-generation-cephalosporins
Cefoperazone	Third-generation-cephalosporins
Ceforanide	Second-generation-cephalosporins
Cefoselis	Fourth-generation-cephalosporins
Cefotaxime	Third-generation-cephalosporins
Cefotetan	Second-generation-cephalosporins
Cefotiam	Second-generation-cephalosporins
Cefoxitin	Second-generation-cephalosporins
Cefozopran	Fourth-generation-cephalosporins
Cefpiramide	Third-generation-cephalosporins
Cefpirome	Fourth-generation-cephalosporins
Cefpodoxime-proxetil	Third-generation-cephalosporins

Ceftizoxime	Third-generation-cephalosporins
Ceftriaxone	Third-generation-cephalosporins
Cefuroxime	Second-generation-cephalosporins
Chlortetracycline	Tetracyclines
Cinoxacin	Quinolones
Ciprofloxacin	Fluoroquinolones
Clarithromycin	Macrolides
Clofocetol	Phenol derivatives
Clomocycline	Tetracyclines
Delafloxacin	Fluoroquinolones
Demeclocycline	Tetracyclines
Dibekacin	Aminoglycosides
Dirithromycin	Macrolides
Doripenem	Carbapenems
Enoxacin	Fluoroquinolones
Ertapenem	Carbapenems
Erythromycin	Macrolides
Fidaxomicin	Macrolides
Fleroxacin	Fluoroquinolones
Flomoxef	Second-generation-cephalosporins
Flumequine	Quinolones
Flurithromycin	Macrolides
Fosfomycin_oral	Phosphonics
Fusidic-acid	Steroid antibacterials
Garenoxacin	Fluoroquinolones
Gatifloxacin	Fluoroquinolones
Gemifloxacin	Fluoroquinolones
Grepafloxacin	Fluoroquinolones
Imipenem/cilastatin	Carbapenems
Isepamicin	Aminoglycosides
Josamycin	Macrolides
Kanamycin_IV	Aminoglycosides
Kanamycin_oral	Aminoglycosides
Lasclufloxacin	Fluoroquinolones

Levofloxacin	Fluoroquinolones
Levonadifloxacin	Fluoroquinolones
Lincomycin	Lincosamides
Lomefloxacin	Fluoroquinolones
Loracarbef	Second-generation-cephalosporins
Lymecycline	Tetracyclines
Meropenem	Carbapenems
Metacycline	Tetracyclines
Mezlocillin	Penicillins
Micronomicin	Aminoglycosides
Midecamycin	Macrolides
Minocycline_oral	Tetracyclines
Miocamycin	Macrolides
Moxifloxacin	Fluoroquinolones
Nemonoxacin	Quinolones
Neomycin_IV	Aminoglycosides
Neomycin_oral	Aminoglycosides
Netilmicin	Aminoglycosides
Norfloxacin	Fluoroquinolones
Ofloxacin	Fluoroquinolones
Oleandomycin	Macrolides
Oxolinic-acid	Quinolones
Oxytetracycline	Tetracyclines
Panipenem	Carbapenems
Pazufloxacin	Fluoroquinolones
Pefloxacin	Fluoroquinolones
Penimepicycline	Tetracyclines
Pheneticillin	Penicillins
Pipemidic-acid	Quinolones
Piperacillin	Penicillins
Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_ant
Piromidic-acid	Quinolones
Pristinamycin	Streptogramins
Prulifloxacin	Fluoroquinolones
Ribostamycin	Aminoglycosides

Rokitamycin	Macrolides
Rolitetracycline	Tetracyclines
Rosoxacin	Quinolones
Roxithromycin	Macrolides
Rufloxacin	Fluoroquinolones
Sarecycline	Tetracyclines
Sisomicin	Aminoglycosides
Sitaflloxacin	Fluoroquinolones
Solithromycin	Macrolides
Sparfloxacin	Fluoroquinolones
Spiramycin	Macrolides
Streptoduocin	Aminoglycosides
Streptomycin_IV	Aminoglycosides
Streptomycin_oral	Aminoglycosides
Sulbenicillin	Penicillins
Tazobactam	Beta-lactamase-inhibitors
Tebipenem	Carbapenems
Teicoplanin	Glycopeptides
Telithromycin	Macrolides
Temafloxacin	Fluoroquinolones
Temocillin	Penicillins
Ticarcillin	Penicillins
Tobramycin	Aminoglycosides
Tosufloxacin	Fluoroquinolones
Troleandomycin	Macrolides
Trovaflloxacin	Fluoroquinolones
Vancomycin_IV	Glycopeptides
Vancomycin_oral	Glycopeptides

# Reserve

Antibiotic	Class
Aztreonam	Monobactams
Carumonam	Monobactams
Cefiderocol	Other-cephalosporins
Ceftaroline-fosamil	Fifth-generation cephalosporins
Ceftazidime/avibactam	Third-generation-cephalosporins
Ceftobiprole-medocaril	Fifth-generation cephalosporins
Ceftolozane/tazobactam	Fifth-generation cephalosporins
Colistin_IV	Polymyxins
Colistin_oral	Polymyxins
Dalbavancin	Glycopeptides
Dalfopristin/quinupristin	Streptogramins
Daptomycin	Lipopeptides
Eravacycline	Tetracyclines
Earopenem	Penems
Fosfomicin_IV	Phosphonics
Iclaprim	Trimethoprim-derivatives
Imipenem/cilastatin/relebactam	Carbapenems
Lefamulin	Pleuromutilin
Linezolid	Oxazolidinones
Meropenem/vaborbactam	Carbapenems
Minocycline_IV	Tetracyclines
Omadacycline	Tetracyclines
Oritavancin	Glycopeptides
Plazomicin	Aminoglycosides
Polymyxin-B_IV	Polymyxins
Polymyxin-B_oral	Polymyxins
Tedizolid	Oxazolidinones
Telavancin	Glycopeptides
Tigecycline	Glycylcyclines

## Levels of Restriction

Antimicrobial restrictions are often categorised in a 'traffic-light system'. Whilst this is not an absolute requirement, such a system is recognised across many Australian healthcare facilities and it is generally considered to be a successful tool for educating prescribers about a local antimicrobial restriction policy.

### **RED - Highly Restricted**

Most red antimicrobials require discussion with an infectious disease (ID) physician or clinical microbiologist (or a nominated medical officer) **prior to use**, however some restriction may be criteria-based where appropriate. Consideration must be given on how to manage requests for highly restricted antimicrobials in life-threatening and/or urgent situations 24 hours a day, 7 days a week.

### **ORANGE - Restricted**

Orange antimicrobial agents are often subject to criteria-based restrictions. Many orange antimicrobials are restricted to use for selected indications or for a limited amount of time (e.g. 24 to 72 hours) prior to seeking approval from an ID physician or clinical microbiologist, or a nominated medical officer. These agents often require approval **after initiation** of therapy. Some agents may be classified as orange for specific indications and red for all other indications.

### **GREEN - Unrestricted**

Green antimicrobial agents should be prescribed sensibly and appropriately, but have no specific restrictions on their use.

# Australia

ANTIMICROBIAL (Systemic)	RESTRICTION LEVEL	RATIONALE*
Ganciclovir	RED	1
Gentamicin (up to 48 hrs)	ORANGE	13
Gentamicin (after 48 hrs)	RED	13
Griseofulvin	GREEN	N/A
Hexamine hippurate	GREEN	N/A
Imipenem	RED	9,10
Isoniazid	ORANGE	12
Itraconazole	ORANGE	1
Ivermectin	ORANGE	1,4
Lincomycin	ORANGE	6,7
Linezolid	RED	1,4
Mebendazole	GREEN	N/A
Mefloquine	ORANGE	4,7
Meropenem	RED	9
Metronidazole (oral)	GREEN	N/A
Metronidazole (inj)	ORANGE	2
Micafungin	RED	1,4,5

ANTIMICROBIAL (Systemic)	RESTRICTION LEVEL	RATIONALE*
Primaquine	RED	4,7
Procaine penicillin	GREEN	N/A
Pyrantel	GREEN	N/A
Pyrazinamide	ORANGE	12
Pyrimethamine	RED	1,7
Quinine	RED	4
Rifabutin	RED	1,4
Rifampicin (used in combination for TB or MRSA)	ORANGE	11,12,15
Rifampicin (all other indications)	RED	11,12,15
Rifaximin	ORANGE	4,5,17
Roxithromycin	GREEN	N/A
Sodium fusidate (used in combination for MRSA)	ORANGE	15
Sodium fusidate (all other indications)	RED	15
Streptomycin	RED	1,4
Sulfadiazine	RED	1,4



Minocycline	GREEN	N/A
Moxifloxacin (oral)	ORANGE	3,9
Moxifloxacin (inj)	RED	2
Neomycin	ORANGE	13
Nitrofurantoin	GREEN	N/A
Norfloxacin	ORANGE	7
Nystatin	GREEN	N/A
Oseltamivir	ORANGE	7
Palivizumab	RED	14
Pentamidine	RED	1,4
Phenoxymethylpenicillin	GREEN	N/A
Piperacillin with tazobactam	ORANGE	3,7,9
Posaconazole	RED	1,2
Praziquantel	ORANGE	1,7

Sulfadiazine	RED	1,4
Teicoplanin	RED	4,6
Terbinafine	GREEN	N/A
Ticarcillin with clavulanic acid	ORANGE	3,7,9
Tigecycline	RED	1,4
Tinidazole	GREEN	N/A
Tobramycin	ORANGE	6,13
Trimethoprim	GREEN	N/A
Trimethoprim + sulfamethoxazole	GREEN+	N/A
Valaciclovir	ORANGE	6
Valganciclovir	RED	1
Vancomycin	ORANGE	15
Voriconazole	RED	1

# Romania

- ORDIN nr. 63 din 10 ianuarie 2024
- privind reglementarea metodologiei de monitorizare a prescrierii și eliberării la nivel național a medicamentelor din categoria antibiotice și antifungice de uz sistemic
- EMITENT
- MINISTERUL SĂNĂTĂȚII
- Publicat în MONITORUL OFICIAL nr. 41 din 17 ianuarie 2024

Nr. crt.	Denumirea comună internațională
1	AMIKACINUM
2	AMOXICILLINUM*
3	AMOXICILLINUM + ACIDUM CLAVULANICUM*
4	AMPICILLINUM*
5	AMPICILLINUM + SULBACTAM
6	AZITHROMYCINUM
7	AZTREONAM
8	BENZATHINI BENZYLPENICILLINUM
9	BENZYLPENICILLINUM
10	CEFACLORUM
11	CEFADROXILUM*
12	CEFALEXINUM*
13	CEFAZOLINUM
14	CEFEPIMUM
15	CEFIXIMUM
16	CEFOPERAZONUM
17	CEFOTAXIMUM
18	CEFPODOXIMUM
19	CEFTAROLINUM FOSMIL
20	CEFTAZIDIMUM
21	CEFTRIAXONUM
22	CEFUROXIMUM
23	CHLORAMPHENICOLUM*
24	CIPROFLOXACINUM
25	CLARITHROMYCINUM*
26	CLINDAMYCINUM*
27	COLISTIMETAT DE SODIU
28	COLISTINUM
29	COMBINAȚII (CEFOPERAZONUM + SULBACTAMUM)
30	COMBINAȚII (CEFTAZIDIMUM + AVIBACTAMUM)
31	COMBINAȚII (CEFTOLOZANUM + TAZOBACTAMUM)
32	CYCLOSERINUM
33	DALBAVANCINUM
34	DAPTOMYCINUM

35	DOXYCYCLINUM*
36	ERAVACICLINUM
37	ERTAPENEMUM
38	ERYTHROMYCINUM*
39	FIDAXOMICINUM
40	FOSFOMYCINUM
41	GENTAMICINUM
42	IMIPENEMUM + CILASTATINUM
43	IMIPENEMUM + CILASTATINUM + RELEBACTAMUM
44	KANAMYCINUM
45	LEVOFLOXACINUM
46	LINEZOLIDUM
47	MEROPENEMUM
48	METRONIDAZOLUM i.v.
49	METRONIDAZOLUM oral*
50	MINOCYCLINUM
51	MOXIFLOXACINUM
52	NITROFURANTOINUM*
53	NITROXOLINUM
54	NORFLOXACINUM
55	OFLOXACINUM
56	OXACILLINUM*
57	PEFLOXACINUM
58	PHENOXYMETHYLPENICILLINUM*
59	PIPERACILLINUM + TAZOBACTAMUM
60	RIFAMPICINUM
61	RIFAXIMINUM
62	SPIRAMYCINUM
63	STREPTOMYCINUM
64	SULFAFURAZOLUM*
65	SULFAMETHOXAZOLUM + TRIMETHOPRIMUM*

66	SULTAMICILLINUM*
67	TEICOPLANINUM
68	TETRACYCLINUM*
69	TIGECYCLINUM
70	TINIDAZOLUM*
71	TOBRAMYCINUM
72	VANCOMYCINUM
73	NYSTATINUM*
74	AMPHOTERICINUM B
75	FLUCONAZOLUM
76	ITRACONAZOLUM
77	VORICONAZOLUM
78	POSACONAZOLUM
79	ISAVUCONAZOLUM
80	CASPOFUNGINUM
81	ANIDULAFUNGINUM
82	MICAFUNGINUM

(la 23-01-2024, Anexa nr. 1 a fost modificată de Punct ORDINUL nr. 183 din 22 ianuarie 2024, publicat în MONIT din 23 ianuarie 2024 )

# Concluzii

- Limitarea rezistenței la antibiotice este o preocupare globală crucială,
- Adoptarea unor măsuri eficiente este esențială pentru
  - a proteja sănătatea publică și pentru
  - a menține eficacitatea antibioticelor.

Va multumesc pentru atentie!

