



PROVOCĂRI ALE TERAPIEI MEDICAMENTOASE ÎN PEDIATRIE

Dr Ana Ștefănescu
Medic pediatru

Terapie medicamentoasă copii vs adulți

- Farmacodinamică diferită
- Efect diferit al “gazdei”
- Efecte secundare diferite
- Stadiul de dezvoltare poate afecta efectul (dorit sau secundar!)
- “Programming by drugs”
- Studii insuficiente la copii

Terapie medicamentoasă copii vs adulți

- Medicamente nerecomandate la copii
- Medicamente folosite off label
- Medicamente recomandate dar fără formulări pediatrice în România

[J Pediatr Pharmacol Ther.](#) 2020; 25(3): 175–191. doi: [10.5863/1551-6776-25.3.175](#)

PMCID: PMC7134587 | PMID: [32265601](#)

Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List

- Aspirină (Kawasaki, AVC ischemic, chirurgie CV)
- Fluorochinolone (FC, ITU complicate, pneumonii severe)
- Sildenafil (HTP)
- Siropuri pt tuse și răceală

Terapie medicamentoasă copii vs adulți

- Medicamente nerecomandate la copii
- Medicamente folosite off label
- Medicamente recomandate dar fără formulări pediatrice în România



Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology

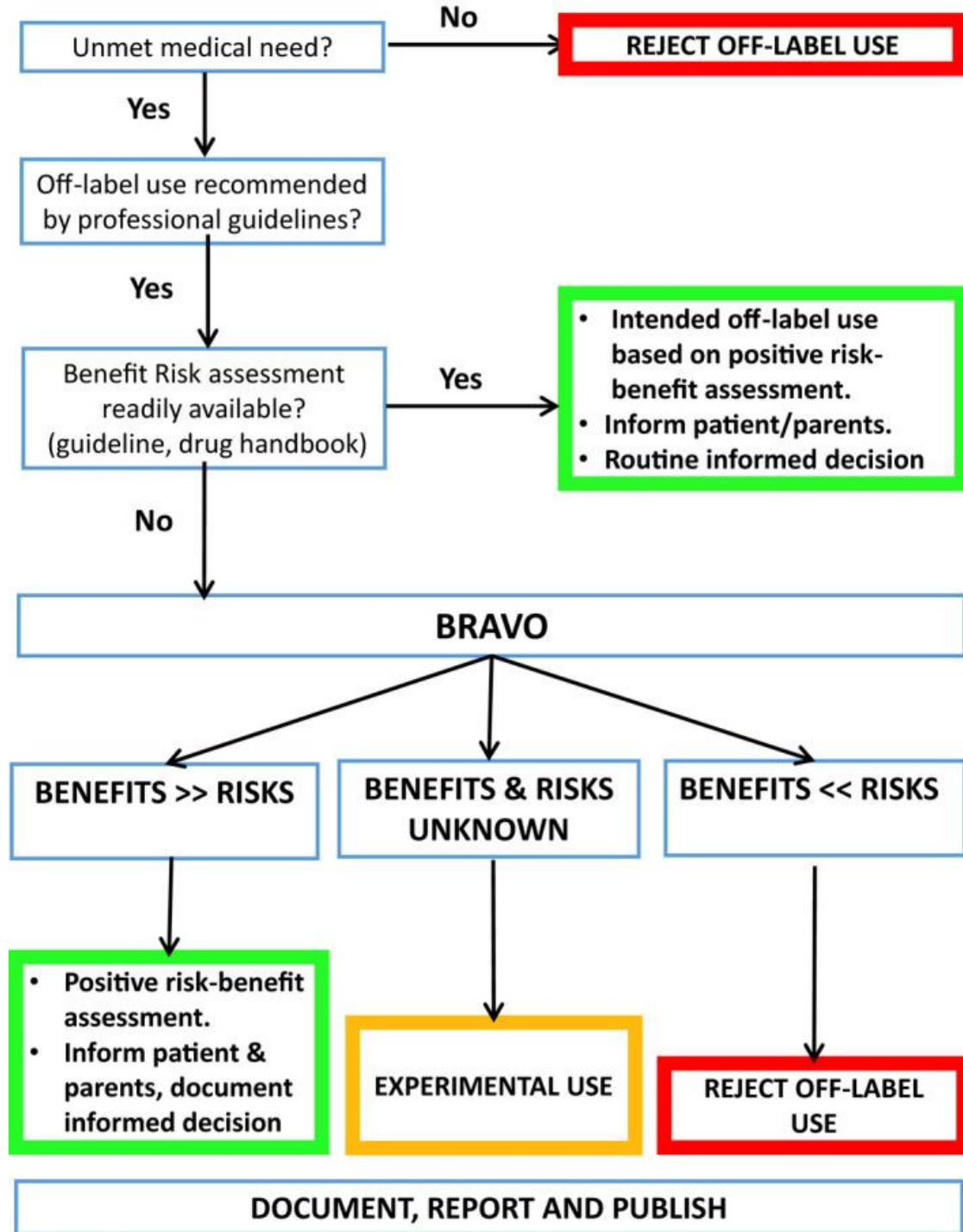
EAP Statement | Published: 03 January 2020 | 179, 839–847 (2020)

- The Academia Europeană de Pediatrie și Societatea Europeană de Farmacologie Perinatală și Pediatrică au emis un document care permite utilizarea medicamentelor în regim off-label la copii când **indicația este rezonabilă** și **beneficiile depășesc riscurile**.

[Clin Pharmacol Ther.](#) 2021 Oct; 110(4): 952–965.

Published online 2021 Jul 29. doi: [10.1002/cpt.2336](https://doi.org/10.1002/cpt.2336)

Benefit-Risk Assessment of Off-Label Drug Use in Children: The Bravo Framework



[Clin Pharmacol Ther.](#) 2021 Oct; 110(4): 952–965.

Published online 2021 Jul 29. doi: [10.1002/cpt.2336](https://doi.org/10.1002/cpt.2336)

Benefit-Risk Assessment of Off-Label Drug Use in Children: The Bravo Framework

RISK TOLERANCE FOR THE USE OF ONDANSETRON FOR GASTROENTERITIS-INDUCED NAUSEA AND VOMITING

The assessment has been reviewed by the DPF's editorial board. The board concluded that in cases where prolonged nausea, vomiting, and diarrhea leads to (risk of) dehydration, drug treatment can be considered to prevent hospital admission and to improve the success rate of oral rehydration. Vomiting and diarrhea are uncomfortable symptoms for both the child and parent, but do not need treatment in general. Editorial board members do not have conflicts of interest (as

Off-Label Use of Drugs in Children **FREE**

COMMITTEE ON DRUGS; Kathleen A. Neville, MD; Daniel A.C. Frattarelli, MD; Jeffrey L. Galinkin, MD; Thomas P. Green, MD; Timothy D. Johnson, DO; MMM; Ian M. Paul, MD; John N. Van Den Anker, MD

Pediatrics (2014) 133 (3): 563–567.

1. Decizia rămâne a medicului.

1. Prospect/ ANM

2. Dovezi științifice – inclusiv rezultatele negative!

2. Utilizare off label în caz de situații legate de medicamentul însuși – de ex lipsa din depozit

Management of Pediatric Chronic Spontaneous Urticaria: A Review of Current Evidence and Guidelines

Cetirizine	• 6 to <12 months: 2.5 mg daily • 1 to <2 years: 2.5 mg once daily • 2 to 5 years: 2.5–5 mg daily • 6 to 11 years: 5–10 mg daily • ≥12 years: 10 mg daily	Hypersensitivity	Drowsiness, headache	Can be used during the last trimester of pregnancy.
Levocetirizine	• ≥6 months to ≤5 years: 1.25 mg daily • 6 to 11 years: 2.5 mg daily • ≥12 years: 5 mg daily	Hypersensitivity, end-stage renal disease, hemodialysis, patients ≤11 years with renal impairment	Diarrhea, drowsiness	

Terapie medicamentoasă copii vs adulți

- Medicamente nerecomandate la copii
- Medicamente folosite off label
- Medicamente recomandate dar fără formulări pediatrice în România

Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

Due to the unpleasant acute illness caused by UTI and the risk of pyelonephritis-induced permanent kidney damage, many children are given long-term antibiotics aimed at preventing recurrence. Cotrimoxazole, nitrofurantoin and trimethoprim are commonly used for this purpose. These medications may cause side effects and promote the development of resistant bacteria.

Drug	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Hexachlorophene ⁹⁶	Neurotoxicity	Avoid in neonates	Strong	High
Indinavir ⁹⁹	Nephrolithiasis	Avoid in children	Strong	High
	Hyperbilirubinemia	Avoid in neonates	Strong	Low
Ivermectin (oral) ^{100,104}	Encephalopathy	Avoid in <1 year	Weak	Low
Lamotrigine ¹⁰²	Serious skin rashes	Caution in children; titration needed	Strong	High
Lidocaine 2% viscous ^{103,104}	Seizures, arrhythmia, death (due to CNS depression, seizures, or dysrhythmias)	Avoid in infants for teething	Strong	High
Linacotide ¹⁰⁵	Death from dehydration	Avoid in <6 years	Weak	Very low
Lindane ^{106,107}	Seizure, spasm	Avoid in <10 years or <50 kg	Moderate	Low
Loperamide ¹⁰⁸	Ileus, lethargy	Avoid in infants for acute infectious diarrhea	Strong	High
Macrolides ^{109–112} Azithromycin Erythromycin (oral and intravenous)	Hypertrophic pyloric stenosis	Avoid in neonates, unless treating <i>Bordetella pertussis</i> (azithromycin), or <i>Chlamydia trachomatis</i> pneumonia (azithromycin and erythromycin) Consider risk/benefit ratio when using for ureaplasma (azithromycin)	Strong	High
Malathion ⁹³	Increased absorption (organophosphate poisoning)	Avoid in <1 year	Weak	Very low
Meperidine ^{94,95}	Respiratory depression	Avoid in neonates Caution in children	Strong	High
Midazolam ⁹⁴	Severe intraventricular hemorrhage, periventricular leukomalacia, or death	Avoid in very low birth weight neonates	Strong	High
Mineral oil, oral ⁹⁷	Lipid pneumonitis	Avoid in <1 year	Strong	Low
Naloxone ^{98,99}	Seizure	Avoid in neonates for postpartum resuscitation	Strong	High
Nitrofurantoin ^{120,121}	Hemolytic anemia	Avoid in neonates	Weak	Very low
Olanzapine ¹²²	Metabolic syndrome (weight gain, hyperlipidemia, hyperglycemia)	Caution long-term use (>24 weeks) in children	Strong	High
Opium tincture ¹²³	Respiratory depression	Avoid in neonates Caution in children	Strong	High



[Exp Ther Med.](#) 2021 Jul; 22(1): 748.

Published online 2021 May 12. doi: [10.3892/etm.2021.10180](https://doi.org/10.3892/etm.2021.10180)

Antibiotic resistance patterns of urinary tract pathogens in children from Central Romania

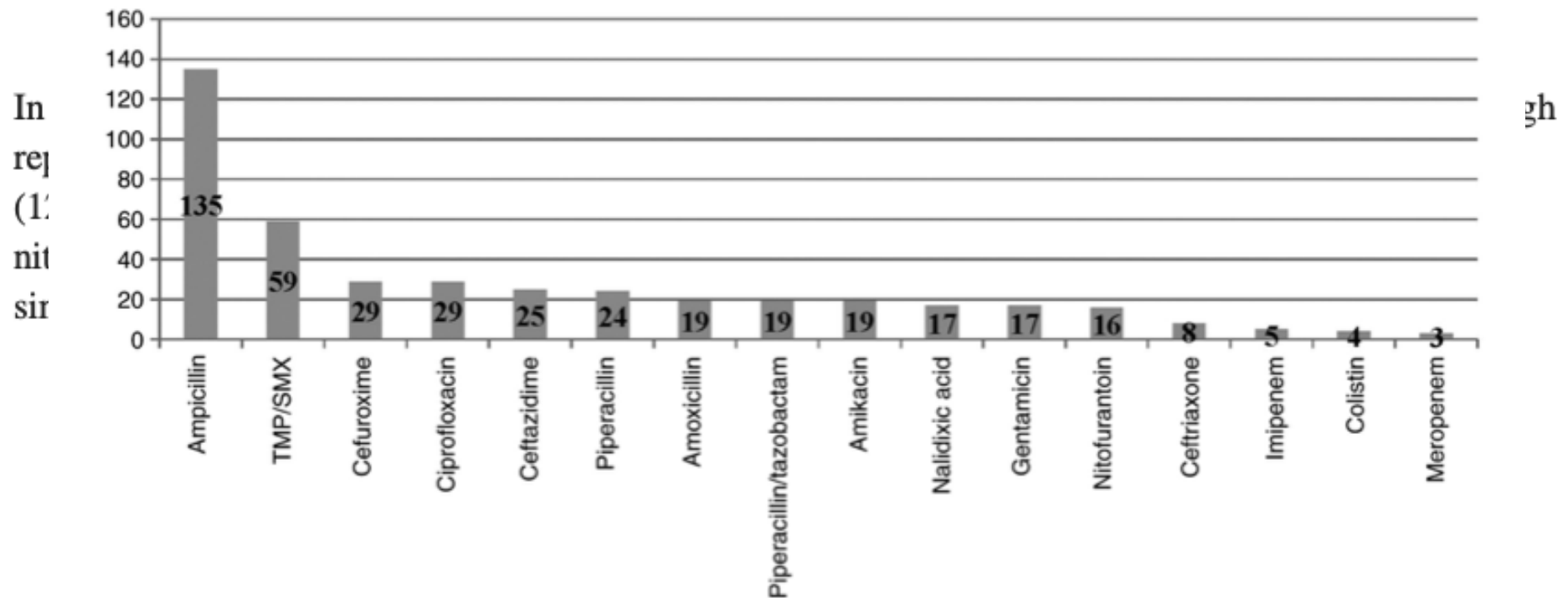
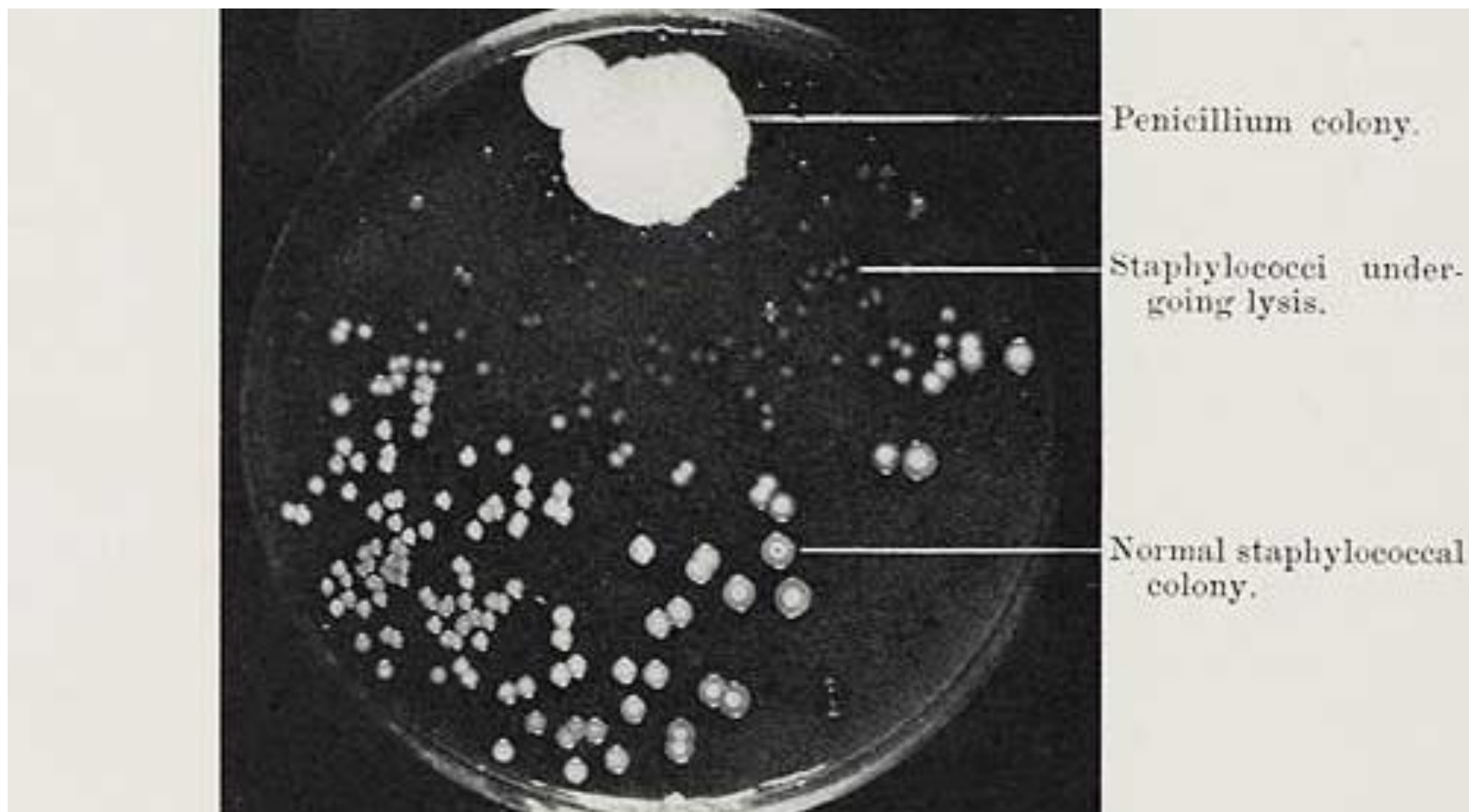


Figure 5. *E. coli* resistance pattern.

ATB/Uropathogen	<i>E. coli</i> (%)	<i>Klebsiella</i> (%)	<i>Pseudomonas</i> (%)	<i>Proteus</i> (%)	<i>Enterococcus</i> (%)	<i>Morganella</i> (%)	<i>Enterobacter</i> (%)
Nalidixic acid	7.11	1.81	<1	<1	<1	<1	<1
Amikacin	7.94	<1	<1	<1	<1	<1	<1
Amoxicillin	33.05	6.04	<1	3.62	<1	1.25	1.81
Ampicillin	56.48	7.85	<1	5.13	<1	1.25	2.09
Cefepime	7.94	4.53	1.25	2.09	<1	<1	2.09
Cefotaxime	10.04	4.53	<1	2.09	1.25	<1	1.81
Ceftazidime	10.46	3.32	1.67	1.25	1.25	<1	2.09
Ceftriaxone	3.34	1.25	<1	<1	1.25	<1	1.67
Cefuroxime	12.13	1.25	1.25	1.67	1.25	<1	2.09
Ciprofloxacin	12.13	3.92	<1	1.25	1.67	<1	1.25
Colistin	1.67	<1	<1	<1	<1	<1	<1
Ertapenem	0.83	2.09	<1	<1	<1	<1	1.25
Gentamicin	7.11	3.02	3.32	1.67	1.81	<1	1.25
Imipenem	2.09	<1	<1	<1	<1	<1	<1
Linezolid	<1	<1	<1	<1	<1	<1	<1
Meropenem	1.25	<1	<1	<1	<1	<1	<1
Netilmicin	<1	<1	<1	<1	<1	<1	<1
Nitrofurantoin	6.69	1.81	<1	1.81	<1	<1	<1
Norfloxacin	15.06	4.23	<1	1.67	<1	<1	<1
Oxacillin	<1	<1	<1	<1	<1	<1	<1
Piperacillin	7.94	0.83	<1	<1	<1	<1	<1
Piperacillin/tazobactam	10.04	2.41	1.25	<1	<1	<1	2.09

Rezistența bacteriană la antibiotice





SURVEILLANCE REPORT

Antimicrobial consumption in the EU/EEA (ESAC-Net)

Annual Epidemiological Report for 2021

România s-a menținut la aceeași rată de utilizare de antibiotic ca în urmă cu 10 ani (> 25 doze zilnice/ 1000 persoane). Consumul la nivelul Uniunii Europene este plafonat la 16 doze zilnice/ 1000 persoane

Table 1. Total consumption (community and hospital sector) of antibacterials for systemic use (ATC group J01), EU/EEA and UK, 2012–2021 (expressed as DDD per 1 000 inhabitants per day)

Country	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Time series, 2012–2021	Trend	Compound annual growth rate (CAGR)
Austria								11.6	8.8	8.8		N/A	N/A
Belgium	25.6	24.2	24.0	24.4	24.2	22.8	22.3	21.4	16.7	17.4		↓	-4.2%
Bulgaria	17.4	18.6	20.0	20.1	19.2	20.5	21.1	20.7	22.7	24.4		↑	3.8%
Croatia	20.0	19.2	19.4	19.7	18.7	18.6	18.8	18.8	15.7	18.2		↓	-1.1%
Cyprus	25.1	23.9	22.2	26.6	28.4	28.9	28.0	30.1	28.9	25.0		-	0.0%
Czechia								16.9	13.4	13.7		N/A	N/A
Denmark	17.4	17.5	17.1	17.5	17.0	16.2	15.6	15.3	14.3	14.4		↓	-2.1%
Estonia	12.2	12.0	11.9	12.1	12.0	11.6	11.8	11.8	10.5	10.1		↓	-2.1%
Finland	20.6	19.6	19.1	18.1	17.4	15.7	15.4	14.7	11.9	11.3		↓	-6.5%
France	25.7	25.9	24.9	25.6	25.6	24.7	25.3	25.1	20.3	21.5		↓	-2.0%
Germany												N/A	N/A
Greece	29.9	29.8	31.0	33.2	33.1	34.2	34.1	34.1	28.1	23.5		-	-2.6%
Hungary	14.1	14.5	15.2	15.8	14.4	14.6	14.8	14.4	11.2	11.9		-	-1.8%
Iceland	19.7	19.4				20.7	20.4	19.3	16.5	16.8		N/A	N/A
Ireland	21.0	21.6	21.0	23.0	22.0	20.9	22.4	22.8	18.6	17.8		-	-1.8%
Italy	24.6	25.2	24.5	24.5	24.0	20.9	21.4	21.7	18.4	17.5		↓	-3.7%
Latvia	12.9	13.3	12.6	13.1	12.9	13.9	13.4	13.9	11.9	11.6		-	-1.2%
Lithuania	15.3	17.1	15.1	15.8	16.6	16.6	16.3	16.1	14.1	13.7		-	-1.3%
Luxembourg	25.0	25.0	23.2	23.5	22.9	22.6	22.1	21.1	16.1	15.9		N/A	N/A
Malta	20.8	22.2	22.4	21.2	20.9	22.6	20.2	20.7	16.6	15.8		↓	-3.0%
Netherlands	10.9	10.5	10.3	10.4	10.1	9.8	9.7	9.5	8.5	8.3		↓	-3.0%
Norway	17.9	17.2	16.9	16.8	16.2	15.7	15.3	14.9	13.9	14.0		↓	-2.7%
Poland			21.2	24.1	22.0	25.4	24.4	23.6	18.5	20.2		-	-0.7%
Portugal	20.1	17.6	18.0	18.8	19.0	18.3	19.1	19.3	15.2	15.3		-	-3.0%
Romania	25.9	26.8	26.6	28.0	24.4	24.5	25.1	25.8	25.2	25.7		-	-0.1%
Slovakia	19.7	23.2	21.2	24.2	23.6	20.0	22.0	19.3	14.4	16.0		↓	-2.3%
Slovenia	13.2	13.3	13.1	13.3	13.0	13.1	13.2	13.0	10.2	10.2		↓	-2.8%
Spain	15.7†	16.2†	17.1†	17.5†	27.5	26.8	26.3	24.9	19.8	20.0		N/A	N/A
Sweden	15.3	14.2	14.0	13.5	13.2	12.8	12.4	11.8	10.4	10.1		↓	-4.5%
EU/EEA*	21.2	21.6	21.2	21.7	20.9	20.4	20.3	19.8	16.4	16.4		↓	-2.8%
United Kingdom		20.5	20.8	20.2	19.7	19.4	18.8	18.2				N/A	N/A
Crude EU/EEA**	22.3	22.0	21.7	22.3	22.2	21.7	21.7	21.1	17.8	18.1		N/A	N/A



All country data are shown as they are reported to The European Surveillance System.

Community consumption of antibacterials for systemic use (ATC group J01)

In 2021, the EU/EEA population-weighted mean consumption of antibacterials for systemic use in the community (i.e. outside of hospitals) was 15.0 DDD per 1 000 inhabitants per day, ranging from 7.2 in Austria to 24.3 in Romania (Figure 2).

Figure 2. Community consumption of antibacterials for systemic use (ATC group J01), EU/EEA countries, 2021 (expressed as DDD per 1 000 inhabitants per day)

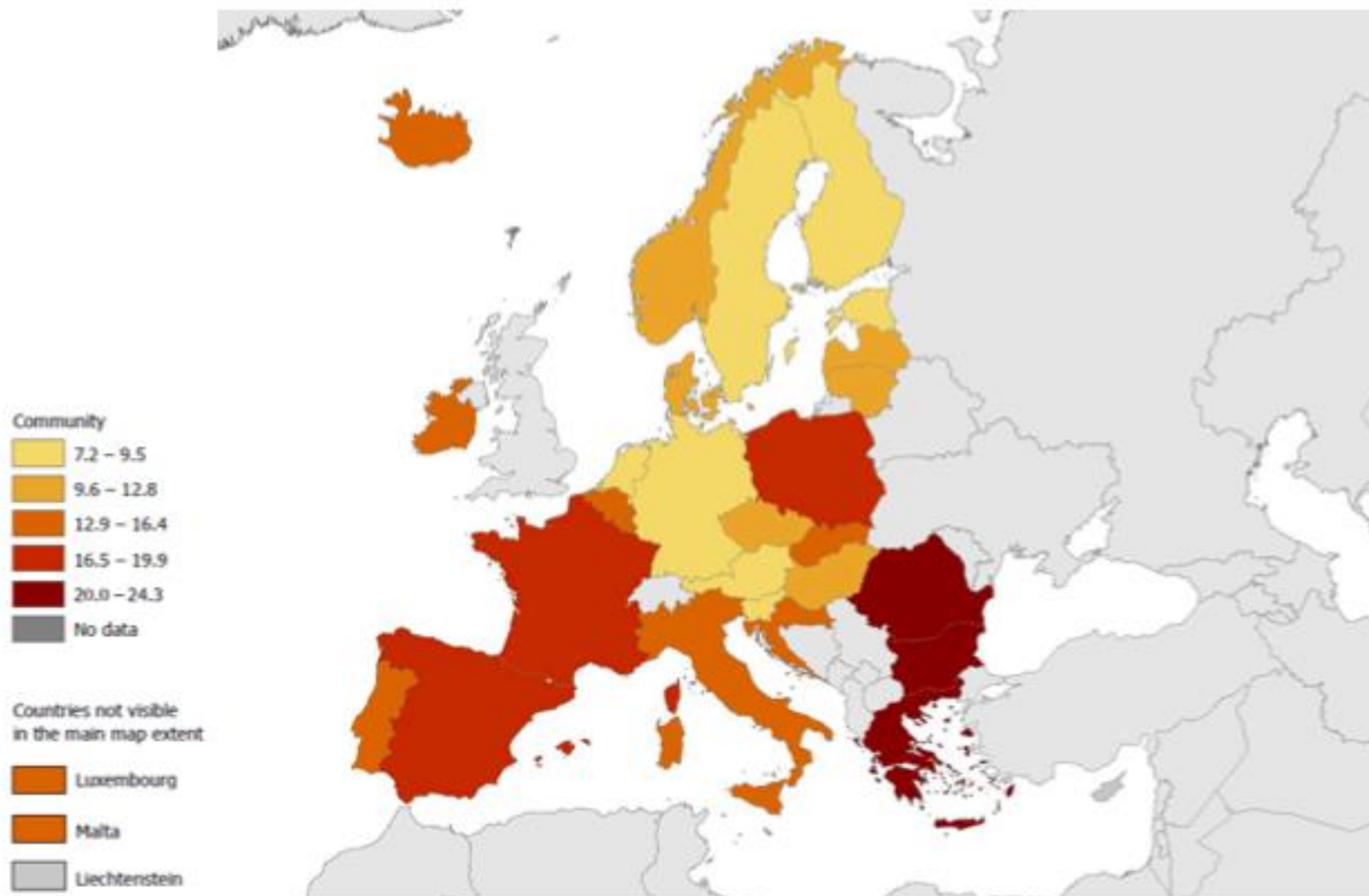
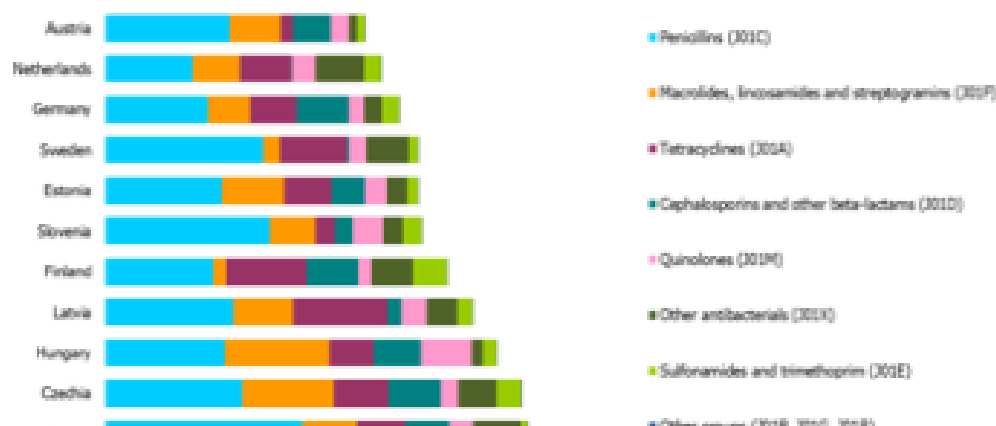
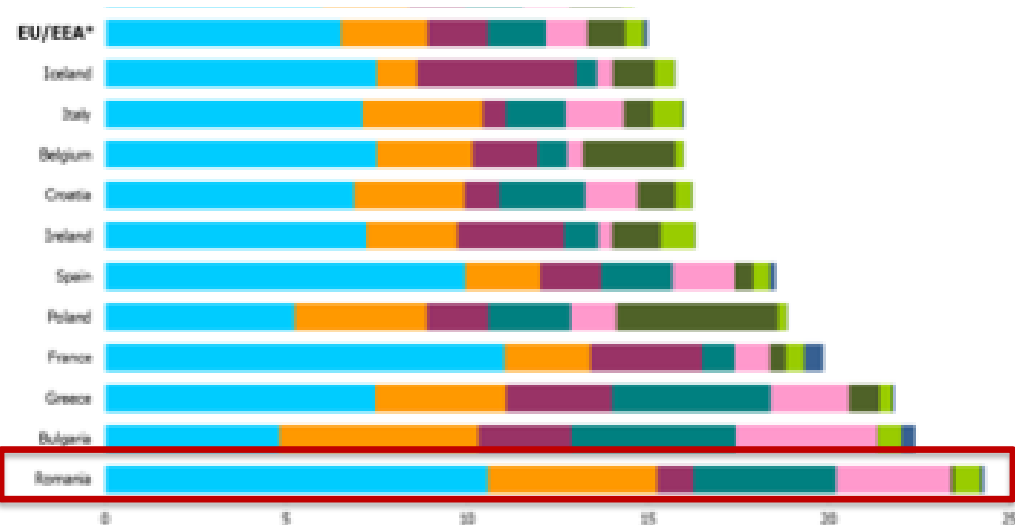


Figure 3. Community consumption of antibacterials for systemic use (ATC group J01) at ATC level 3 sub-group, EU/EEA countries, 2021 (expressed as DDD per 1 000 inhabitants per day)



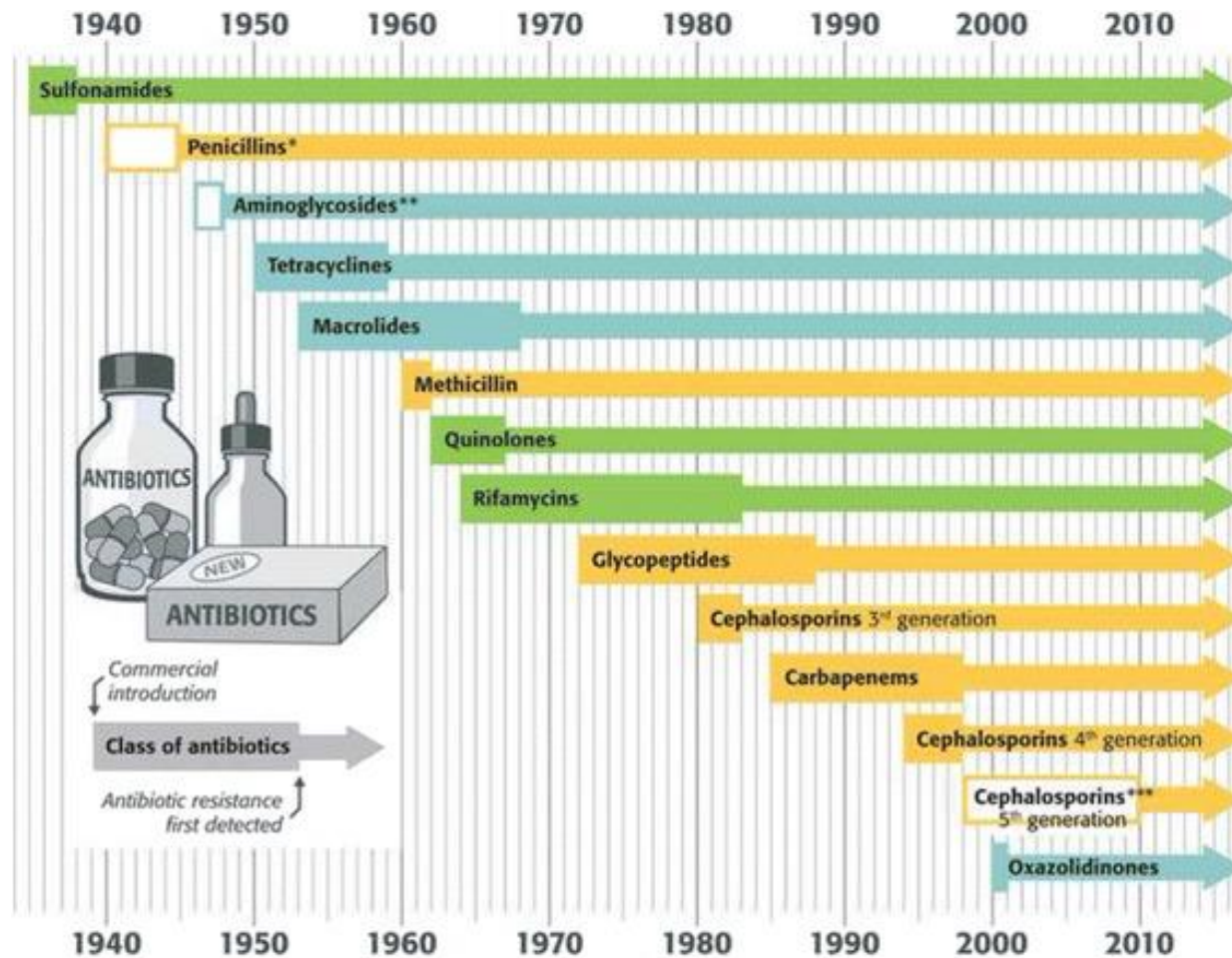
The two countries that exceeded their 2019 community consumption in 2021 (Bulgaria and Romania) were also the two countries with the highest community consumption, exhibiting a worrying divergence from improvements shown in the other EU/EEA countries. Examination of trends in consumption of ATC level 3 sub-groups for the community sector (downloadable tables D1–D7) and proportional consumption of these groups compared to the EU/EEA mean (Table 2, Figure 3) can help countries determine where there is potential for reductions.



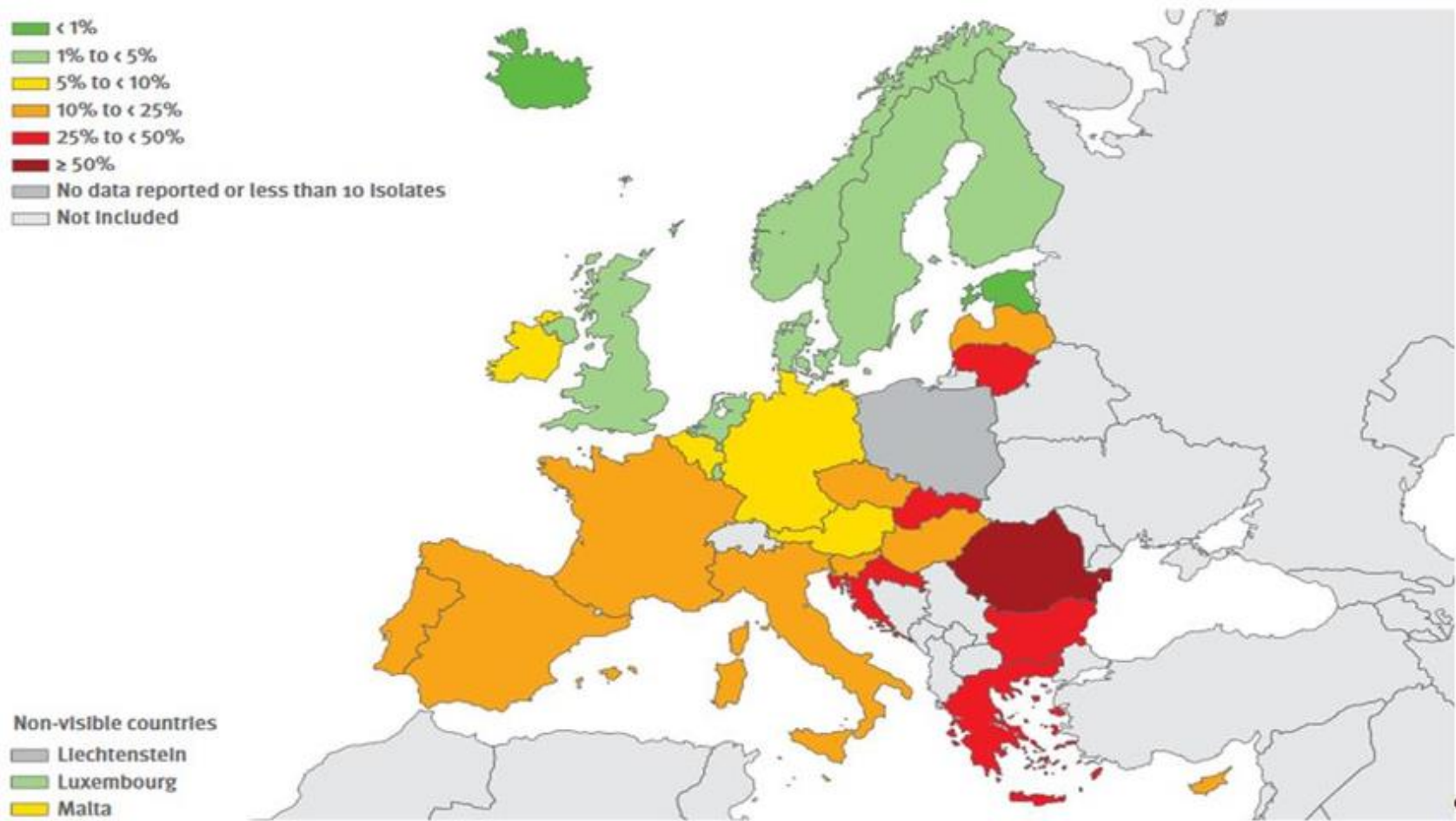
Studiul STAR 2022

- 49% - antibioticele = eficiente pentru durerile în gât;
- 23% s-ar simți anxioși să fie tratați pentru boli respiratorii fără antibiotice;
- 54% sunt de acord că antibioticele sunt eficiente pentru răceli și gripă; 63% sunt îngrijorați de rezistența la antibiotice;
- 54% sunt de acord că antibioticele ameliorează rapid simptomele;
- 49% ar fi interesați să afle mai multe despre rezistența la antibiotice.
- 42% antibioticele ar trebui să fie disponibile la cerere de la farmacie;
- 35% cred că ar trebui să fie disponibile fără prescripție medicală;
- 46% sunt de acord că ar trebui păstrate antibioticele rămase pentru data viitoare când familia se îmbolnăvește

Comercializare și prima detectare a rezistenței



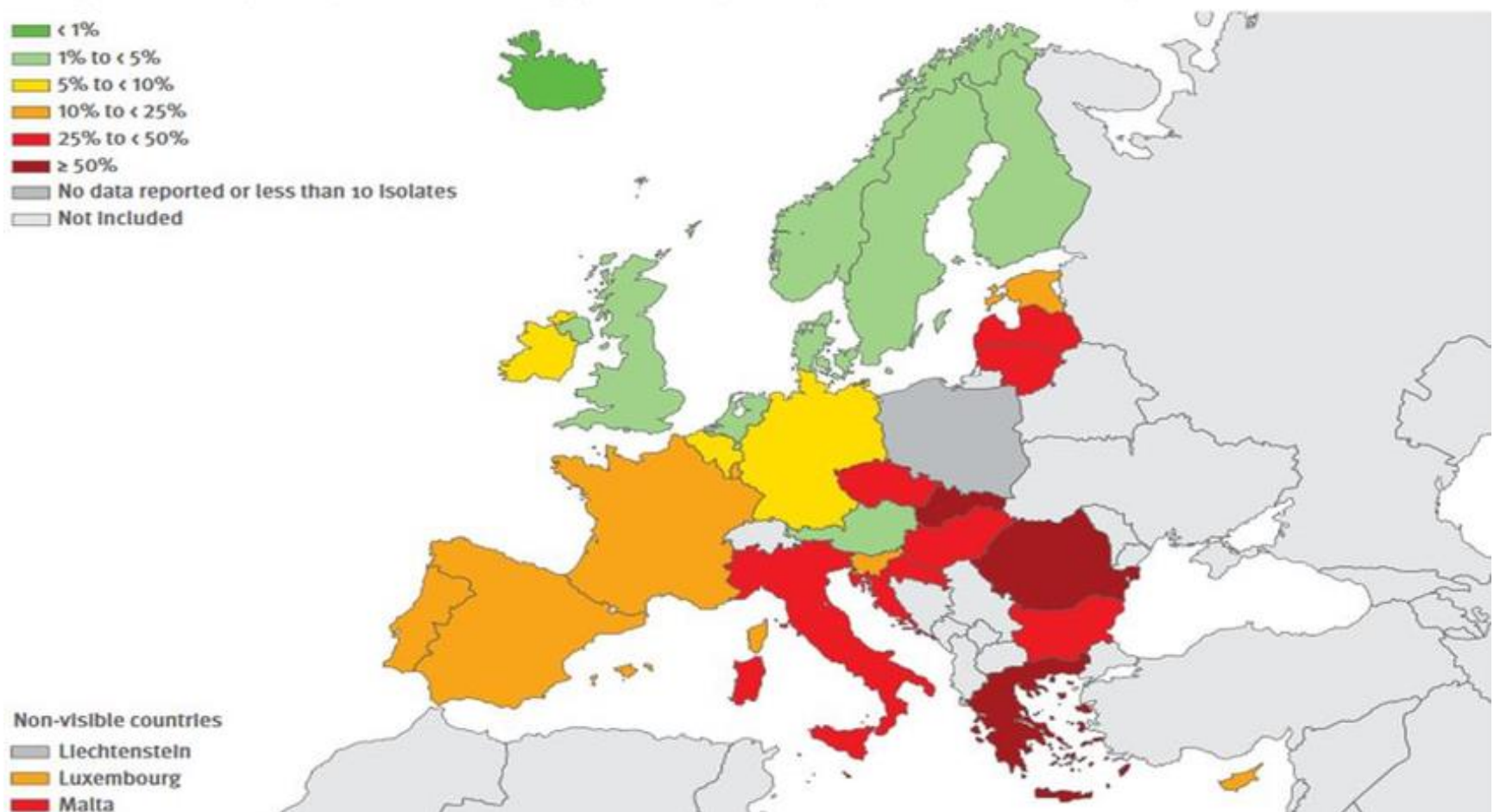
Harbarth et al, Antimicrob Resist Infect Control. 2015; 4: 49.



(Antimicrobial resistance surveillance in Europe, ECDC, 2014).

***Pseudomonas aeruginosa*.**

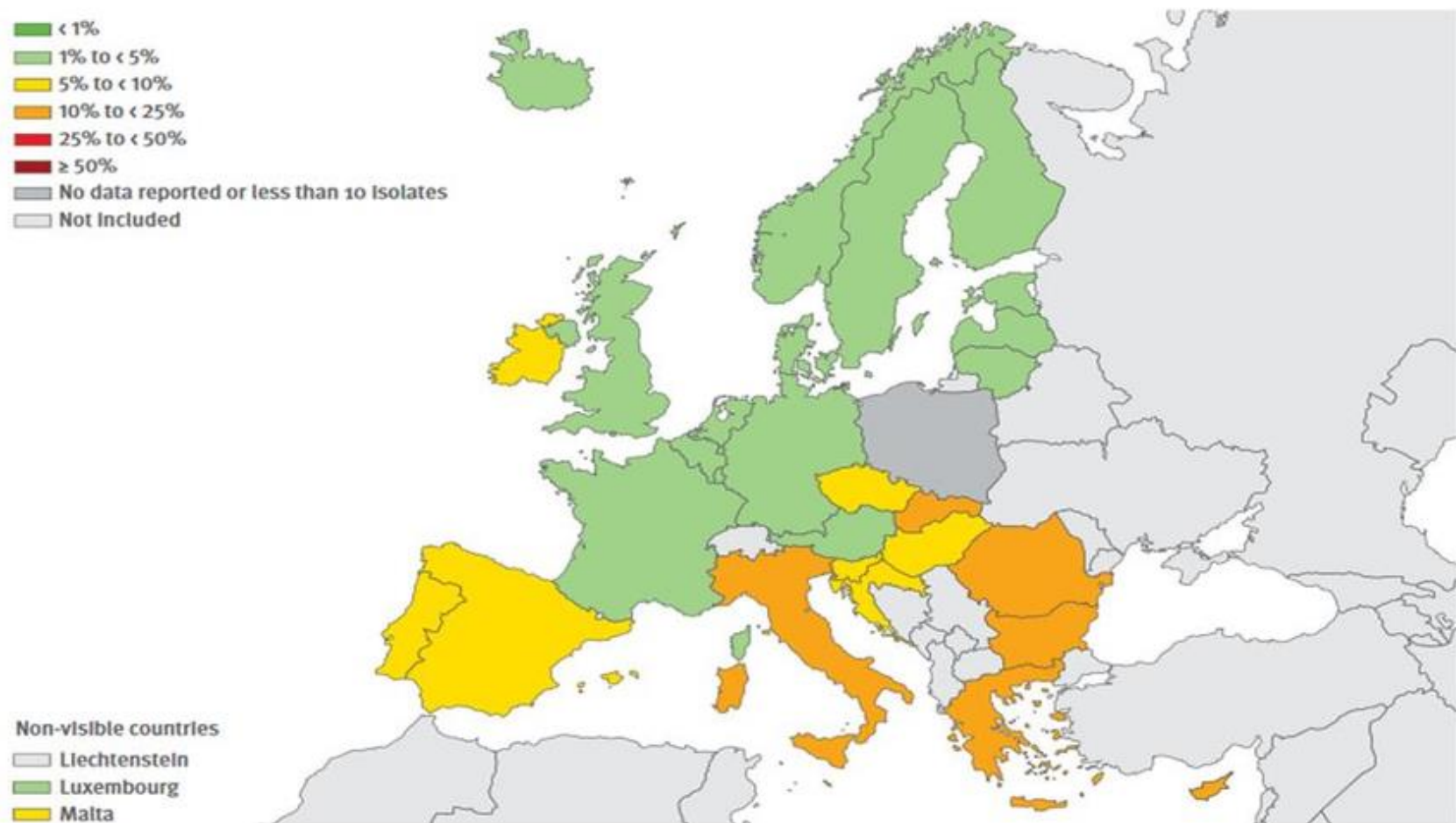
Percentage (%) of invasive isolates with combined resistance (≥ 3 antimicrobial groups among piperacillin + tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems)



(Antimicrobial resistance surveillance in Europe, ECDC, 2014).

Klebsiella pneumoniae

Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, third generation cephalosporins and aminoglycosides



(Antimicrobial resistance surveillance in Europe, ECDC, 2014).

Escherichia coli

Percentage (%) of invasive isolate with combined resistance to third generation cephalosporin, fluoroquinolones and aminoglycosides

Ce e de făcut?

Respiratory tract infections (self-limiting): prescribing antibiotics

Clinical guideline

Published: 23 July 2008

nice.org.uk/guidance/cg69

A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions:

- acute otitis media
- acute sore throat/acute pharyngitis/acute tonsillitis
- common cold
- acute rhinosinusitis
- acute cough/acute bronchitis.

Ce e de făcut?

Respiratory tract infections (self-limiting): prescribing antibiotics

Clinical guideline

Published: 23 July 2008

nice.org.uk/guidance/cg69

Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy):

- bilateral acute otitis media in children younger than 2 years
- acute otitis media in children with otorrhoea
- acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.

Ce e de făcut?

Sinuzită și otită medie:

- **virusuri** - 40-75%
- **Pneumococ** – 25-50%

- 
- *Atb nu au efect pe durere*
 - *1/4000 șansă de protecție față de complicații*

- **Hib** 15-30% - 50% *beta lactamază* +
- **Moraxella** 3-20% - 100% *beta lactamază*



De obicei
remit
spontan

Ce e de făcut?

FROM THE AMERICAN ACADEMY OF PEDIATRICS | CLINICAL PRACTICE GUIDELINE | NOVEMBER 01 2014

Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis **FREE**

8. Clinicians should not administer antibacterial medications to infants and children with a diagnosis of bronchiolitis unless there is a concomitant bacterial infection, or a strong suspicion of one (Evidence Quality: B; Recommendation Strength: Strong Recommendation).



European Society for Pediatric Gastroenterology,
Hepatology, and Nutrition/European Society for Pediatric
Infectious Diseases Evidence-Based Guidelines for the
Management of Acute Gastroenteritis in Children in
Europe: Update 2014

**9.4.1 Antimicrobial Therapy of Bacterial
Gastroenteritis**

Antibiotic therapy for acute bacterial gastroenteritis is not needed routinely but only for specific pathogens or in defined clinical settings (Va, D) (strong recommendation, low-quality evidence).

Salmonella Gastroenteritis

Antibiotic therapy is not effective on symptoms and does not prevent complications. It is associated with a prolonged fecal excretion of *Salmonella*. Therefore, antibiotics should not be used in an otherwise healthy child with *Salmonella* gastroenteritis (I, A) (strong recommendation, moderate-quality evidence).

Ce e de făcut?

- *Atb de spectru îngust*
- *Atb conform antibiogramei*
- *Atb conform intervalului recomandat – minim necesar*

NU moldaminizare
NU Azitromicină în angine/
infecții streptococice
dovedite

Ce e de făcut?

- *Atb doar pe rețetă*
- *Atb doar la doza corectă pt vârstă*
- *Verificarea dozei în funcție de concentrație!*

Recomandări off label?
Greșeli?

Colaborare medic-farmacist

