

Uso di antibiotici e antibiotico-resistenza in Europa: a che punto siamo?

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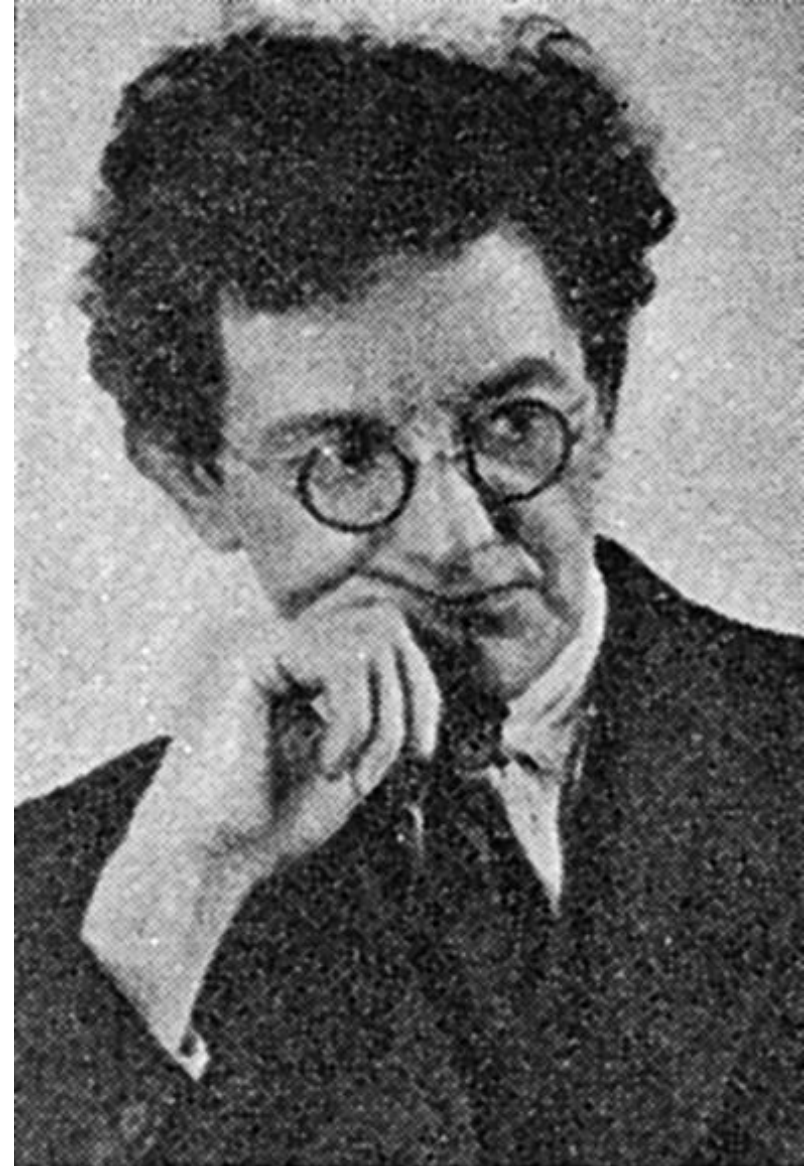
I am full-time staff member of WHO

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IT IS MUCH EASIER TO MAKE
MEASUREMENTS THAN TO
KNOW EXACTLY WHAT YOU ARE
MEASURING.

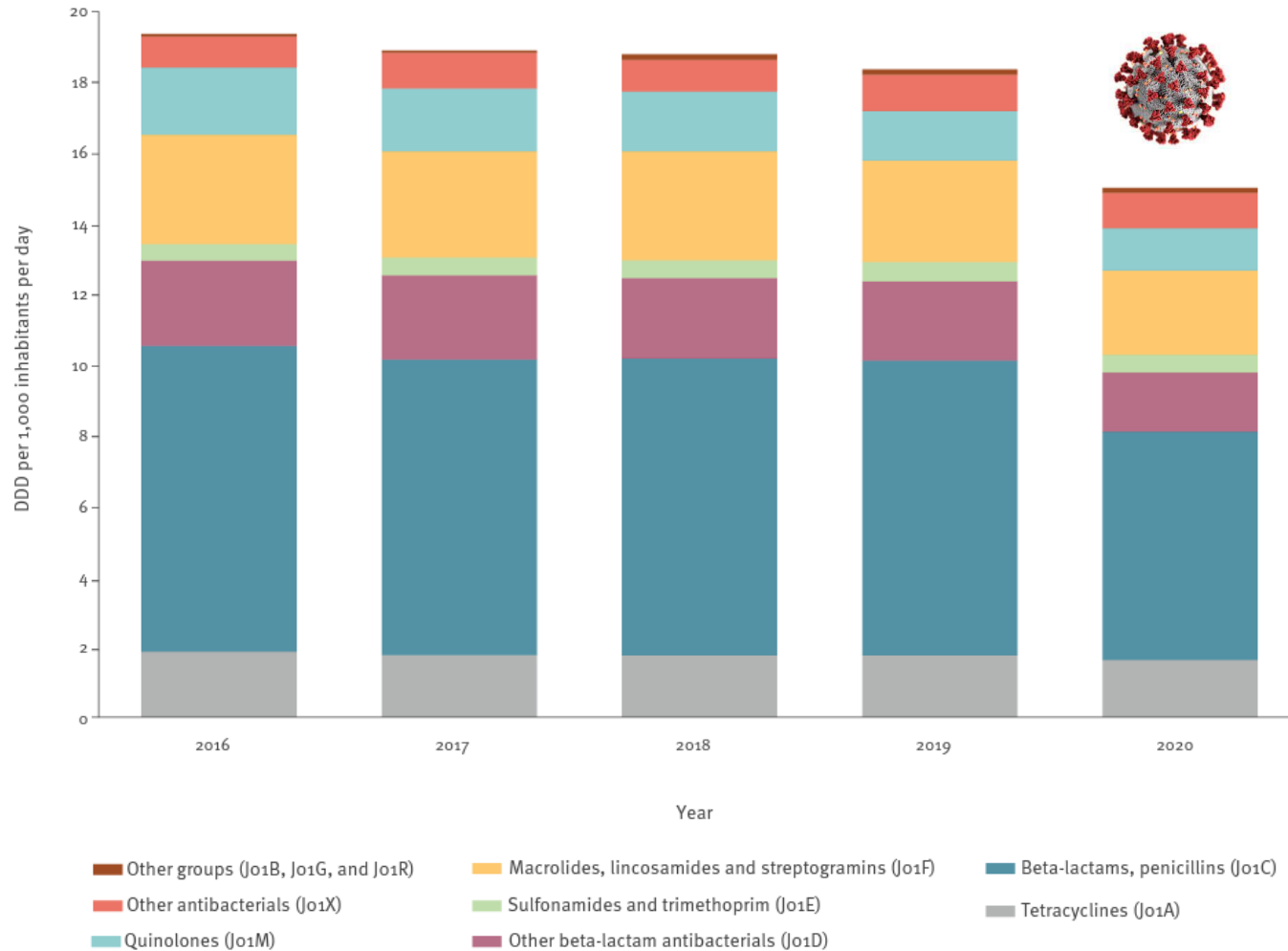
- J. W. N. SULLIVAN -

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2020 was a “special” year

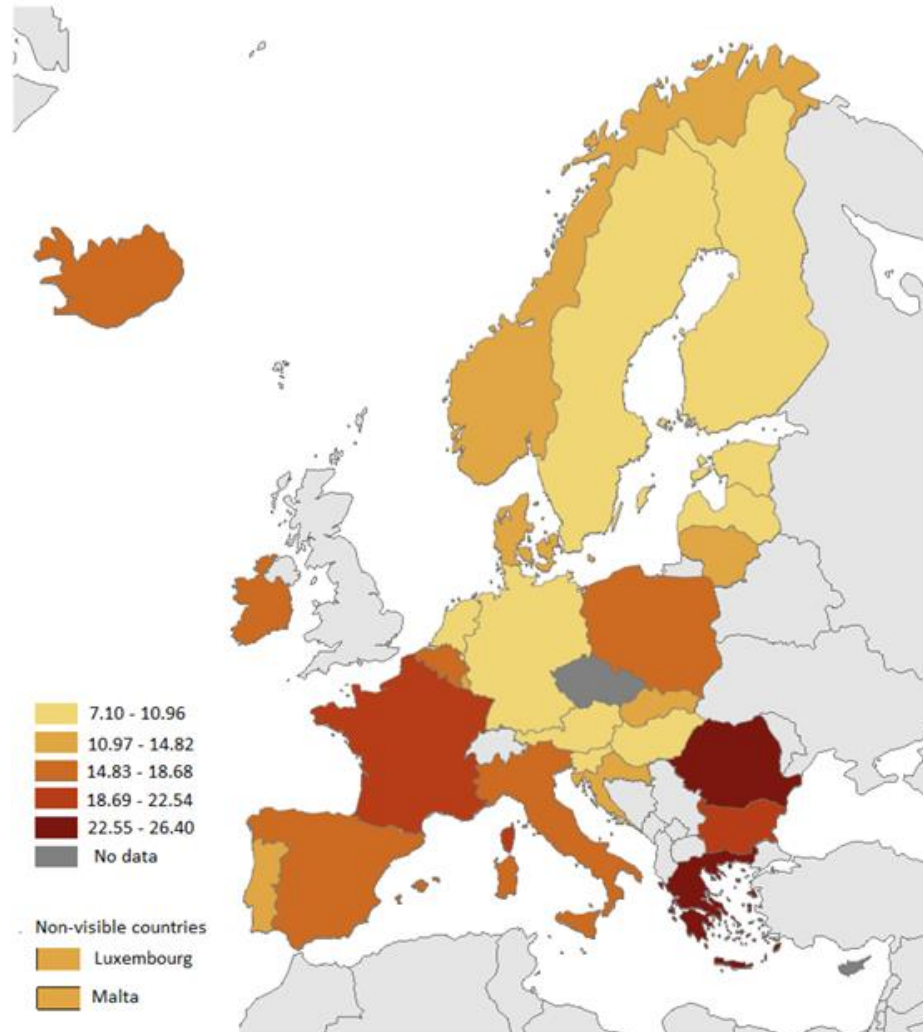
Consumption of antibacterials for systemic use (ATC group J01) in the community, population-weighted mean, by ATC group, 29 EU/EEA countries, 2016–2020



- 18.3% decrease in antibiotic consumption between 2019 and 2020
- –3.35 DDD/1000 inhabitants/day
- Largest annual decrease in the ESAC’s two-decade history
- Decrease observed in 26 of 27 countries reporting data on community use in 2019 and 2020
- Larger decrease in countries with high baseline use
- Reduced access to primary care as main driver ?

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

Figure 1. Community consumption of antibacterials for systemic use (ATC group J01), by country, EU/EEA countries, 2020 (expressed as DDD per 1 000 inhabitants per day)



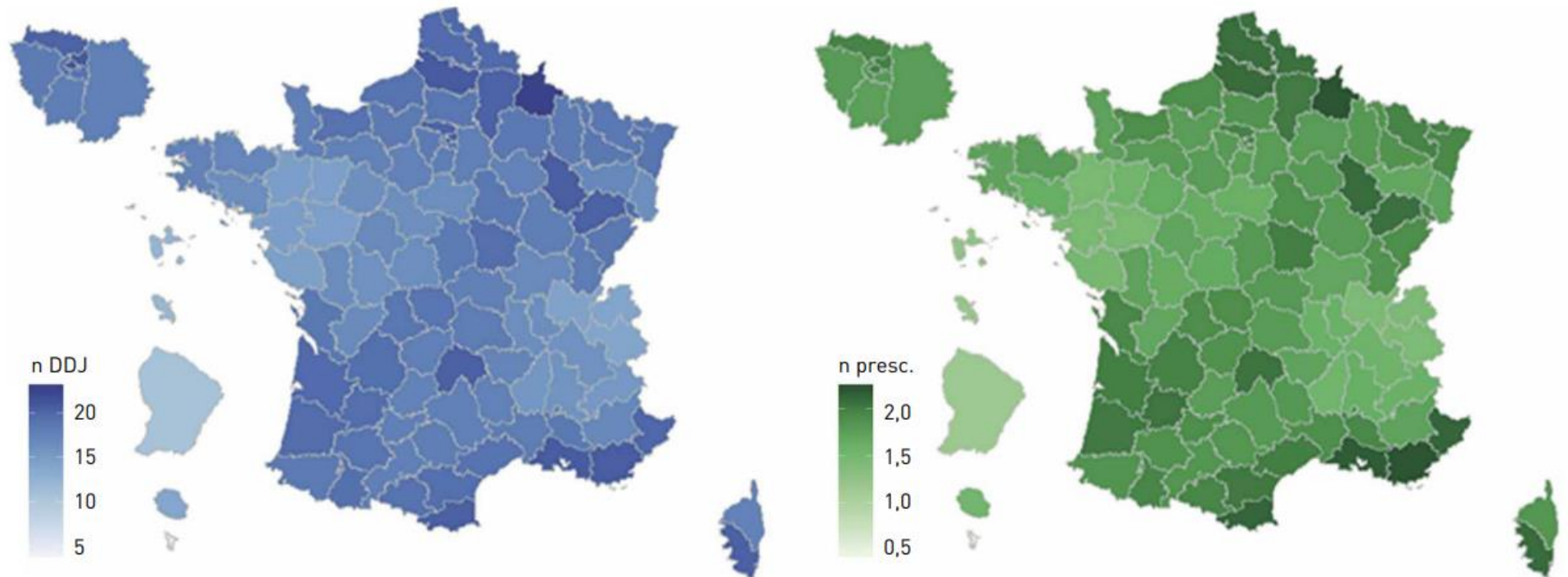
- Mean consumption of antibacterials for systemic use*: **16.4 DDD** per 1000 inhabitants per day



- Country range: 8.5–28.9
 - Variation by a factor of 3.4
- Italy: 18.4 DID

Regional variation in antibiotic use

FIGURE 9 | Nombre de DDJ/1 000H/J et de nombre de prescriptions/1 000H/J par département en 2020



But what
about
quality of
use ?



Antibiotics are categorized into three groups

Essential Access, Watch and Reserve antibiotics need to be accessible and affordable for those who need them!

Reserve

“Last-resort” options
against MDRO

Watch

Higher
“resistance potential”

Often 1st or 2nd choice
for common infectious
syndromes

Access

Lower
“resistance potential”



WHO's 13th General Program of Work antibiotic use indicator

- Access group antibiotics at ≥60% of overall antibiotic consumption

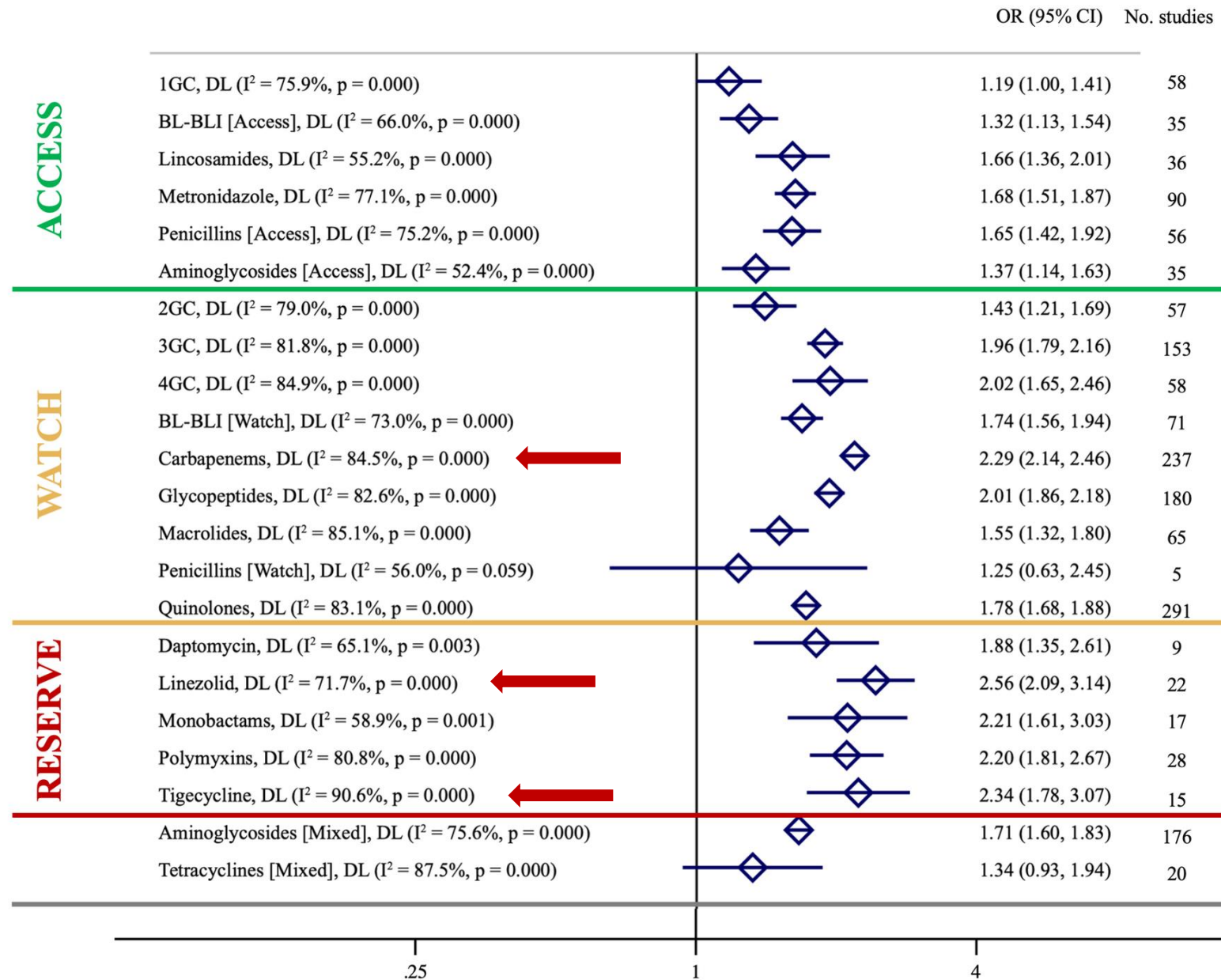
		ACCESS GROUP	WATCH GROUP	RESERVE GROUP
Amikacin Amoxicillin Amoxicillin/clavulanic-acid Ampicillin Benzathine-benzylpenicillin Benzylpenicillin Cefalexin Cefazolin Chloramphenicol Clindamycin Cloxacillin Doxycycline Gentamicin Metronidazole Nitrofurantoin Phenoxymethylpenicillin Procaine-benzylpenicillin Spectinomycin Sulfamethoxazole/TMP Trimethoprim	Azithromycin			
	Cefixime			
	Cefotaxime			
	Ceftazidime			
	Ceftriaxone			
	Cefuroxime			
	Ciprofloxacin			
	Clarithromycin			
	Meropenem			
	Piperacillin/tazobactam			
	Vancomycin (IV)			
	Vancomycin (oral)			
	Cefiderocol			
	Ceftazidime/avibactam			
	Colistin (IV)			
	Fosfomycin (IV)			
	Linezolid			
	Meropenem/vaborbactam			
	Plazomicin			
	Polymyxin B (IV)			

**Antibiotics on the WHO model
list of essential medicines - 22nd
list, 2021**

Evaluation of the association of prior exposure to WHO AWaRe antibiotics and isolation of multidrug-resistant bacteria: a systematic review and meta-analysis

Results of primary analysis (all MDROs combined)

- **Weakest** association for 1° gen. cephalosporins (Access)
- **Strongest** associations for:
 - linezolid (Reserve)
 - carbapenems (Watch)
 - tigecycline (Reserve)



Variations in the Consumption of Antimicrobial Medicines in the European Region, 2014-2018: Findings and Implications from ESAC-Net and WHO Europe

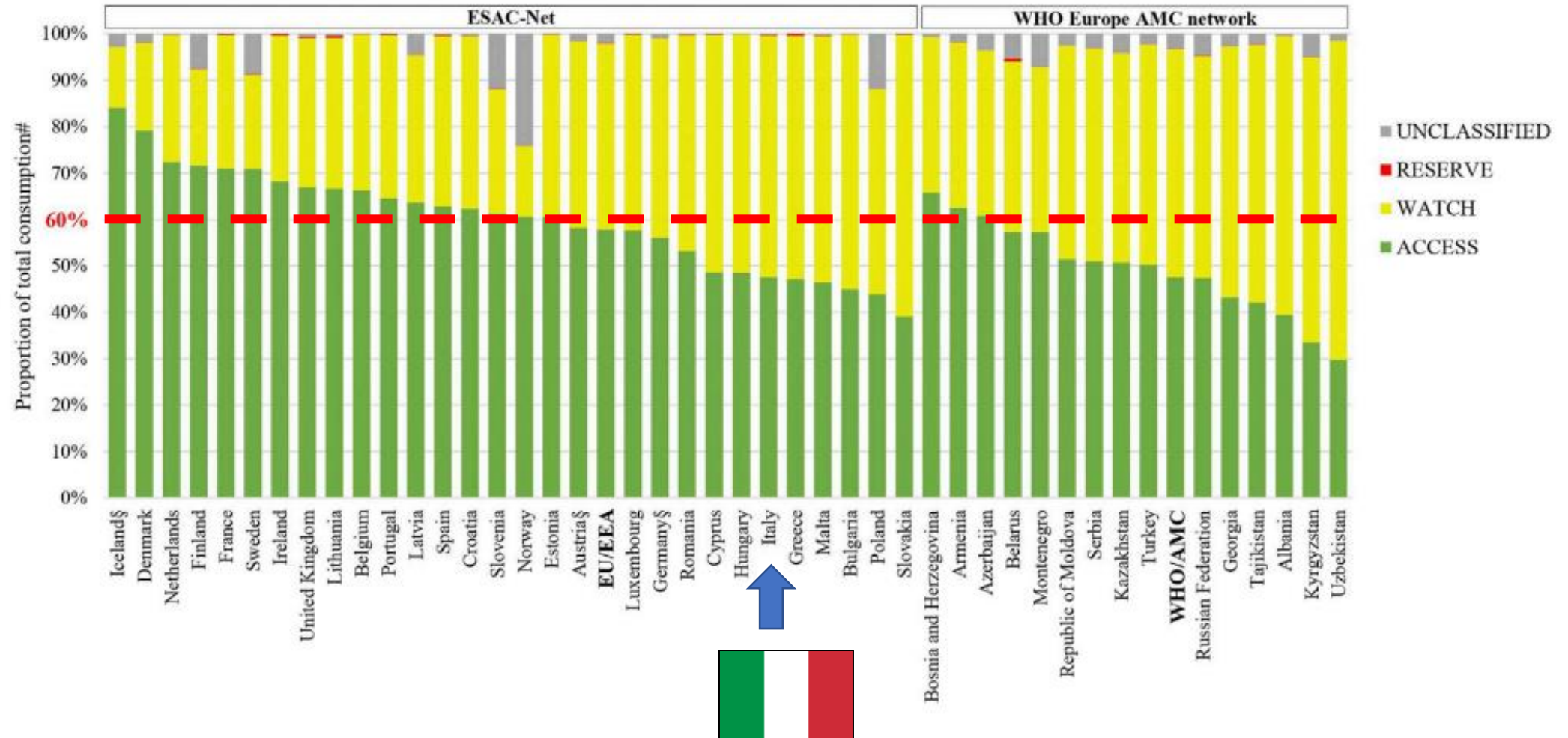


FIGURE 3 | Patterns of consumption of antibacterials according to the AwaRe classification of antimicrobial agents, 2018. AwaRe: Access, Watch and Reserve classification of antimicrobials (World Health Organization 2019).





Antibacterial agent (ATC code)	Austria	Belgium	Bulgaria	Croatia	Cyprus	Denmark	Estonia	Finland	France	Germany	Greece	Hungary	Iceland	Ireland	Italy	Latvia	Lithuania	Luxembourg	Malta	Netherlands	Norway	Poland	Portugal	Romania	Slovakia	Slovenia	Spain	Sweden	United Kingdom	Albania	Armenia	Azerbaijan	Belarus	Bosnia and Herzegovina	Georgia	Kazakhstan	Kyrgyzstan	Montenegro	Republic of Moldova	Russian Federation	Serbia	Tajikistan	Turkey	Uzbekistan	Number of countries*	EU/EEA	WHO/AMC	
Amoxicillin/enzyme inhibitor (J01CR02)	1	1	3	1	1	4	1	6	2	4	1	1	3	1	1	3	3	1	1	4	3	1	2	2	1	1	1	7	1	5	3	2	1	1	4	8	2	1	3	3	1	3	7	3	40	1	1	
Amoxicillin (J01CA04)	6	2	2	3	5	5	3	2	1	1	3	8	2	2	3	1	1	2	2	6	1	2	2	2	2	2	1	2	1	1	1	2	3	7	1	2	1	1	1	3	7	3	40	2	2			
Doxycycline (J01AA02)			6	5	3	6	4	1	3	3	5	5	1	4	2	4	5	7	1	3	6			6		5	5	2	3	2	3	5	5	6	4	7		4	6		6		34	3	5			
Nitrofurantoin (J01XE01)	3			7										6			5		3			5			6		5	6	7	10			6	10	2		7	9		5		15	9	10				
Sulfamethoxazole/Trimethoprim (J01EE01)										6			4		6								7		6				2	7		4		9			4		2				11		8			
Phenoxymethylpenicillin (J01CE02)	8					1		5		5			5	7						2					3		1	8																10	8			
Pivmecillinam (J01CA08)						2		9					6							4							7																		5			
Flucloxacillin (J01CF05)														5									6				2	5																		4		
Cefalexin (J01DB01)	9							3																									7				3								4			
Trimethoprim (J01EA01)						7		8																										2											3			
Clindamycin (J01FF01)	5								8			6																																		3		
Metronidazole (P01AB01)																																				8	5		8					3				
Tetracycline (J01AA07)																													5		4															2		
Ampicillin (J01CA01)																																															1	
Dicloxacillin (J01CF01)						3																																									1	
Roxithromycin (J01FA06)						7																																									1	
Azithromycin (J01FA10)	3	4	5	4					5	9		3	7		5			4	5			7	4	5	7	4	3		7	4	5	4	8	3	5	3	4	8	2	2				2	30	6	4	
Clarithromycin (J01FA09)	2	6	4	6	6		2				4			3	2	4	2	4	2			2	3	3	3			4			8	5				10		6	7	4		2			25	4	6	
Ciprofloxacin (J01MA02)	7					6			7	6	7				5		6	5	6				4	5	5		6		4	6		6	3		2	1	5		5	5	1	4	1		25	7	3	
Cefuroxime (J01DC02)	4	5	1	2	2		5		2	2	2						3	3			5	7		1		4		3				6	7				3				3			20	5	9		
Levofloxacin (J01MA12)			7		4							4			4			6					6					8		6			4	1			5	6	7	6		4	15	10	7			
Lymecycline (J01AA04)							7													5							3	3																		4		
Cefixime (J01DD08)														6										4													6			8					4			
Erythromycin (J01FA01)																																						6	8						3			
Cefaclor (J01DC04)																													6																	1		
Cefdinir (J01DD15)																																															1	
Pristinamycin (J01FG01)									4																																					1		
Ofloxacin (J01MA01)									7																																					1		
Spiramycin/Metronidazole (J01RA04)									6																																					1		
Rifampicin (J04AB02)																																															1	
Methenamine (J01XX05)							4																																							3		
Furazidin (J01XE03)																																															2	
Nitroxoline (J01XX07)																																															1	



The WHO AWaRe antibiotic book

- A more comprehensive resource to improve antibiotic use

- First & second choice essential antibiotics

	Ear infection (otitis media)	Sore throat (pharyngitis)
First line treatment	No antibiotic therapy	
1 First choice	 ACCESS e.g. Amoxicillin	 ACCESS e.g. Amoxicillin
2 Second choice	 ACCESS e.g. Amoxicillin + clavulanic acid	 WATCH e.g. Clarithromycin

- Additional general information regarding

- Definition(s)
- Epidemiology
- Diagnosis (link with essential diagnostics list)
- Dose (standard; not taking into account renal dosing)
- Duration (favoring shorter duration)
- Based on review of literature and guidelines and expert input (antibiotic working group)
- Separate chapters for Reserve antibiotics on the EML

Variations in the Consumption of Antimicrobial
Medicines in the European Region, 2014-2018:
Findings and Implications from ESAC-Net and WHO

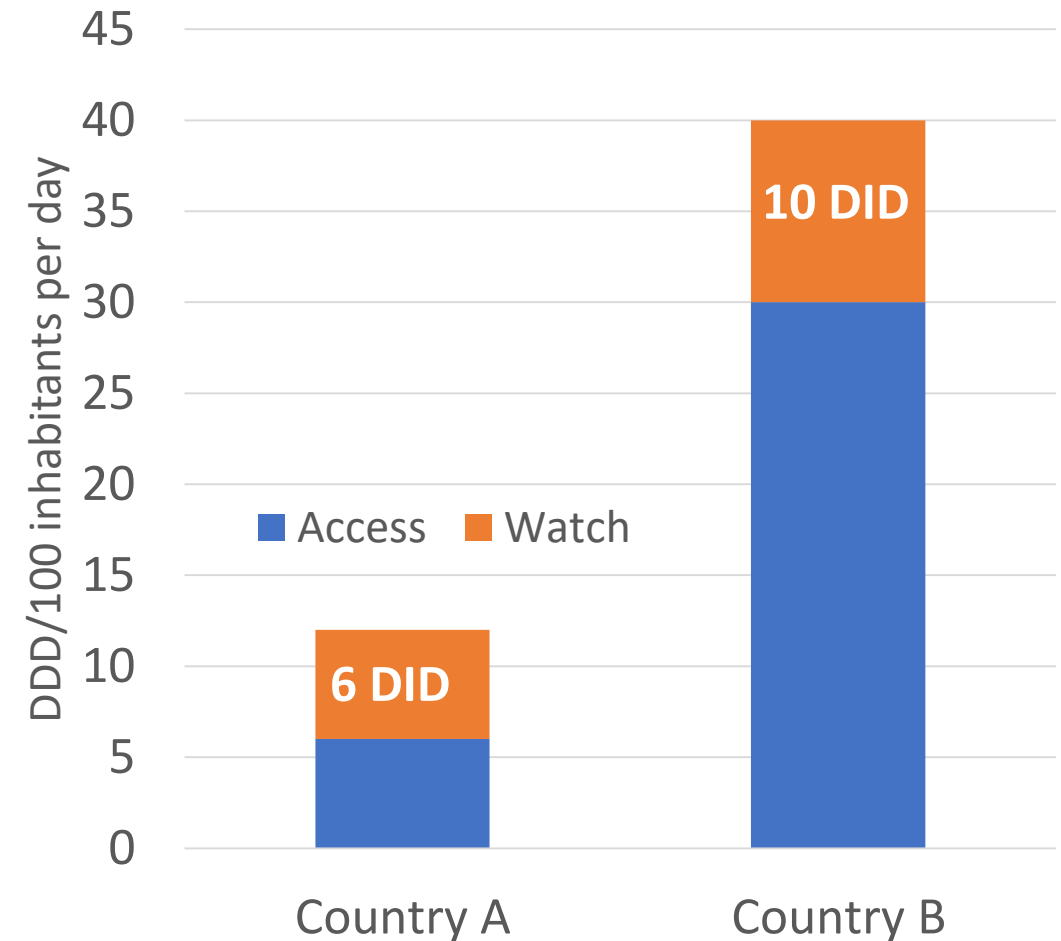
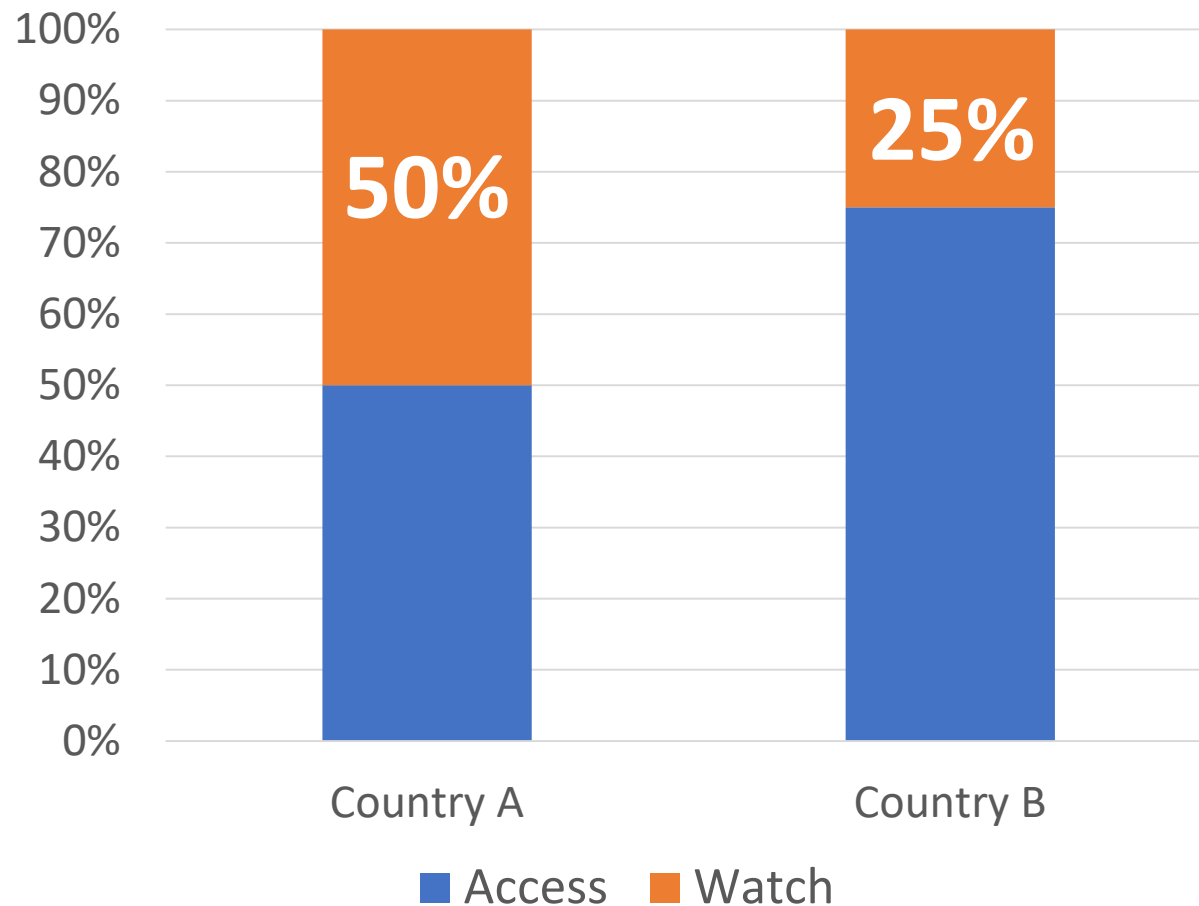
Country	Access agents as proportion (%) of total consumption ^a				
	2014	2015	2016	2017	2018
ESAC-Net					
Austria	57	57	58	58	58
Belgium	57	57	58	61	66
Bulgaria	49	46	44	45	45
Croatia	61	63	65	63	62
Cyprus	55	52	48	49	49
Czechia	61	60			
Denmark	78	79	79	79	79
Estonia	59	58	60	59	61
Finland	71	72	72	73	72
France	66	68	70	71	71
Germany	52	51	52	54	56
Greece	40	44	48	46	47
Hungary	49	48	48	48	49
Iceland	84	83	82	83	84
Ireland	62	66	65	65	68
Italy	46	47	48	48	48
Latvia	69	68	68	65	64
Lithuania	70	70	69	68	67
Luxembourg	53	54	53	47	58
Malta	43	43	46	49	46
Netherlands	71	72	71	71	72
Norway	63	63	62	61	61
Poland	64	63	61	59	44
Portugal	60	59	60	64	65
Romania	56	58	56	54	53
Slovakia	47	43	46	42	39
Slovenia	60	63	63	61	61
Spain	63	63	63	63	63
Sweden	71	70	71	71	71
United Kingdom	65	65	66	66	67

The 60% target is conservative!

Infection (in alphabetical order)	Can it be safely treated without antibiotics?	Type of antibiotic (if indicated)
Bronchitis	Yes	
COPD exacerbations	Yes, in most mild cases	Access
Dental infections	Yes, in most mild cases	Access
Otitis media	Yes, in most mild cases	Access
Pharyngitis	Yes, in most mild cases	Access
Sinusitis	Yes, in most mild cases	Access
Skin and soft tissue infections (mild)	Only for certain conditions and in certain patients	Access
Urinary tract infection (lower)	Only in a few patients with no risk factors for complicated infections	Access

WHO AWaRe Antibiotic Book (draft)

Single metrics should not be overinterpreted



Large variation also in antibiotic use among hospitals

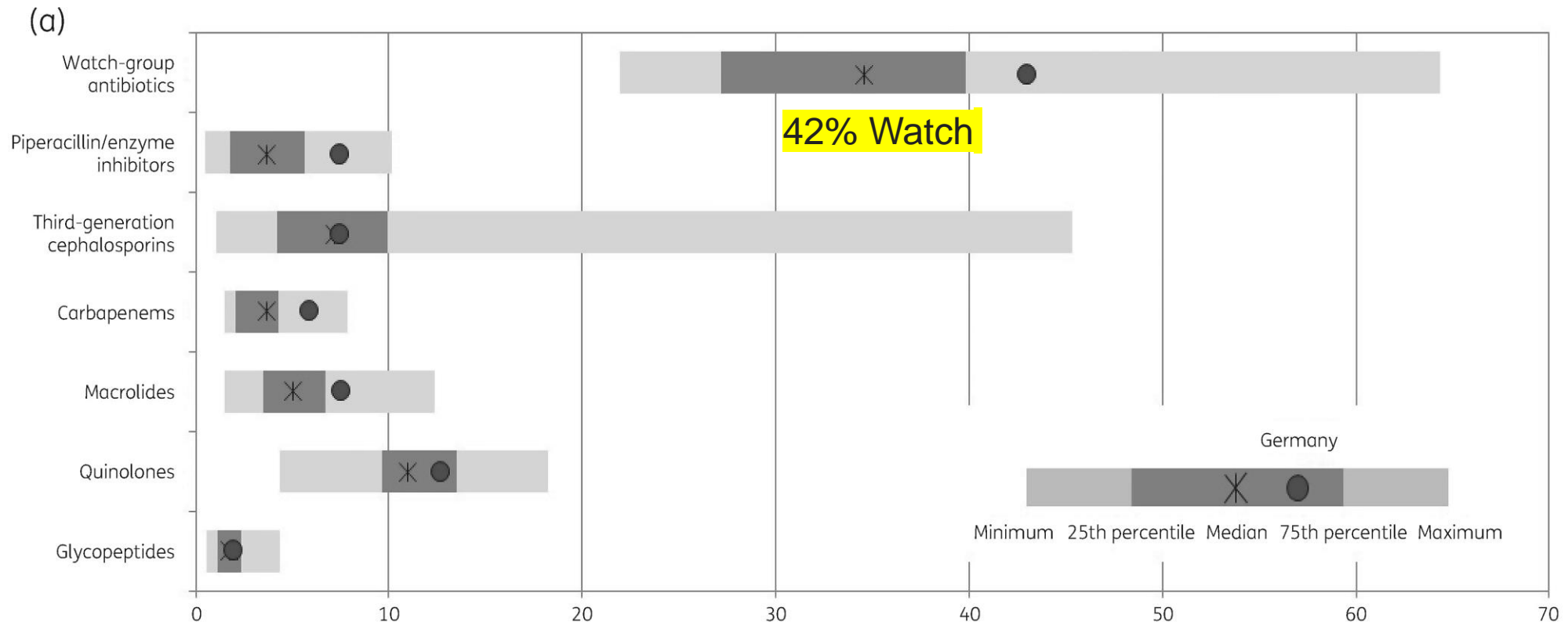
Antibiotic use data from 137 German acute care hospitals (2015/16)

	All hospital types			Primary and secondary care hospitals			Tertiary care hospitals		
	DDD/100 PD		%	DDD/100 PD		%	DDD/100 PD		%
	median	IQR		median	IQR		median	IQR	
Overall use	55.4	48.4–62.2		53.5	47.8–60.6		60.7	49.9–66.1	
Watch antibiotics	22.9	18.8–26.8	42.2	22.8	18.7–26.7	43.3	23.6	19.1–28.8	41.2

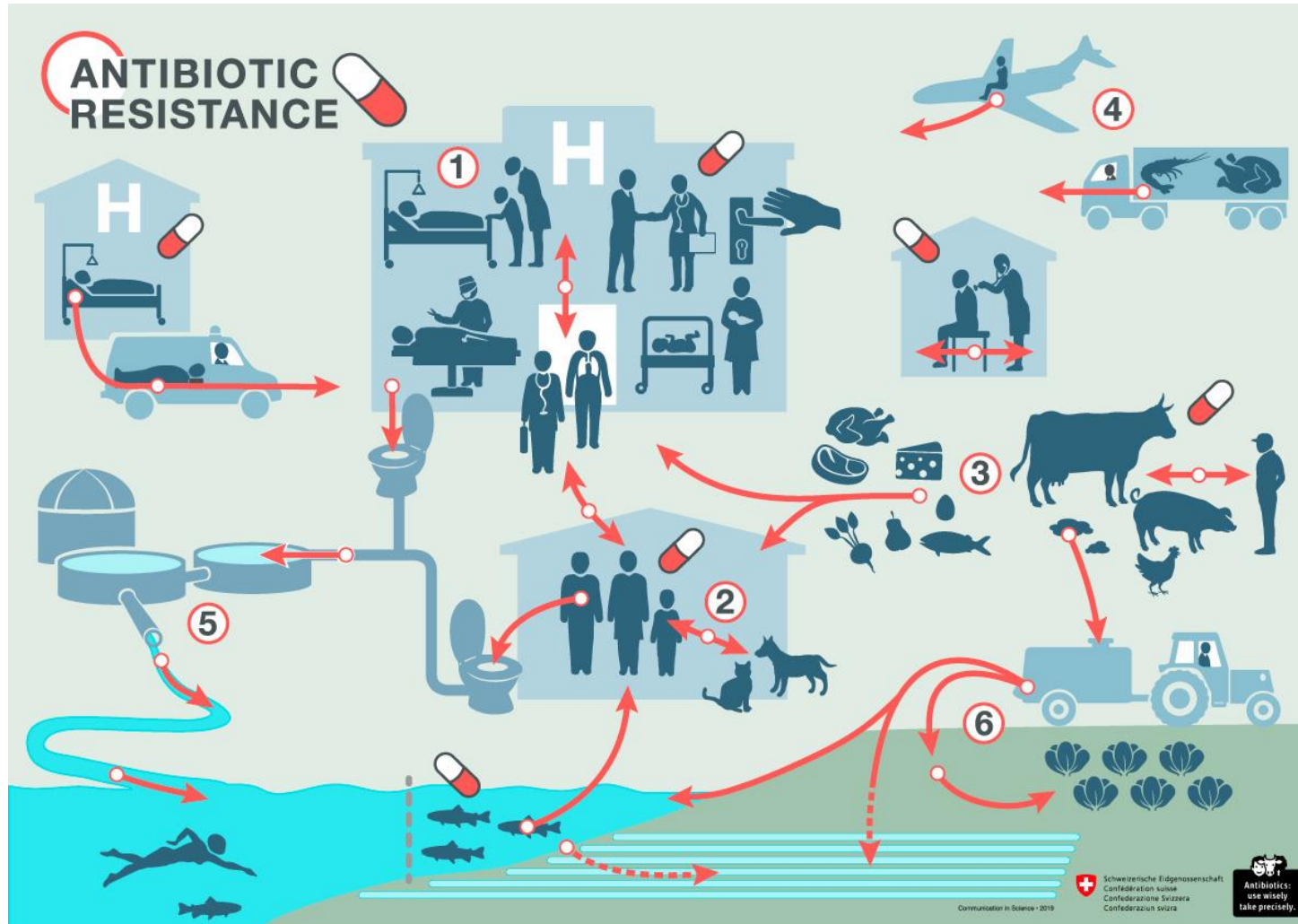
DDD= defined daily doses; PD= patient days

Large variation also in antibiotic use among hospitals

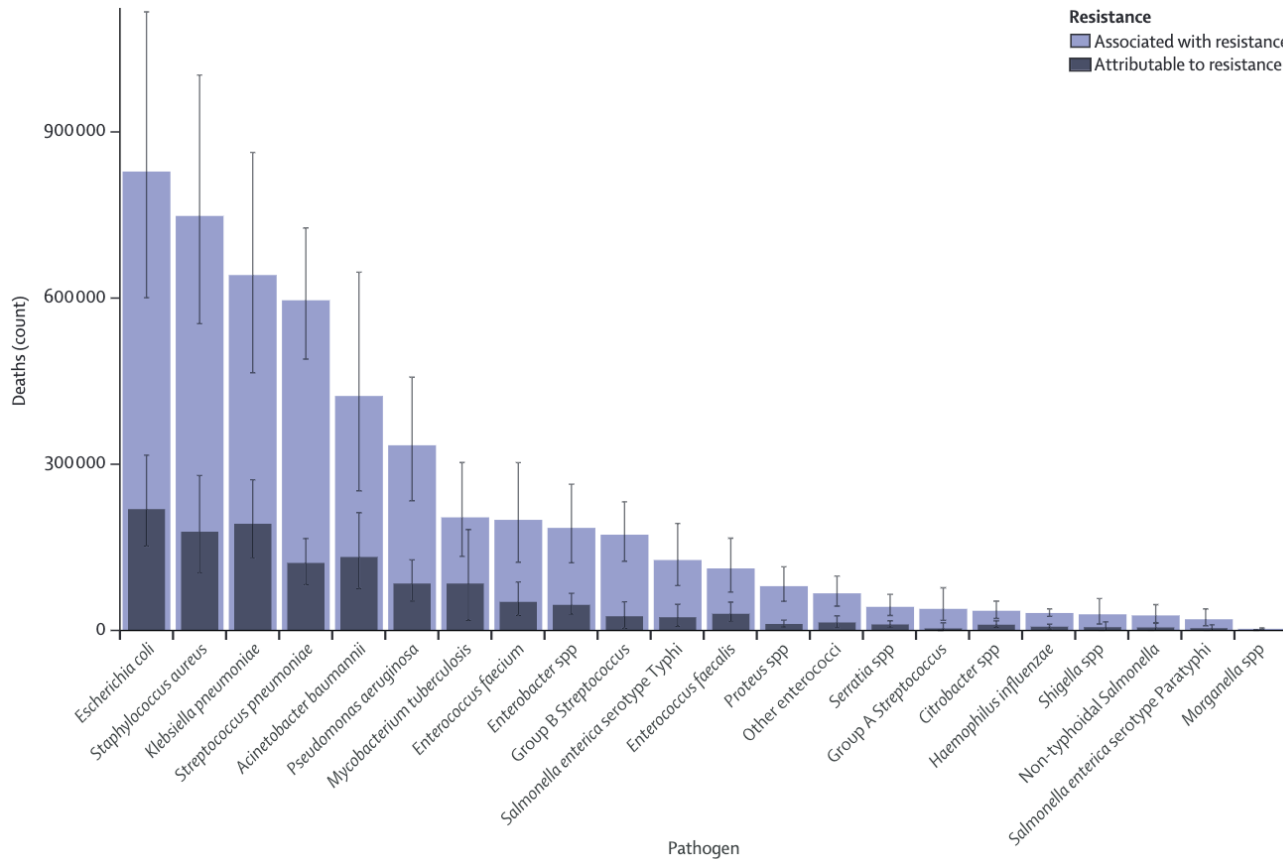
Antibiotic use data from 137 German acute care hospitals (2015/16)



Antimicrobial resistance



Estimating the impact of AMR on clinical outcomes is difficult



Global deaths (counts) attributable to bacterial antimicrobial resistance by pathogen, 2019

Lancet. 2022 Feb 12;399(10325):629-655.

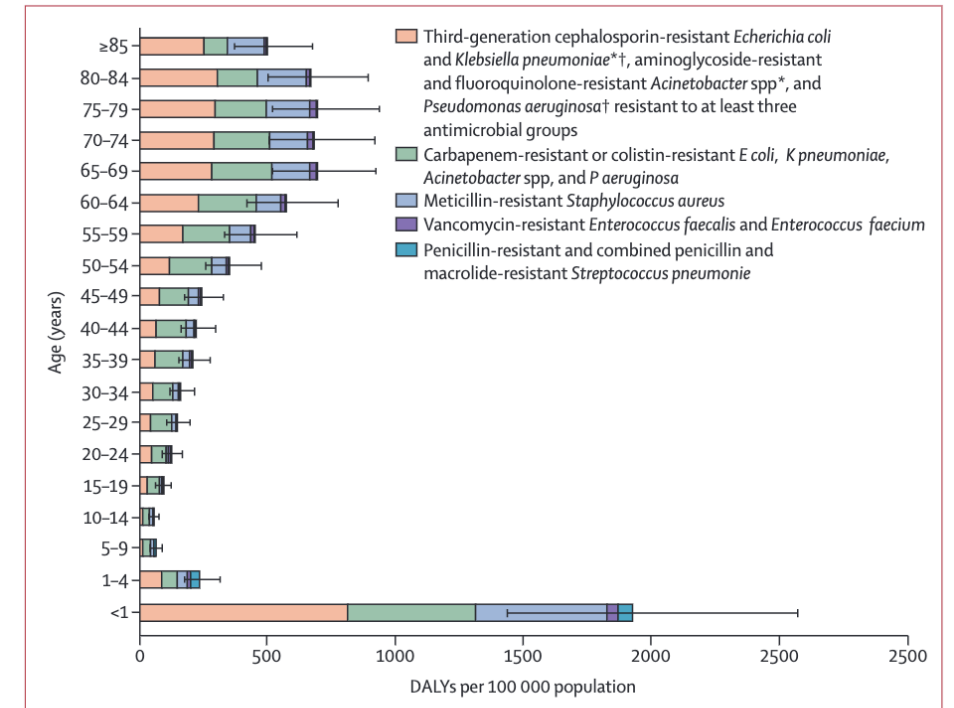


Figure 2: Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015

Cassini et al. Lancet Infect Dis. 2019 Jan;19(1):56-66.

Hospital-acquired pathogens are probably the key concern in Europe*

*With the exception of 3rd generation cephalosporin-resistant *E. coli*

- High percentages of resistance to third-generation cephalosporins and carbapenems in *K. pneumoniae*
- High percentages of carbapenem resistant *Acinetobacter* spp.

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

*Enterobacteriaceae**, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

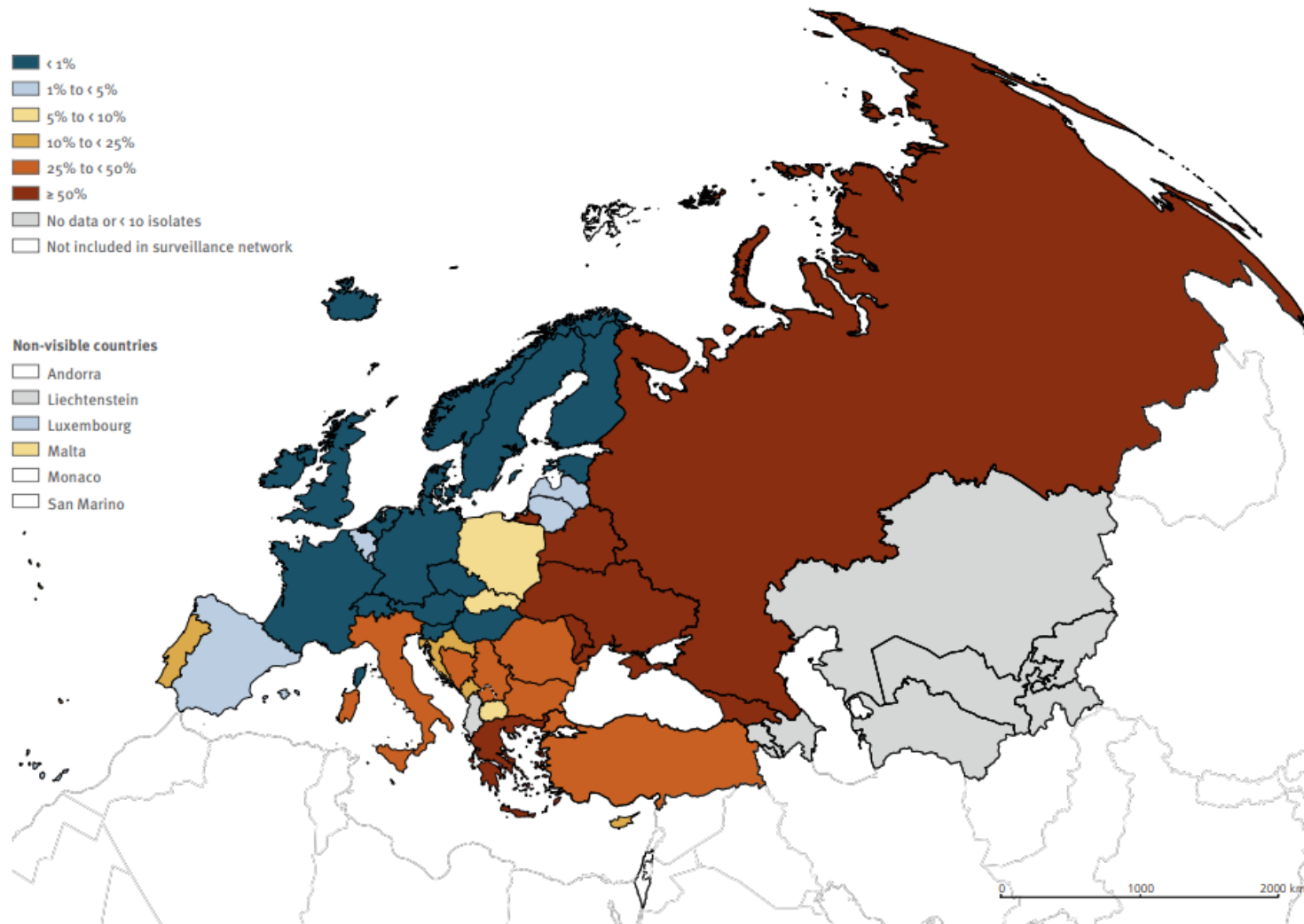
Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Carbapenem-resistant *Klebsiella pneumoniae*

Fig. 5 *K. pneumoniae*: percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



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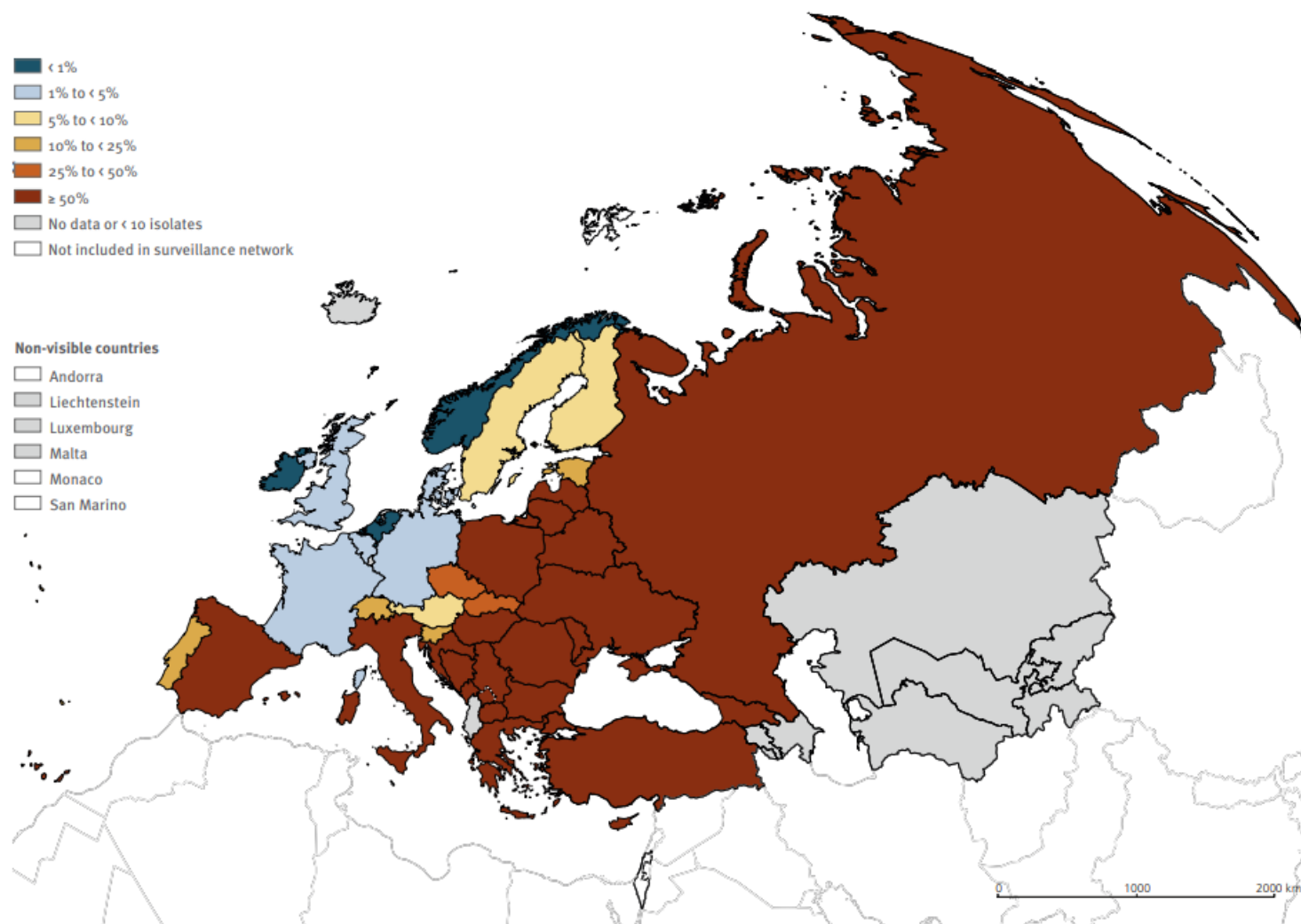
Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Carbapenem-resistant *Acinetobacter* spp.

Fig. 7 *Acinetobacter* spp.: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



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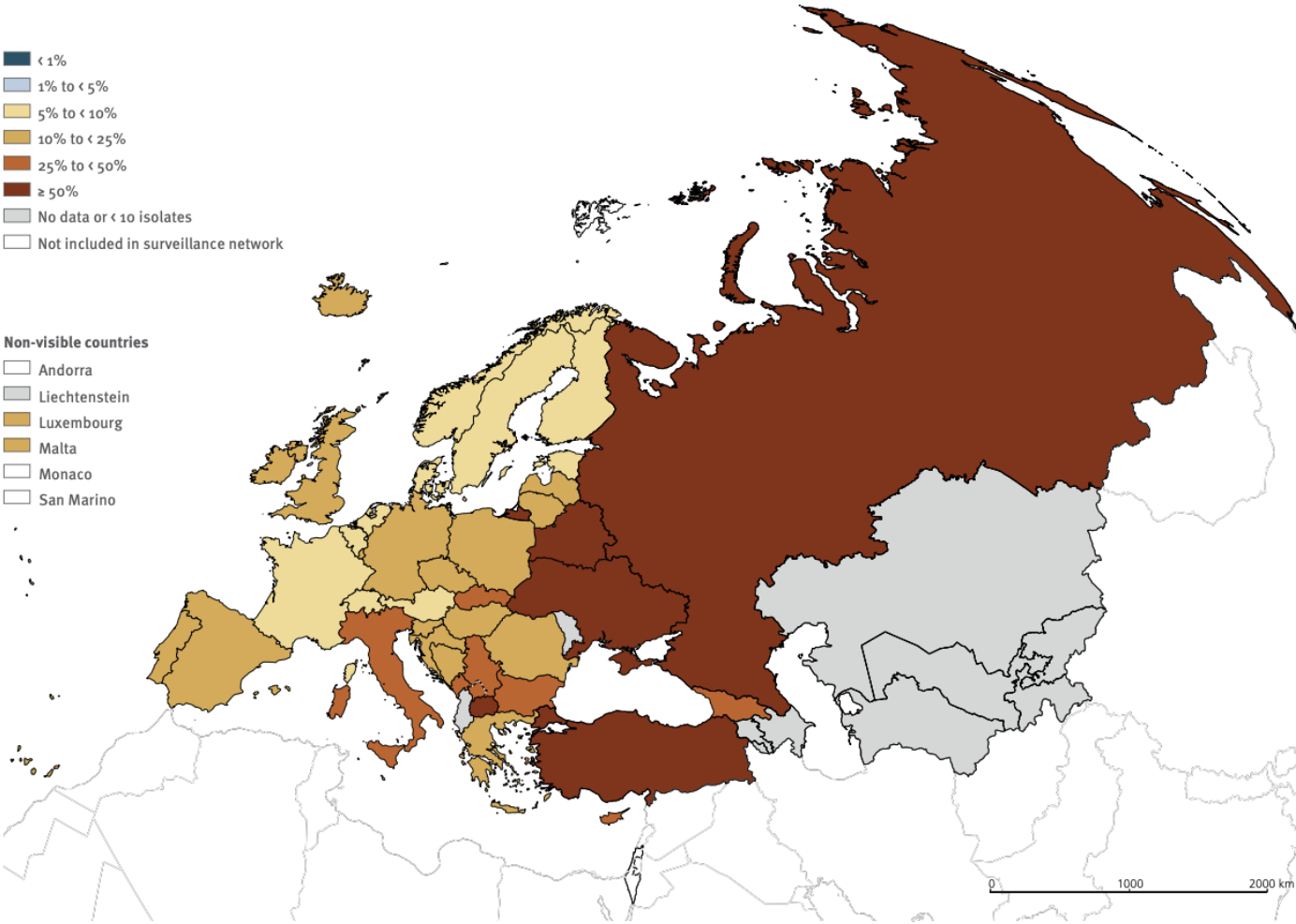
Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Third generation cephalosporin-resistant *E. coli*

Fig. 2 *E. coli*: percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country/area, WHO European Region, 2020



WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

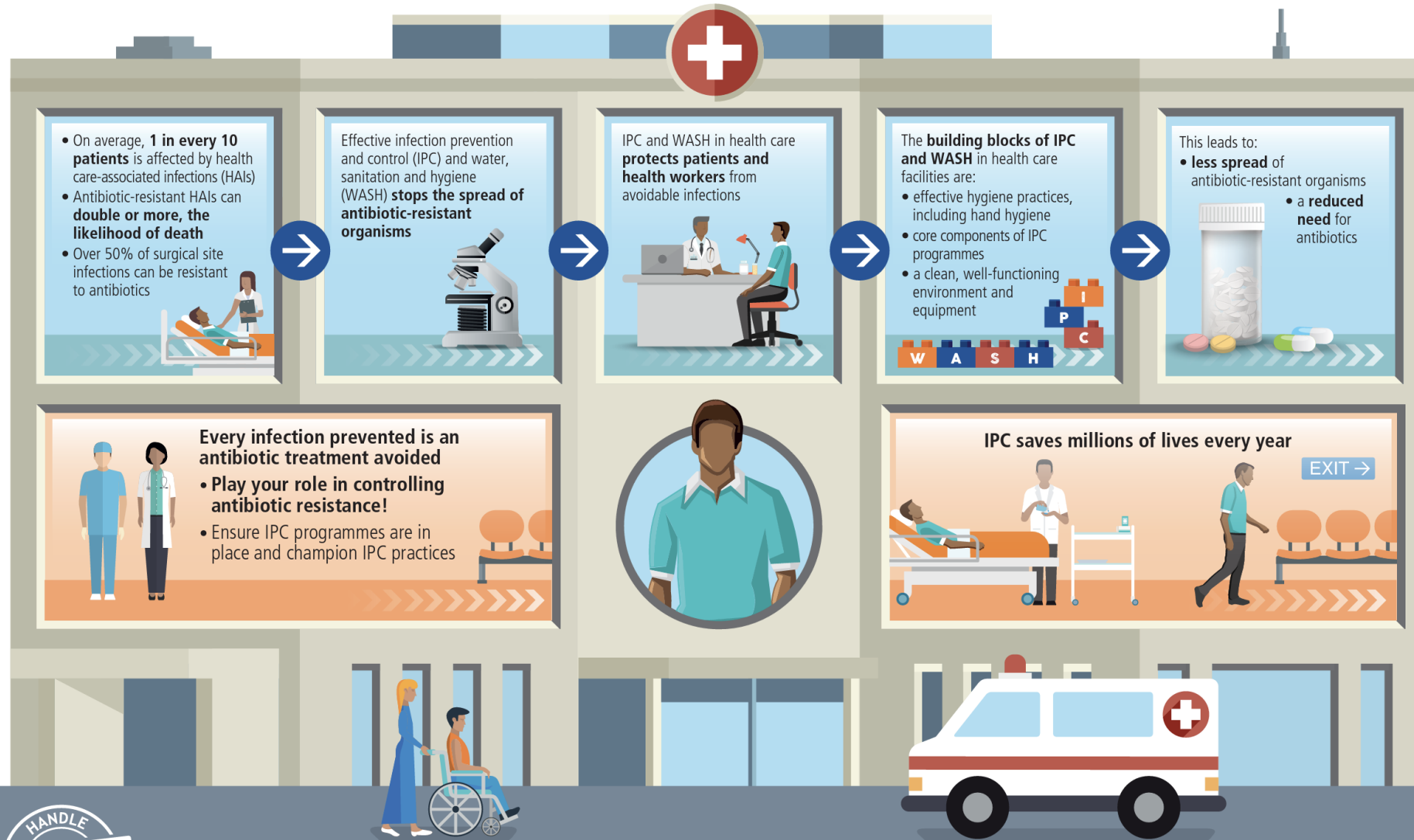
Priority 1: CRITICAL[#]

- Acinetobacter baumannii*, carbapenem-resistant
- Pseudomonas aeruginosa*, carbapenem-resistant
- Enterobacteriaceae**, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

- Enterococcus faecium*, vancomycin-resistant
- Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
- Helicobacter pylori*, clarithromycin-resistant
- Campylobacter*, fluoroquinolone-resistant
- Salmonella* spp., fluoroquinolone-resistant
- Neisseria gonorrhoeae*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

THE ROLE OF INFECTION PREVENTION AND CONTROL IN PREVENTING ANTIBIOTIC RESISTANCE IN HEALTH CARE



Sources: World Health Organization. Infection prevention and control. Available at: <http://www.who.int/infection-prevention/en/> | World Health Organization. Water sanitation and hygiene. Available at: http://www.who.int/water_sanitation_health/en/

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Antibiotic use and antibiotic resistance in Europe - conclusions

- Large, mostly unexplained variation in the quantity and quality of antibiotic use among countries and regions
- Too many countries do not reach the (conservative) 60% Access target
- There is a need for metrics that better capture the quality of antibiotic use
- For many countries the aim should probably be to
 - Reduce overall antibiotic use to the level of lowest use in Europe in primary care and the hospital
 - Decrease the use of Watch antibiotics
 - Improve infection control
- How to do it (the more difficult question): guidance, education, campaigns, incentives, audit and feedback, decision support, antimicrobial stewardship programs, etc.

Grazie !



Antibiotics

Antivirals

Antifungals

Antiparasitics