

Antimicrobial Resistance (AMR) in Republic of Macedonia

*Nikola Panovski, Biljana Kakaraskoska Boceska,
Ana Kaftadziewa, Zaklina Cekovska, Golubinka
Boshevaska, Kristina Hristova, Neda Milevska*

*Institute of Microbiology and Parasitology, Medical Faculty,
Institute of Public Health, Health Insurance Fund, Studiorum,
Skopje, Republic of Macedonia*



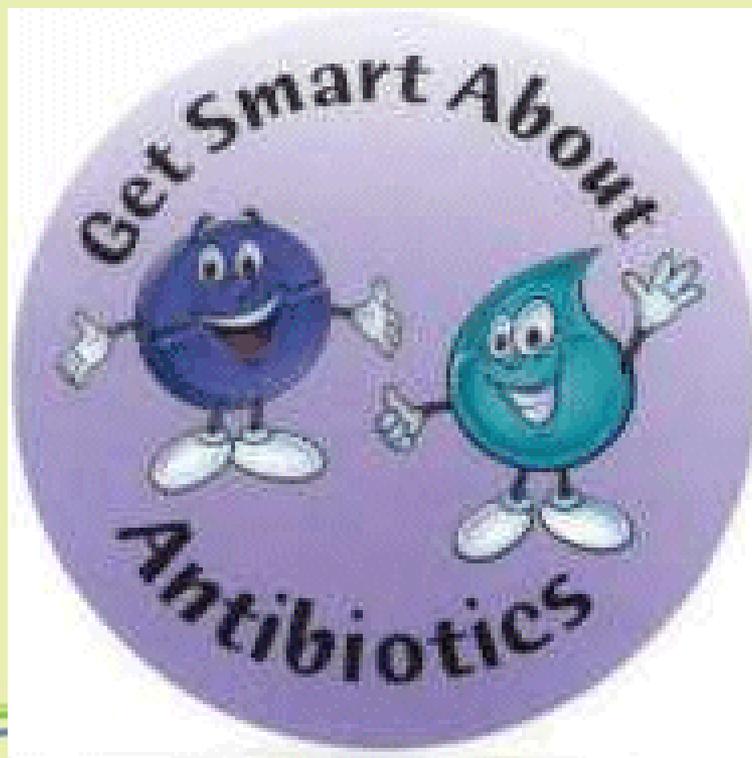
Aims of the study

- To overview the antimicrobial resistance in Republic of Macedonia, to compare with the AMR in Europe and the Balkan region, it's close relation with the consumption of antibacterials.
- Fortunately, we have finally gathered enough relevant data to answer the question: Where does our country stand on this issue, what is the situation like in the neighboring countries and in the Balkans in general?

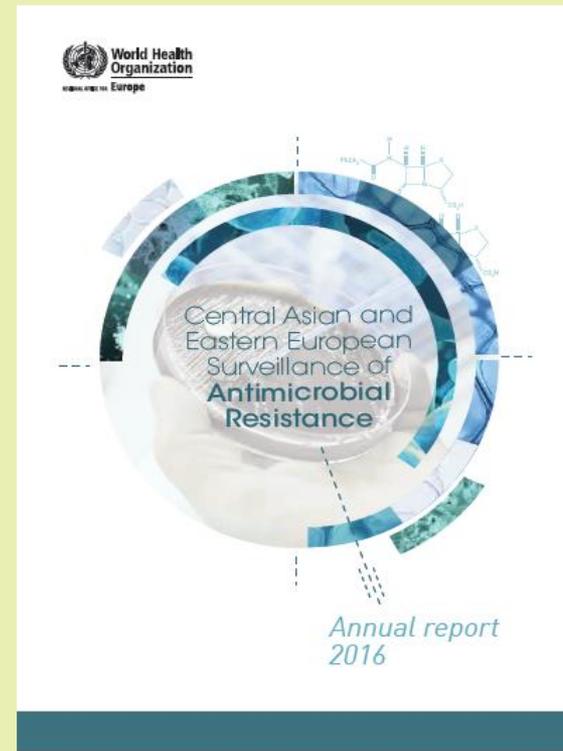


***“The more you use it,
- the faster you lose it”***

Burke JP, Lancet 1995;345:977



Source of data



ECDC (2015): Antimicrobial resistance surveillance in Europe 2014

CAESAR (2016): Antimicrobial resistance surveillance in 2014-15



Target countries of EARS-Net

- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*

defined in the EARS-Net reporting protocol.

5 EARS-Net Reporting Protocol Version 3, 2013. Available from http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Documents/2013_EARS-Net_Reporting-Protocol.pdf

Figure 2.1. Countries contributing AMR data for 2012 to EARS-Net

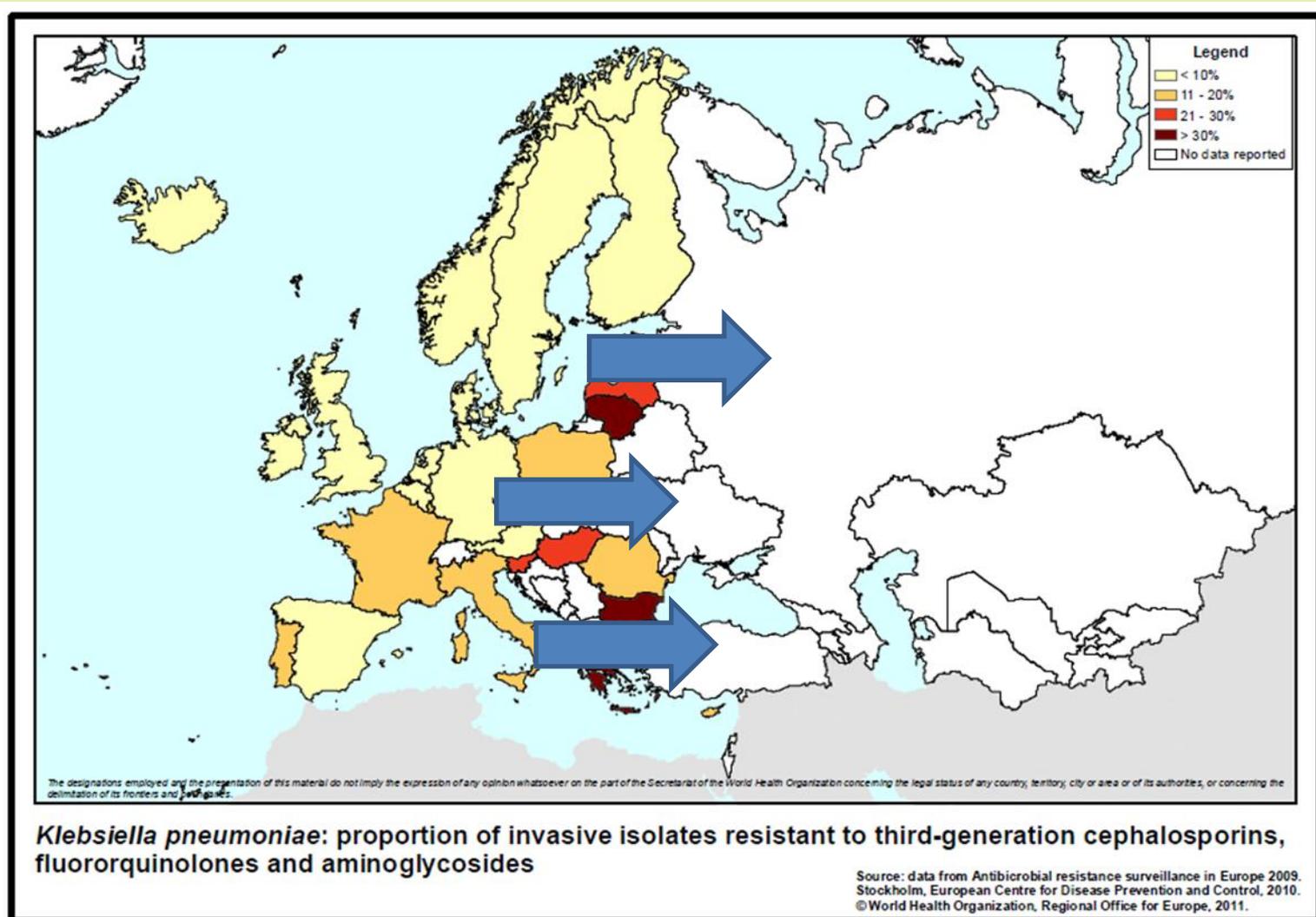
- Participating countries
- Non participating countries



AT	Austria	FI	Finland	MT	Malta
BE	Belgium	FR	France	NL	Netherlands
BG	Bulgaria	HR	Croatia	NO	Norway
CY	Cyprus	HU	Hungary	PL	Poland
CZ	Czech Republic	IE	Ireland	PT	Portugal
DE	Germany	IS	Iceland	RO	Romania
DK	Denmark	IT	Italy	SE	Sweden



Target countries of CAESAR



What is CAESAR?

- CAESAR= Central Asian and Eastern European Surveillance of Antimicrobial Resistance
- The initiators and founders: WHO, ESCMID, RIVM in close collaboration with ECDC.
- The methodology of collecting, checking and processing of data is in accordance with the EARS-Net



CAESAR - methodology

- Microorganisms that should be reported:
 - *S. aureus* (MRSA)
 - *Str. pneumoniae* (Pen R)
 - *E. coli* (ESBL+, carbapenemase +)
 - *K. pneum.* (ESBL +, carbapenemase +)
 - *E. faecium and faecalis* (VRE)
 - *Ps. aeruginosa* (multiresistant)
 - *Acinetobater spp.*

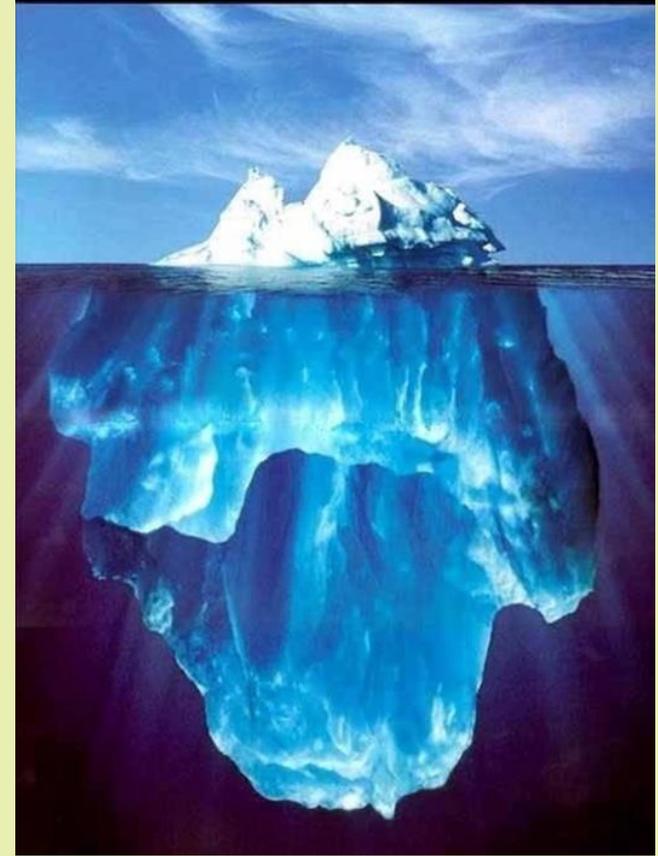


CAESAR - methodology

- The site of isolation of the strains indicates they are the cause of infection with high degree of probability.
- All isolated strains of these species should be reported, but only one strain from one patient.
- The results are shown as a percent of resistant strains from all isolated strains.



CAESAR - methodology



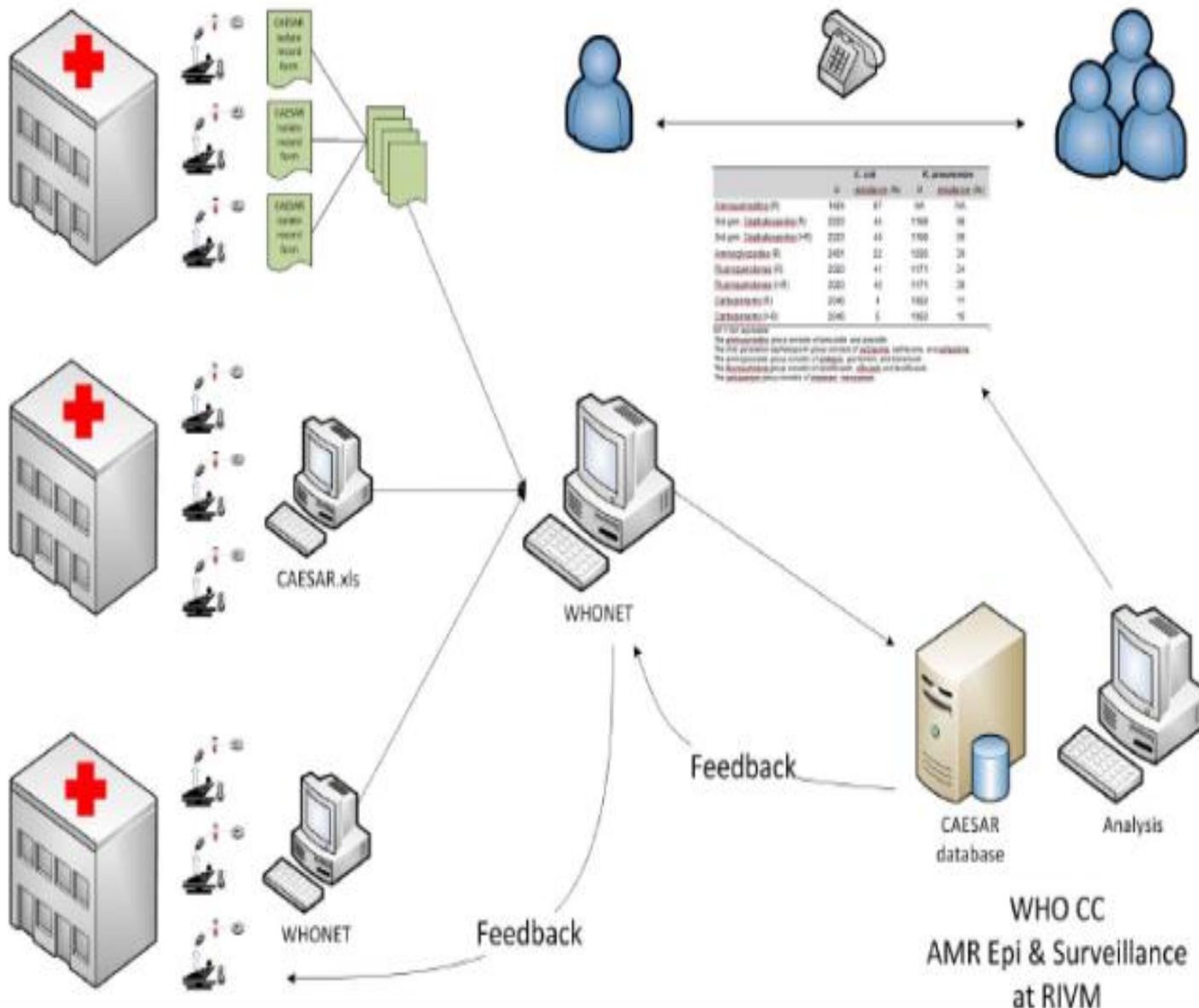
(Cornaglia, G., W. Hryniewicz, et al. (2004). "European recommendations for antimicrobial resistance surveillance." Clin Microbiol Infect **10**(4): 349-383.)



AMR surveillance network

National AMR surveillance coordinator

CAESAR project group WHO/ESCMID/RIVM



CAESAR Network in Macedonia

Institution/lab- oratory	Total number of blood cultures/CSF		
	Year		
	2013	2014	2015
IMP MF Skopje	3777 / 314	3556 / 426	3122 / 174
IPH of RM	846 / 0	906 / 9	1042 / 4
CH Achib. Sistina	982 / *	1005 / *	1100 / *
Clinic of Inf.diseases			859 / 222
CPH Bitola	296 / 22	323 / 10	337 / 6
Nephrology Struga	161 / 0	169 / 0	209 / 0
CPH Prilep	78 / 4	126 / 5	
CPH Shtip			20 / 5
IPD Kozle			155 / 0
PHH Remedica			43 / 0
CPH Tet./PE Gostiv.			23 / 0
* No data for CSF CPH Veles			17 / 0

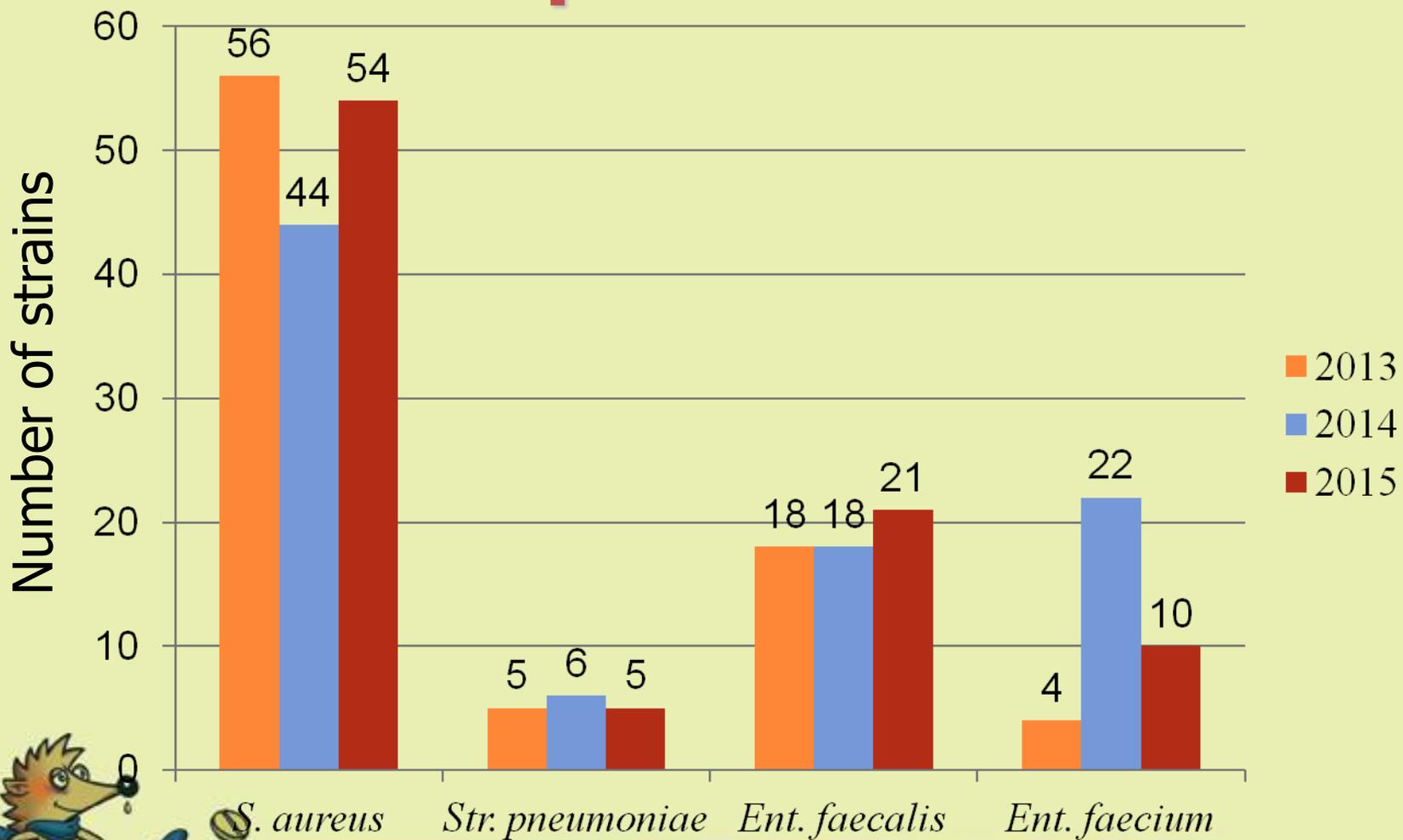
Invasive isolates reported to CAESAR 2013-2015

Institution/ laboratory	Number (%) of reported isolates to CAESAR			
	Year			Total (%)
	2013	2014	2015	
IMP MF Skopje	155 (81,6%)	158 (72,5%)	147 (67,7%)	460 (73,6%)
IPH of RM	11 (5,8%)	24 (11,0%)	10 (2,2%)	45 (7,2%)
CPH Bitola	12 (6,3%)	11 (5,0%)	13 (6,0%)	36 (5,8%)
Clin.of Inf.diseas.			28 (12,9%)	28 (4,5%)
Nephrology Struga	3 (1,6%)	15 (6,9%)	7 (3,2%)	25 (4,0%)
CH Achib. Sistina	8 (4,2%)	8 (3,7%)	2 (0,9%)	18 (2,9%)
CPH Veles			4 (1,8%)	4 (0,6%)
CPH Prilep	1 (0,5%)	2 (0,9%)	0	3 (0,5%)
CPH Tet./PE Gostiv			2 (0,9%)	2 (0,3%)
CPH Shtip	0	0	1 (0,5%)	1 (0,2%)
IPD Kozle	0	0	1 (0,5%)	1 (0,2%)
PHH Remedica			1 (0,5%)	1 (0,2%)
CPH Strumica			1 (0,5%)	1 (0,2%)
Total	190	218	217	625

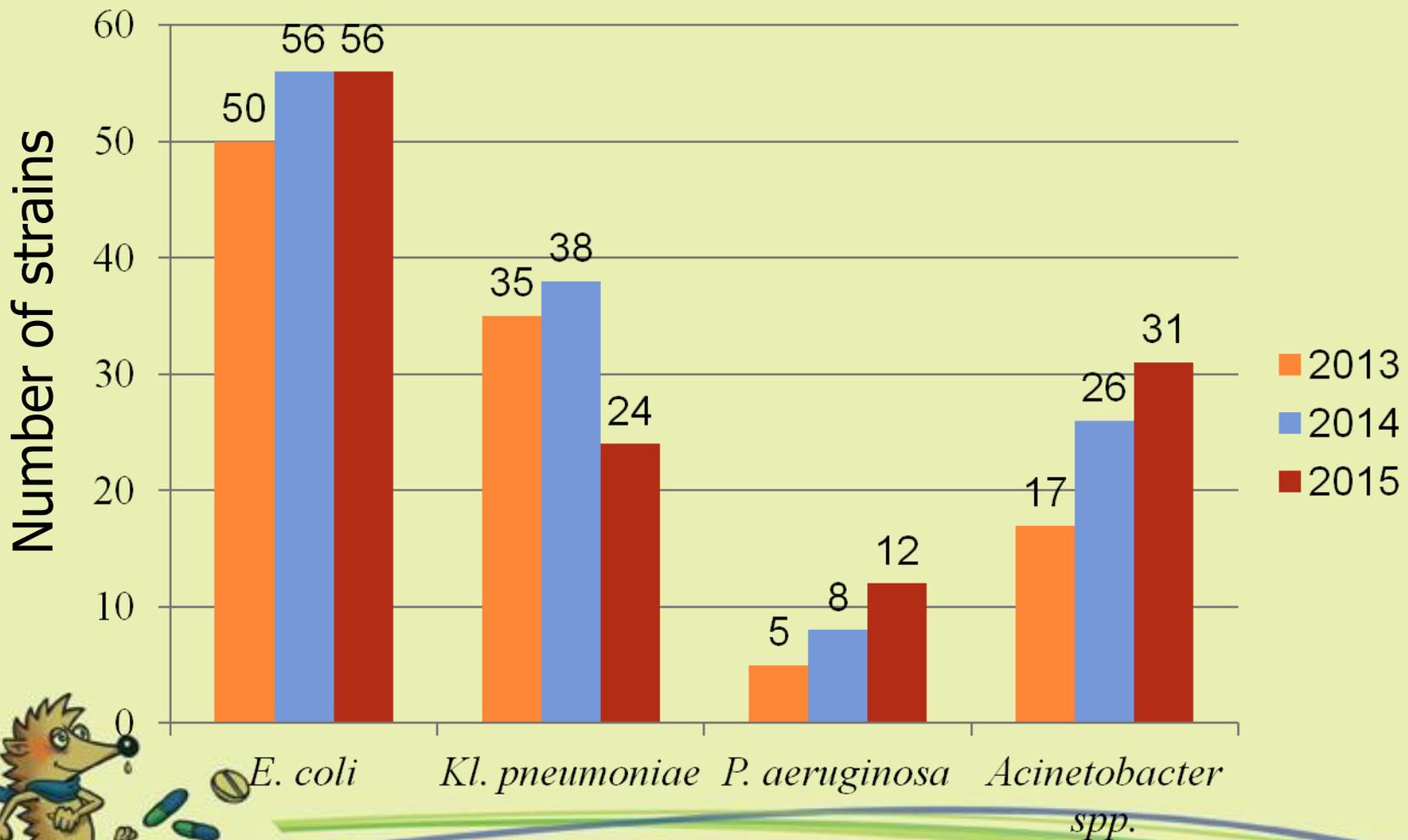
Total number of invasive isolates and percents of resistance

2013 2014 2015	<i>S. aureus</i>	<i>Str. pneumon.</i>	<i>Ent. faecalis</i>	<i>Ent. faecium</i>	<i>E. coli</i>	<i>Kl. pneumon.</i>	<i>Acinetobacter</i>	<i>P. aeruginosa</i>
Total number	156	16	60	37	162	97	74	25
Kind of resistance	MRSA	PNSP	VRE	VRE	ESBL	ESBL	CRAB	CRPA
% of resistance	40,4	18,8	1,7	62,2	66,0	85,6	74,3	36,0

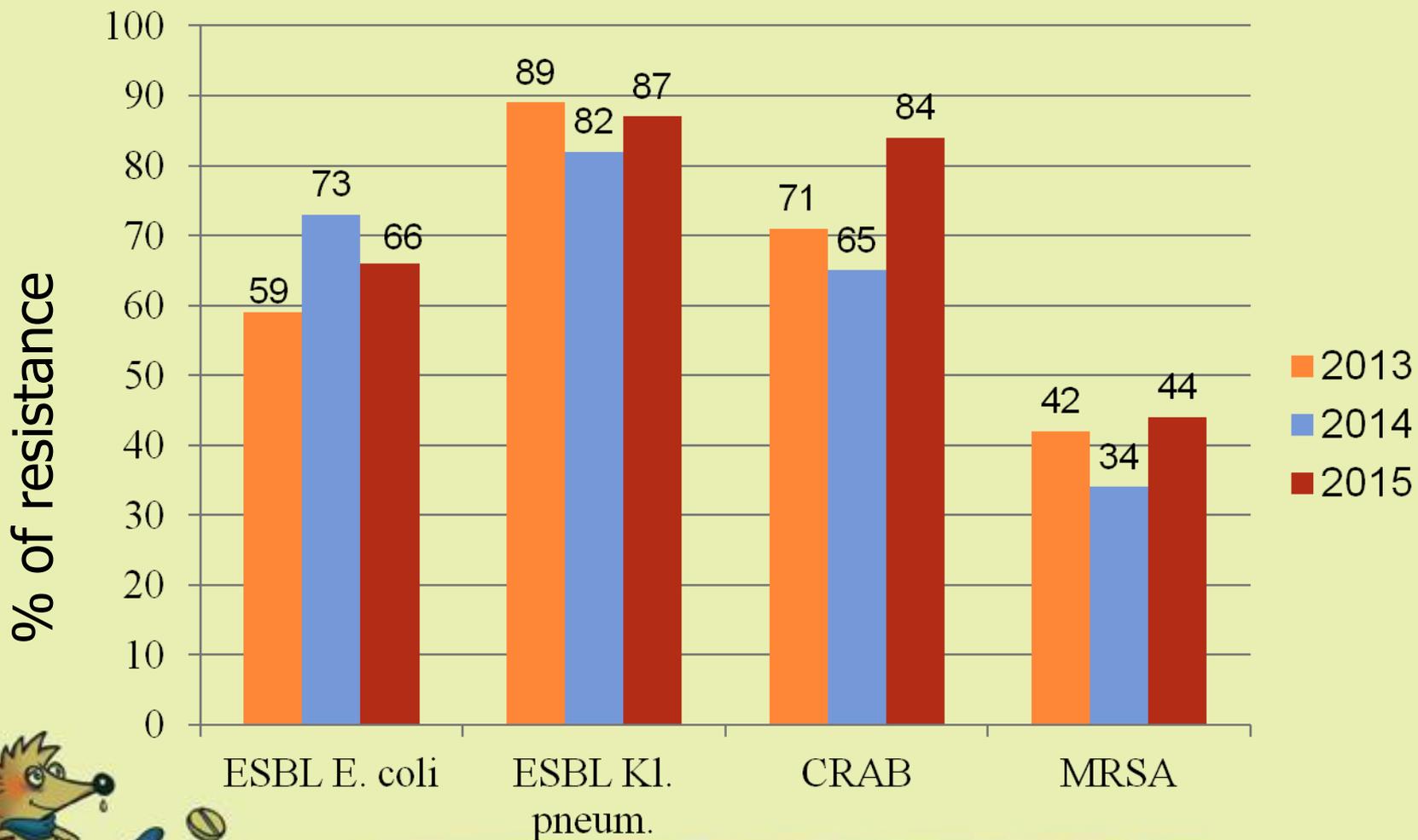
Gram positive bacteria



Gram negative bacteria



Resistance of isolates



Kind of resistance

Resistance of *E. coli* and *K.pneumoniae* to aminoglycosides, fluoroquinolones and carbapenems



Klebsiella pneumoniae



Invasive strains in EU-EEA and in Macedonia in 2014

Bacteria	Number of isolates		
	EU-EEA	Min.-max.	MCD/EU average
<i>S.aureus</i>	40414	61-5484	44/162
<i>S.pneumoniae</i>	10456	8-1288	6/42
<i>E.faecalis</i>	9560	12-1741	18/38
<i>E.faecium</i>	8142	11-882	22/32
<i>E.coli</i>	82815	141-10307	56/331
<i>K.pneumoniae</i>	19536	28-2175	38/78
<i>P.aeruginosa</i>	11447	11-1779	8/46
<i>Acinetobacter</i>	4058	3-806	26/16
Вкупно	186428	-	218/745

Five hospitals with the most number of invasive isolates in Macedonia

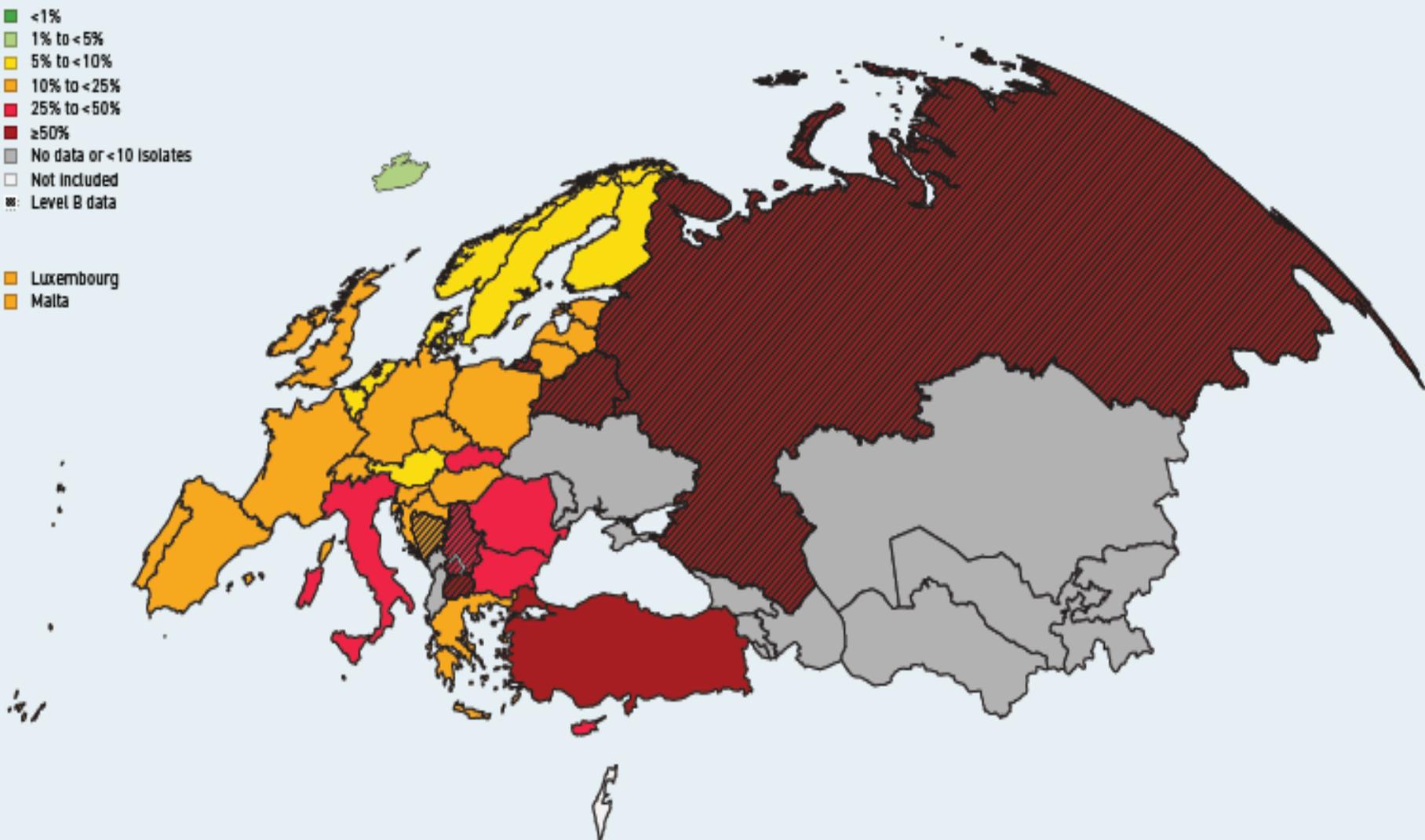
Hospital (clinic)	Number of specimens / reported isolates to CAESAR			
	Year			
	2013	2014	2015	Total
Pediatric diseases	1484 / 33	1323 / 28	1650 / 42	4457 / 103
Infective diseases	1023 / 25	1040 / 19	1277 / 32	3436 / 76
Gynecol./obstet.	839 / 12	906 / 23	1046 / 10	2781 / 45
Nephrology	462 / 52	517 / 42	460 / 64	1439 / 168
Hematology	228 / 12	214 / 18	190 / 29	632 / 59



Resistance of the most frequent isolates in the five hospitals in Macedonia

Hospital (clinic)	Nuber of isolates/% of resistance (2013,2014,2015)				
	<i>S. aureus</i> (MRSA)	<i>E. coli</i> (ESBL)	<i>Kl. pnemoniae</i> (ESBL)	<i>E. faecium</i> (VRE)	<i>Acinetobact.</i> (CRAB)
Nephrology	67 (29,8%)	47 (57,4%)	8 (100%)	5 (20%)	9 (100%)
Pediatric diseases	1 (0%)	8 (50.0%)	32 (93,7%)	0	2 (50%)
Infective diseases	28 (39,3%)	15 (73,3%)	33 (74,4%)	2 (100%)	14 (68,8%)
Hematology	6 (50%)	28 (82,1%)	1 (0%)	13 (76,9%)	5 (100%)
Gynecol./obstet.	7 (42,8%)	28 (50%)	4 (75%)	9 (0%)	11 (72,7%)



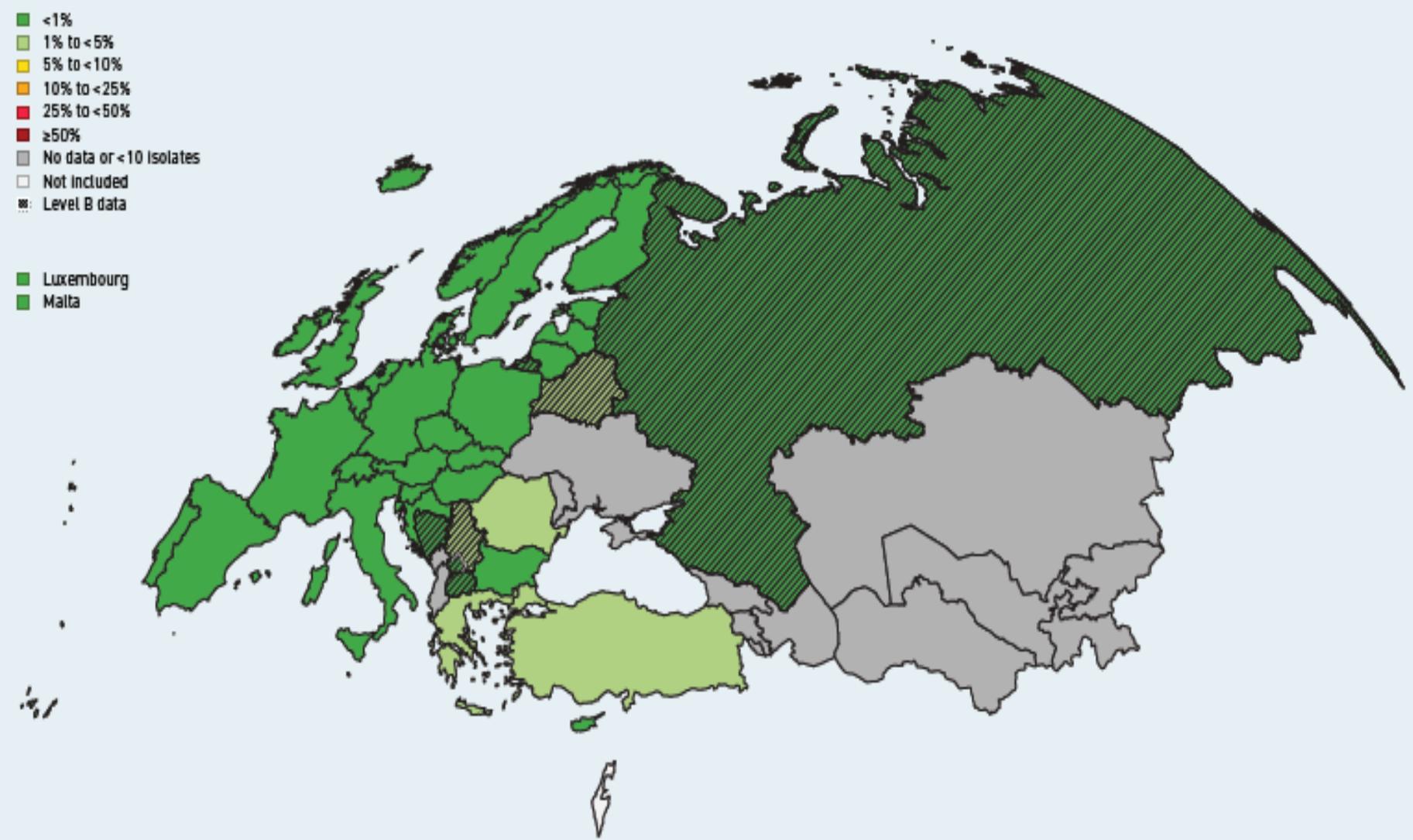


Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of antimicrobial resistance in the country. For more information about levels of evidence, see section 5.2. Levels of evidence are only provided for CAESAR countries and areas.

EARS-Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, 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.

CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, Republic of Moldova, Russian Federation, Serbia, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244(1999))

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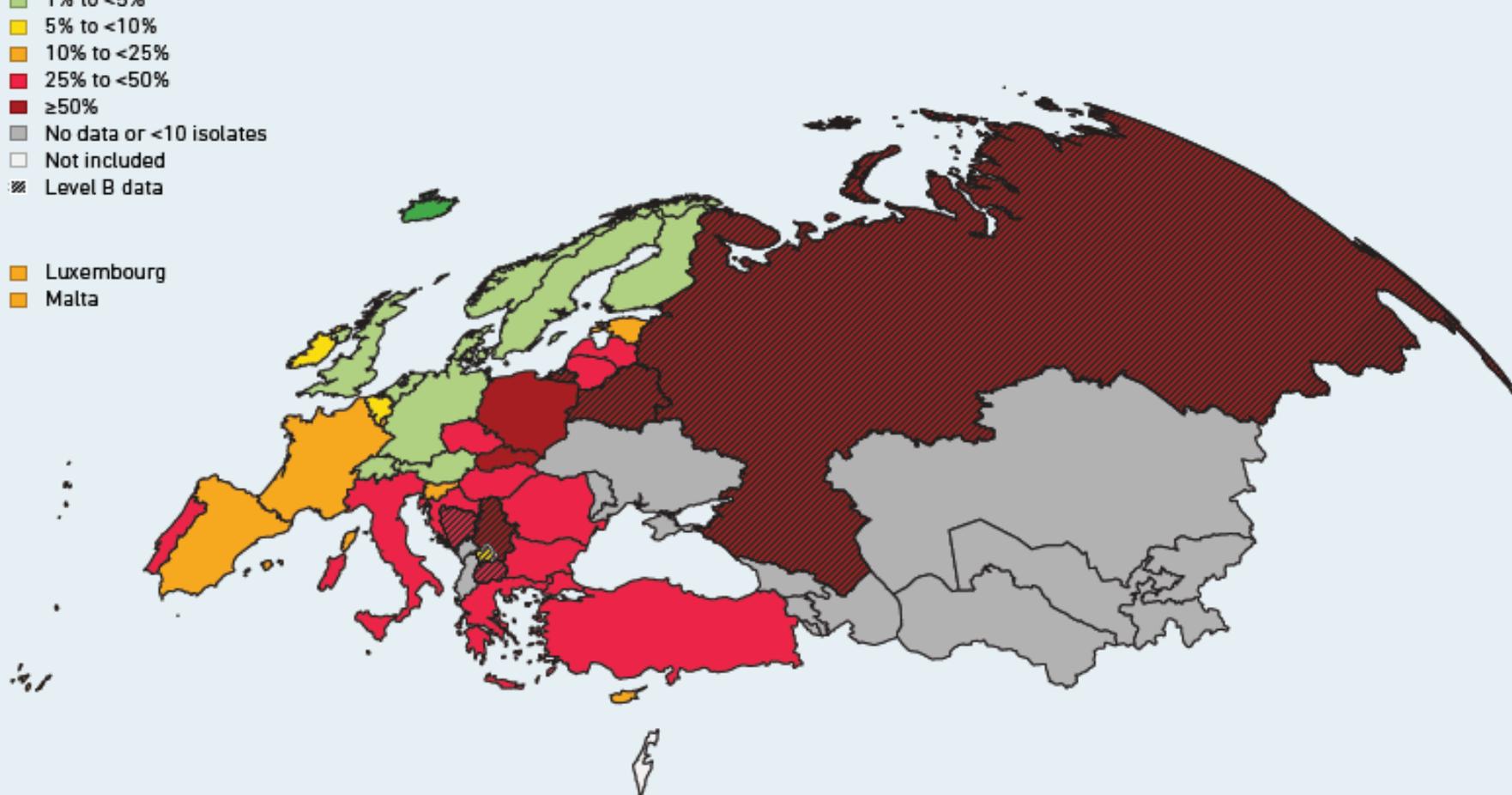


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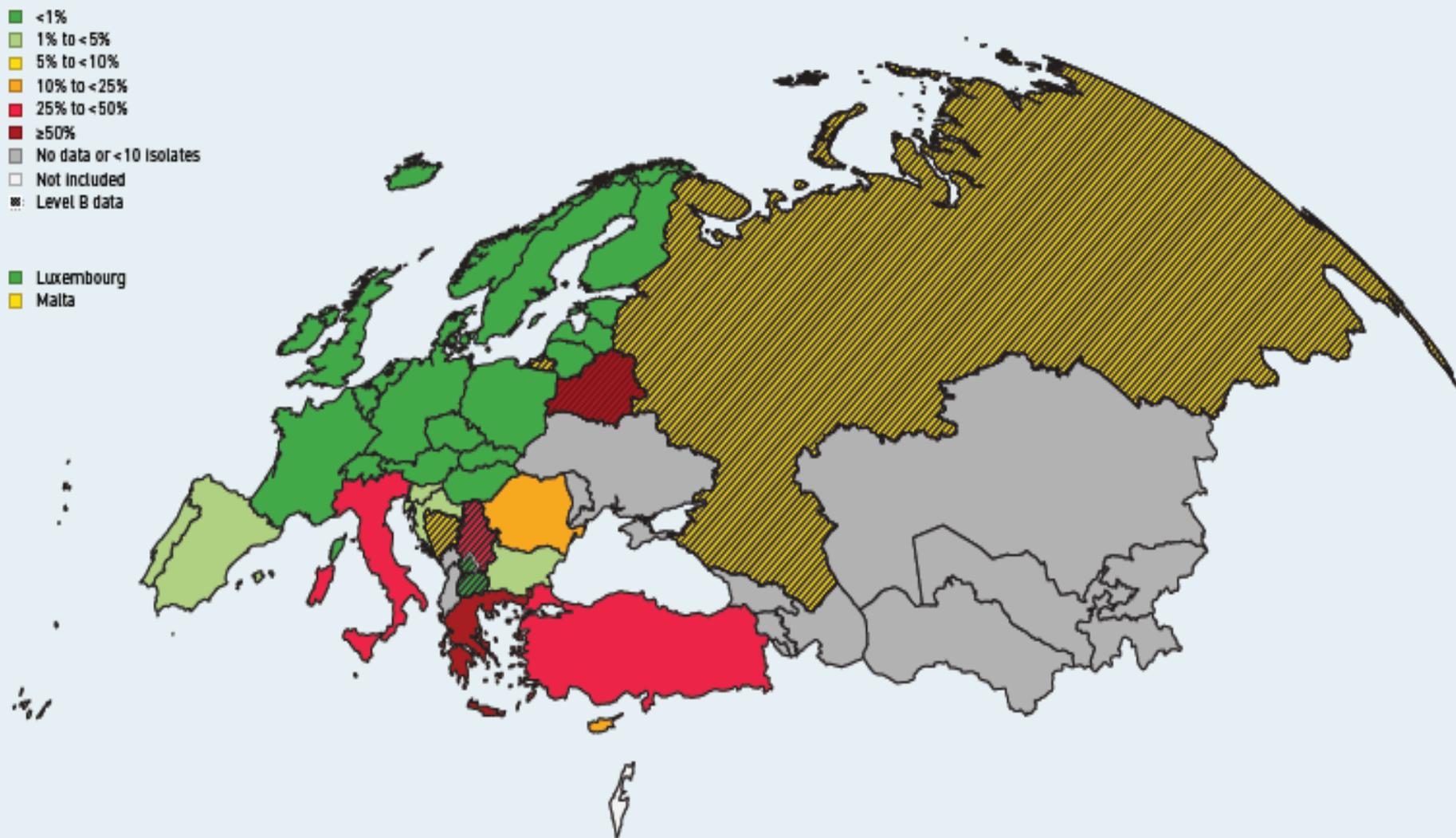


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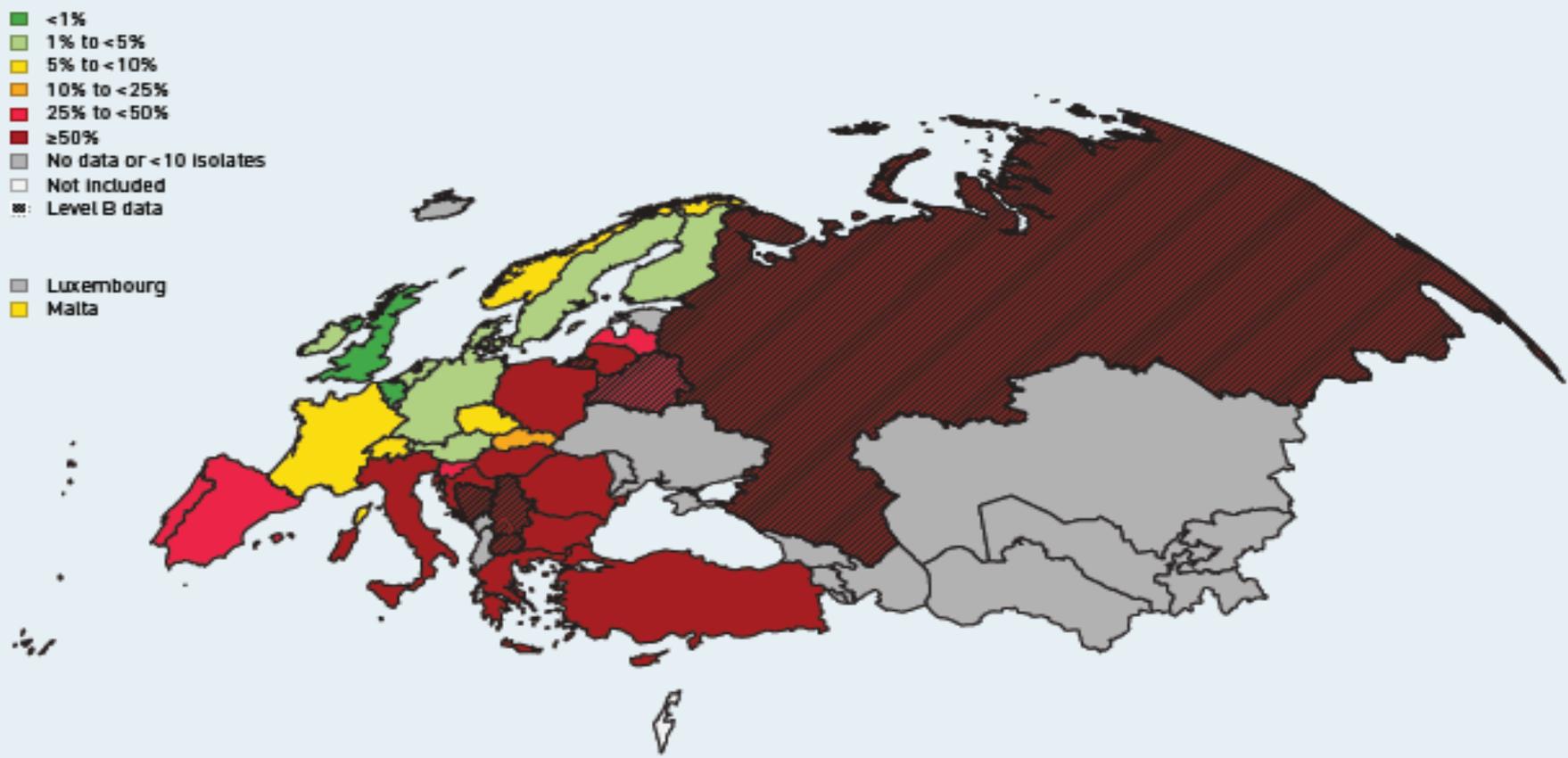


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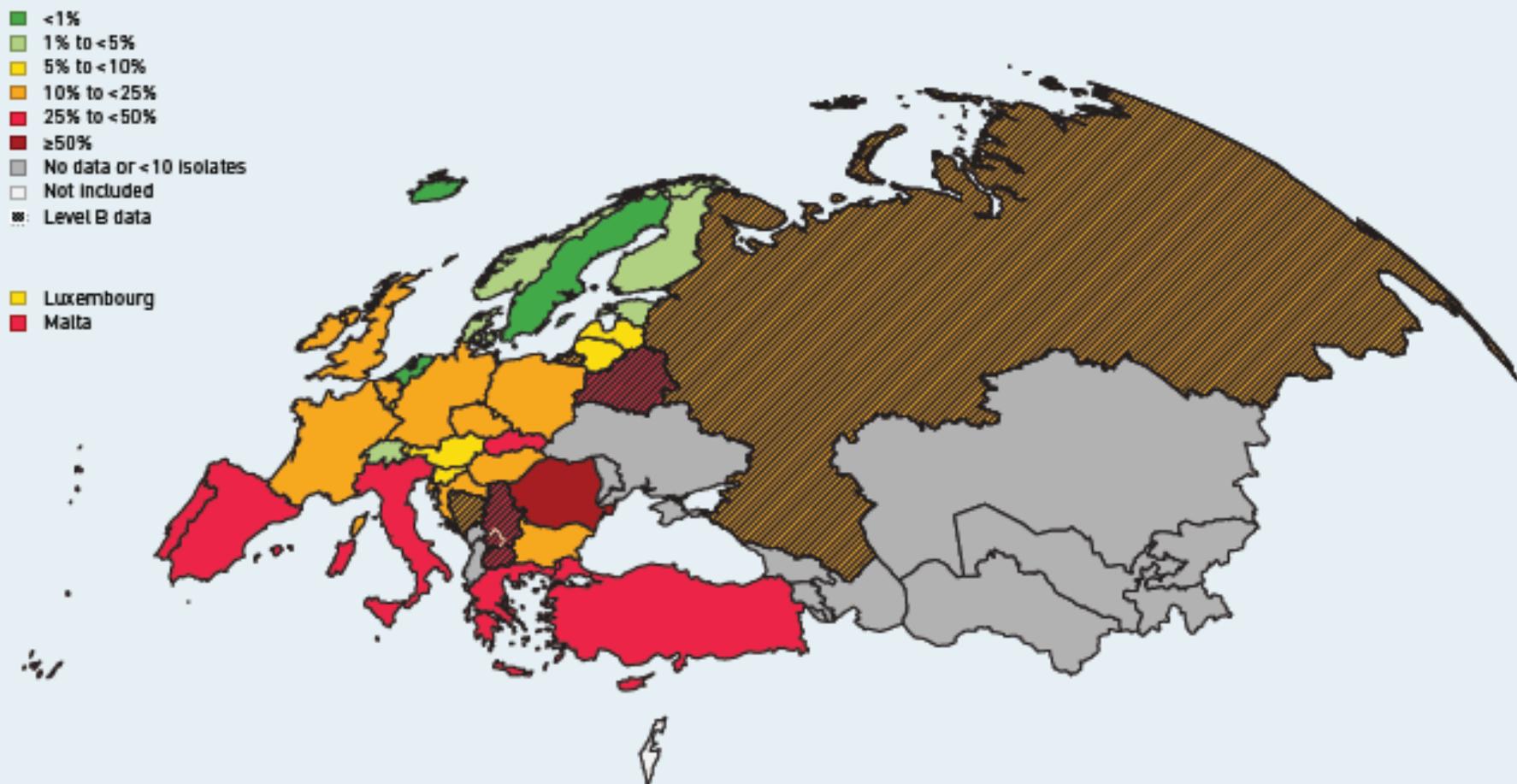
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Comparison of AMR in Macedonia (CAESAR) with AMR in EU-EEA countries (EARS-Net)

Result for year 2014



Escherichia coli =

- Results from EARS –Net 2014
- EU-EEA 82815 isolates (141-10307/min-max)
- Macedonia 56 isolates

- **Fluoroquinolones –resistant-E.coli (R-Ec)**
- 7.8% - Iceland – 46.4% Cyprus
- EU-EEA average 22.4%
- Macedonia – 71%



Escherichia coli

=

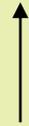


- Aminoglycozides. R-Ec
- 4.6% Finland – 28.2% Bulgaria
- EU-EEA average 9.8%
- Macedonia 64%

- 3rd Gen.Ceph. – R-Ec
- 3.3% Iceland – 40.4% Bulgaria
- EU-EEA trend 2011-2014 = 9.6% - 12 %
- Macedonia 73%



Klebsiella pneumoniae

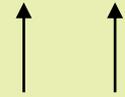


- Results from EARS-Net 2014
- EU-EEA 19536 isolates (28-2175)
- Macedonia 35 isolates

- Fluoroquinol. resistant *K.pneumoniae* (R-Kp)
- 3.6% Iceland – 70.8% Slovakia
- EU-EEA trend 2011-2014 = 24.5% - 27.4%
- Macedonia 32%



Klebsiella pneumoniae



- Aminoglycozides. R-Kp
- 2.3% Finland – 68.2% Slovakia
- EU-EEA trend 2011-2014 = 20.1% - 23.1%
- Macedonia 78%

- 3rd Gen.Ceph. – R-Kp
- 0% Iceland – 74.8% Bulgaria
- EU-EEA trend 2011-2014 = 23.6% - 28%
- Macedonia 82%



Klebsiella pneumoniae



- Carbapenems R-Kp (CRKP)
- 0% Estonia, Finland, Iceland, Norway, Sweden – 62.3% Greece
- EU-EEA trend 2011-2014 = 6% - 7.3%
- Macedonia 0%

- Polimixin (Colistin) R-Kp
- 0% - 25.8% Romania
- EU-EEA average 8.2%
- 29% of CRKP resistant to polmixin



Acinetobacter

- Results from EARS-Net 2014
- EU-EEA 4058 isolates (3-806)
- Macedonia 26 isolates
- **Fluoroquinolones resistant *Acinetobacter* (R-A)**
- 2.9% Denmark – 95.3% Greece
- Macedonia 84.6%
- **Aminoglycosides. R-A**
- 1.7% Denmark – 95.3% Greece
- Macedonia 88%



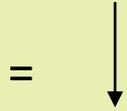
Acinetobacter

- Carbapenems R-A
- 0% Netherlands – 93.2% Greece
- Macedonia 65.4%

- Polimixin (Colistin) R-A
- 0% - 80.1% Greece and Italy
- EU-EEA average 4%



Pseudomonas aeruginosa



- Results from EARS-Net 2014
- EU-EEA 11447 isolates (11-1779)
- Macedonia 8 isolates
- **Fluoroquinolones resistant *P.aeruginosa*-(R-Pa)**
- 0% Iceland – 55.4% Romania
- EU-EEA -trend 2011-2014 = 22.1%-19.4%
- **Ceftazidime – R-Pa**
- 2.4% Luxembourg – 59.1% Romania

EU-EEA trend 13.1%



Pseudomonas aeruginosa



- **Aminoglycozides. R-Pa**
- 0% Iceland – 63.4% Romania
- EU-EEA trend 2011-2014 = 16.7% - 14.8%
- **Carbapenems R –Pa**
- 4.4% Netherlands – 58.5% Romania
- EU-EEA trend 2011-2014 = 16.8%-18.3%
- **Piperacillin-Tazobactam R-Pa**
- 4.4% Denmark – 62.2% Romania
- EU-EEA trend 2011-2014 = 16%-16.9%



Staphylococcus aureus



- Results from EARS-Net 2014
- EU-EEA 40414 isolates (61-5484)
- Macedonia 44 isolates

- **MRSA**
- 0.9% Netherlands – 56% Romania
- EU-EEA trend 2011-2014 = 18.6% - 17.4%
- 34% Macedonia



Streptococcus pneumoniae =

- Results from EARS-Net 2014
- EU-EEA 10456 isolates (8-1288)
- Macedonia 6 isolates

- **Penicillin resistant (PRSP)**
- 0% Cyprus – 46.7% Romania
- **Macrolides resistant (MRSP)**
- 0% Cyprus – 48% Romania



Enterococcus faecalis =

- Results from EARS-Net 2014
- EU-EEA 9560 isolates (12-1741)
- Macedonia 18 isolates
- **High level aminoglycosides resistant (HLARE)**
- 8.3% Iceland – 76.5% Romania
- EU-EEA-average – 28.8%
- Macedonia – 88.9%



Enterococcus faecium



- Results from EARS-Net 2014
- EU-EEA 8142 isolates (11-882)
- Macedonia 22 isolates
- **Vancomycin resistant (VRE)**
- 0% Iceland, Finland, Estonia, Malta – 45.1% Ireland
- EU-EEA trend – 2011-2014 – 6.2% - 7.9%
- Macedonia – 68.2%



Comparison of invasive strains isolated in 2013

Country (popul., in millions)	<i>S.pneum.</i>	<i>S.aureus</i>	<i>Enterocc.</i>	<i>E.coli</i>	<i>K.pneum.</i>	<i>P.aerug</i>
	Number of strains					
Macedonia (2)	5	55	22	50	35	5
Slovenia (2)	279	465	135	1224	245	133
Estonia (1.3)	79	171	77	342	91	21
Luxembourg (0.5)	49	135	61	322	53	34
Denmark (5.5)	789	1685	1224	3967	875	414
Serbia (8.5)	42	270	146	199	307	109
Romania (21.5)	44	384	135	302	221	94
Bulgaria (7.5)	29	214	154	187	138	60



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	Isolated strains per 1 mil.cit.					
Macedonia (2)	2.5	27.5	11	25	17.5	2.5
Slovenia (2)	139.5	232.5	67.5	612	122.5	66.5
Estonia (1.3)	60.8	131.5	59.2	263.1	70	16.1
Luxembourg (0.5)	98	270	122	644	106	68
Denmark (5.5)	143.5	306.4	222.5	721.3	159.1	75.3
Serbia (7.2)	5.8	37.5	20.3	27.6	42.6	15.1
Romania (21.5)	2	17.9	6.3	14	10.3	4.4
Bulgaria (7.5)	3.9	28.5	20.5	24.9	18.4	8



The resistance in Macedonia is very high, but not very real – what is the reason?

Example – hypothetical

- Slovenia 2000 pt with E.coli x 3 = 6000 hc
- 60% isolates = 1200 strains, ESBL 5% 60 strains

- Macedonia 2000 pt with E.coli 50 hc
- 60% isolates = 30 strains (6 ESBL+), after failure of treatment, another 50 hc, 26 strains 20 of them ESBL+ (total 52% ESBL +).



Summary – Europe

- The antimicrobial resistance situation in Europe displays **large variations depending on bacteria, antimicrobial group and geographical region.**
- For several antimicrobial group and bacterium combinations, **a north-to-south and west-to-east gradient** is evident in Europe. In general, lower resistance percentages are reported by countries in the north and higher percentages reported by countries in the south and east of Europe.



Conclusion

- The % of resistance in invasive strains isolated in the Republic of Macedonia are significantly higher than the average ones in the EU and similar to those in SE and SEE countries. This is due to the long-lasting irrational antibiotic use.
- The lower number of isolated strains in Macedonia is not due to the successful disease prevention but rather to the fact that blood cultures are examined ten times less than in EU countries. This is the main reason that detected resistance of invasive strains is unreal very high, because laboratories test selective strains. One specific characteristic attributed to the Republic of Macedonia is the exceptionally low number of strains of *S.pneumoniae*. Another one is that 40% of the taken blood cultures are in children aged 0-4.



Благодарам на вниманието

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