



Gram Pozitif Bakterilerde Antibiyotik Duyarlılığı : Epidemiyoloji



Önemli Patojenler

- Stafilocoklar
 - Metisiline dirençli stafilocoklar
- Streptokoklar
 - Penisiline dirençli pnömokoklar
- Enterokoklar
 - Vankomisin dirençli enterokoklar



Tarihçe

- İlk kullanılan antibiyotiklerden
 - Penisilin
- İlk tanımlanan dirençler arasında
 - Penisilin direnci= beta laktamaz

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ*.

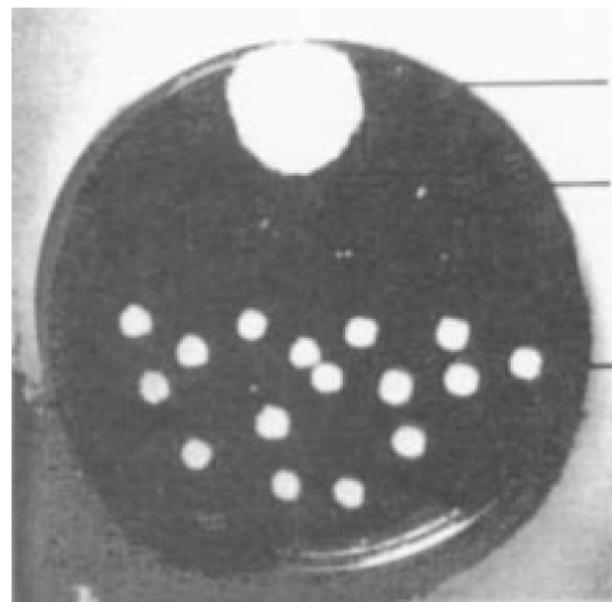
ALEXANDER FLEMING, F.R.C.S.

From the Laboratories of the Inoculation Department, St. Mary's Hospital, London.

Received for publication May 10th, 1929.

WHILE working with staphylococcus variants a number of culture-plates

BRITISH JOURNAL OF EXPERIMENTAL PATHOLOGY, VOL. X, NO. 3



Penicillium colony.

Staphylococci undergoing lysis.

Normal staphylococcal colony.

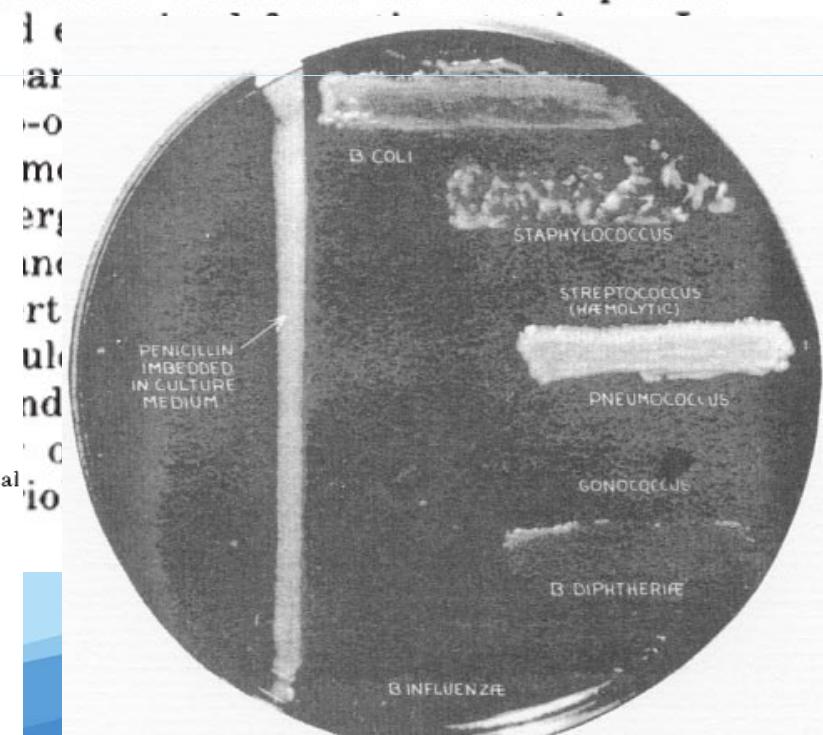


FIG. 1.—Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.

LETTERS TO THE EDITORS

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This column is open to all who have something to say on subjects of interest to the scientific world.

in constituents and pus.⁴ That the anti-bacterial
Is activity of penicillin is not affected under these con-
ditions gives this substance a definite advantage over
the sulphonamide drugs from the chemotherapeutic
point of view. The fact that a number of bacteria
contain an enzyme acting on penicillin points to the
possibility that this substance may have a function
in their metabolism.

E. P. ABRAHAM.

E. CHAIN.

Sir William Dunn School of Pathology,
Oxford.
Dec. 5.

¹ Fleming, A., *Brit. J. Exp. Path.*, **10**, 226 (1929).

² Booth, V. H., and Green, D. E., *Biochem. J.*, **32**, 855 (1938).

³ Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G., *Lancet*, **226** (1940).

⁴ MacLeod, C., *J. Exp. Med.*, **72**, 217 (1940).





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Science. 1944 Jun 2;99(2579):452-453.

EXTRACTION OF A HIGHLY POTENT PENICILLIN INACTIVATOR FROM PENICILLIN RESISTANT STAPHYLOCOCCI.

Kirby WM.

A highly potent penicillin inactivator has been extracted from 7 strains of Staph. aureus (coagulase positive), all of which were naturally penicillin resistant. No such inhibitor was present in extracts of 7 penicillin sensitive strains of Staph. aureus.

PMID: 17798398 [PubMed - as supplied by publisher]

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Staphylococcus aureus

Table 16. Antimicrobial resistance rates in the ICUs of the International Nosocomial Infection Control Consortium

Pathogen, antimicrobial	No. of pathogenic isolated tested, pooled	Resistance percentage, %	No. of pathogenic isolated tested, pooled	Resistance percentage, %	No. of pathogenic isolated tested, pooled	Resistance percentage, %
	(CLAB)	(CLAB)	(VAP)	(VAP)	(CAUTI)	(CAUTI)
<i>Staphylococcus aureus</i>						
OXA	761	84.1	715	77.5	43	74.4
<i>Enterococcus faecalis</i>						
VAN	115	8.7	277	0.72	277	2.9
<i>Pseudomonas aeruginosa</i>						
FQs	963	50.0	963	49.8	188	56.4
PIP or PTZ	703	78.0	1525	35.1	277	37.9
AMK	304	31.0	990	30.4	185	35.1
IMI or MERO	526	44.0	1636	38.6	288	34.7
CPM	30	73.3	118	66.9	30	73.3
<i>Klebsiella pneumoniae</i>						
CTR or TAZ	394	76.1	584	70.4	213	70.0
IMI, MERO, or ETP	444	3.8	632	3.8	237	3.4
<i>Acinetobacter baumannii</i>						
IMI or MERO	605	46.3	1209	52.4	113	38.9
<i>Escherichia coli</i>						
CTR or TAZ	193	53.9	274	67.9	343	41.7
IMI, MERO, or ETP	214	3.7	299	3.0	302	4.6
FQs	181	46.4	142	59.9	300	35.0

AMK, amikacin; CPM, cefepime; CTR, ceftriaxone; ETP, ertapenem; FQs, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, or ofloxacin); IMI, imipenem; MERO, meropenem; OXA, oxacillin; PIP, piperacillin; PTZ, piperacillin-tazobactam; TAZ, ceftazidime; VAN, vancomycin.



CLAB: Central Veneus Catheter Associated Blood Stream Infection

VAP : Ventilator Associated Pneumoniae

CAUTI : Catheter Associated Urinary tract infections

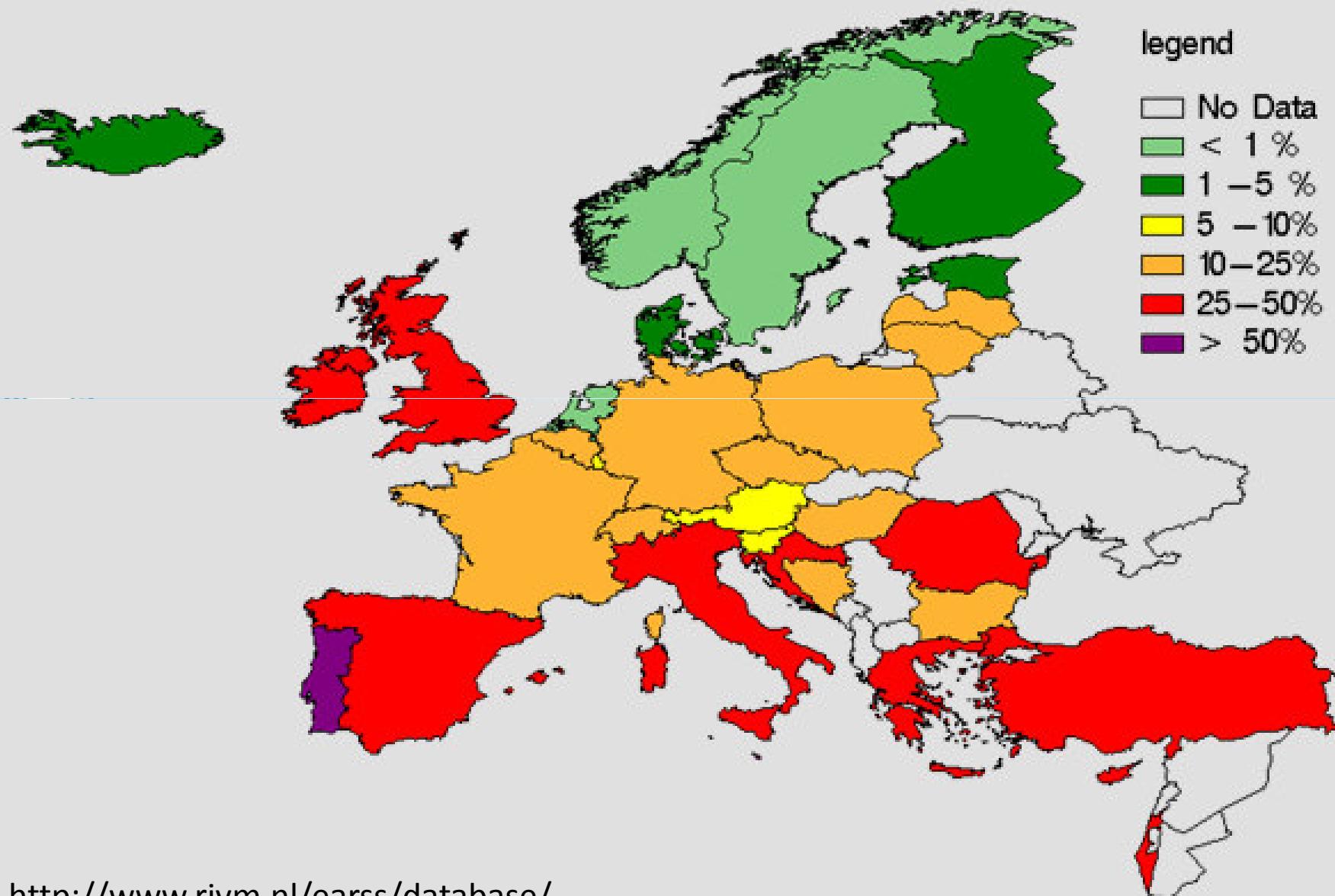
Table 2

Comparative activity of linezolid tested against 6113 Gram-positive pathogens isolated during the 2008 LEADER Program

Organism/resistance group (no. tested/antimicrobial agents)	MIC (μg/mL)			% by category Susceptible/resistant ^a	
	50%	90%	Range		
<i>Staphylococcus aureus</i>					
Oxacillin-susceptible (1404)					
Linezolid	2	2	0.25 to 2	100.0 /–	
Oxacillin	0.5	0.5	≤0.25 to 2	100.0/0.0	
Ceftriaxone	4	4	0.5 to 32	99.6/0.0	
Ciprofloxacin	0.5	>4	≤0.03 to >4	85.6/11.6	
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	92.2/7.5	
Daptomycin	0.25	0.5	≤0.06 to 1	100.0/–	
Erythromycin	≤0.25	>2	≤0.25 to >2	62.8/36.5	
Gentamicin	≤2	≤2	≤2 to >8	99.4/0.6	
Levofloxacin	≤0.5	4	≤0.5 to >4	88.3/11.3	
Penicillin	4	32	≤0.015 to >32	19.5/80.5	
Quinupristin/dalfopristin	0.5	0.5	≤0.25 to 2	99.9/0.0	
Teicoplanin	≤2	≤2	≤2 to 4	100.0/0.0	
Tetracycline	≤2	≤2	≤2 to >8	95.7/3.6	
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >2	98.1/1.9	
Vancomycin	1	1	0.5 to 2	100.0/0.0	
Oxacillin-resistant (1752)					
Linezolid	2	2	0.25 to >8	99.8/–	
Ciprofloxacin	>4	>4	≤0.03 to >4	25.9/72.2	
Clindamycin	≤0.25	>2	≤0.25 to >2	62.7/37.0	
Daptomycin	0.25	0.5	0.12 to 4	99.8/–	
Erythromycin	>2	>2	<0.25 to >2	6.8/92.6	
Gentamicin	≤2	≤2	≤2 to >8	97.1/2.6	
Levofloxacin	>4	>4	≤0.5 to >4	27.7/72.0	
Quinupristin/dalfopristin	0.5	1	≤0.25 to 2	99.8/0.0	
Teicoplanin	≤2	≤2	≤2 to 4	100.0/0.0	
Tetracycline	≤2	≤2	≤2 to >8	94.5/5.3	
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >2	98.2/1.8	
Vancomycin	1	1	≤0.12 to 2	100.0/0.0	

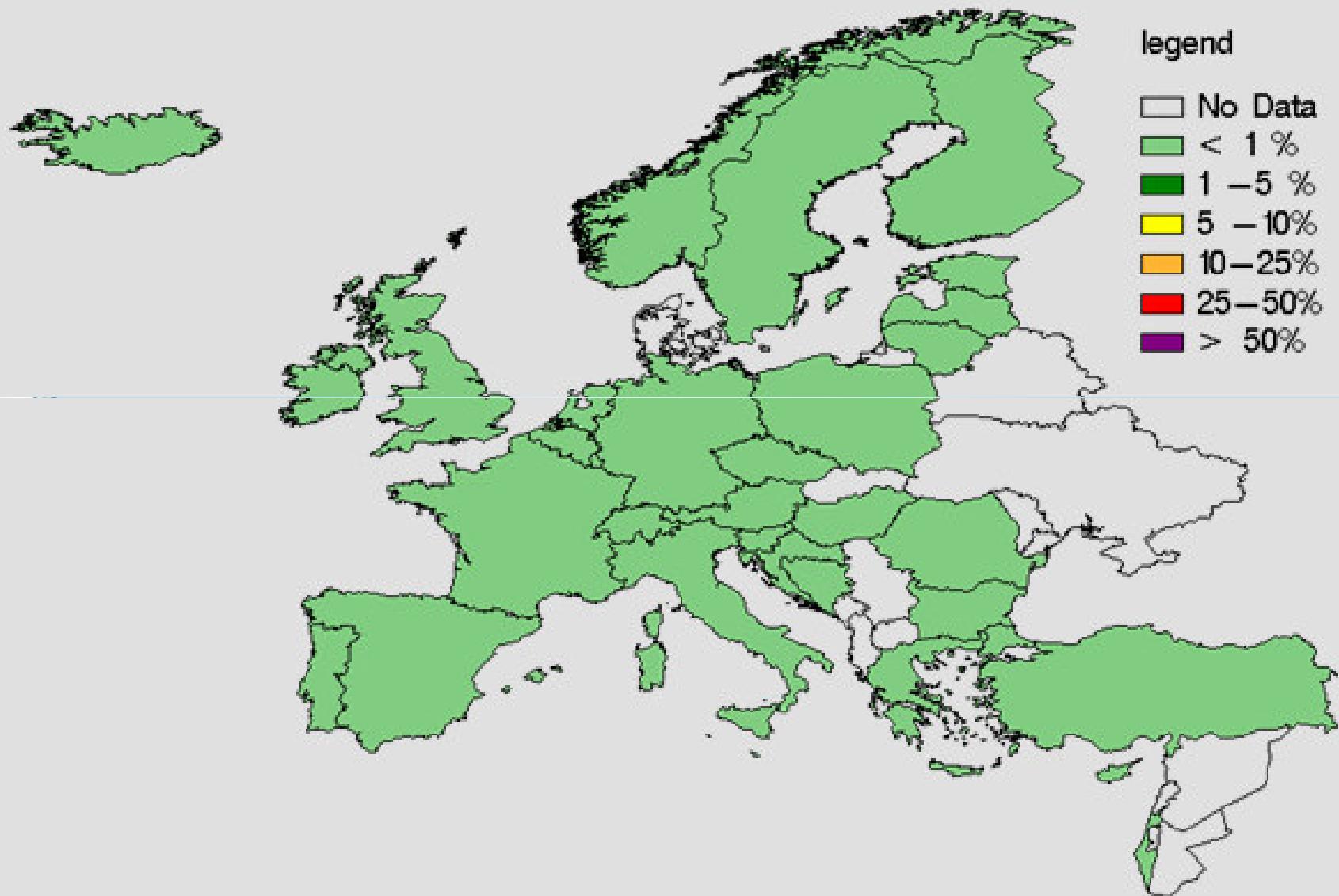
Proportion of MRSA isolates in participating countries in 2008

(c) EARSS



Proportion of Vancomycin non susceptible *S. aureus* isolates in participating countries in 2008

(c) EARSS





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Molecular epidemiology of 399 Methicillin Resistant Staphylococcus aureus isolated from 12 hospitals in Turkey

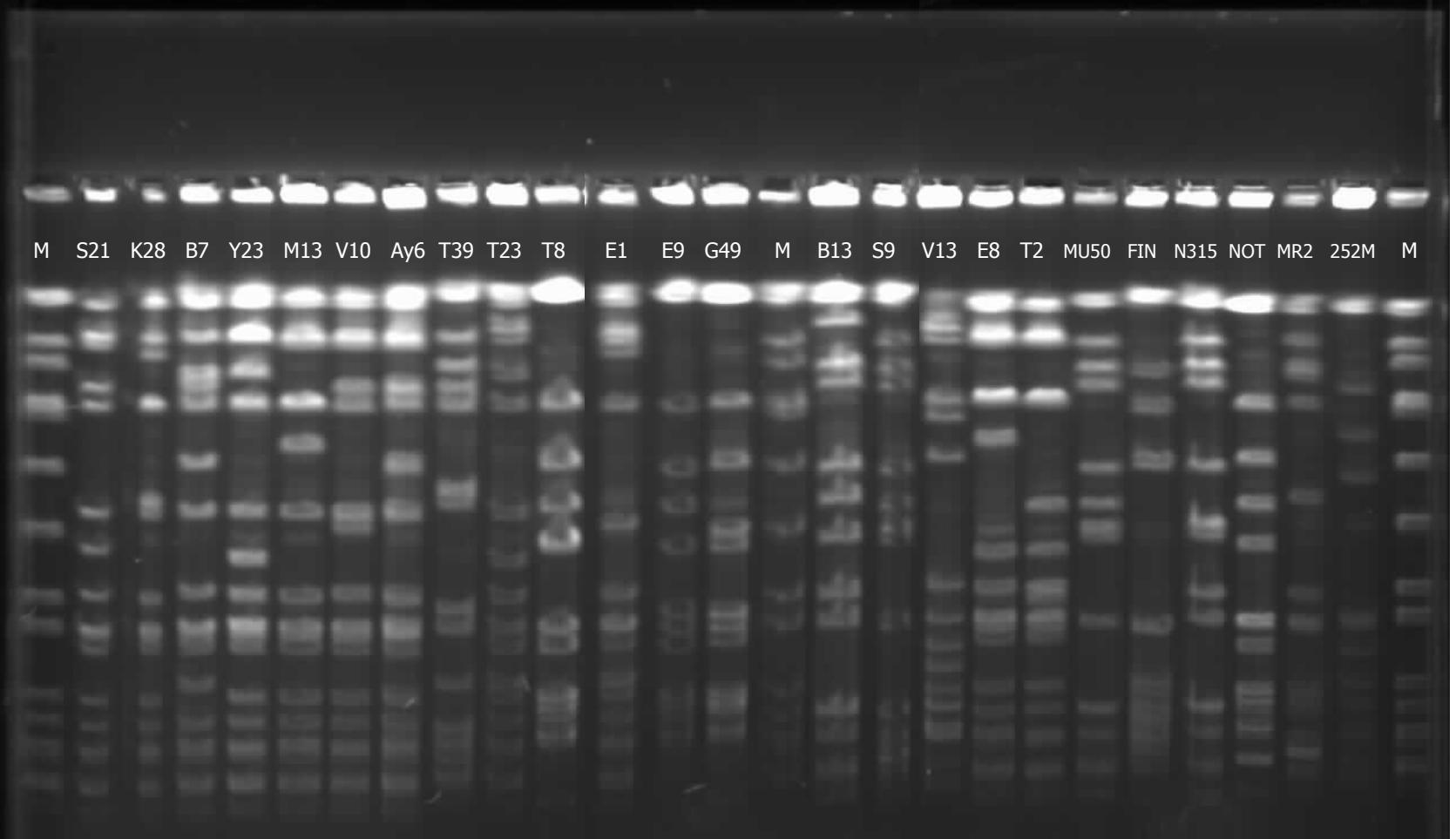
Author Block: O. Yildiz¹, S. Kirdar², B. Gulcu¹, O. Aktepe³, N. Karabiber⁴, S. Oncu², M. Tatman Otkun⁵, M. Ozyurt⁶, A. G. Sener⁷, A. Coskuner⁸, A. Y. Coban⁹, U. Arslan¹⁰, N. Ozkutuk¹¹, G. Bayramoglu¹², H. Guducuoglu¹³, B. Bozdogan^{2,1};

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Abstract:

Background. *S. aureus* is a common pathogen that causes a variety of infections in a large spectrum including skin infections, meningitis, endocarditis, food poisoning, osteomyelitis. This pathogen is one of the most common hospital infection agent. *S. aureus* has a great ability to adapt itself to variety of conditions and successful clones can be epidemic and even pandemic by its ability spread from one continent to another. Since 1980 the rates of infections due to methicillin resistant *S. aureus* gradually increased. These strains are also resistant to other groups of antimicrobials which causes difficulty for the treatment of MRSA infections. With the isolation of *S. aureus* resistant to vancomycin at 2002 treatment alternative of clinicians decreased further. **Methods.** A total of 12 centers sent 399 *S. aureus* strains for their molecular epidemiologic analysis. These centers were from different geographical area of Turkey and strains were isolated from 2005 to 2007. Epidemiologic studies with 399 strains are done and their pulsed field gel electrophoresis types (PFGE),





PFGE analizi 6 ulusal klon, 8 suş bölgesel klon ve 7 suş farklı PFGE, SCC veya PVL özelliklerine sahip. Enzim Smal. Marker *S. aureus* NCTC8325.

CLONES	SCC	PVL (+)	MLST	Number of Strains	Pulsotype
TR 01	Type III	3	ST239	359	A
TR 02	Type I	0	ST239	4	A
TR03	Type IV	0	ST737	16	B
TR04	Type IV	2	ST80	2	B
TR05	Type IV	0	ST97	11	C
TR06	Type IV	0	ST8	1	D
Singletons				4	
Total				397	



Spa tipleri

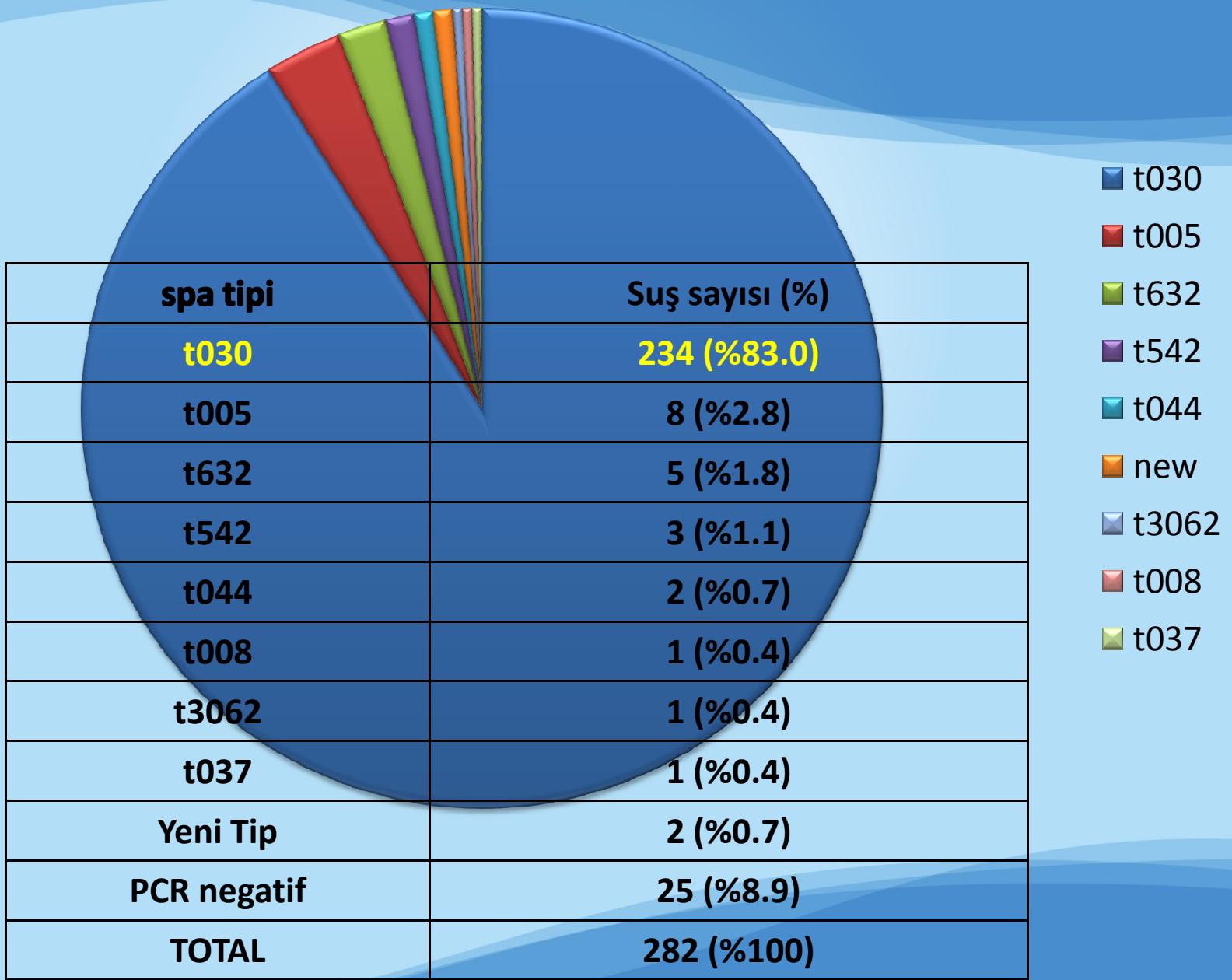


TABLE 2. Distribution of clonal complexes of MRSA in Asian countries

Country (no. of isolates)	No. of isolates with clonal complex and <i>SCCmec</i> type:							
	CC5		CC239			CC59 (IV)	Other ^b (IV)	
	II	IV	II	III	IIIA			
Japan (6)	6							
Korea (13)	10	2	1					
China (6)				3	3			
India (6) ^a				1	4			
Indonesia (7)						7		
Philippines (6)			1		4		1	
Saudi Arabia (5)						5		
Singapore (5)				1	4			
Sri Lanka (5)						5		
Taiwan (5)				1	1	1	2	
Thailand (5)				1	4			
Vietnam (5)						5		
Total (74) ^c	16	2	2	7	42	1	2	
							1	

^a One isolate (193), which was included in CC239, showed the nontypeable *SCCmec* type.

Staphylococcus aureus





S. aureus

- Metisilin direnci yayılmakta
- Genellikle çoklu dirençli
- Glikopeptid direnci nadir



Streptococcus pneumoniae

Table 2 (continued)

Organism/resistance group (no. tested/antimicrobial agents)	MIC ($\mu\text{g/mL}$)			% by category Susceptible/resistant ^a
	50%	90%	Range	
<i>Streptococcus pneumoniae</i> (619)				
Linezolid	1	1	≤ 0.12 to 2	100.0/-
Amoxicillin/clavulanate	≤ 1	8	≤ 1 to 16	83.4/12.9
Ceftriaxone	≤ 0.25	1	≤ 0.25 to 8	91.4/1.6
Clindamycin	≤ 0.25	>2	≤ 0.25 to >2	80.1/19.5
Erythromycin	≤ 0.25	>2	≤ 0.25 to >2	65.3/34.2
Levofloxacin	1	1	≤ 0.5 to 4	99.4/0.5
Penicillin ^f	≤ 0.03	4	≤ 0.03 to >4	86.9/1.1
Penicillin ^g	≤ 0.03	4	≤ 0.03 to >4	60.1/22.0
Quinupristin/dalfopristin	0.5	0.5	≤ 0.25 to 1	100.0/0.0
Tetracycline	≤ 2	>8	≤ 2 to >8	77.9/21.6
Trimethoprim/sulfamethoxazole	≤ 0.5	>2	≤ 0.5 to >2	67.9/24.1
Vancomycin	≤ 1	≤ 1	≤ 1	100.0 /-

^f CLSI (2008) criteria for "penicillin parenteral (nonmeningitis)" (susceptible at $\leq 2 \mu\text{g/mL}$ and resistant at $\geq 8 \mu\text{g/mL}$).

^g CLSI (2008) criteria for "Penicillin parenteral (oral penicillin V)" (susceptible at $\leq 0.06 \mu\text{g/mL}$ and resistant at $\geq 2 \mu\text{g/mL}$).

Penisilin direnci

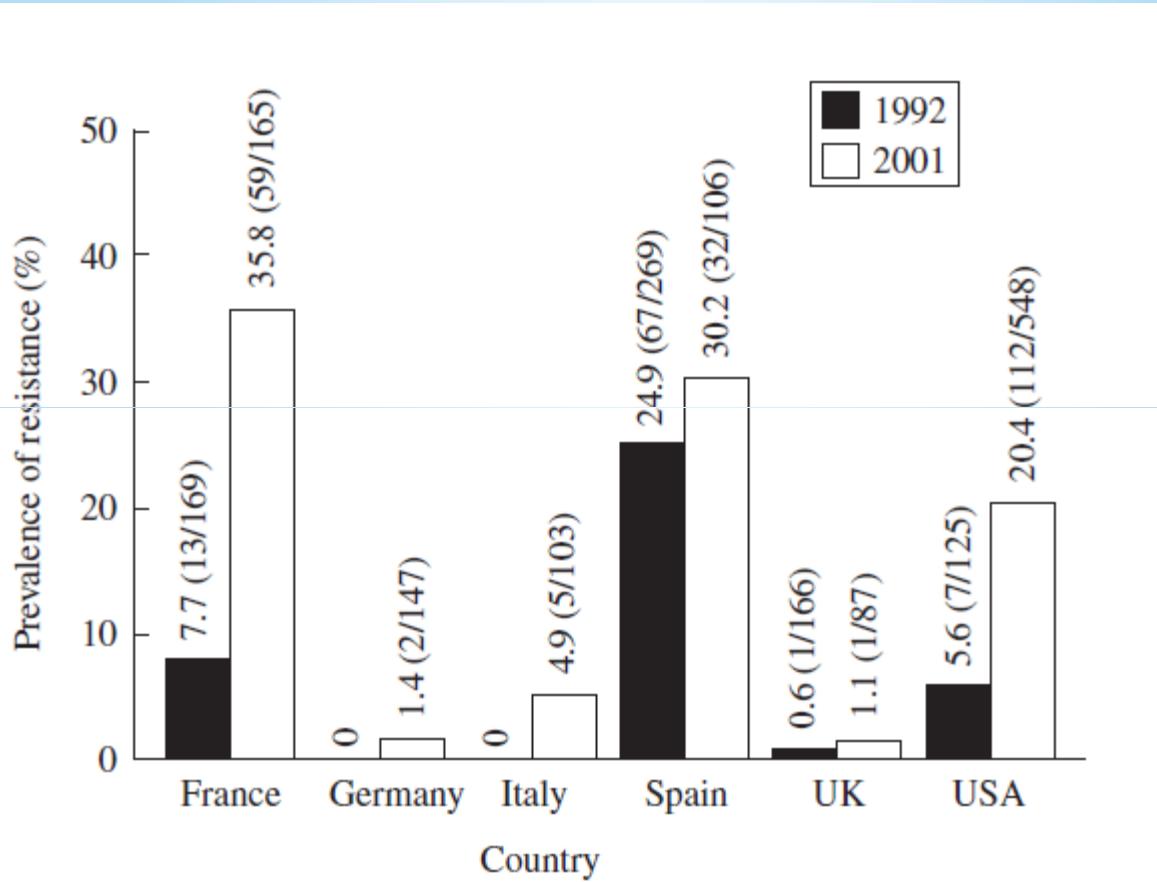
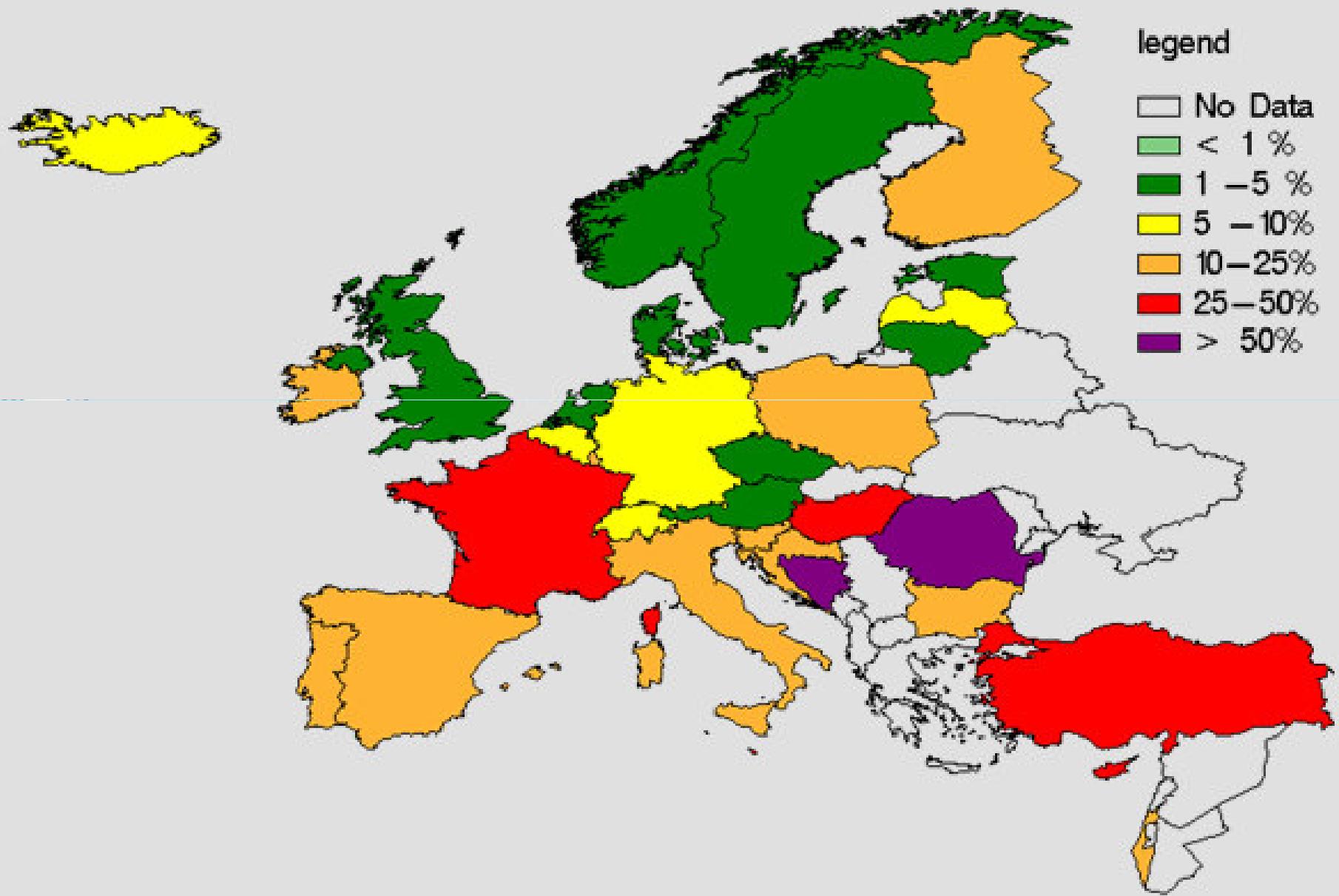


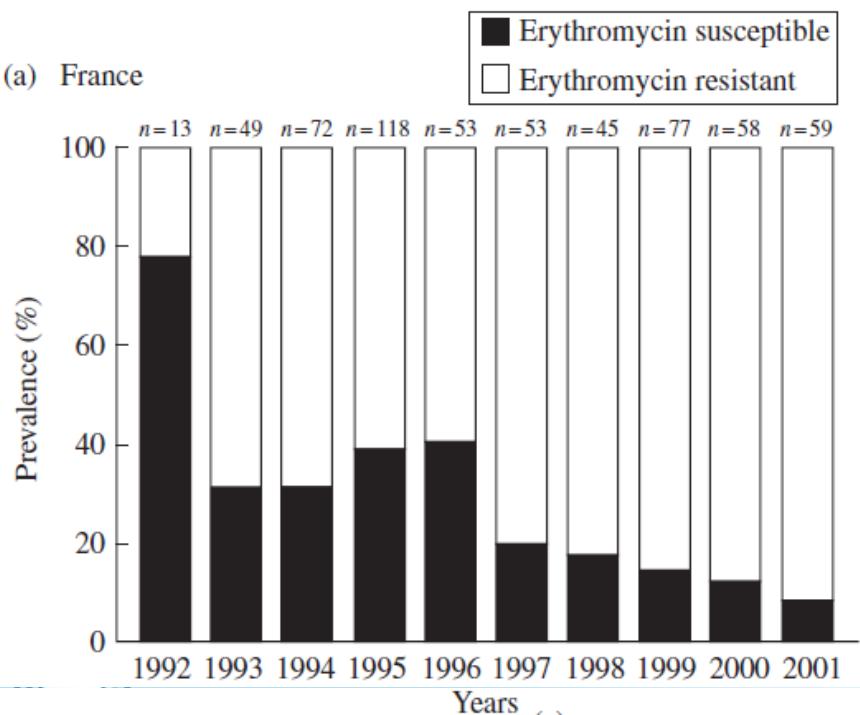
Figure 3. Changes in the prevalence of penicillin-resistant *S. pneumoniae* from 1992 to 2001 for the six countries included in the Alexander Project since 1992.

Proportion of PNSP isolates in participating countries in 2008

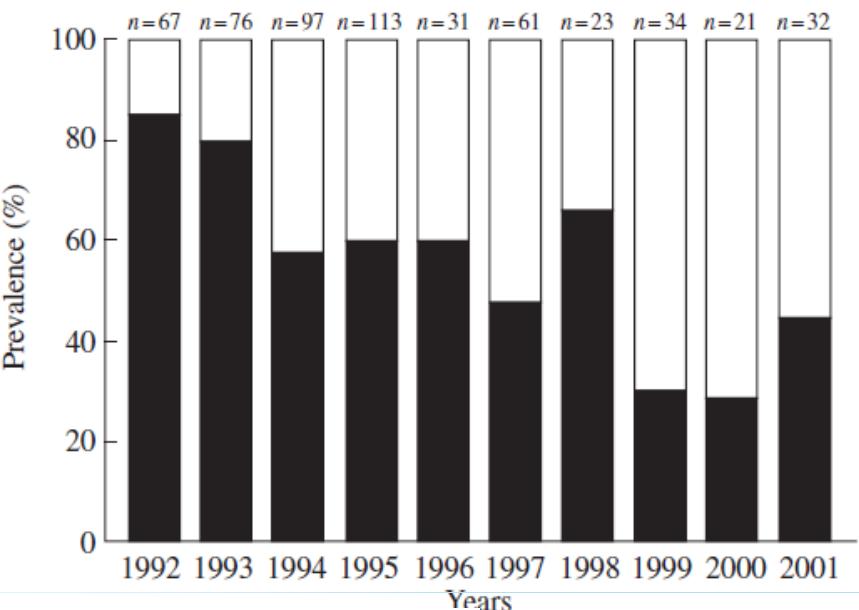
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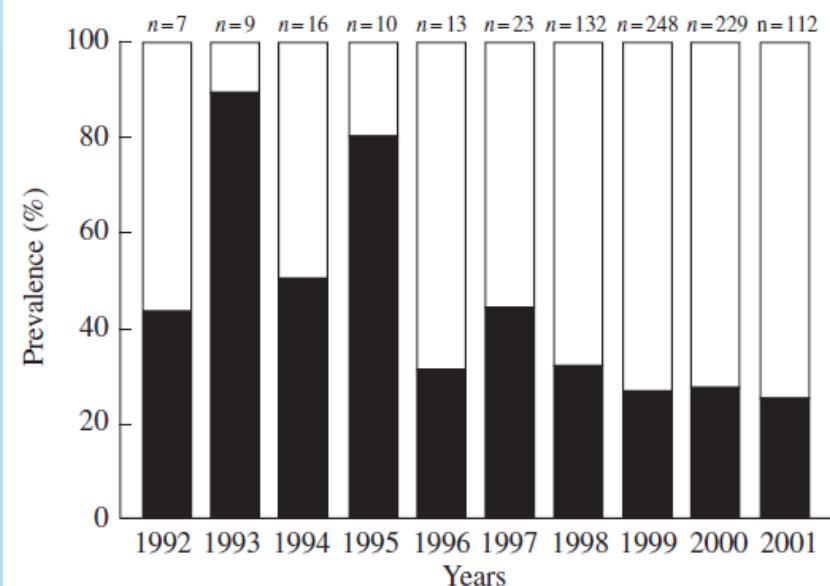
(a) France



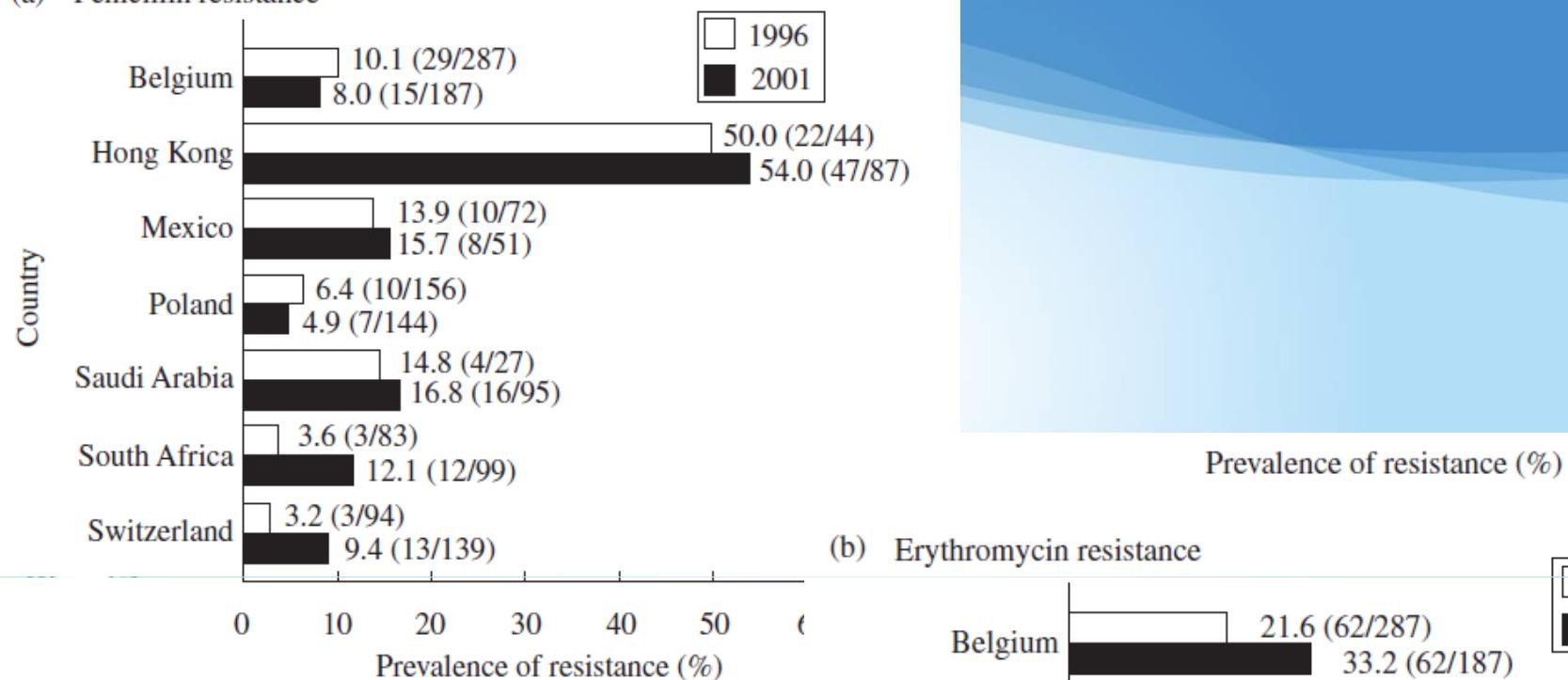
(b) Spain



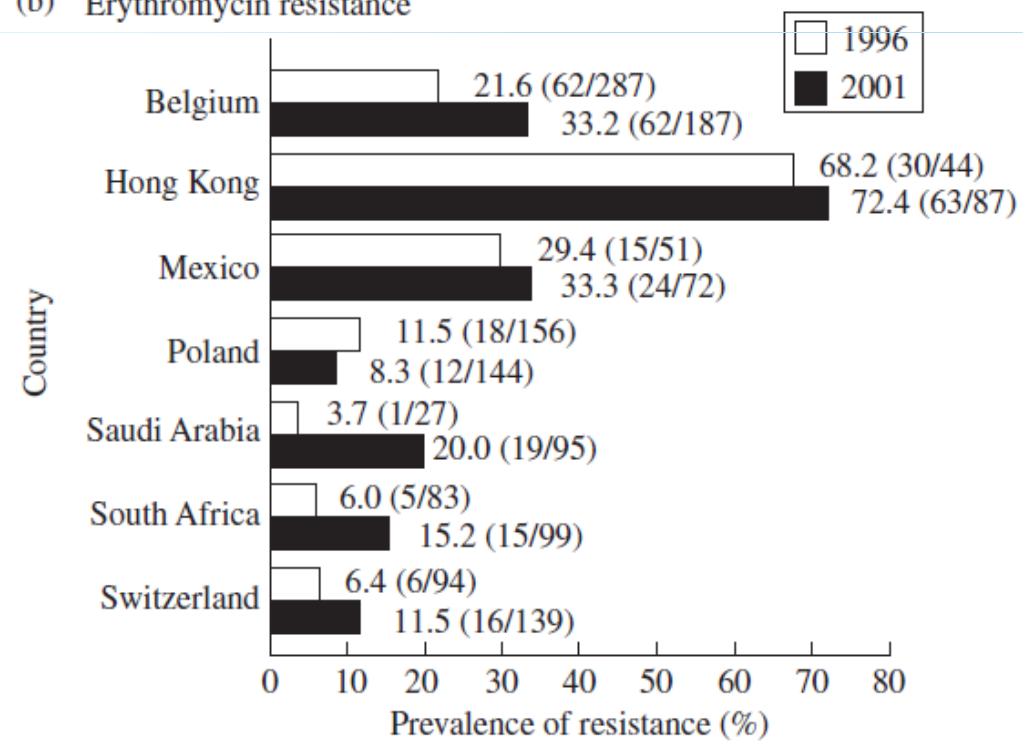
(c) USA



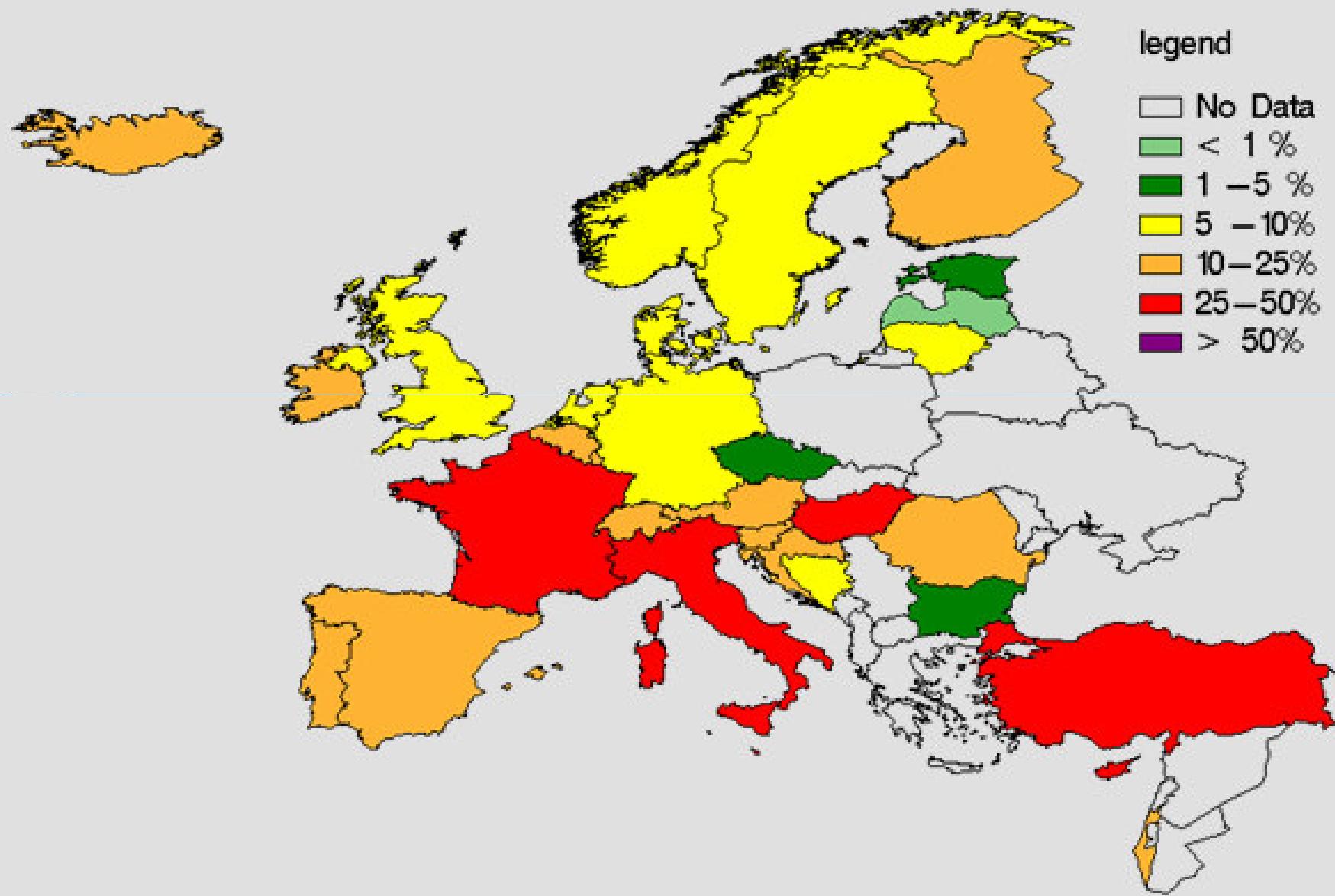
(a) Penicillin resistance



(b) Erythromycin resistance

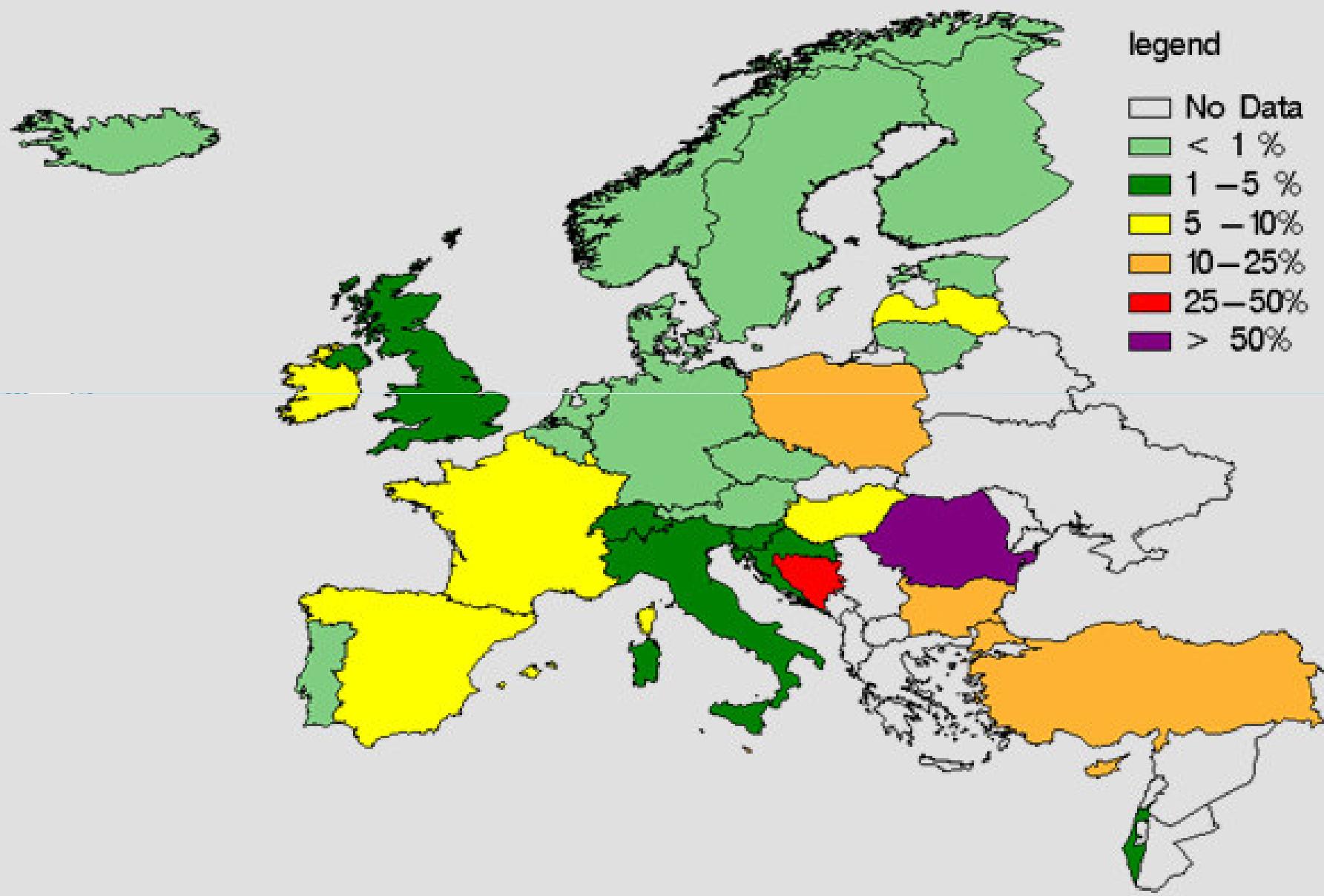


Proportion of Erythromycin non susceptible *S. pneumoniae* isolates in participating countries in 2008
(c) EARSS

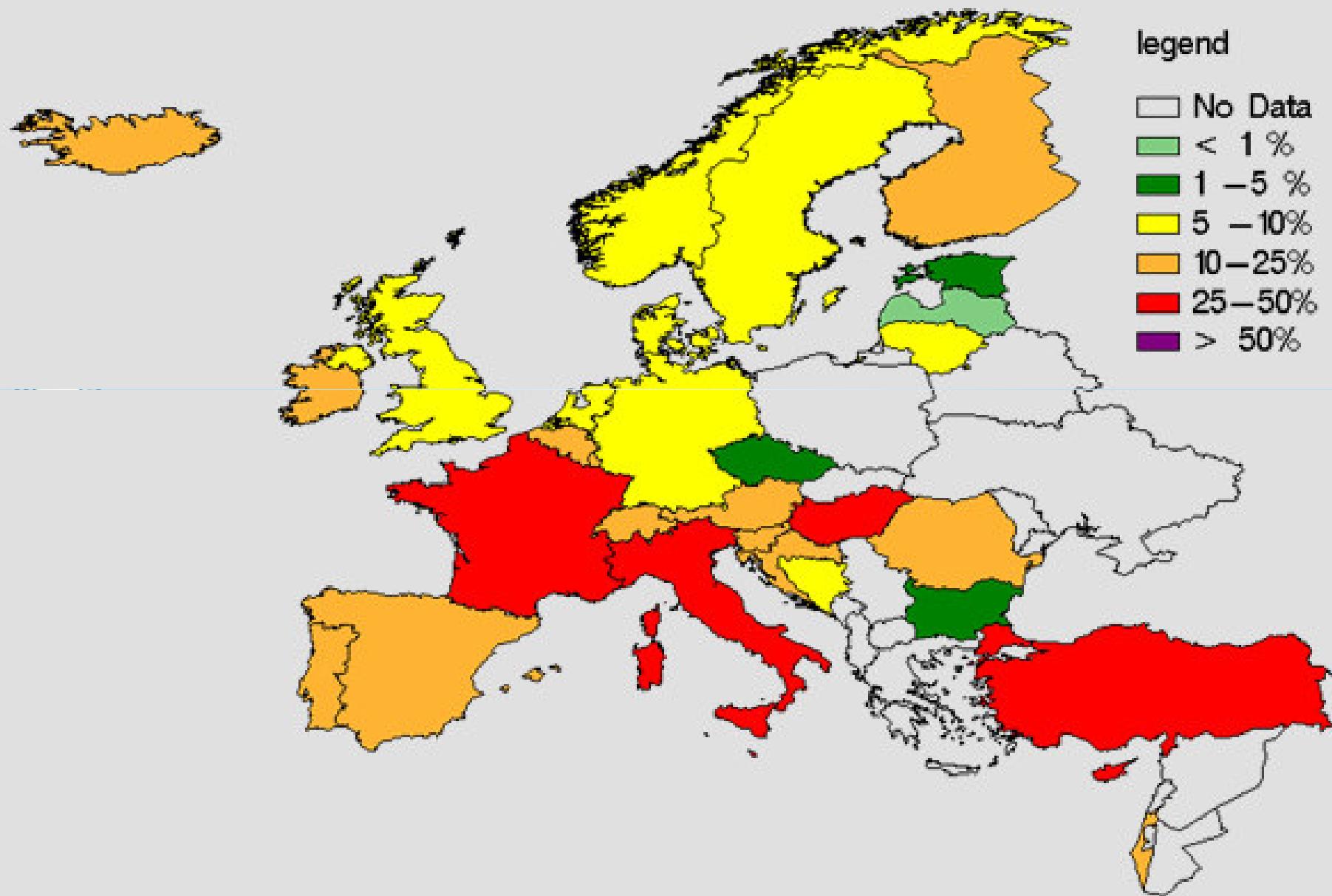


Proportion of Penicillin high resistant *S. pneumoniae* isolates in participating countries in 2008

(c) EARSS



Proportion of Erythromycin non susceptible *S. pneumoniae* isolates in participating countries in 2008
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*S. pneumoniae* Antibiyotik Direnci

BELÇİKA Çok merkezli çalışma Vanhoof R et al 2009 Pathol Biol (Paris)

Table 2

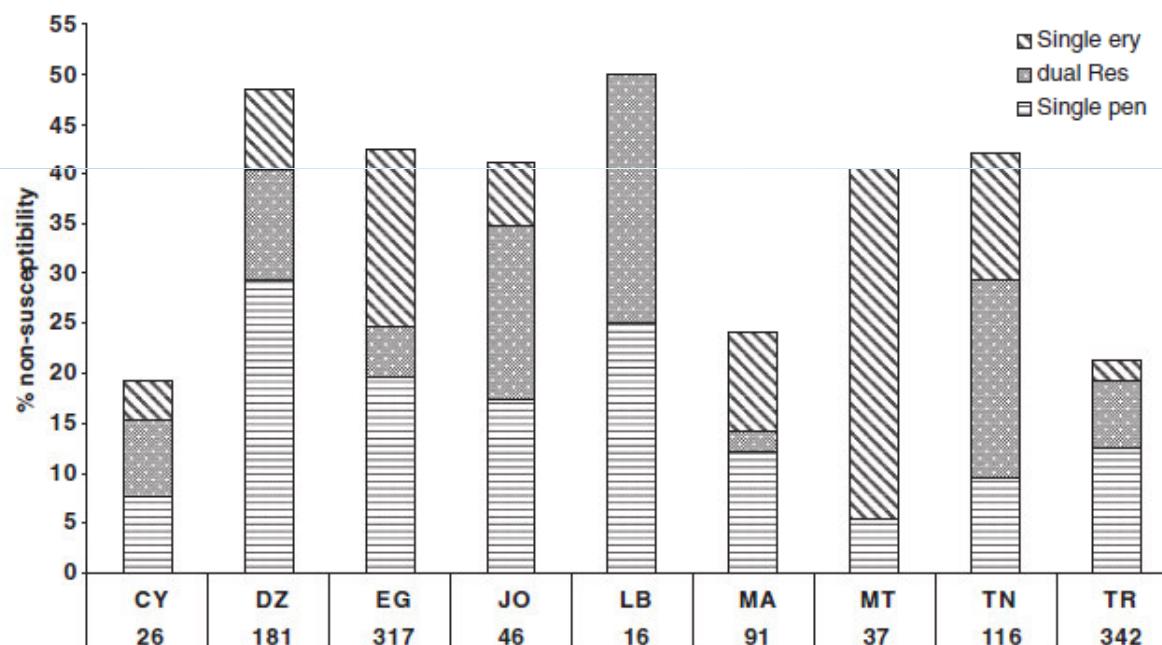
Susceptibility rates following CLSI criteria of 448 isolates of *S. pneumoniae*.

Antibiotic	Susceptibility rates (in %)		
	Susceptible	Intermediate	Resistant
Penicillin	88.4	7.6	4.0
Ampicillin	88.8	7.4	4.0
Amoxicillin	100	0	0
Amoxicillin/clavulanate	100	0	0
Cefaclor	89.7	0.7	9.6
Cefuroxime	90.8	0.5	8.7
Cefuroxime-axetil	91.3	0.9	7.8
Cefotaxime	98.0	2.0	0
Ceftazidime	98.0	2.0	0
Cefepime	98.0	2.0	0
Imipenem	97.5	2.5	0
Ciprofloxacin	94.9	4.7	0.4
Levofloxacin	99.3	0.2	0.5
Moxifloxacin	99.6	0.2	0.2
Oflloxacin	94.9	4.7	0.4
Erythromycin	70.3	0.5	29.2
Azithromycin	70.3	0.9	28.8
Telithromycin	100	0	0
Clindamycin	73.7	0.9	25.4
Tetracycline	78.1	5.4	16.5

TABLE 4. Antibiotic resistance profiles (no. (%)) of *Streptococcus pneumoniae* and *Listeria monocytogenes*

	PEN	AMP	CXN	E	CLN	CLA	RIF	LEV	SXT
<i>S. pneumoniae</i>	14/110 (13)		1/110 (1%)	5/55 (9)	0/38 (0)	2/34 (6)	2/101 (2)	0/29 (0)	9/39 (23)
<i>L. monocytogenes</i>	0/14 (0)	0/14 (0)	14/14 (100)						

PEN, penicillin; AMP, ampicillin; CXN, ceftriaxone; E, erythromycin; CLN, clindamycin; CLA, chloramphenicol; RIF, rifampicin; LEV, levofloxacin; SXT, trimethoprim-sulphamethoxazole.

**FIG. 1.** Single erythromycin, single penicillin and dual resistance (intermediate or resistant) proportions found within the indicated number of isolates, tested for both antibiotics during the 3-year study period by laboratories in the ARMed participating countries: Cyprus (CY), Algeria (DZ), Egypt (EG), Jordan (JO), Lebanon (LB), Morocco (MA), Malta (MT), Tunisia (TN) and Turkey (TR).



S. pneumoniae Antibiyotik Direnci
TÜRKİYE Çok merkezli çalışma

Sener et al. Journal of Antimicrobial Chemotherapy (2007) 60, 587–593

Table 3. Susceptibility (%) of penicillin-susceptible (PSSP), -intermediate (PISP) and -resistant (PRSP) *S. pneumoniae* to 12 antimicrobials using CLSI interpretive breakpoints

Antimicrobial	All		PSSP		PISP		PRSP	
	n	S (%)	n	S (%)	n	S (%)	n	S (%)
Penicillin	301	67.8	204	100	74	0	23	0
Amoxicillin/ clavulanate	301	98.7	204	100	74	98.6	23	87.0
Cefaclor	301	78.7	204	100	74	44.6	23	0
Cefprozil	299	90.6	203	100	74	86.5	22	18.2
Erythromycin	301	83.1	204	97.1	74	59.5	23	34.8
Azithromycin	296	78.0	199	92.0	74	55.4	23	30.4
Clarithromycin	301	82.7	204	96.6	74	59.5	23	34.8
Clindamycin	301	87.7	204	98.0	74	73.0	23	43.5
Ofloxacin	301	72.1	204	78.4	74	62.2	23	47.8
Co-trimoxazole	301	53.2	204	62.7	74	36.5	23	21.7
Tetracycline	301	81.4	204	93.1	74	59.5	23	47.8
Chloramphenicol	300	94.7	204	98.5	74	91.9	22	68.2



S. pneumoniae

- Penisilin direncinde artış
- Makrolid direncinde artış
- Türkiye'de makrolid direnç oranı düşük



Enterokoklar



Enterokoklarda direnç sorunu

- Penisilin direnci
- Aminoglikozid direnci
- Vankomisin direnci

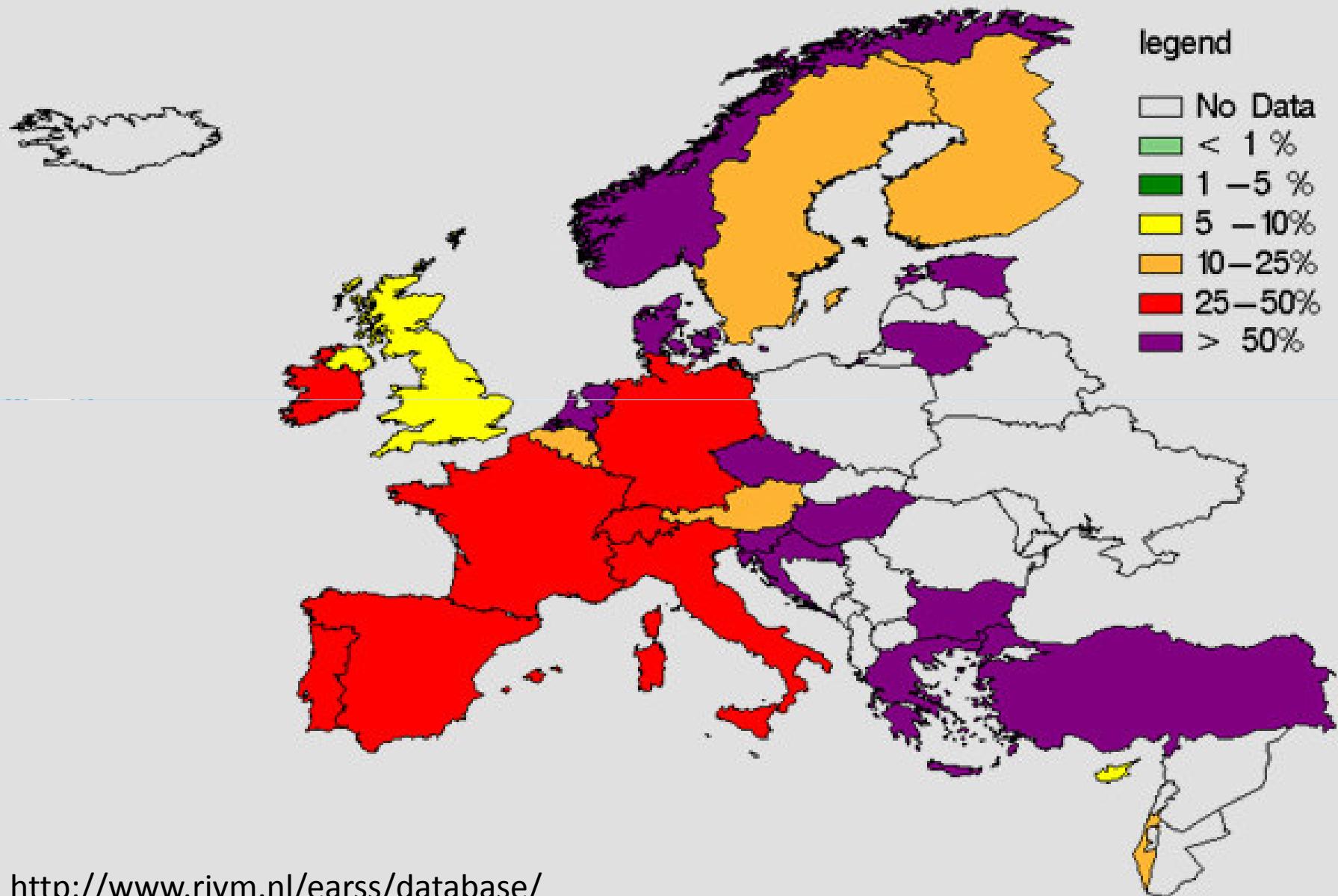
Table 2 (continued)

Organism/resistance group (no. tested/antimicrobial agents)	MIC ($\mu\text{g/mL}$)			% by category Susceptible/resistant ^a
	50%	90%	Range	
<i>Enterococcus spp.</i> (901) ^c				
Linezolid	1	2	0.25 to >8	99.3/0.6
Ampicillin	≤ 1	>16	≤ 1 to >16	71.3/28.7
Ciprofloxacin	>4	>4	0.06 to >4	41.3/54.1
Daptomycin	1	2	≤ 0.06 to 8	99.8/ ^b
Erythromycin	>2	>2	≤ 0.25 to >2	8.5/75.2
Gentamicin (HL) ^f	≤ 500	>1000	≤ 500 to >1000	75.4/24.6
Levofloxacin	>4	>4	≤ 0.5 to >4	46.3/52.2
Quinupristin/dalfopristin	>2	>2	≤ 0.25 to >2	28.6/66.3
Streptomycin (HL)	≤ 1000	>2000	≤ 1000 to >2000	69.6/30.4
Teicoplanin	≤ 2	>16	≤ 2 to >16	74.0/25.1
Vancomycin	1	>16	0.25 to >16	72.0/27.3

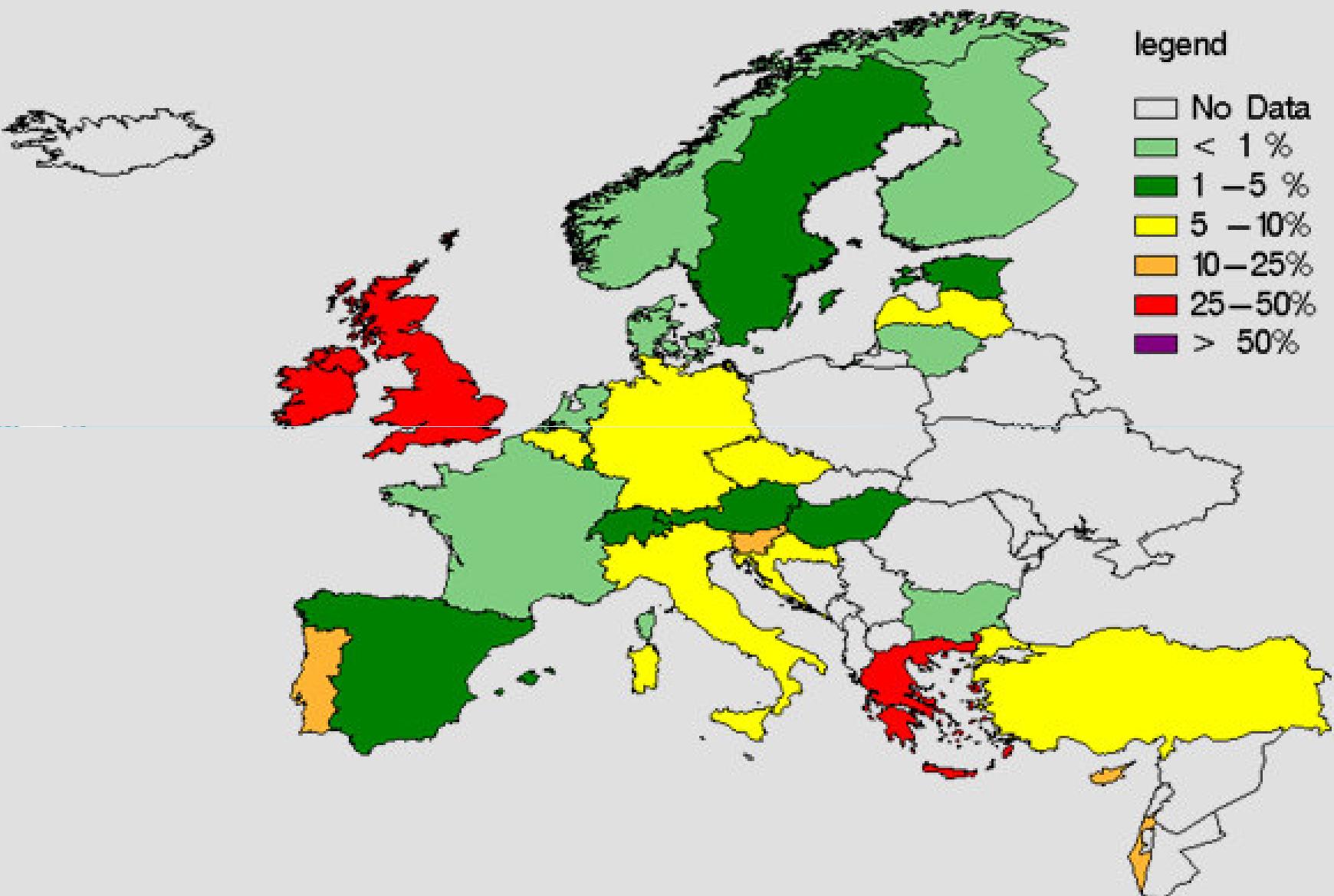


Proportion of Aminoglyc High resistant *E. faecium* isolates in participating countries in 2008

(c) EARSS

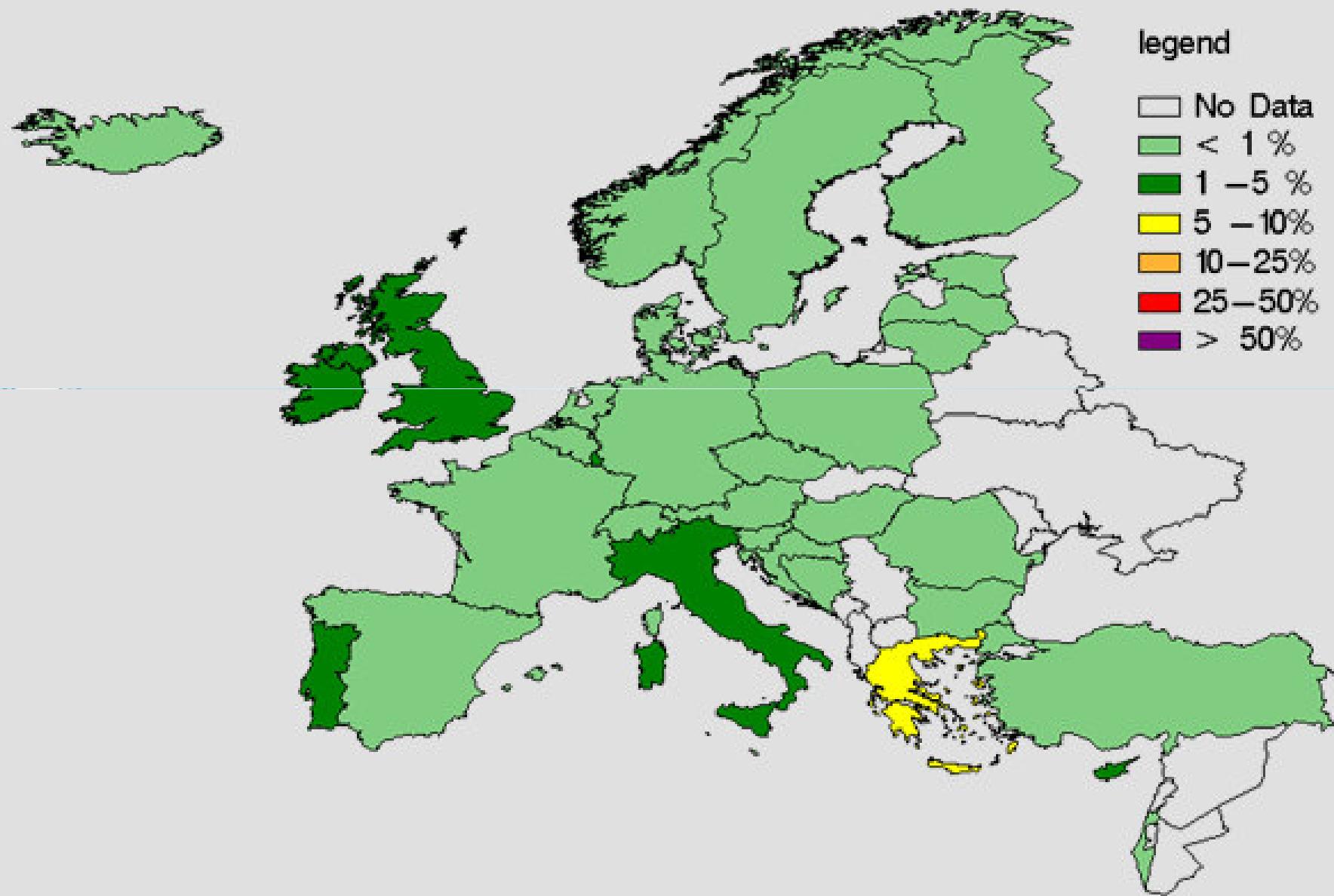


Proportion of Vancomycin resistant *E. faecium* isolates in participating countries in 2008
(c) EARSS



Proportion of Vancomycin resistant *E. faecalis* isolates in participating countries in 2008

(c) EARSS



VANKOMİSİNİNE DİRENÇLİ ENTEROKOK KOLONİZASYONU ARAŞTIRILMASI VE DİĞER ANTİMİKROBİYALLERE DUYARLILIKLARI

THE INVESTIGATION OF THE COLONIZATION AND ANTIBIOTIC SUSCEPTIBILITY OF VANCOMYCIN RESISTANT ENTEROCOCCI

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Tablo 1. İzole edilen enterokok şuşlarının tür ve vankomisin duyarlılığına göre dağılımı

İzole edilen enterokok türü	Şuş sayısı	(%)	Vankomisine duyarlı şuş		Vankomisine dirençli şuş	
			Sayı	(%)	Sayı	(%)
<i>E. faecium</i>	37	(54.4)	27	(73.0)	10	(27.0)
<i>E. faecalis</i>	29	(42.6)	26	(89.7)	3	(10.3)
<i>E. avium</i>	2	(3.0)	2	(100.0)	0	(0.0)
Toplam	68	(100.0)	55	(80.9)	13	(19.1)

KLİNİK ÖRNEKLERDEN İZOLE EDİLEN ENTEROKOK SUŞLARININ ANTİBİYOTİK DİRENCİ

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ÖZET

Enterokok türleri toplum veya hastane kökenli infeksiyon etkenleri arasında giderek önem kazanmaktadır. Son yıllarda ampicilin, penisilin ve vankomisine dirençli suşlara rastlanmaktadır. Bu çalışmada Ağustos 2004 - Nisan 2005 arasında hastanemiz Merkez Mikrobiyoloji Laboratuvarına gönderilen çeşitli örneklerden izole edilen enterokok suşlarının penisilin, ampicilin, vankomisin ve teikoplanine direnç durumu araştırılmıştır. Örneklerin 96'sı (% 60) polikliniklerden, 64'ü (% 40) yataklı servislerden gönderilmiştir. Polikliniklerden gönderilen örneklerde penisilin direnci % 48, ampicilin direnci % 43 iken, vankomisin ve teikoplanin direnci saptanmamıştır. Yataklı servislerden gönderilen örneklerde penisilin direnci % 84, ampicilin direnci % 70, vankomisin ve teikoplanin direnci % 5 olarak saptanmıştır. Sonuç olarak ciddi enterokok infeksiyonlarının empirik tedavisinde olası penisilin, ampicilin, vankomisin ve teikoplanin direncinin dikkate alınması gerektiği düşünülmüştür.

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Antibiyotik	Poliklinik n:96	Yataklı servis n:64	İdrar n: 125	Dışkı n:22	Kan n: 6	Vajinal sürüntü n: 4	Cerahat n: 2	Dren n: 1	Toplam n: 160
Penisilin	46 (48)	54 (84)	68 (54)	22	5	2	2	1	100 (63)
Ampicilin	41 (43)	45 (70)	61 (49)	18	5	2	-	-	86 (54)
Vankomisin	-	3 (5)	-	3	-	-	-	-	3 (2)
Teikoplanin	-	3 (5)	-	3	-	-	-	-	3 (2)

Fekal ve Klinik Örneklerden İzole Edilen Enterokok Suşlarının Antibiyotiklere Duyarlılıkları

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ÖZET

Çalışmamızda, Ocak 2001-Şubat 2002 tarihleri arasında yatan hasta/poliklinik hastası klinik örneklerinden ve gaita/rektal sürüntü örneklerinden izole edilen 292 enterokok suşu API 20 Strep ile tiplendirilmiştir. Standart agar tarama yöntemi ile yüksek düzey aminoglikozid (YDAD), E-test yöntemi ile glikopeptid ve disk diffüzyon yöntemi ile penisilin direnci incelenmiştir. *E.faecalis* (%85.2) en sık izole edilen enterokok türü olarak saptanmıştır. Klinik örneklerden izole edilen enterokok suşlarının %68.4'ü, fekal örneklerden izole edilenlerin ise %56.3'ü penisiline dirençli olarak saptanmıştır. İzole edilen suşlarda vankomisine veya teikoplanine direnç saptanmamıştır. Sadece fekal suşların %12.6'sında vankomisine orta duyarlılık tespit edilmiştir. Klinik ve fekal örneklerden izole edilen suşların yüksek düzey streptomisin direnci(YDSD) ve yüksek düzey gentamisin direnci (YDGD) sırası ile %41(39/95), %51.5(49/95) ve %13 (26/197), %25.3 (50/197) olarak saptanmıştır. Her iki aminoglikozid antibiyotiğe birden yüksek düzey direnç, *Efaecium* suşlarında %38, *Efaecalis* suşlarında %10 oranında ($P=0.000$), bütün enterokok suşlarında ise %14 oranında saptanmıştır. *Efaecium* suşlarının tüm antibiyotiklere direnci *Efaecalis*'ten daha yüksek oranda bulunmuştur. Enterokok suşlarında glikopeptid direnci saptamamış olmamıza rağmen, yüksek düzey aminoglikozid direnci ve penisilin direncinin yüksek oluşu bu cinse ait suşların duyarlılık profillerinin yakından izlemeni gereklili kılmaktadır.

Anahtar kelimeler; *Enterococcus*, antibiyotiklere duyarlılıkları, yüksek düzey aminoglikozid direnci





Sonuç

- Gram pozitif suşlarda antibiyotik direnci önemli sorun.
- Direnç durumu bölgesel, ulusal ve uluslararası düzeyde izlenmeli

