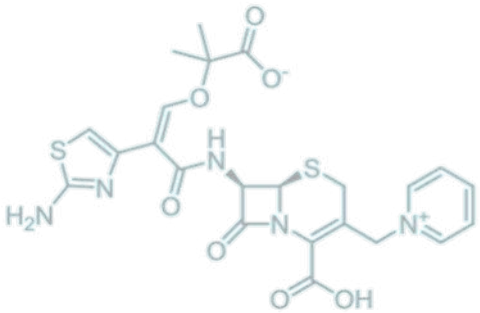
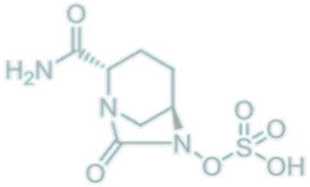
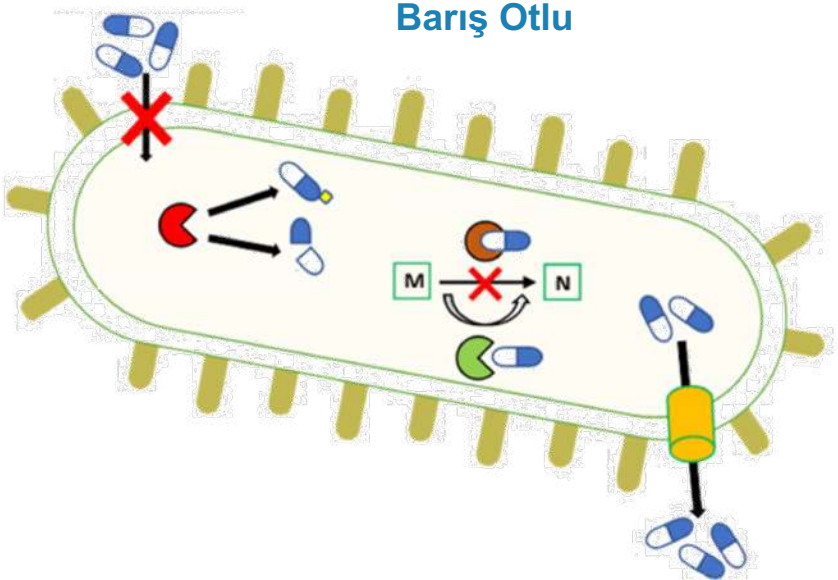




Antimikrobiyal Direnç Aslında Nedir?

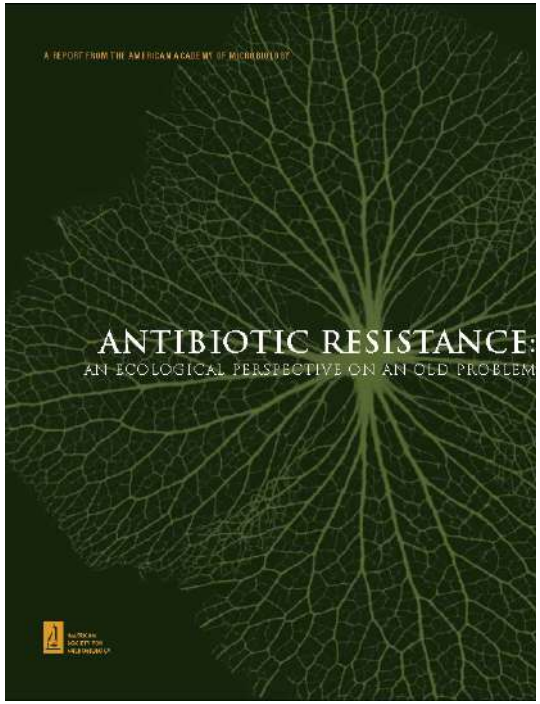
Antimikrobiyal Duyarlılık Testlerinin Sınır Değerleri Nasıl Belirlenir?

Barış Otlu



Kazanamayacağız!

- Tirilyonlarca mikroorganizmanın gücü, sürekli evrimin kadim kuvveti ve dirençli varyasyon ile birleşerek, kaçınılmaz olarak ilaçlarımıza üstün gelecektir.



INTRODUCTION

The struggle against antibiotic resistance is a war we will never win. The strength of trillions upon trillions of microorganisms, combined with the ancient force of evolution by constant, unrelenting variation, will inevitably overpower our drugs. Their spectrum is selected to include pathogenic bacteria; antibiotics always select naturally resistant bacteria and the strains which have acquired resistance (e.g., Nafcillin resistant staphylococci which acquire resistance readily and *Burkholderia cepacia* which is naturally resistant).

Tuberculosis illustrates just how lopsided the battle with resistance is. Tuberculosis (TB) is a disease we should have well in hand; effective antibiotics for this condition have been available for decades. In developing countries, TB should be considered a thing of the past. However, largely because of antibiotic resistance, TB is on the march.

The treatment regimen for TB lasts as long as six months, and if a patient discontinues treatment or takes prescribed antibiotics sporadically, resistance can get a foothold. Once a patient has acquired a resistant form of TB, re-starting them on the same therapy no longer works. Antibiotic resistant TB is curable, but treatment requires lengthy and expensive regimens of chemotherapy—something many patients, particularly those in developing countries, can not afford. Strains resistant to the two most powerful anti-TB drugs and multidrug resistant TB have become more common. Now, extensively drug resistant (XDR) TB strains, which are resistant to all major TB drugs, have arrived on the scene. TB is finding a way around all of the best antibiotics, and, at the present time, the World Health Organization (WHO) estimates that 30% of the world's population is infected with the tuberculosis bacterium. This is an impressive statistic for a disease that should be treatable with antibiotics.

The specific meaning of "antibiotic resistance" depends entirely on context. The clinical definition used in this document refers to the ability of a microorganism—a bacterium, virus, fungus, or parasite—to survive concentrations of antibiotics that kill sensitive cells of the same strain. It is important to note that for every antibiotic, there are sensitive strains, which are killed or inhibited by the drug, and naturally resistant strains. When a sensitive strain gains the ability to withstand an antibiotic, it is "antibiotic resistant."

In biological terms, antibiotic resistance simply means that a pathogen is less susceptible than its counterparts and may not respond to the antibiotic administered. In genomics, organisms that possess a resistance gene are resistant. Like all other living things, the evolution of microorganisms is Darwinian: in the face of change, the fittest survive. Antibiotics represent an evolutionary challenge that microorganisms must surmount or perish.

Resistance is commonly considered simplistically—either an organism is resistant or it's not. In reality, resistance exists as a gradient that reflects phenotypic and

THE STRUGGLE AGAINST ANTIBIOTIC RESISTANCE IS A WAR WE WILL NEVER WIN.

Antibiotic Resistance: An Ecological Perspective on an Old Problem 3

« Antibiyotik direnci ile mücadele bir savaştır ve biz asla kazanamayacağız »

Kazanamayacağız!

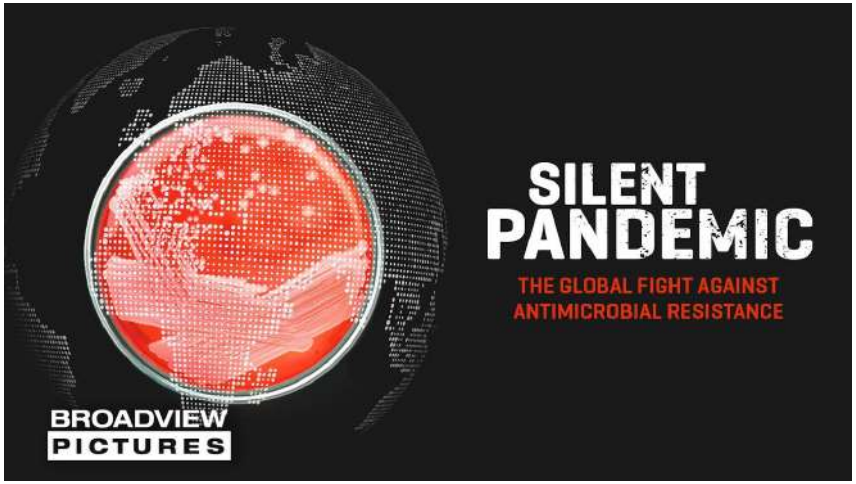
- Progresif familyal intrahepatik kolestaz tip 3 nedeniyle;24/04/2024 tarihinde nakil olmuş. Batından kaynaklı olduğu düşünülen, peritoneal kateter trombozu var, revizyon düşünülüyor, meropenem 6. günü

NUMUNE BİLGİLERİ	TAM OTOMATİZE KAN KÜLTÜRÜ	Barkod No : 13270376	
MİKROSKOBİK İNCELEME	KLEBSIELLA PNEUMONIAE ÜRED .		
MİKROORGANİZMA	1. KLEBSIELLA PNEUMONIAE	Koloni Sayısı :	
ANTİBİYOGRAM	Antibiyotik Adı	1	
	AMIKACIN	Dirençli	
	AMPICILLIN	Dirençli	
	CEFTRIAXONE	Dirençli	
	COLISTIN	Dirençli	4
	MEROPENEM	Dirençli	>32
	TRIMETHOPRIM / SULFAMETHOXAZOL	Dirençli	
	TİGESİKLİN	Dirençli	4
	CEFTAZIDIME-AVIBACTAM	Dirençli	
	AMOXICILLIN/CLAVULANATE	Dirençli	
	AZTREONAM	Dirençli	
	CEFEPIME	Dirençli	
	CEFOTAXIME	Dirençli	
	CEFOXITIN	Dirençli	
	CEFTAZIDIME	Dirençli	
	ERTAPENEM	Dirençli	
	IMIPENEM	Dirençli	>32
	PIPERACILIN/TAZOBACTAM	Dirençli	

Tıbbi Laboratuvar Yorum :

Antibiyotik Direnci / Sessiz Salgın

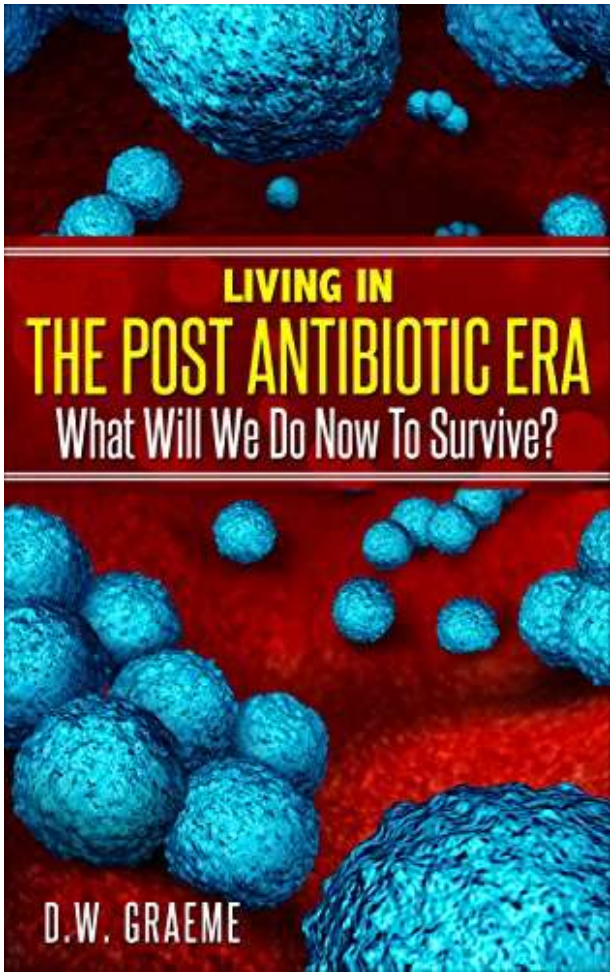
- Antibiyotik direnci, insanlığı tehdit eden en büyük sorunlardan biridir.
- DSÖ'nün "sessiz salgın" olarak adlandırmasının nedeni, bunun çok ciddi bir halk sağlığı krizi olmasına rağmen göz ardı edilmesidir.



Antibiyotik Sonrası Çağ Başladı!

- Artık buna sessiz bir salgın dememeliyiz.

  Yüksek sesle ve net olmalıyız: bu gerçekten bir salgın. DSÖ



Hayatta kalmak için ne yapmalıyız?

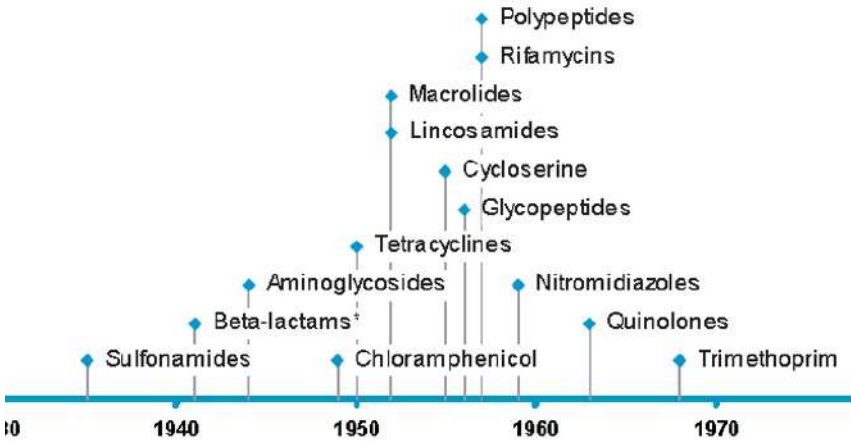
Oysa Her Şey Güzel Başlamıştı ?

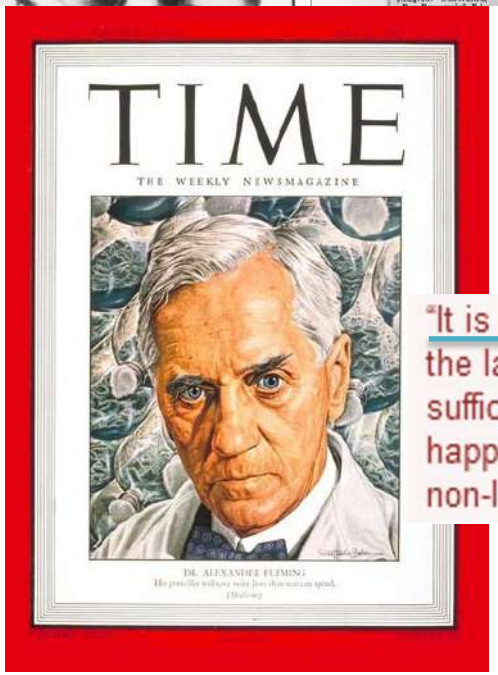
- Mucize ilaçlar zamanı

Salvarsan

Beta Laktamlar

The horror of diseases such as blood poisoning is easily forgotten. These pictures, taken in 1942 shortly after the introduction of penicillin, showthe improvment in a child with a bacterial infection four (photo 3) and nine (photo 4) days after treatment, and fully recovered (5&6)





"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body... ...and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Sömürülen Mucize

- 1954, Hekimler bu önemli ilaçları kullanırken dikkatli olmalıdır, aksi takdirde birçok ciddi enfeksiyonun kontrolünün imkansız hale gelebileceği zamanlar gelebilir.

California MEDICINE
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Volume 81 JULY 1954 Number 1

Consequences of the Widespread Use of Antibiotics

LOWELL A. RANTZ, M.D., San Francisco

PHYSICIANS, to a greater extent than any persons, know of the impact of antimicrobial therapy on the practice of medicine and the natural history of infectious disease. Even they are not fully aware of the enormous quantities of these agents that are used in the United States each year. Penicillin is now being manufactured at a rate of well over 300 tons per annum—equivalent to 150 million courses of 3 million units each year. More than 100 tons of streptomycin are made, which would permit the administration of 100 million 1-gram doses of this agent.[8] The broad spectrum drugs are also produced in enormous quantities. It is believed that the rate is not less than 250 tons per annum. This is enough to permit the administration of 25 million 10-gram courses each year.

• Great quantities of antibiotics are used each year. A direct result has been the appearance of large numbers of infections caused by organisms that are resistant to the action of one or more of these drugs. A new syndrome, that of superinfection by bacteria resistant to an antibiotic being administered, has become common. Its recognition is of great importance.

The control of resistant infections requires the development of new antimicrobial agents and new knowledge about the use of older ones in combination.

The medical profession must be circumspect in its use of these important drugs or the time may come when the control of many serious infections may become impossible.

- Yılda 300 ton penisilin,

  100 ton streptomisin,

  250 ton oxytetracyline kullanılıyor.

TABLE 1.—*Sensitivity of Gram-negative bacilli to antibiotics*

Organisms	Per Cent Sensitive		
	Streptomycin	Oxytetracycline	Chloramphenicol
E. coli	65.3	76.5	76.0
Paracolon	43.9	51.2	58.6
Proteus	64.6	6.2	16.7
Pseudomonas	19.7	14.5	6.6

Sömürülen Mucize

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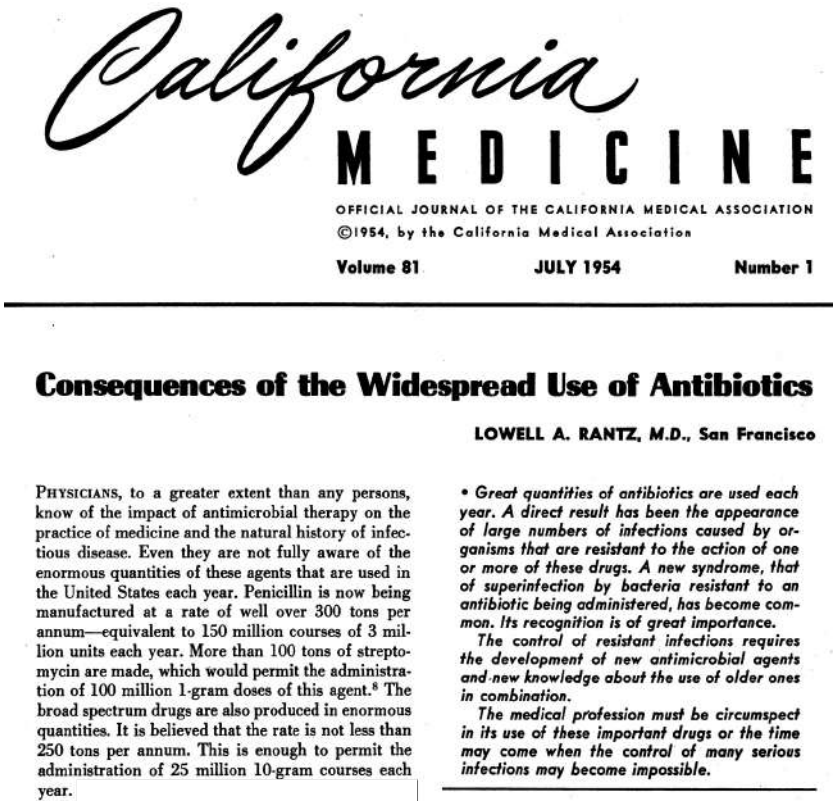

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The control of resistant infections requires the development of new antimicrobial agents and new knowledge about the use of older ones in combination.

The medical profession must be circumspect in its use of these important drugs or the time may come when the control of many serious infections may become impossible.

- Bu verilerden açıkça görülüyor ki, çok az Amerikalı antibiyotikten kaçabilir.
- Antibiyotiklerin yaygın kullanımının iki doğrudan sonucu olacaktır.
  - dirençli organizmalar artacak
  - hiç bilinmeyen organizmaların neden olduğu enfeksiyonlar

Sömürülen Mucize

- 1930, Antibiyotiklerin hayvanlarda kullanımının tarihi

  bu kullanım, hayvanların daha hızlı büyümesini sağlamak ve yemden daha iyi verim almak için giderek yaygınlaşmıştır.

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HUMANITIES | SOCIAL SCIENCES | BUSINESS

ARTICLE

DOI: 10.1057/s41599-018-0152-2 OPEN

Pharming animals: a global history of antibiotics in food production (1935–2017)

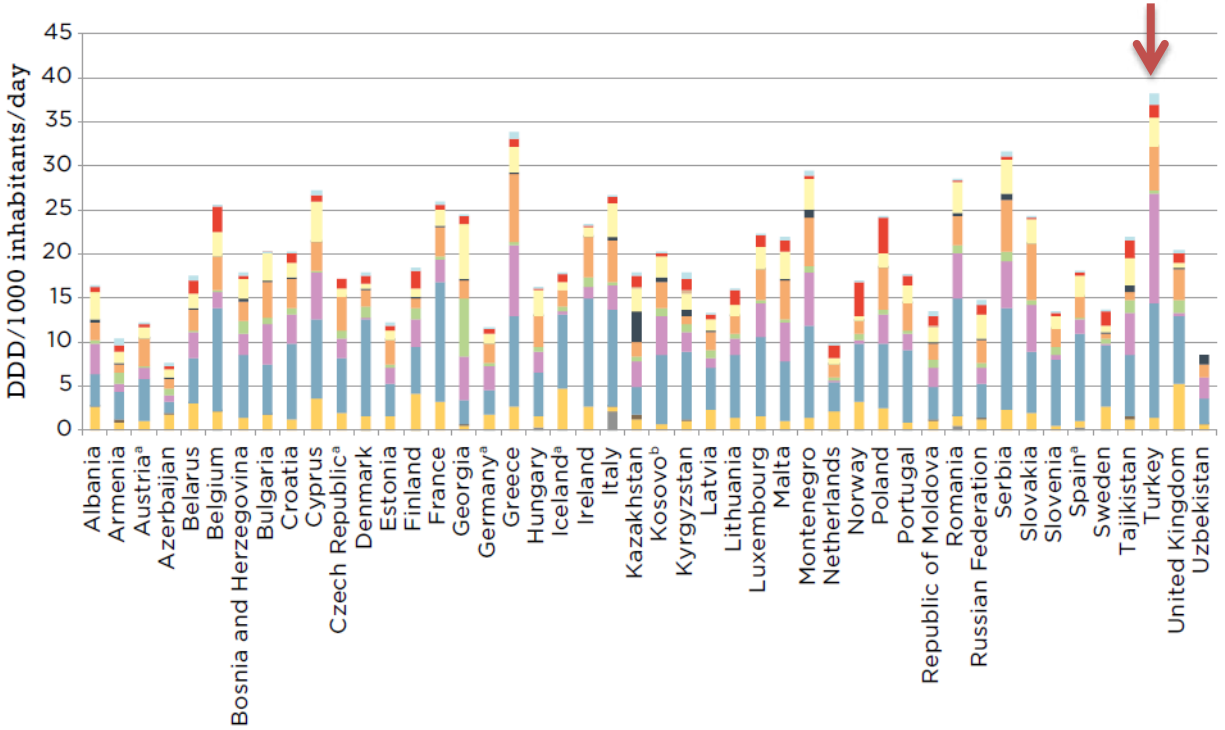
Claas Kirchhelle[1]

ABSTRACT Since their advent during the 1930s, antibiotics have not only had a dramatic impact on human medicine, but also on food production. On farms, whaling and fishing fleets as well as in processing plants and aquaculture operations, antibiotics were used to treat and prevent disease, increase feed conversion, and preserve food. Their rapid diffusion into nearly all areas of food production and processing was initially viewed as a story of progress on both sides of the Iron Curtain. However, from the mid-1950s onwards, agricultural antibiotic use also triggered increasing conflicts about drug residues and antimicrobial resistance (AMR). Significantly, antibiotic concerns did not develop evenly but instead gave rise to an international patchwork of different regulatory approaches. During a time of growing concerns about AMR and a post-antibiotic age, this article reconstructs the origins, global proliferation, and international regulation of agricultural antibiotics. It argues that policymakers need to remember the long history of regulatory failures that has resulted in current antibiotic infrastructures. For effective international stewardship to develop, it is necessary to address the economic dependencies, deep-rooted notions of development, and fragmented cultural understandings of risk, which all contribute to drive global antibiotic consumption and AMR.

Türkiye'de Antimikrobiyal Direnç

- Türkiye 1000 kişi başına günlük tanımlanmış günlük doz (DDD) olarak en yüksek antibiyotik tüketimine sahip ülke durumundadır.

Fig. 4.6 Consumption of antibiotics (DDD per 1000 inhabitants per day) by pharmacological subgroup in 45 countries and Kosovo[3] of the European Region, 2015



Türkiye'de Antimikrobiyal Direnç

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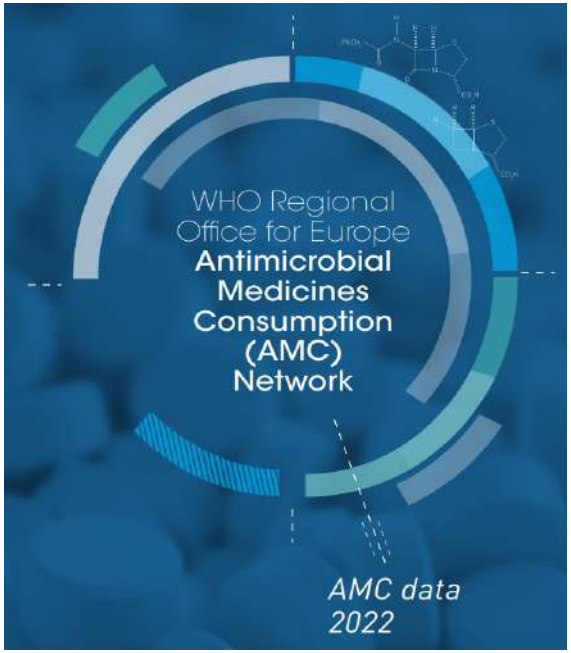
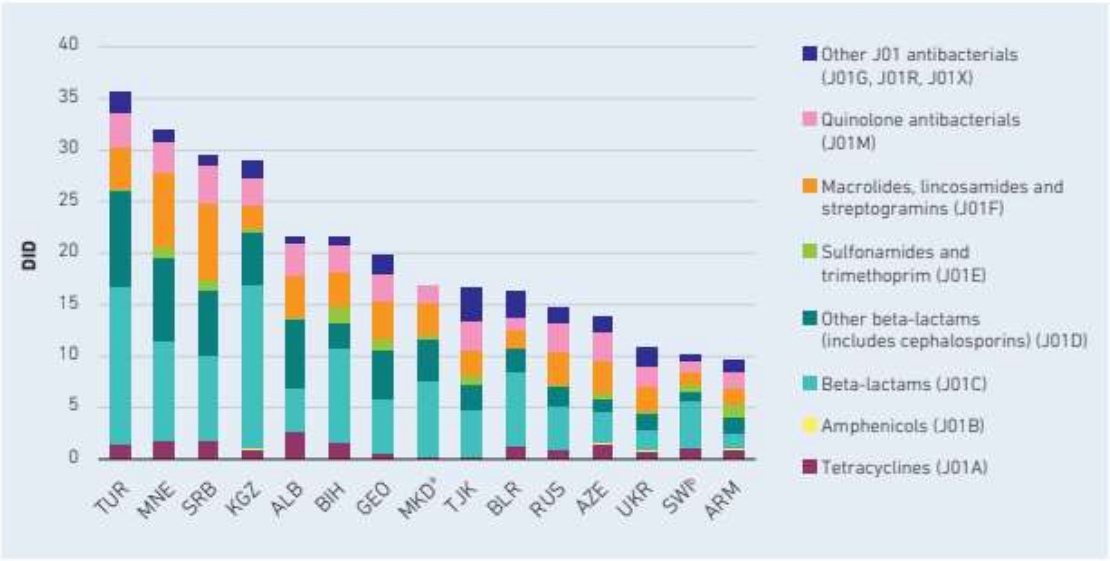


Fig. 3 Total consumption of J01 antibacterials by pharmacological subgroup, 2022



[a] Community consumption. [b] Estimates include consumption data of Liechtenstein.

Antibiyotik direncine, antibiyotiklerle savaş açtık

- Bu beyhude savaş giderek artan antibiyotik direncine neden oldu.

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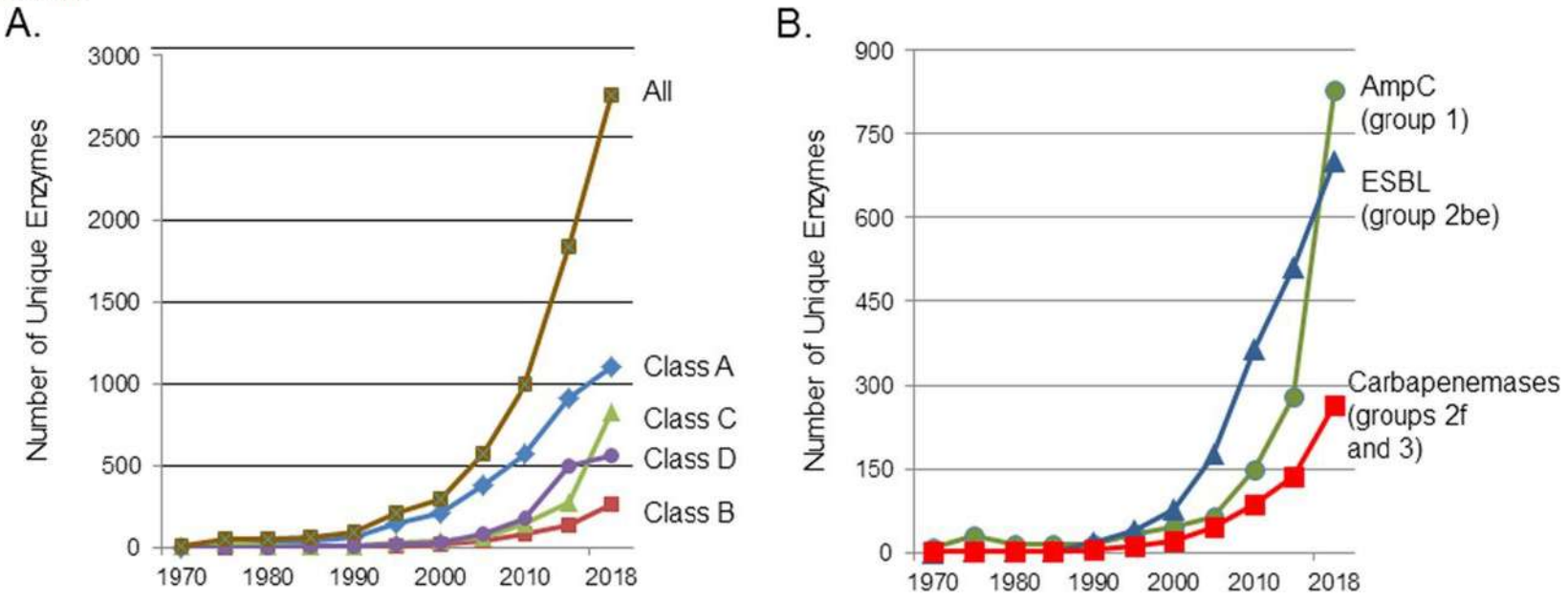
MINIREVIEW

Check for updates

Past and Present Perspectives on β-Lactamases

Karen Bush[a]

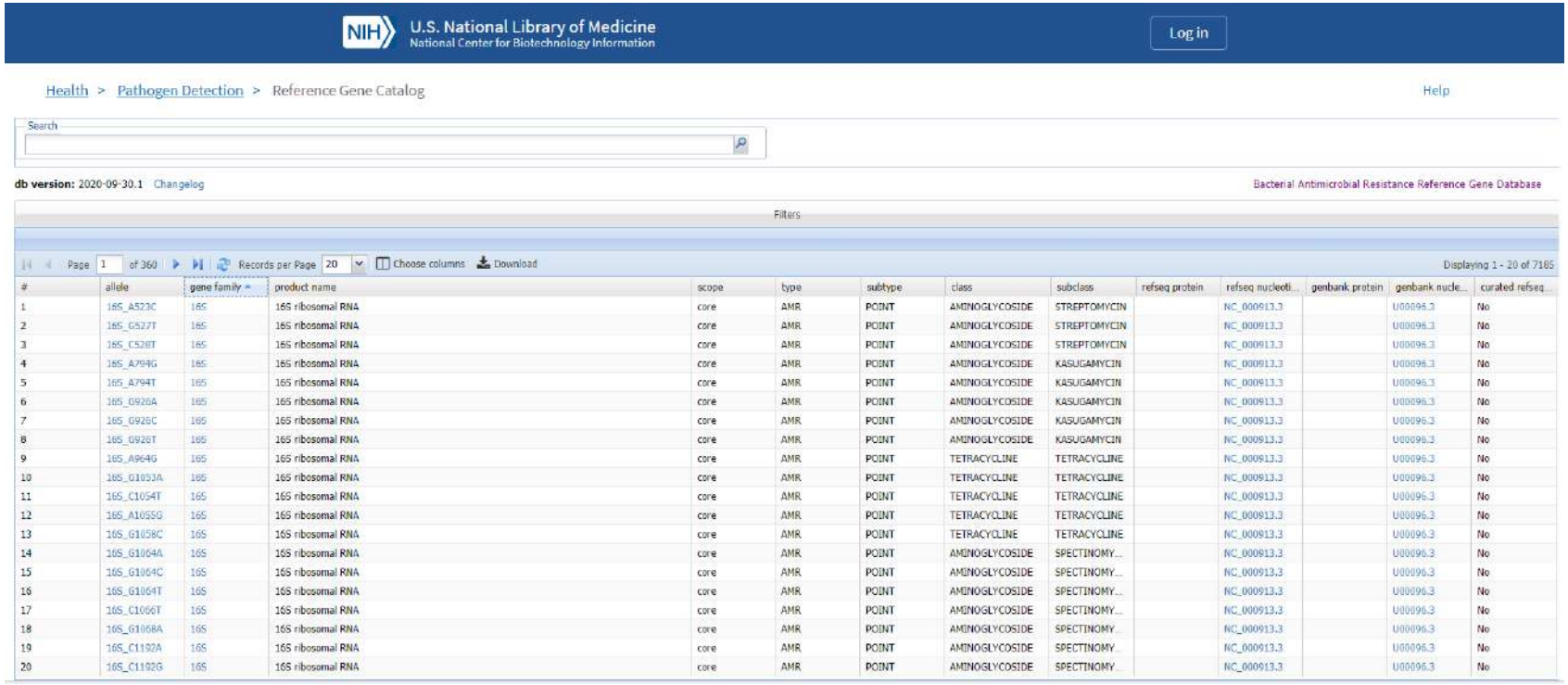


Antibiyotik direncine, Antibiyotiklerle savaş açtık

- Antimikrobiyal direnç referans gen veri tabanı
- Patojen izolatlardan elde edilen 7185 kazanılmış direnç geni / proteinlerini

Bacterial Antimicrobial Resistance Reference Gene Database Accession: PRJNA313047 ID: 313047

This Bioproject contains annotated sequence records for representative DNA sequences that encode proteins conferring or contributing to resistance to various antibiotics. More...



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3	16S_C528T	16S	16S ribosomal RNA	core	AMR	POINT	AMINOGLYCOSIDE	STREPTOMYCIN		NC_000913.3		U00096.3	No
4	16S_A794G	16S	16S ribosomal RNA	core	AMR	POINT	AMINOGLYCOSIDE	KASUGAMYCIN		NC_000913.3		U00096.3	No
5	16S_A794T	16S	16S ribosomal RNA	core	AMR	POINT	AMINOGLYCOSIDE	KASUGAMYCIN		NC_000913.3		U00096.3	No
6	16S_G926A	16S	16S ribosomal RNA	core	AMR	POINT	AMINOGLYCOSIDE	KASUGAMYCIN		NC_000913.3		U00096.3	No
7	16S_G926C	16S	16S ribosomal RNA	core	AMR	POINT	AMINOGLYCOSIDE	KASUGAMYCIN		NC_000913.3		U00096.3	No
8	16S_G926T	16S	16S ribosomal RNA	core	AMR	POINT	AMINOGLYCOSIDE	KASUGAMYCIN		NC_000913.3		U00096.3	No
9	16S_A964G	16S	16S ribosomal RNA	core	AMR	POINT	TETRACYCLINE	TETRACYCLINE		NC_000913.3		U00096.3	No
10	16S_G1053A	16S	16S ribosomal RNA	core	AMR	POINT	TETRACYCLINE	TETRACYCLINE		NC_000913.3		U00096.3	No
11	16S_C1054T	16S	16S ribosomal RNA	core	AMR	POINT	TETRACYCLINE	TETRACYCLINE		NC_000913.3		U00096.3	No
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13	16S_G1058C	16S	16S ribosomal RNA	core	AMR	POINT	TETRACYCLINE	TETRACYCLINE		NC_000913.3		U00096.3	No
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Kazanılan her direnç mekanizması direnç havuzuna eklendi

- Antimikrobiyal direnç referans gen veri tabanı
- Patojen izolatlardan elde edilen 8201 kazanılmış direnç geni

Filters

Page 2 of 3 | Records per Page 20 | Choose columns | Download | Displaying 21 - 40 of 46

#	Allele	Gene family	Product name	Scope	Type	Subtype	Class	Subclass	RefSeq pr...	RefSeq nu...	GenBank p...	GenBank ...	Curated R...
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34	blaOXA-10...	blaOXA	OXA-48 family carbapenem-hydrolyzing class D beta-lactamase OXA-1039	core	AMR	AMR	BETA-LAC...	BETA-LAC...	WP_03741...	NG_07804...	UBJ91324.1	OK180618.1	No
35	blaOXA-162	blaOXA	OXA-48 family carbapenem-hydrolyzing class D beta-lactamase OXA-162	core	AMR	AMR	BETA-LAC...	CARBAPE...	WP_06061...	NG_04946...	ADG27454.1	HM015773...	No
36	blaOXA-163	blaOXA	OXA-48 family extended-spectrum class D beta-lactamase OXA-163	core	AMR	AMR	BETA-LAC...	CEPHALO...	WP_06213...	NG_04946...	ADY06444.1	HQ700343.1	No
37	blaOXA-181	blaOXA	OXA-48 family carbapenem-hydrolyzing class D beta-lactamase OXA-181	core	AMR	AMR	BETA-LAC...	CARBAPE...	WP_01506...	NG_04948...	AEP16366.1	JN205800.1	No
38	blaOXA-199	blaOXA	OXA-48 family carbapenem-hydrolyzing class D beta-lactamase OXA-199	core	AMR	AMR	BETA-LAC...	CARBAPE...	WP_06386...	NG_04949...	AFC95894.1	JN704570.1	No
39	blaOXA-204	blaOXA	OXA-48 family carbapenem-hydrolyzing class D beta-lactamase OXA-204	core	AMR	AMR	BETA-LAC...	CARBAPE...	WP_03249...	NG_04950...	AFU91598.1	JQ809466.1	No
40	blaOXA-232	blaOXA	OXA-48 family carbapenem-hydrolyzing class D beta-lactamase OXA-232	core	AMR	AMR	BETA-LAC...	CARBAPE...	WP_04390...	NG_04952...	AGD91915.1	JX423831.1	No

Link to Protein

Feedback

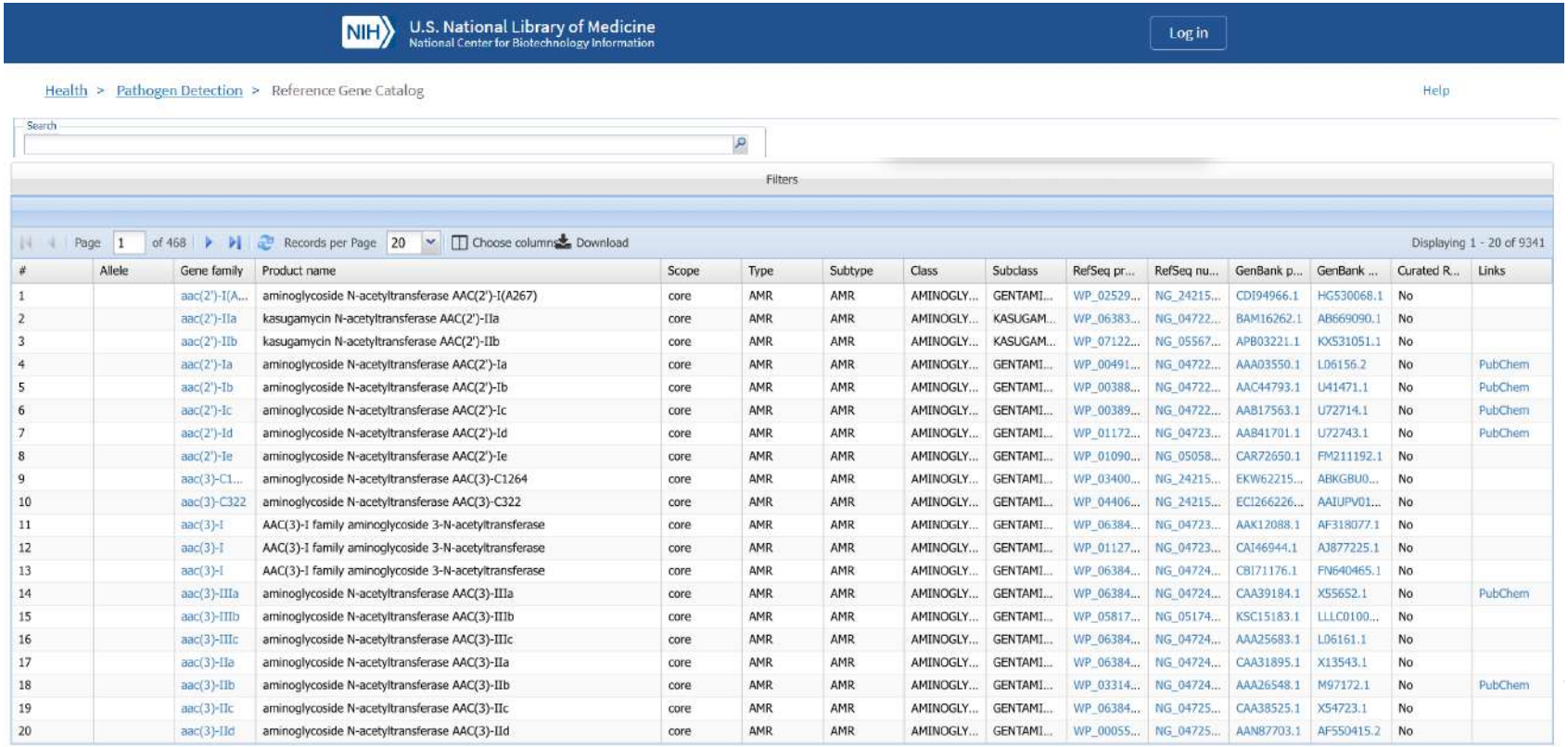
Antibiyotik direncine, Antibiyotiklerle savaş açtık

- Antimikrobiyal direnç referans gen veri tabanı
- Patojen izolatlardan elde edilen 9341 kazanılmış direnç geni / proteinlerini

Bacterial Antimicrobial Resistance Reference Gene Database

Accession: PRJNA313047 ID: 313047

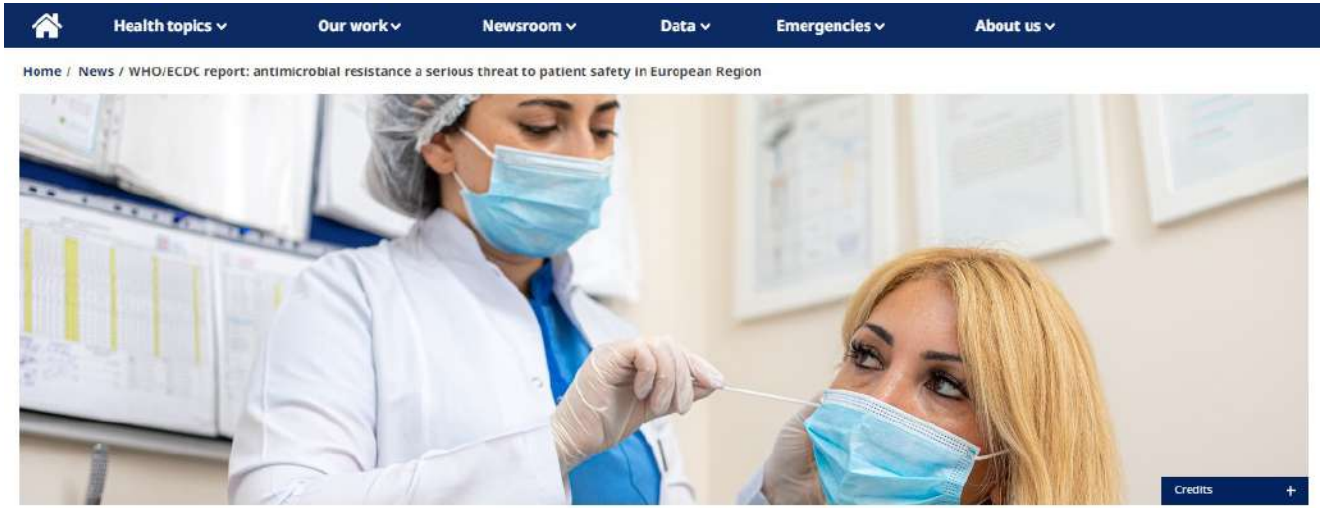
This Bioproject contains annotated sequence records for representative DNA sequences that encode proteins conferring or contributing to resistance to various antibiotics. More...



#	Allele	Gene family	Product name	Scope	Type	Subtype	Class	Subclass	RefSeq pr...	RefSeq nu...	GenBank p...	GenBank ...	Curated R...	Links
1		aac(2')-I(A...	aminoglycoside N-acetyltransferase AAC(2')-I(A267)	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_02529...	NG_24215...	CDI94966.1	HG530068.1	No	
2		aac(2')-IIa	kasugamycin N-acetyltransferase AAC(2')-IIa	core	AMR	AMR	AMINOGLY...	KASUGAM...	WP_06383...	NG_04722...	BAM16262.1	AB669090.1	No	
3		aac(2')-IIb	kasugamycin N-acetyltransferase AAC(2')-IIb	core	AMR	AMR	AMINOGLY...	KASUGAM...	WP_07122...	NG_05567...	APB03221.1	KX531051.1	No	
4		aac(2')-Ia	aminoglycoside N-acetyltransferase AAC(2')-Ia	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_00491...	NG_04722...	AAA03550.1	L06156.2	No	PubChem
5		aac(2')-Ib	aminoglycoside N-acetyltransferase AAC(2')-Ib	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_00388...	NG_04722...	AAC44793.1	U41471.1	No	PubChem
6		aac(2')-Ic	aminoglycoside N-acetyltransferase AAC(2')-Ic	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_00389...	NG_04722...	AAB17563.1	U72714.1	No	PubChem
7		aac(2')-Id	aminoglycoside N-acetyltransferase AAC(2')-Id	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_01172...	NG_04723...	AAB41701.1	U72743.1	No	PubChem
8		aac(2')-Ie	aminoglycoside N-acetyltransferase AAC(2')-Ie	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_01090...	NG_05058...	CAR72650.1	FM211192.1	No	
9		aac(3)-C1...	aminoglycoside N-acetyltransferase AAC(3)-C1264	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_03400...	NG_24215...	EKW62215...	ABKGBU0...	No	
10		aac(3)-C322	aminoglycoside N-acetyltransferase AAC(3)-C322	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_04406...	NG_24215...	ECI266226...	AAIUPV01...	No	
11		aac(3)-I	AAC(3)-I family aminoglycoside 3-N-acetyltransferase	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_06384...	NG_04723...	AAK12088.1	AF318077.1	No	
12		aac(3)-I	AAC(3)-I family aminoglycoside 3-N-acetyltransferase	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_01127...	NG_04723...	CAI46944.1	AJ877225.1	No	
13		aac(3)-I	AAC(3)-I family aminoglycoside 3-N-acetyltransferase	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_06384...	NG_04724...	CBI71176.1	FN640465.1	No	
14		aac(3)-IIIa	aminoglycoside N-acetyltransferase AAC(3)-IIIa	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_06384...	NG_04724...	CAA39184.1	X55652.1	No	PubChem
15		aac(3)-IIIb	aminoglycoside N-acetyltransferase AAC(3)-IIIb	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_05817...	NG_05174...	KSC15183.1	LLLC0100...	No	
16		aac(3)-IIIc	aminoglycoside N-acetyltransferase AAC(3)-IIIc	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_06384...	NG_04724...	AAA25683.1	L06161.1	No	
17		aac(3)-IIa	aminoglycoside N-acetyltransferase AAC(3)-IIa	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_06384...	NG_04724...	CAA31895.1	X13543.1	No	
18		aac(3)-IIb	aminoglycoside N-acetyltransferase AAC(3)-IIb	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_03314...	NG_04724...	AAA26548.1	M97172.1	No	PubChem
19		aac(3)-IIc	aminoglycoside N-acetyltransferase AAC(3)-IIc	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_06384...	NG_04725...	CAA38525.1	X54723.1	No	
20		aac(3)-IId	aminoglycoside N-acetyltransferase AAC(3)-IId	core	AMR	AMR	AMINOGLY...	GENTAMI...	WP_00055...	NG_04725...	AAN87703.1	AF550415.2	No	

Nereden nereye geldik?

- WHO ve ECDC tarafından yayınlanan antimikrobiyal direnç raporunda Avrupa bölgesinde hasta güvenliğine ciddi bir tehdit olarak antimikrobiyal direncin arttığını bildiriyor.



WHO/ECDC report: antimicrobial resistance a serious threat to patient safety in European Region

18 November 2022 | News release |Reading time: 1 min (312 words)

The second "Surveillance of antimicrobial resistance in Europe" report, published jointly by the European Centre for Disease Prevention and Control (ECDC) and WHO/Europe, shows high percentages of resistance to last-line antibiotics, such as carbapenems, in several countries of the WHO European Region. The report features data from 2021.

As observed in previous regional reports, there is a north-to-south and west-to-east gradient of resistance, with higher rates observed in the southern and eastern parts of the European Region, indicating that antimicrobial resistance (AMR) is a serious threat to patient safety.

More countries reporting data but standardized approach needed

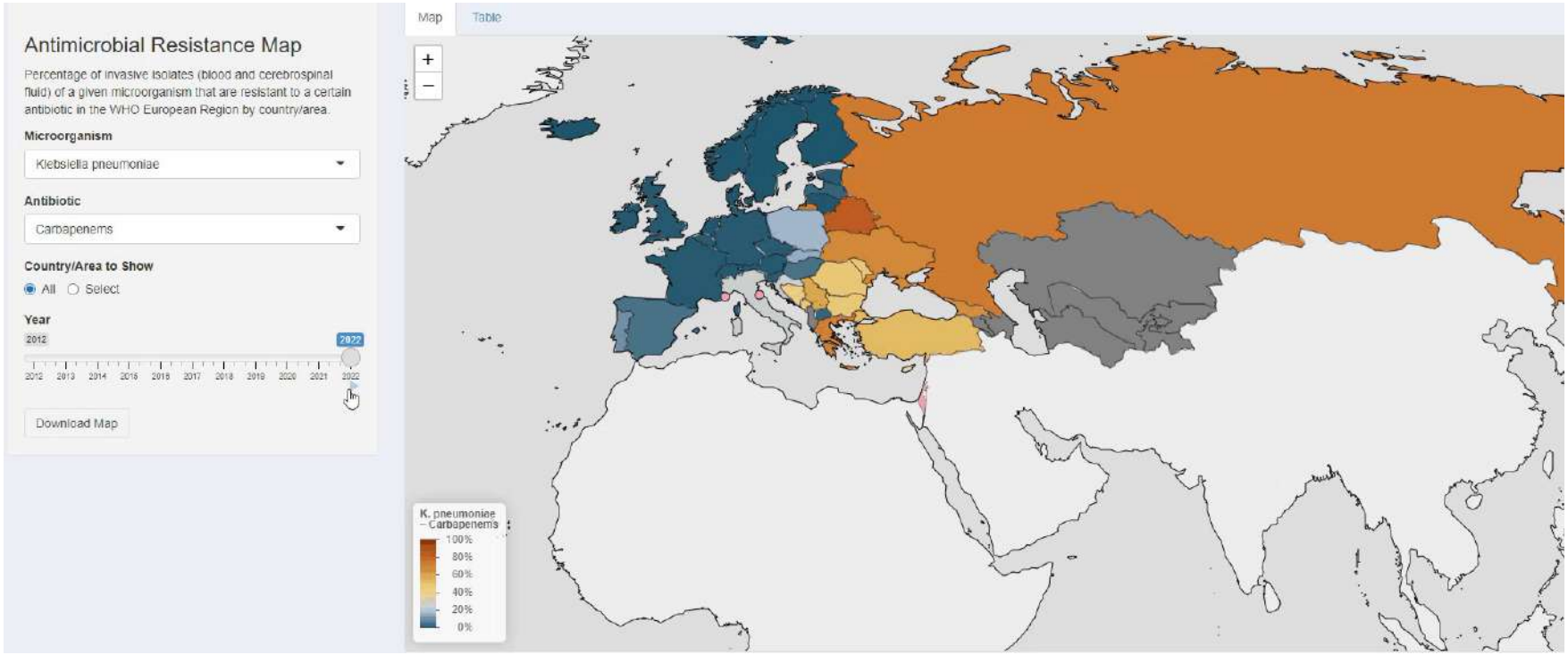
Related

Antimicrobial Resistance Dashboard

Surveillance of antimicrobial resistance in Europe, 2021 data: executive summary

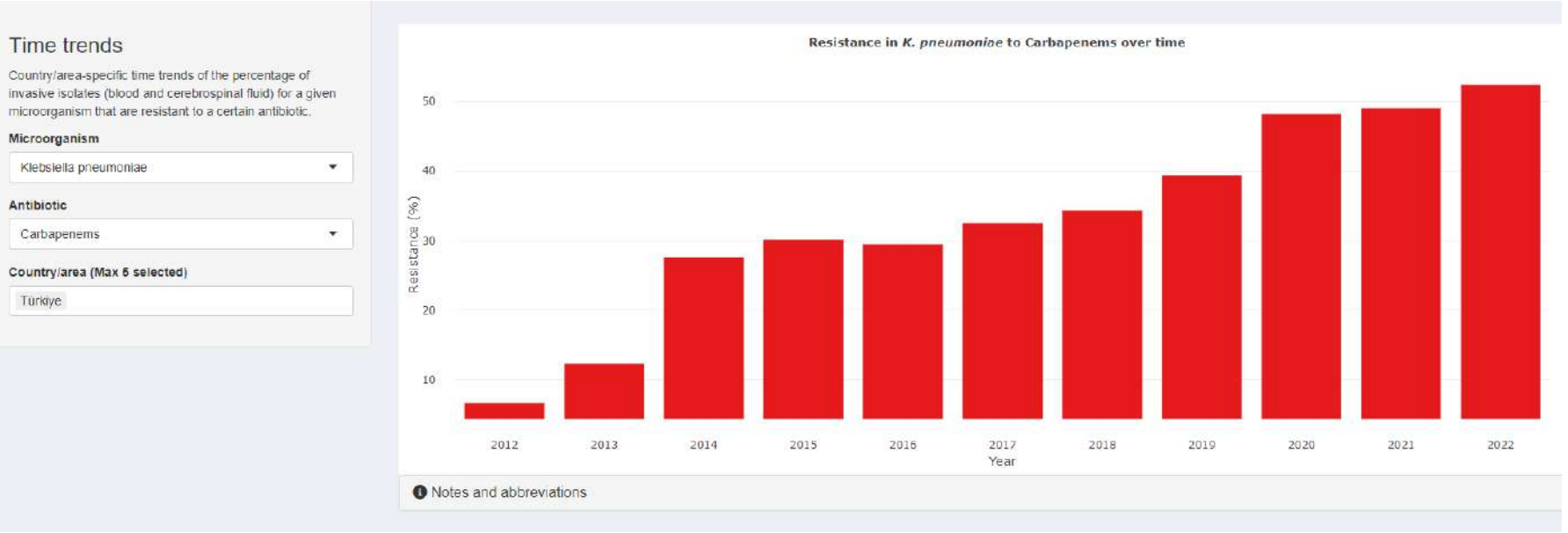
Nereden nereye geldik?

- Antimikrobiyal direnç haritası



Nereden nereye geldik?

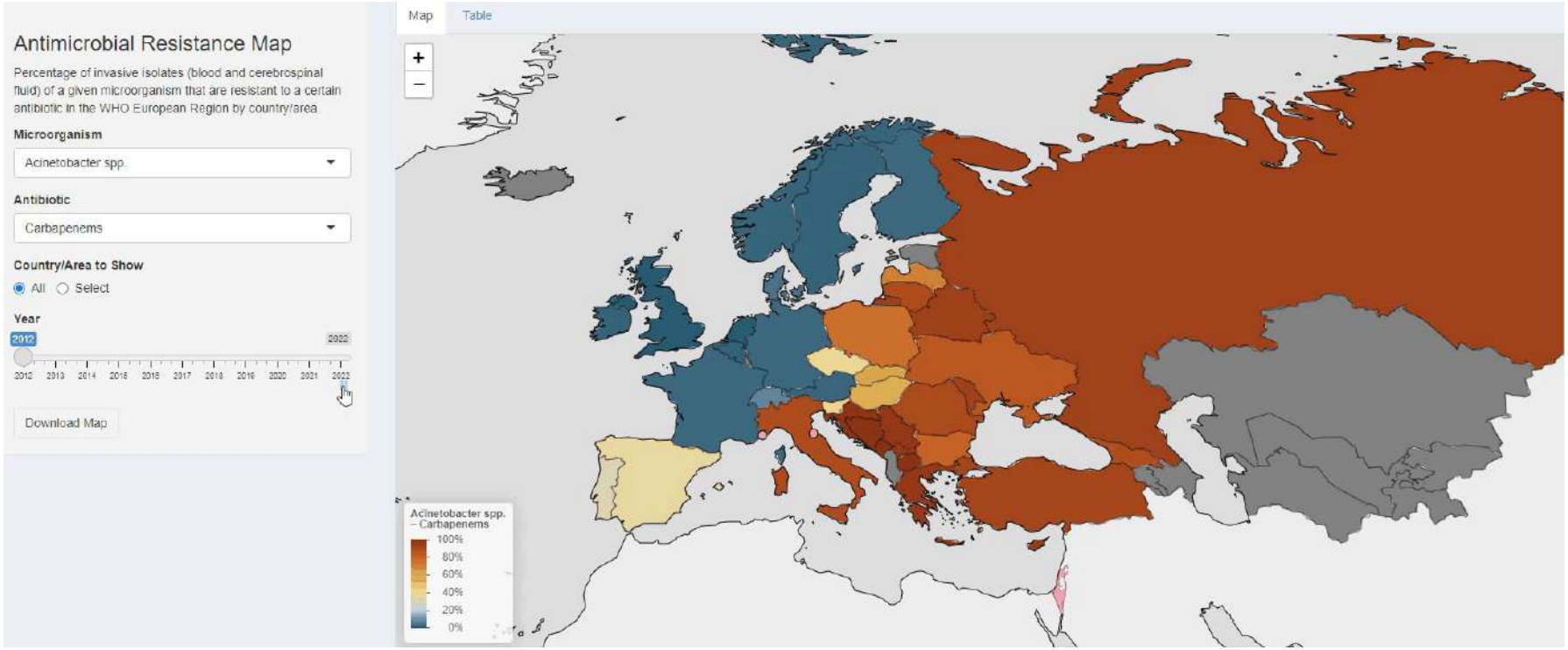
- Türkiye'deki *K. pneumoniae* izolatlarının karbapenem direnci giderek daha da artıyor.



Nereden nereye geldik?

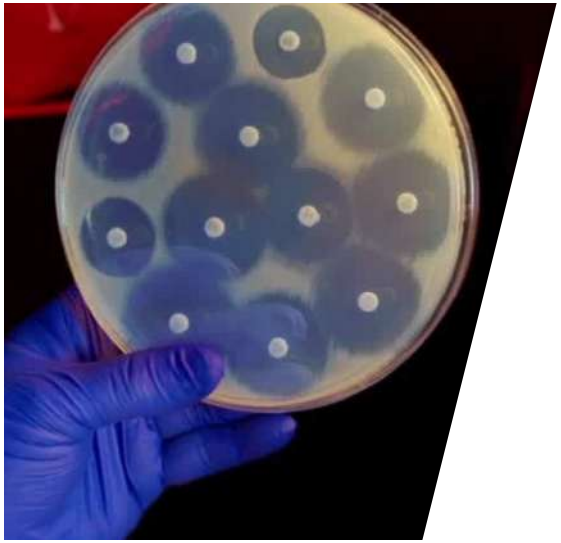
- Antimikrobiyal direnç haritası,

  Acinetobacter spp.'de karbapenem direnci



Nereden nereye geldik?

Antimikrobiyal duyarlılık testleri



OXA-48

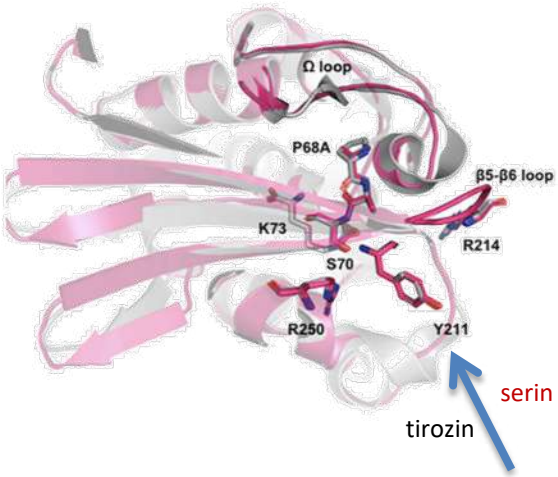
NDM

KPC

IMP

VIM

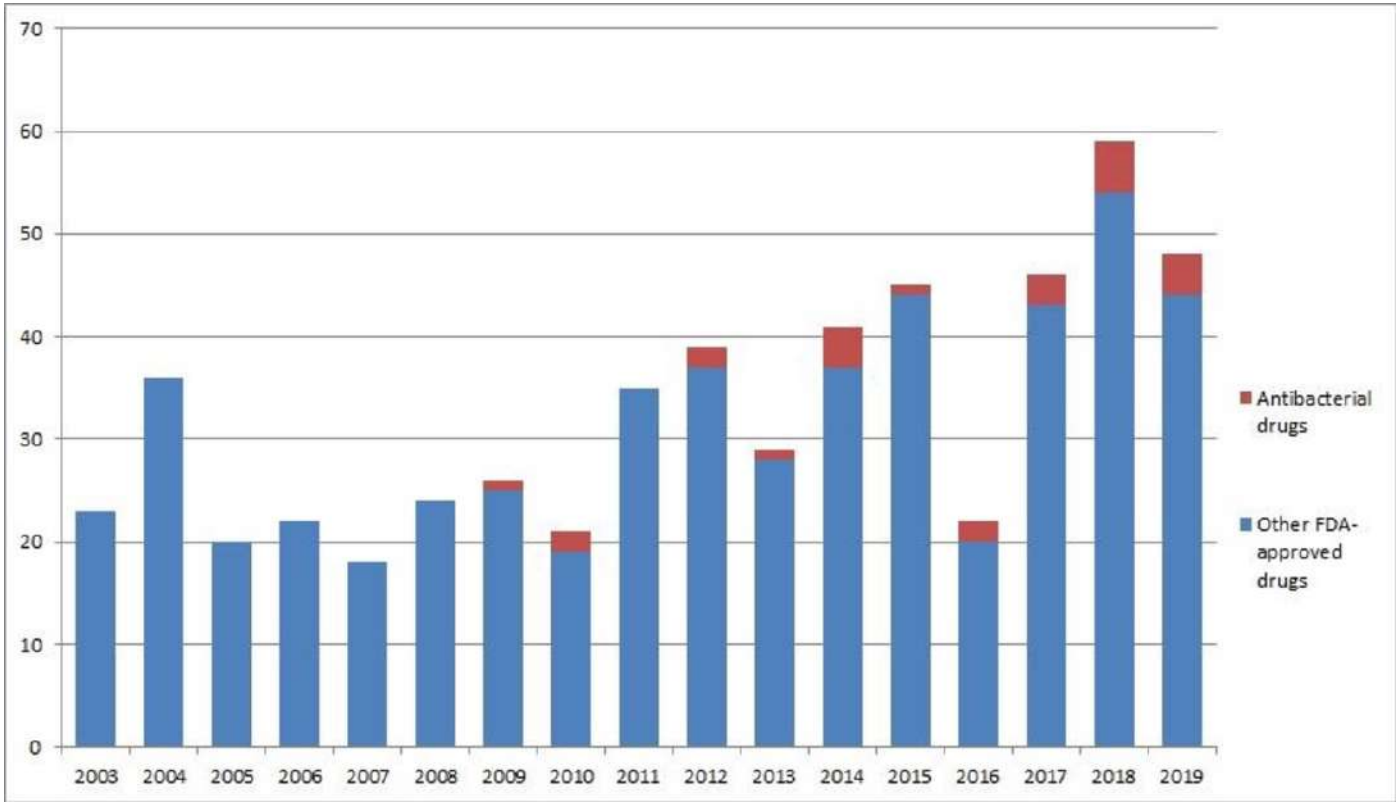
GES



Yeni antibakteriyel moleküller keşfedilmiyor mu?

- Yeni antimikrobiyal üretilmiyor.

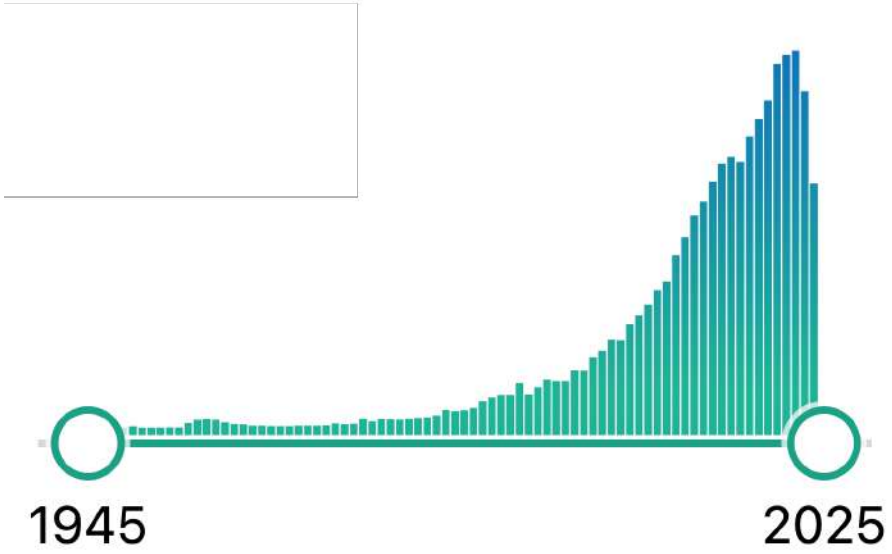
Elde kalan sınırlı kaynağı daha etkin kullanmak için tüm imkanlar seferber edilmeli.



Discoveries (Craiova). 2019 Dec 31;7(4):e102. doi: 10.15190/d.2019.15.

Yeni antibakteriyel moleküller keşfedilmiyor mu?

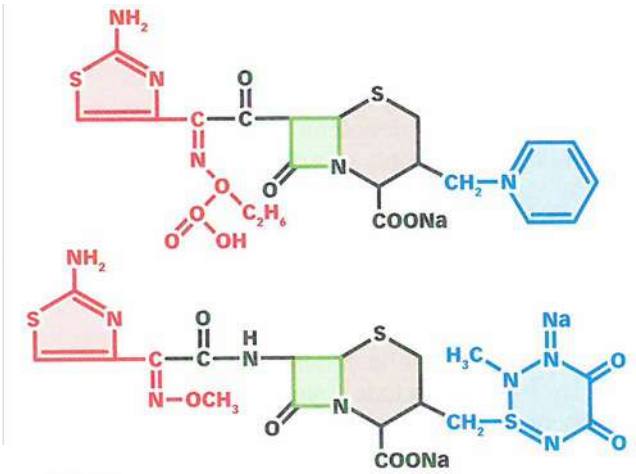
- «New antimicrobial compounds», 57,070 sonuç
- Antibiyotik üretimi direnç yüzünden riskli ve karsız



Using **new** born mouse skin slice culture, we studied the effects on certain antiseptic **agents** on the

Farklı yaklaşımlara ihtiyaç var

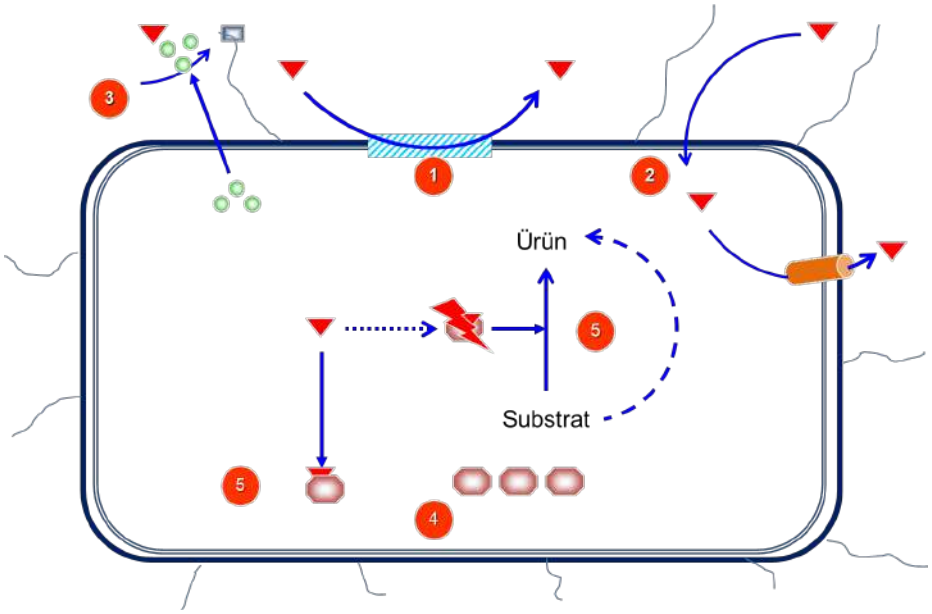
- Salvarsandan bugünkü modern sefalosorinlere kadar geçen süreç ve artan direnç göz önüne alındığında, bakış açımızı değiştirmemizin gerekliliği açıktır.



Direnci önlemek

- Direnci önlenmesi için;

  mikroorganizmaları ve antimikrobiyalleri daha iyi anlamak gerekli.



Antimikrobiyal direnç mekanizmaları

Bir Zamanlar Dünya, 4.5 milyar önce

- Dünya bir gaz ve toz buluydu,

Bir zamanlar Dünya, yaklaşık 4 milyar önce

- Dünyada sadece mikroorganizmalar ve antibiyotikler vardı!

Streptomyces griseus → streptomisin

Streptomyces roseosporus → daptomisin

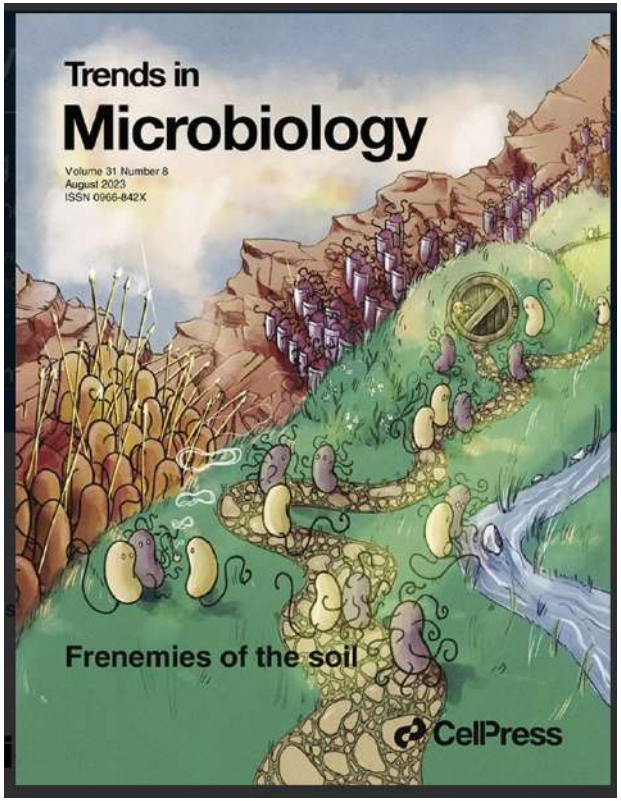
Bacillus colistinus → kolistin

Streptomyces clavuligerus → β-laktamaz inhibitörleri

Streptomyces orientalis → vankomisin

Actinoplanes teichomyceticus → teicoplanin

Eleftheria terrae → teixobactin



Antibiyotik Direnci!

Bakteri

Antibiyotik

Antik Direnç Genleri

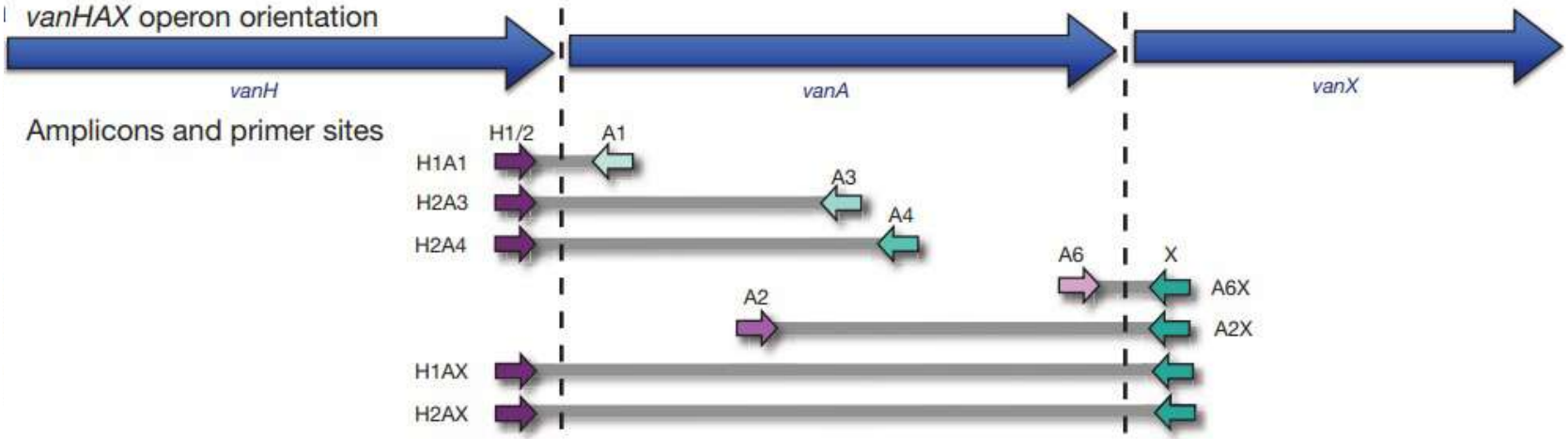
- 30.000 yıllık Beringian permafrost çökeltilerinden β-laktam, tetrasiklin ve glikopeptid gibi antibiyotik direnci kodlayan genler tespit edildi.

LETTER

doi:10.1038/nature10388

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

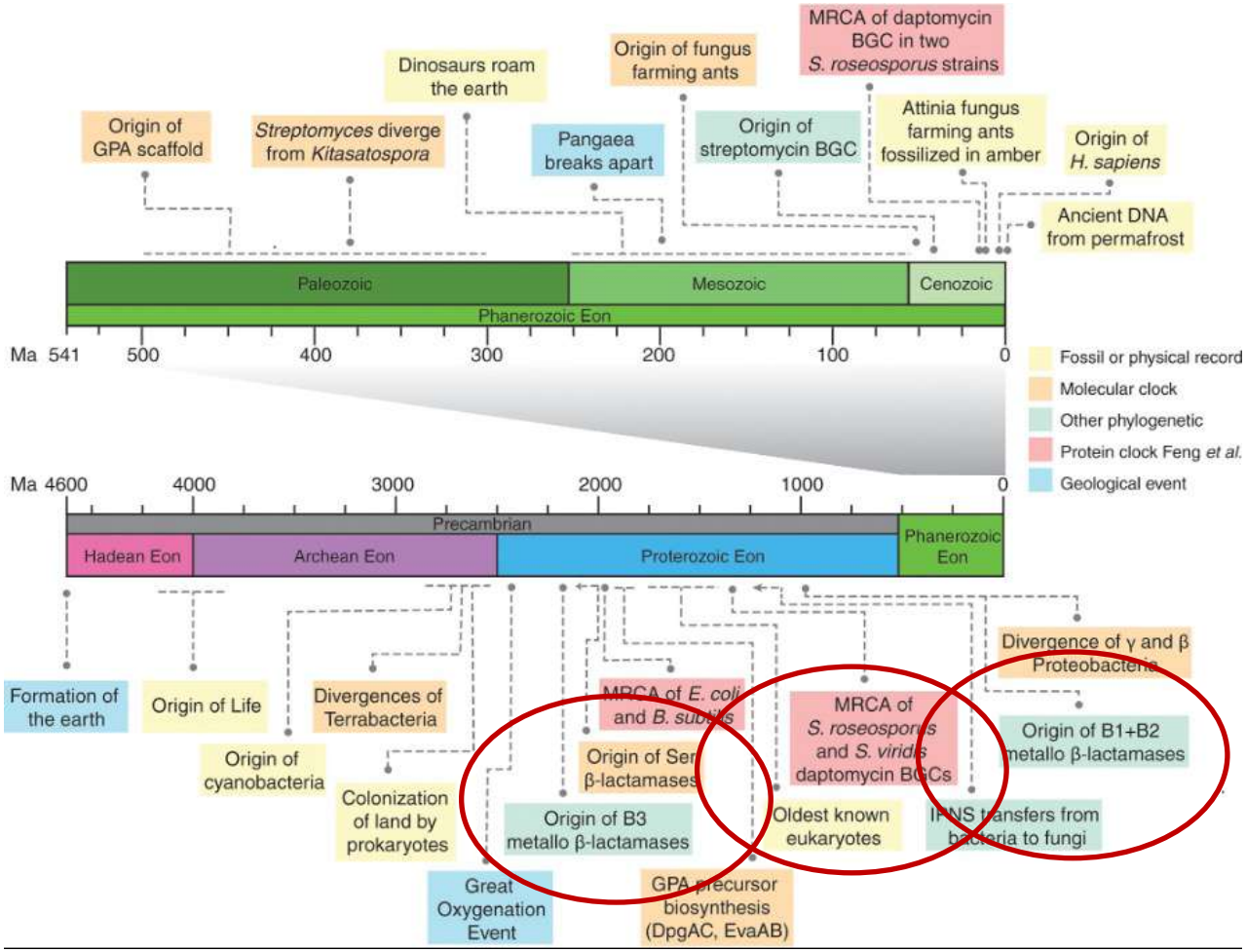


Antik direnç genleri

- Attini karıncaları, en yaygın olarak Actinomyces spp. tarafından üretilen antibiyotiklerin yardımıyla, yiyecek için mantar bahçeleri yetiştirirler .

Antik direnç genleri

- Bu kehribar fosilleri filogenetik düğümleri kalibre etmek için kullanıldığında, mantar çiftçiliği yapan karıncaların 50 milyon yıl önce ortaya çıktığı düşünülüyor



Antik direnç genleri

- Mackay Buzulu bölgesindeki 17 yüzey toprağında, 177 direnç geni tanımlandı.

  Aminoglikozidler, kloramfenikol ve β-laktam antibiyotiklerin inaktivasyonuna yönelik direnç mekanizmaları yaygındı.

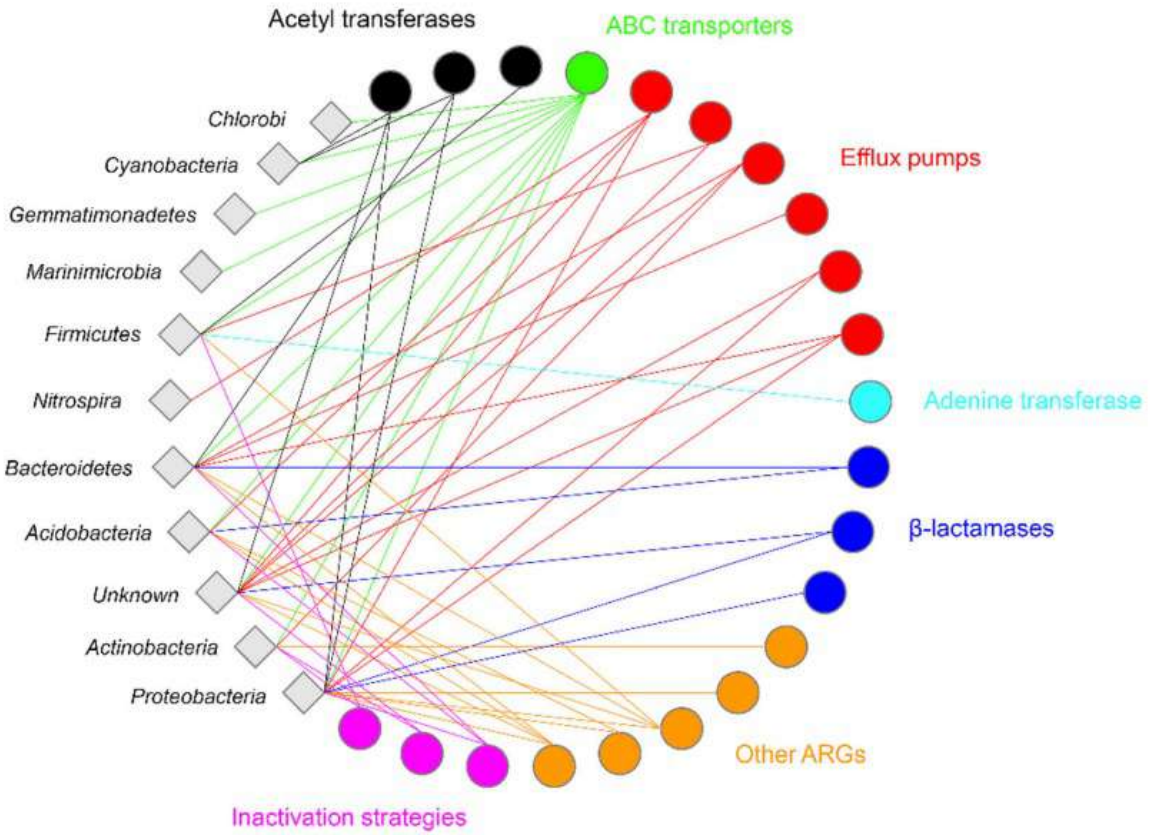


Fig. 3 Co-occurrence network of ARG mechanisms showing resistance mechanisms encoded by diverse soil bacterial phyla. Phyla from all 17 soils that were assigned an ARG are presented here (diamond-shaped nodes), with significant co-occurrences with a specific ARG (circles) indicated (edges)

Antik direnç genleri

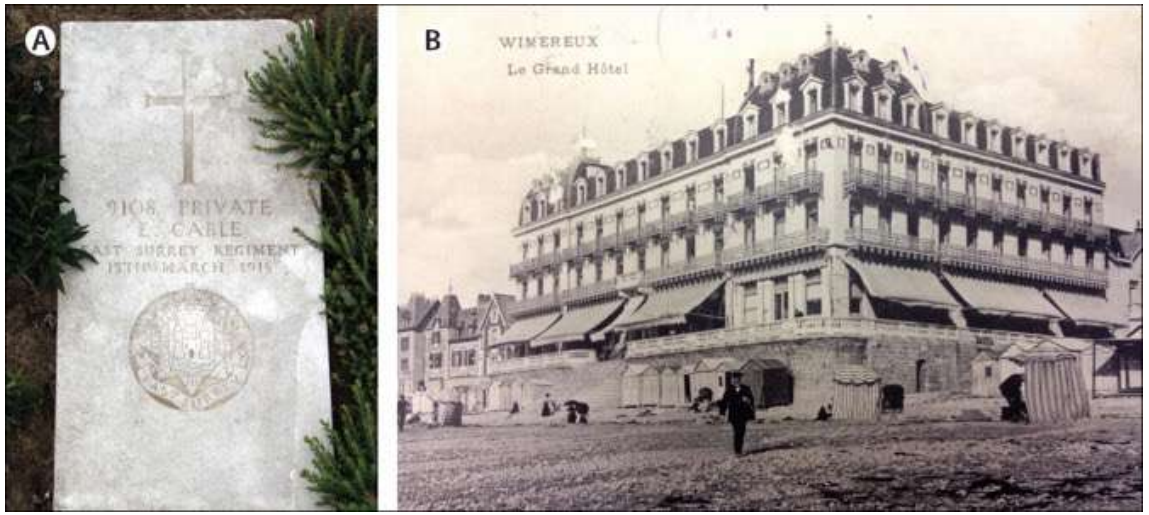
- 1915'in başlarında, 28 yaşında bir asker Fransa'nın Wimereux kentindeki hastaneye ishal ve şiddetli karın krampları ile başvurmuş ve Shigella flexneri serotip 2a bakterisi izole edilmiş. Hem penisiline hem de eritromisine dirençliydi.

Case Report

Bacillary dysentery from World War 1 and NCTC1, the first bacterial isolate in the National Collection

Alison E Mather, Kate S Baker*, Hannah McGregor, Paul Coupland, Pamela L Mather, Ana Deheer-Graham, Julian Parkhill, Philippa Bracegirdle, Julie E Russell, Nicholas R Thomson*

Askerin adı Er Ernest Cable



Antik Direnç Genleri

- 1949 yılında Filipinli bir doktor olan Dr. Abelardo B. Aguilar
- Eli Lilly and Company'de ilaç temsilcisi

Streptomyces erythraea

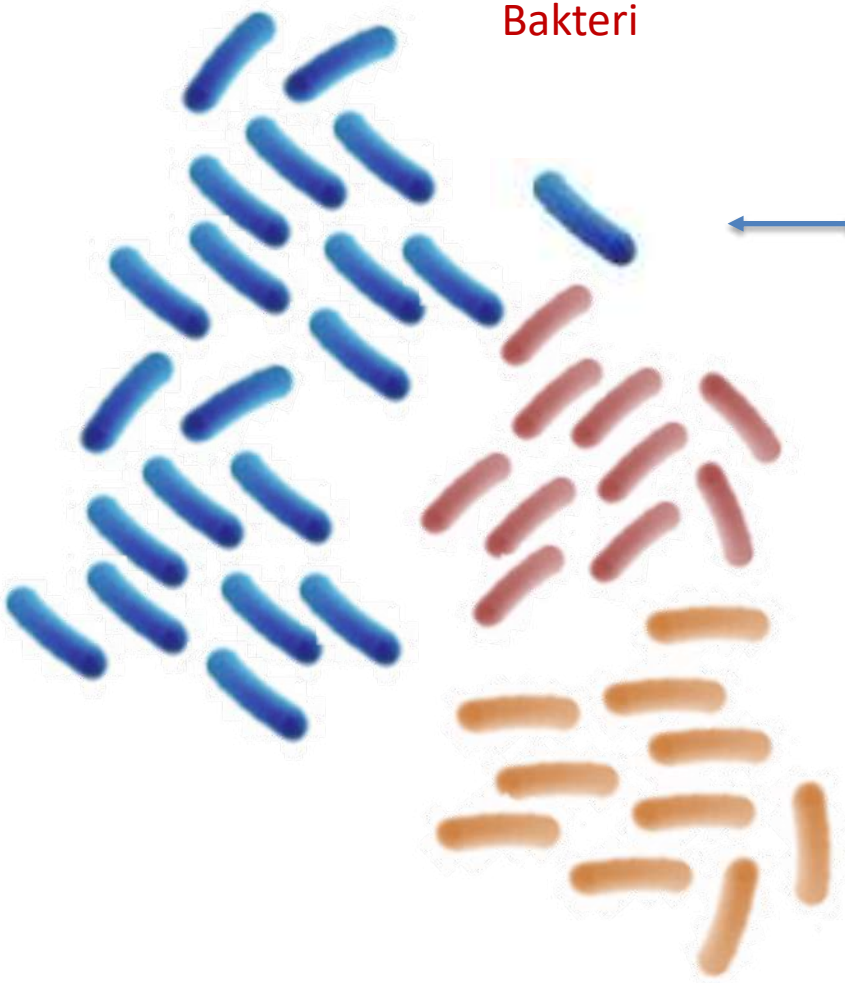
Eli Lilly

Streptomyces orientalis

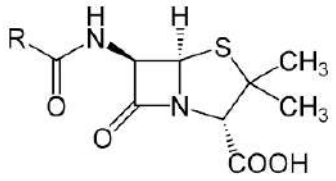
Mikroorganizmalar vs Antibiyotikler

- Bakterinin bu sorunu çözüp hayatta kalması gerekiyor.

Bakteri

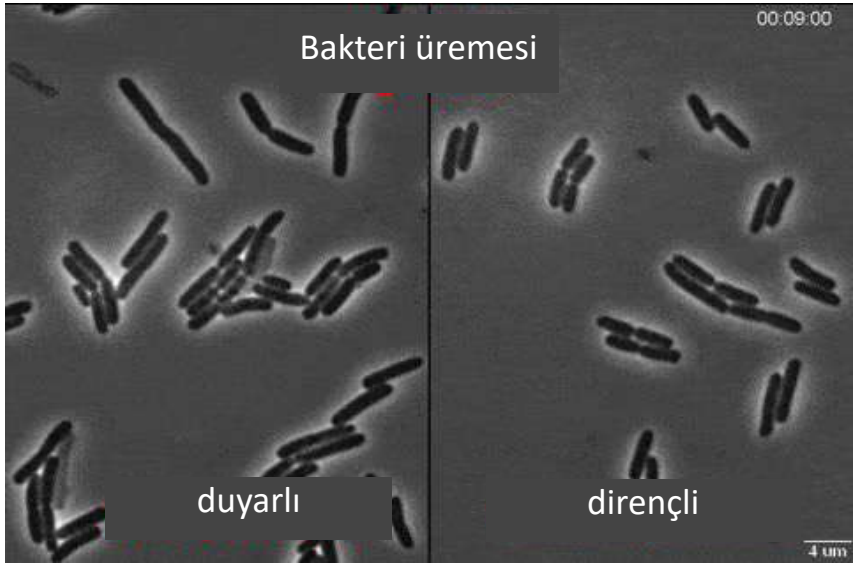


Antibiyotik



Mikroorganizmalar vs Antibiyotikler

- Mikroorganizmanın içinde kopan fırtına.
- Mikroorganizmalar hayatta kalmak için stratejileri nelerdir?



Mikroorganizmalar vs Antibiyotikler

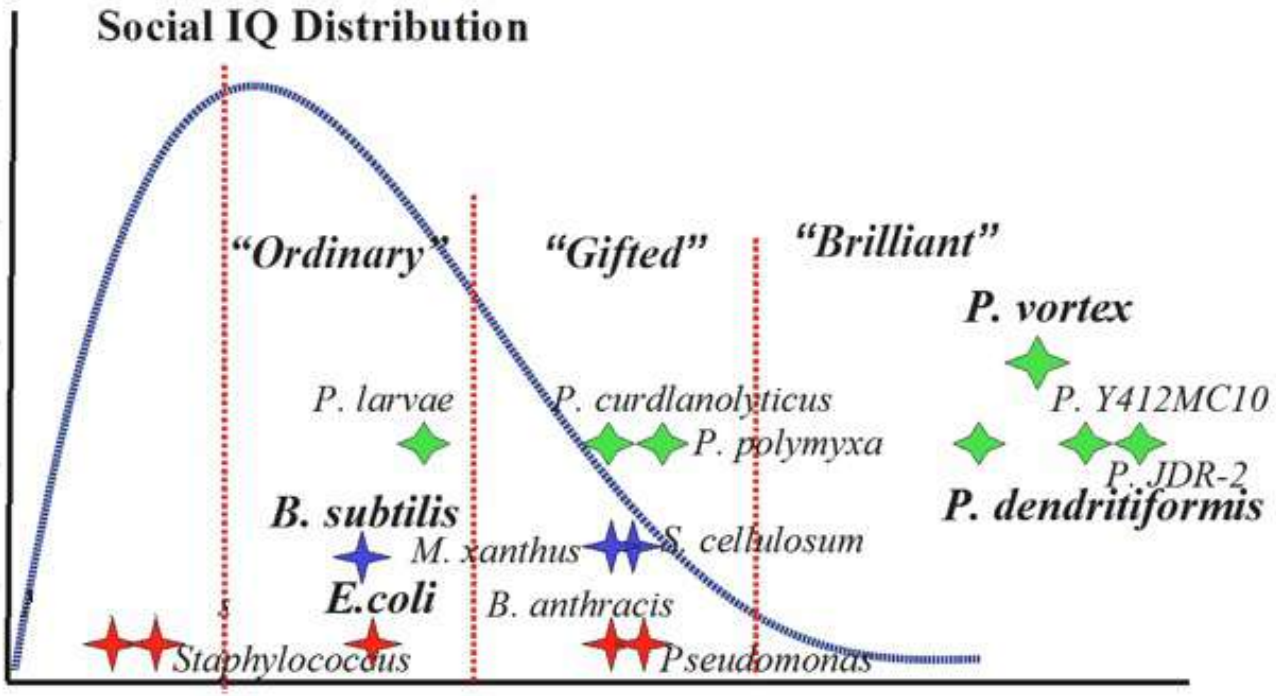
- Bakteriyel IQ

BMC Microbiology

Research article

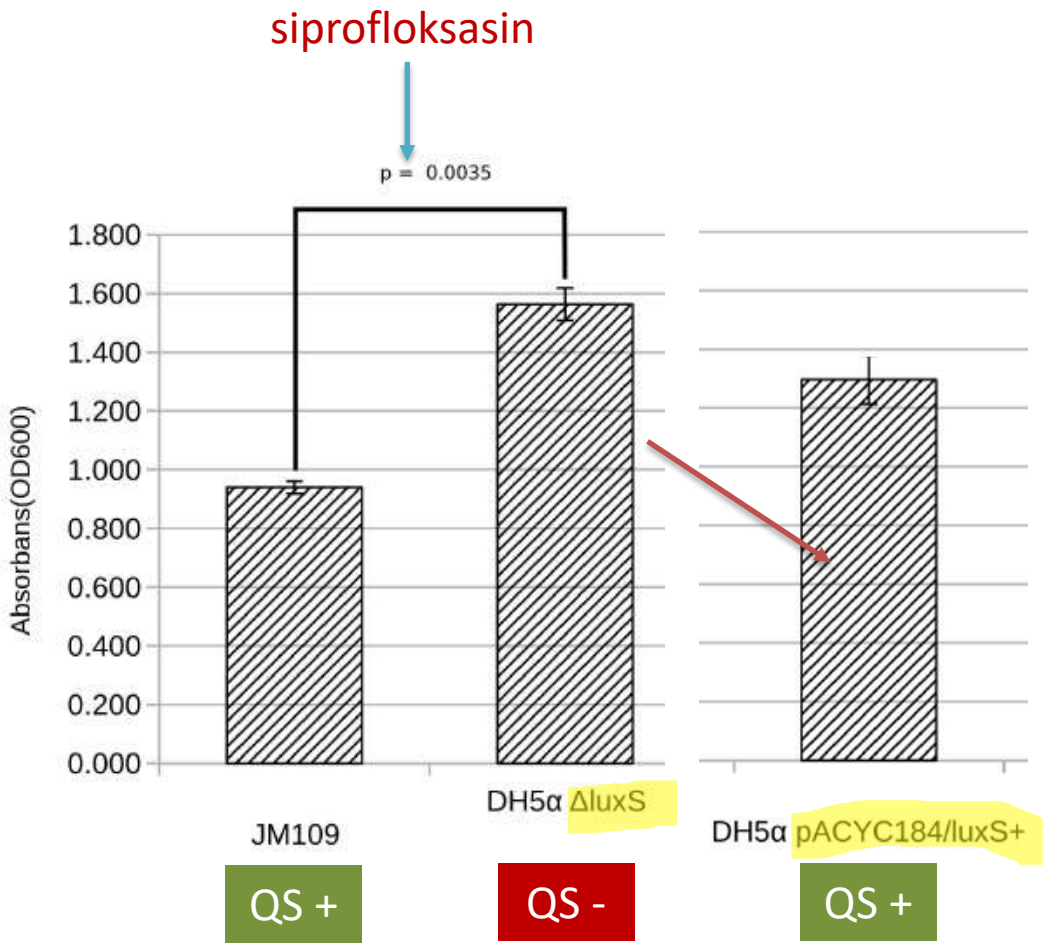
A census of membrane-bound and intracellular signal transduction proteins in bacteria: Bacterial IQ, extroverts and introverts

Michael Y Galperin*



Mikroorganizmalar vs Antibiyotikler

- Quorum sensing; popülasyonun kontrol altında olması önemli



Ozturk AD, Engin D. İnvestigation of the role of quorum sensing in the development of antimicrobial resistance mutations in Eschericia coli

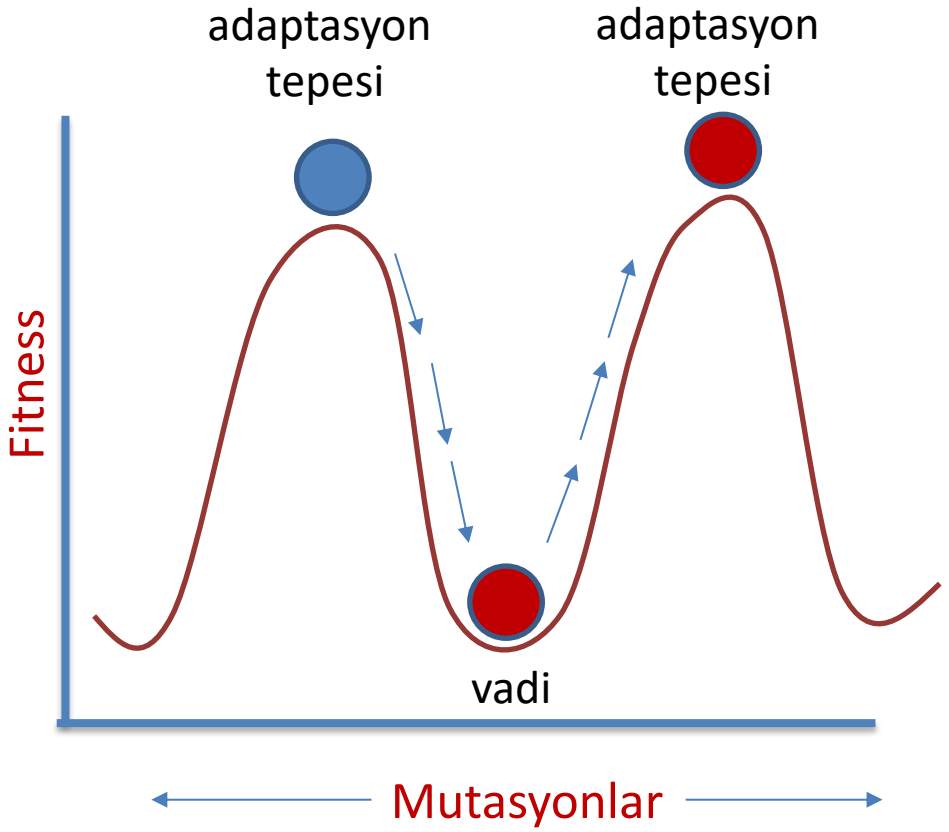
Mikroorganizmalar vs Antibiyotikler

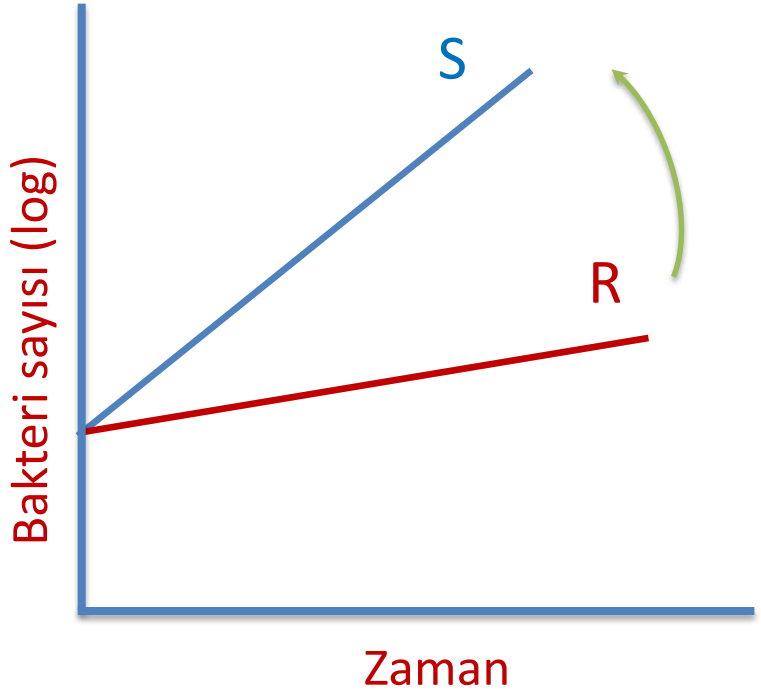
- Quorum sensing mekanizması ilk olarak siprofloksasin tehdidi savuşturuluyor.

Ozturk AD, Engin D. İnvestigation of the role of quorum sensing in the development of antimicrobial resistance mutations in Eschericia coli

Mikroorganizmalar vs Antibiyotikler

- Fitness / gürbüzlük
- Antibiyotiklerin bakteriler üzerine stres etkisi ve direnç

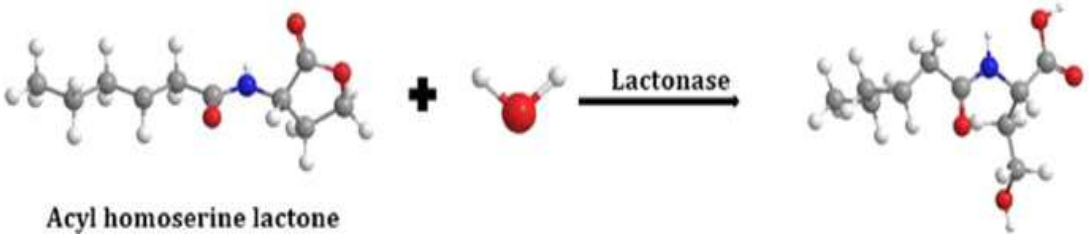




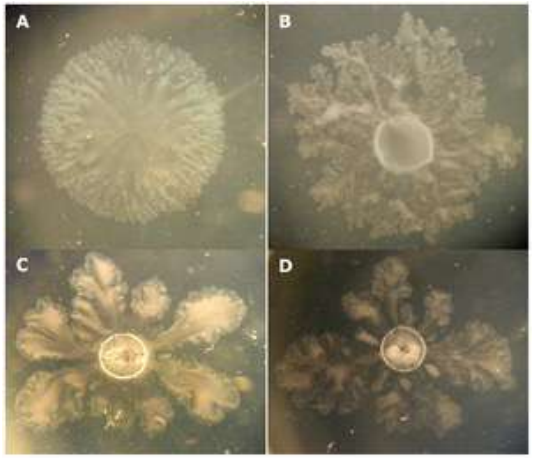
Mikroorganizmalar vs Antibiyotikler

- Bakteriler AHL (N-acyl homoserine lactone) moleküllerini hedef alan

AHL-laktonaz ve AHL-asilaz gibi enzimler bu sinyalleri parçalayarak birbirlerinin quorum sensing mekanizmasını devre dışı bırakabilir.



Variovorax paradoxus, quorum quenching



Mikroorganizmalar vs Antibiyotikler

- İdrarda *E. coli* suşları, hücre duvarını hedefleyen bir antibiyotik ile tehdit sırasında hücre duvarlı halden L-formuna kolayca geçer.

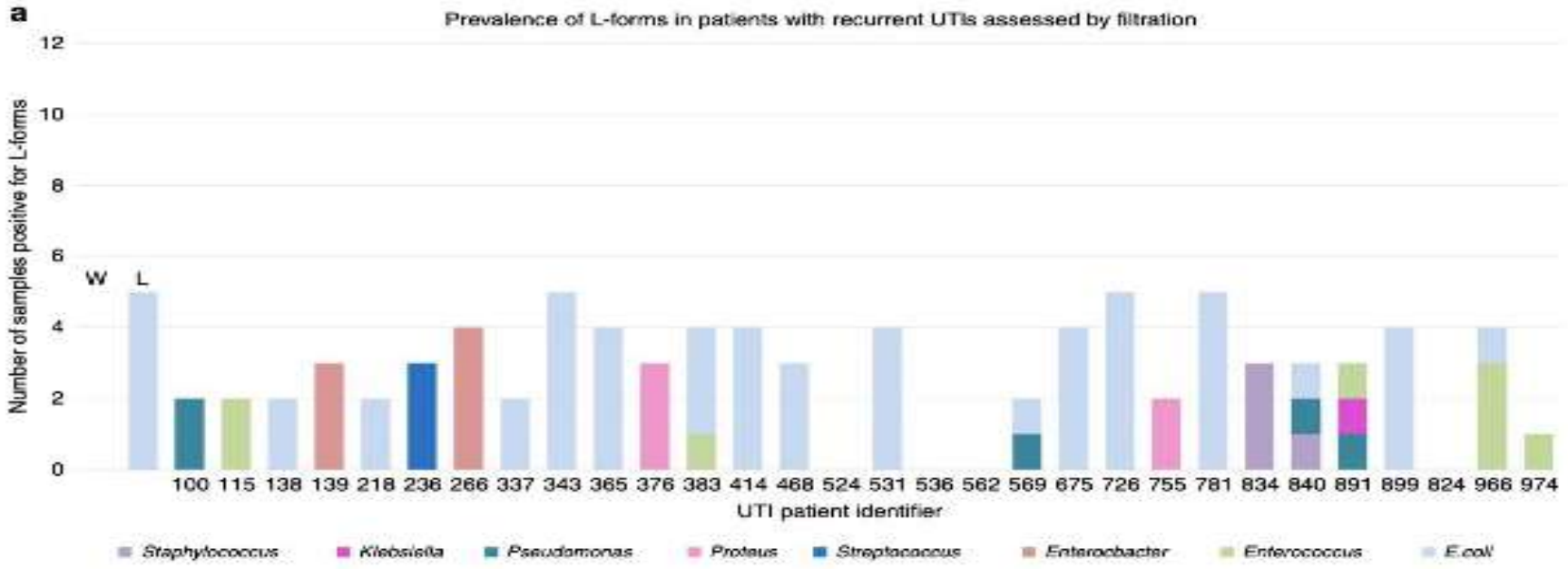
ARTICLE

https://doi.org/10.1038/s41467-019-12359-3 OPEN

Possible role of L-form switching in recurrent urinary tract infection

Viable but nonculturable

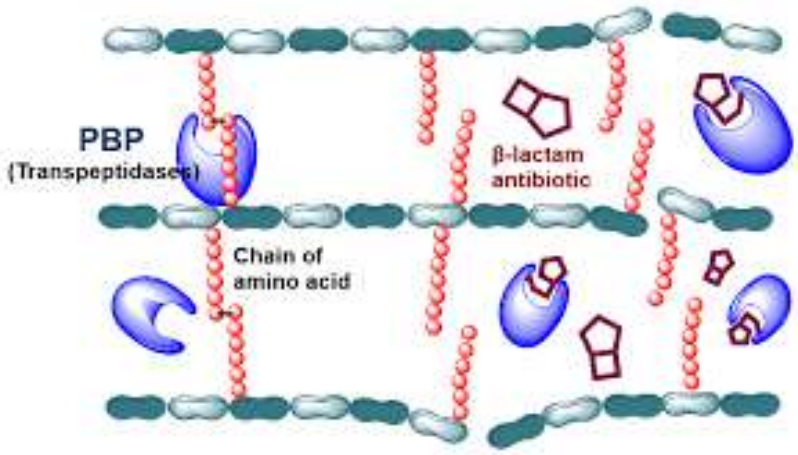
Katarzyna M. Mickiewicz[1]*, Yoshikazu Kawai[1], Lauren Drage[1], Margarida C. Gomes[2], Frances Davison[1], Robert Pickard[3], Judith Hall[4], Serge Mostowy[2], Phillip D. Aldridge[1] & Jeff Errington[1]*



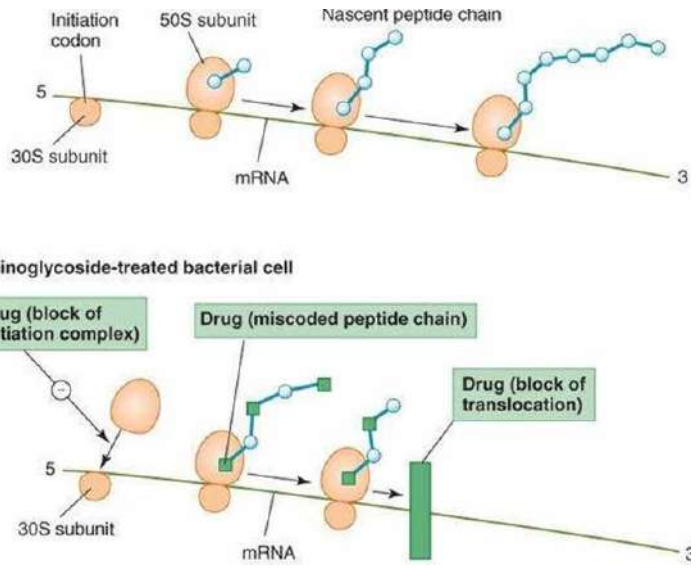
Mikroorganizmalar vs Antibiyotikler

- Seçilen antibiyotiğe bağlı olarak bakterinin stres algısı ve mücadele stratejisi değişir.

Hücre duvarının hedeflenmesi

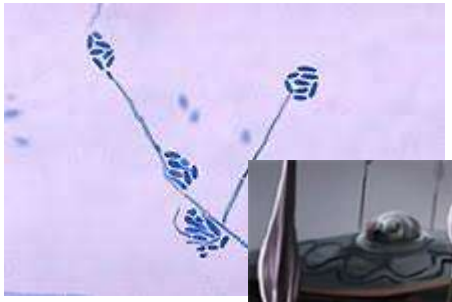


Protein sentezinin hedeflenmesi



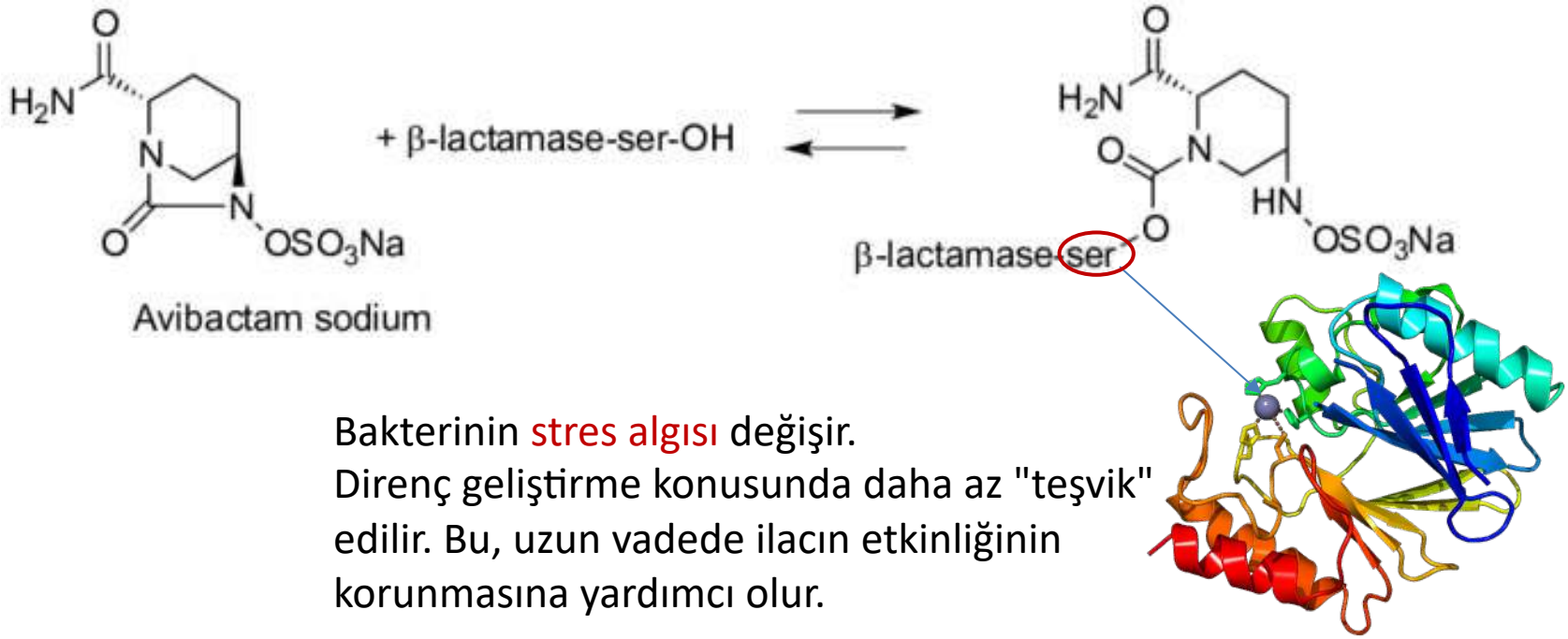
Mikroorganizmalar vs Antibiyotikler

Cephalosporium acremonium



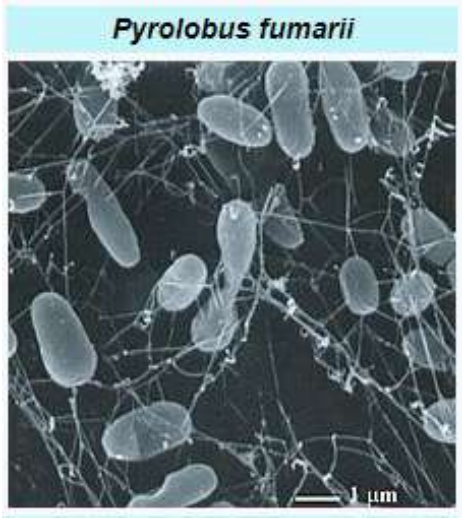
Mikroorganizmalar vs Antibiyotikler

- Avibaktam, diğer beta-laktamaz inhibitörlerinden farklı olarak geri dönüşümlü (reversibl) bir inhibitördür. Bu enzim beta-laktamaz enzimlerini kalıcı olarak bloke etmez. Bu eşsiz özellik, geniş spektrumlu etkinliğinin bir parçasıdır.

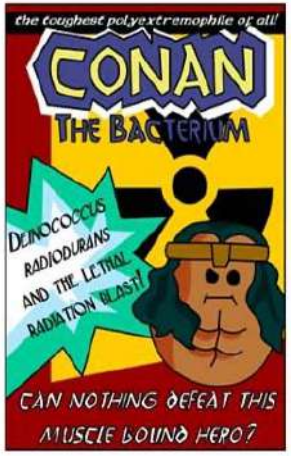


Bakterinin stres algısı değişir.
Direnç geliştirme konusunda daha az "teşvik" edilir. Bu, uzun vadede ilacın etkinliğinin korunmasına yardımcı olur.

121 derece 10 saat otoklavda

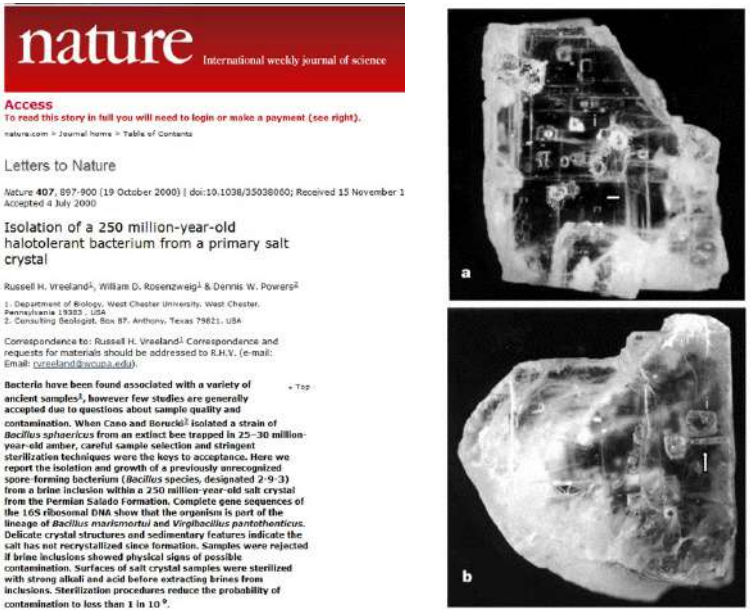


Nükleer reaktör soğutma havuzlarında yaşar



Uçak yakıtını besin kaynağı olan bakteriler

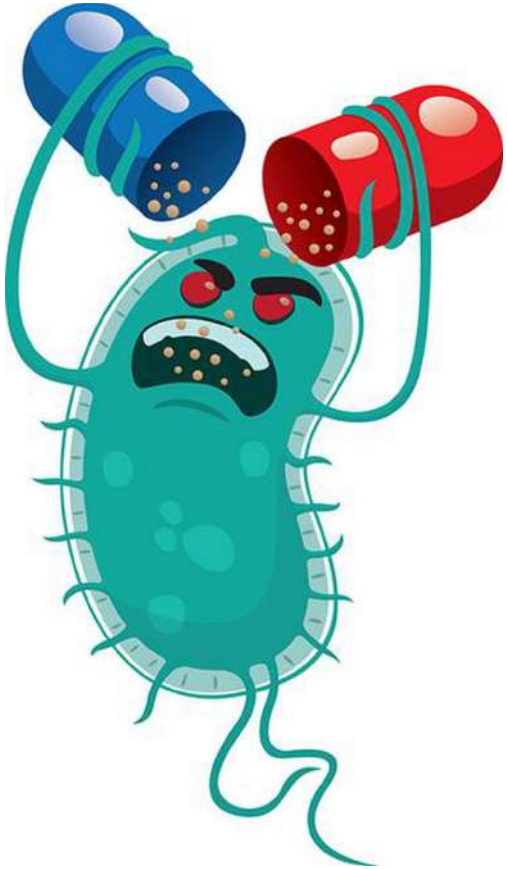
Gerekirse yaşamını 250 milyon yıl dondur



Yeryüzünde yaşamış canlıların %99'u yok oldular. Yaklaşık 4 milyar yıldır dünyadalar

Mikroorganizmalar vs Antibiyotikler

- Böyle bir canlıyı antibiyotikler durdurabilir mi?



Mikroorganizmalar vs Antibiyotikler

- Antibiyotik baskısında önce dirençli sonra antibiyotik bağımlı hale gelen mikroorganizmalar.

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SCIENTIFIC REPORTS

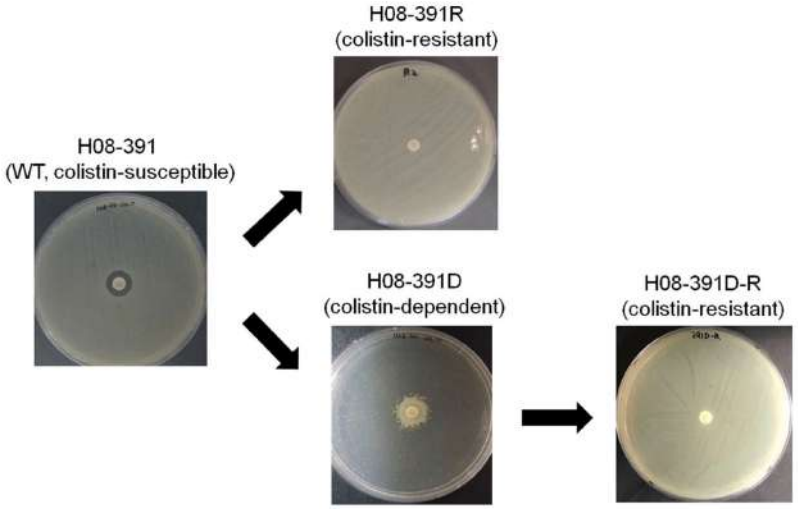

Figure 1. Colistin disc diffusion assays showing the development of colistin-dependent and -resistant mutants from the colistin-susceptible wild-type (WT) strain, H08-391. From a colistin-susceptible strain, H08-391, a colistin-resistant (H08-391R) and -dependent mutant (H08-391D) were selected *in vitro* using culture media containing 10 mg/L colistin. H08-391D-R was derived from the colistin-dependent mutant, H08-391D, through subsequent passages in the absence of colistin selection pressure, and exhibited the colistin-resistant phenotype.

Mikroorganizmalar vs Antibiyotikler

- Antibiyotik baskısında, önce dirençli sonra antibiyotik bağımlı hale gelen mikroorganizmalar.

FULL PAPER

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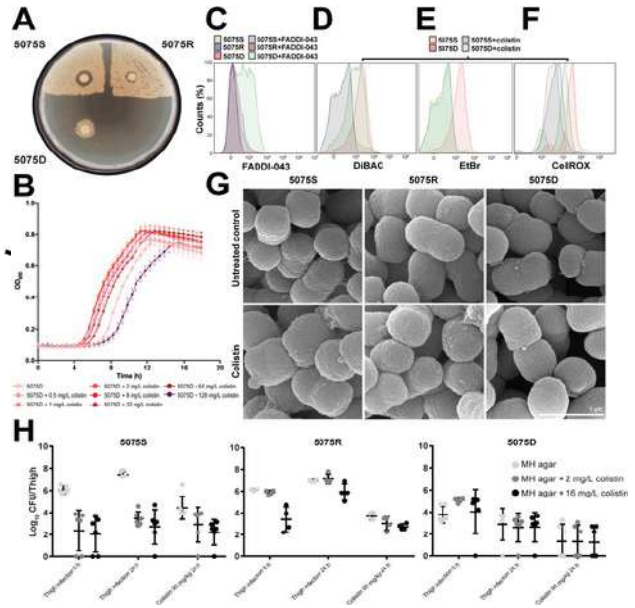
Polymyxins Bind to the Cell Surface of Unculturable *Acinetobacter baumannii* and Cause Unique Dependent Resistance



Mikroorganizmalar vs Antibiyotikler

- Antibiyotik baskısında önce dirençli sonra antibiyotik bağımlı hale gelen mikroorganizmalar.

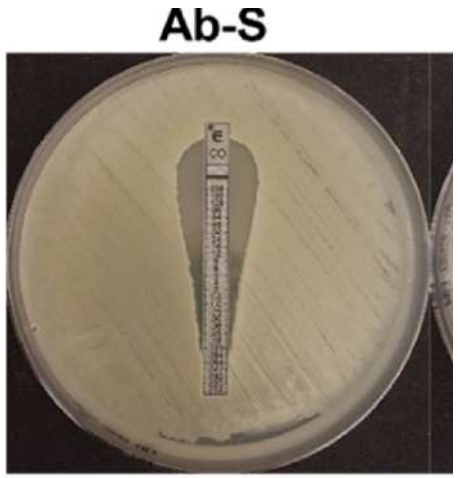
International Journal of
Molecular Sciences

MDPI

Article

Colistin Dependence in Extensively Drug-Resistant *Acinetobacter baumannii* Strain Is Associated with IS*Ajo2* and IS*Aba13* Insertions and Multiple Cellular Responses

Sherley Chamoun [1], Jenny Welander [2], Mihaela-Maria Martis-Thiele [1,3], Maria Ntzouni [4], Carina Claesson [2], Elena Vikström [1] and Maria V. Turkina



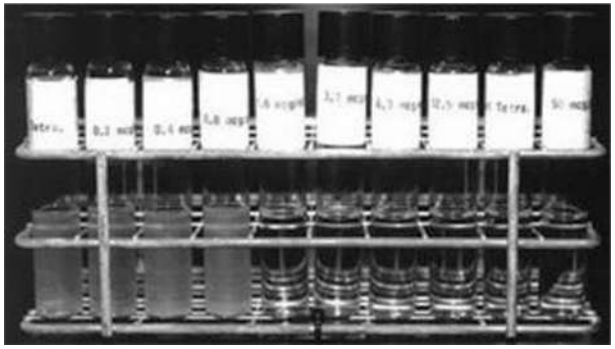
Mikroorganizmalar vs Antibiyotikler

- Antibiyotik baskısında önce dirençli sonra antibiyotik bağımlı hale gelen mikroorganizmalar.
    - Beta-laktam Bağımlılığı
    - Glikopeptid Bağımlılığı
    - Aminoglikozid Bağımlılığı
    - Rifampisin Bağımlılığı
    - Fluorokinolon Bağımlılığı

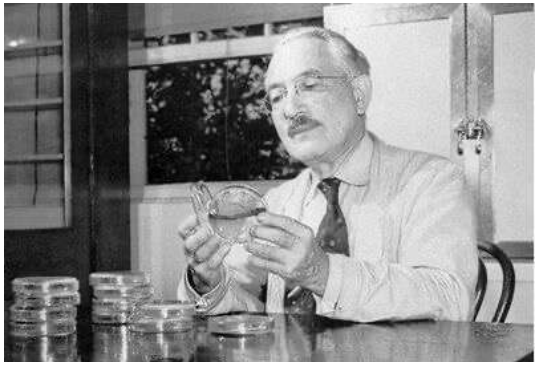
Duyarlılık testlerinin sınır değerleri nasıl belirlenir?

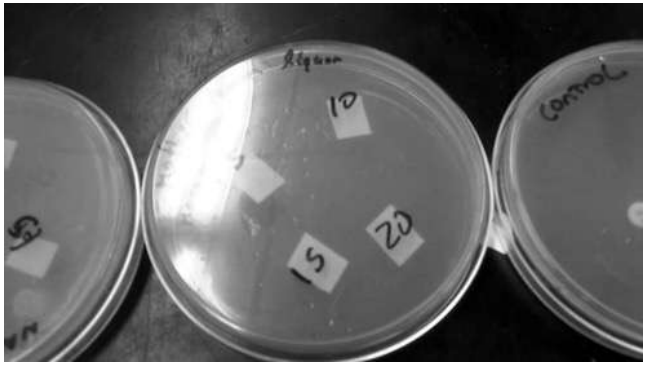
- Sınır değerlerin belirlenmesi, farmakolojik, klinik ve mikrobiyolojik verilerin karmaşık bir analizini gerektirir.

- 1929 “Broth dilution” tekniği ve MIC tespiti



- 1940 “Antimikrobiyal emdirilmiş absorbent kağıtlar





Duyarlılık testlerinin sınır değerleri nasıl belirlenir?

- Sınır değerlerin belirlenmesi, farmakolojik, klinik ve mikrobiyolojik verilerin karmaşık bir analizini gerektirir.

1967

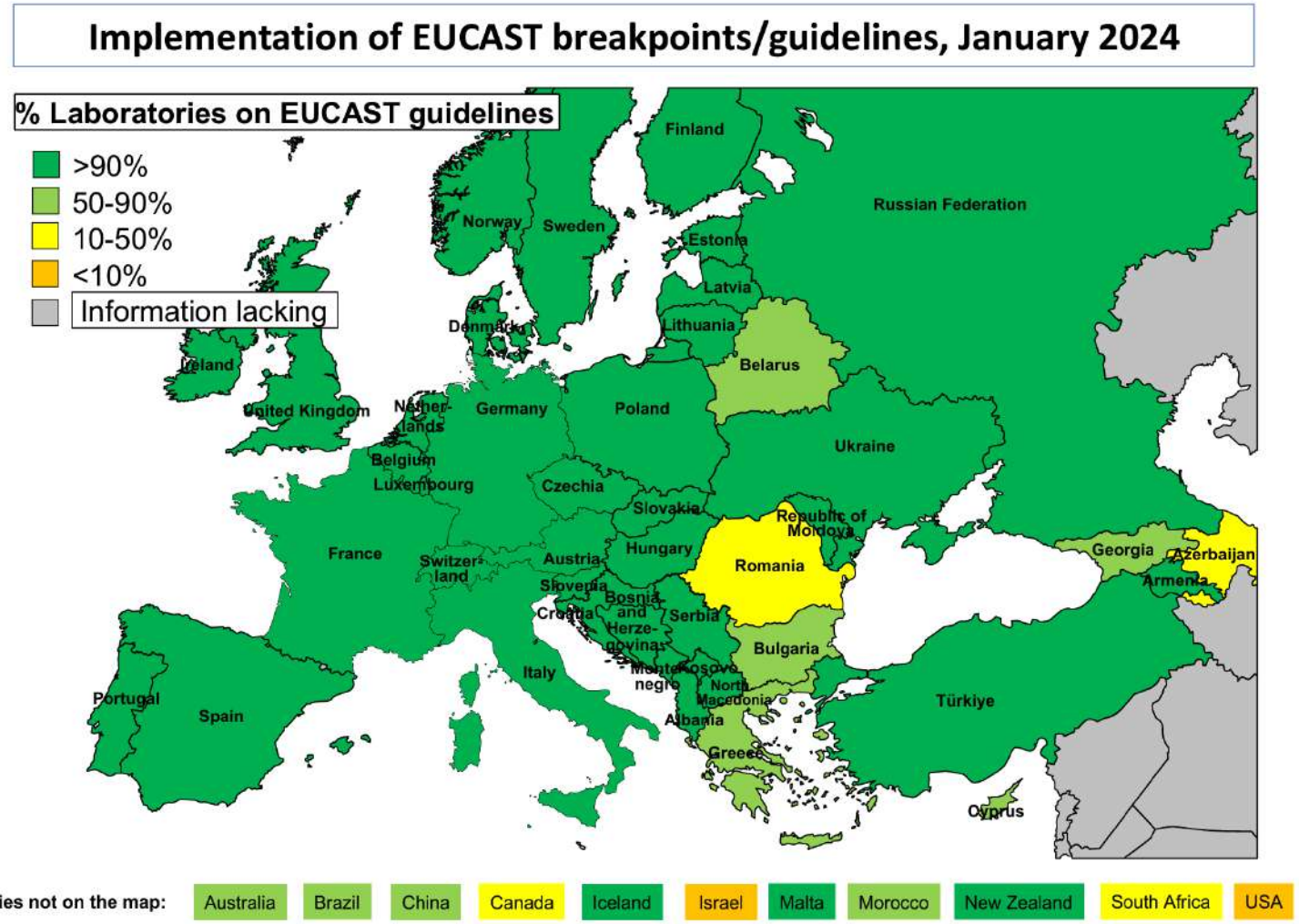
2005

1997 → 2009

EUCAST klinik eşik değerleri Türkiye'de ilk olarak 2014 yılından itibaren kullanılmaya başlanmıştır.

Duyarlılık testlerinin sınır değerleri nasıl belirlenir?

- EUCAST kılavuzunun kullanıldığı ülkeler



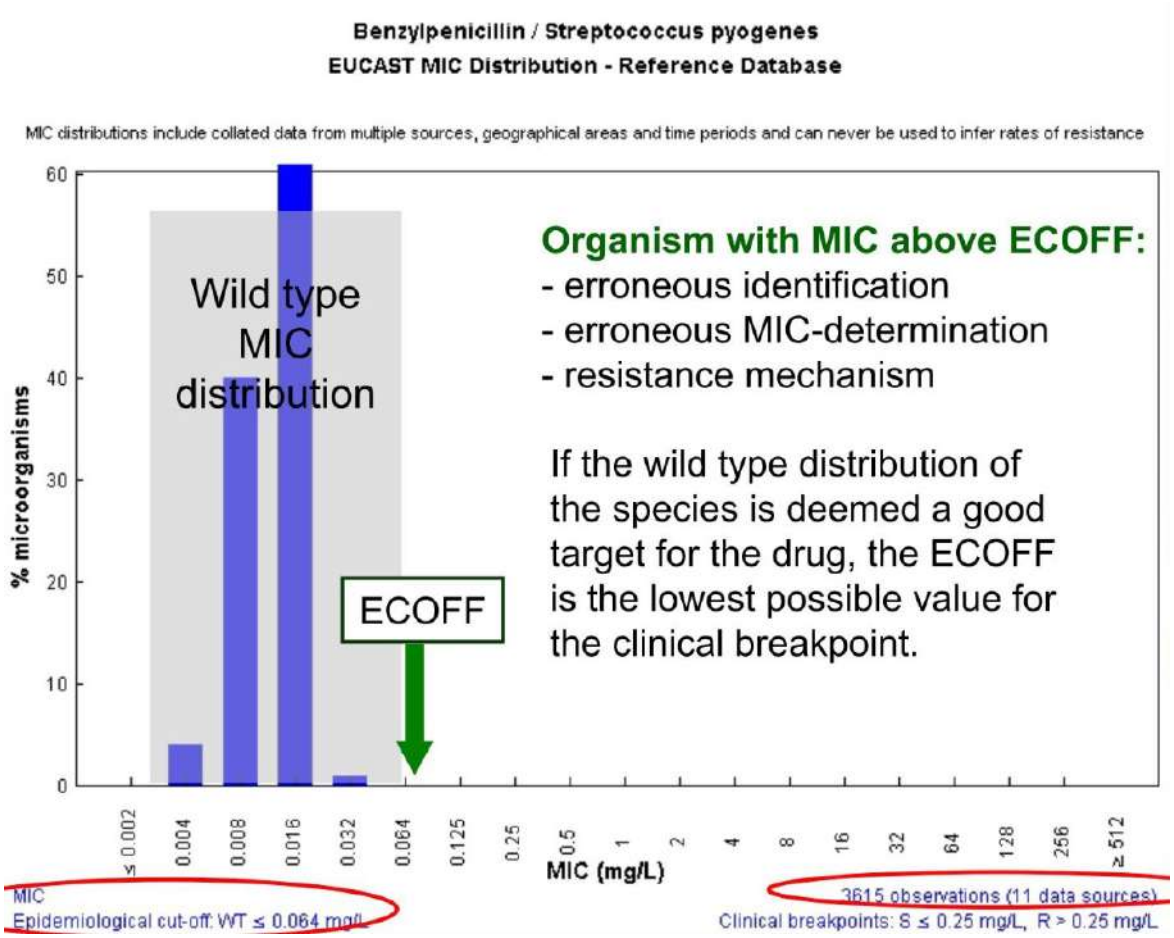
Duyarlılık testlerinin sınır değerleri nasıl belirlenir?

- Benzersiz eşik değer belirleme yöntemi ile EUCAST baskınlığı artıyor
- Epidemiolojik Kesme Değerleri (ECOFF) hesaplaması, antimikrobiyal duyarlılık testlerinde çok önemli bir rol oynar.

Fig. 9.3 Trends in AST guidelines used by CAESAR EQA participating laboratories, 2013–2017

ECOFF (Epidemiological Cutoff Value)

- ECOFF, bir antibiyotiğe karşı doğrudan direnç mekanizması olmayan (doğal popülasyona ait) mikroorganizmaların en yüksek minimum inhibitör konsantrasyonu (MIC) değerini ifade eder.



ECOFF (Epidemiological Cutoff Value)

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

How to: ECOFFs—the why, the how, and the don'ts of EUCAST epidemiological cutoff values

Gunnar Kahlmeter [1,*], John Turnidge [2]

[1] Klinisk Mikrobiologi, Centrallasarettet, Växjö, Sweden
[2] Adelaide Medical School, University of Adelaide, Adelaide, Australia

- EUCAST veritabanı, 1950'lerden bu yana toplanan izolatların verilerini içerir.
  - Toplum sağlığı merkezlerinden ya da halktan alınan örnekler
  - Tarım ve hayvancılık sektöründen alınan örnekler
  - Çevresel suşlar, doğrudan doğal ortamlardan (toprak, su kaynakları vb.)
  - Antibiyotik kullanımının yaygınlaşmadığı dönemlerde toplanmış olan izolatlar

ECOFF (Epidemiological Cutoff Value)

- ECOFF verileri

MIC EUCAST

Login

MIC distributions for Klebsiella pneumoniae, 2024-09-27

Species: Klebsiella pneumoniae (Method: MIC)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
Amikacin	0	0	0	0	0	0	0	14	373	5348	4478	566	386	612	104	21	6	25	77	15	12010	8	2 - 8
Amoxicillin-clavulanic acid (fixed)	0	0	0	0	0	0	0	0	0	543	704	334	175	77	46	33	47	105	86	2	2150	ID	
Ampicillin	0	0	0	0	0	0	2	1	5	44	118	174	655	2821	10665	609	126	863	99	10	16182	ID	0.06 - 256
Ampicillin-sulbactam (fixed)	0	0	0	0	0	0	0	0	2	10	24	4	5	3	0	0	2	0	0	1	50	ID	
Ampicillin-sulbactam (ratio)	0	0	0	0	0	0	6	4	24	836	653	1659	727	273	299	655	22	167	88	3	5413	ID	
Aztreonam	0	0	0	0	83	127	79	25	10	4	8	3	7	5	12	53	0	0	0	1	416	ID	
Aztreonam-avibactam	0	0	0	2051	7615	7938	4514	2651	938	285	127	54	4	6	3	7	6	0	0	5	26199	0.5	0.25 - 1
Cefadroxil	0	0	0	0	0	0	0	0	0	0	0	0	21	31	12	0	0	0	0	1	64	ID	
Cefalexin	0	0	0	0	0	0	0	0	0	0	0	4	44	7	9	0	0	0	0	1	64	ID	
Cefaloridine	0	0	0	0	0	0	0	0	2	32	14	2	4	0	10	0	0	0	0	1	64	ID	
Cefalothin	0	0	0	0	0	0	0	0	6	38	150	229	93	48	48	118	3	1	4	4	738	(16)	4 - 32
Cefazolin	0	0	0	0	0	0	0	0	5	71	82	17	8	6	12	1	5	1	0	5	208	4	1 - 8
Cefepime	0	0	35	170	1940	1980	513	278	168	150	138	143	176	243	283	323	352	215	723	32	7830	0.125	0.06 - 0.25
Cefepime-clavulanate	0	0	0	4	13	30	10	2	0	0	0	0	0	0	0	0	0	0	0	2	59	ID	
Cefepime-enmetazobactam-8	0	0	13	151	2172	1217	322	204	113	48	25	25	31	19	32	52	68	0	0	8	4492	0.125	0.06 - 0.125

© MIC EUCAST 2024.

ECOFF (Epidemiological Cutoff Value)

- Örneğin, *E. coli* ve gentamisin üzerine yapılan bir çalışmada, 82 farklı katkı ile toplanan 80.000'e yakın MIC değeri analiz edilmiştir. ECOFF değerlerinin güvenilir olması için bu tarz büyük veri setleri gereklidir.

MIC EUCAST

Login

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
Enterobacter agglomerans	0	0	0	0	0	1	5	43	5	0	0	0	0	0	0	0	0	0	0	1	54	ID	
Enterobacter cloacae	1	0	1	2	13	77	292	1178	3642	1383	159	87	124	91	19	103	50	52	60	34	7334	2	0.5 - 2
Enterococcus avium	0	0	0	0	0	0	0	1	0	9	7	2	1	0	0	0	0	0	0	1	20	-	
Enterococcus casseliflavus	0	0	0	0	0	0	0	0	0	0	12	8	0	0	0	0	0	0	0	1	20	-	
Enterococcus durans	0	0	0	0	0	0	0	0	0	1	3	10	6	0	0	0	0	0	0	1	20	-	
Enterococcus faecalis	0	0	0	0	0	2	2	7	18	37	73	156	880	1761	704	61	57	69	686	25	4513	64	32 - 128
Enterococcus faecium	0	0	0	0	0	0	0	1	5	14	83	555	1147	575	93	13	11	46	320	24	2863	32	16 - 64
Enterococcus gallinarum	0	0	0	0	0	0	0	0	0	0	6	8	6	0	0	0	0	0	0	1	20	-	
Enterococcus hirae	0	0	0	0	0	0	0	0	1	4	50	99	253	151	28	0	0	0	2	9	588	32	4 - 32
Enterococcus lactis	0	0	0	0	0	0	0	0	0	0	0	4	16	0	0	0	0	0	0	1	20	-	
Enterococcus mundtii	0	0	0	0	0	0	0	0	0	0	0	4	7	0	0	0	0	0	0	1	11	-	
Enterococcus raffinosus	0	0	0	0	0	0	0	0	0	4	12	1	3	0	0	0	0	0	0	1	20	-	
Escherichia coli	0	0	4	6	25	49	522	8516	32023	20499	3360	799	1362	3725	6360	512	138	166	70	82	78136	2	1 - 2
Escherichia coli ATCC 25922	0	0	0	0	0	0	0	1	63	34	7	0	0	0	0	0	0	0	0	2	105	ID	
Escherichia coli NCTC 13846	0	0	0	0	0	0	0	0	54	58	8	0	0	0	0	0	0	0	0	2	120	ID	

ECOFF (Epidemiological Cutoff Value)

- Direnç ve Duyarlılığın Ayrımı: ECOFF değerleri, antibiyotiğe dirençli olan izolatları tespit etmek için temel bir referans noktası sağlar.
  - ECOFF'un altında kalan bakteriler, doğal popülasyona aittir ve antibiyotiğe karşı dirençli değildir.
  - ECOFF'un üzerinde kalan bakteriler ise potansiyel olarak direnç mekanizmasına sahip olabilir.

- ECOFF, klinik kırılma noktası (clinical breakpoint) ile aynı anlama gelmez.
  ECOFF, yalnızca doğal popülasyonları belirlemeye odaklanırken,
  klinik kırılma noktaları hem farmakokinetik (PK) hem de farmakodinamik (PD) verileri dikkate alarak klinik etkinliği değerlendirir.

ECOFF (Epidemiological Cutoff Value)

- CLSI'nin antimikrobiyal duyarlılık testlerinde belirlediği eşik değerler (breakpoints), genellikle klinik izolatların sonuçlarına dayanır.
- Bu çalışmalar, çeşitli klinik izolatlar üzerinde elde edilen verileri, farmakokinetik ve farmakodinamik verilerle birleştirir.
- Klinik sonuçlar ve tedavi başarısına odaklanır.

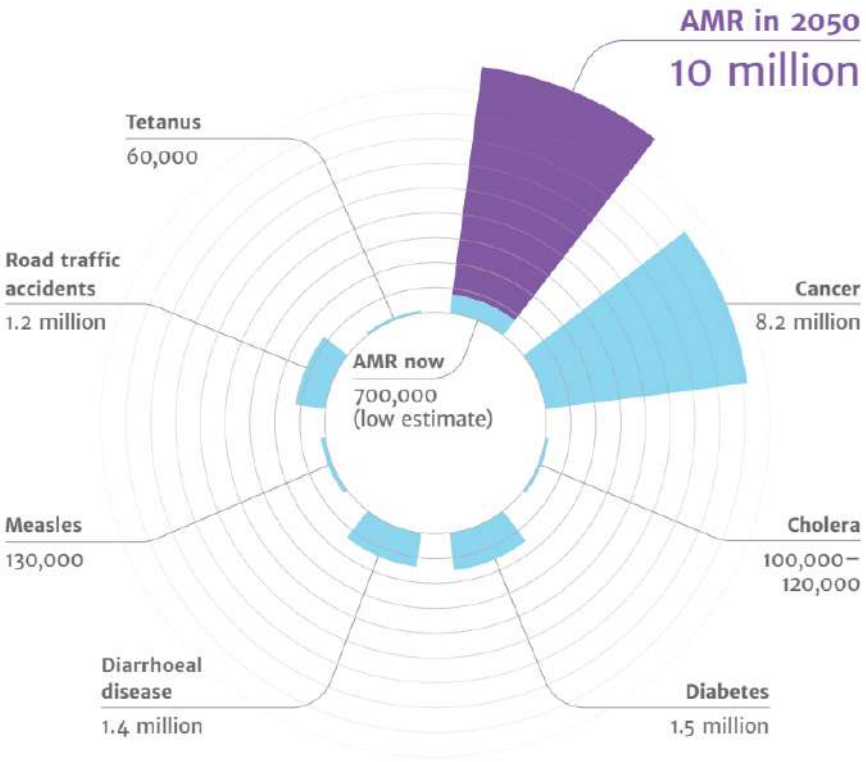
EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

CLINICAL AND LABORATORY STANDARDS INSTITUTE

EUCAST vs. CLSI

Tehlike kapımızda!

- 2050 yılında beklenen ölüm yılda 10 milyon kişi.



Direnci Nasıl Yavaşlatabiliriz?

3. Türk-Alman Transplantasyon Günleri, 2015

Trinad Chakraborty
Institute for Medical Microbiology
German Centre for Infection Research Justus-Liebig-University Giessen Germany

Direnci Nasıl yavaşlatabiliriz?

Etkin Antimikrobiyal tedavi için daha fazla veri

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

DZIF

Diagnostic Report: *Acinetobacter baumannii*

Isolate number	113	Date isolated	2012-09-04
Origin	Throat swab	Pat. ID	XXXX-XXGiXXX

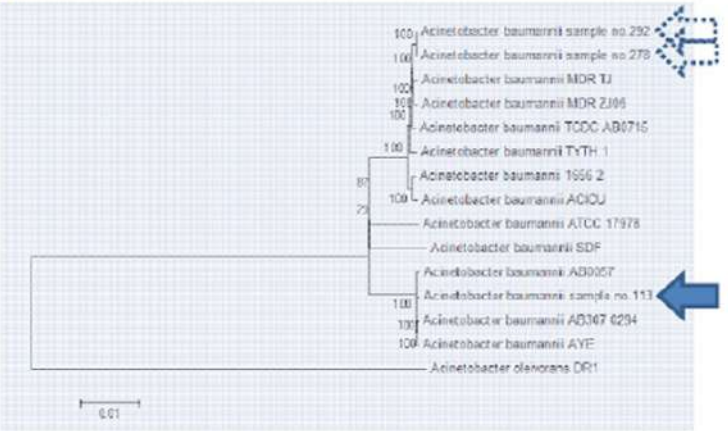
MLST type

1

Resistance genes	Antibiotic group	Location
bla_{oxa-72}	Beta-Lactam	Plasmid 1
bla_{oxa-66}	Beta-Lactam	Chromosome
aadA1	Aminoglycoside	Chromosome
sul1	Sulfonamid	Chromosome

Virulence genes detected	Location
Type IV secretion system	Plasmid 2

Phylogeny



Assessment

CAVE: Strain with two carbapenemase genes detected. Classified as multiresistant. Phylogeny relation traced to known outbreak strain AB0057. No significant relation to other clinical isolates in recent time frame.
Hygiene: Single patient isolation recommended.
Treatment options: Tetracyclin, Tigecyclin, Colistin (inhalative)