A 3D scientific illustration showing a large, blue, rod-shaped bacterium with numerous red flagella on the left. It is positioned near a host cell, which is depicted with a red, textured surface and internal organelles. The bacterium appears to be interacting with the host cell, possibly through a pore or channel. The background is a dark, teal color with some faint, glowing structures.

İnfeksiyonun Erken Adımları: İnvazyon, Serum Direnci ve Virülans Odaklı Bağışıklıktan Kaçış Mekanizmaları

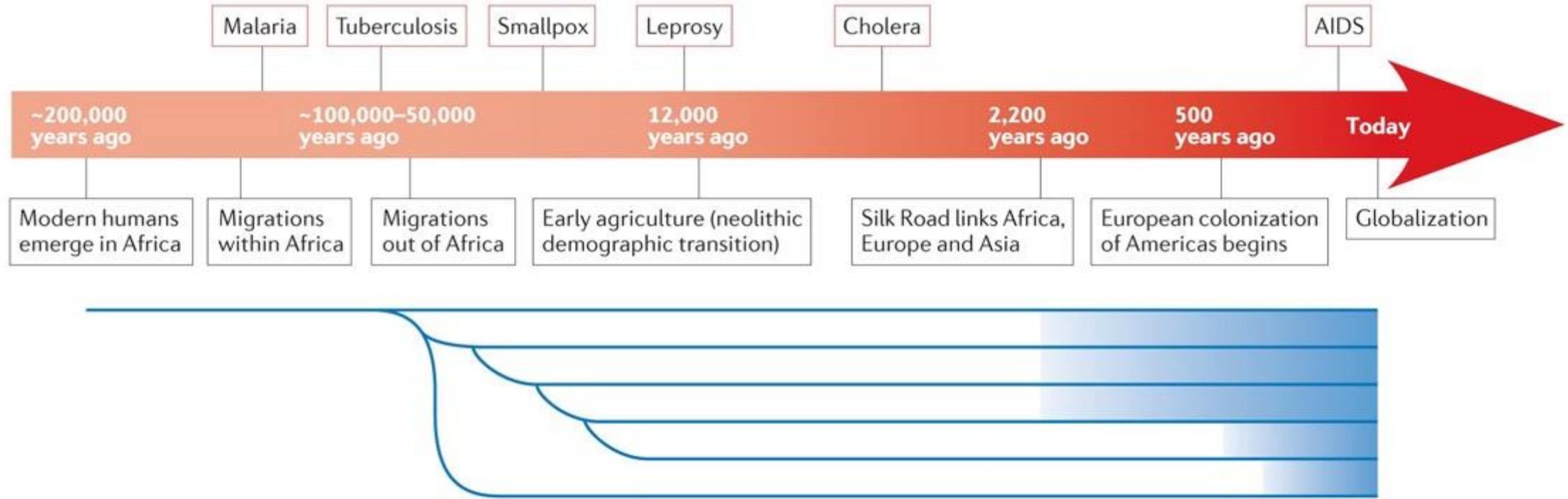
Prof. Dr. Füsün CAN

Koç Üniversitesi Tıp Fakültesi

Tıbbi Mikrobiyoloji AD

Koç Üniversitesi İş Bankası Enfeksiyon Hastalıkları Merkezi (KUISCID)

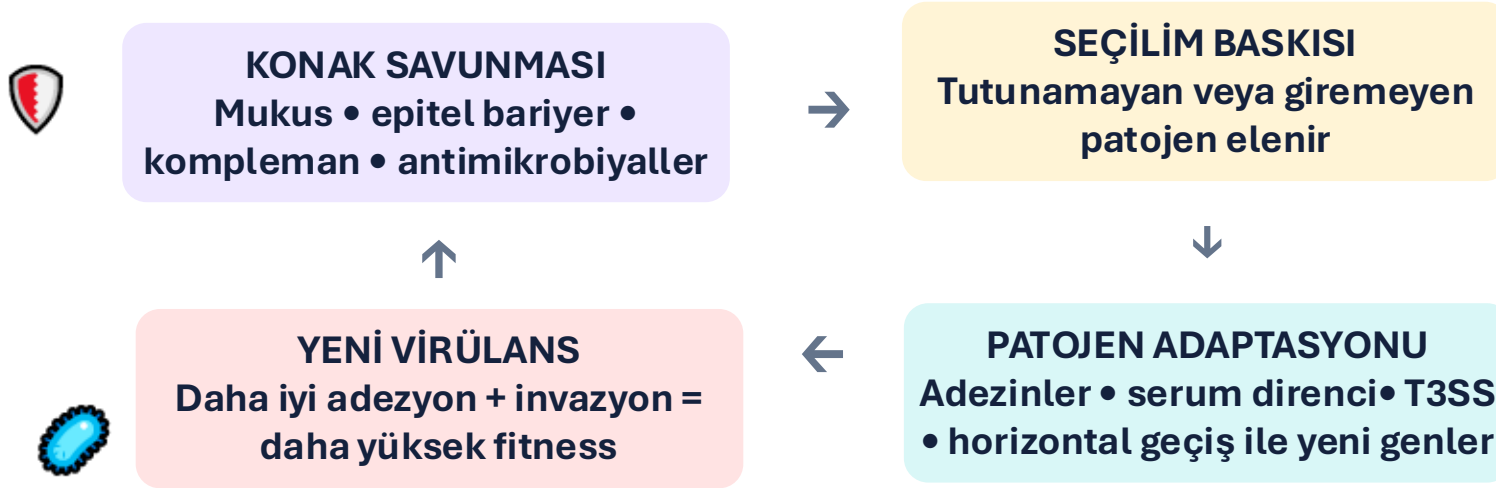
Patojenlerin ve İnsanların Ortak Evrimi ve Enfeksiyonlar



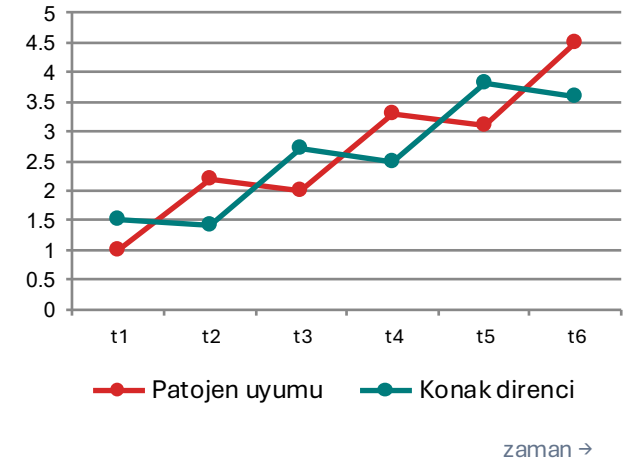
Nature Reviews | **Genetics**

İnsan–Patojen Ortak Erim Süreci

“Attack–defense” döngüsü: konak savunması güçlendikçe, patojenin adezyon–invazyon ve kaçış stratejileri güçlenir



Basitleştirilmiş arms race grafiği



Bakterilerde hızlı adaptasyon;
virülans genleri patojenite
adaları/plazmidlerle yayılabilir.

Ko-evrim “tek yönlü” değildir: hem konak hem patojen genotipleri,
karşı tarafın baskısına göre seçilir.

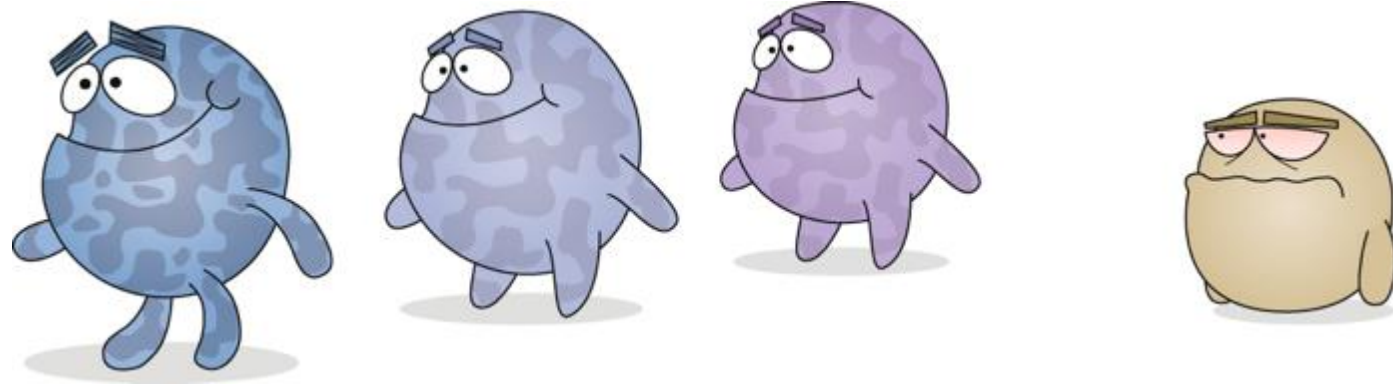
Bakterilerin Yaşam Stratejisi: Evrimsel sürecini başlat, adapte ol yada yok ol



Niye virülanlar???



- Küresel Antibiyotik Direnci Sorunu
- Virülansı artmış Klonlar



Virülans mekanizmaları

- Bağlanma
- Toksinler
- Dış membran proteinleri
- Demir alım
- Sekresyon sistemleri
- Quorum sensing

- Mutasyonlar
- Horizontal gen transferi

Antivirülans Tedavi ile ilgili çalışmalar artıyor

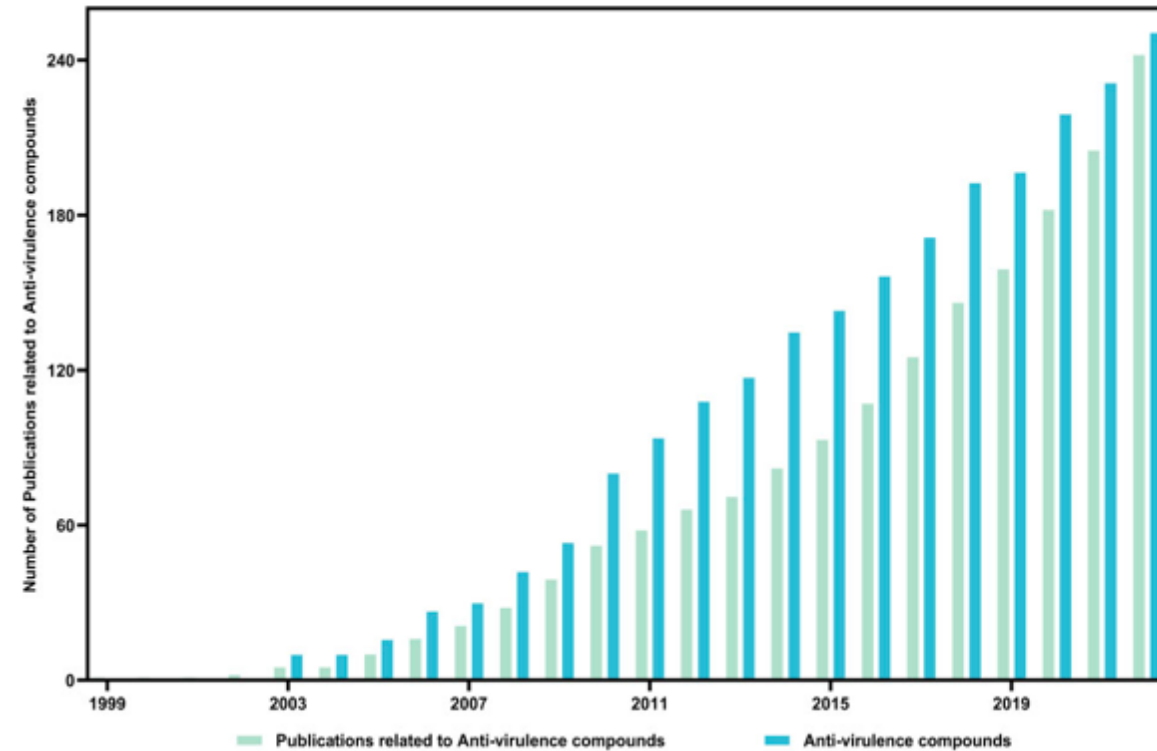
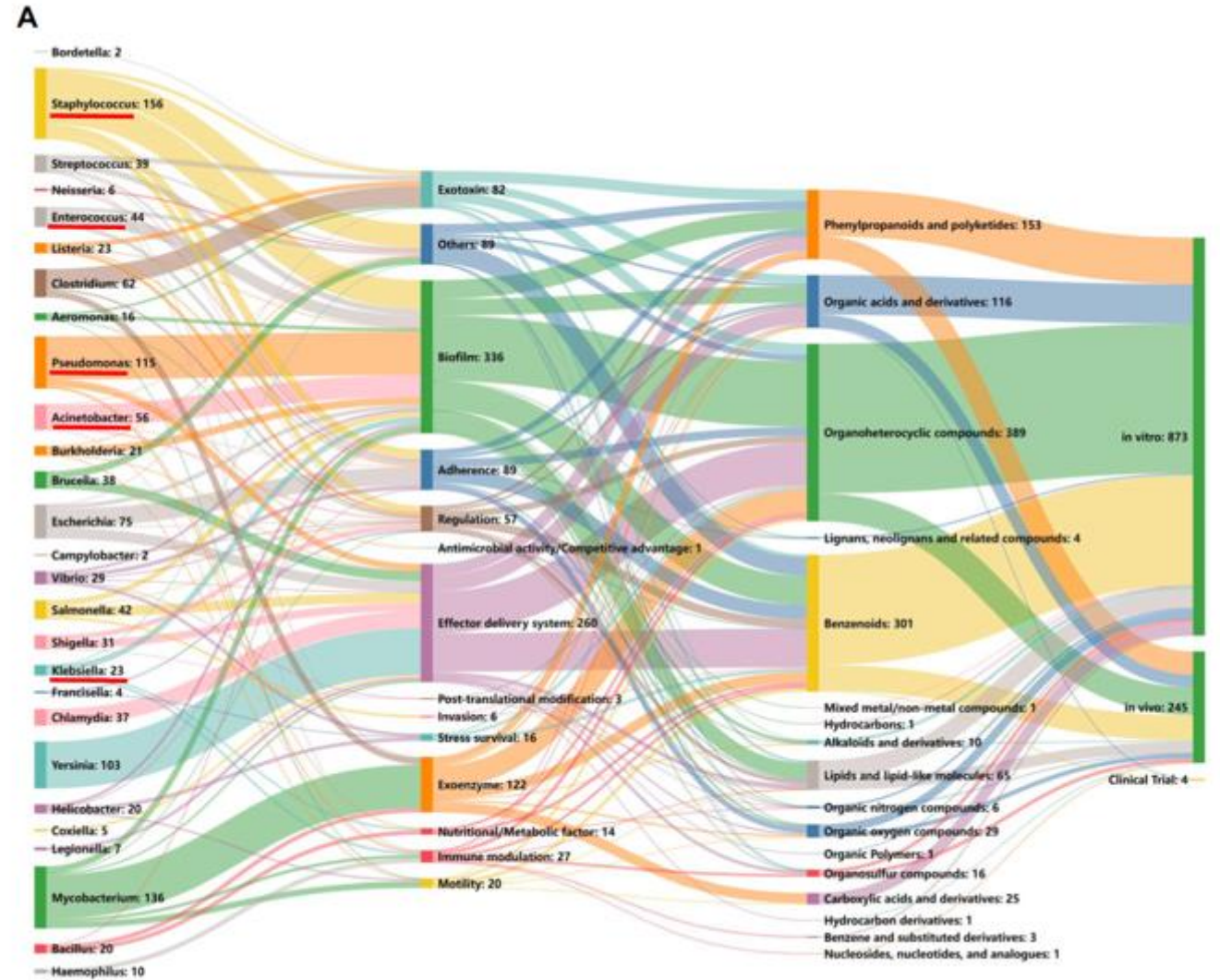


Figure 1. Overview of the current resources for the exploration of anti-virulence compounds.



Zhou S, ve ark: Nucleic acid research, 2024

Bakteriyel virülans klinikte ne anlama geliyor

- Aynı tür farklı klinik yanıt olur mu?
 - Düşük virülans daha hafif klinik
- Artmış virülans mortaliteyi artırır mı?
- Tedavide farklı protokoller gerekir mi?
 - Daha agresif tedavi
- Genetik virülans fenotipe nasıl yansıyor?
- Virülans faktörlerini hedef alan tedavi protokolleri olabilir mi?
 - FDA onayı alan ürünler var

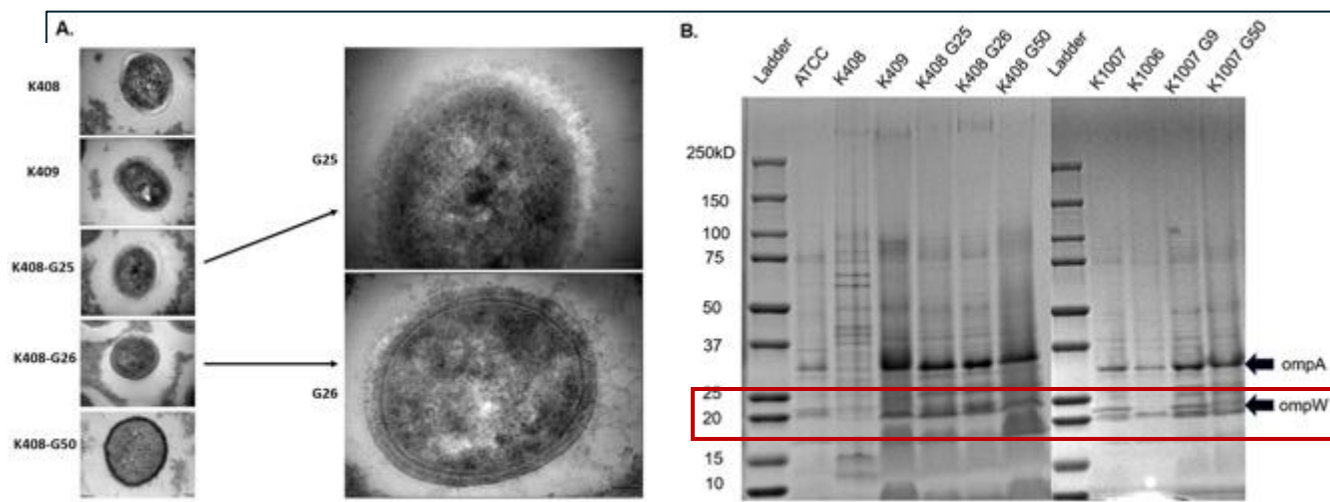
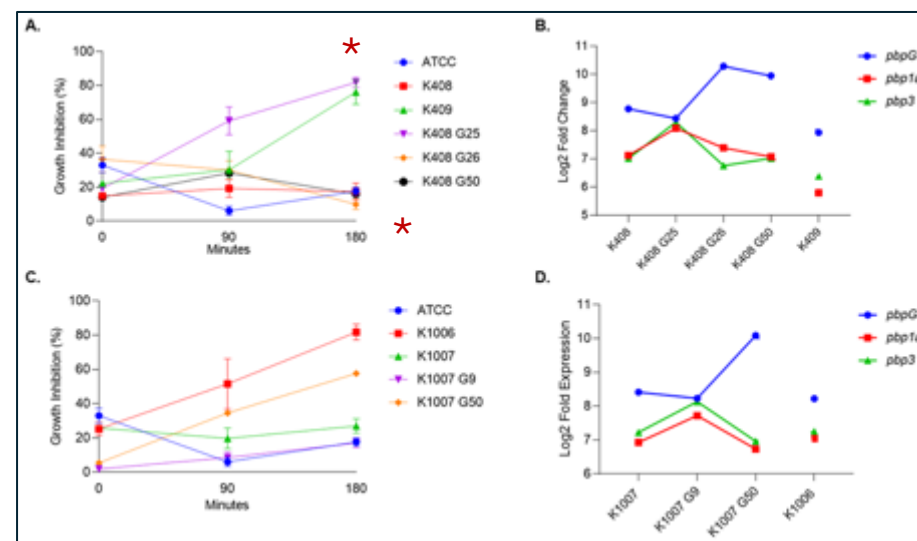
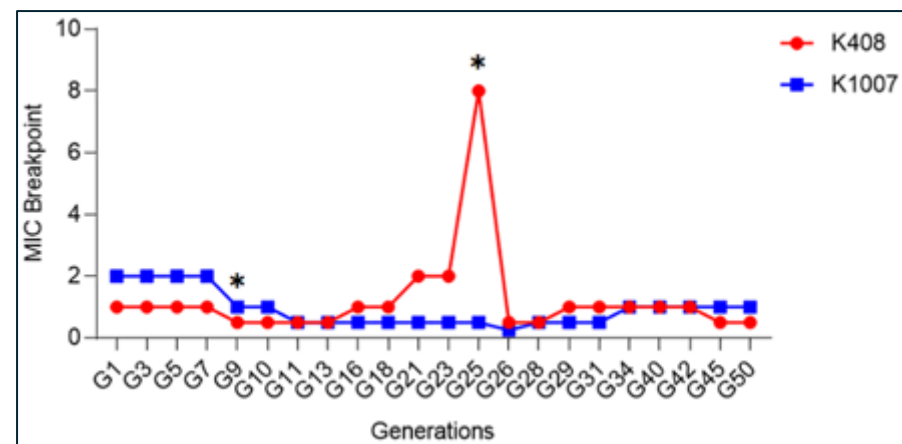
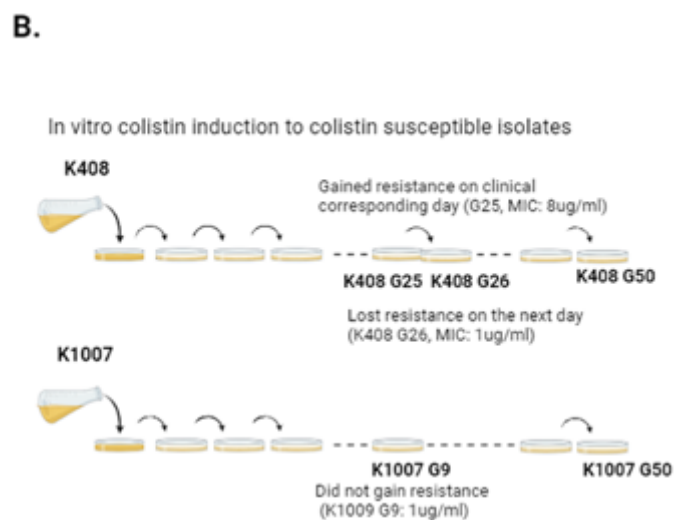
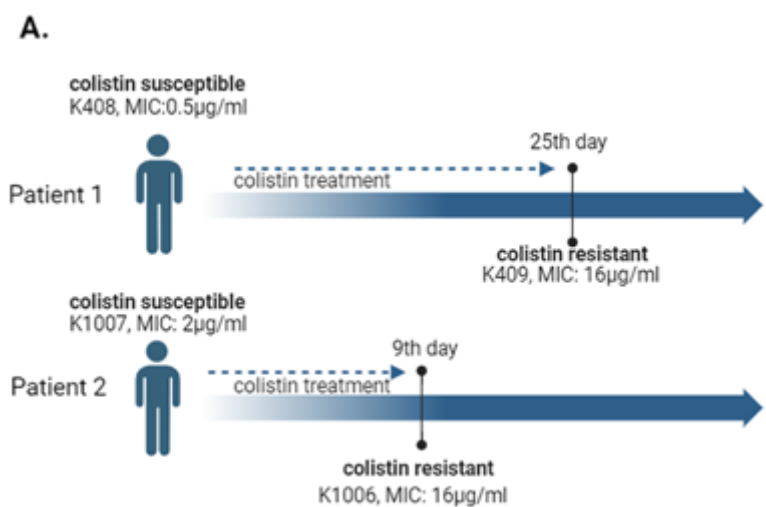
Dirençli hipervirü lent bakteriler güç kaybediyor mu?

- ❖ In vitro çalışmalarda bakteri ve antibiyotik tipine göre değişiyor
- ❖ Klinik çalışma eksikliği nedeniyle klinik yansımaları bilmiyoruz
- ❖ İnvazyon kapasitesini bilmiyoruz.

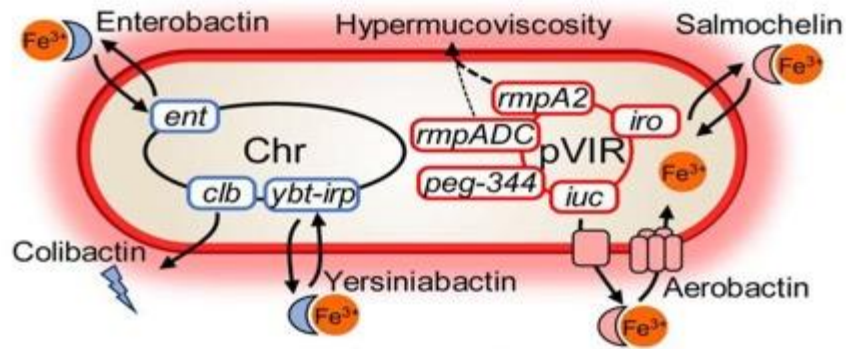
RESEARCH ARTICLE

Resensitization to colistin results in rapid and stable recovery of adherence, serum resistance and ompW in *Acinetobacter baumannii*

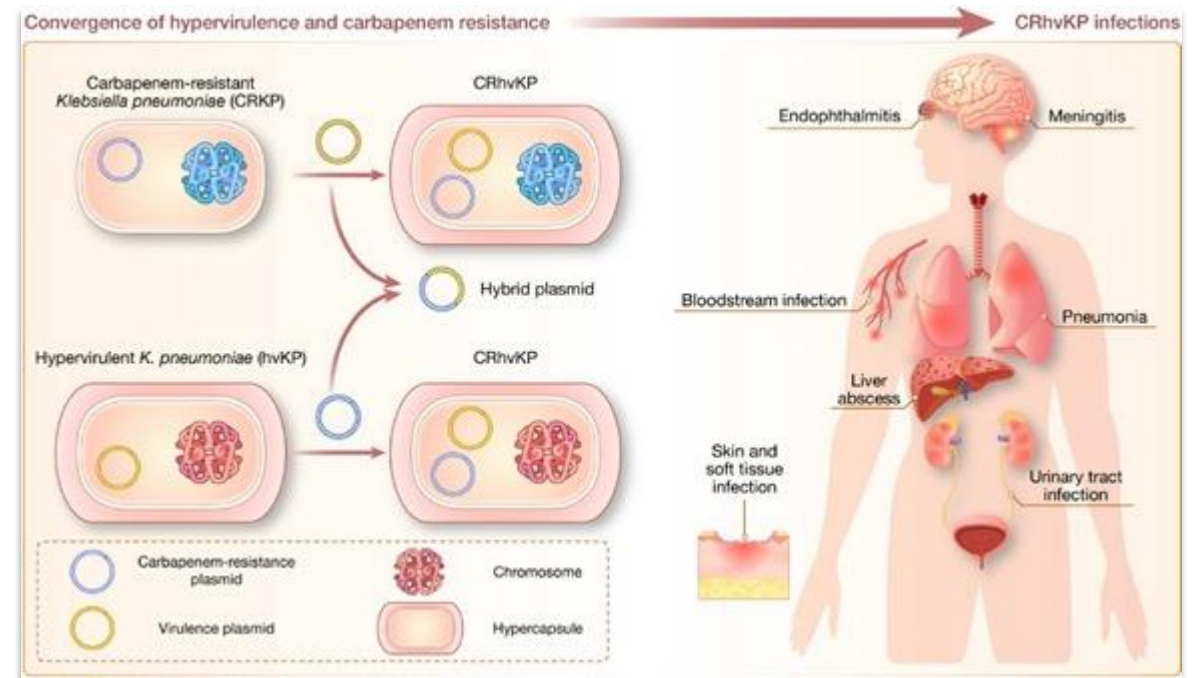
Jale Borrali^{1,2}, Cansel Vatandaş², Gulin Ozcan^{1,2}, Siran Keske², Sirin Menekse², Mehmet Gonen^{2,3}, Fusun Can^{1,2*}



Hipervirülan K.pneumoniae (HvKp) ve Karbapenem Dirençli HvKp



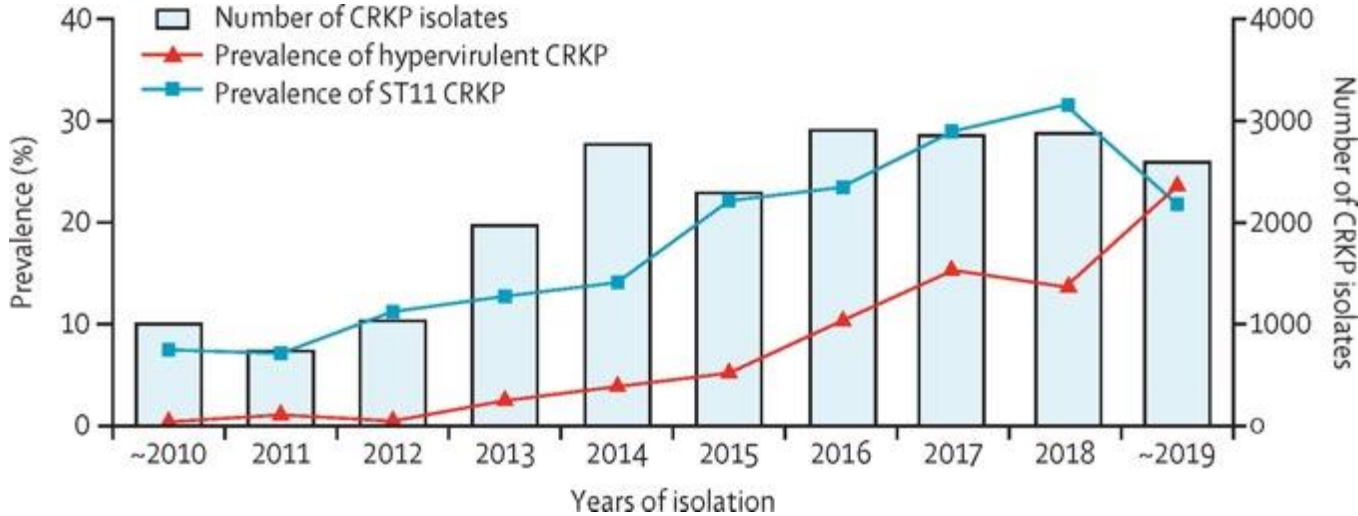
Convergence of CrKp to HvKp



Feature	CKp	HvKp
Capsule	Thin	Very thick
Virulence factors	Rare	Common
Resistance profile	High	Low, but increasing
Source	Nosocomial	Community-acquired
Infected	Immunocompromised	Healthy individuals with no comorbidities

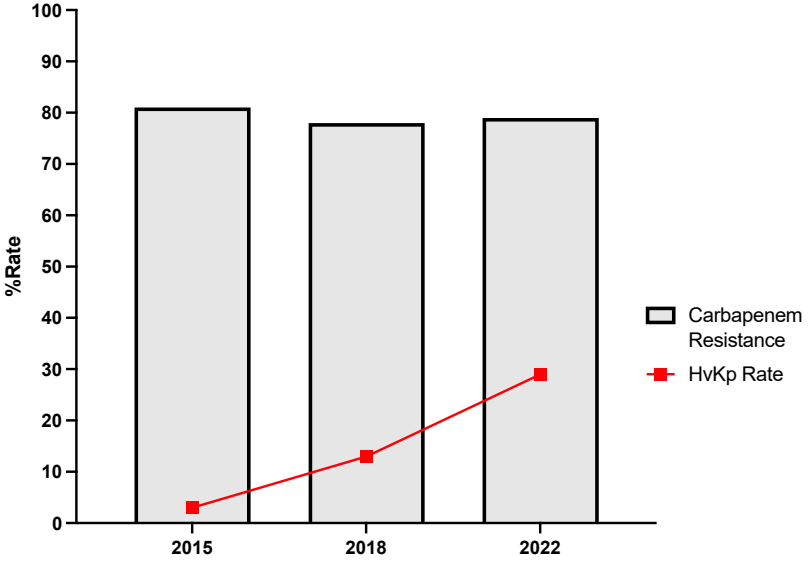
Global and Regional Prevalence of HvKp

Global evolution and geographic diversity of hypervirulent carbapenem-resistant *Klebsiella pneumoniae*



Wu Y, et al. *Lancet Infectious Dis* 22 (6): 761-762,2022

Carbapenem-resistance and evolution of HvKp in Turkiye

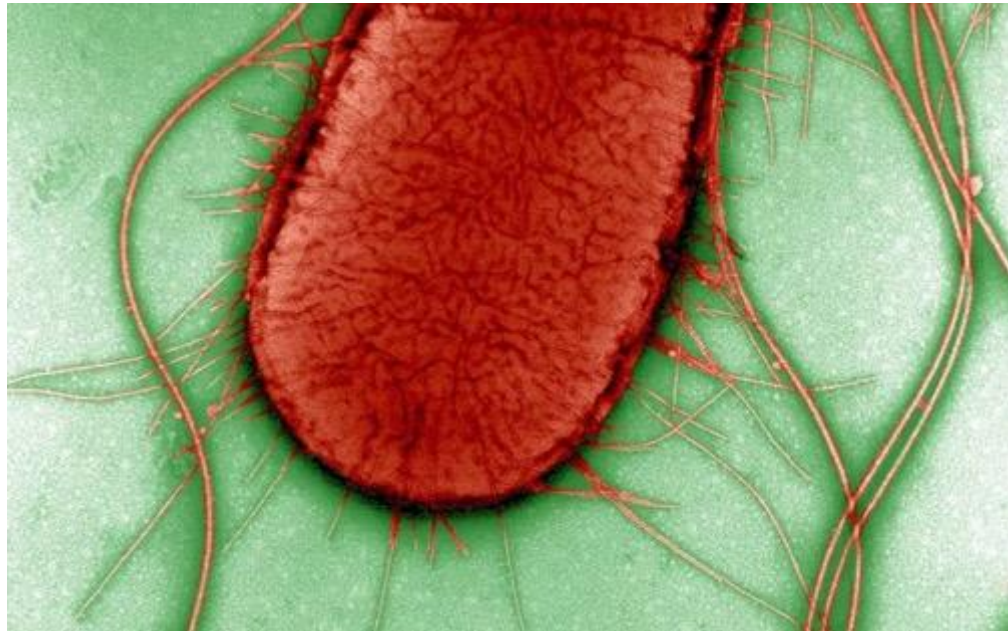


Can F, et al. Unpublished Data

Global emergence of a hypervirulent carbapenem-resistant *Escherichia coli* ST410 clone

[Xiaoliang Ba](#), [Yingyi Guo](#), [Robert A. Moran](#), [Emma L. Doughty](#), [Baomo Liu](#), [Likang Yao](#), [Jiahui Li](#), [Nanhao He](#), [Siqun Shen](#), [Yang Li](#), [Willem van Schaik](#), [Alan McNally](#), [Mark A. Holmes](#) & [Chao Zhuo](#)

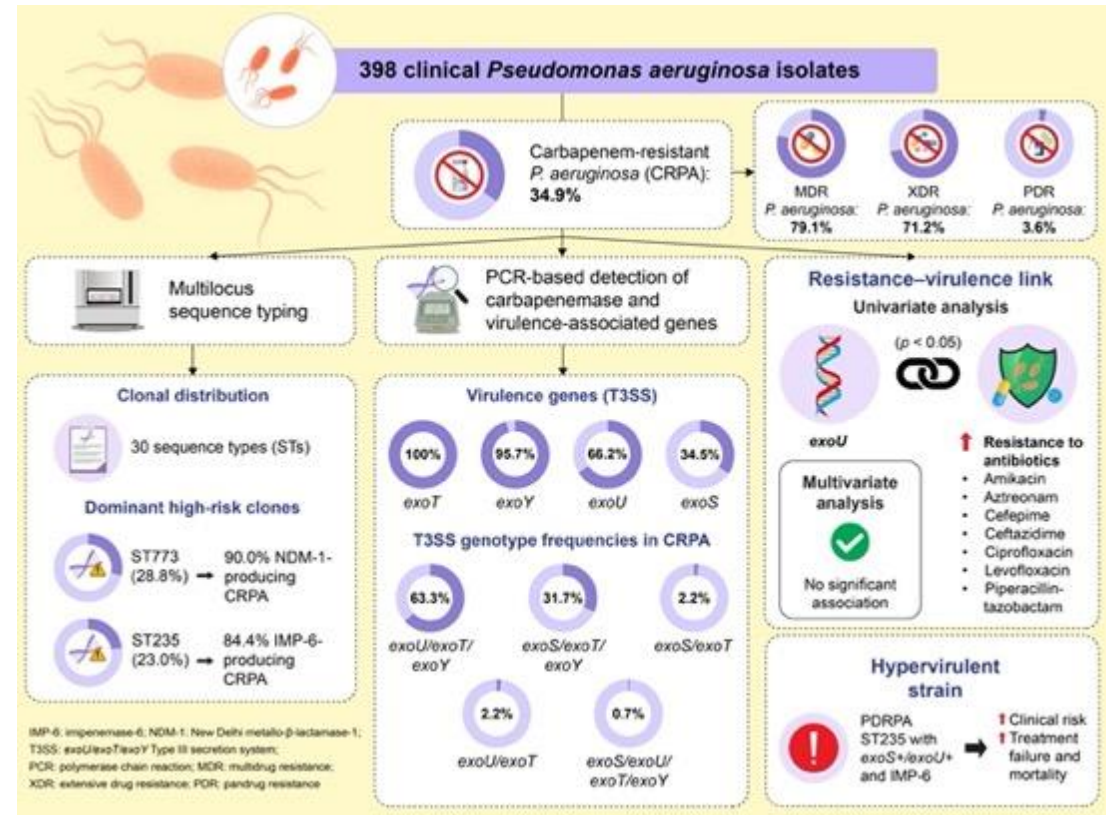
Nature Communications **15**, Article number: 494 (2024) | [Cite this article](#)



K1 kapsüllü carbapenem dirençli E.coli yayılıyor

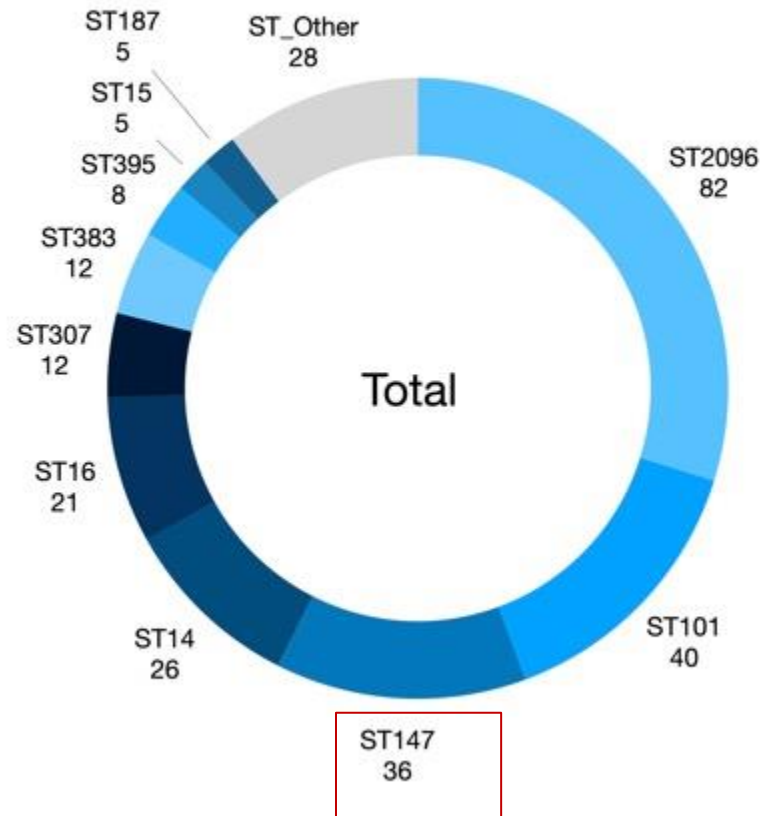
Coexistence of Multidrug Resistance and Hypervirulence-Associated Genes in Clinical Carbapenem-Resistant *Pseudomonas aeruginosa*

[Hye Hyun Cho](#)¹, [Yumi Park](#)²

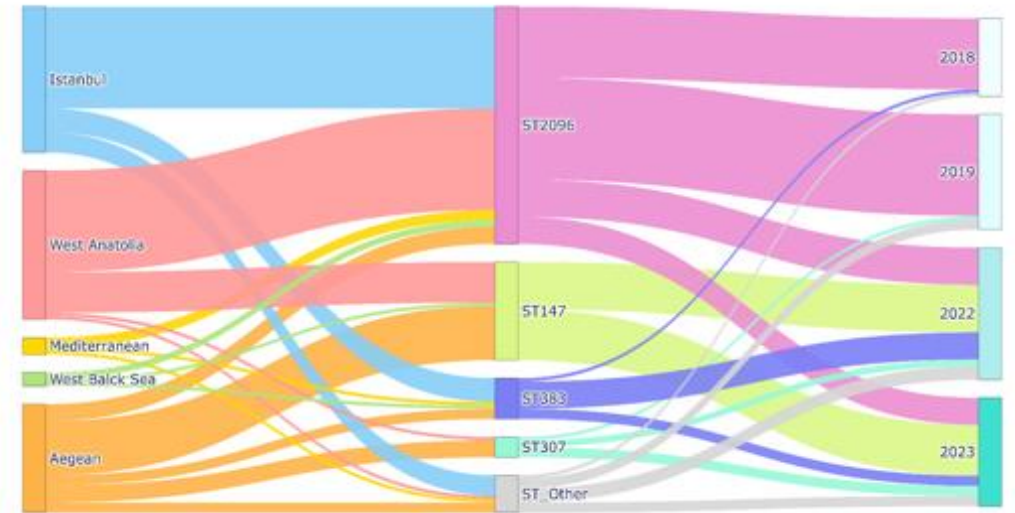
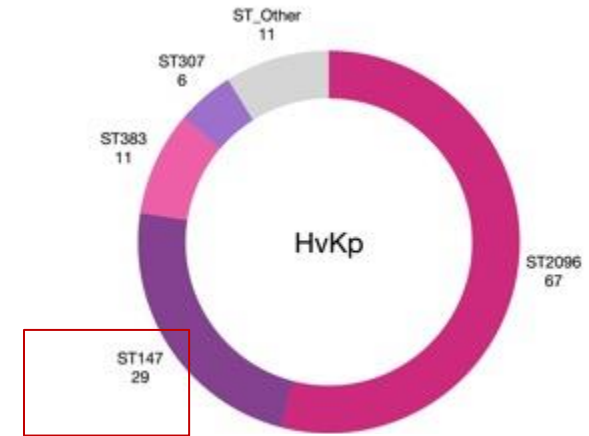


K.pneumoniae ST Types across years in Turkiye

CRKp



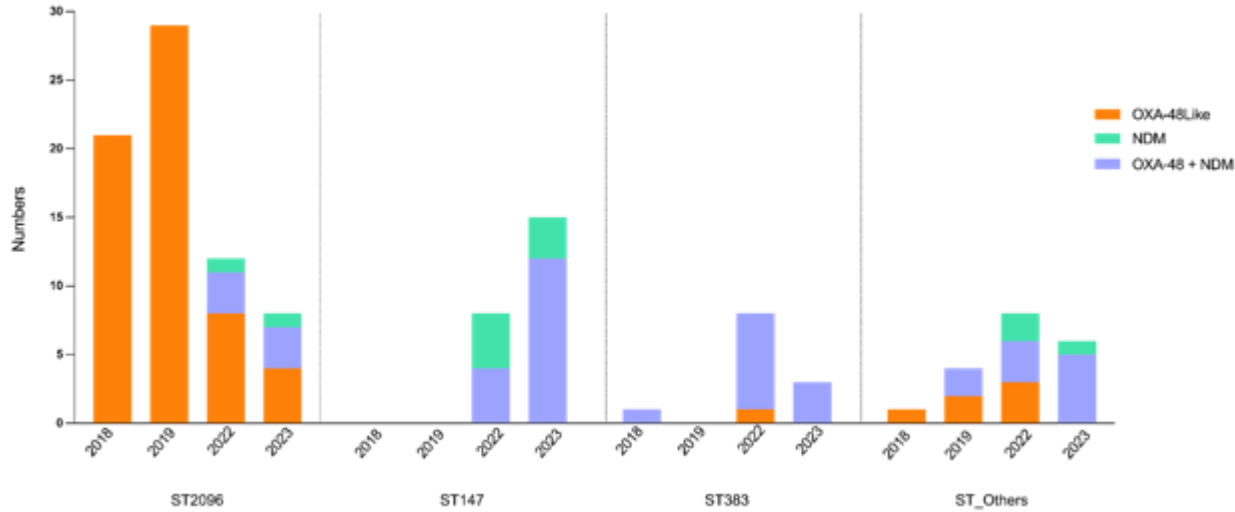
CR-HvKp



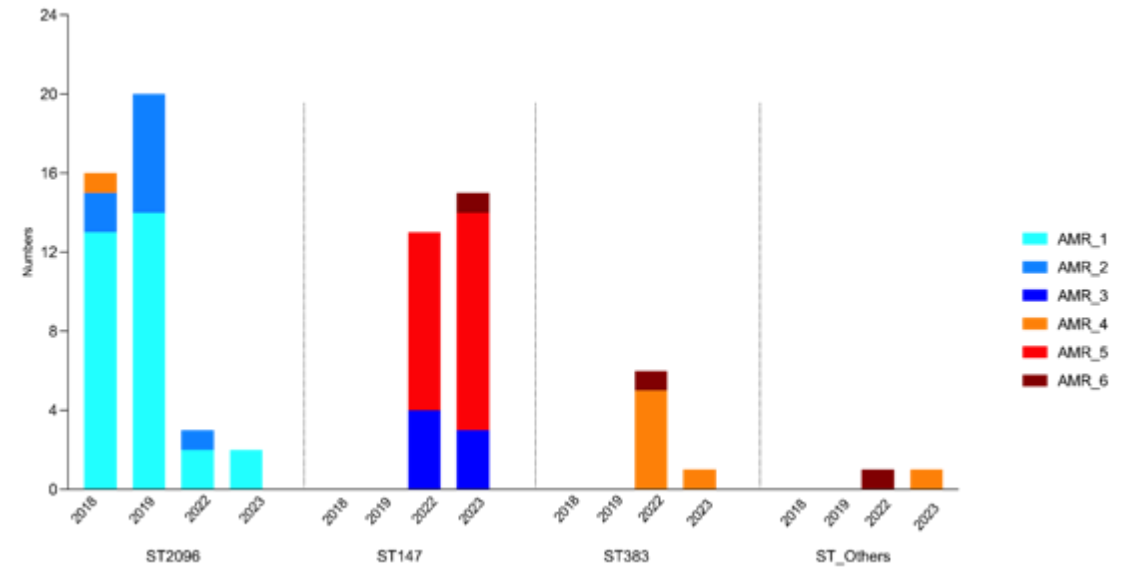
Regional distribution of sequence types in hypervirulent *Klebsiella pneumoniae*.

HvKp ST Types: Carbapenemases and Antibiotic Resistance score

Carbapenemases



AMR Score



AMR_1: *aac(6')*_AGly, *aadA*_AGly, *blaCTX*, *blaOXA*, *dfrA*_Tmt, *gyrA*_Quin, *ompK36*_Carb, *tet*_TetCyc.

AMR_2: AMR_1 + *pmrB*_Col.

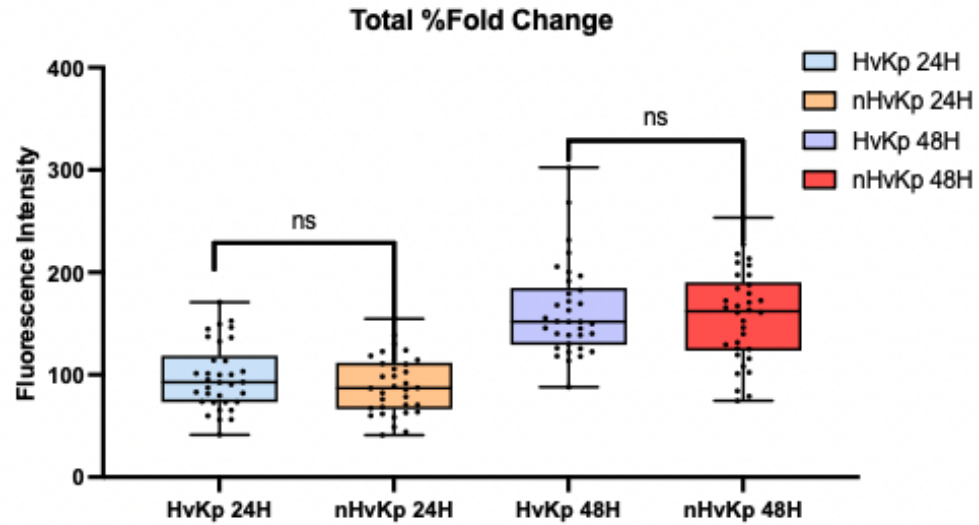
AMR_3: *aac(6')*_AGly, *aadA*_AGly, *aph(3')*_AGly, *blaCTX*, *blaNDM*, *dfrA*_Tmt, *gyrA*_Quin, *ompK36*_Carb, *pmrB*_Col, *qnrB*_Quin.

AMR_4: AMR_3 + *blaOXA*, *tet*_TetCyc.

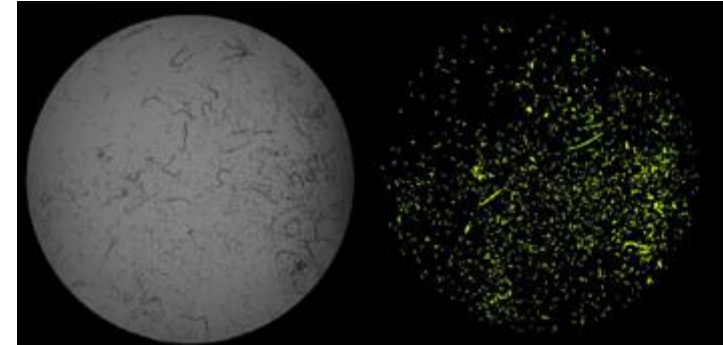
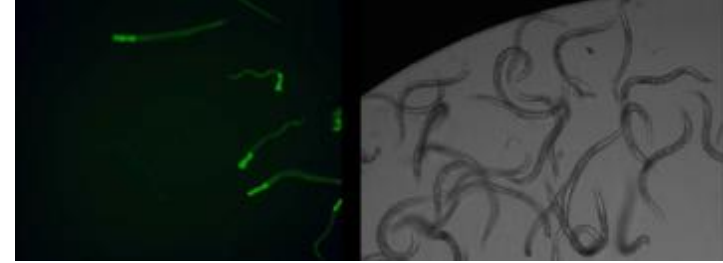
AMR_5: AMR_4 - *tet*_TetCyc.

AMR_6: AMR_5 + *tet*_TetCyc

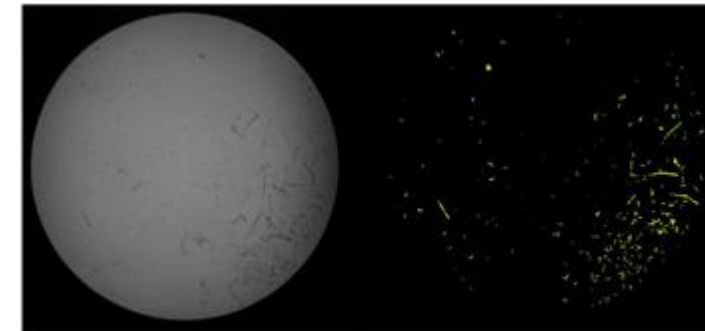
Karbapenem Dirençli HvKp C.elegans toksisitesi



Karbapenem Dirençli HvKp C.elegans mortalitesinde artış yok



OP50

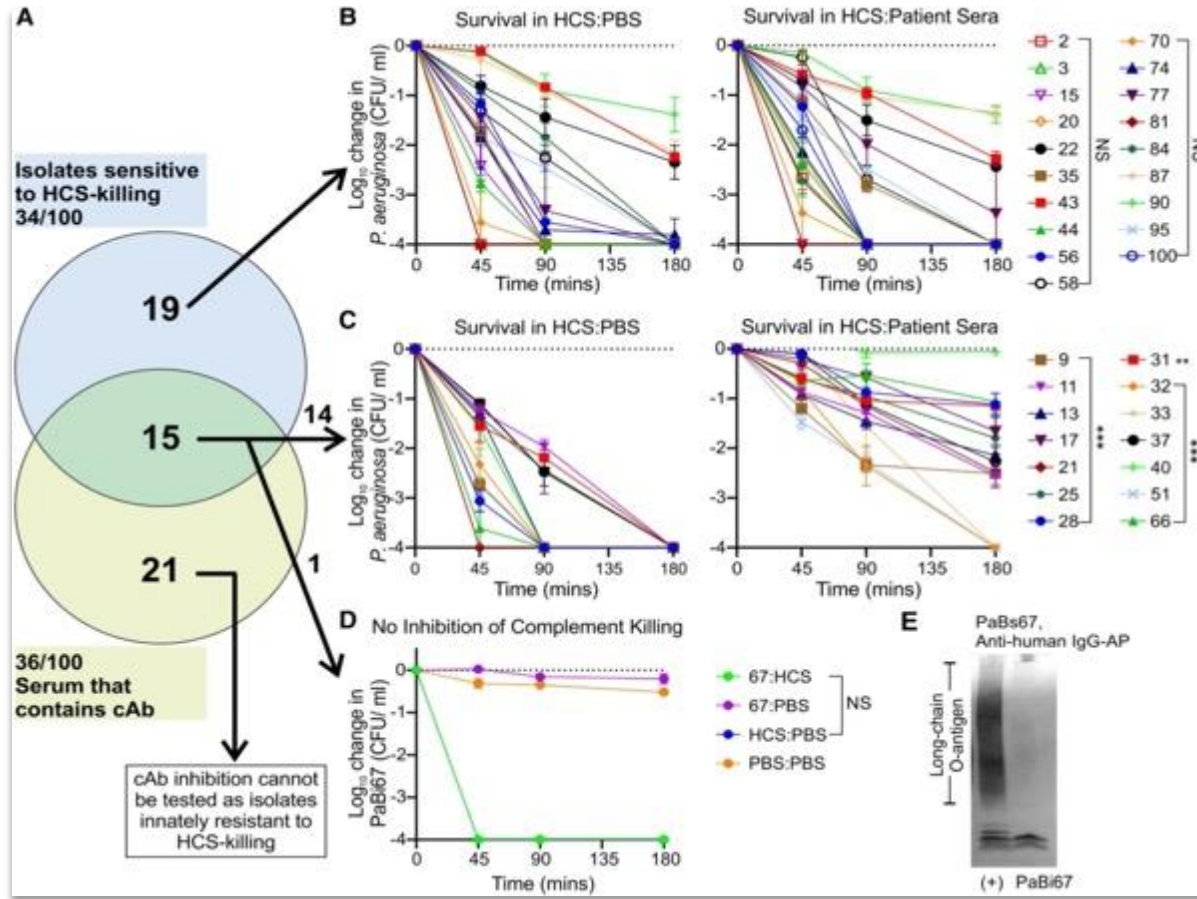


HvKp

Antibody-Mediated Serum Resistance Protects *Pseudomonas aeruginosa* During Bloodstream Infections

Sarah M Hickson, Johannes K Hoehensteiger, Johanna Mayer-Coverdale, Von Vergel L Torres, Wenkang Feng, Joshua N Monteith, Ian R Henderson, Kate L McCarthy, Timothy J Wells ✉ Author Notes

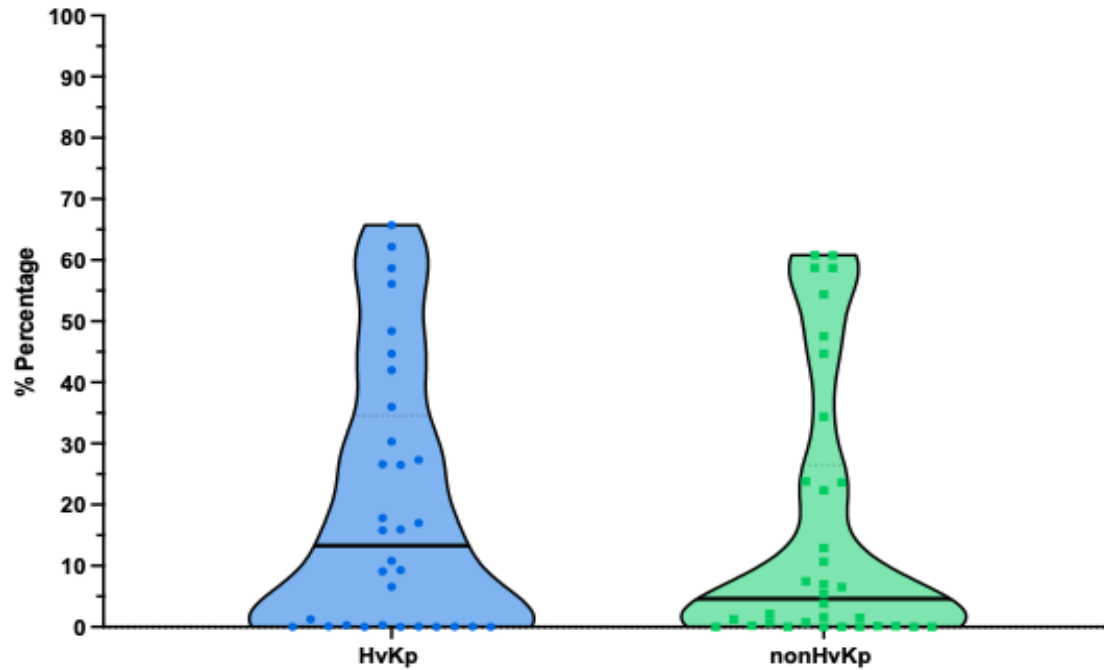
The Journal of Infectious Diseases, Volume 230, Issue 2, 15 August 2024, Pages e221–e229,



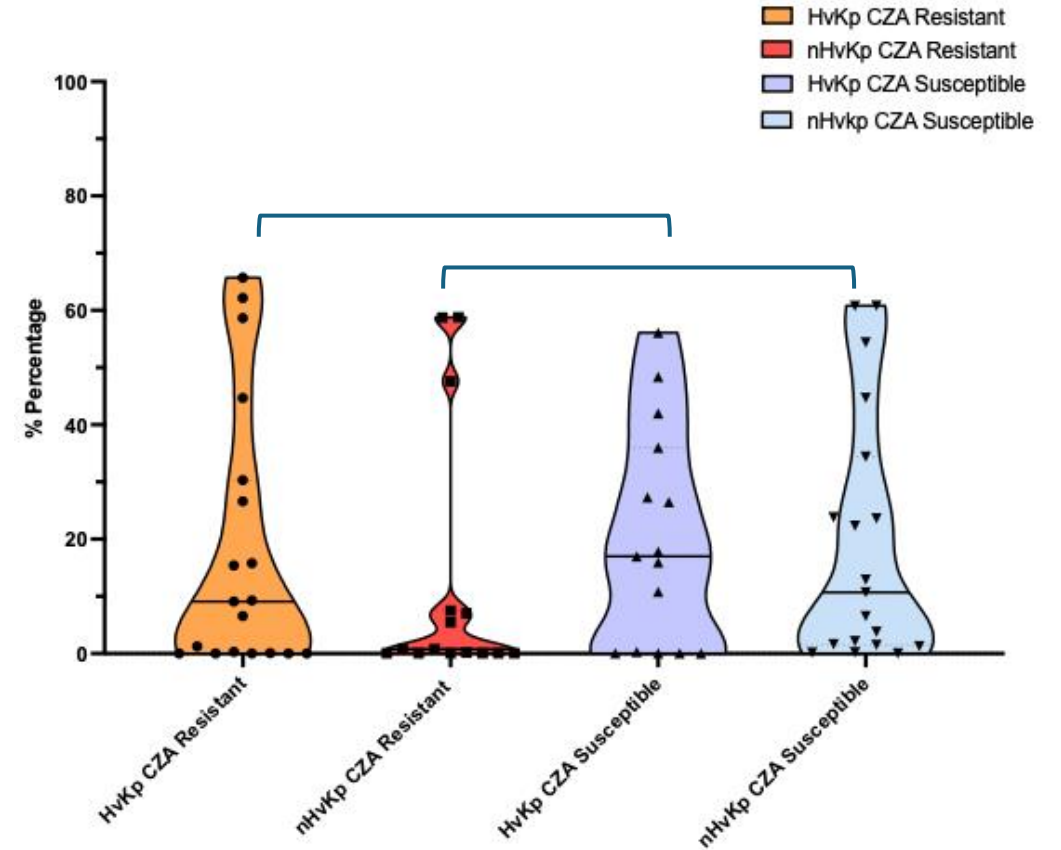
- ❖ Kan enfeksiyonu olan 100 hasta
- ❖ 14'ünde serumda clacking Ab (gizleyen Ab) pozitif
- ❖ Yapıları, O antijen spesifik IgG2 or IgA
- ❖ Bakterinin LPS'ine bağlanıp komplemandan gizliyorlar
- ❖ Kan enfeksiyon riskini artırıyorlar

Karbapenem ve Seftazidim Dirençli HvKp Serum Direnci


Survival in Active Serum



Survival in Active Serum



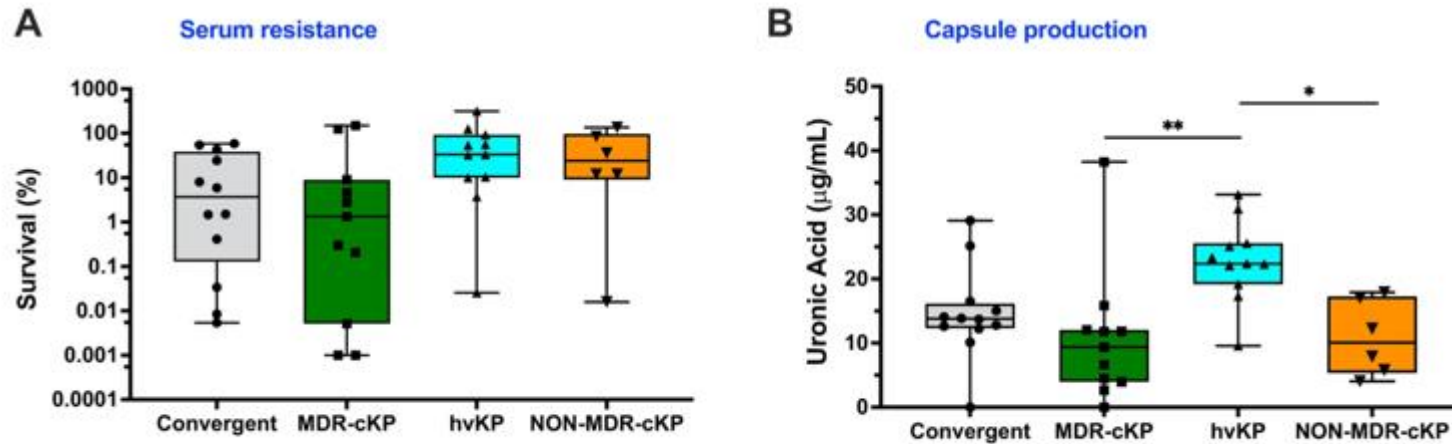
Klebsiella pneumoniae clinical isolates with features of both multidrug-resistance and hypervirulence have unexpectedly low virulence

Travis J. Kochan , Sophia H. Nozick, Ailki Valdes, Sumitra D. Mitra, Bettina H. Cheung, Marine Lebrun-Corbin, Rachel L. Medernach, Madeleine B. Vessely, Jori O. Mills, Christopher M. R. Axline, Julia A. Nelson, Ethan M. VanGosen, Timothy J. Ward, Egon A. Ozer, David van Duin, Liang Chen, Barry N. Kreiswirth, S. Wesley Long, James M. Musser, Zackery P. Bulman, Richard G. Wunderink & Alan R. Hauser

Nature Communications 14, Article number: 7962 (2023) | [Cite this article](#)

Fig. 5: Phenotypic comparison of convergent, MDR-cKP, hvKP, and NON-MDR-cKP isolates.

From: *Klebsiella pneumoniae* clinical isolates with features of both multidrug-resistance and hypervirulence have unexpectedly low virulence

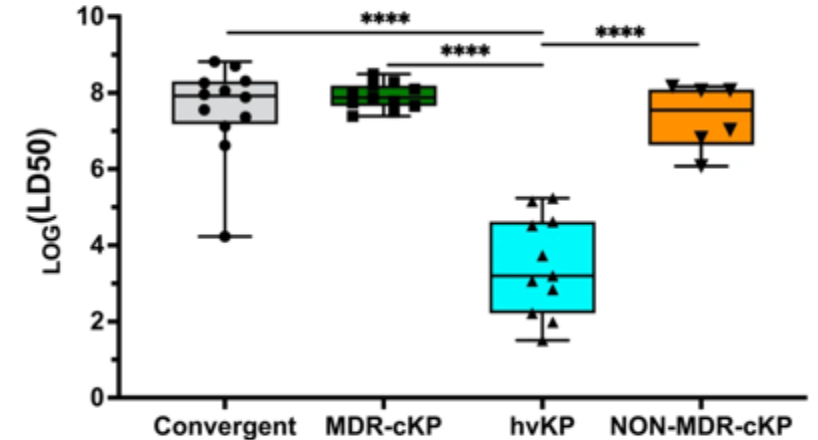


Serum Direnci HvKp'de farklı değil

Kapsül üretimi HvKp'de yüksek
Ancak MDR-HvKp'de azalıyor.

Fig. 6: Virulence comparison of convergent, MDR-cKP, hvKP, and NON-MDR-cKP isolates.

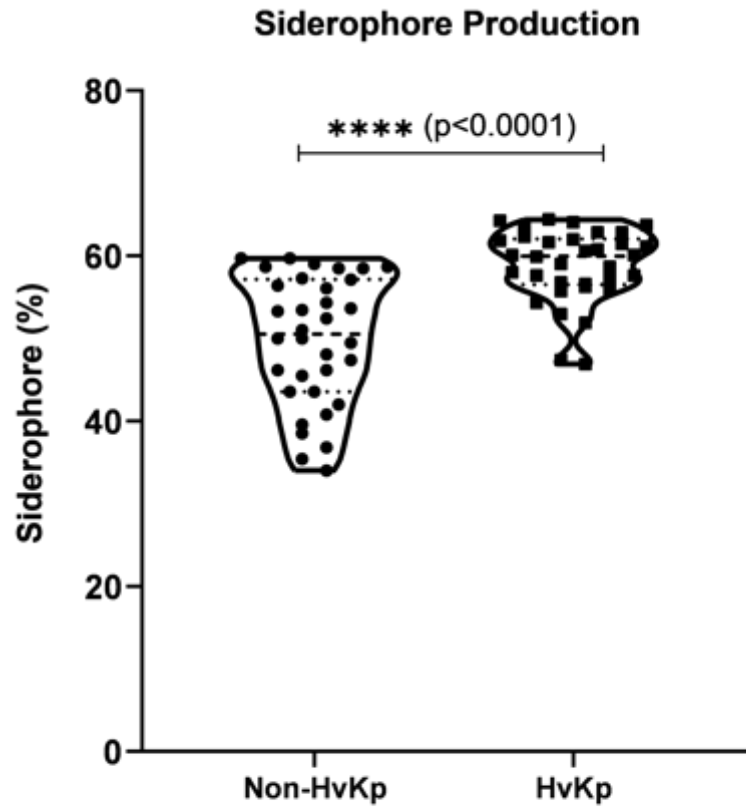
From: *Klebsiella pneumoniae* clinical isolates with features of both multidrug-resistance and hypervirulence have unexpectedly low virulence



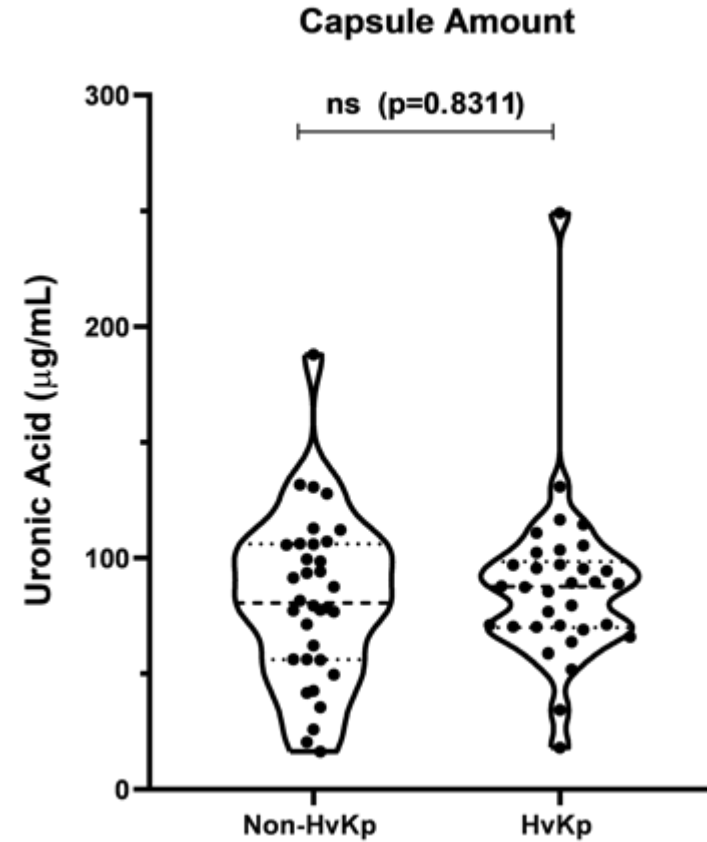
Virulence in a murine model of pneumonia was measured for each of the 40 representative isolates. Each symbol represents an isolate ($n = 40$). The middle lines represent medians, the boxes represent the interquartile range, and the outer bars represent the minimum and maximum. Number of mice and dosing used to determine LD₅₀ values are included in Supplementary Data 5. Statistical analysis was performed using one-way ANOVA; **** $p \leq 0.0001$. Source data are provided as a Source data file.

LD50 HvKp'de belirgin düşük
MDR HvKp'de artıyor

Karbapenem Dirençli HvKp Siderofor ve Kapsül Üretimi



Hangi Tip Siderofor??



Baskın Kapsül Hangisi??

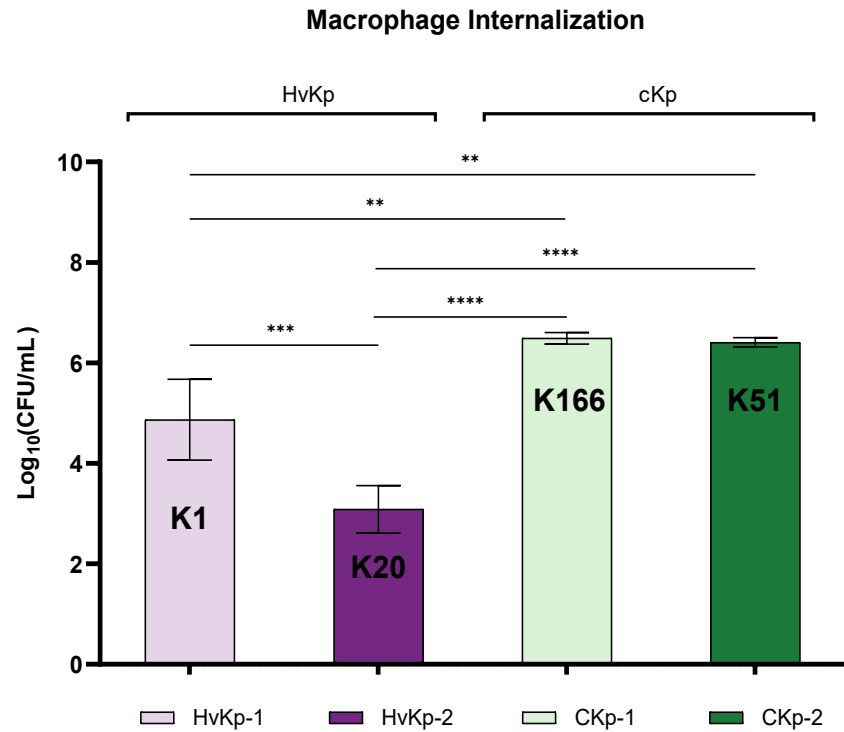


Figure 3. Internalization of *K. pneumoniae* strains within murine macrophages.

Data are presented as Log_{10} (CFU/mL) \pm SD. The experiment was performed in triplicate. A one-way ANOVA indicated statistically significant difference among the means of groups ($P < 0.0001$). Differences between specific groups were analyzed post-hoc (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.0001$).

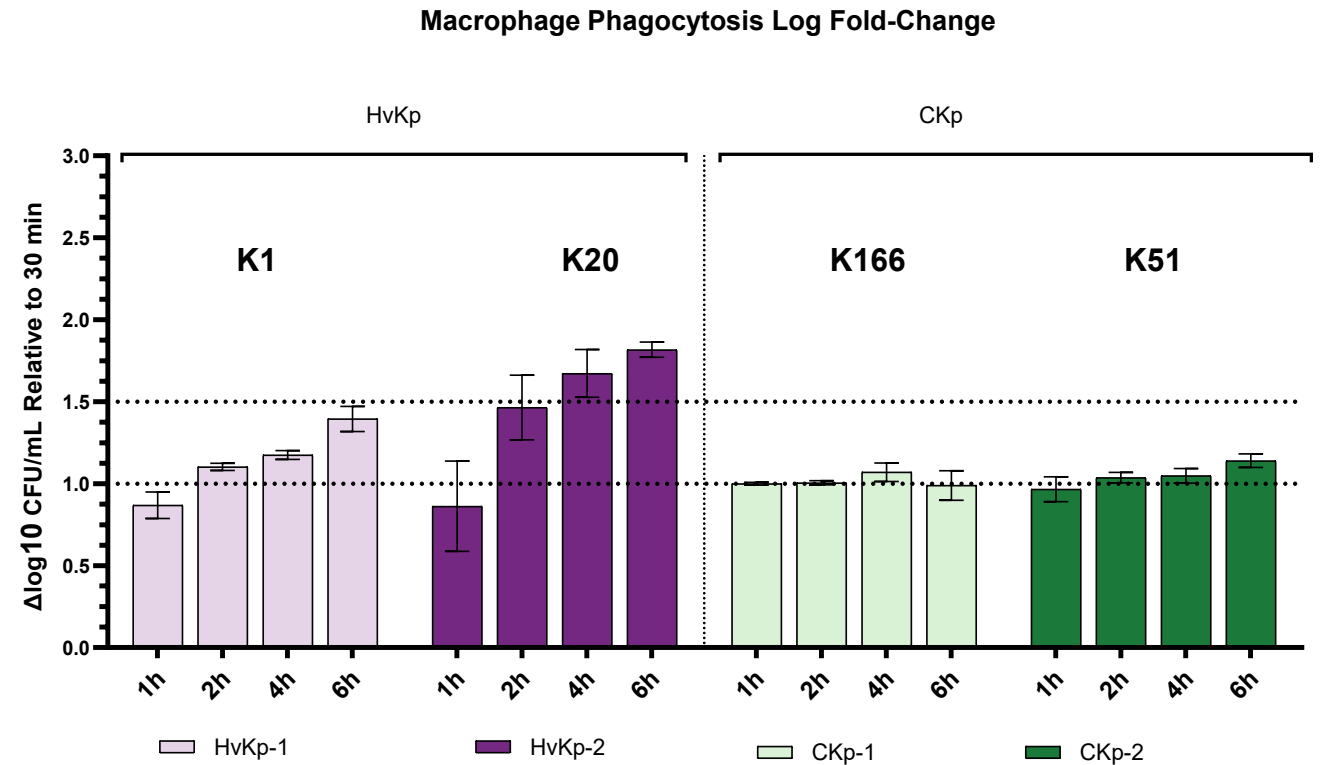


Figure 4. Log_{10} Fold-Change of *K. pneumoniae* strains to 30-min reference within murine macrophages

The graph illustrates the change in bacterial load (Log_{10} CFU/mL) inside macrophages over a 6-hour period (1h, 2h, 4h, 6h) relative to 30-minute internalization time point (ΔLog_{10} CFU/mL relative to 30min). All data points represents the mean \pm SD of three independent experiments.

Result

Murine macrophage response: Localization of *K. pneumoniae* at 6hpi

HvKp-1 (K1)

HvKp-2 (K20)

CKp-1 (K166)

CKp-2 (K51)

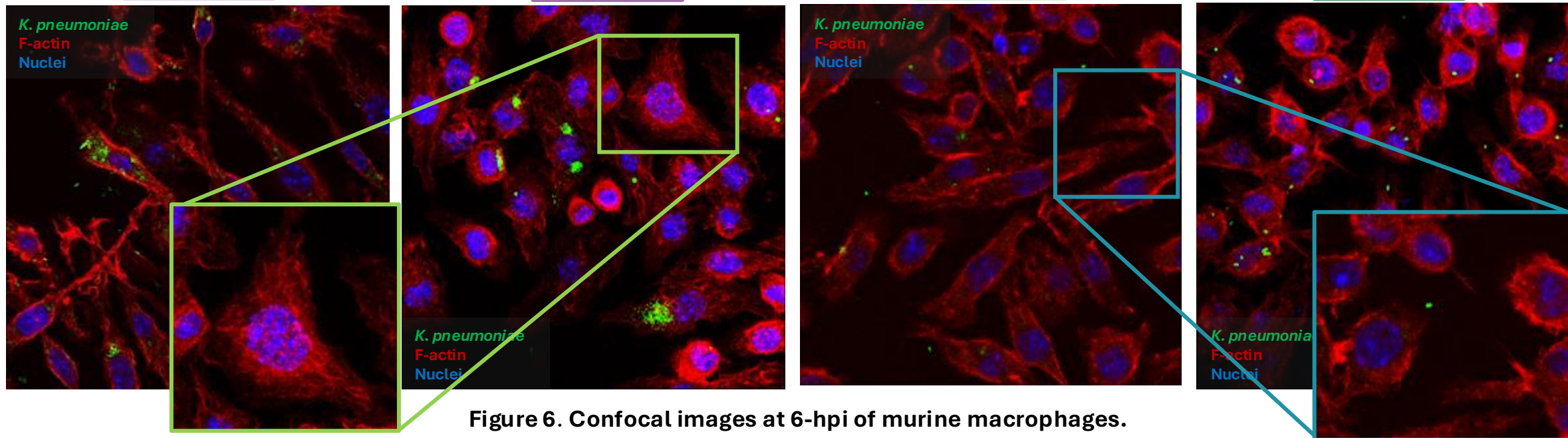


Figure 6. Confocal images at 6-hpi of murine macrophages.

(Representative images were captured from 10-20 randomly selected fields of view per slide.)

- HvKp strains had **high bacterial load** within macrophages.
- HvKp strains induced **ruffled membrane morphology**.
- HvKp-1 induced a unique **elongated macrophage** morphology.

At 6h post-infection, HvKp induced extracellular, F-actin-rich accumulations, indicating **impaired engulfment and compromised phagocytic function**.

- CKp isolates exhibited **lower intracellular bacterial load**.
- CKp infection induced **pseudopodia**.

CKp isolates induced pseudopodia, F-actin-driven protrusions that facilitate efficient macrophage engulfment and clearance.

Sonuç olarak,

- Konağa ait ve çevresel faktörler virülansı artmış bakterilerin selektif çoğalmasını hızlandırıyor
- Bu bakteriler invitro çalışmalarda özellikle kapsül, serum direnci ve siderofor yapılarındaki farklılıklar ile ortaya çıkıyor
- Artmış virülans artmış invazyon ile ilişkili olabilir
- Kritik önemi olan bakterilerin antibiyotik direnci yanısıra virülans surveyansı yapılmalıdır
- Antivirülans tedaviler yakın gelecekte pratikte uygulamalarda yerini alacaktır