Klebsiella pneumoniae genomic epidemiology and antimicrobial resistance

Convergence of hypervirulence and antimicrobial resistance

11 September 2025

Intended Learning Objectives

Specific objectives of this session:

1. Discuss typical distributions of AMR and (hyper)virulence genes in different *K. pneumoniae* clones
   a. *Geographical/clonal trends of resistance to 3rd generation cephalosporins and carbapenems*
2. Learn about AMR and virulence convergence
   a. *What is convergence and how does it arise?*
3. Demonstrate how Kleborate can be used to identify genomes of convergent isolates
4. Learn about prevalence of AMR and virulence convergence from public genome data

Outline

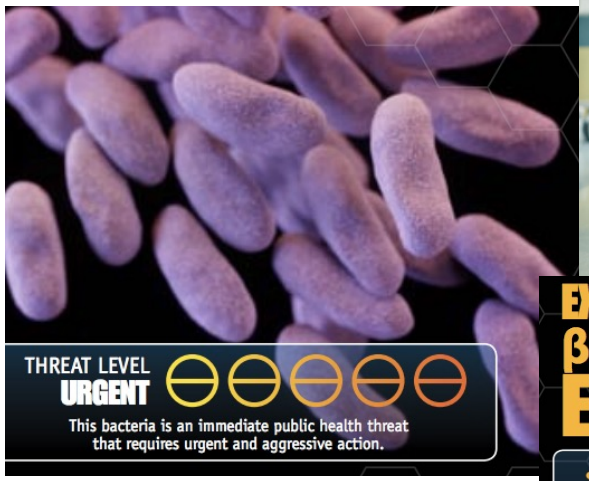
This session consists of the following elements

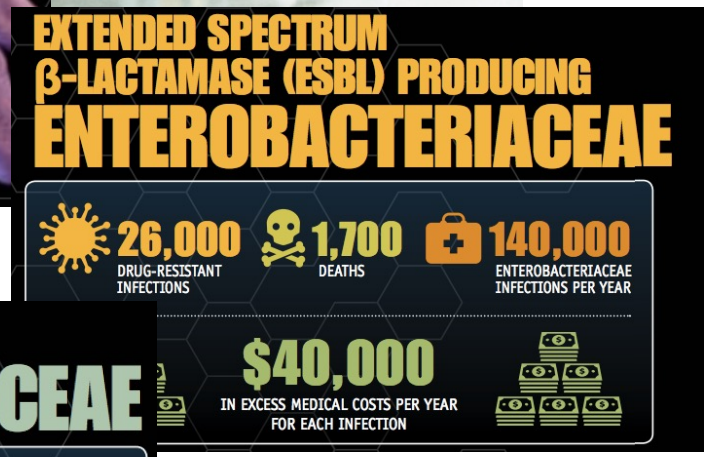
1. Overview of typical AMR and (hyper)virulence gene distribution in different *K. pneumoniae* clones
2. Trends of ESBL and carbapenemase distributions in different geographies and *K. pneumoniae* clones
3. Overview of AMR and virulence convergence
4. Application of Kleborate to detect potential convergent genomes
5. Global snapshot of AMR and virulence convergence from public genome data
6. Challenges around the lack of consensus definition of hypervirulence
7. Summary

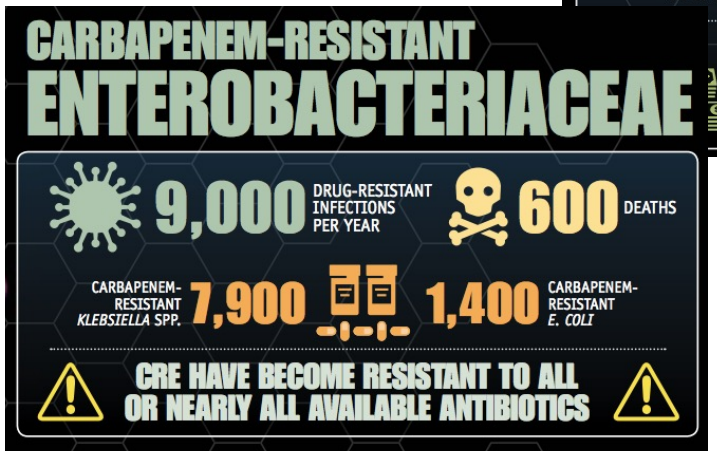
K. pneumoniae – two distinct public health threats

Healthcare-associated infections

- Classical Kp strains (cKp)
- Multi-drug resistance (MDR) from AMR plasmids
- Common MDR clones: ST258, ST147, ST307 etc.
- "Last-line" drug resistance:
  - 3rd generation cephalosporins (3GC)
  - carbapenems



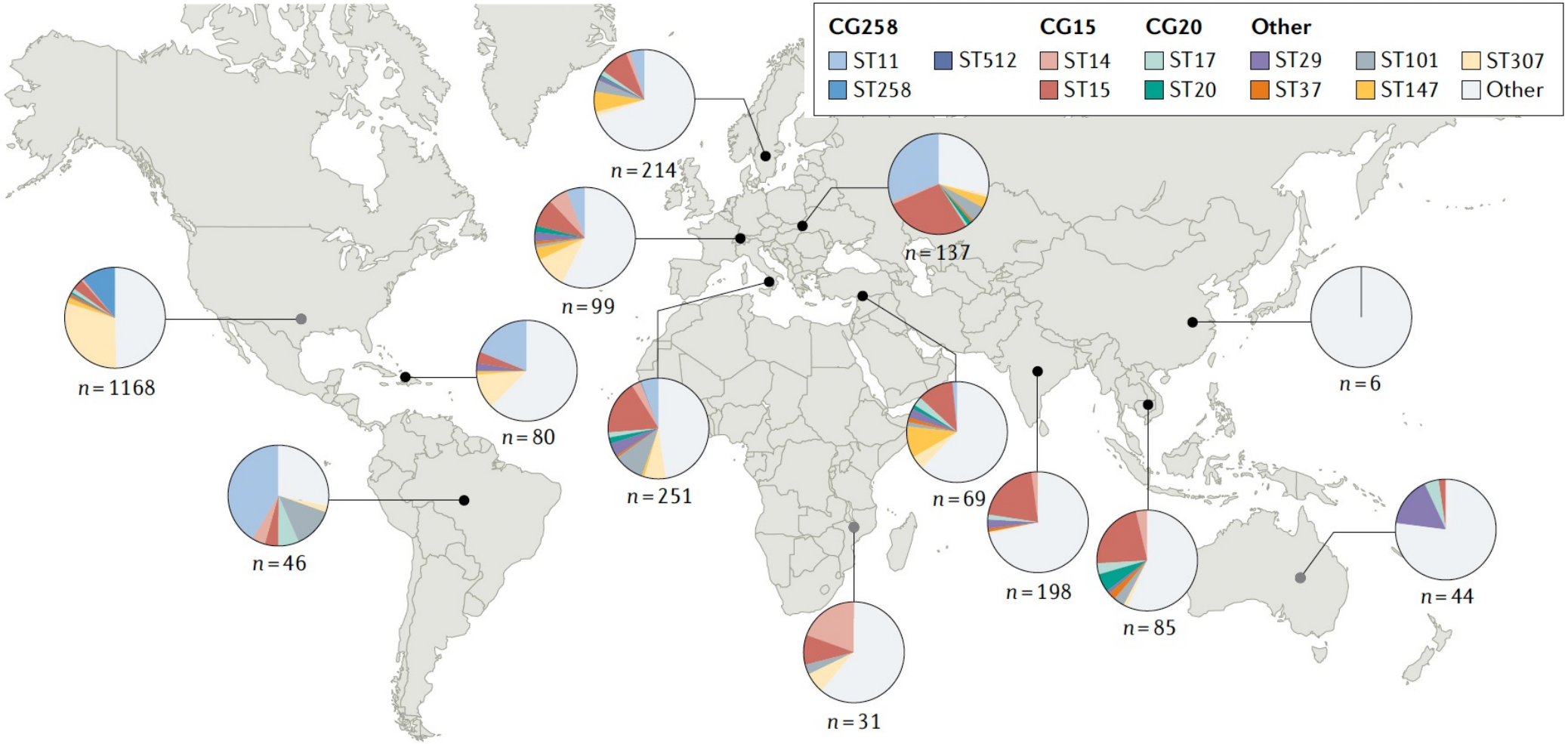




Source: CDC 2013

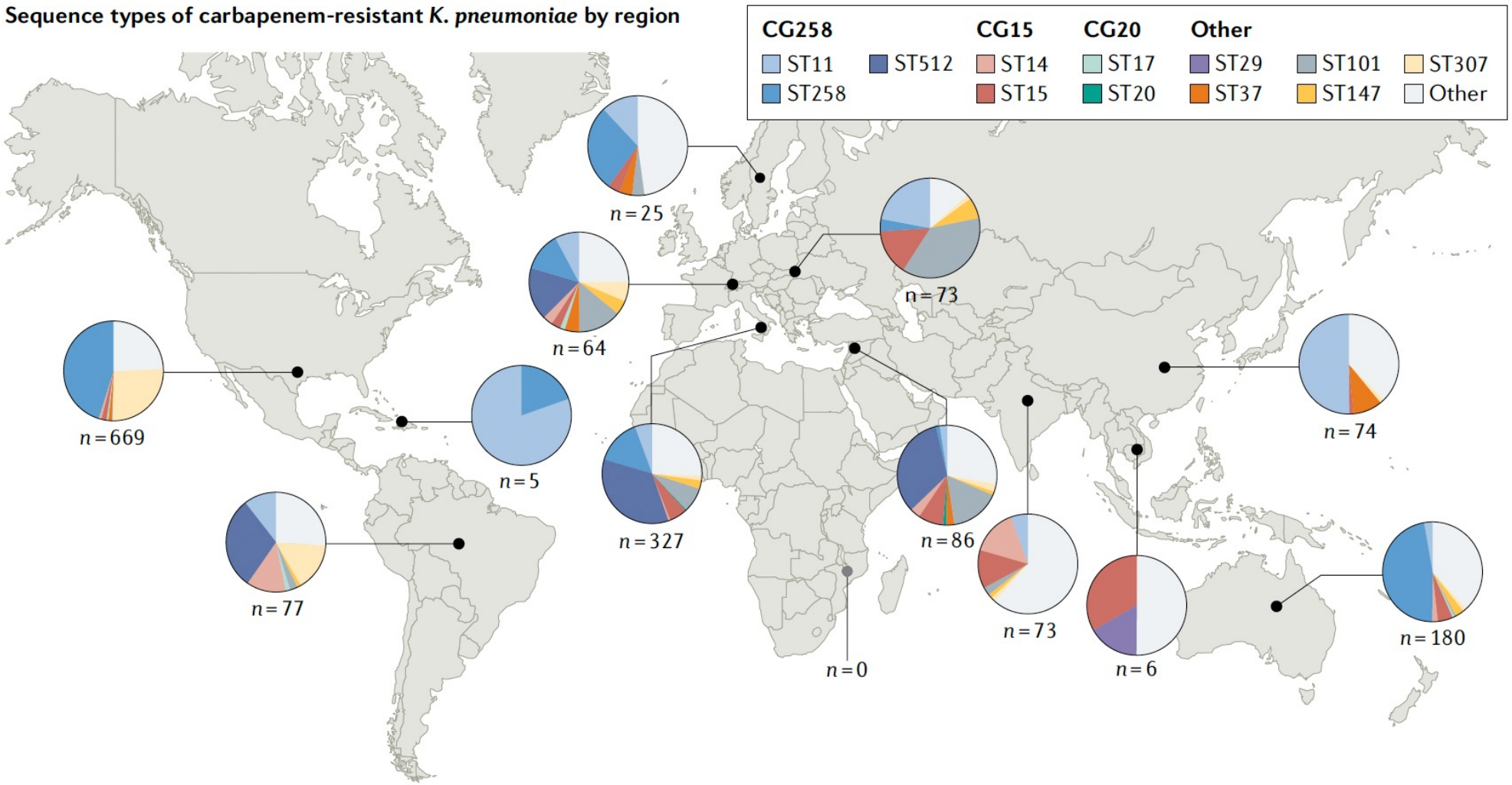
3GC resistance in *K. pneumoniae*

Sequence types of third-generation cephalosporin-resistant, carbapenem-susceptible *K. pneumoniae* by region



Wyres, Lam & Holt, *Nature Reviews Microbiology* 2020.

Carbapenem resistance in *K. pneumoniae*



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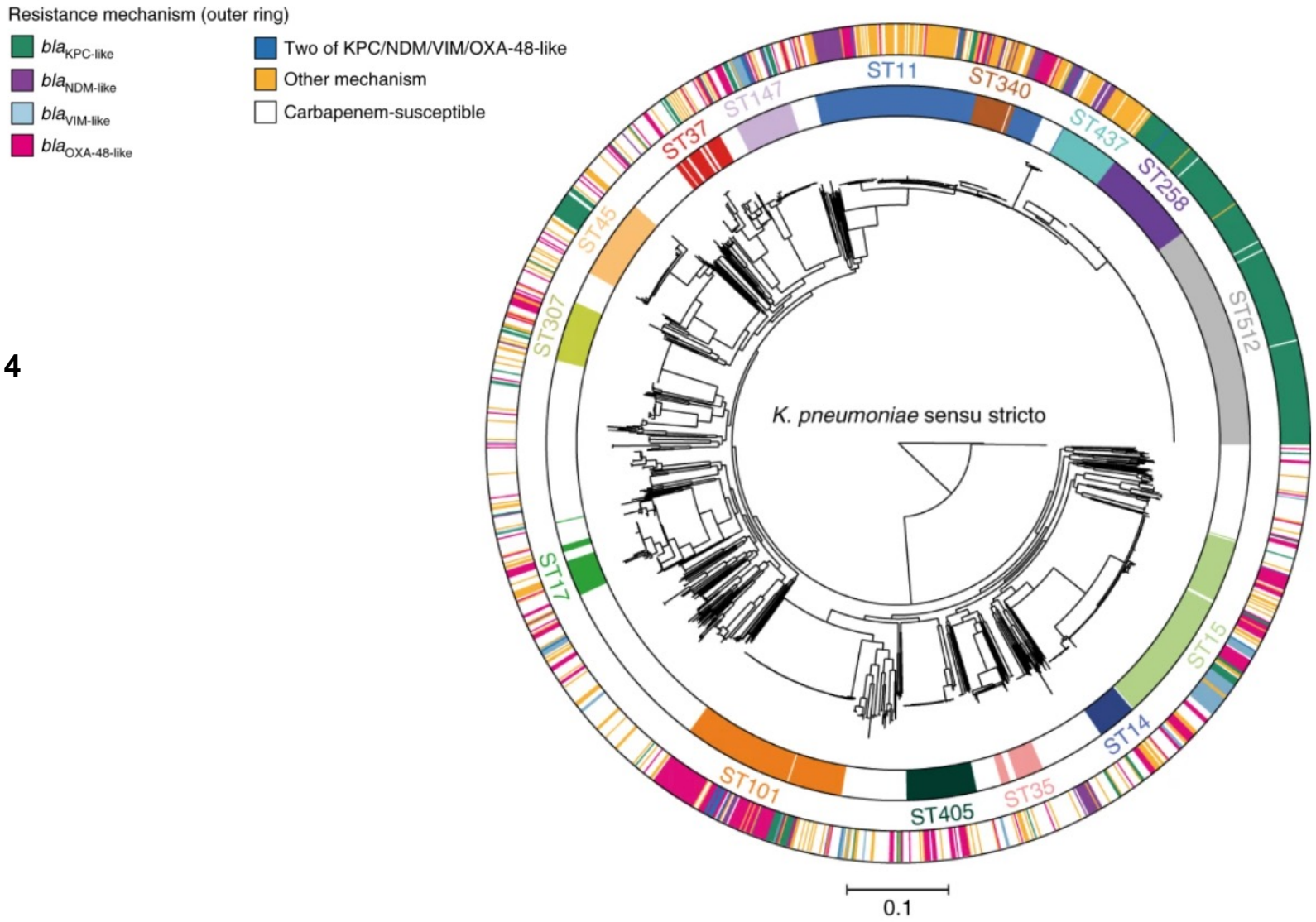
Carbapenem resistance in *K. pneumoniae*



EuSCAPE, 2013 – 2014

David et al, *Nature Microbiology* 2019.

Carbapenem resistance in *K. pneumoniae*

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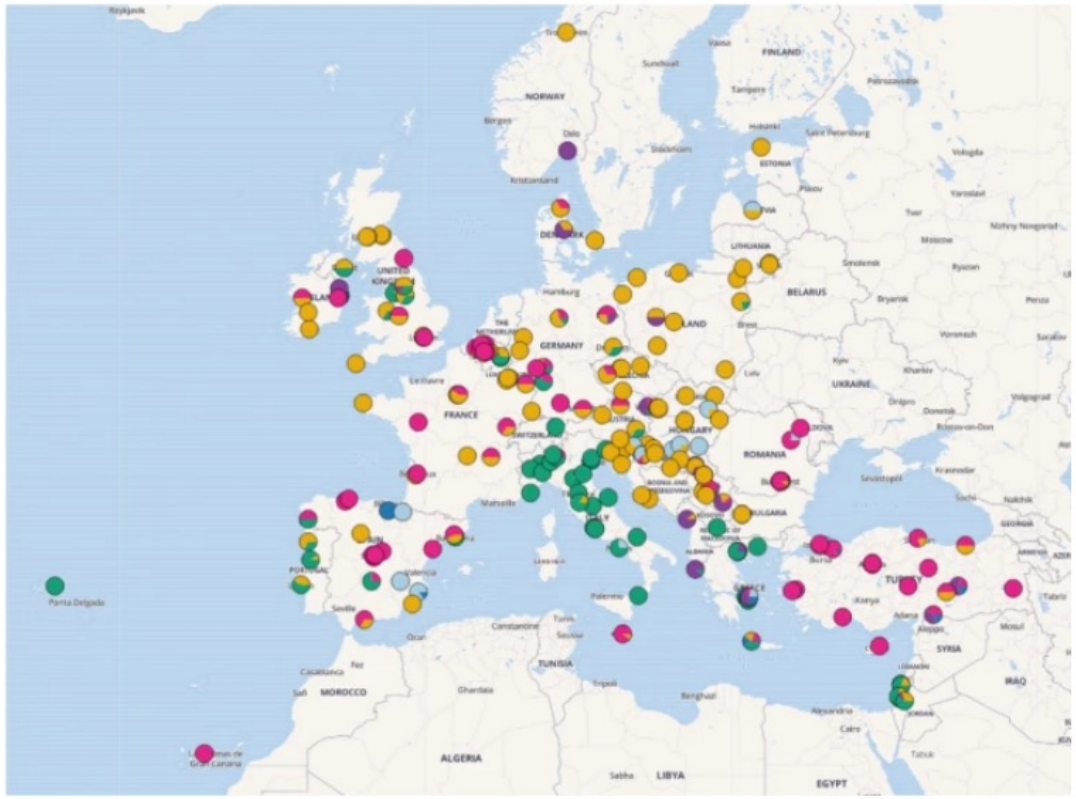
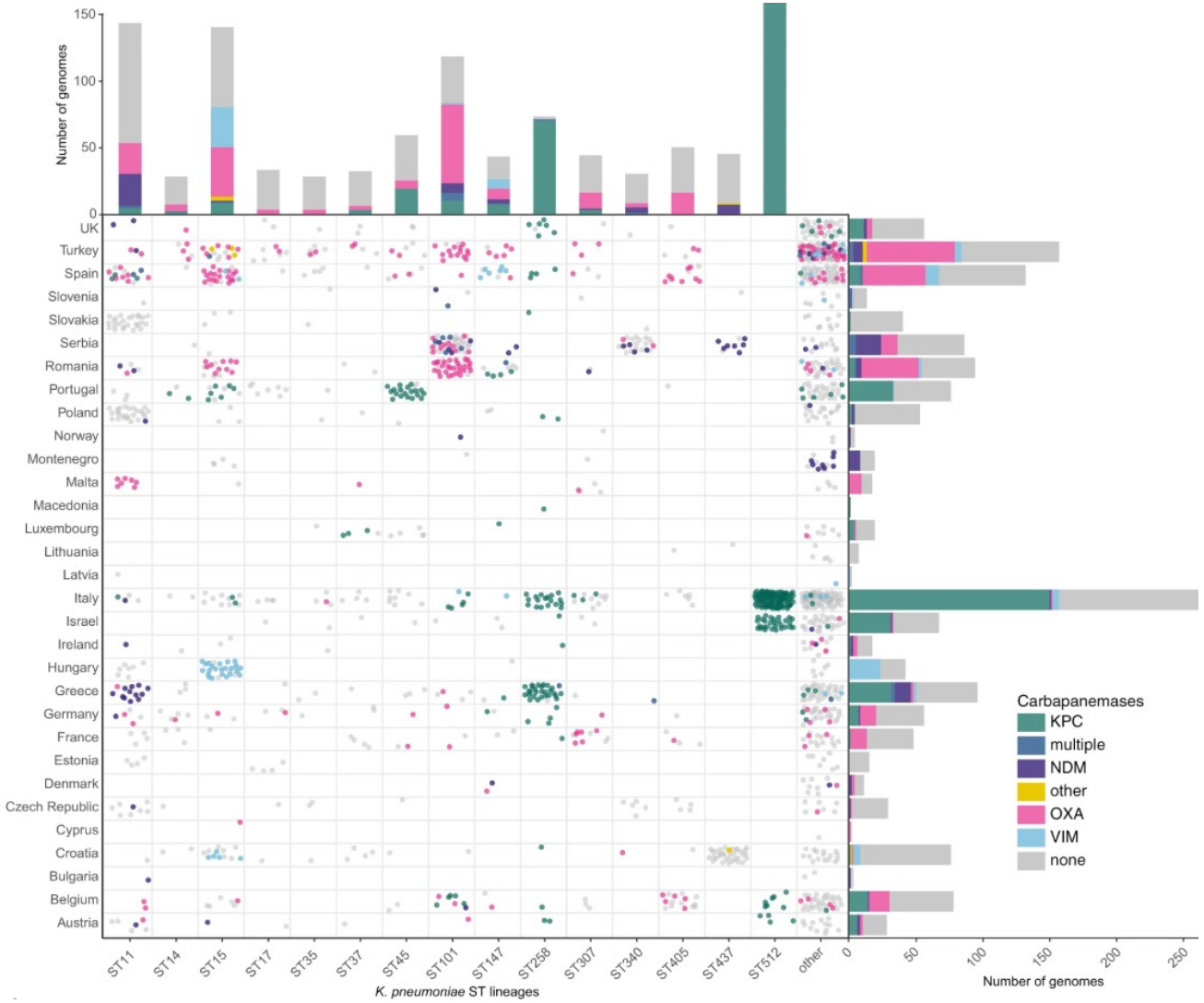




David et al, *Nature Microbiology* 2019.
Lam et al, *Nature Communications* 2021.

K. pneumoniae – two distinct public health threats

Healthcare-associated infections

- Classical Kp strains (cKp)
- Multi-drug resistance (MDR) from AMR plasmids
- Common MDR clones: ST258, ST147, ST307 etc.
- "Last-line" drug resistance:
  - carbapenems
  - 3rd generation cephalosporins (3GC)

Community-acquired infections

- Often invasive, multiple body sites - distinct from cKp infections
- "Hypervirulent" strains (hvKp)
- Common hvKp clones:

  ST23 > ST86 > ST65

- Virulence plasmids – *iuc, iro, rmpADC, rmpA2*

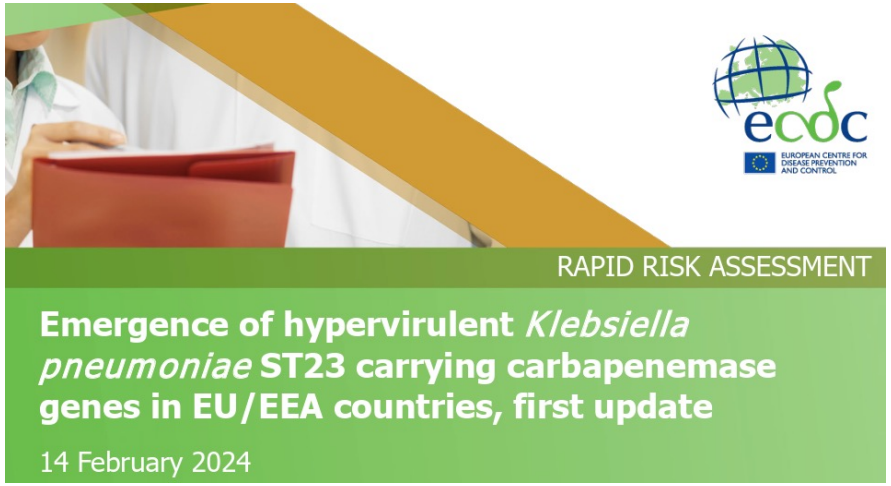
Hypervirulent *K. pneumoniae*

World Health Organization

Disease Outbreak News

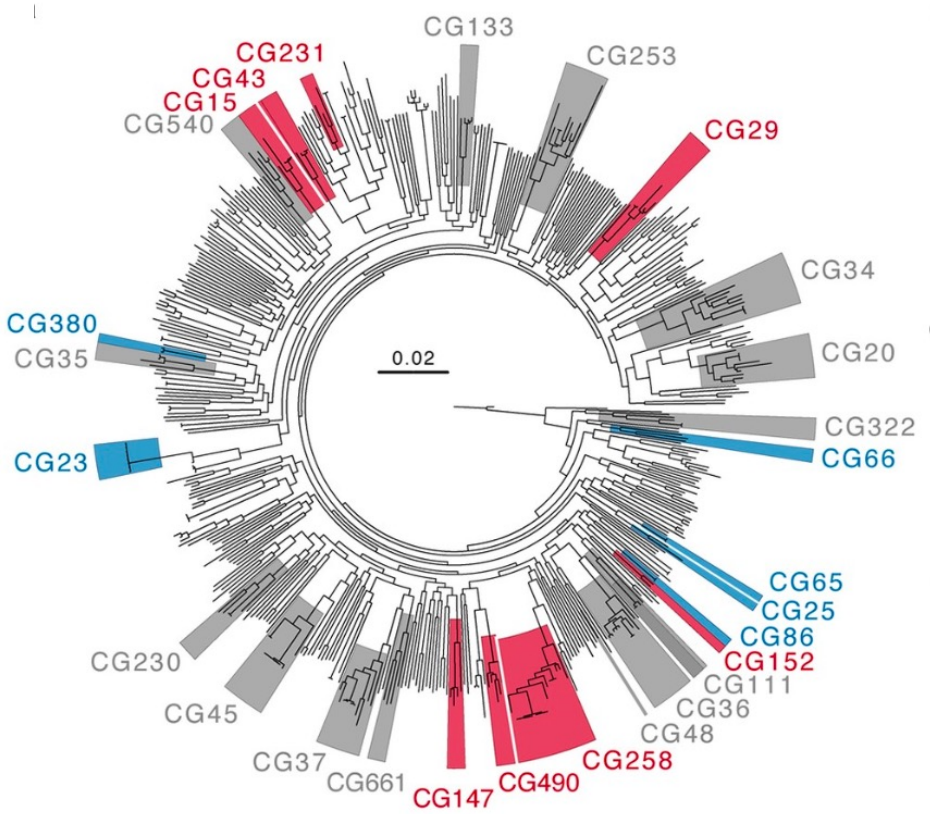
Antimicrobial Resistance, Hypervirulent Klebsiella pneumoniae - Global situation

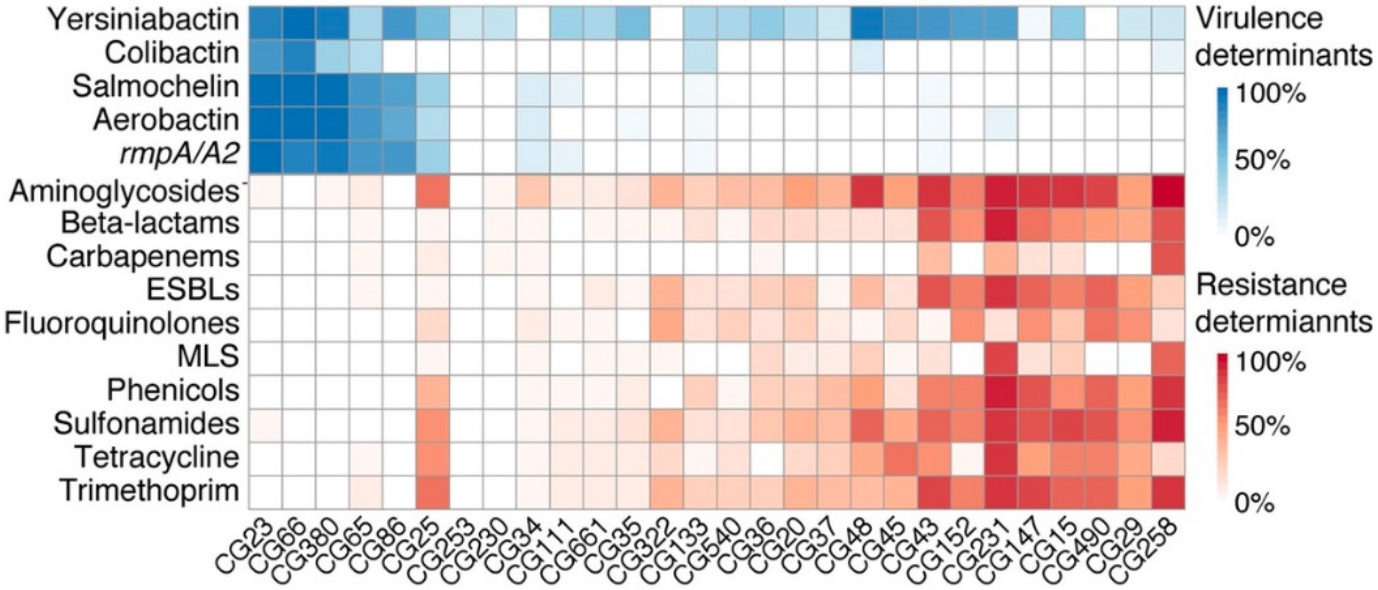
31 July 2024



- HvKp strains (e.g. ST23) initially and primarily observed in Asia
- Recent reports by WHO/ECDC demonstrate increased detection of ST23 outside of Asia

Distribution of AMR and virulence genes – typically segregated





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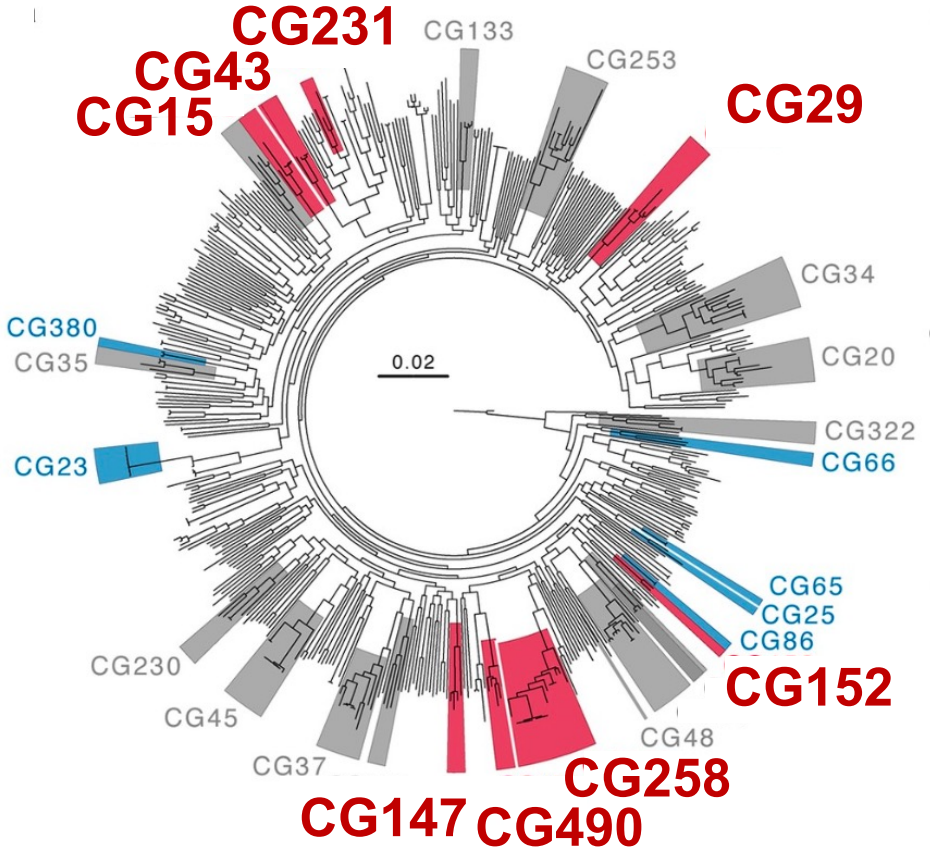

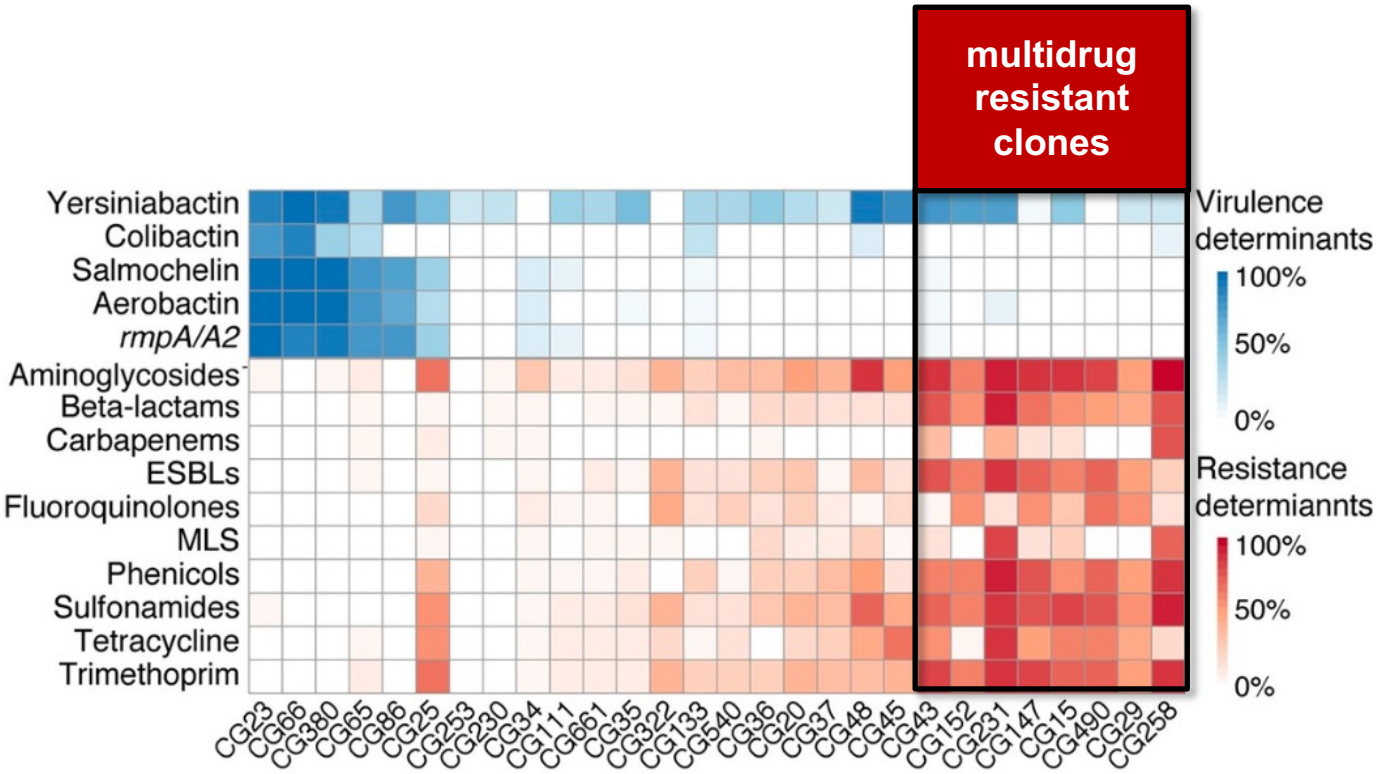

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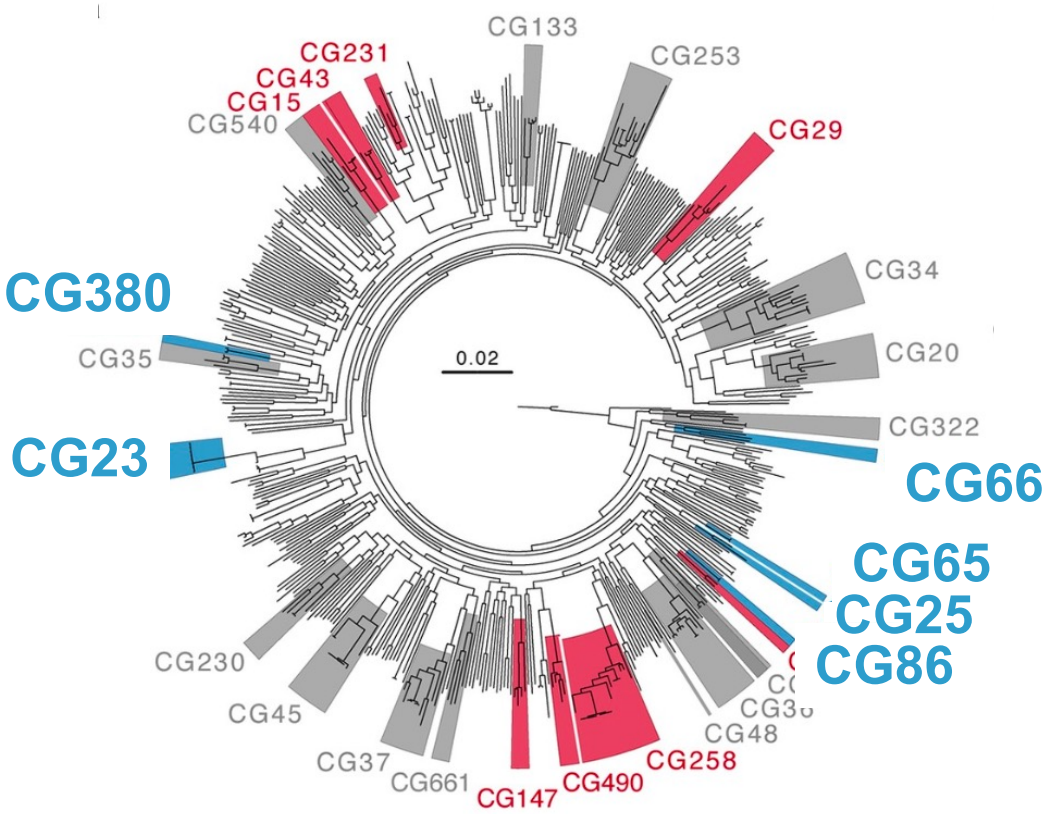
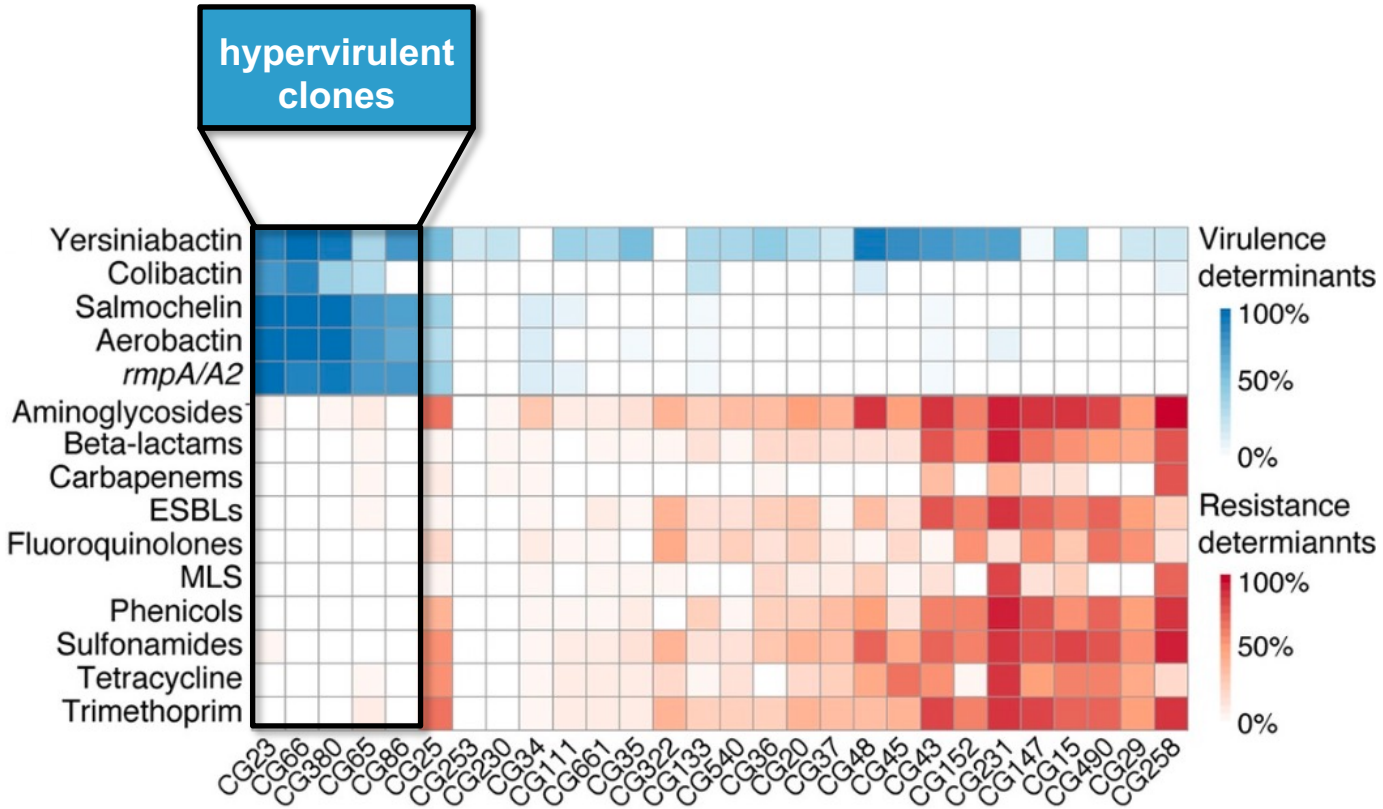


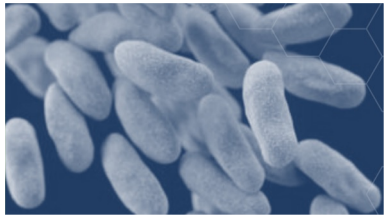


Wyres et al, *PLoS Genetics* 2019.

Convergence of AMR and virulence

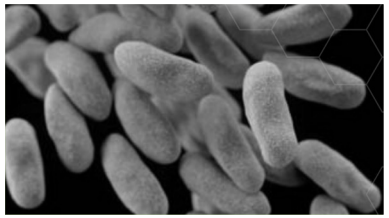
virulence plasmid

MULTIDRUG RESISTANT *Kp*



AMR plasmid

HYPERVIRULENT *Kp*



virulence plasmid

AMR plasmid

'OTHER' *Kp*

Convergence of AMR and virulence has happened

A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study

Danxia Gu*, Ning Dong*, Zhiwei Zheng, Di Lin, Man Huang, Lihua Wang, Edward Wai-Chi Chan, Lingbin Shu, Jiang Yu, Rong Zhang, Sheng Chen

virulence plasmid
(+*iuc*, +*rmpA2*)

MULTIDRUG RESISTANT *Kp*
(ST11 with KPC)

Convergence of AMR and virulence has happened, multiple times

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Danxia Gu*, Ning Dong*, Zhiwei Zheng, Di Lin, Man Huang, Lihua Wang, Edward Wai-Chi Chan, Lingbin Shu, Jiang Yu, Rong Zhang, Sheng Chen

Biomedical Research 2018; 29 (11): 2438-2441
ISSN 0970-938X
www.biomedres.info

The threat of carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (CR-HvKP).

Chang-Ro Lee[1#], Kwang Seung Park[1#], Jung Hun Lee[1], Jeong Ho Jeon[1], Young Bae Kim[2], Byeong Chul Jeong[1], Sang Hee Lee[1*]

t of Biological Sciences, Myongji

s, USA

PMCID: PMC10619465
PMID: 37842870

Convergent *Klebsiella pneumoniae* strains belonging to a sequence type 307 outbreak clone combine cefiderocol and carbapenem resistance with hypervirulence

Katharina Schaufler,[a,b,c,d] Thaddäus Echelmeyer,[b] Michael Schwabe,[b] Sebastian Guenther,[e] Jürgen A. Bohnert,[f] Karsten Becker,[f] Helmut Fickenscher,[a] Aike Bueter,[a] Gregor Maschkowitz,[a] Andi Krumbholz,[a,g] Dennis Nurjadi,[h] Stefan E. Heiden,[c] and Elias Eger[a,c]

J Antimicrob Chemother 2019; **74**: 1218–1222
doi:10.1093/jac/dkz028 Advance Access publication 15 February 2019

Journal of Antimicrobial Chemotherapy

Convergence of virulence and MDR in a single plasmid vector in MDR *Klebsiella pneumoniae* ST15

Margaret M. C. Lam[1], Kelly L. Wyres[1], Ryan R. Wick[1], Louise M. Judd[1], Aasmund Fostervold[2,3], Kathryn E. Holt[1,4]† and Iren Høyland Löhr[2]*†

RAPID COMMUNICATION

Cross-border spread of a mosaic resistance (OXA-48) and virulence (aerobactin) plasmid in *Klebsiella pneumoniae*: a European Antimicrobial Resistance Genes Surveillance Network investigation, Europe, February 2019 to October 2024

Genome Med. 2024 Apr 18;16:58. doi: 10.1186/s13073-024-01332-5

The emergence of highly resistant and hypervirulent *Klebsiella pneumoniae* CC14 clone in a tertiary hospital over 8 years

Sharif Hala [1,2,3,4], Mohammed Malaikah [1,5], Jiayi Huang [5,6], Wesam Bahitham [2,3,4], Omniya Fallatah [2,3,4], Samer Zakri [2,3,4], Chakkiath Paul Antony [1,10], Mohammed Alshehri [2,3,4], Raeece Naeem Ghazzali [1], Fathia Ben-Rached [1], Abdullah Alsahafi [2,3,4], Asim Alsaedi [2,3,4], Ghadeer AlAhmadi [7], Mai Kaaki [2,3,4], Meshari Alazmi [6,8], Baraa AlhajHussein [2,3,4], Muhammad Yaseen [2,3,4], Hosam M Zowawi [9,2,3,4], Majed F Alghoribi [2,3,4], Abdulhakeem O Althaqafi [2,3,4], Abdulfattah Al-Amri [2,3,4], Danesh Moradigaravand [5,6,✉], Arnab Pain [1,9,✉]

Detection of convergence with Kleborate

KLEBORATE

Virulence score:

0	negative for all of yersiniabactin (ybt), colibactin (clb), aerobactin (iuc)
1	yersiniabactin only
2	yersiniabactin and colibactin (or colibactin only)
3	aerobactin (without yersiniabactin or colibactin)
4	aerobactin with yersiniabactin (without colibactin)
5	yersiniabactin, colibactin and aerobactin

Virulence score > 3

Presence of aerobactin, typically indicates presence of virulence plasmid
***iro, rmp not included in score**

Resistance score:

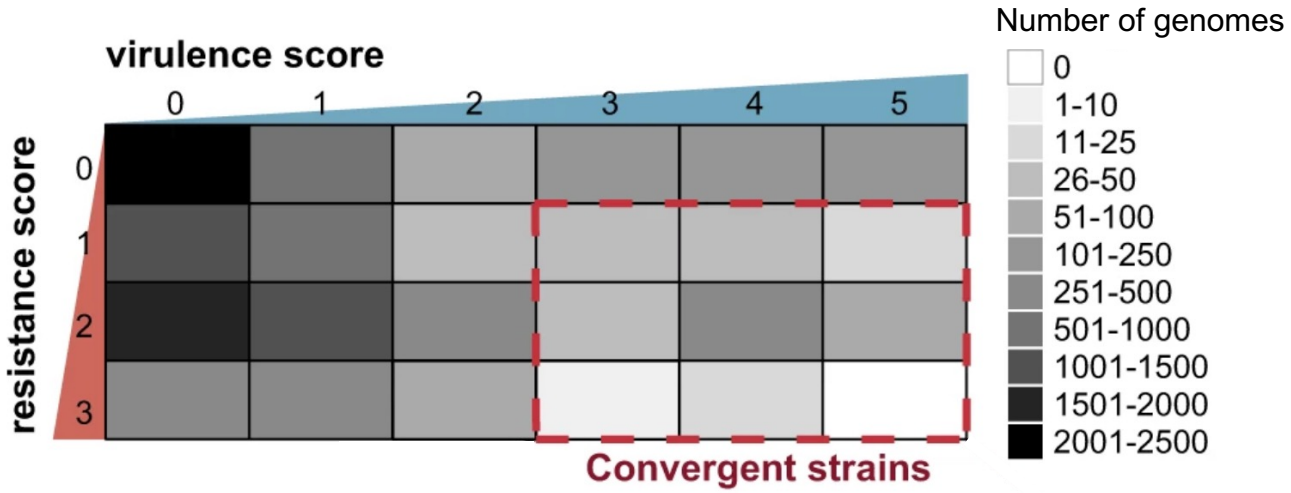
0	no ESBL, no carbapenemase (regardless of colistin resistance)
1	ESBL, no carbapenemase (regardless of colistin resistance)
2	Carbapenemase without colistin resistance (regardless of ESBL genes or OmpK mutations)
3	Carbapenemase with colistin resistance (regardless of ESBL genes or OmpK mutations)

Resistance score > 1

3rd gen cephalosporin or carbapenem resistance

Use the scores as a way to quickly screen for <u>potential</u> convergent genomes

Detection of convergence with Kleborate

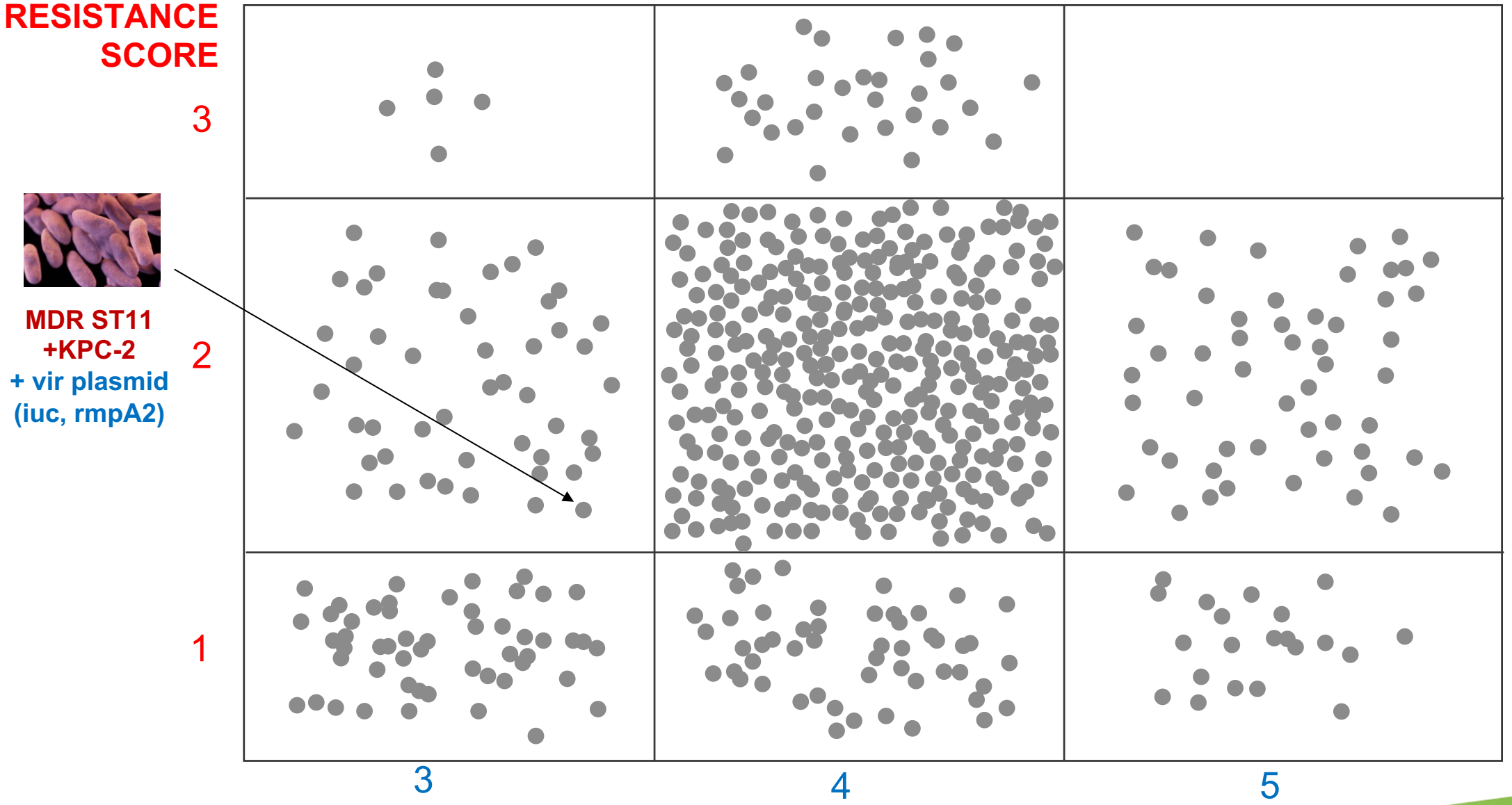


Screen of 14000 public genomes

N=601 convergent genomes (4.3%) based on virulence score ≥3, resistance score ≥1

Lam et al, *Nature Communications* 2021

Global snapshot of convergence events



Data from Lam et al, *Nature Communications* 2021

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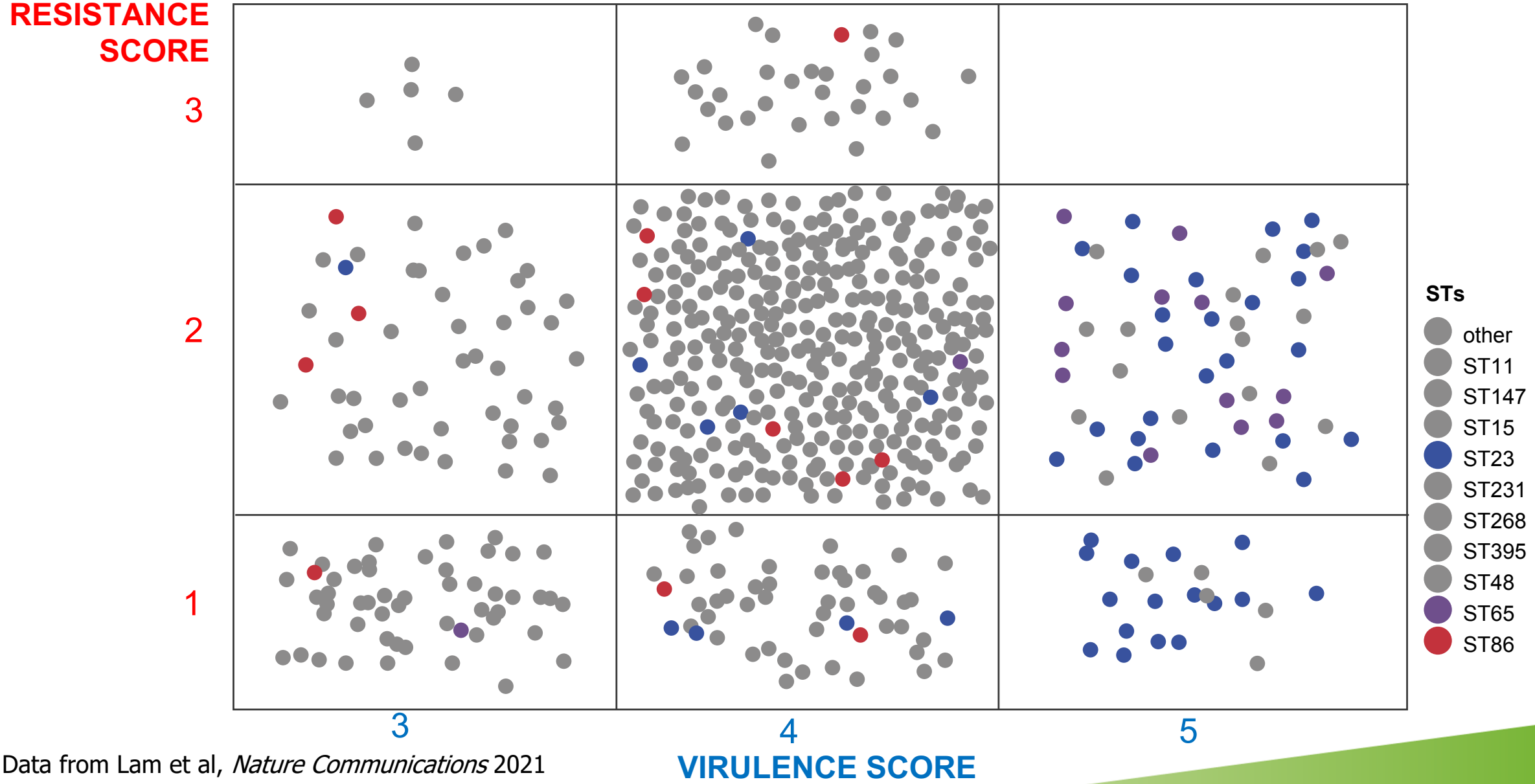

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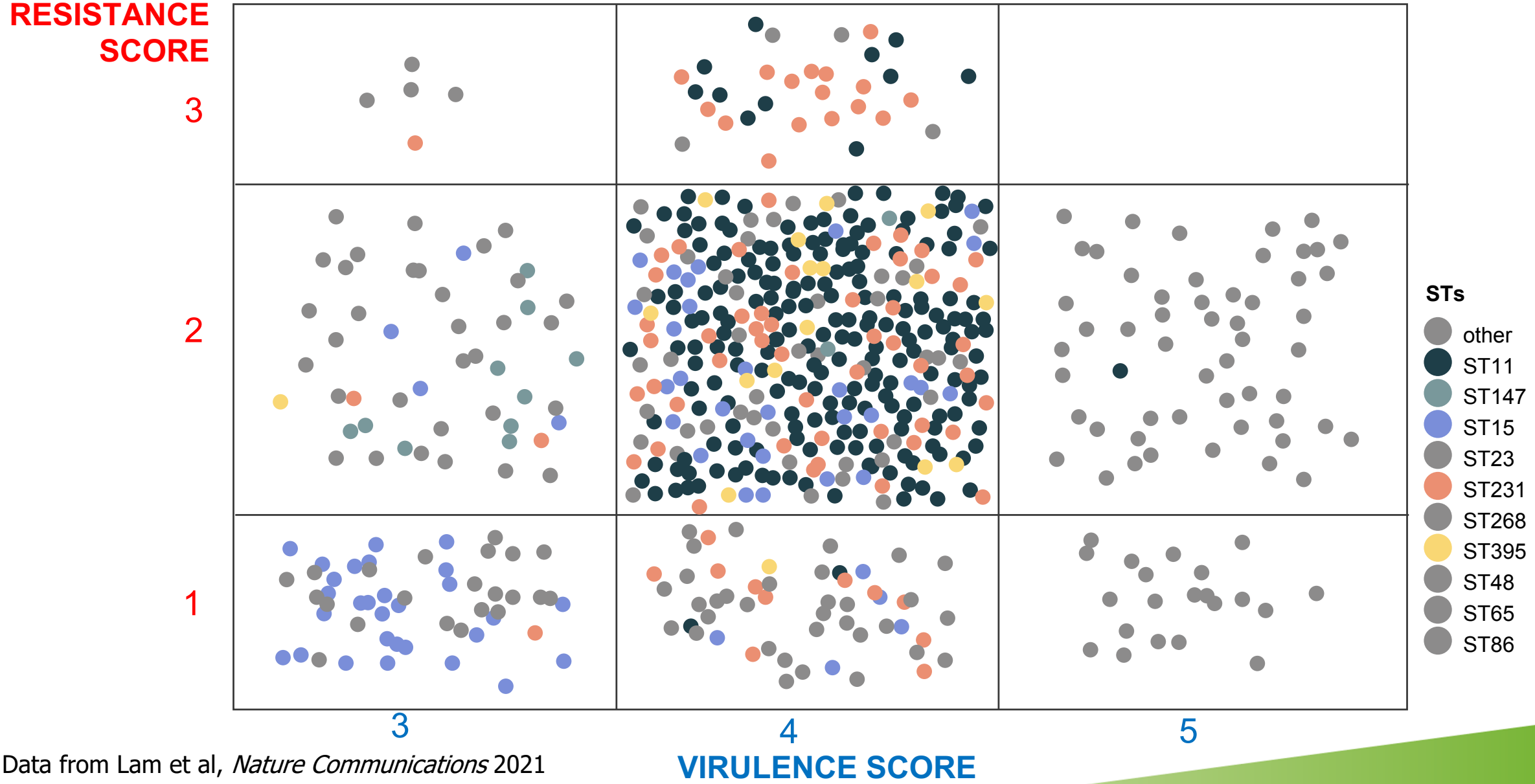
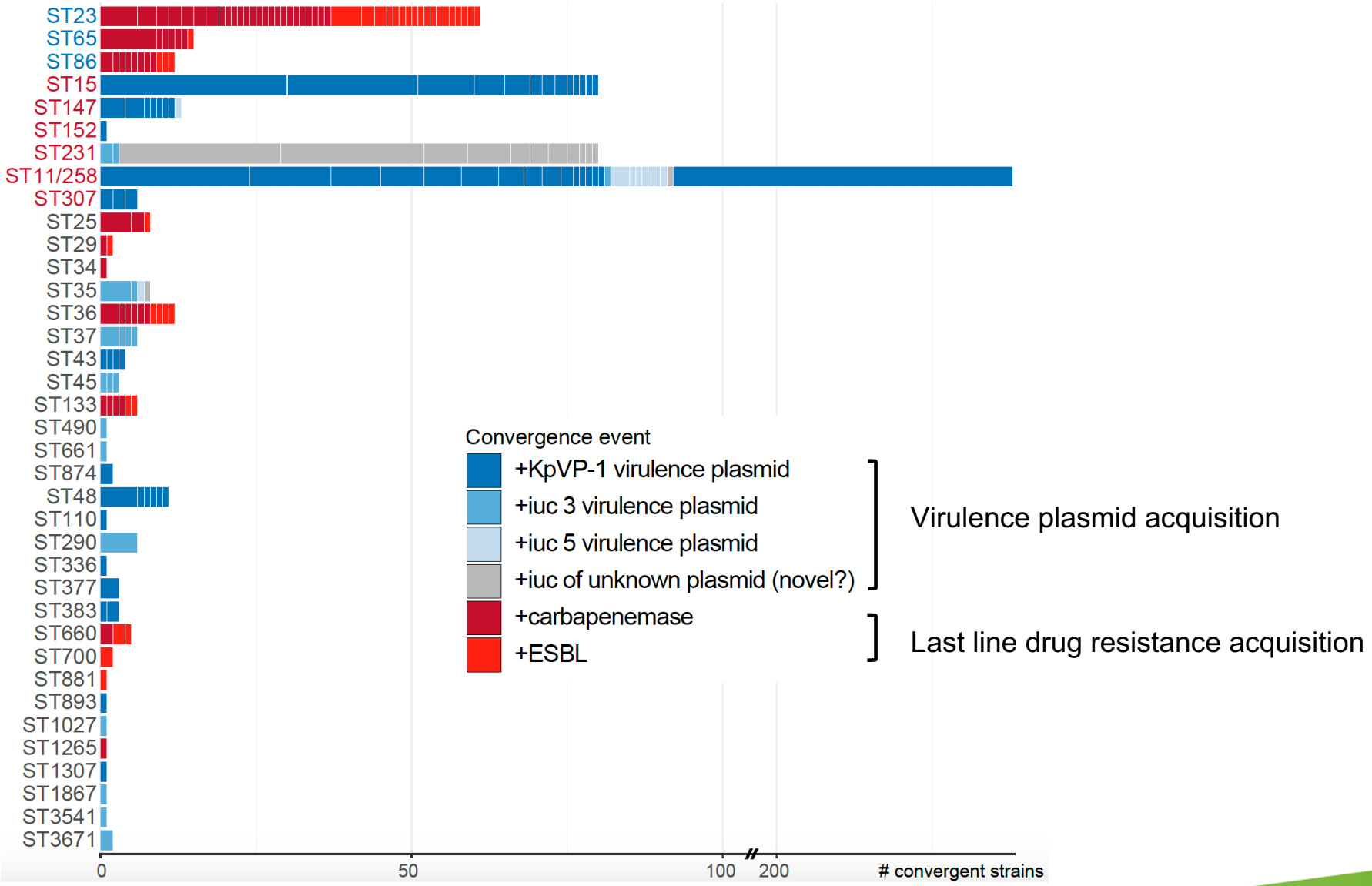


Data from Lam et al, *Nature Communications* 2021

Global snapshot of convergence events

Hypervirulent clones

MDR clones



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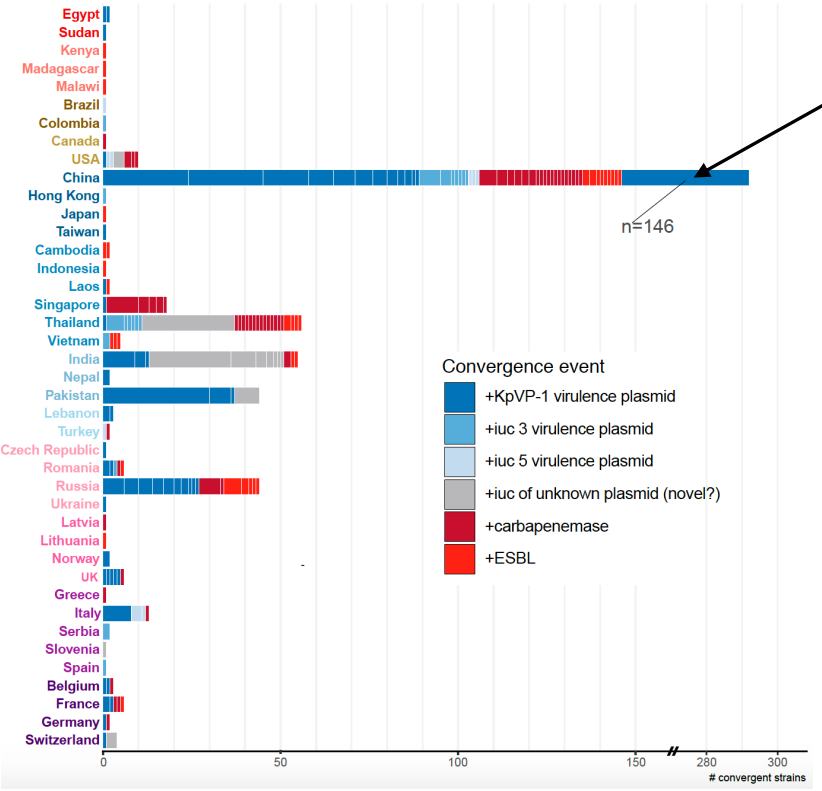

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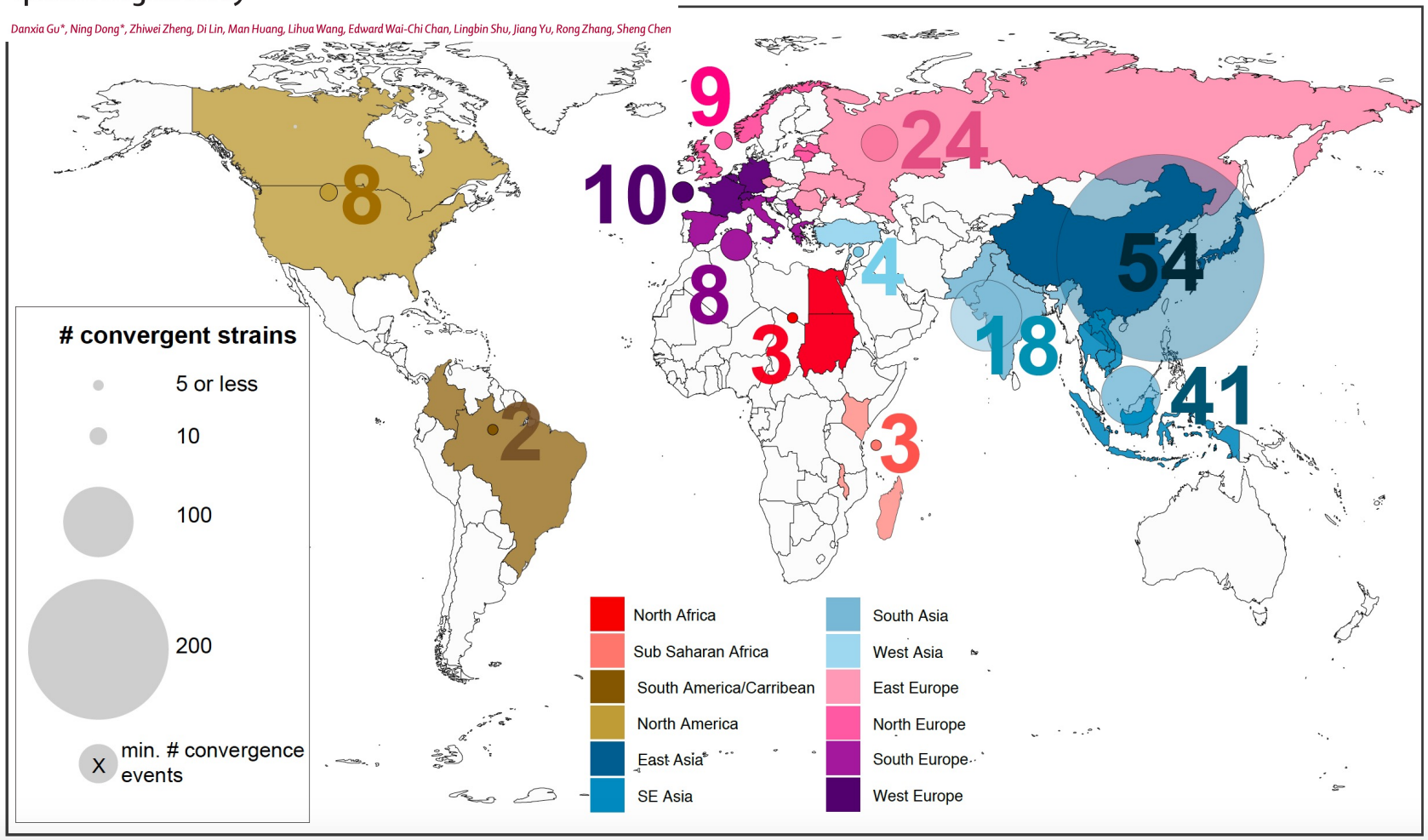
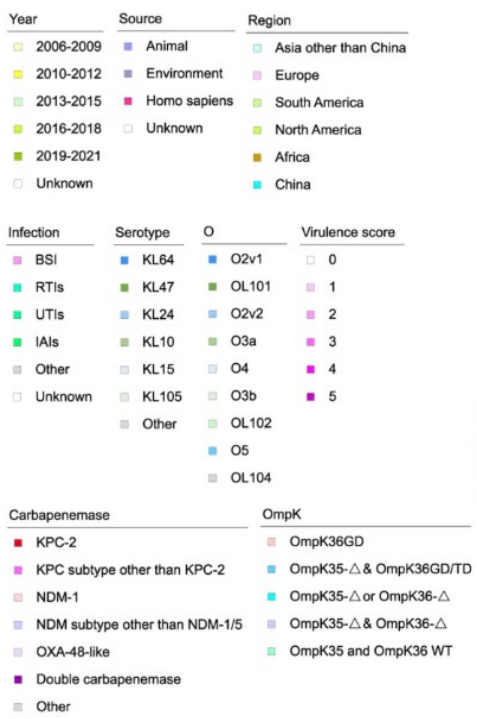


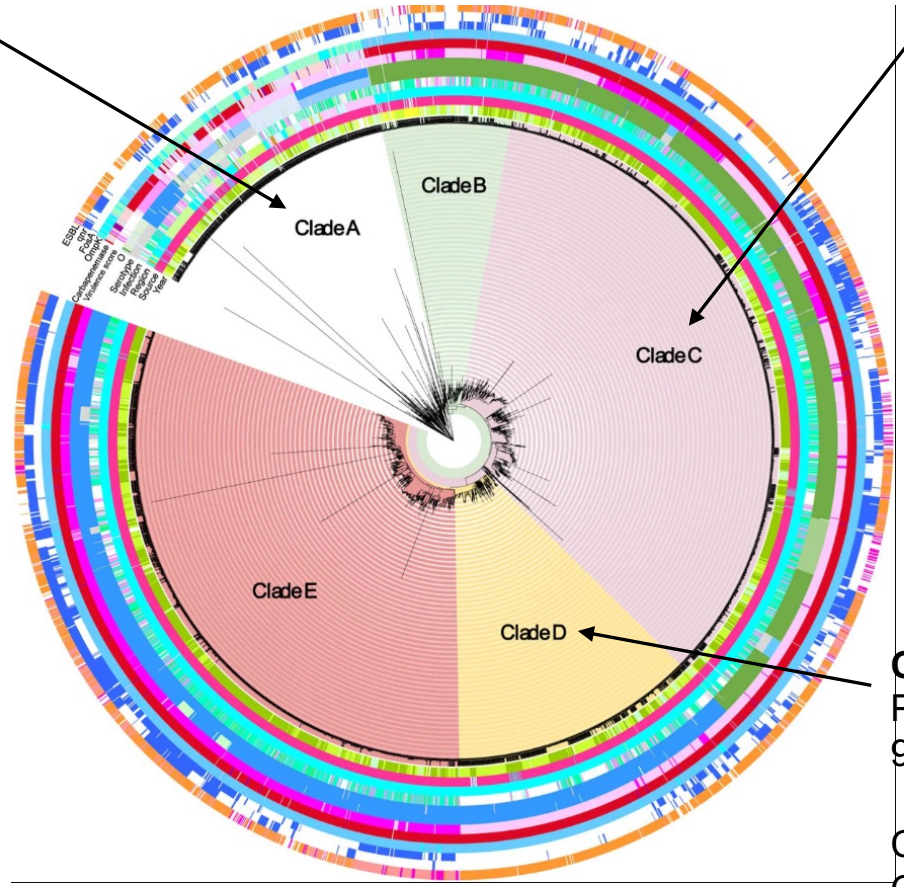
Lam et al, *Nature Communications* 2021

Global snapshot of convergence events - China

N=3386 ST11 CRKp, 2006-2022

Clade A:
Global distribution
Various serotypes
Various carbapenemases





Clades B+C:
Predominantly **KL47/OL101**
98.3% KPC

Clade B: 43.8% with vir score >=4
Clade C: 24.7% with vir score >=4

Clades D+E:
Predominantly **KL64/O2v1**
98.1% KPC

Clade D: 5.3% iuc 1.6% iro 0.2% rmp 4.9% rmpA2
Clade E: 95.2% iuc 14.4% iro 71.1% rmp 91.6% rmpA2

Wang et al, *Drug Resistance Updates* 2024

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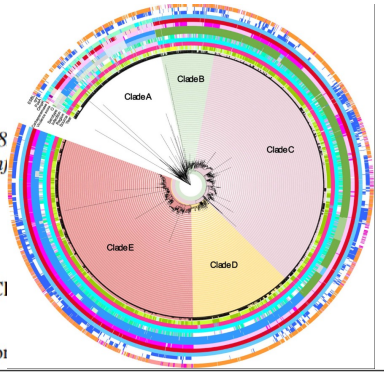
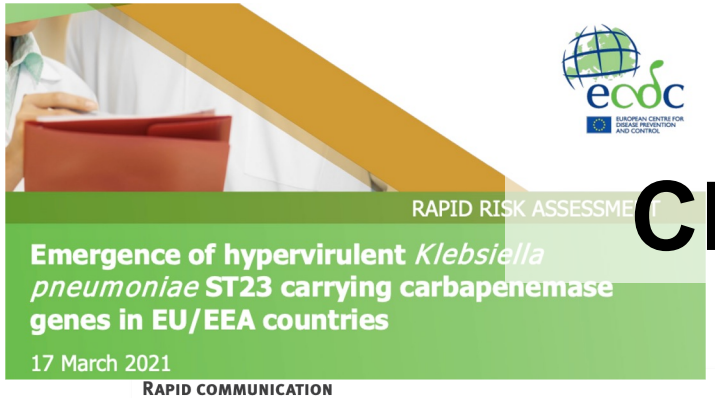
[1]National Leading Research Laboratory of Drug Resistance Proteomics, Department of Biological Sciences, Myo
University, 116 Myongjiro, Yongin, Gyeonggido, Republic of Korea

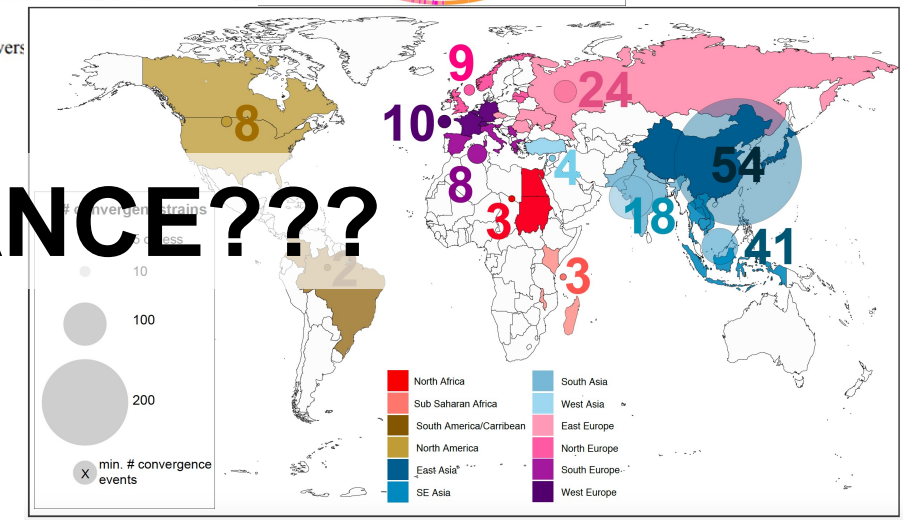
[2]Biotechnology Program, North Shore Community College, 1 Ferncroft Road, Danvers

[#]These authors contributed equally to this work





CLINICAL SIGNIFICANCE???



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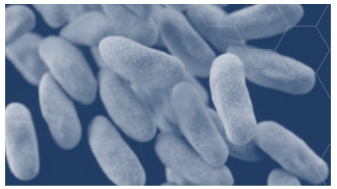
Journal of Antimicrobial Chemotherapy

Convergence of virulence and MDR in a single plasmid vector in MDR *Klebsiella pneumoniae* ST15

Margaret M. C. Lam[1], Kelly L. Wyres[1], Ryan R. Wick[1], Louise M. Judd[1], Aasmund Fostervold[2,3], Kathryn E. Holt[1,4]† and Iren Høyland Löhr[2]*†



Hv*Kp*

+ AMR plasmid

same risk/ threat???

MDR *Kp*

+ virulence plasmid

Convergence of AMR and virulence

THE LANCET
Microbe

Call for prudent use of the term hypervirulence in carbapenem-resistant *Klebsiella pneumoniae*

Yang, McNally & Zhong, 2025.

- No formal/consensus definition for hvKp
- The following features in various combinations have been used to define hvKp:
  - String test
  - Presence of virulence genes
  - **Clinical evidence (infection type, mortality)**
  - **Virulence in infection models**

How to understand convergence?

In the absence of a formal definition for hypervirulence, propose to define convergence of <u>hypervirulence</u> and resistance as:

- Presence of a complete <u>virulence plasmid with intact *iuc*, *rmp*, and *iro*</u> in a MDR strain

Presence of partial virulence plasmid with *iuc+rmpA2* in AMR clones is common, but these are likely not hypervirulent.

More clinical research is needed to understand whether such strains are associated with:

- increased clinical risk? (e.g. disease severity, metastasis, mortality)
- increased dissemination risk? (e.g. increased colonization efficiency, or transmission efficiency/R_0 in different patient groups)

In summary

- AMR (including 3GC and carbapenem resistance) and virulence remain largely segregated in the population i.e. detected in separate strains/clones
- However, convergence of AMR and virulence can occur due to the movement of mobile elements, and appear to be increasingly detected/reported
- Kleborate can be used to identify potential convergent genomes – using virulence/resistance scores AND checking for presence of AMR and virulence genes (intact *iuc+iro+rmp*)
- Genome data demonstrates convergence in multiple clones: MDR strains with intact/deletion variants of the virulence plasmid dominate
- Lack of consensus definition of 'hyper'virulence impacts interpretation of AMR+hypervirulence convergence

References

Gu et al. The Lancet Infectious Diseases 2018, PMID: 28864030.
Wyres et al. PloS Genetics 2019, PMID: 30986243.
David et al. Nature Microbiology 2019, PMID: 31358985.
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