

KlebNET-GSP

LECTURE SERIES

Klebsiella pneumoniae Genomic Epidemiology and Antimicrobial Resistance

Seroepidemiology of *Klebsiella*

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Intended Learning Objectives



Specific objectives of this session:

1. Understand the relationship between K/O antigen diversity and *Kpn* population structure i.e. diversity within/between clones
2. Understand the diversity of K/O antigens among clinical *Kpn* isolates
3. Discuss key considerations for *Kpn* sero-epidemiology analyses

Outline

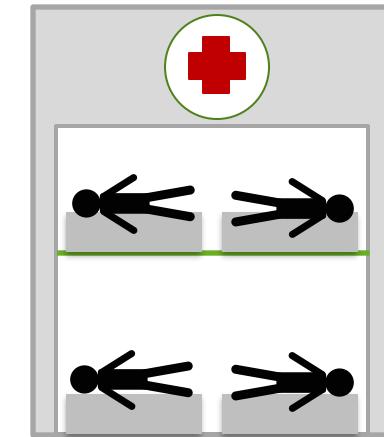
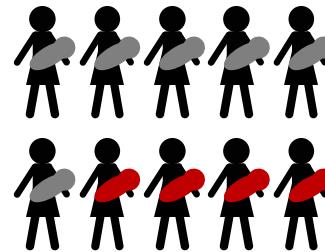
This session consists of the following elements

1. The *Kpn* vaccine value profile
2. Brief recap on *Kpn* K and O antigen genetics
3. K and O diversity in hypervirulent and multidrug resistant clones
4. K and O diversity in clinical *Kpn* collections:
 - Geographic differences
 - Temporal fluctuations
5. Meta-analysis of neonatal sepsis isolates
6. Sero-epi app
7. Summary

WHO *Kpn* vaccine value profile

Use cases:

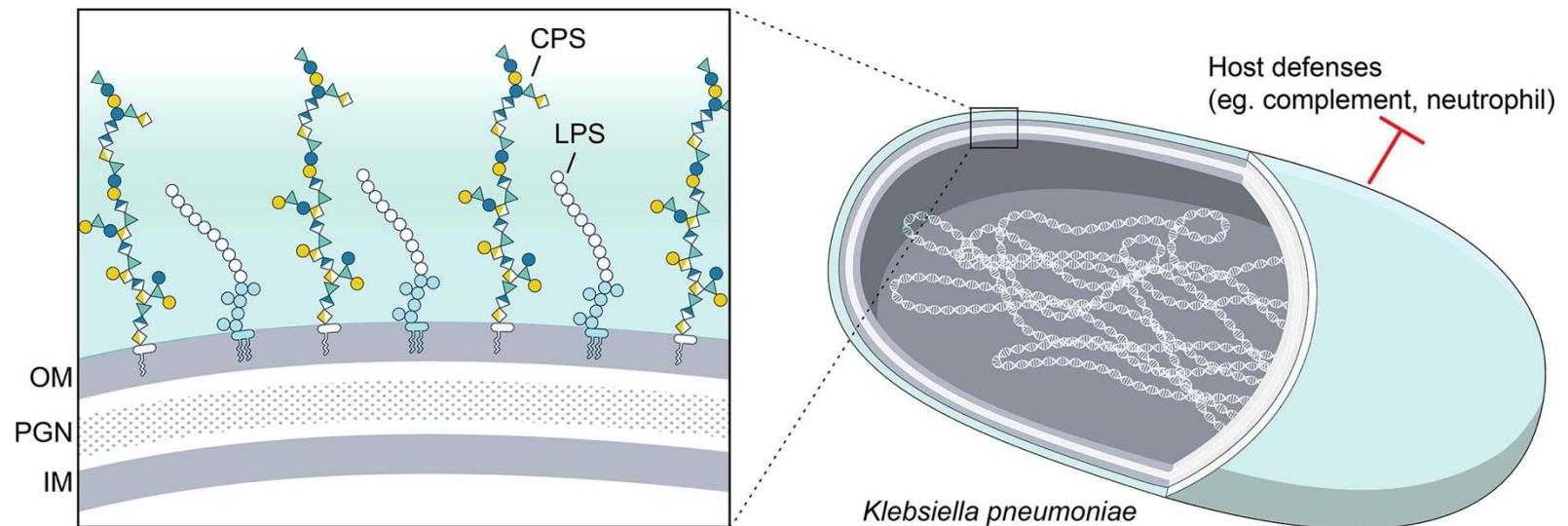
- Neonatal sepsis
- Adult HAIs



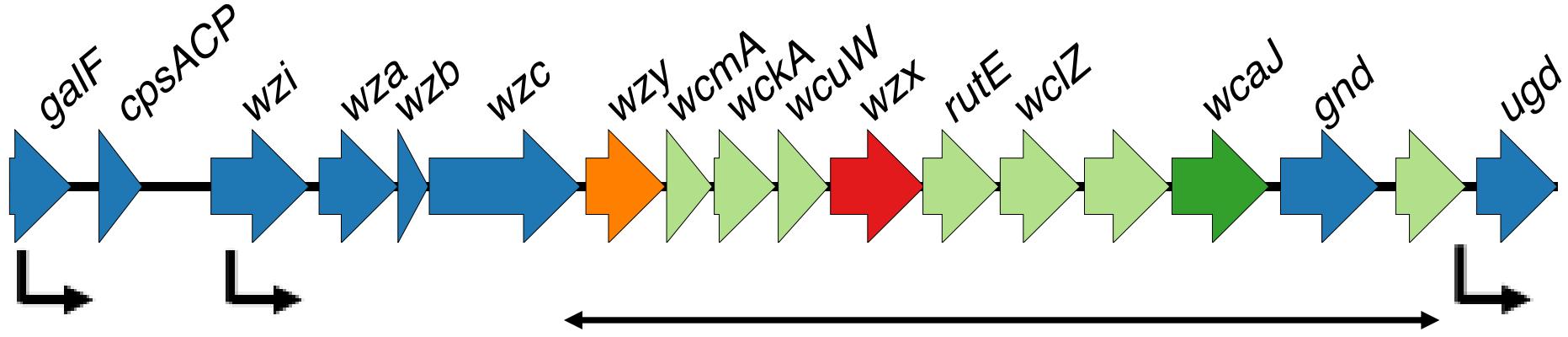
Major antigen targets:

- Capsule (K)
- Outer-LPS (O)

Coverage target:
≥70% infections



Klebsiella K loci are defined by unique gene content



**>160 K loci
defined to-date**

█ Common proteins
inc. core assembly
machinery

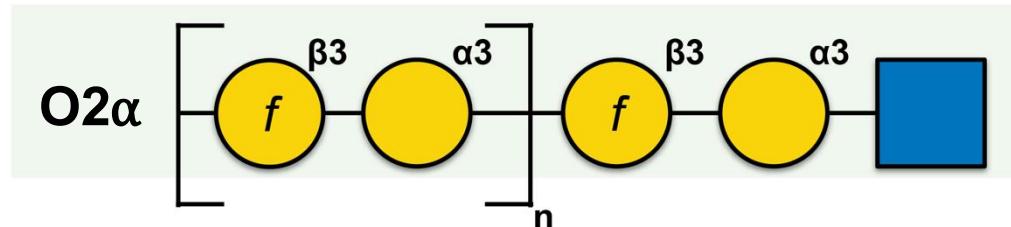
█ Wzy capsule repeat
unit polymerase

█ WbaP / WcaJ initiating
glycosyltransferase

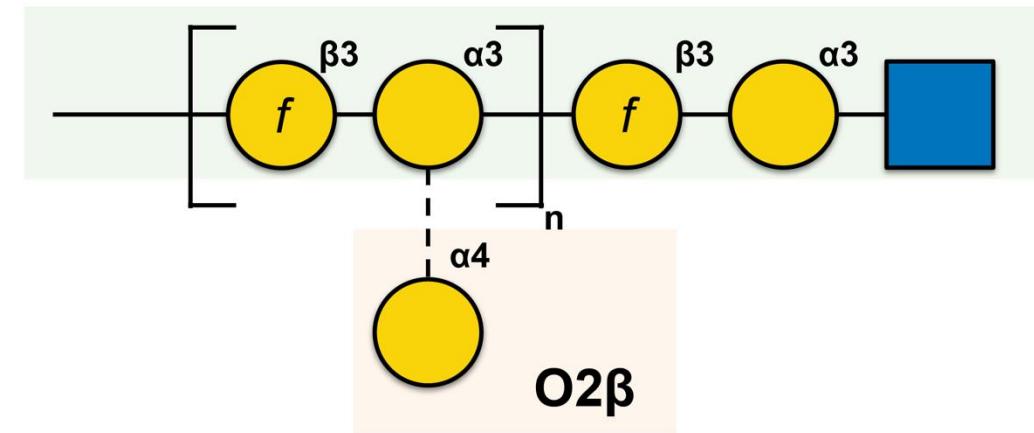
█ Wzx flippase

█ Other sugar synthesis
and processing

O types determined by O loci & additional genes



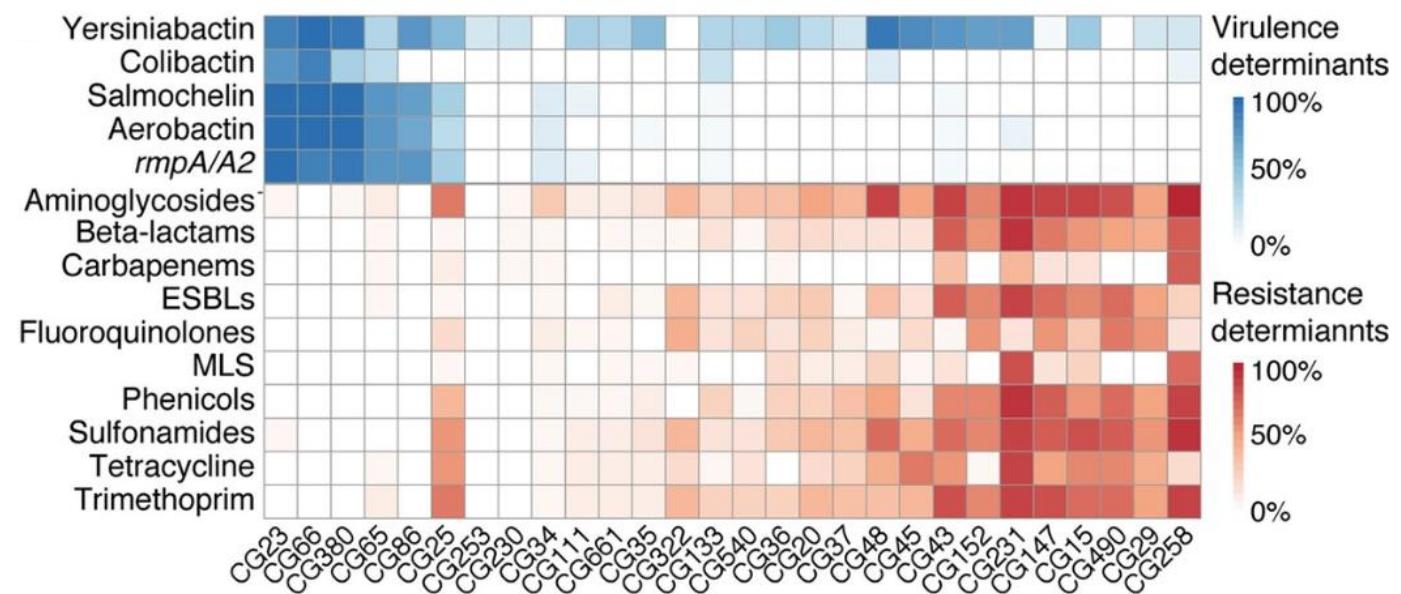
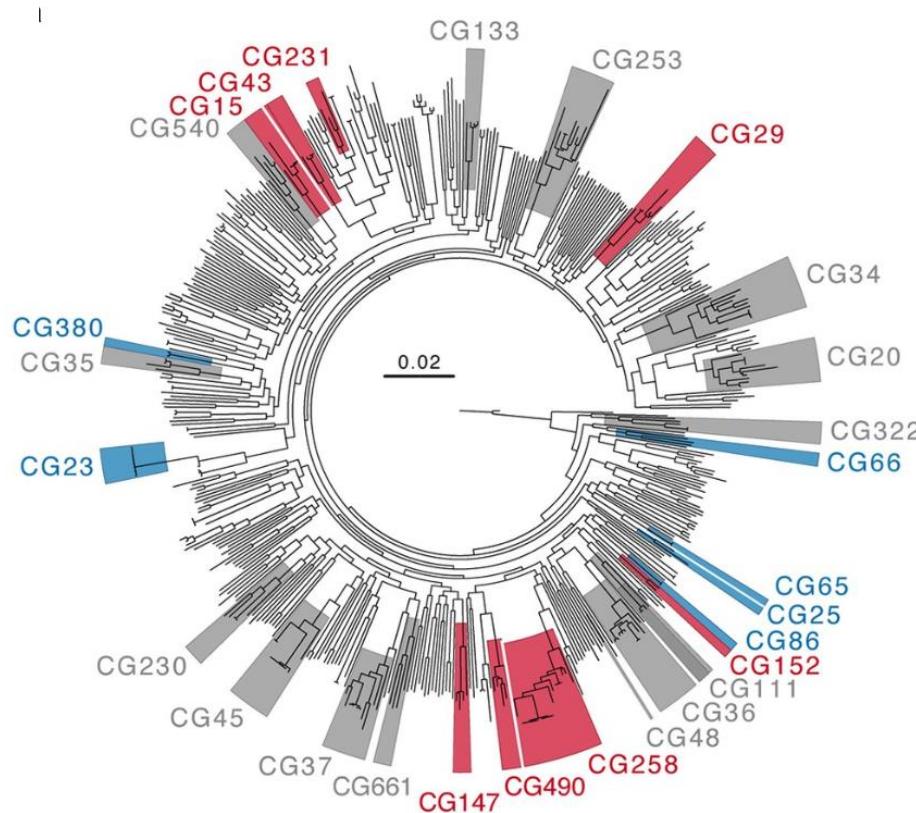
OL2 α



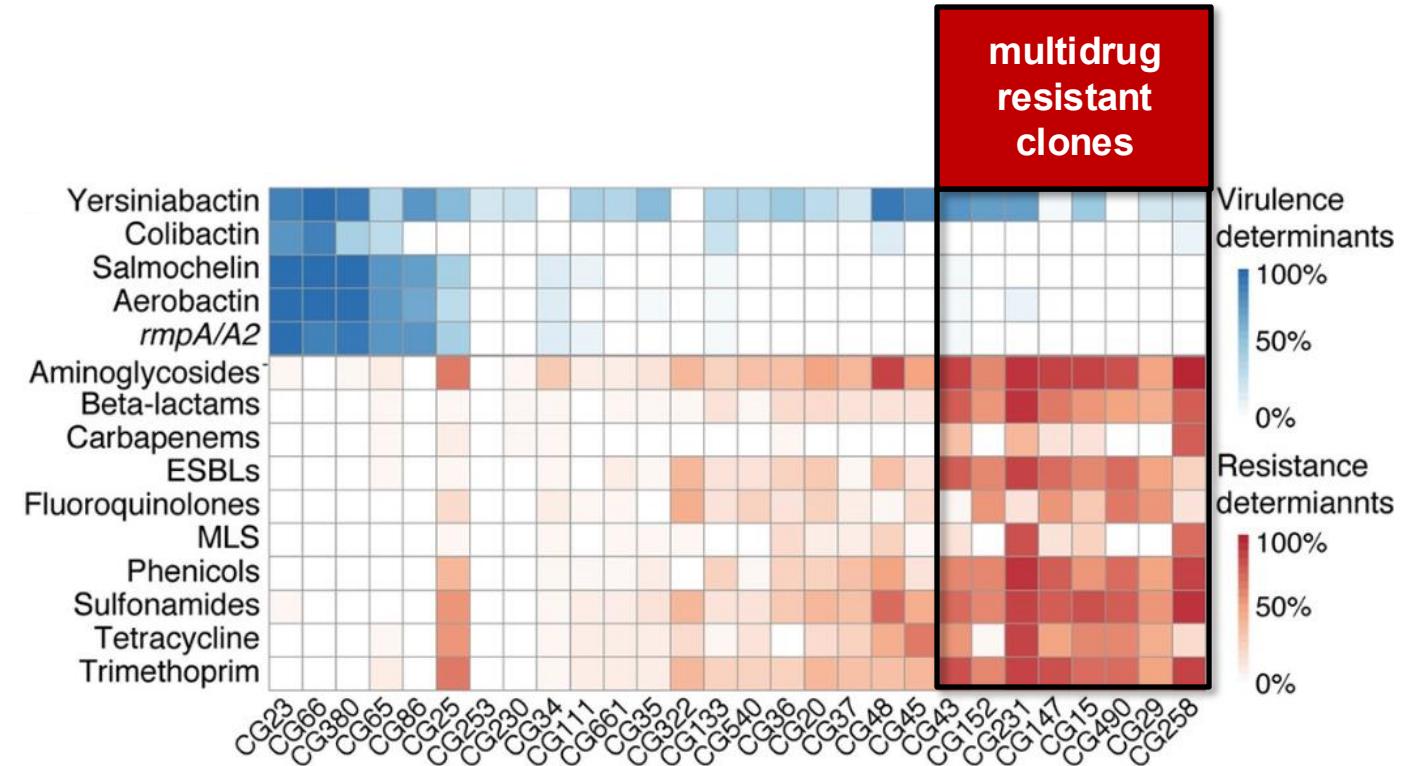
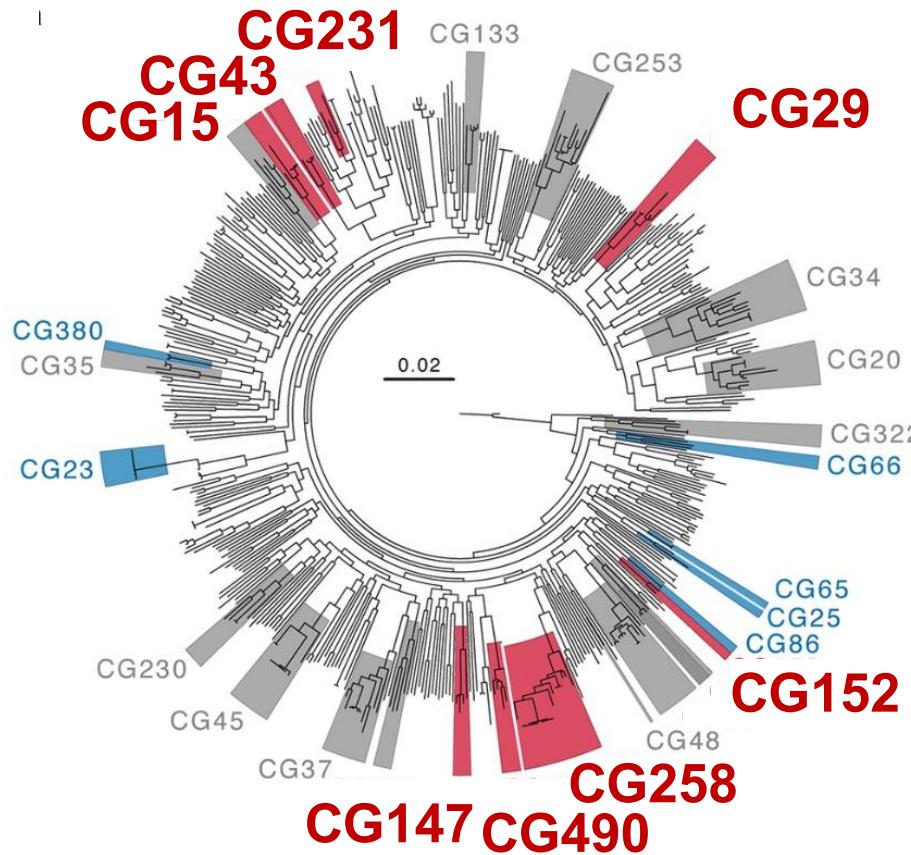
OL2 α + *gm|2β*

>20 combinations
identified to-date

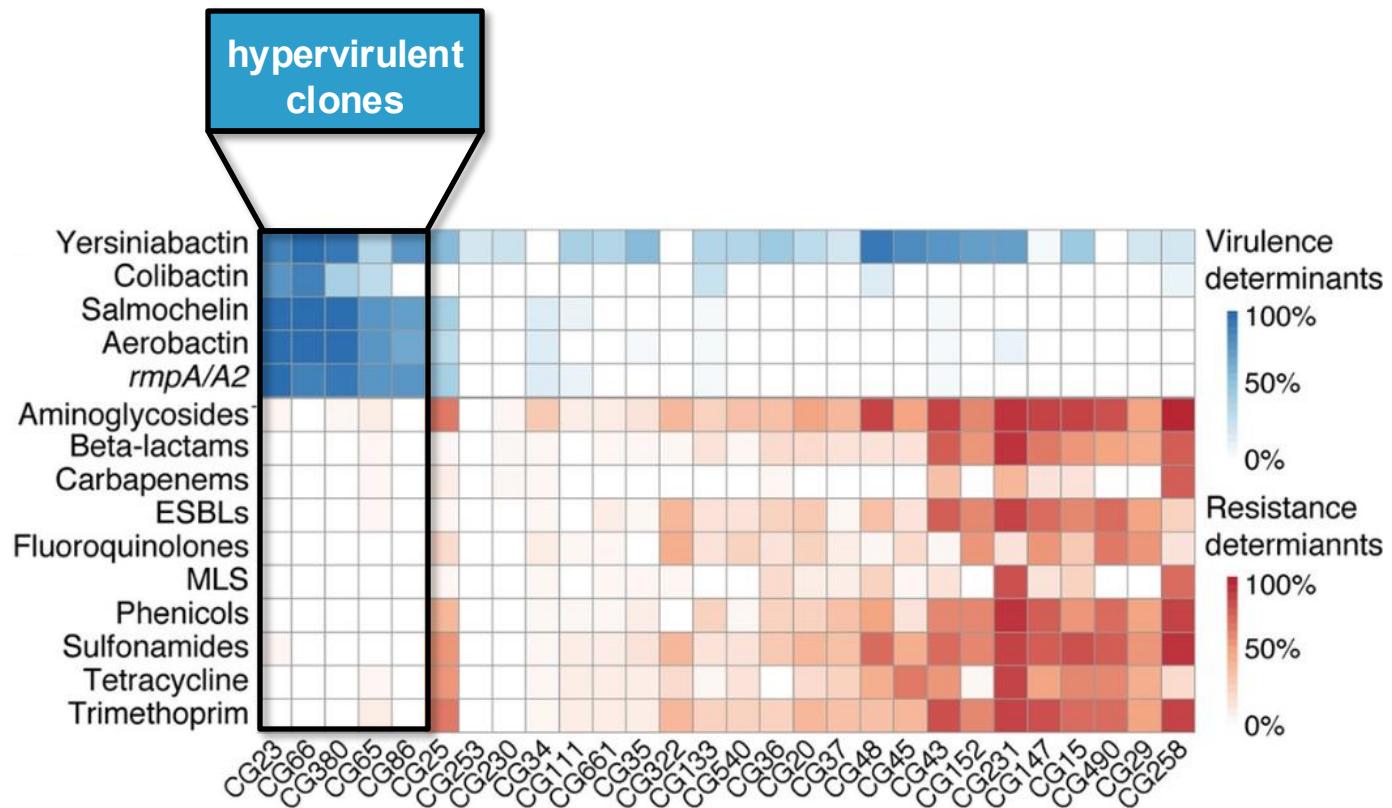
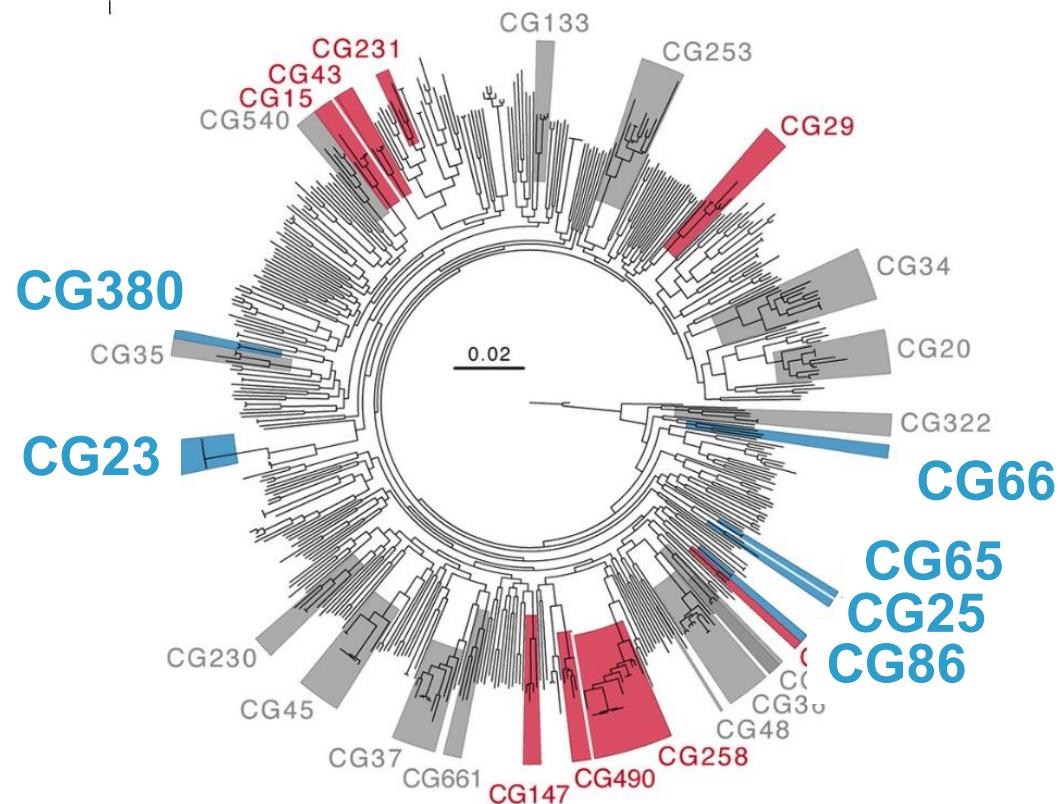
Distribution of AMR and virulence genes



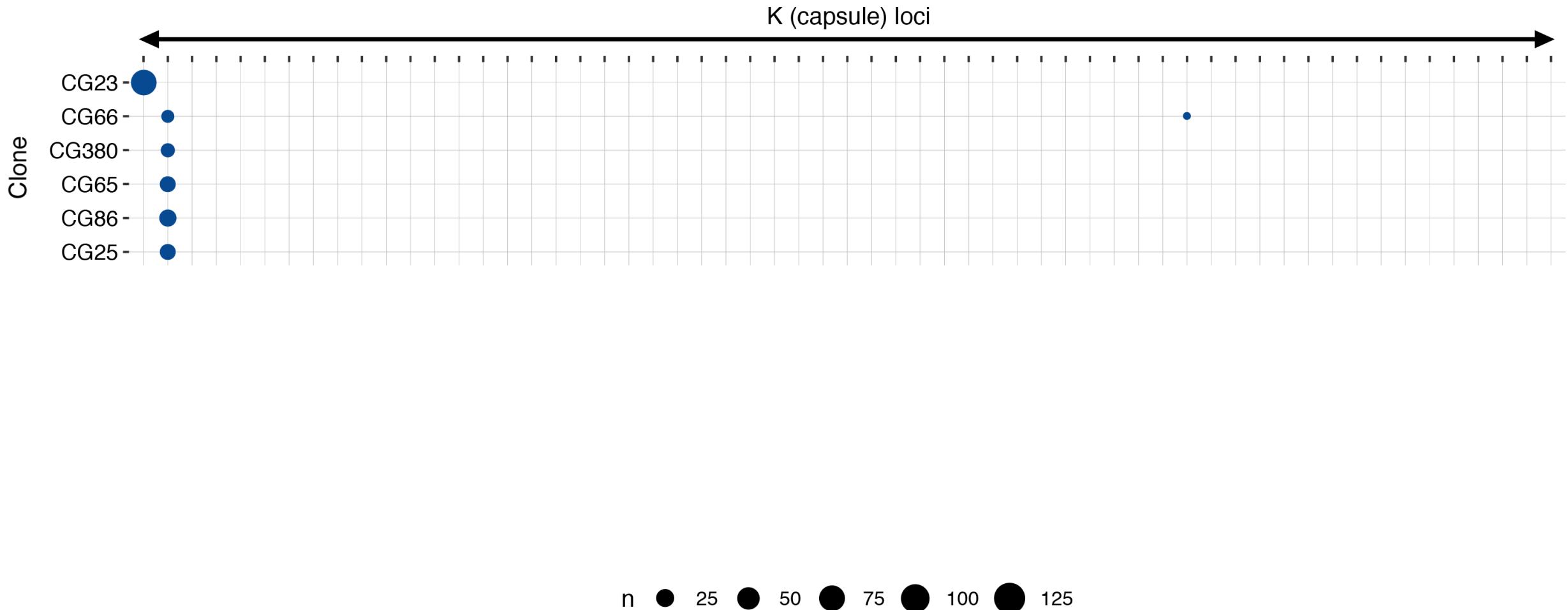
Distribution of AMR and virulence genes



Distribution of AMR and virulence genes



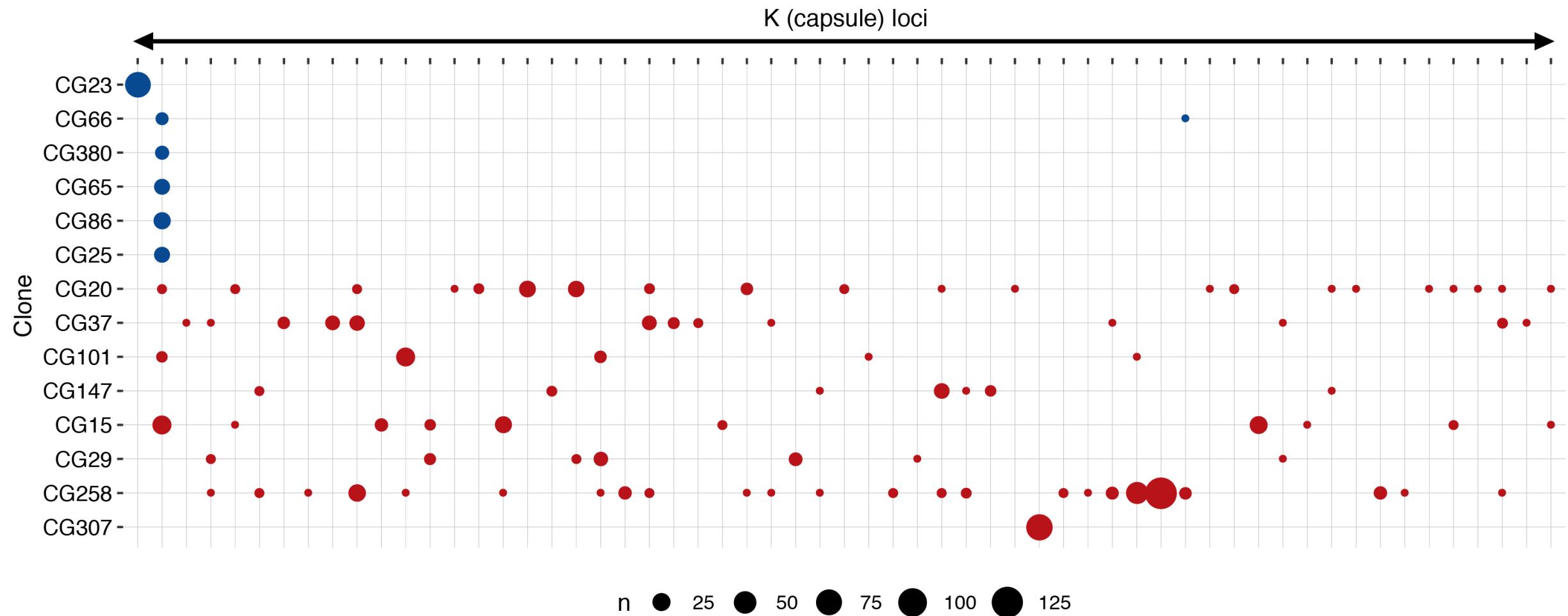
Hypervirulent clones carry either KL1 or KL2



$n \geq 20$ per clone

Data from Wyres *et al* PLoS Genetics 2019

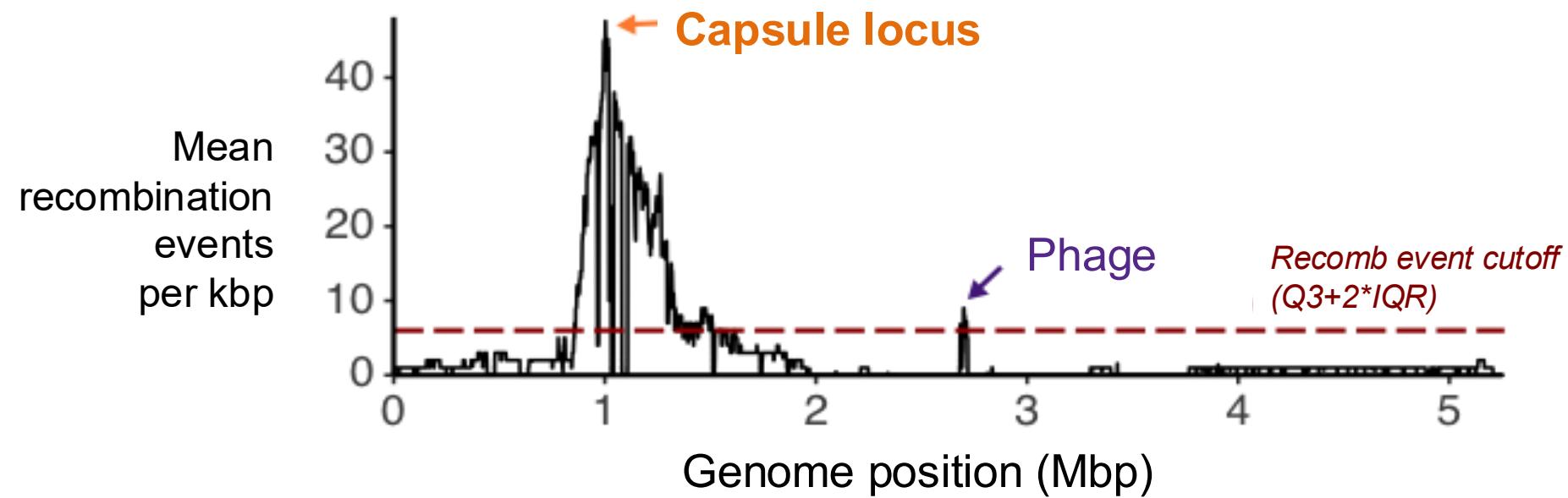
MDR clones carry diverse K loci



$n \geq 20$ per clone

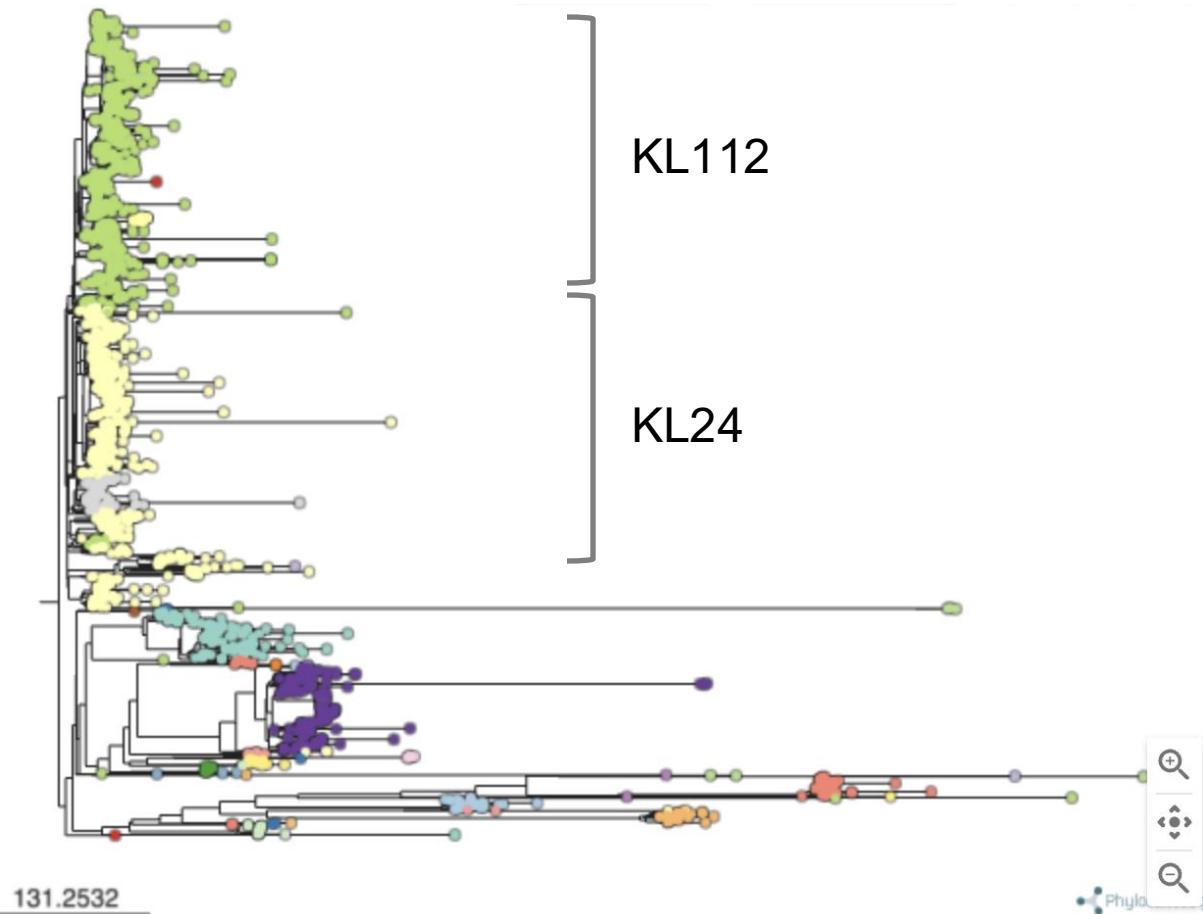
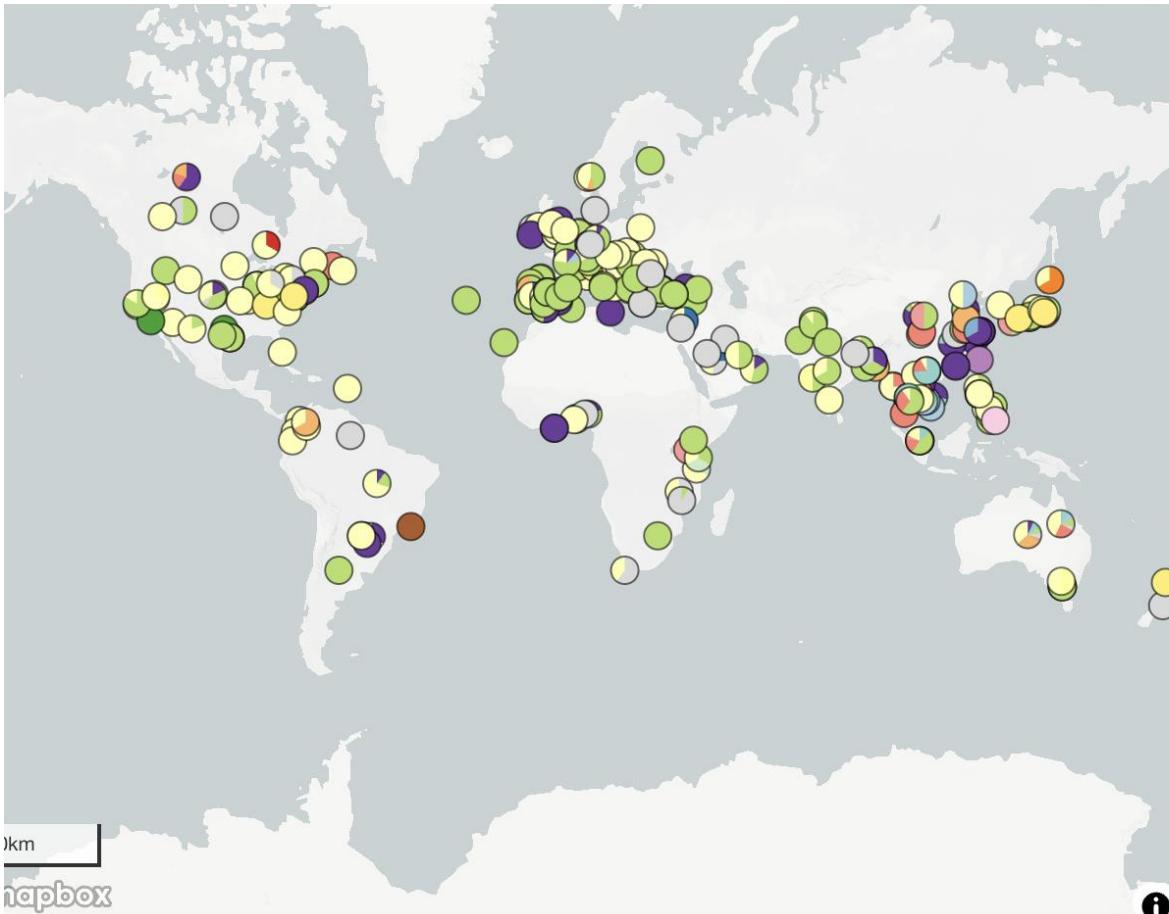
Data from Wyres *et al* PLoS Genetics 2019

K locus is a recombination hotspot in MDR clones



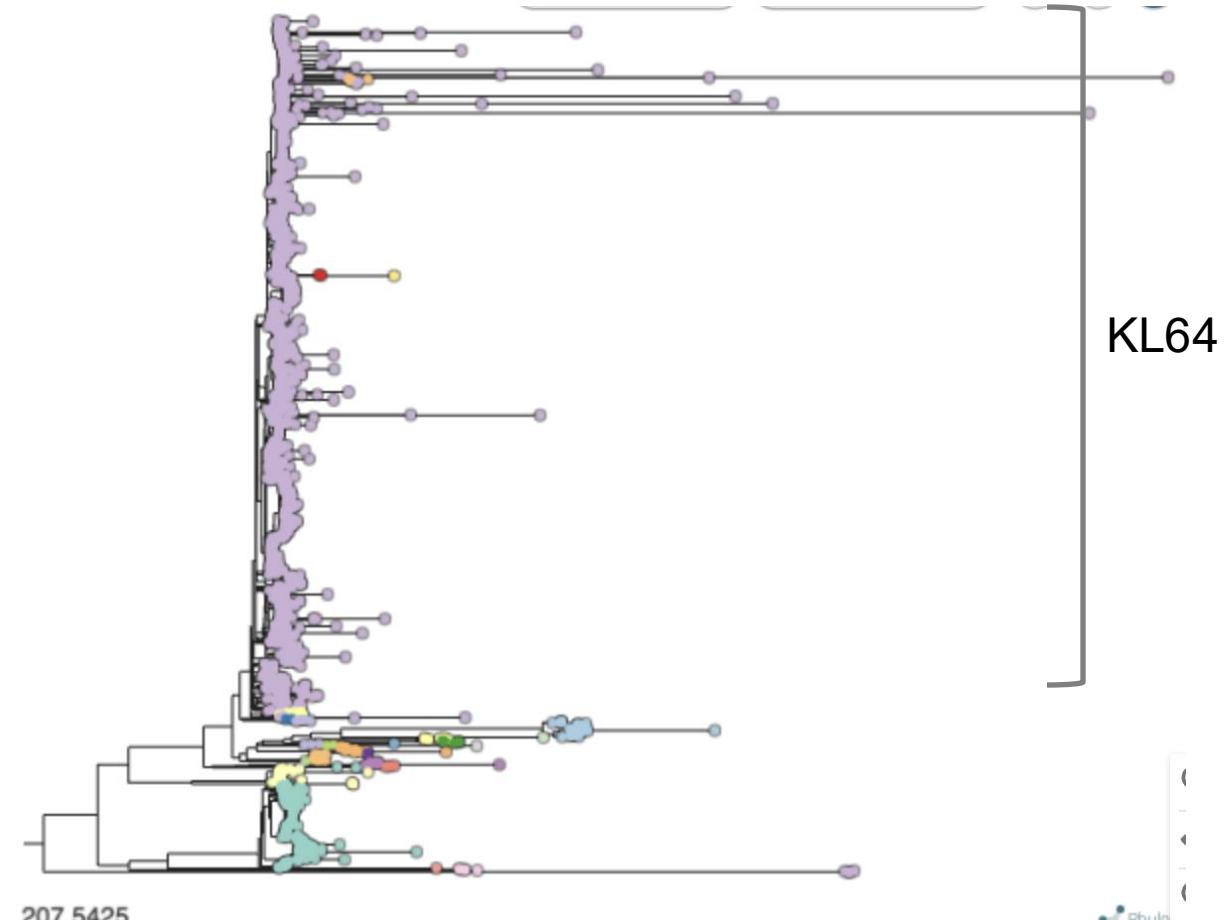
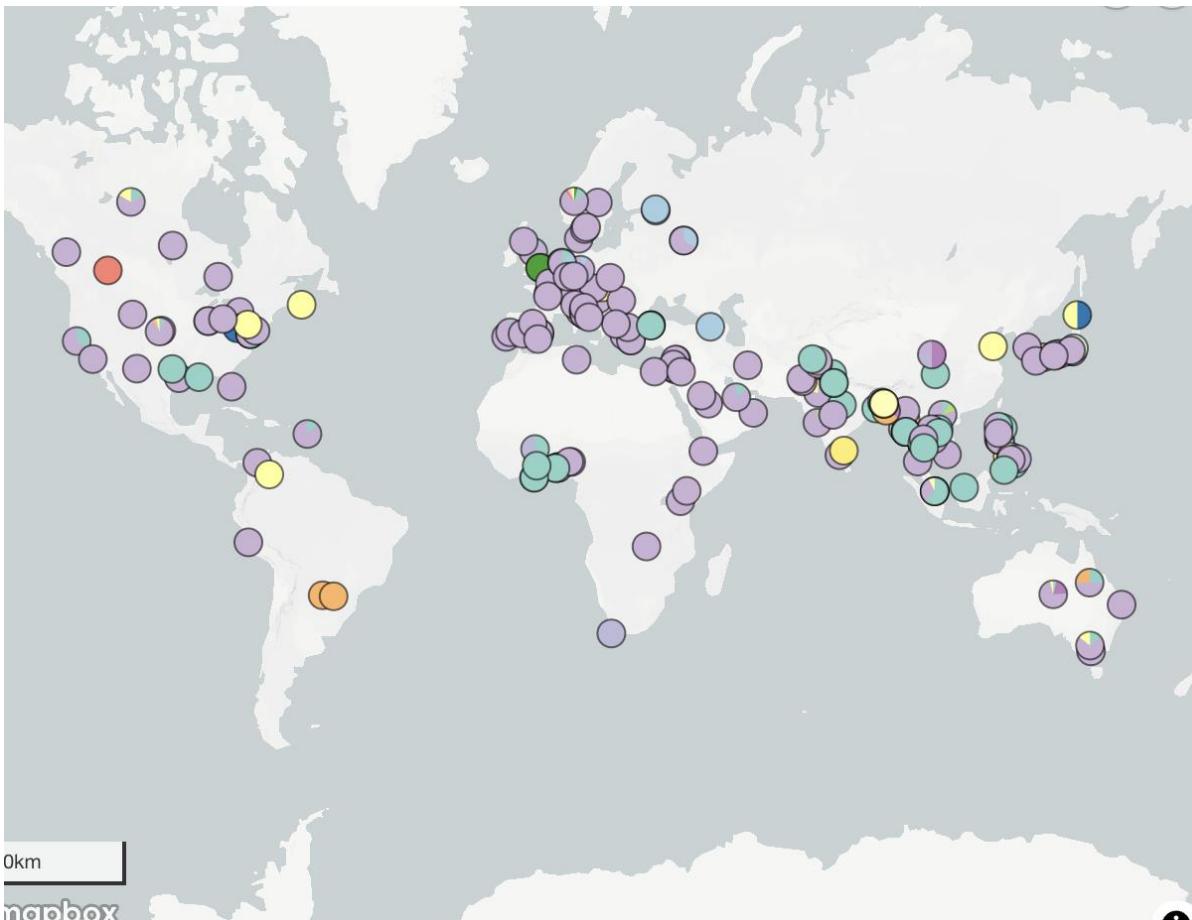
Some ST + KL combinations have proliferated

~1800 ST15 genomes, 1968-2023

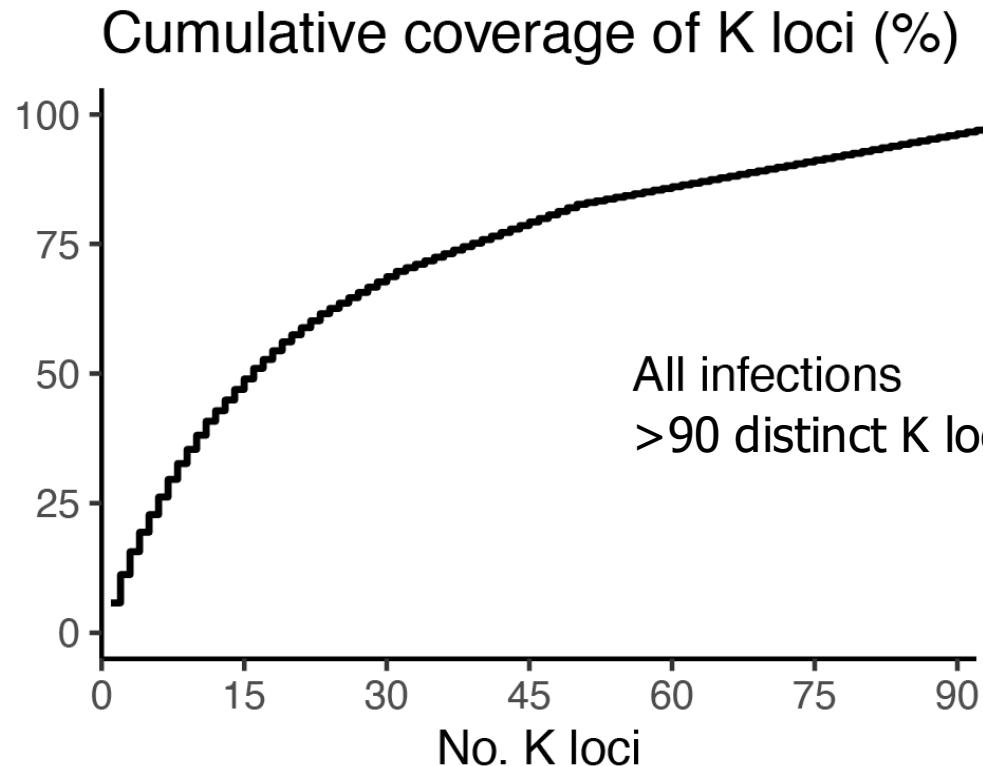


Some ST + KL combinations have proliferated

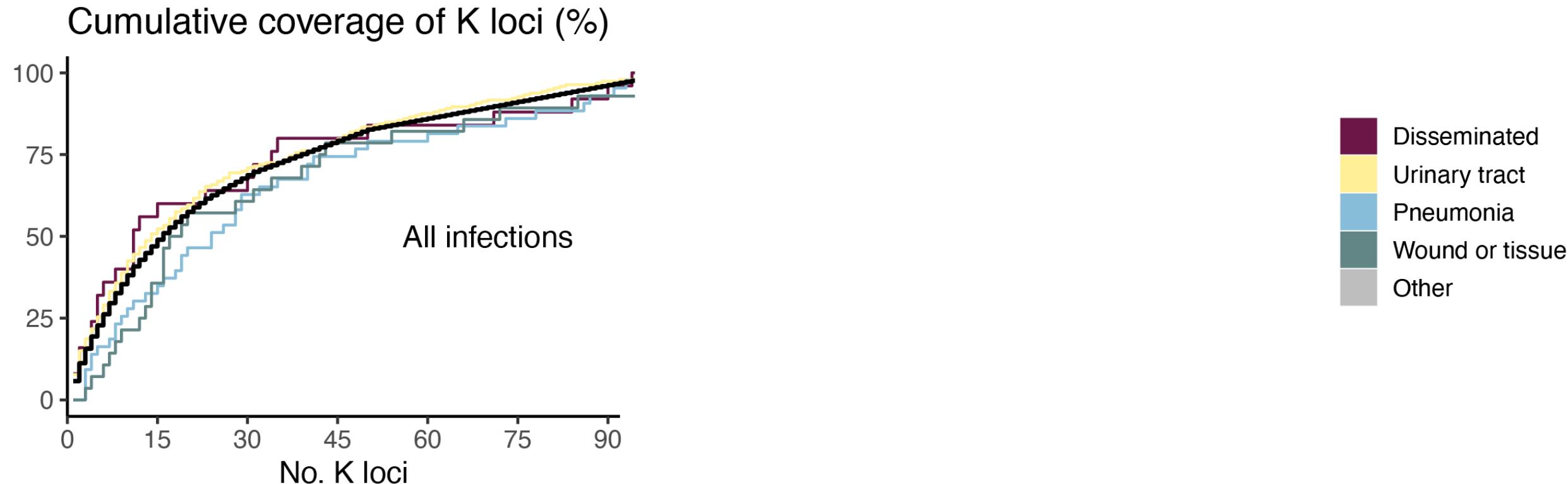
~2000 ST147 genomes, 2014-2023



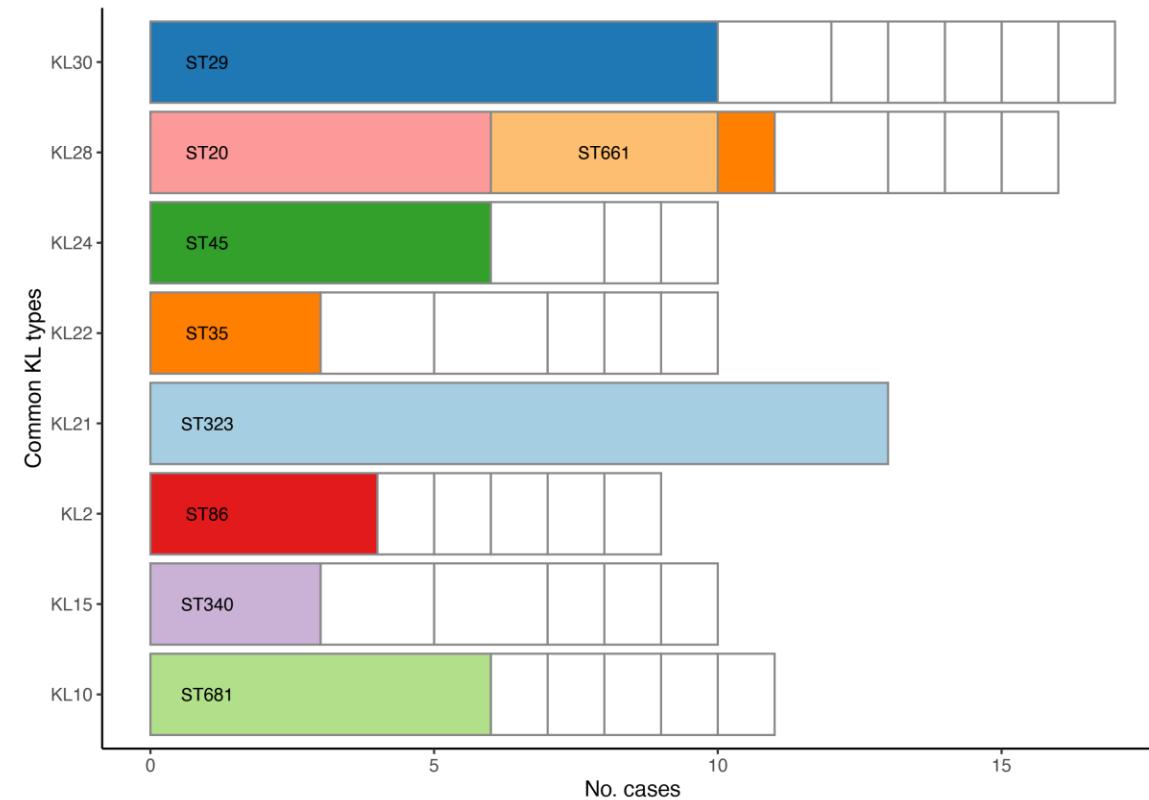
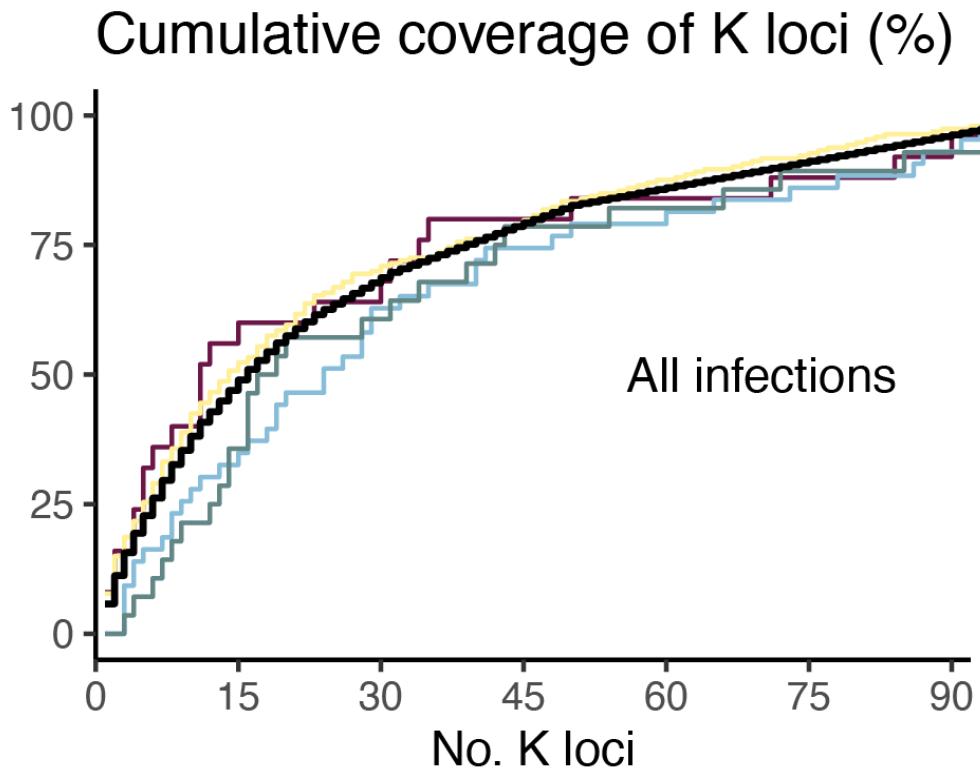
Substantial K diversity in 1 year of *Kpn* infections (n=294)



Diversity similar by infection type

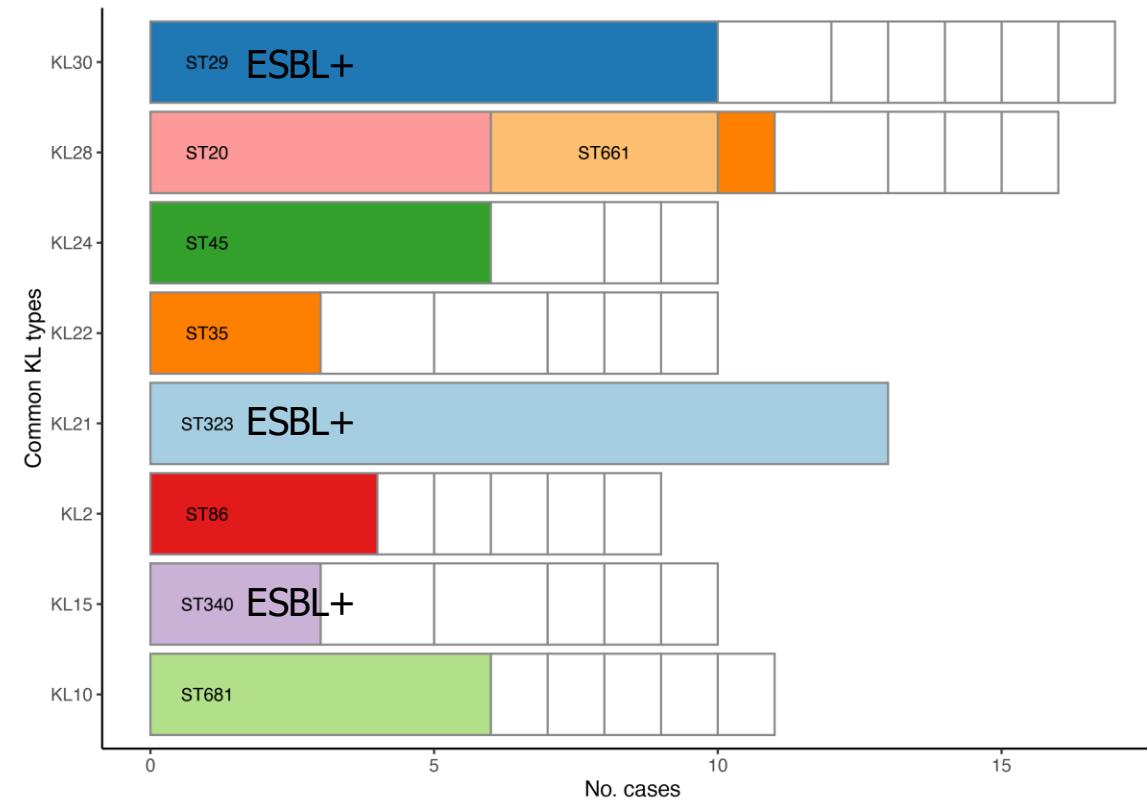
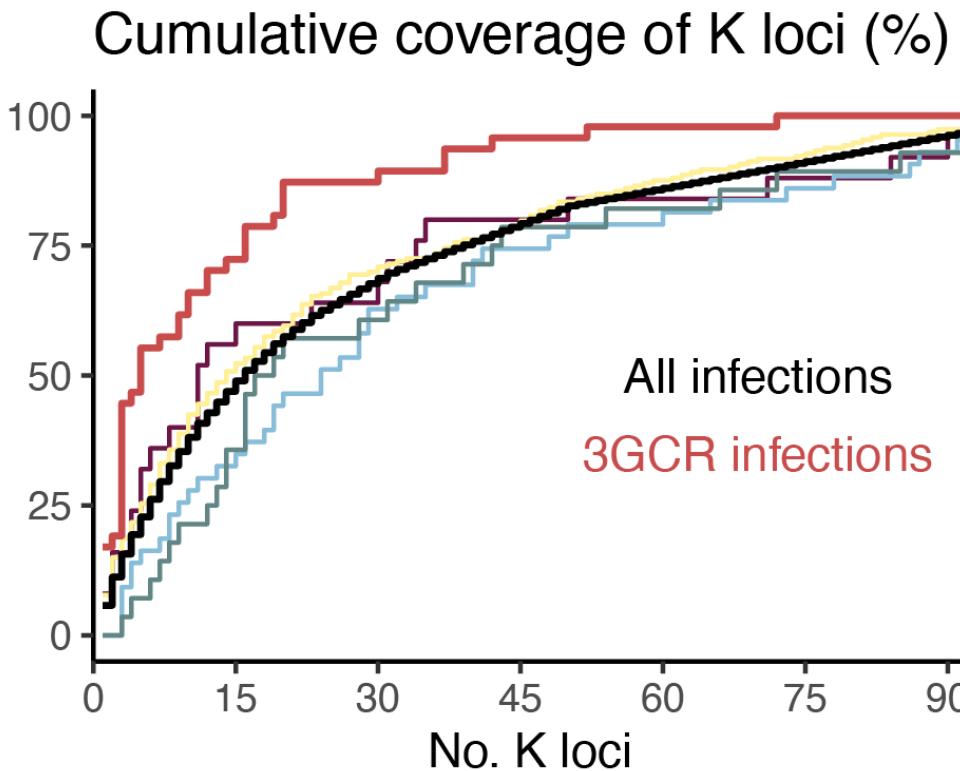


Common K loci associated with specific clones



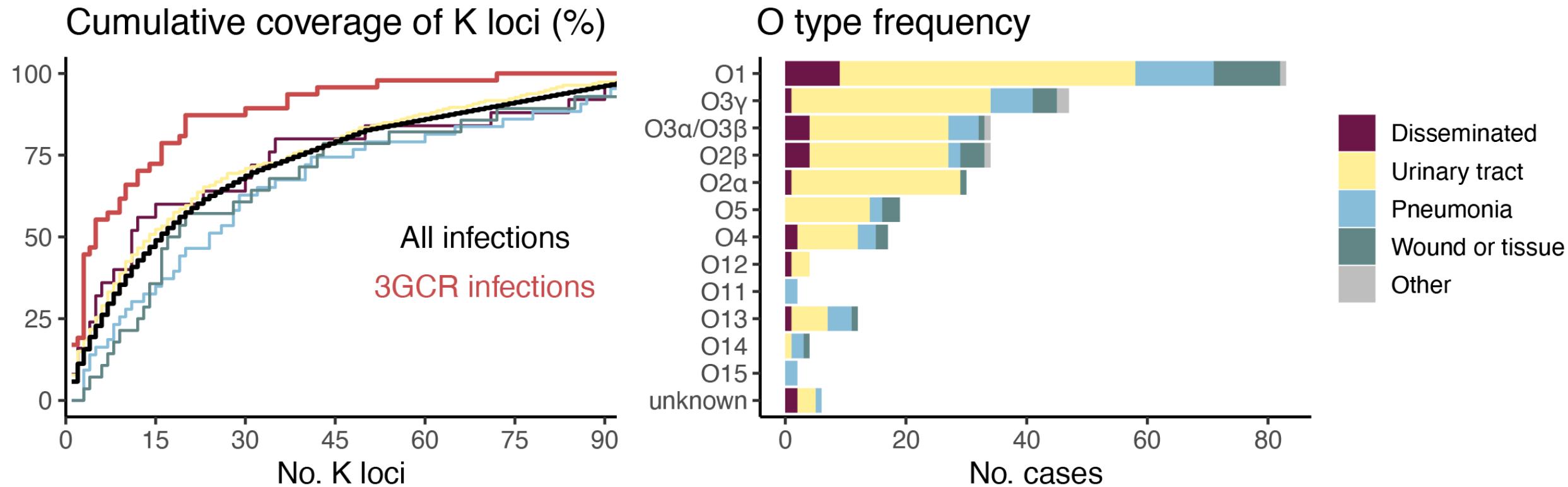
Note: few hypervirulent ST23 infections → KL1 not common

Lower diversity among 3GC resistant infections



Note: few hypervirulent ST23 infections → KL1 not common

Comparable O diversity by infection type

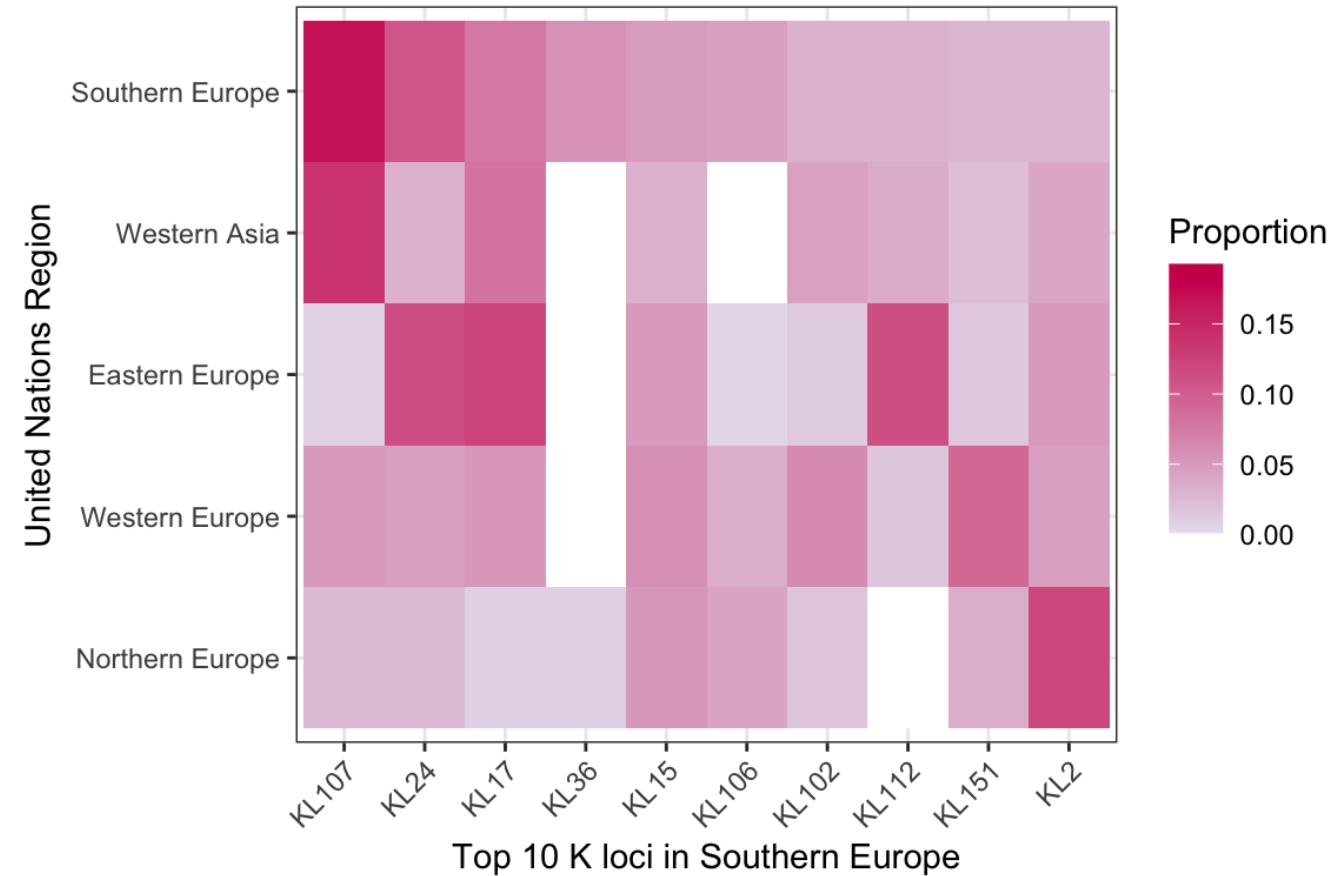


K frequencies differ by geography



The screenshot shows a journal article from *nature microbiology*. The title is "ARTICLES" followed by the DOI: <https://doi.org/10.1038/s41564-019-0492-8>. The main title of the article is "Epidemic of carbapenem-resistant *Klebsiella pneumoniae* in Europe is driven by nosocomial spread". The authors listed are Sophia David¹, Sandra Reuter², Simon R. Harris³, Corinna Glasner⁴, Theresa Feltwell³, Silvia Argimon¹, Khalil Abudahab¹, Richard Goater¹, Tommaso Giani⁵, Giulia Errico⁶, Marianne Aspbury⁷, Sara Sjunnebo⁸, the EuSCAPE Working Group⁹, the ESGEM Study Group¹⁰, Edward J. Feil¹¹, Gian Maria Rossolini^{5,12}, David M. Aanensen^{1,13,14*} and Hajo Grundmann^{1,2,4,14*}.

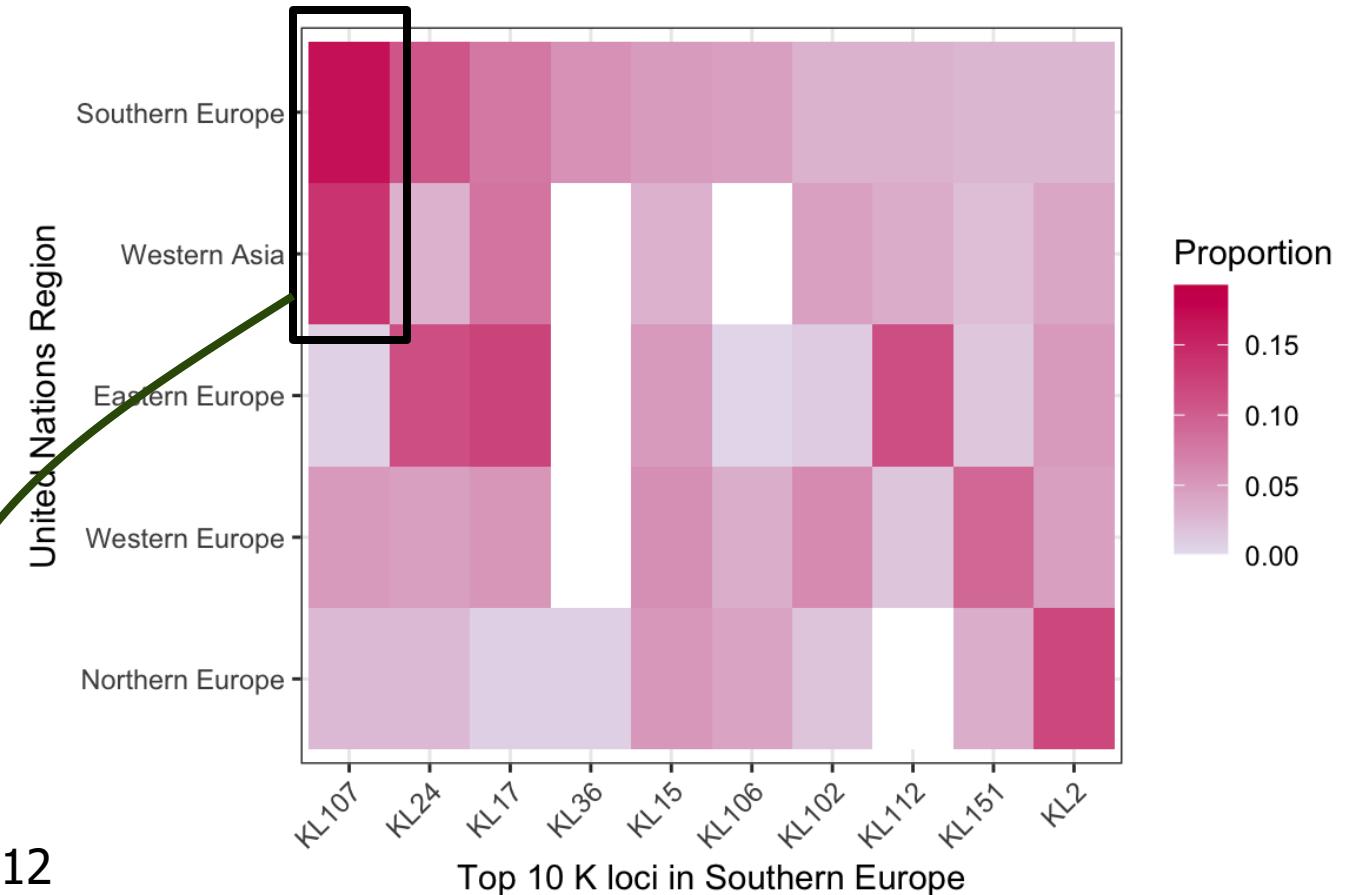
K frequencies differ by geography



Geographic differences driven by clone associations

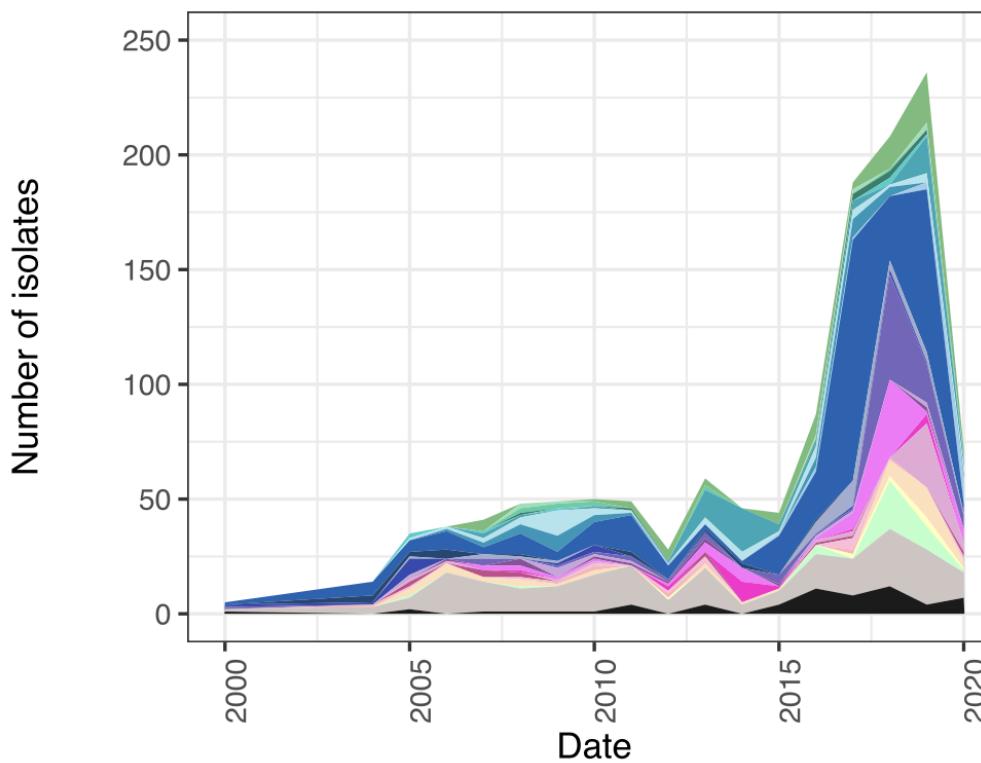


ST258 / ST512
 (Italy and Israel)

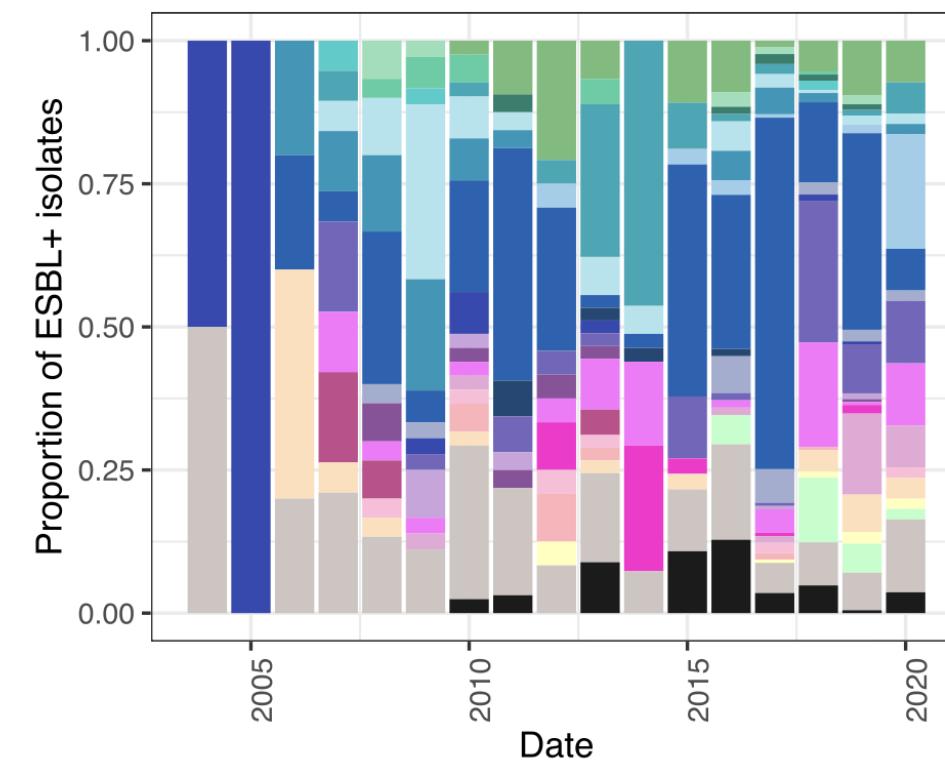


K frequencies fluctuate through time

K-locus over time



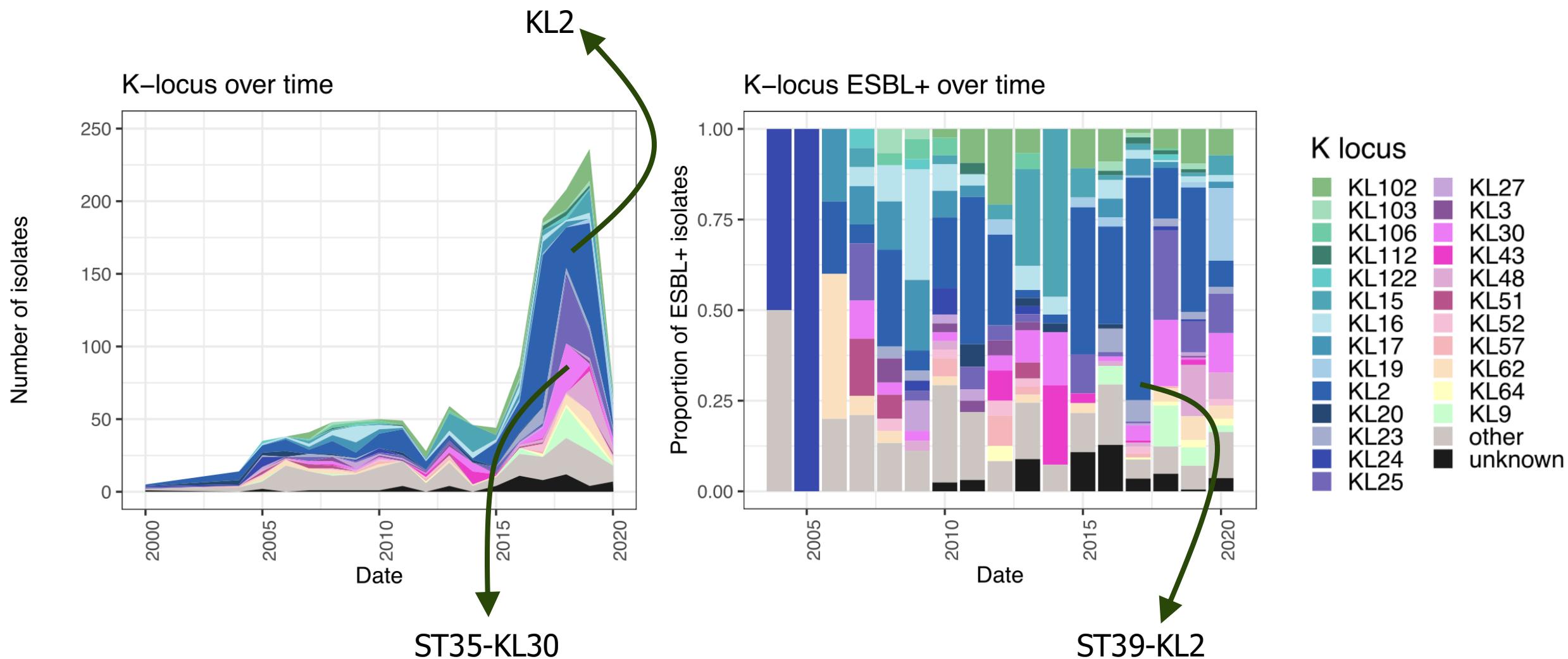
K-locus ESBL+ over time



K locus

KL102	KL27
KL103	KL3
KL106	KL30
KL112	KL43
KL122	KL48
KL15	KL51
KL16	KL52
KL17	KL57
KL19	KL62
KL2	KL64
KL20	KL9
KL23	other
KL24	KL25
KL25	unknown

K frequencies impacted by successive clonal expansions



Considerations for robust *Kpn* sero-epidemiology analyses



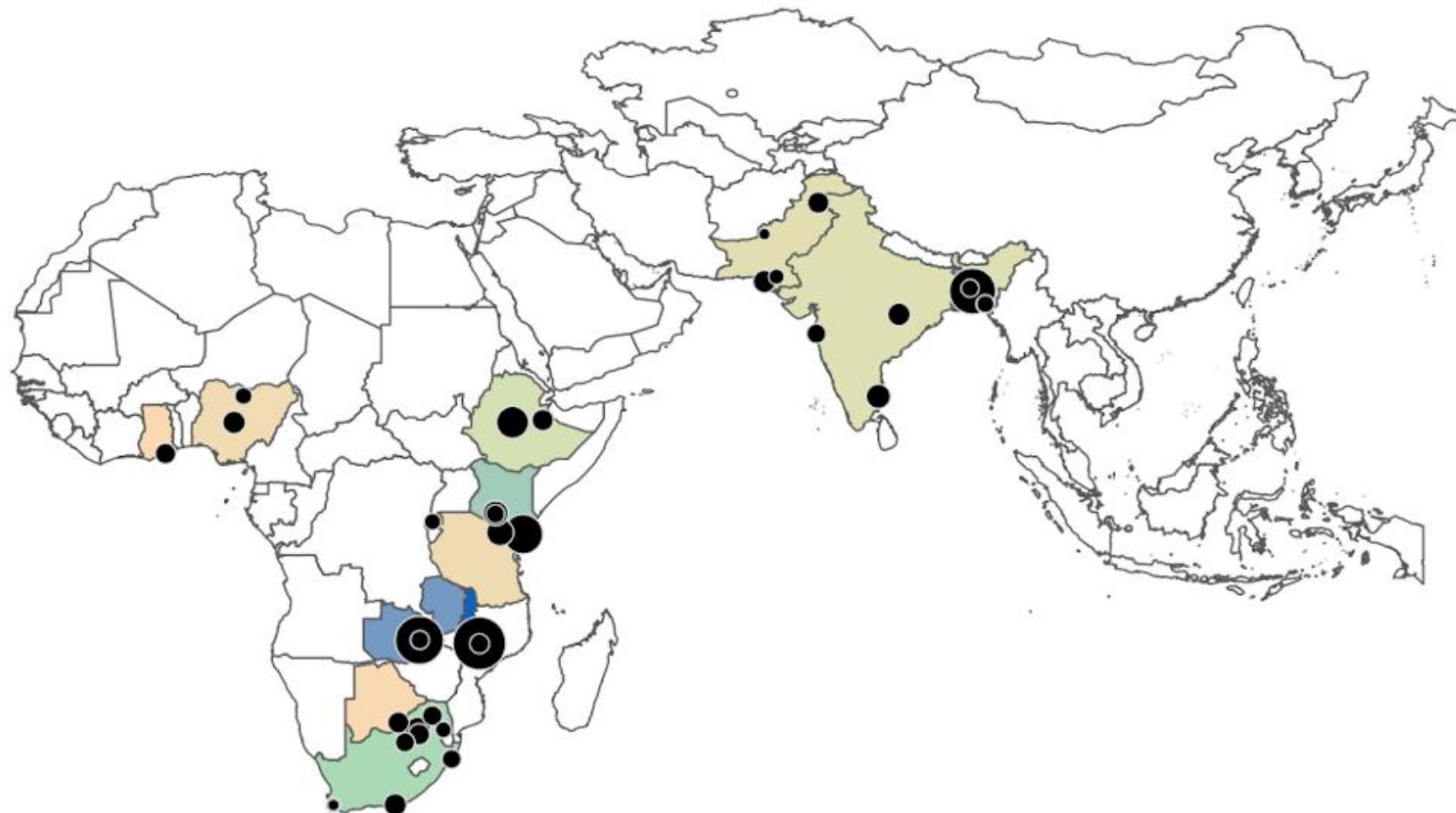
Sampling:

- Large sample sizes
- Broad representation:
 - target infections
 - target geographies

Analysis approach:

- Account for sampling differences between sites
- Adjust for local clonal expansions

Kpn neonatal sepsis isolate meta-analysis



N ~2000
total isolates

N isolates
per country

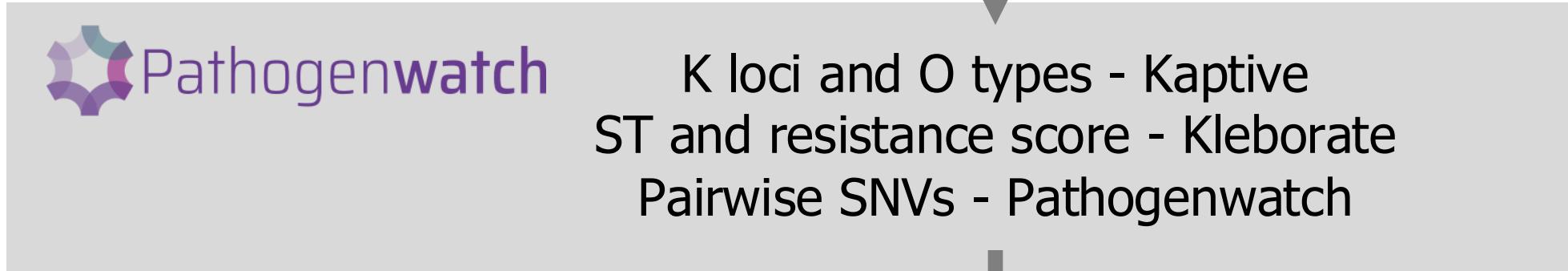
300
200
100

N isolates
per site

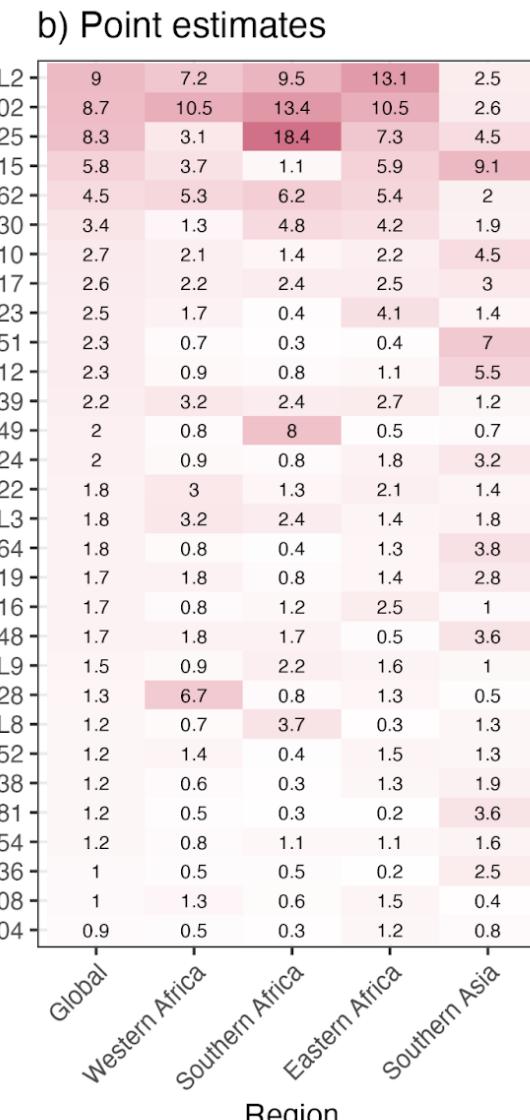
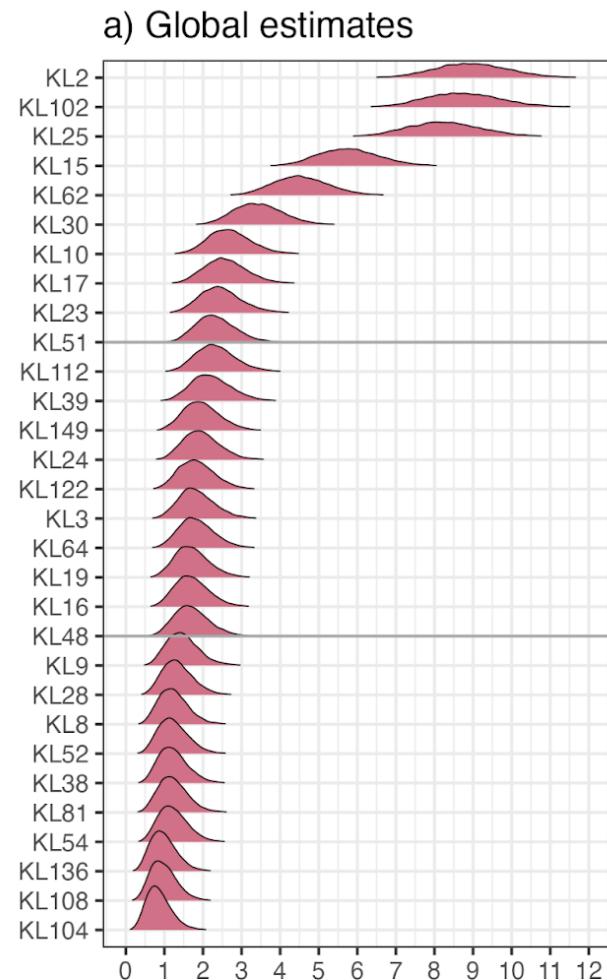
● 100
● 200
● 300

HUGE collaborative effort – 82 coauthors!

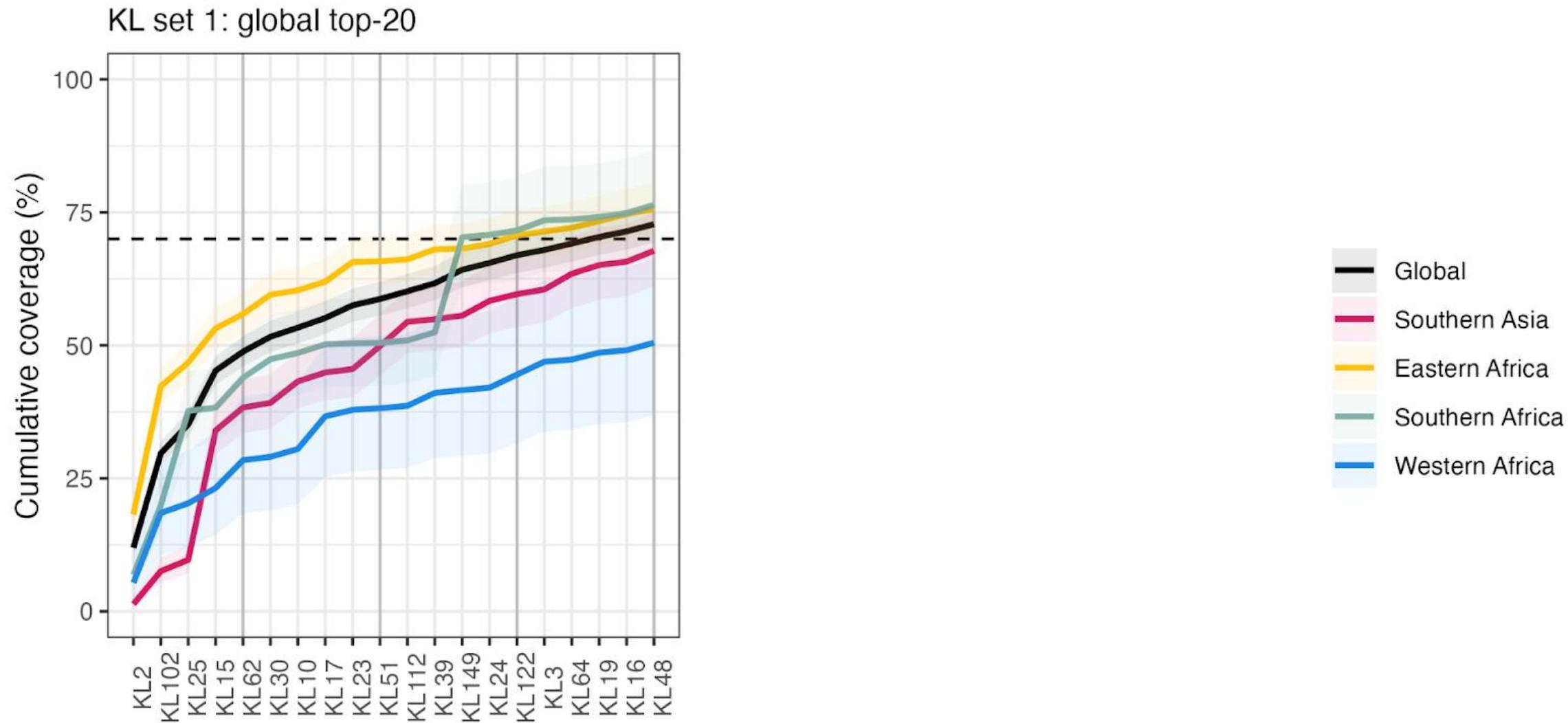
Bayesian prevalence estimates, adjusted for outbreaks



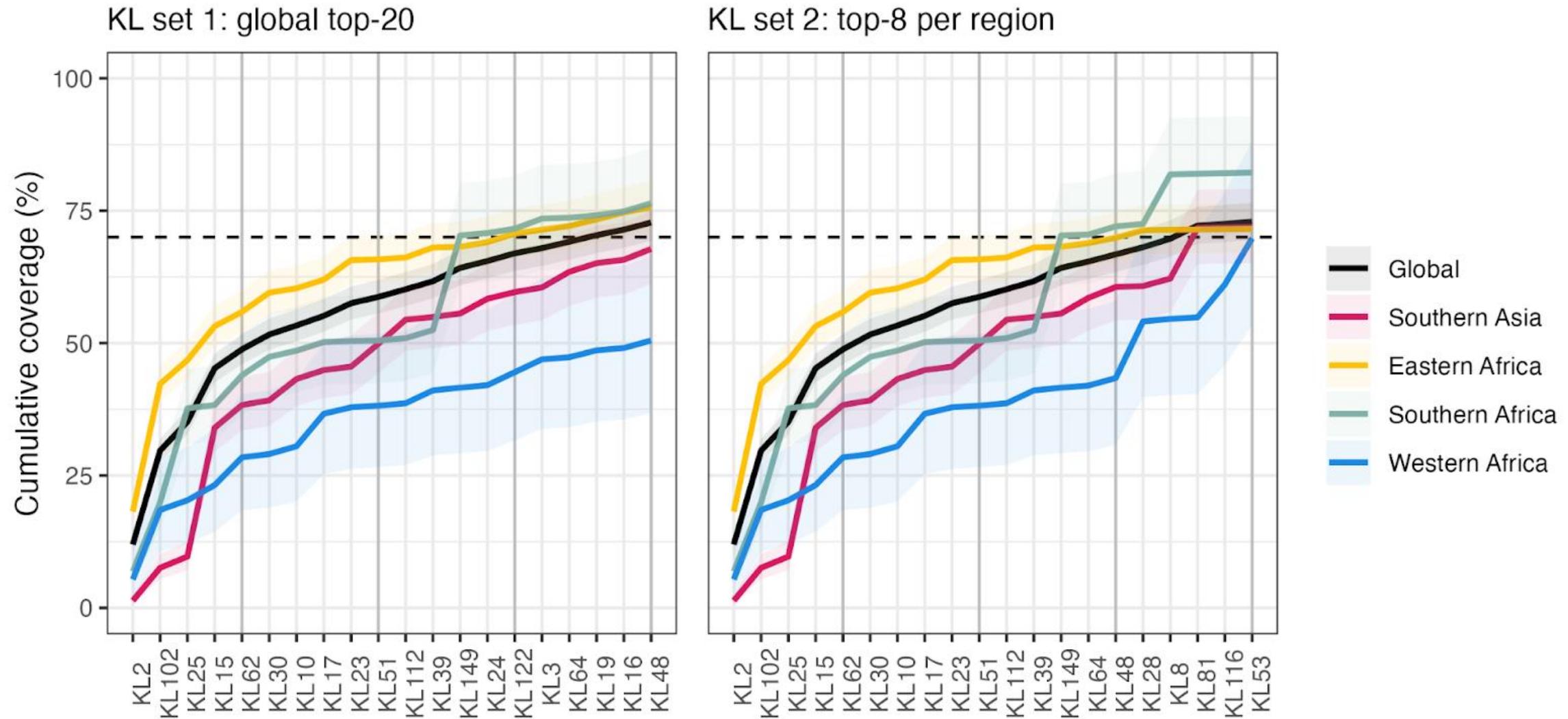
Bayesian prevalence estimates, adjusted for outbreaks



Cumulative coverage for top 20 K varies by region

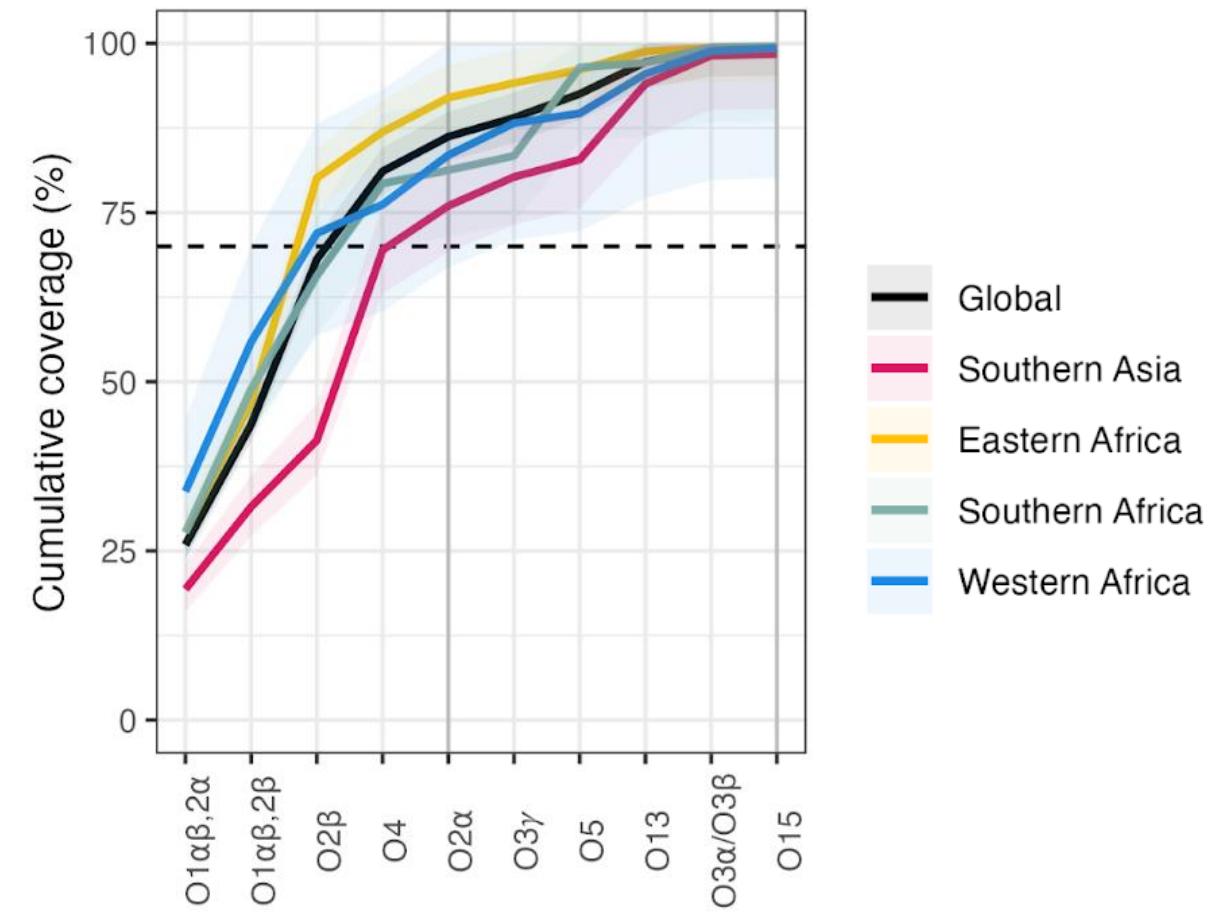
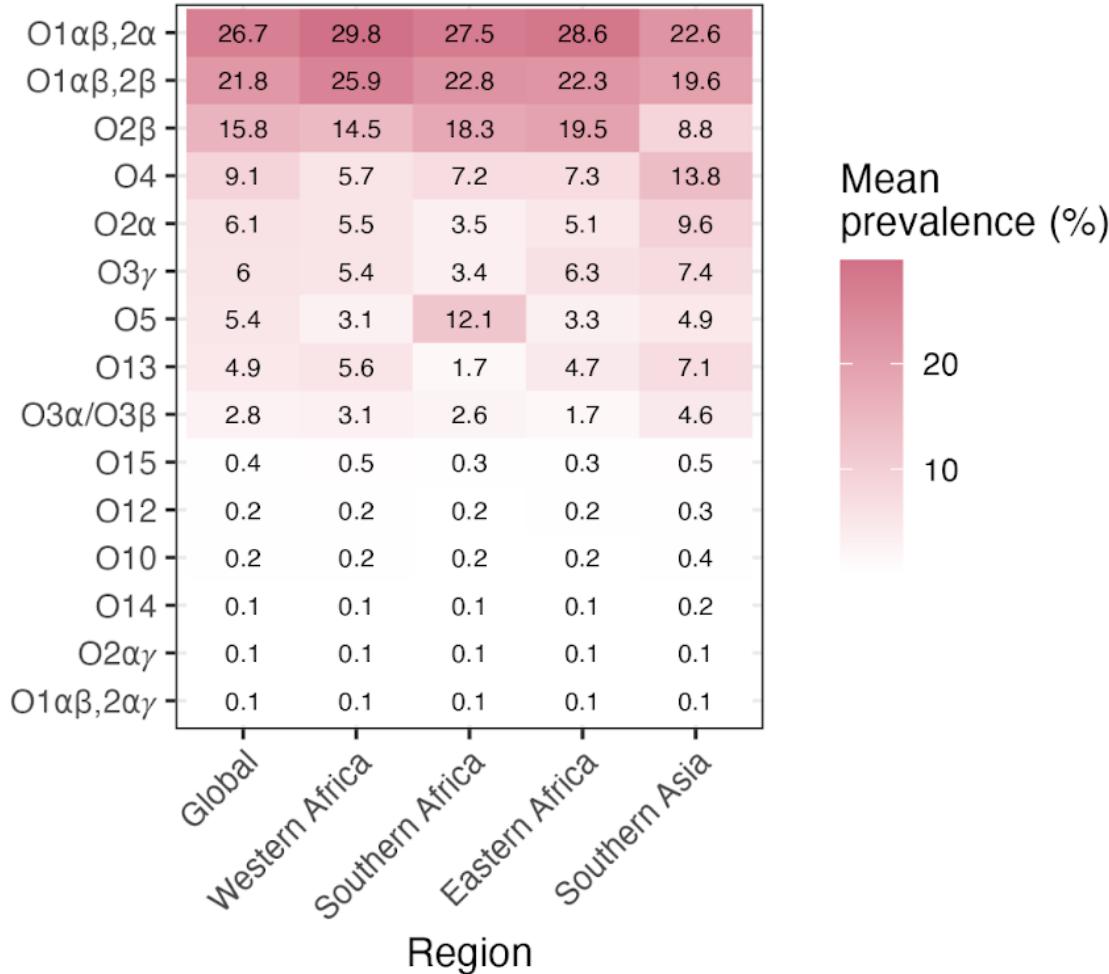


Can achieve $\geq 70\%$ coverage for all regions if select top loci from each

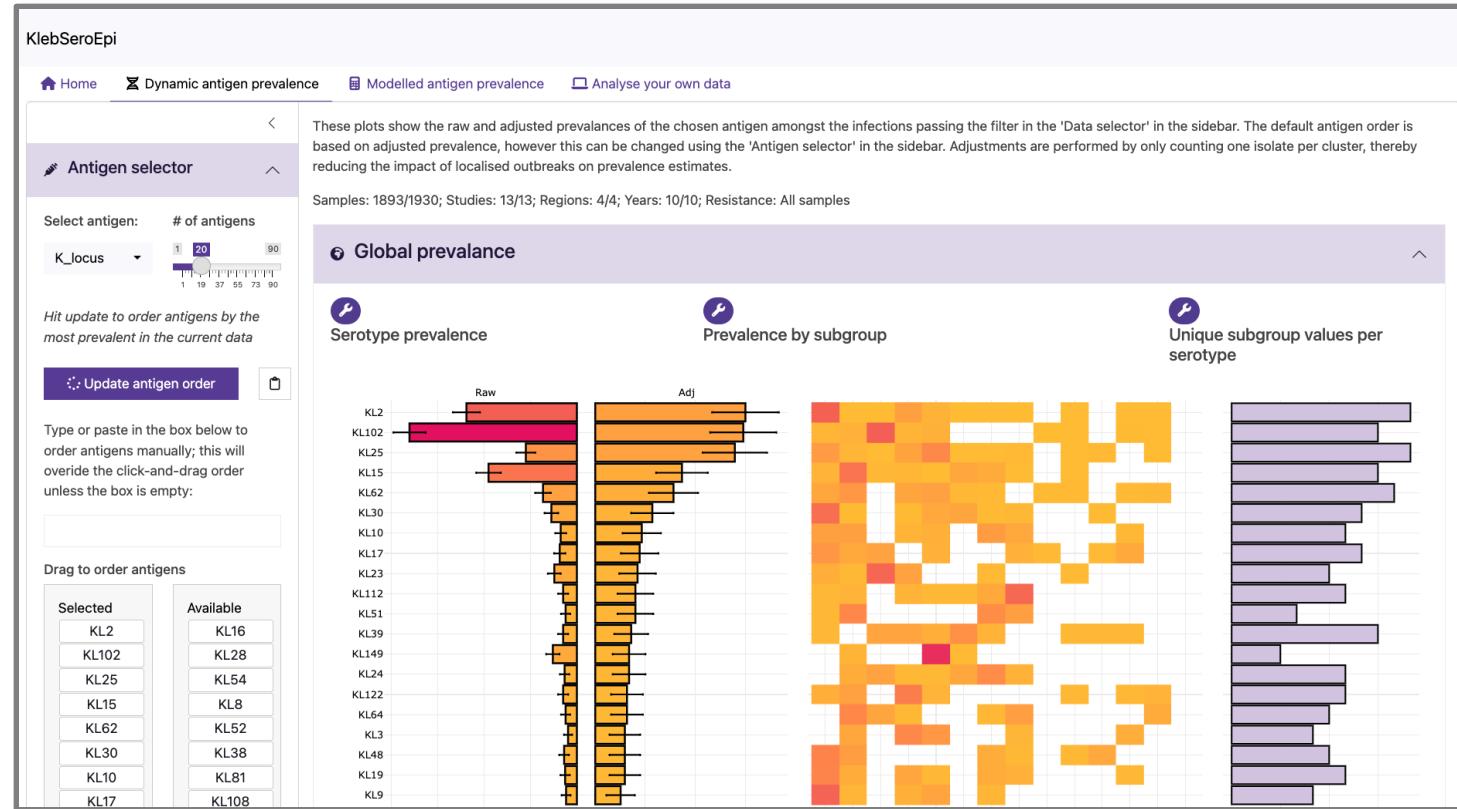




O types much less diverse, top 4 achieves $\geq 70\%$ coverage in all regions



Sero-epi app for data exploration



<https://klebsiella.shinyapps.io/neonatal/>

In summary

List of learning points in this session:

- *Kpn* causing opportunistic human infections produce diverse K and O antigens
- MDR clones associated with diverse K and O loci, but some combinations have proliferated globally
- Hypervirulent clones (and infections) associated with KL1 and KL2
- K loci vary through space and time among opportunistic infections
- O types are less variable
- To prioritise antigens for vaccines and other interventions we need broadly representative data, and we need to adjust for localised clonal outbreaks
- Despite the extensive diversity it may be possible to produce a single anti-K vaccine with $\geq 70\%$ theoretical population coverage

Further reading



Specific further reading for this session

Stanton / Keegan *et al.* Distribution of capsule and O types in *Klebsiella pneumoniae* causing neonatal sepsis in Africa and South Asia: meta-analysis of genome-predicted serotype prevalence and potential vaccine coverage. *medRxiv* 2025
doi: <https://doi.org/10.1101/2025.06.28.25330253>

References

- Opoku-Temeng *et al* *Comput Struct Biotechnol J* 2019. PMID: 31762959
- Zangor *et al* *Vaccine* 2024. PMID: 38503661
- Pan *et al* *Sci Rep* 2015. PMID: 26493302
- Wyres *et al* *Microb Genom* 2016. PMID: 28348840
- Lam *et al* *Microb Genom* 2022. PMID: 35311639
- Whitfield *et al* *MMBR* 2025. PMID: 40116577
- Wyres *et al* *PLoS Genetics* 2019. PMID: 30986243
- Gorrie *et al* *Nature Communications* 2022. PMID: 35641522
- David *et al* *Nature Microbiology* 2019. PMID: 31358985
- Lam *et al* *Nature Communications* 2021. PMID: 34234121
- Heinz *et al* *Genome Medicine* 2024. PMID: 38711148



Acknowledgements

The creation of this training material was commissioned by Associate Professor Kelly Wyres at Monash University