Klebsiella pneumoniae genomic epidemiology and antimicrobial resistance

Seroepidemiolgy of *Klebsiella*

9th September 2025

How do you assess your current knowledge about Kpn seroepidemiology?

Are you working on, or interested in, novel anti-Kpn control strategies?

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* seroepidemiology analyses

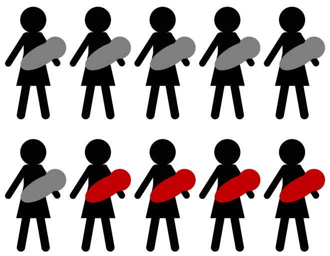
Outline

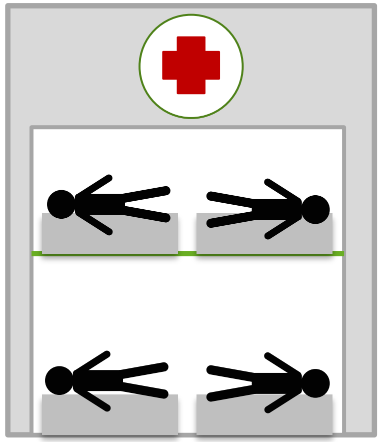
This session consists of the following elements

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. Summary

WHO *Kpn* vaccine value profile

Use cases:
- Neonatal sepsis
- Adult HAIs





Major antigen targets:
- Capsule (K)
- Outer-LPS (O)

Coverage target:
≥70% infections

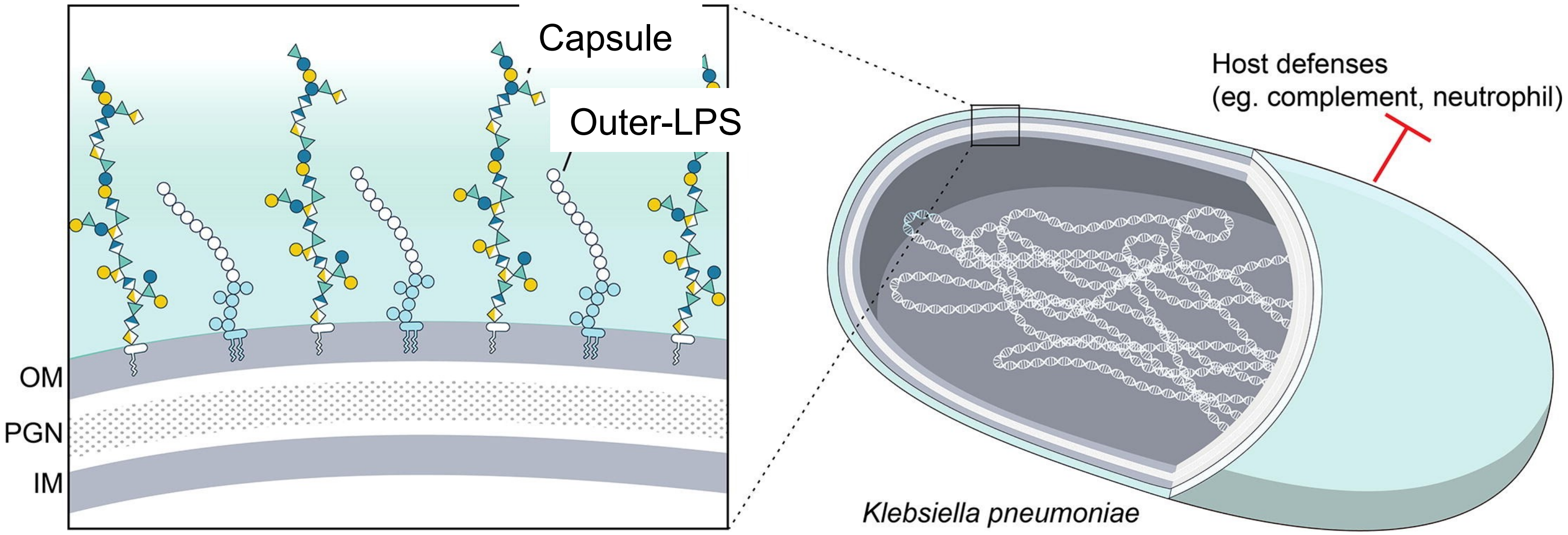
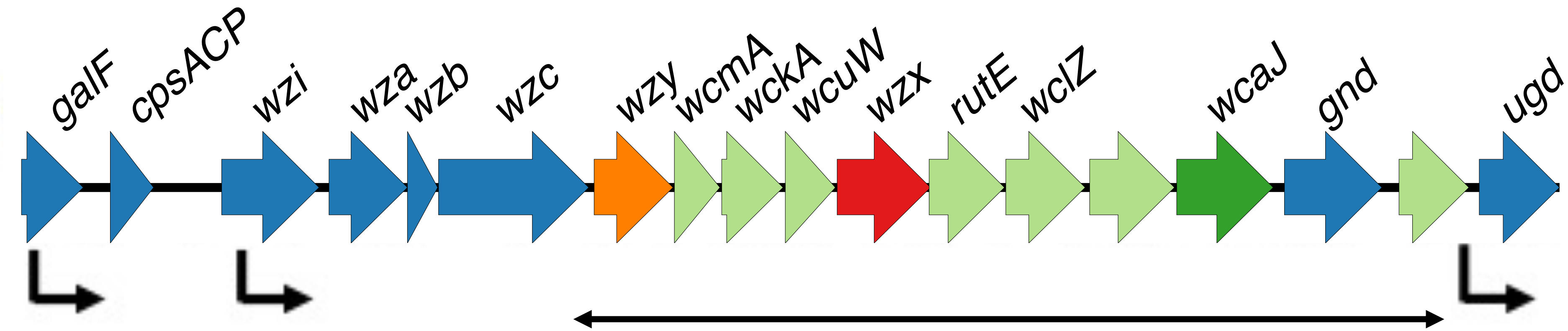


Image from: Opoku-Temeng *et al Comput Struct Biotechnol J* 2019
Vaccine Value Profile: Zangor *et al Vaccine* 2024

Klebsiella K loci are defined by unique gene content



Capsule specific
sugar synthesis
(highly variable)

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

KAPTIVE

🟦 Common proteins inc. core assembly machinery

🟧 Wzy capsule repeat unit polymerase

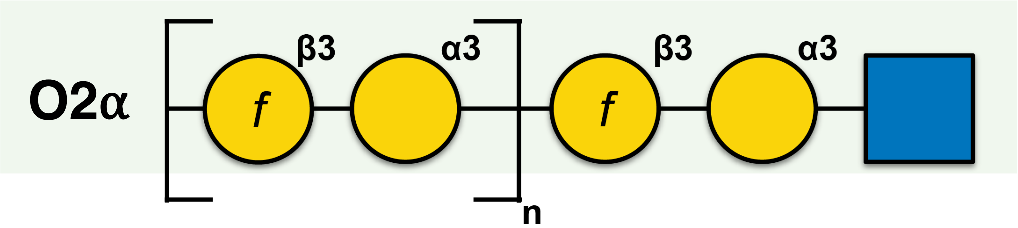
🟩 WbaP / WcaJ initiating glycosyltransferase

🟥 Wzx flippase

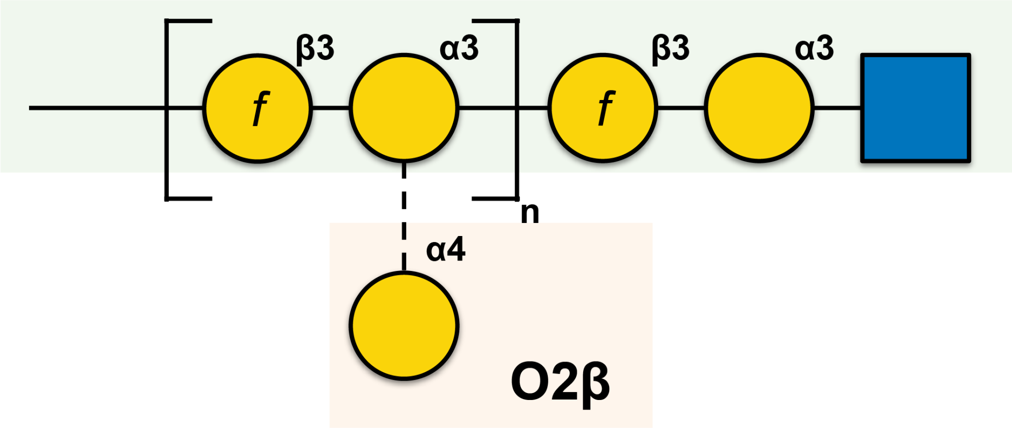
🟩 Other sugar synthesis and processing

Pan *et al Sci Rep* 2015
Wyres *et al Microb Genom* 2016
Lam *et al Microb Genom* 2022

O types determined by O loci & additional genes



OL2α

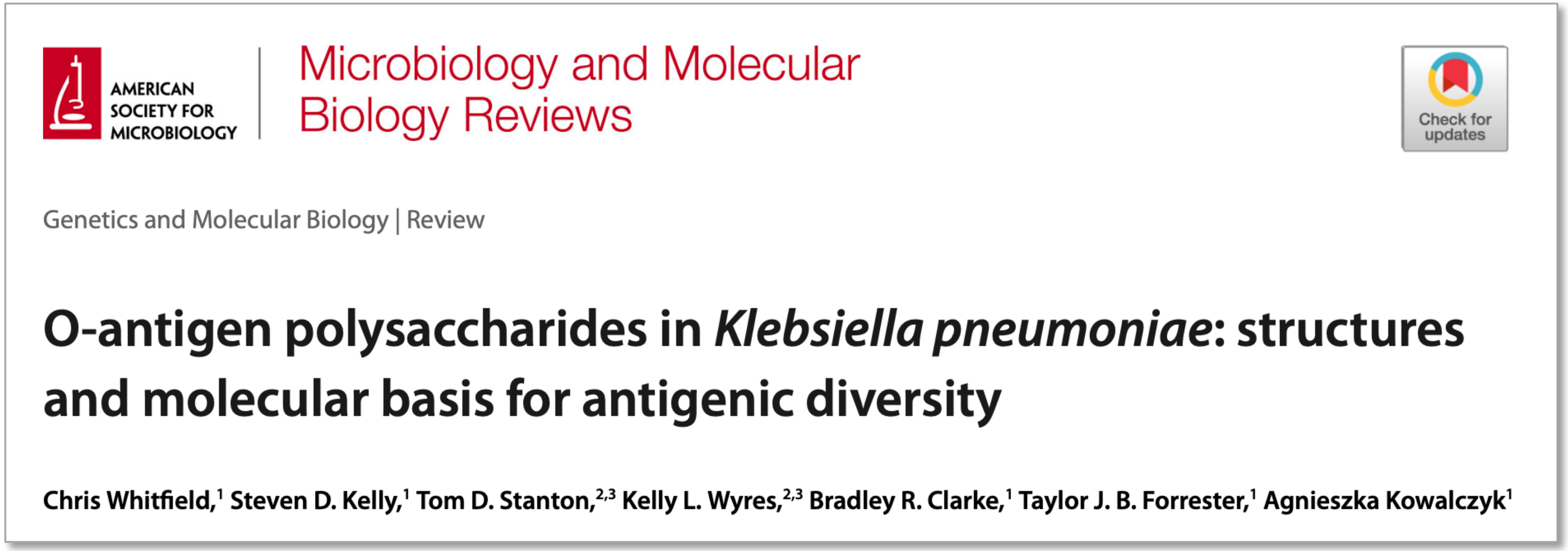


OL2α + *gml2β*

>20 combinations identified to-date

Whitfield *et al MMBR* 2025

Updated O type nomenclature, from 2025



AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology and Molecular Biology Reviews

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Genetics and Molecular Biology | Review

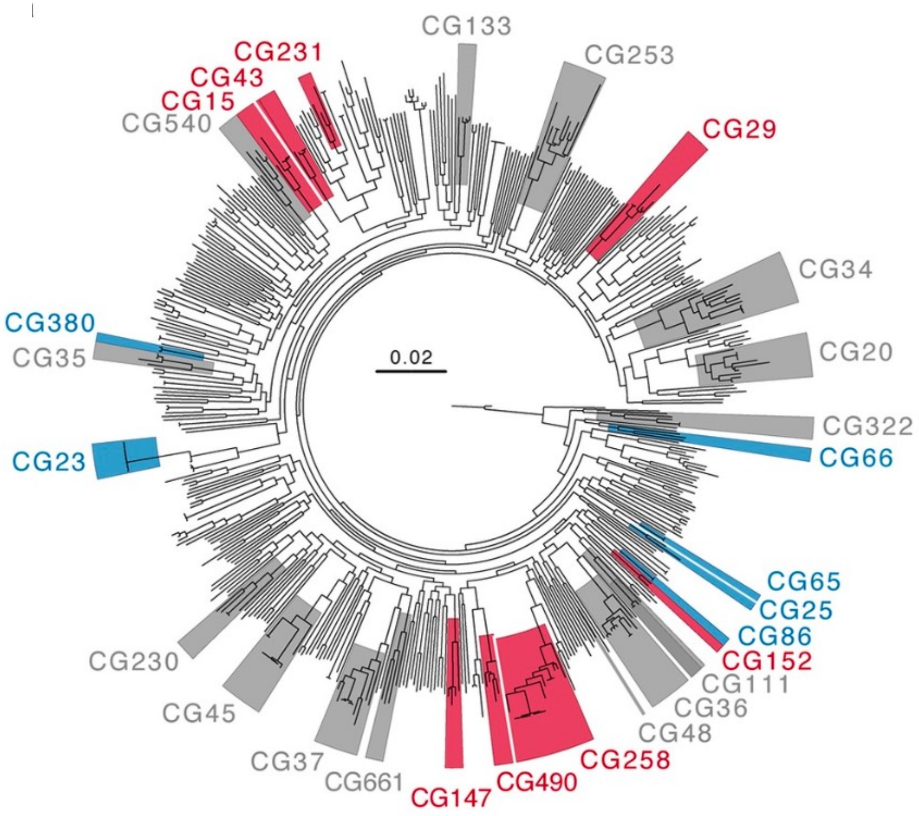
O-antigen polysaccharides in *Klebsiella pneumoniae*: structures and molecular basis for antigenic diversity

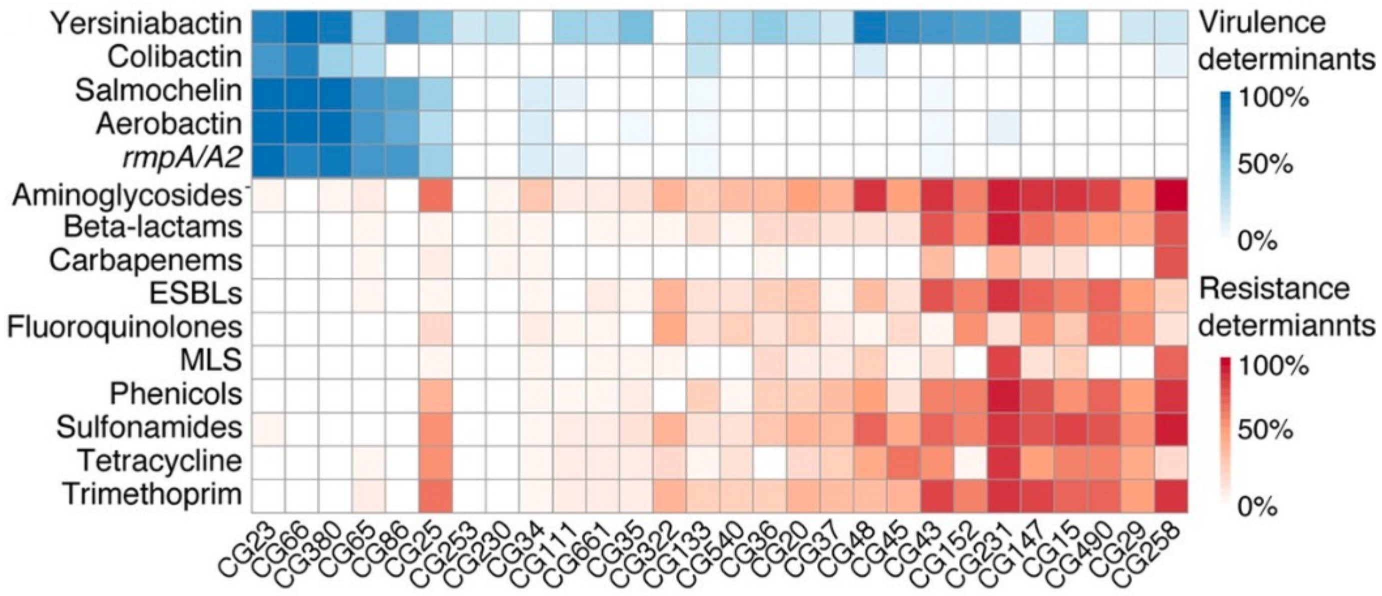
Chris Whitfield,[1] Steven D. Kelly,[1] Tom D. Stanton,[2,3] Kelly L. Wyres,[2,3] Bradley R. Clarke,[1] Taylor J. B. Forrester,[1] Agnieszka Kowalczyk[1]

Nomenclature explainer

Whitfield *et al MMBR* 2025

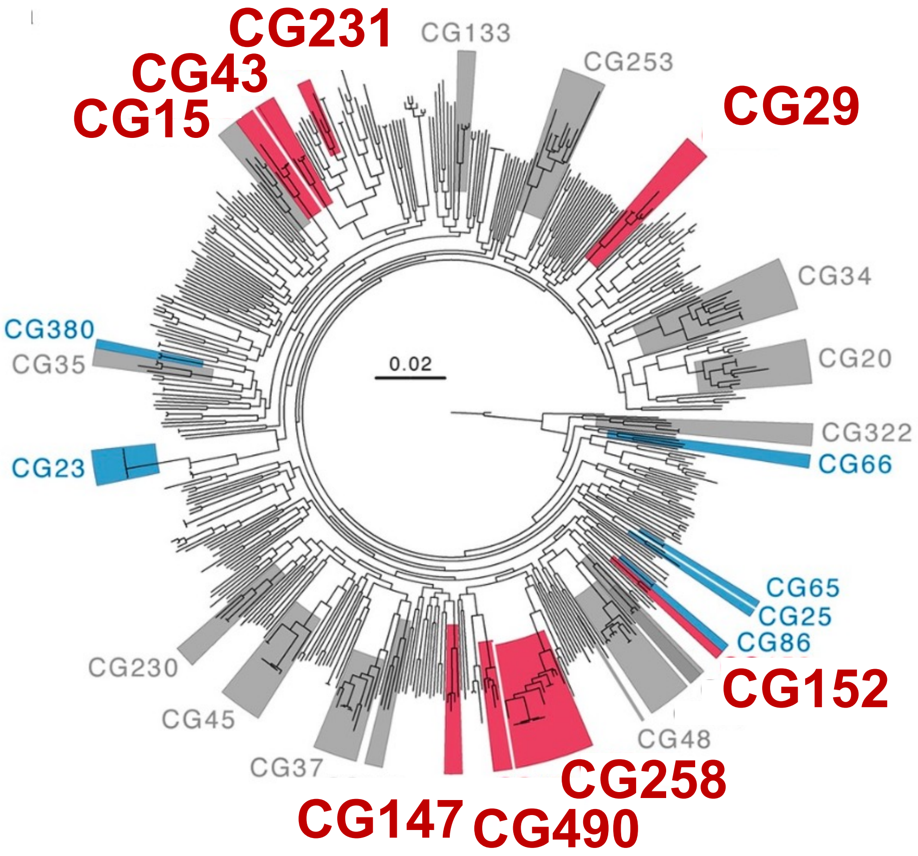
Distribution of AMR and virulence genes

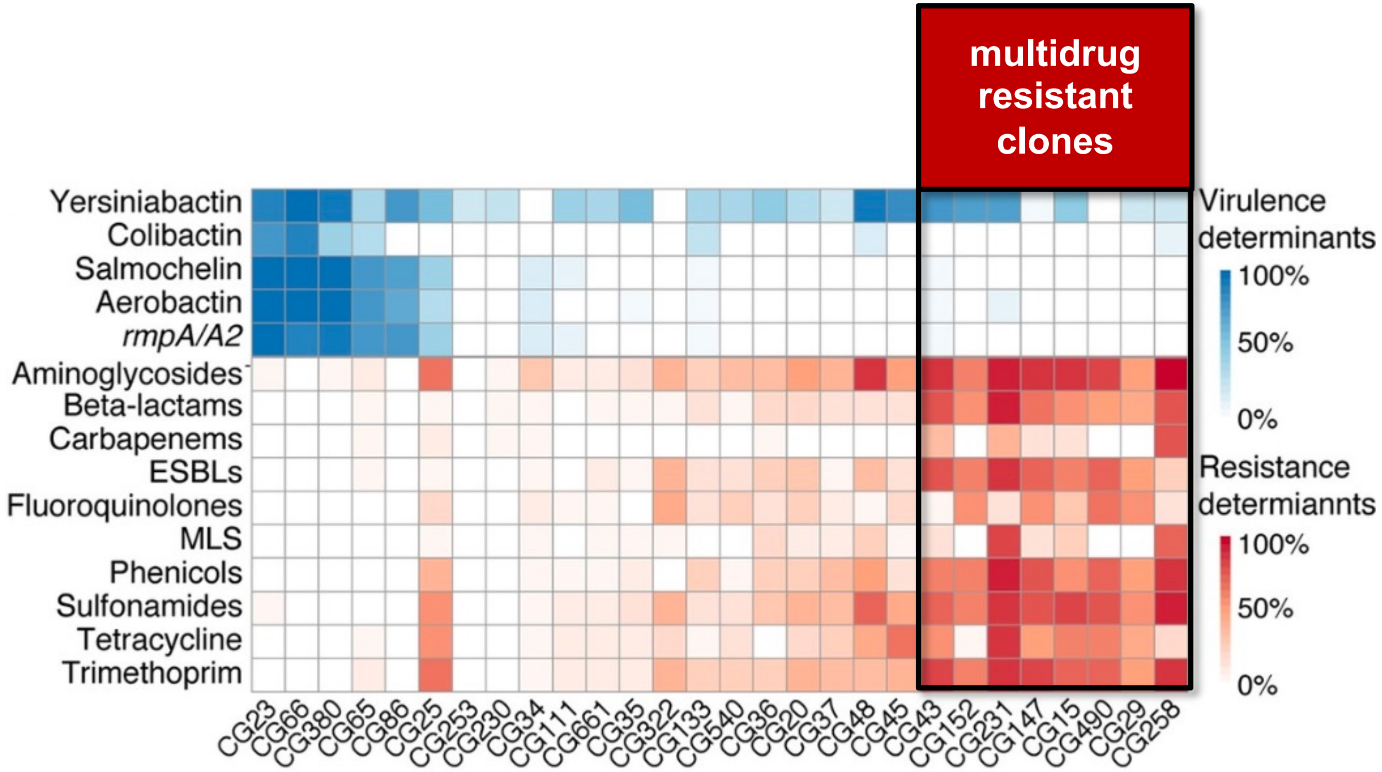




Wyres et al, *PLoS Genetics* 2019.

Distribution of AMR and virulence genes





Wyres et al, *PLoS Genetics* 2019.

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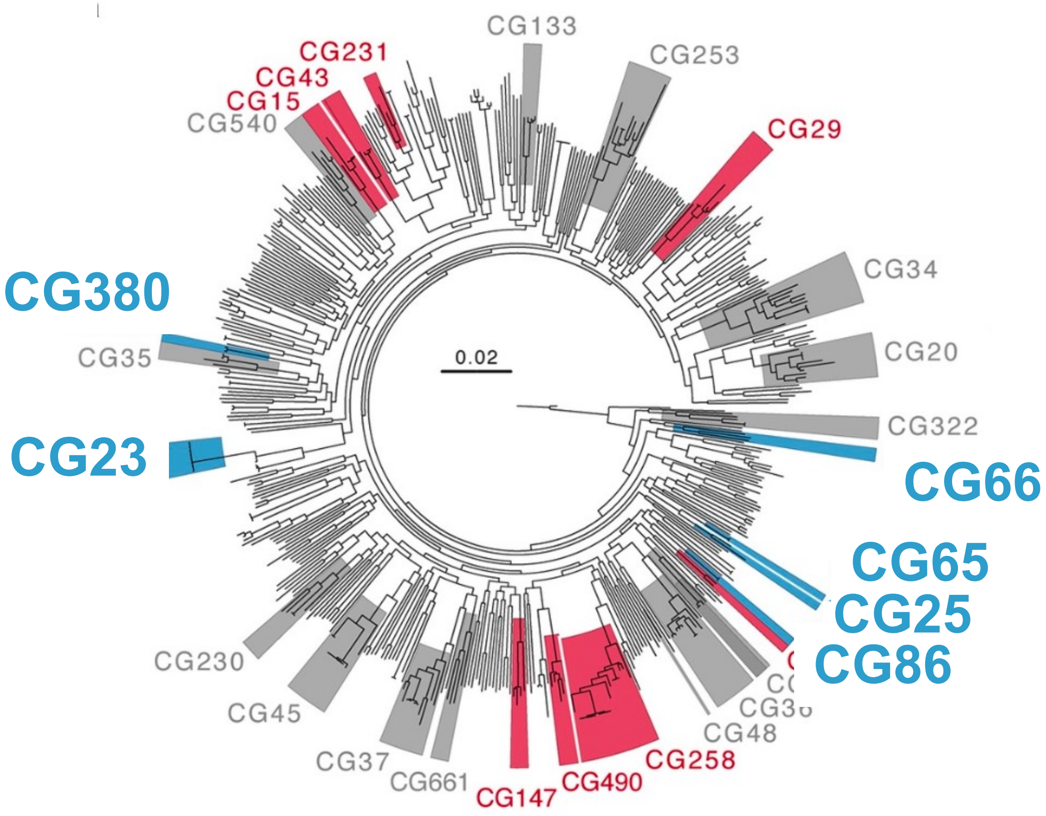
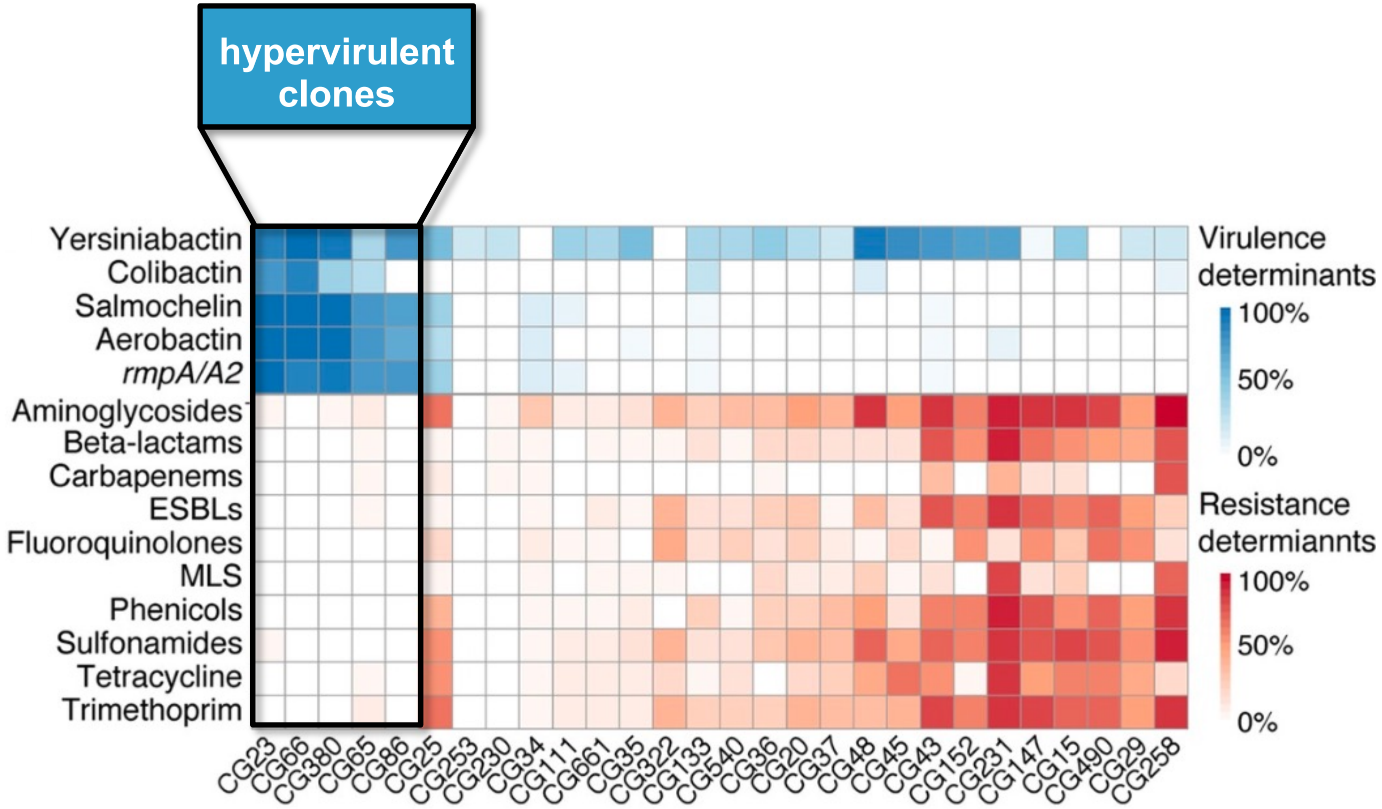
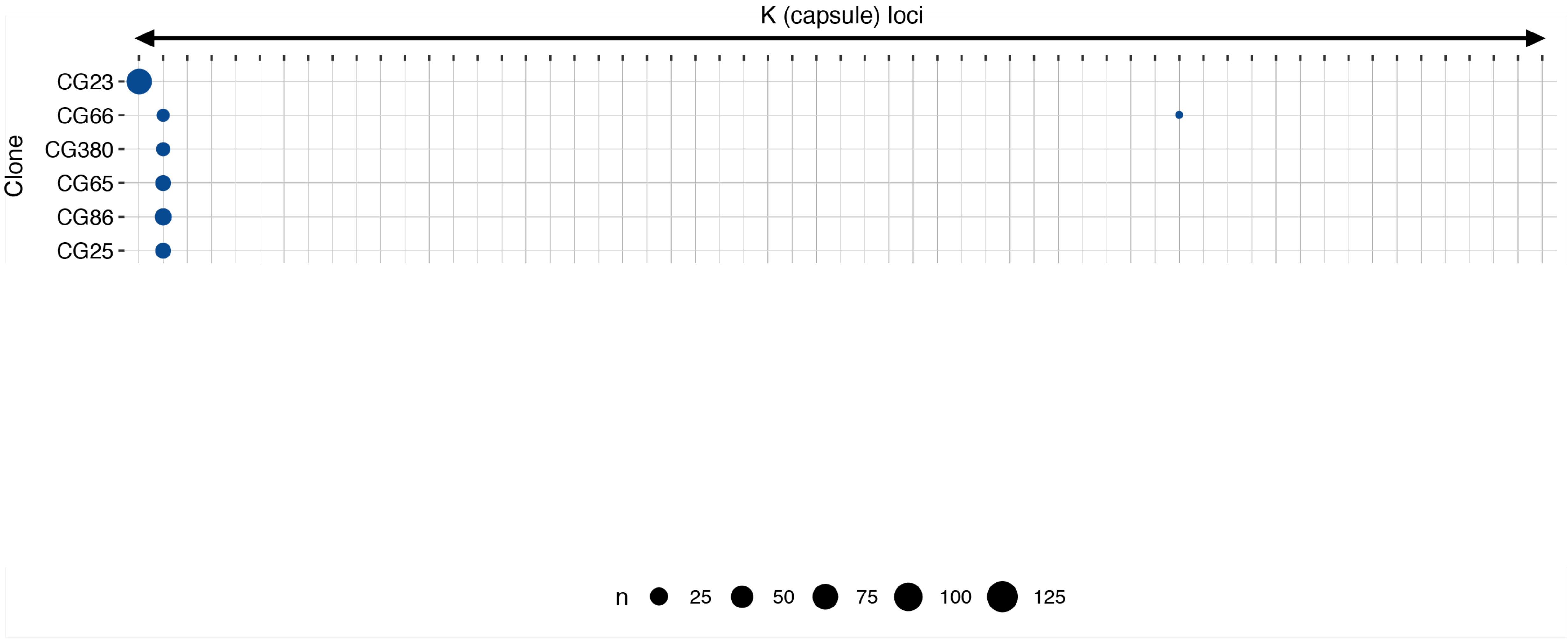




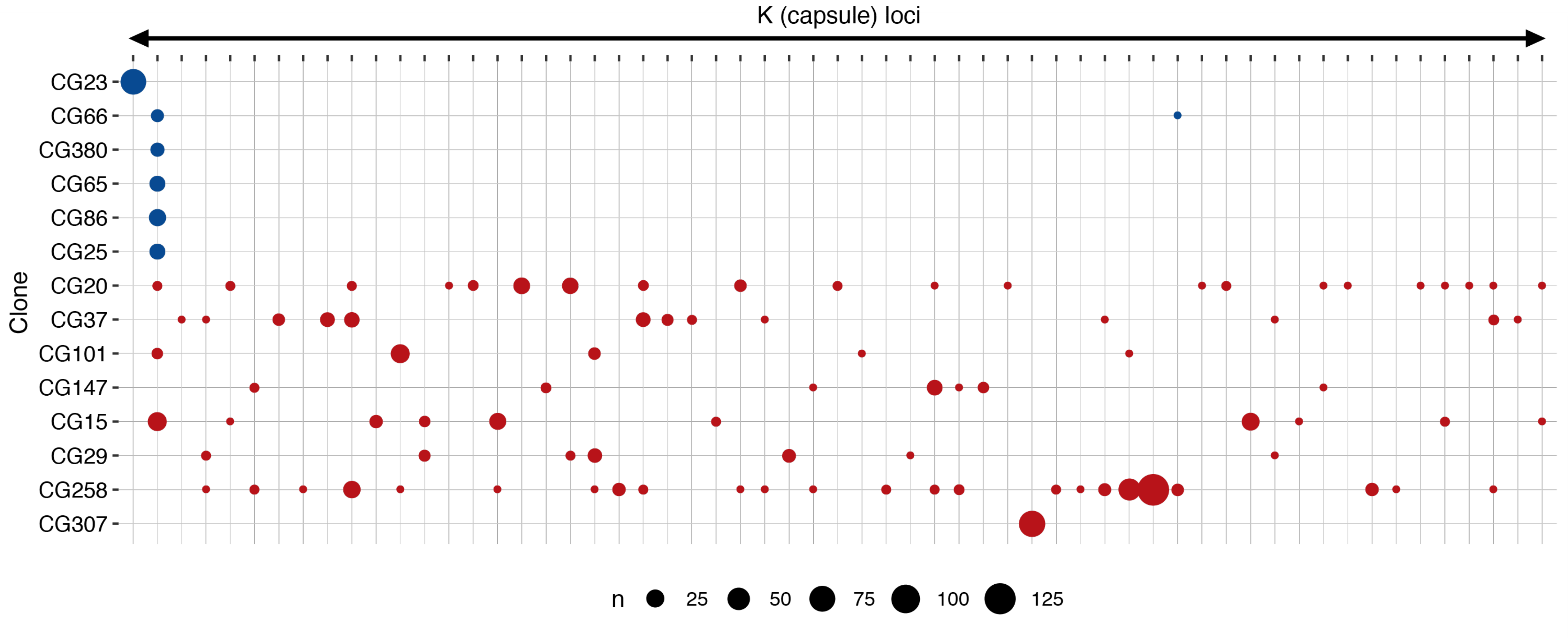
Wyres et al, *PLoS Genetics* 2019.

Hypervirulent clones carry either KL1 or KL2



n≥20 per clone
Data from Wyres *et al PLoS Genetics* 2019

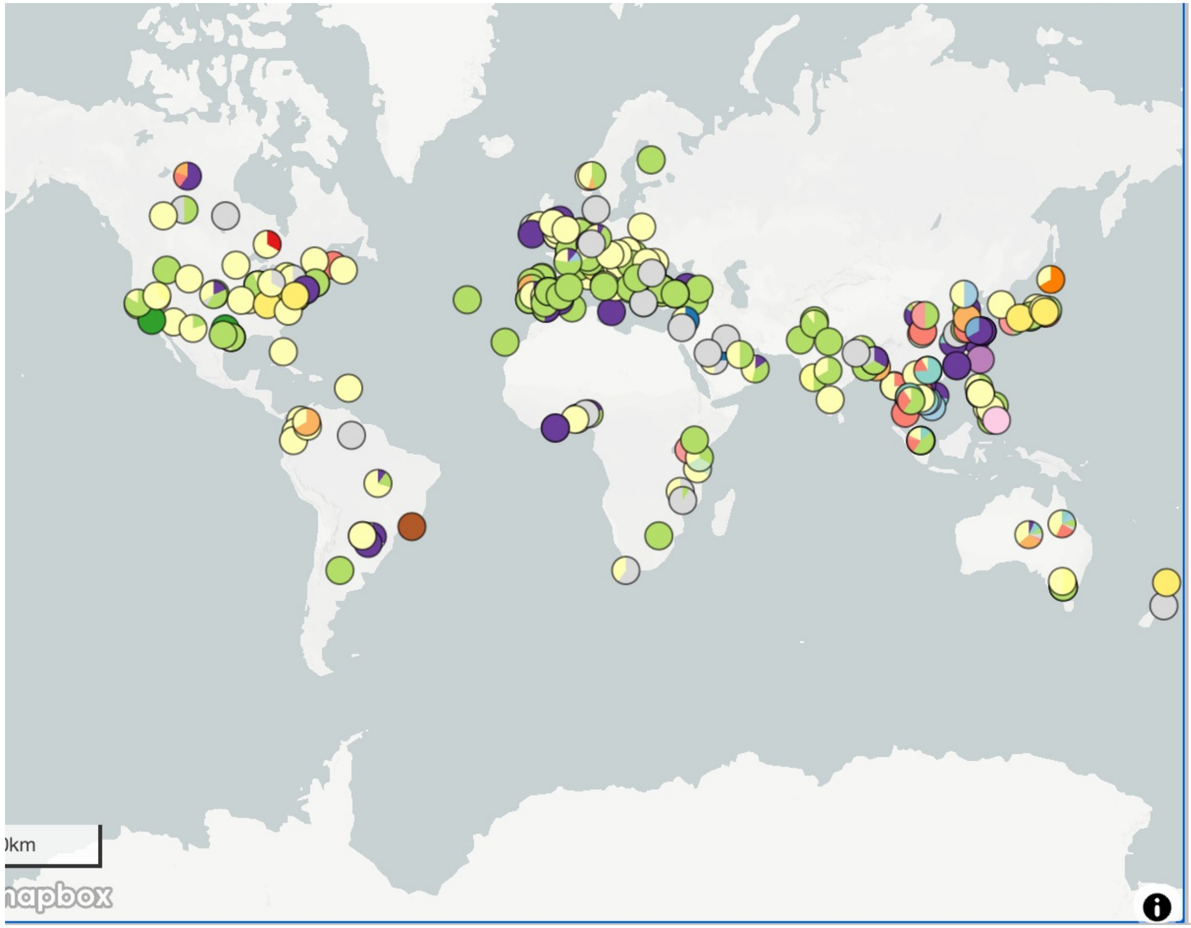
MDR clones carry diverse K loci

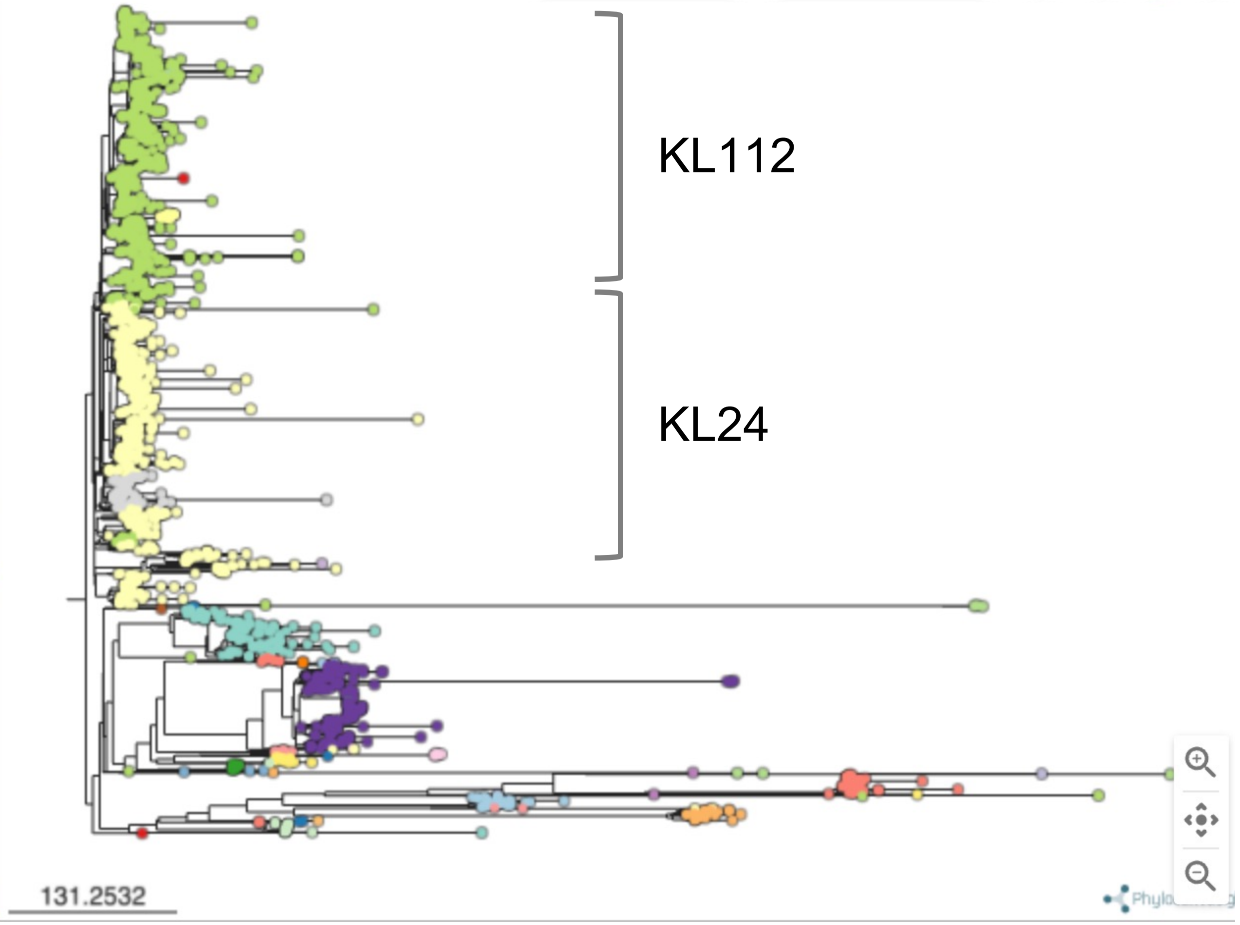


n≥20 per clone
Data from Wyres *et al PLoS Genetics* 2019

Some ST + KL combinations have proliferated

~1800 ST15 genomes, 1968-2023

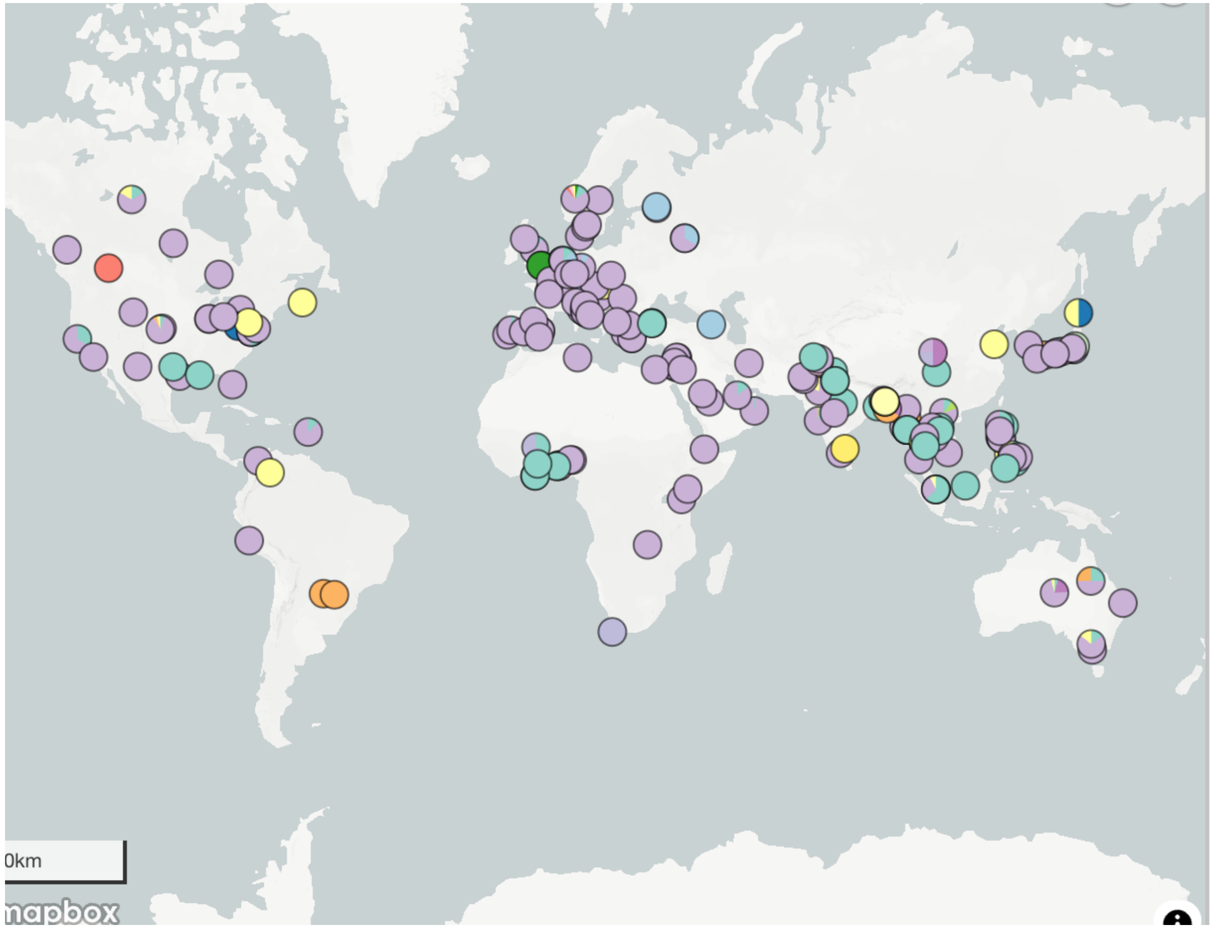


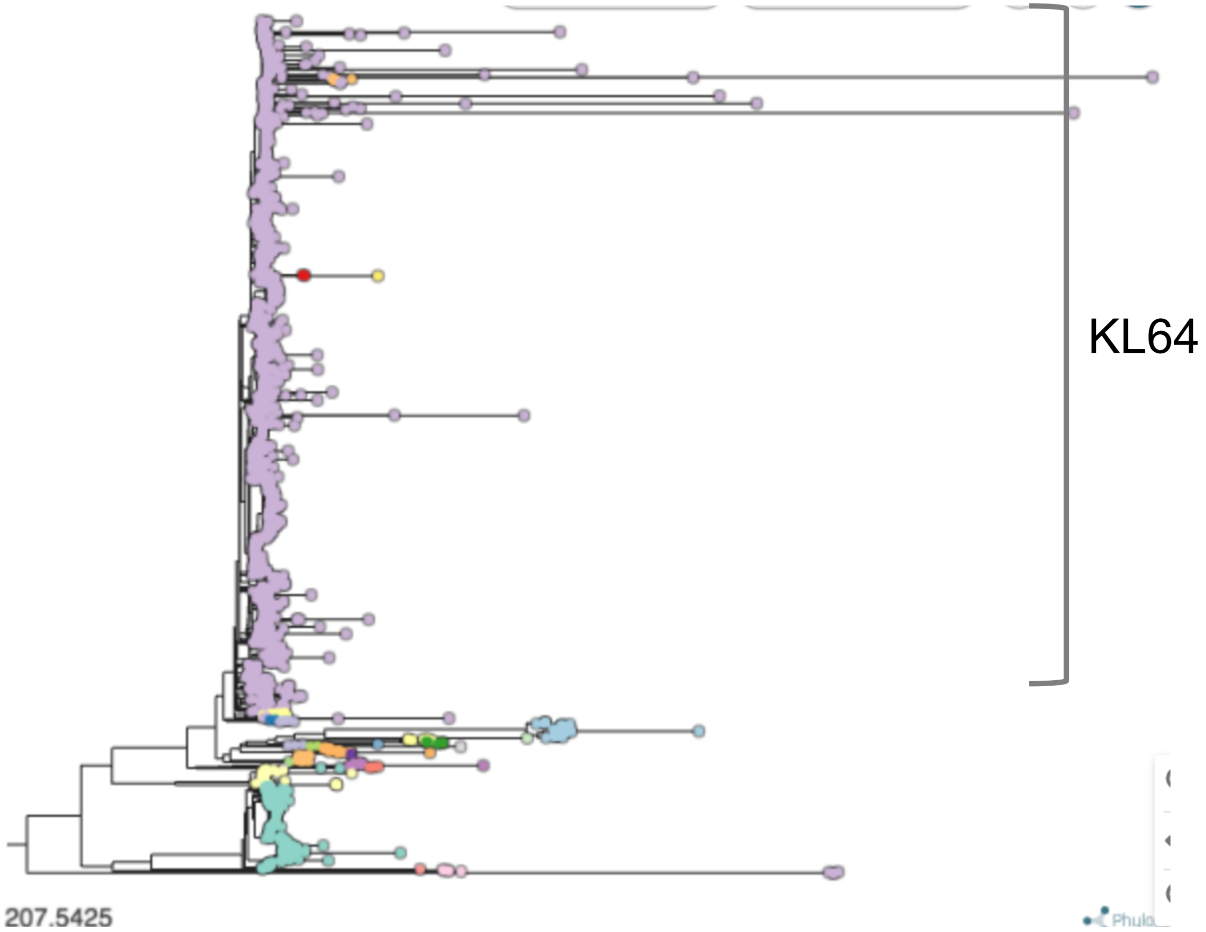


Data are public genomes accessed via Pathogenwatch.org (5 Sep 2025), visualised via Microreact.org

Some ST + KL combinations have proliferated

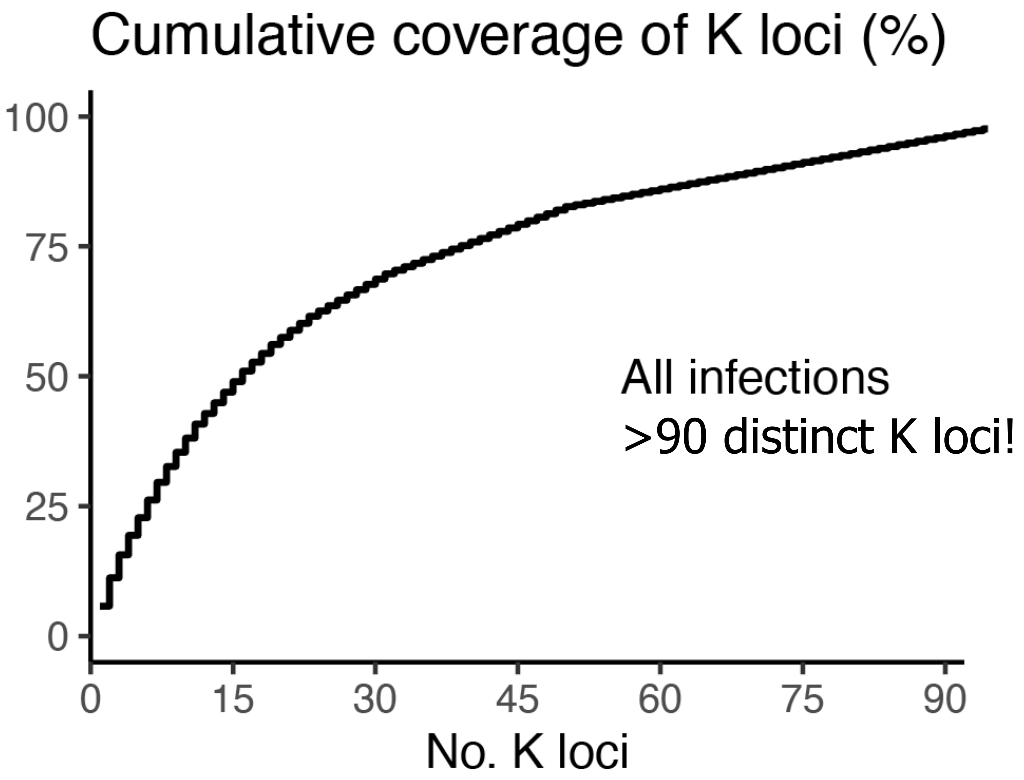
~2000 ST147 genomes, 2014-2023





Data are public genomes accessed via Pathogenwatch.org (5 Sep 2025), visualised via Microreact.org

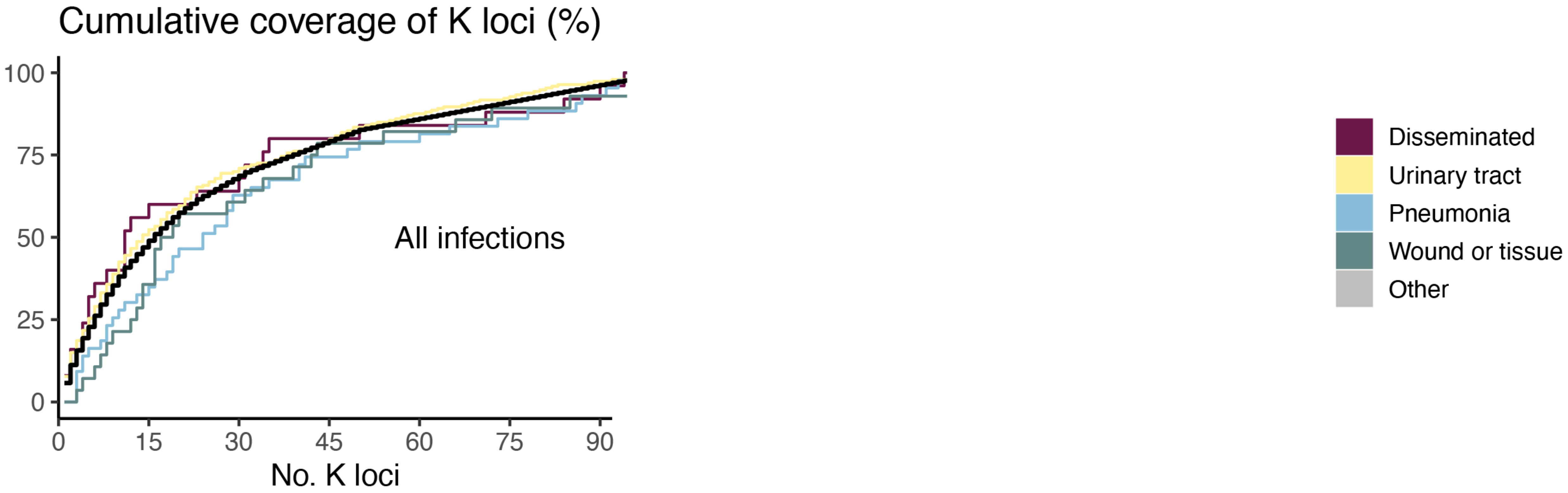
Substantial K diversity in 1 year of *Kpn* infections (n=294)



All infections
>90 distinct K loci!

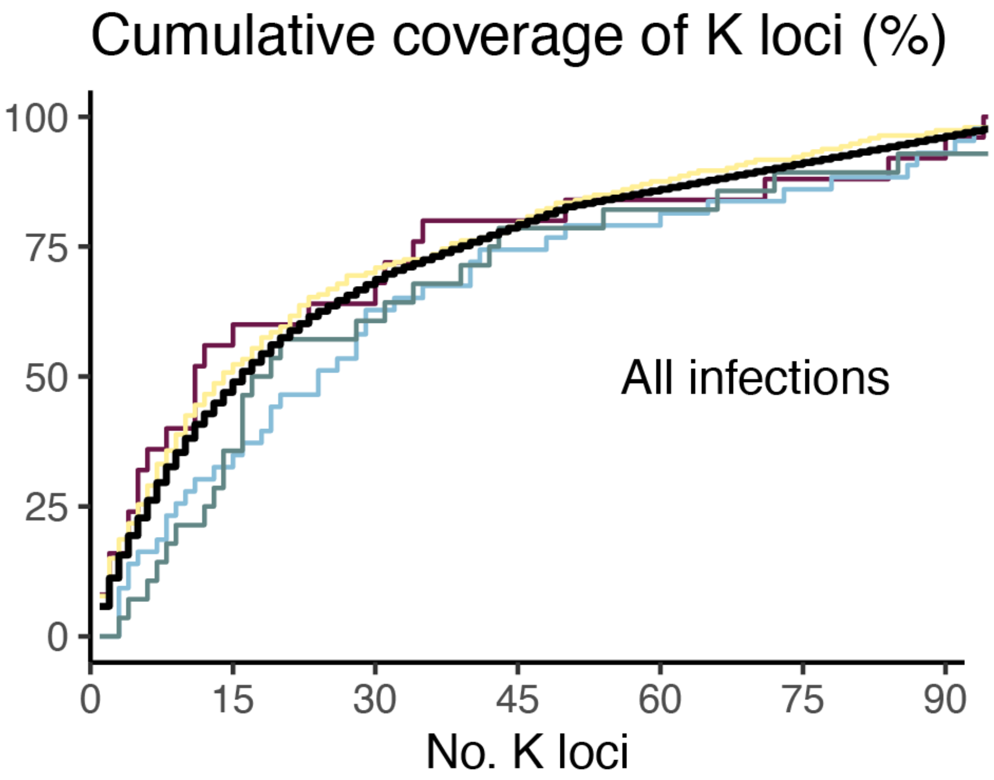
Adapted from Gorrie *et al Nature Communications* 2022; Alfred Hospital Network, Melbourne, Australia

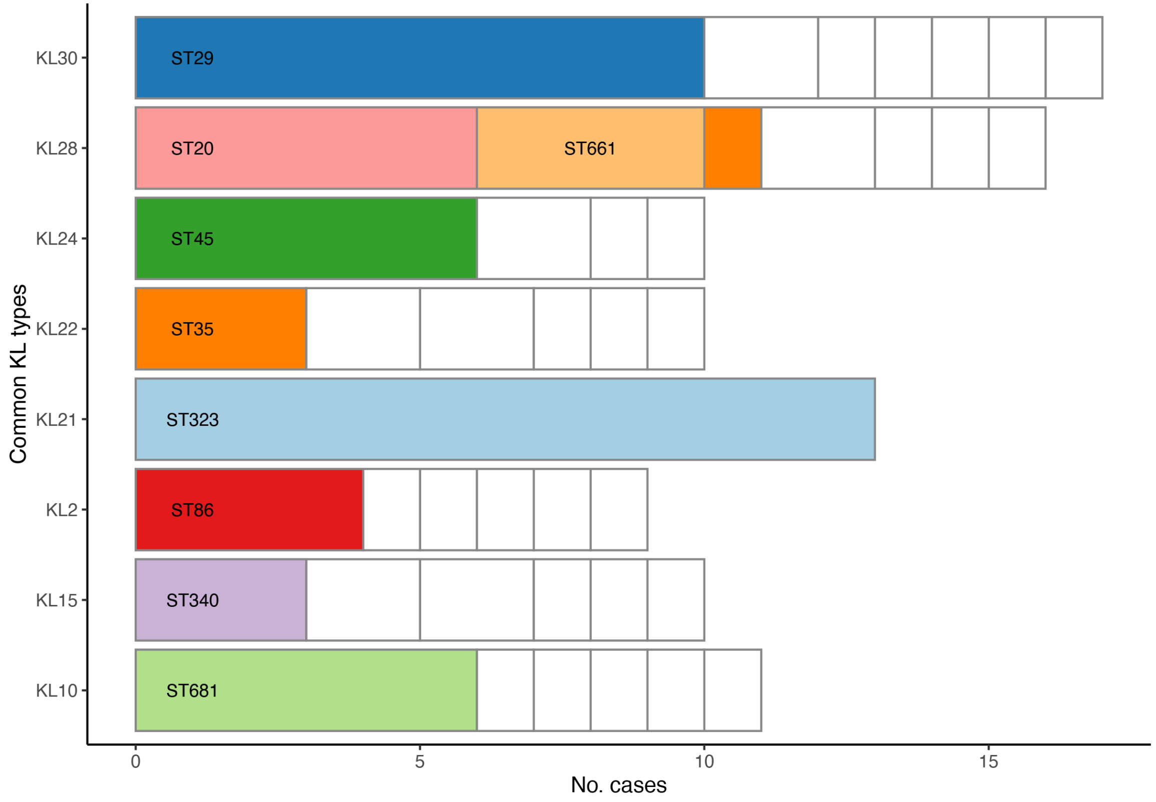
Diversity similar by infection type



Adapted from Gorrie *et al Nature Communications* 2022; Alfred Hospital Network, Melbourne, Australia

Common K loci associated with specific clones

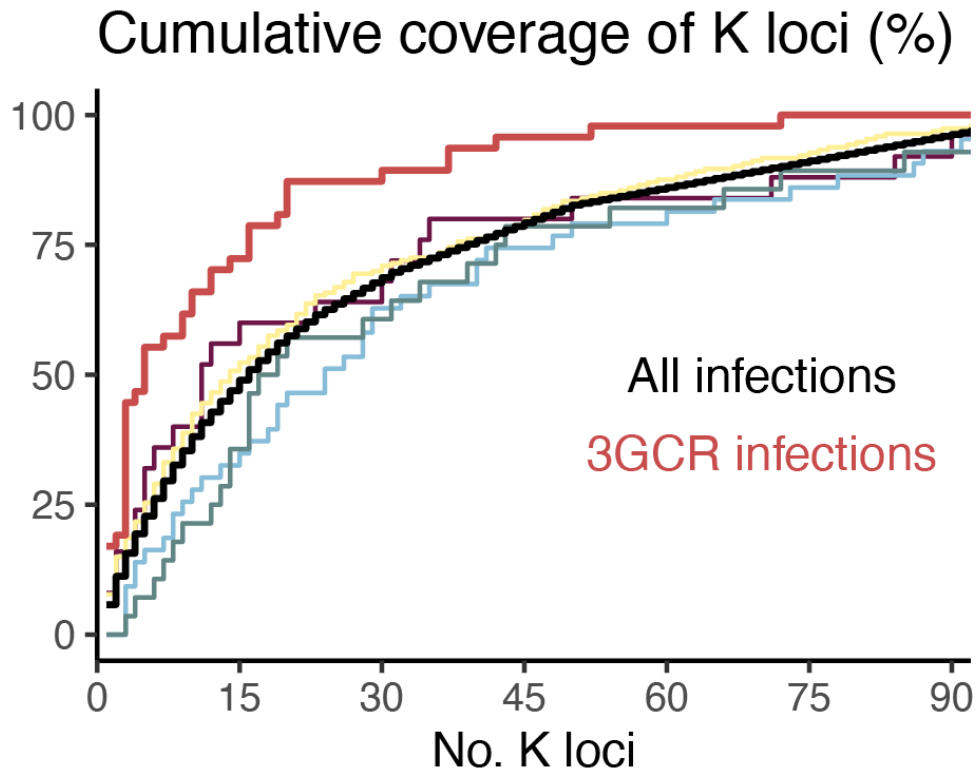


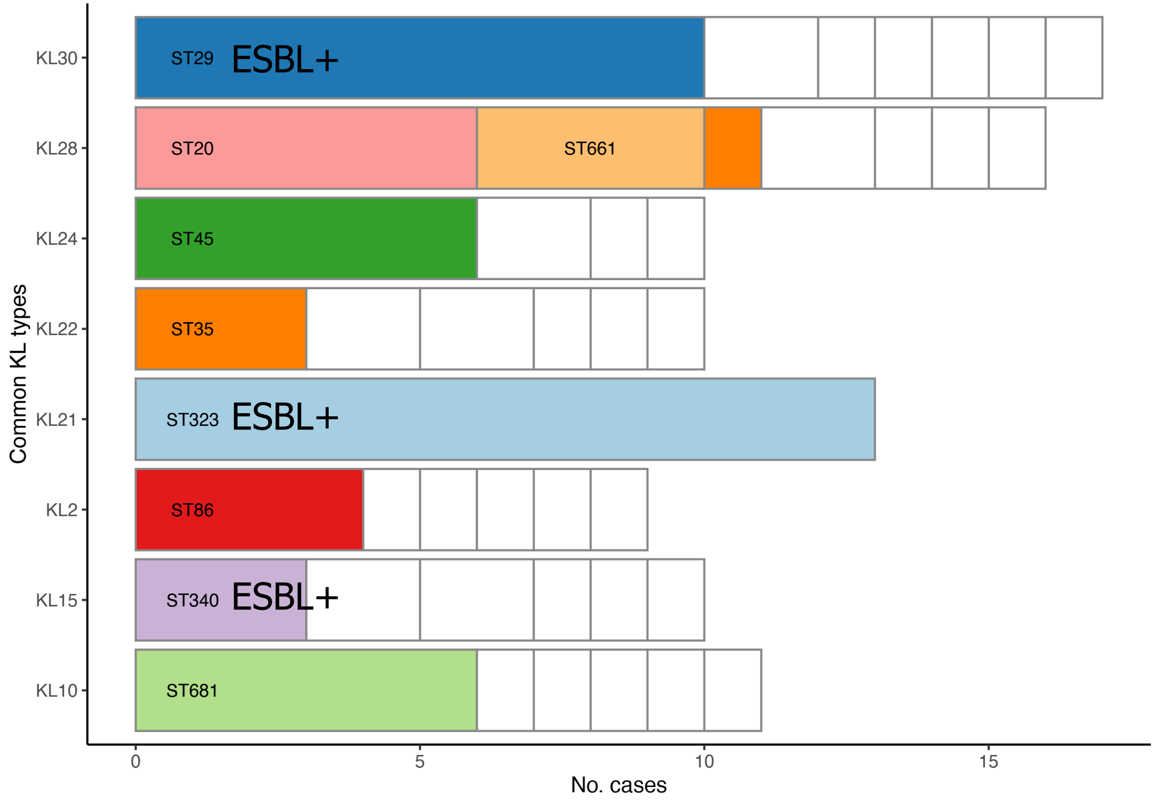


Note: few hypervirulent ST23 infections ➔ KL1 not common

Adapted from Gorrie *et al Nature Communications* 2022; Alfred Hospital Network, Melbourne, Australia

Lower diversity among 3GC resistant infections

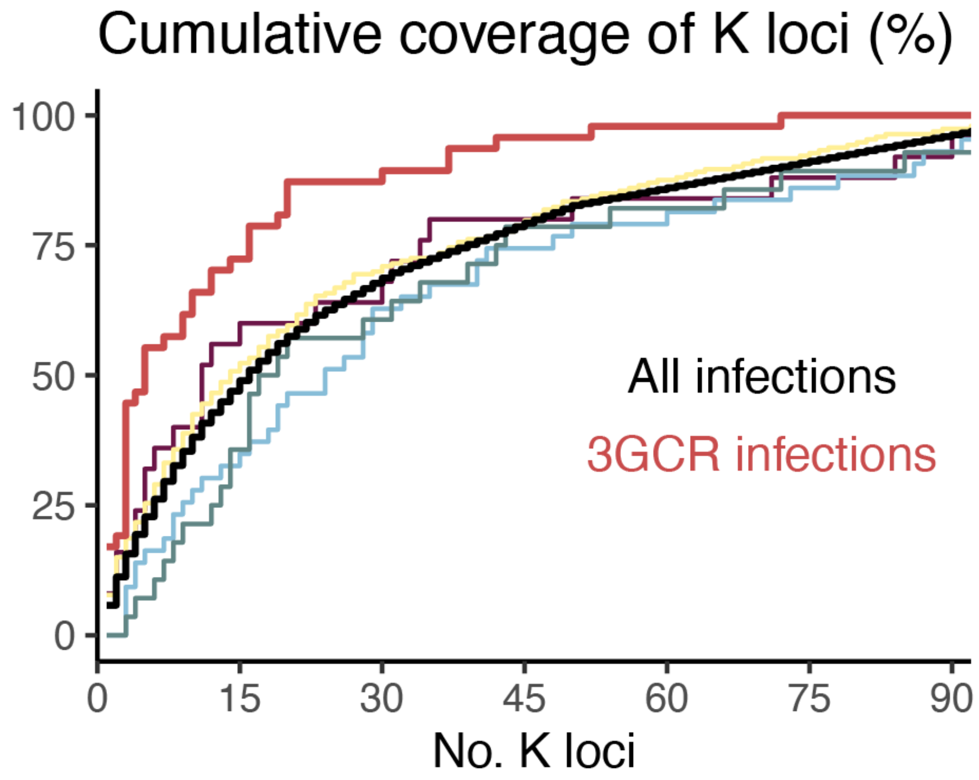


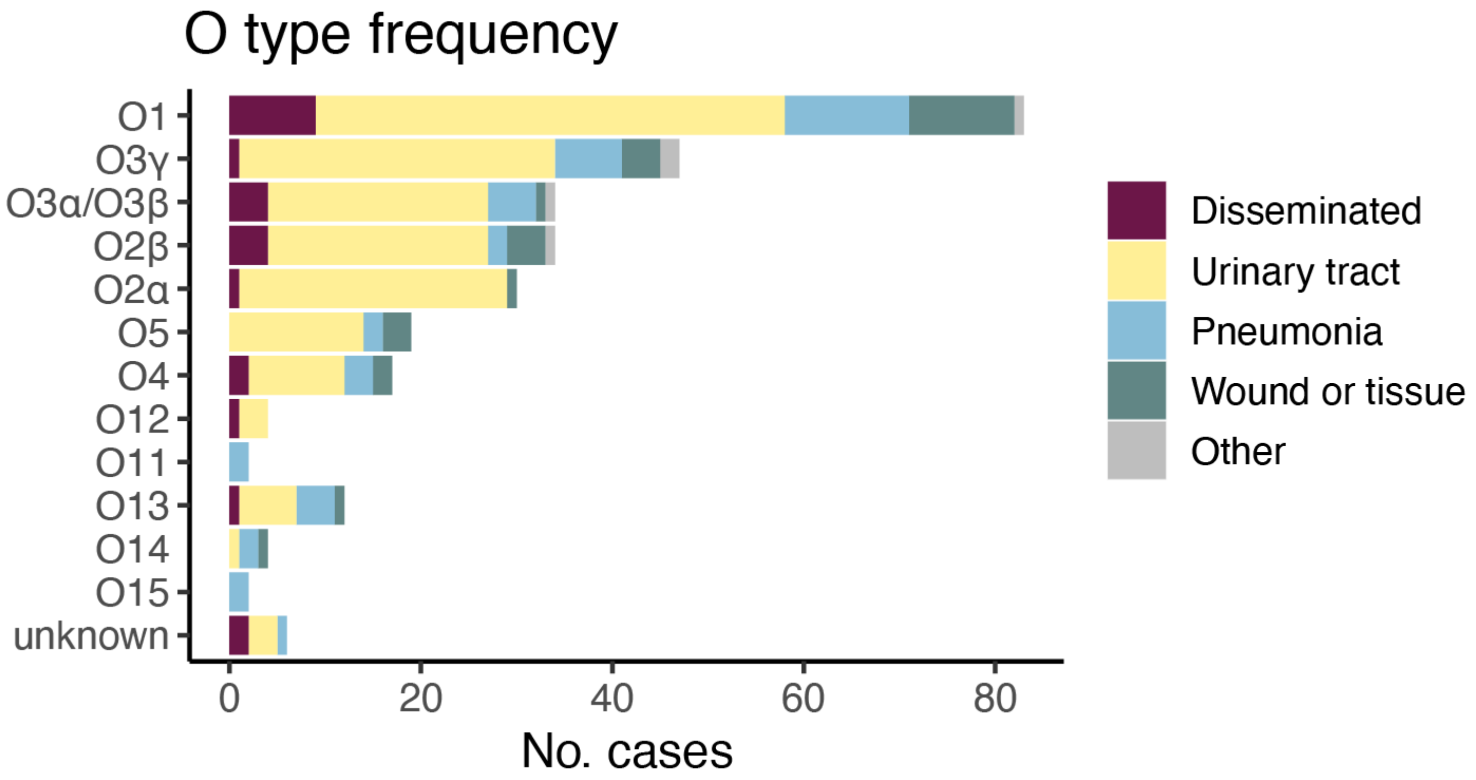


Note: few hypervirulent ST23 infections ➔ KL1 not common

Adapted from Gorrie *et al Nature Communications* 2022; Alfred Hospital Network, Melbourne, Australia

Comparable O diversity by infection type





Adapted from Gorrie *et al Nature Communications* 2022; Alfred Hospital Network, Melbourne, Australia

K frequencies differ by geography

nature microbiology

ARTICLES

https://doi.org/10.1038/s41564-019-0492-8

Epidemic of carbapenem-resistant *Klebsiella pneumoniae* in Europe is driven by nosocomial spread

Sophia David[1], Sandra Reuter[2], Simon R. Harris[3], Corinna Glasner[4], Theresa Feltwell[3], Silvia Argimon[1], Khalil Abudahab[1], Richard Goater[1], Tommaso Giani[5], Giulia Errico[6], Marianne Aspbury[7], Sara Sjunnebo[8], the EuSCAPE Working Group[9], the ESGEM Study Group[10], Edward J. Feil[11], Gian Maria Rossolini[5,12], David M. Aanensen[1,13,14]* and Hajo Grundmann[2,4,14]*

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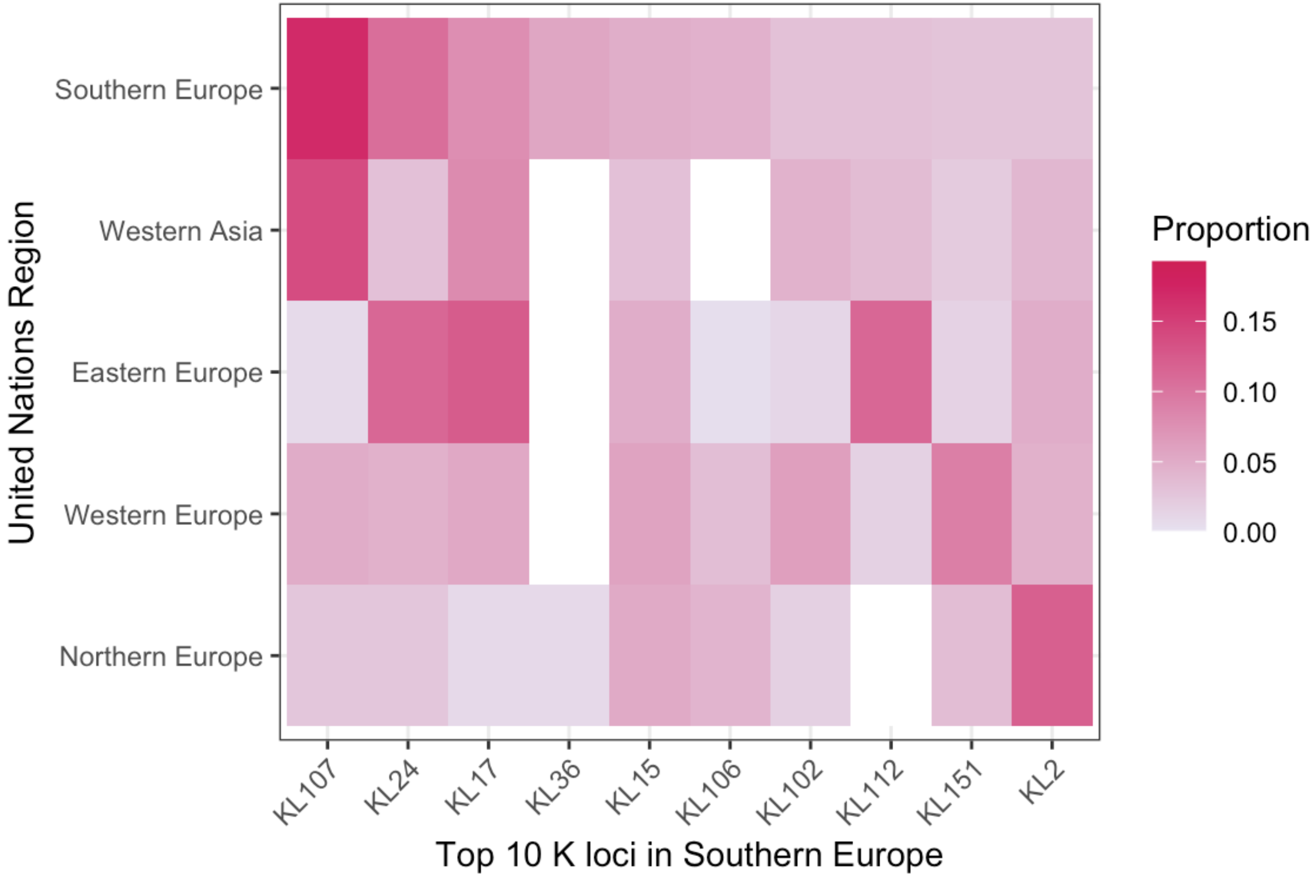

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Geographic differences driven by clone associations

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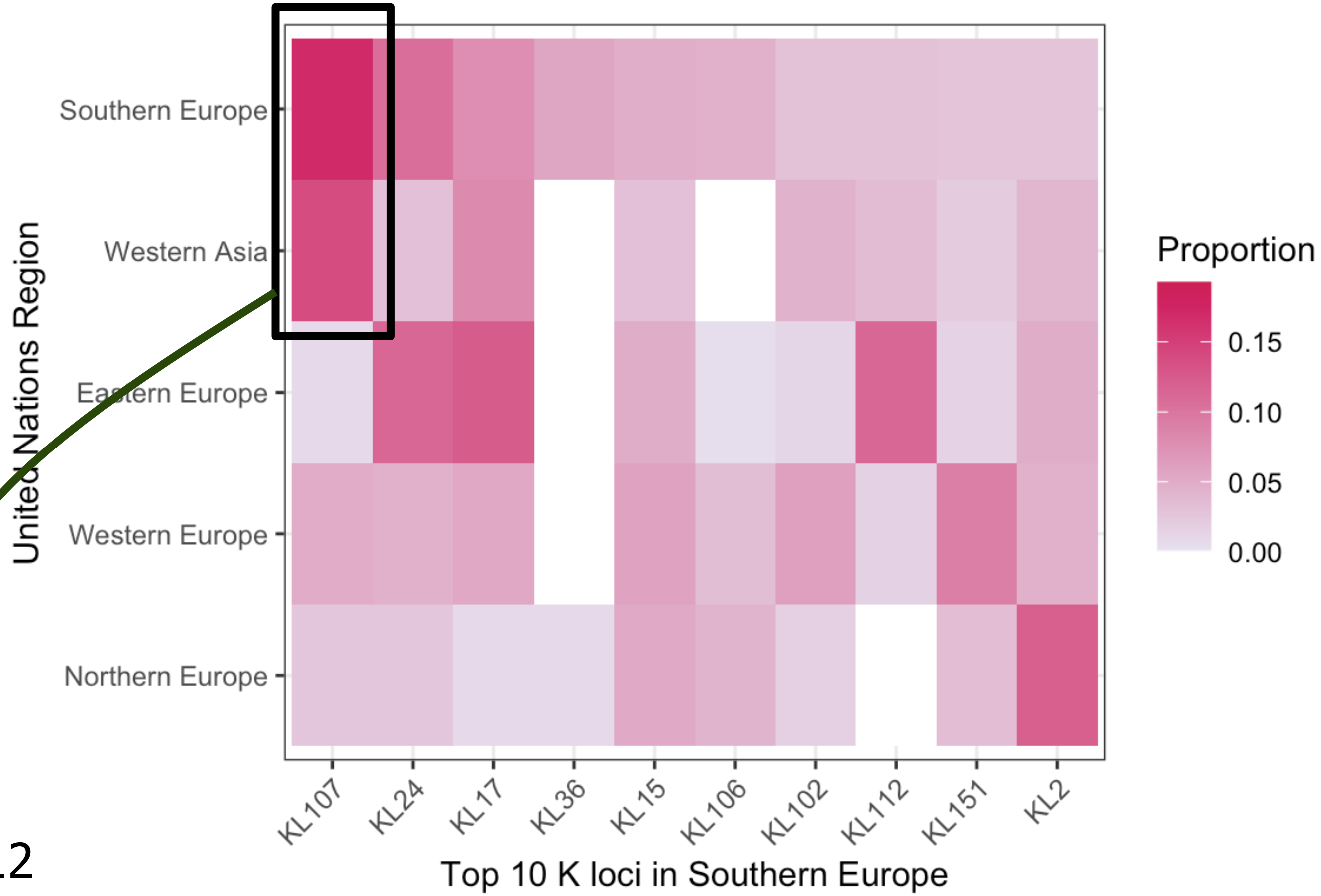
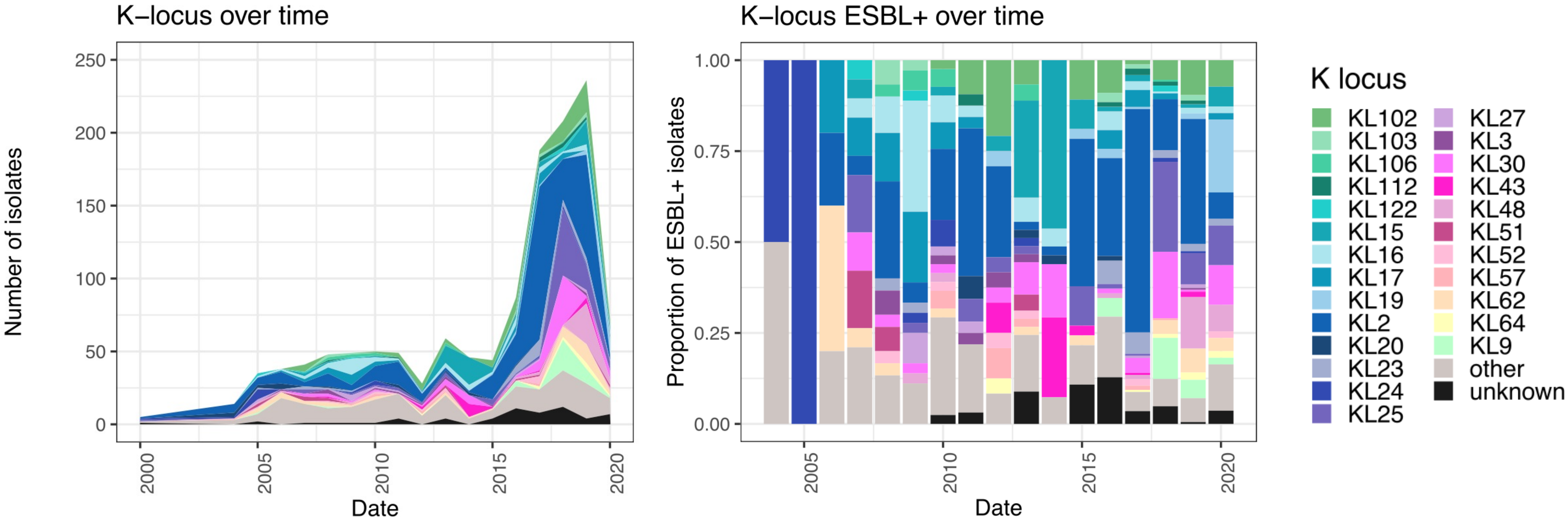


ST258 / ST512
(Italy and Israel)

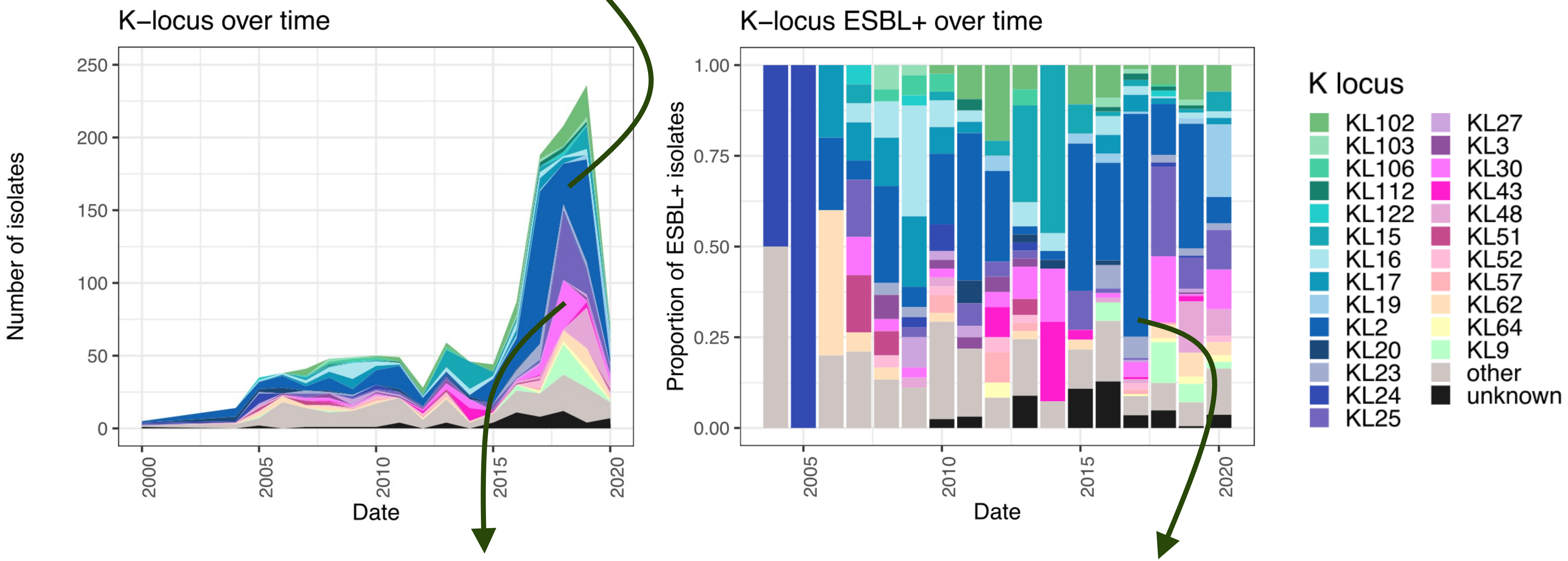
Data from David *et al Nature Microbiology* 2019; Genotypes from Lam *et al Nature Communications* 2021

K frequencies fluctuate through time



Heinz *et al Genome Medicine* 2024; Queen Elizabeth Central Hospital, Blantyre, Malawi

K frequencies impacted by successive clonal expansions



KL2

ST35-KL30

ST39-KL2

Heinz *et al Genome Medicine* 2024; Queen Elizabeth Central Hospital, Blantyre, Malawi

What should we consider when designing Kpn seroepidemiology analyses?

Considerations for robust *Kpn* seroepidemiology analyses

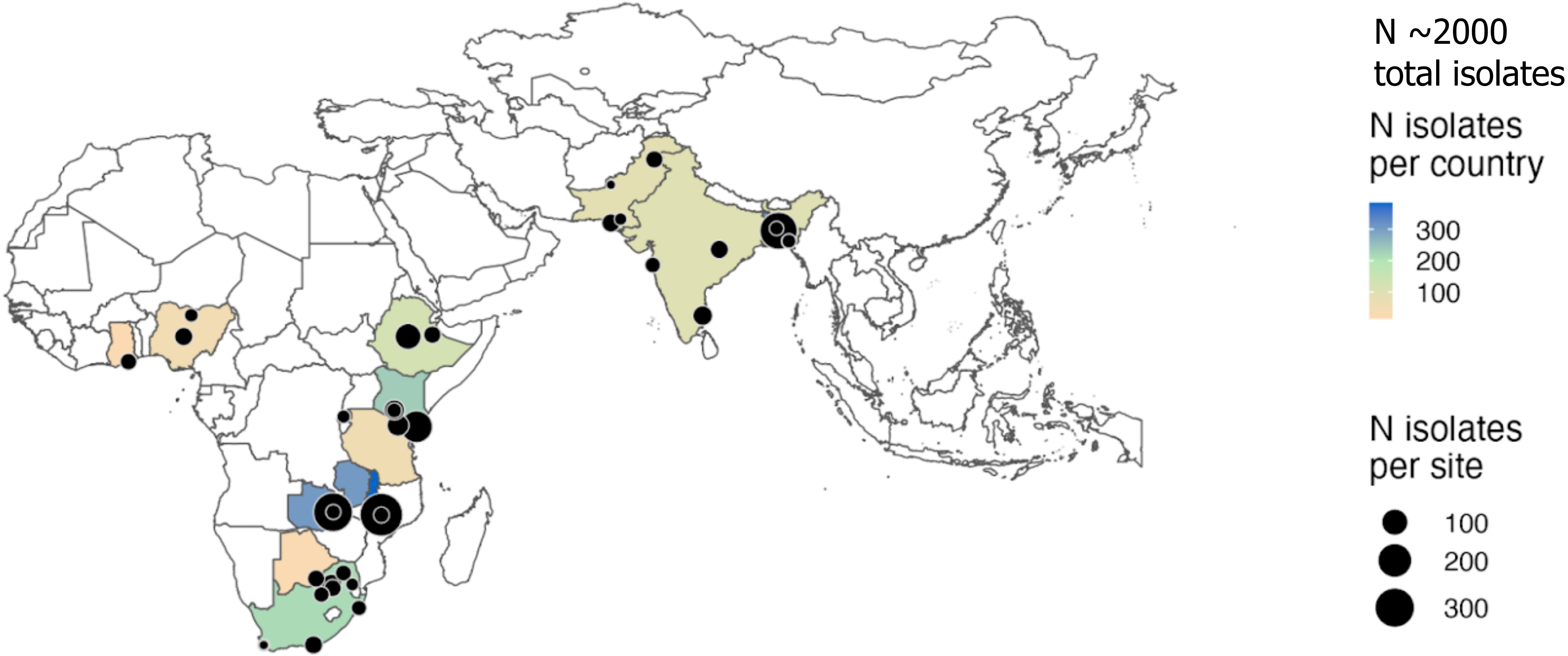
Sampling:

- 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



HUGE collaborative effort – 82 coauthors!

Stanton / Keegan *et al medRxiv* 2025
DOI: 10.1101/2025.06.28.25330253

Bayesian prevalence estimates, adjusted for outbreaks

One WGS per infection

↓

K loci and O types - Kaptive
ST and resistance score - Kleborate
Pairwise SNVs - Pathogenwatch

↓

Cluster genomes ≤10 SNVs, same site, same year

↓

Bayesian prevalence estimates, global and regional
ESBL+, CP+, fatal cases

Stanton / Keegan *et al medRxiv* 2025
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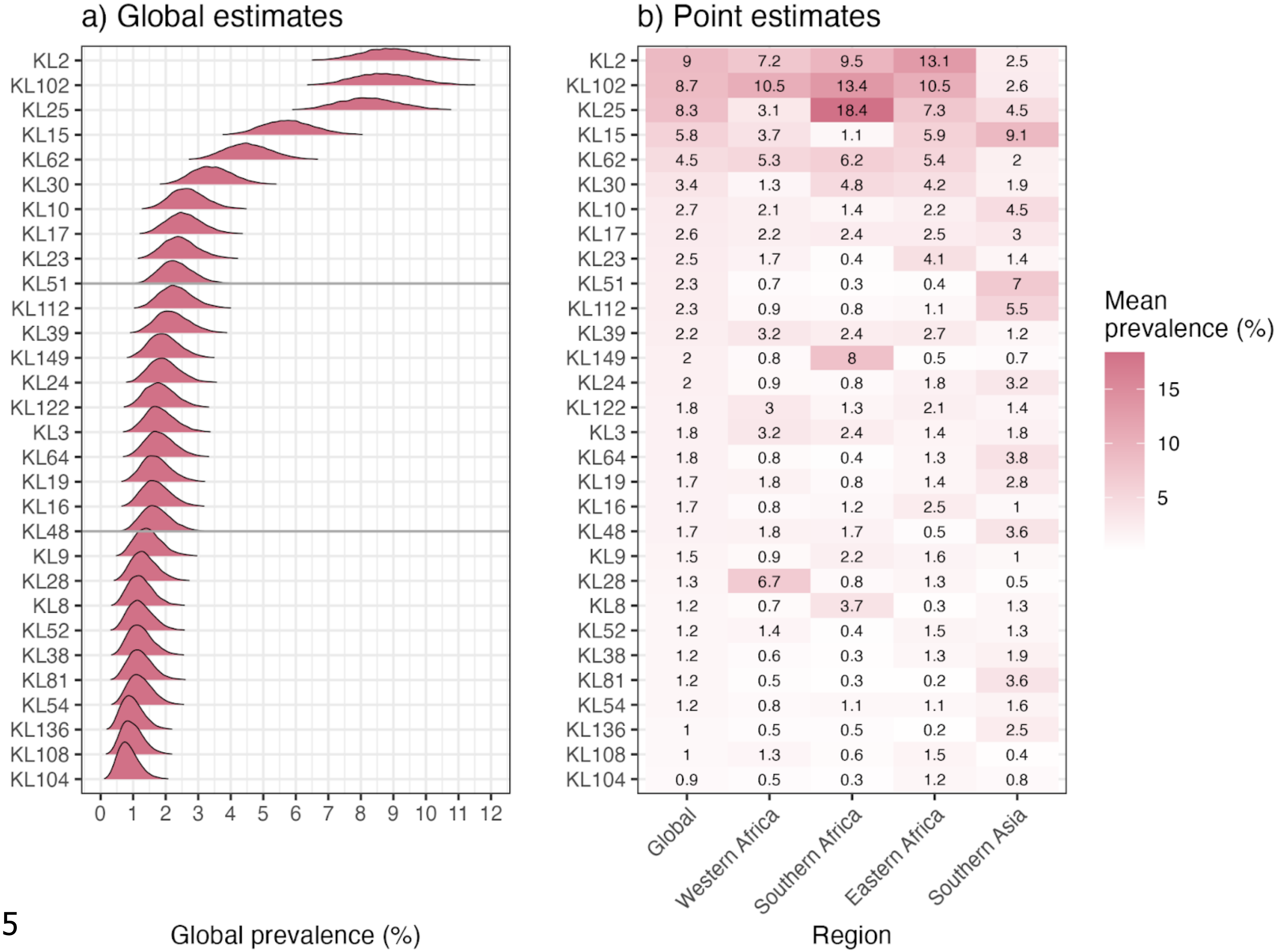
Bayesian prevalence estimates, adjusted for outbreaks



	Global	Western Africa	Southern Africa	Eastern Africa	Southern Asia
KL2	9	7.2	9.5	13.1	2.5
KL102	8.7	10.5	13.4	10.5	2.6
KL25	8.3	3.1	18.4	7.3	4.5
KL15	5.8	3.7	1.1	5.9	9.1
KL62	4.5	5.3	6.2	5.4	2
KL30	3.4	1.3	4.8	4.2	1.9
KL10	2.7	2.1	1.4	2.2	4.5
KL17	2.6	2.2	2.4	2.5	3
KL23	2.5	1.7	0.4	4.1	1.4
KL51	2.3	0.7	0.3	0.4	7
KL112	2.3	0.9	0.8	1.1	5.5
KL39	2.2	3.2	2.4	2.7	1.2
KL149	2	0.8	8	0.5	0.7
KL24	2	0.9	0.8	1.8	3.2
KL122	1.8	3	1.3	2.1	1.4
KL3	1.8	3.2	2.4	1.4	1.8
KL64	1.8	0.8	0.4	1.3	3.8
KL19	1.7	1.8	0.8	1.4	2.8
KL16	1.7	0.8	1.2	2.5	1
KL48	1.7	1.8	1.7	0.5	3.6
KL9	1.5	0.9	2.2	1.6	1
KL28	1.3	6.7	0.8	1.3	0.5
KL8	1.2	0.7	3.7	0.3	1.3
KL52	1.2	1.4	0.4	1.5	1.3
KL38	1.2	0.6	0.3	1.3	1.9
KL81	1.2	0.5	0.3	0.2	3.6
KL54	1.2	0.8	1.1	1.1	1.6
KL136	1	0.5	0.5	0.2	2.5
KL108	1	1.3	0.6	1.5	0.4
KL104	0.9	0.5	0.3	1.2	0.8

Stanton / Keegan *et al medRxiv* 2025
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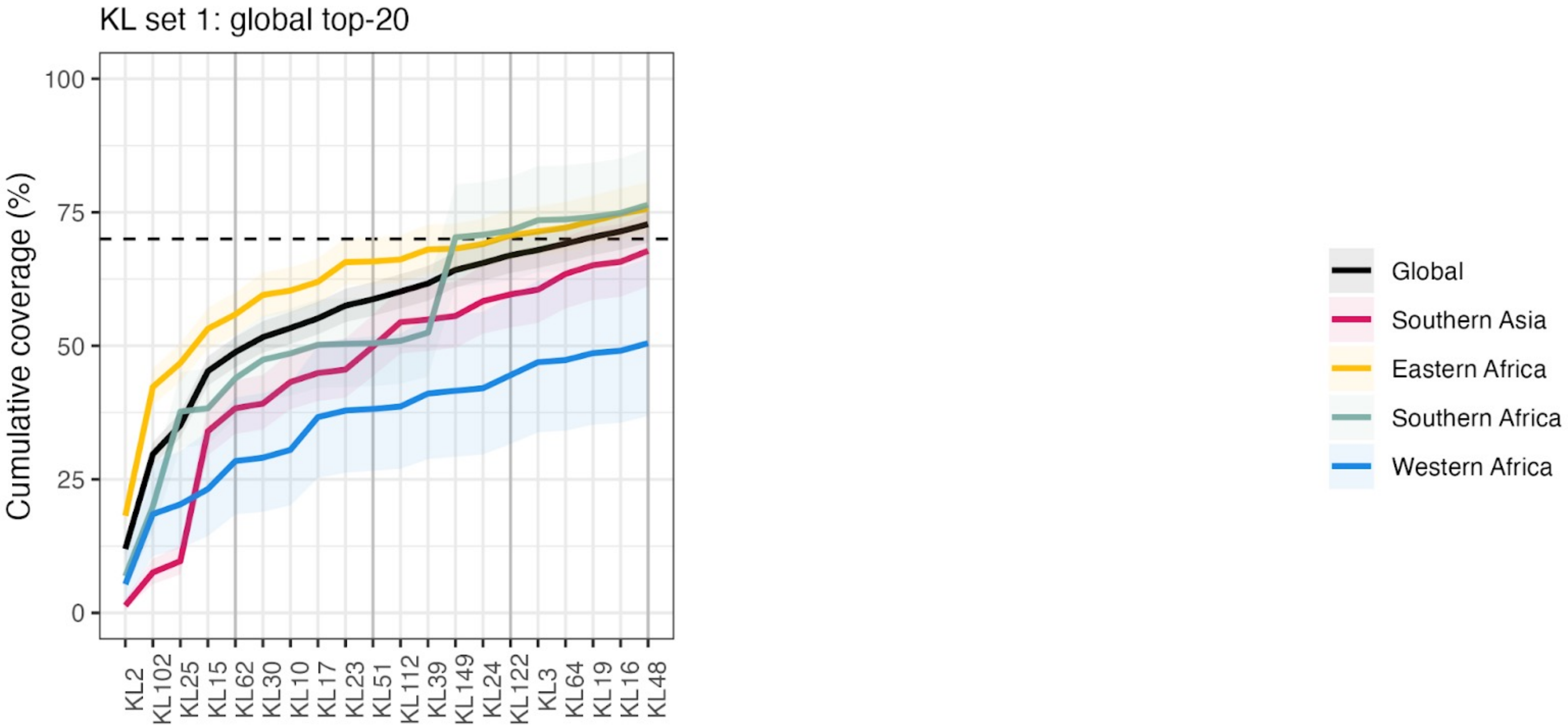
Cumulative coverage for top 20 K varies by region



Stanton / Keegan *et al medRxiv* 2025
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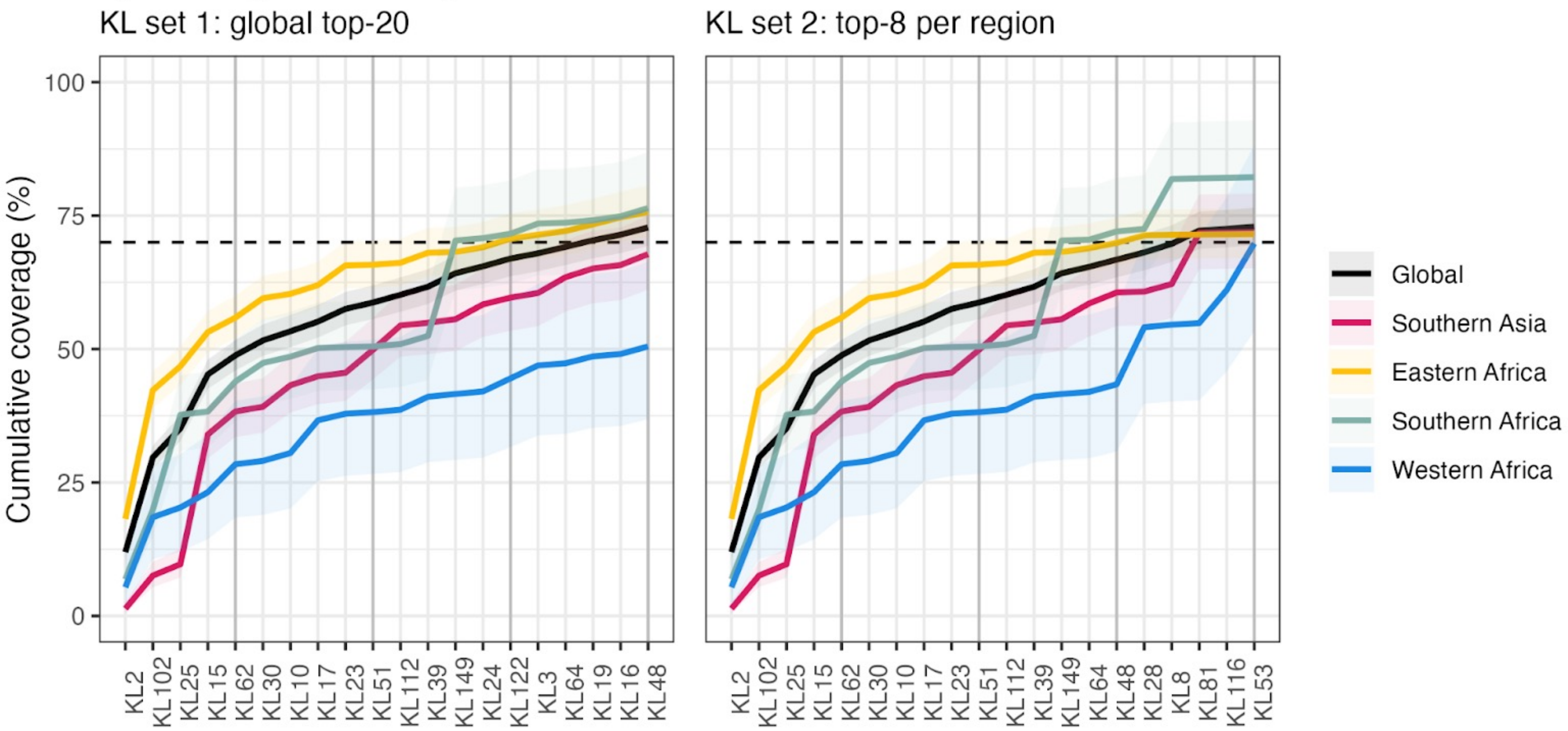
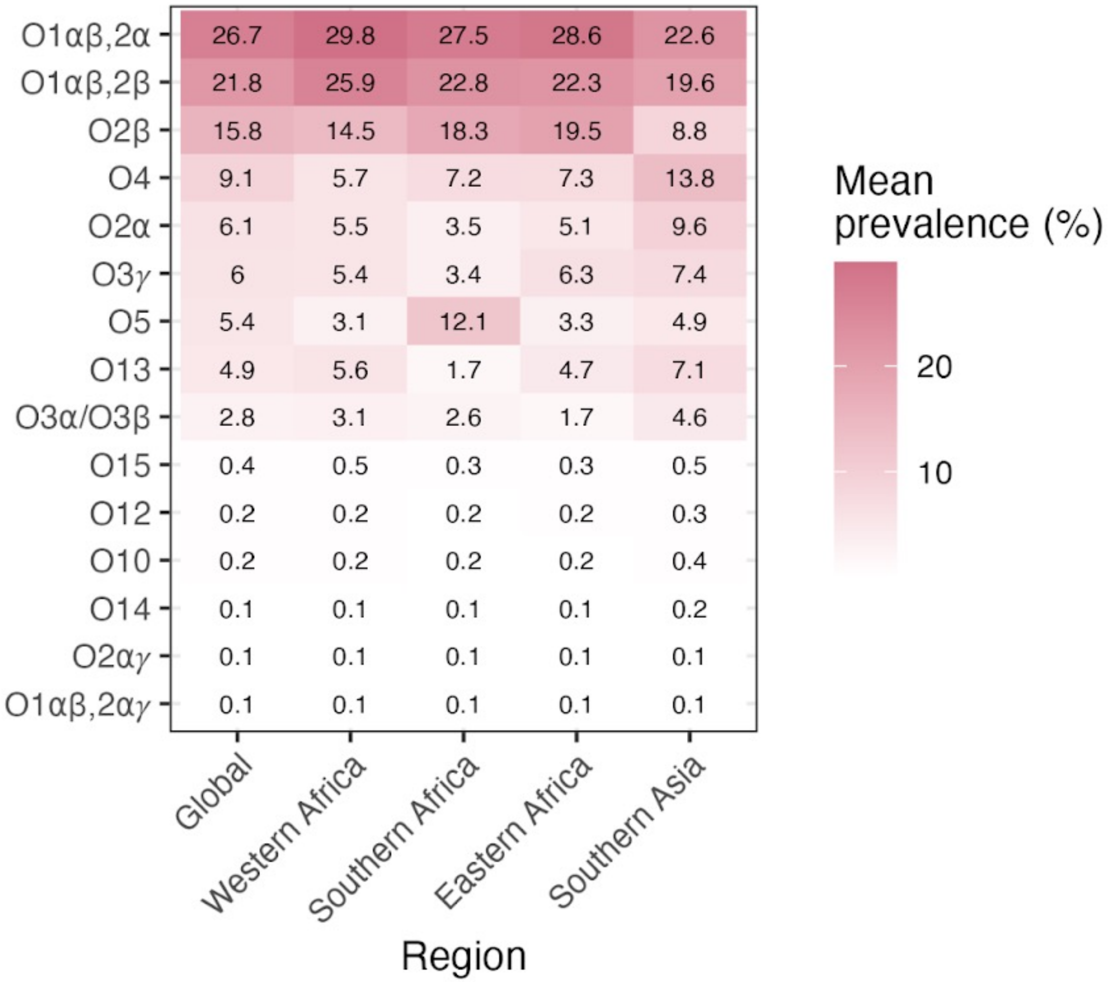
Can achieve ≥70% coverage for all regions if select top loci from each



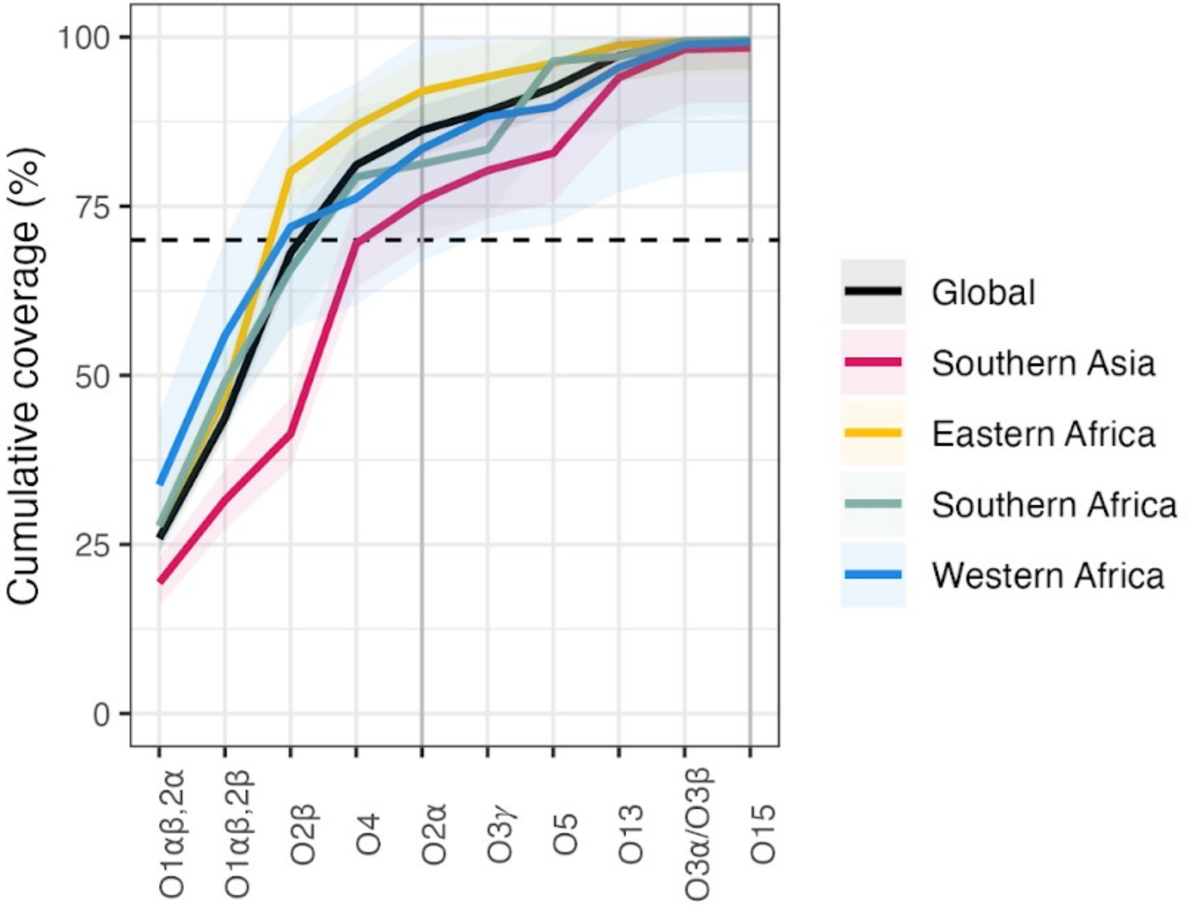
Stanton / Keegan *et al medRxiv* 2025

DOI: 10.1101/2025.06.28.25330253

O types much less diverse, top 4 achieves ≥70% coverage in all regions



	Global	Western Africa	Southern Africa	Eastern Africa	Southern Asia
O1αβ,2α	26.7	29.8	27.5	28.6	22.6
O1αβ,2β	21.8	25.9	22.8	22.3	19.6
O2β	15.8	14.5	18.3	19.5	8.8
O4	9.1	5.7	7.2	7.3	13.8
O2α	6.1	5.5	3.5	5.1	9.6
O3γ	6	5.4	3.4	6.3	7.4
O5	5.4	3.1	12.1	3.3	4.9
O13	4.9	5.6	1.7	4.7	7.1
O3α/O3β	2.8	3.1	2.6	1.7	4.6
O15	0.4	0.5	0.3	0.3	0.5
O12	0.2	0.2	0.2	0.2	0.3
O10	0.2	0.2	0.2	0.2	0.4
O14	0.1	0.1	0.1	0.1	0.2
O2αγ	0.1	0.1	0.1	0.1	0.1
O1αβ,2αγ	0.1	0.1	0.1	0.1	0.1



Stanton / Keegan *et al medRxiv* 2025
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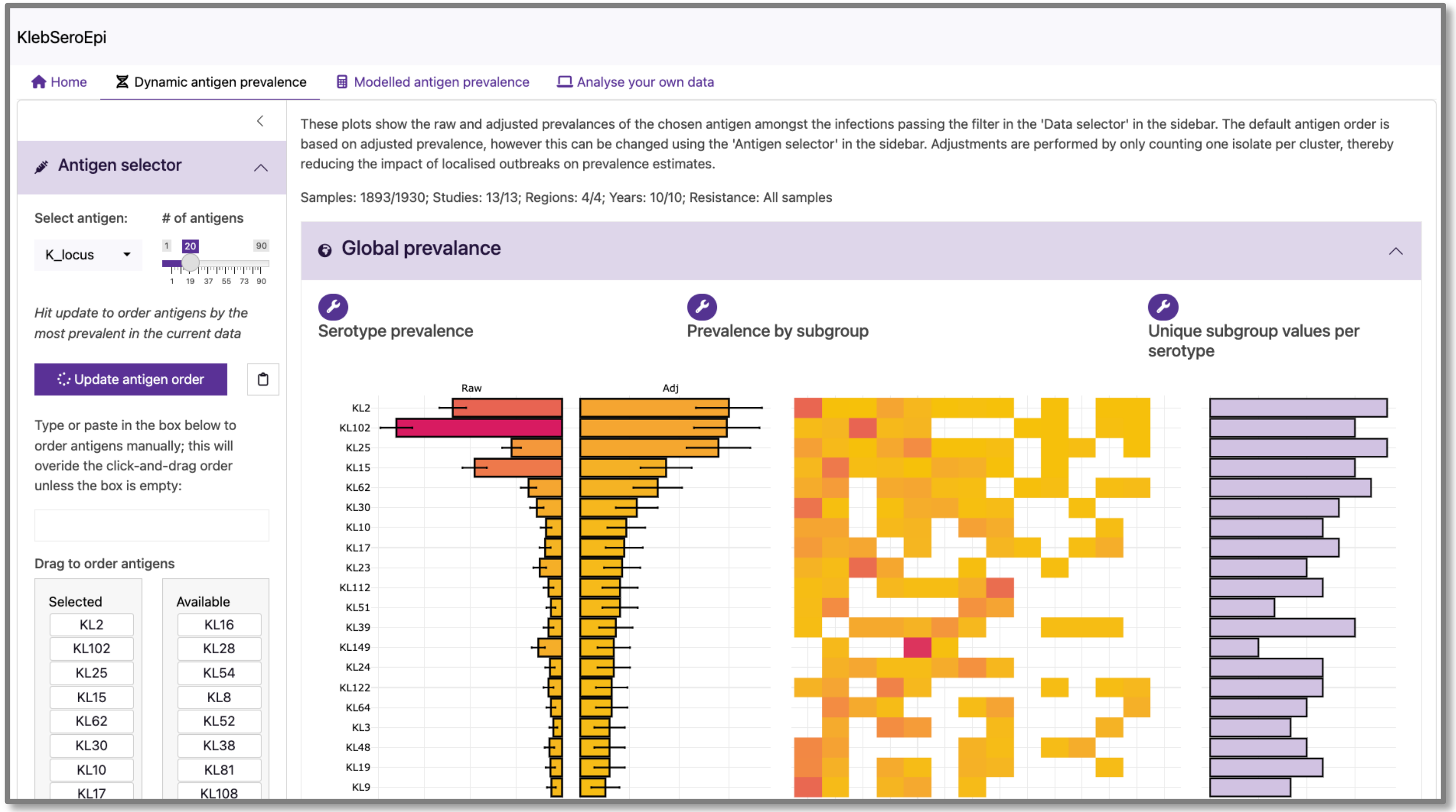
Sero-epi app for data exploration



Hit update to order antigens by the most prevalent in the current data

Type or paste in the box below to order antigens manually; this will overide the click-and-drag order unless the box is empty:

These plots show the raw and adjusted prevalances of the chosen antigen amongst the infections passing the filter in the 'Data selector' in the sidebar. The default antigen order is based on adjusted prevalence, however this can be changed using the 'Antigen selector' in the sidebar. Adjustments are performed by only counting one isolate per cluster, thereby reducing the impact of localised outbreaks on prevalence estimates.

Samples: 1893/1930; Studies: 13/13; Regions: 4/4; Years: 10/10; Resistance: All samples

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

Stanton / Keegan *et al medRxiv* 2025
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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 ≥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
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Pan *et al Sci Rep* 2015. PMID: 26493302
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