Understanding spread of AMR: genomics and modelling perspectives

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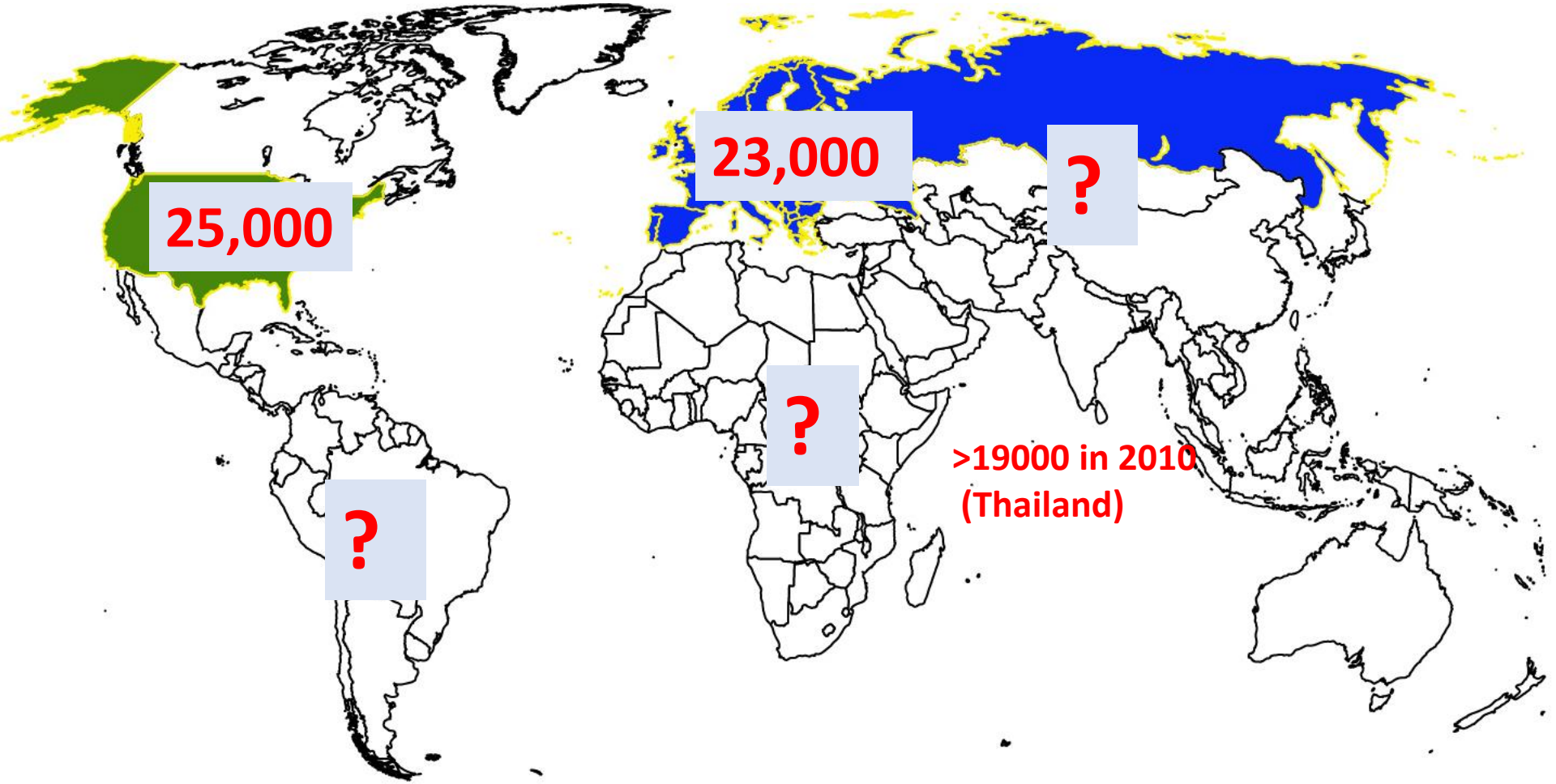
29 November 2019

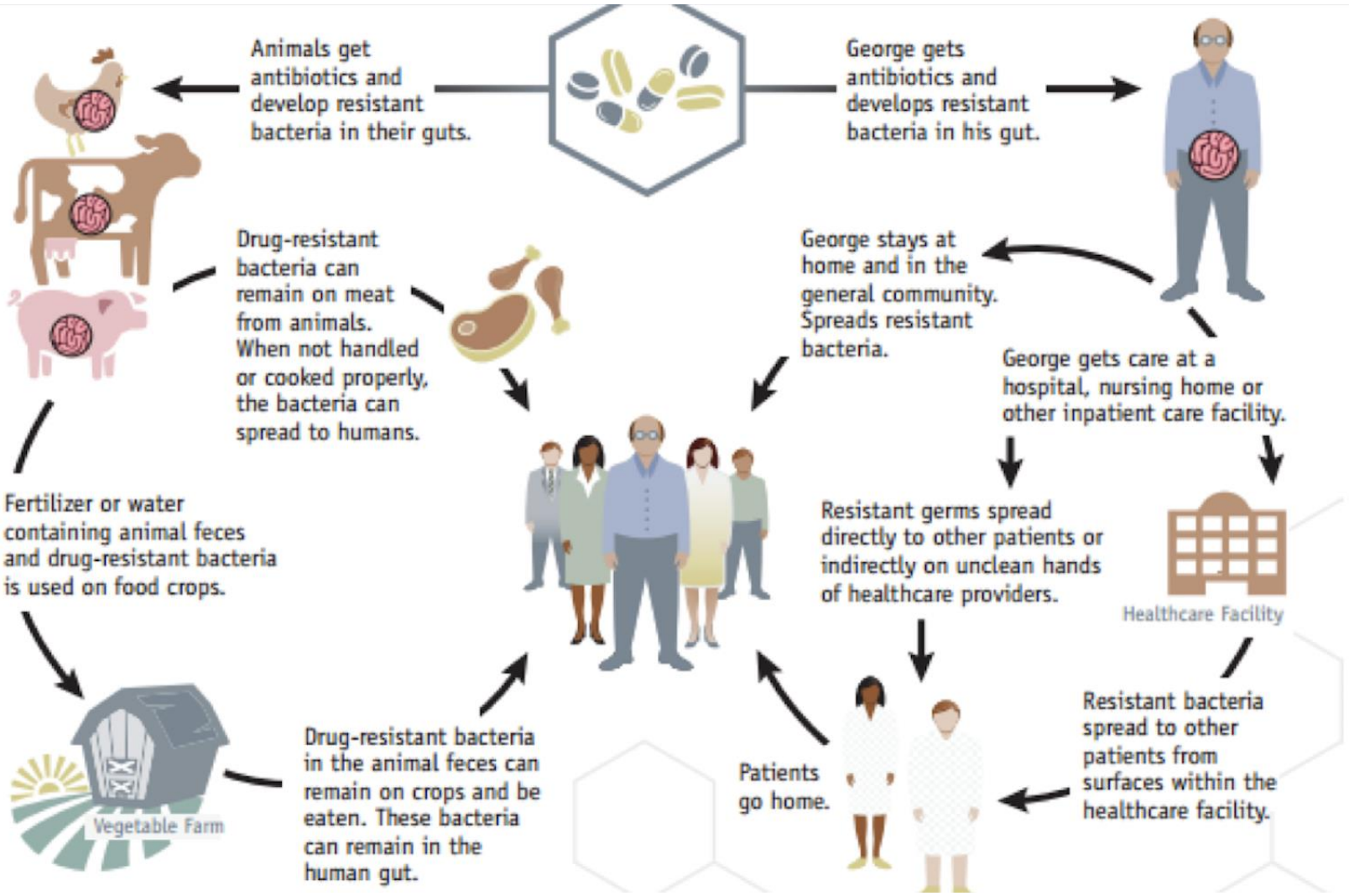
Antimicrobial resistance- A major threat to human health

0.7 million (2016)

10 million (2050)



Sources and routes of AMR spread



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Background

- Understanding of how AMR spreads is critical in guiding development of strategies to control AMR spread

- Both genomics and epidemiological models can help to understand spread of AMR

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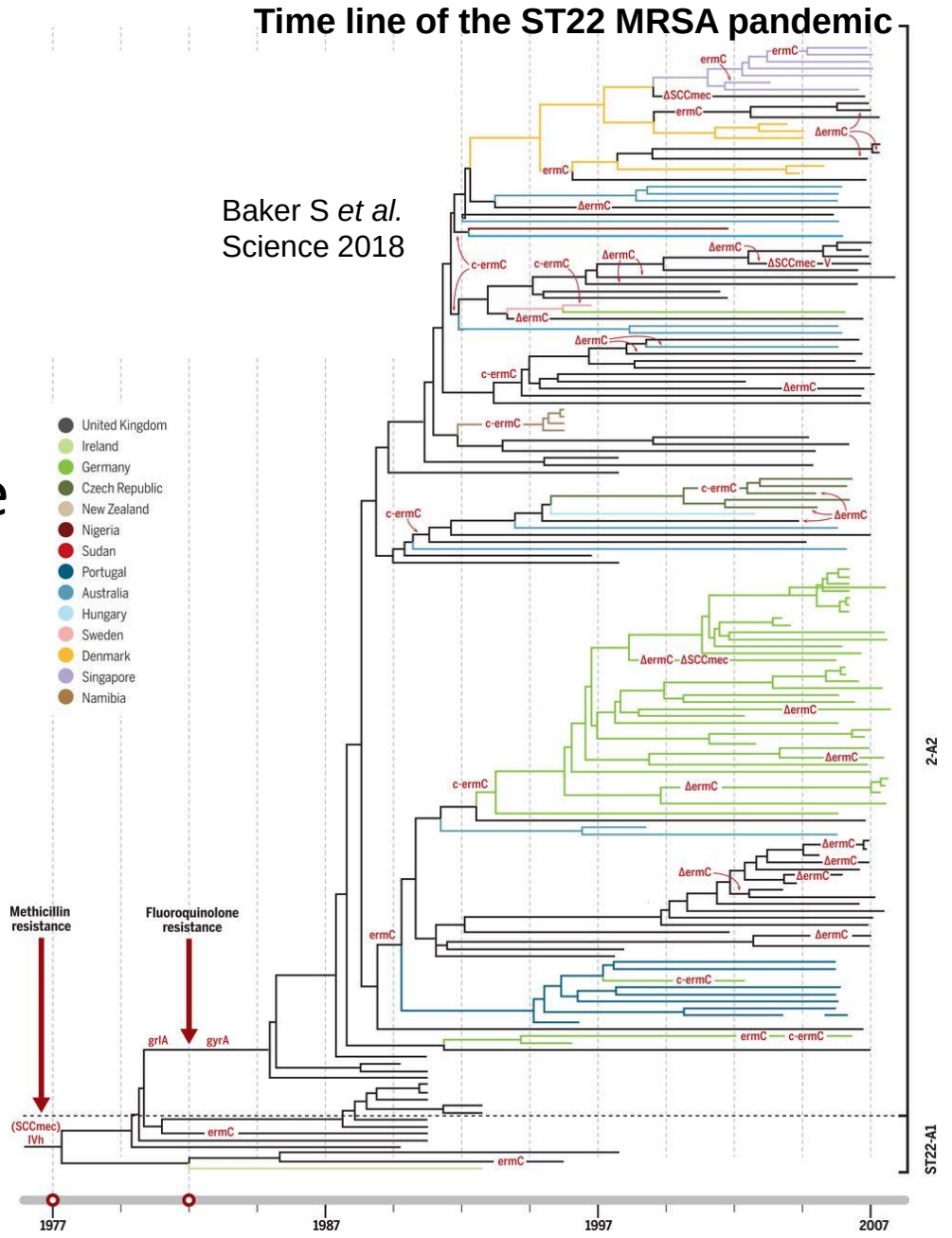
What can we learn about AMR with genomics?

- Spread and maintenance of AMR depends on Organism's lifestyle
  - colonization, and pathogenicity
- genetic basis for resistance
  - intrinsic,
  - mutation associated,
  - horizontal gene transfer



… from epidemiological models

- Quantifying transmission dynamics
  - Rates of acquiring drug resistant bacteria
  - Routes of transmission
  - Identify risk factors
- Identification and evaluation of potential interventions

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Case studies

- Spread of *bla*$_{\text{CTX-M-15}}$ in Malawian *E. coli* population (Genomics only)

- Bayesian Markov models for colonisation and carriage dynamics of FQR-E (epidemiological data only)

- Estimation of carriage duration of carbapenemase producing Enterobacteriaceae (epidemiological+ genomic data)

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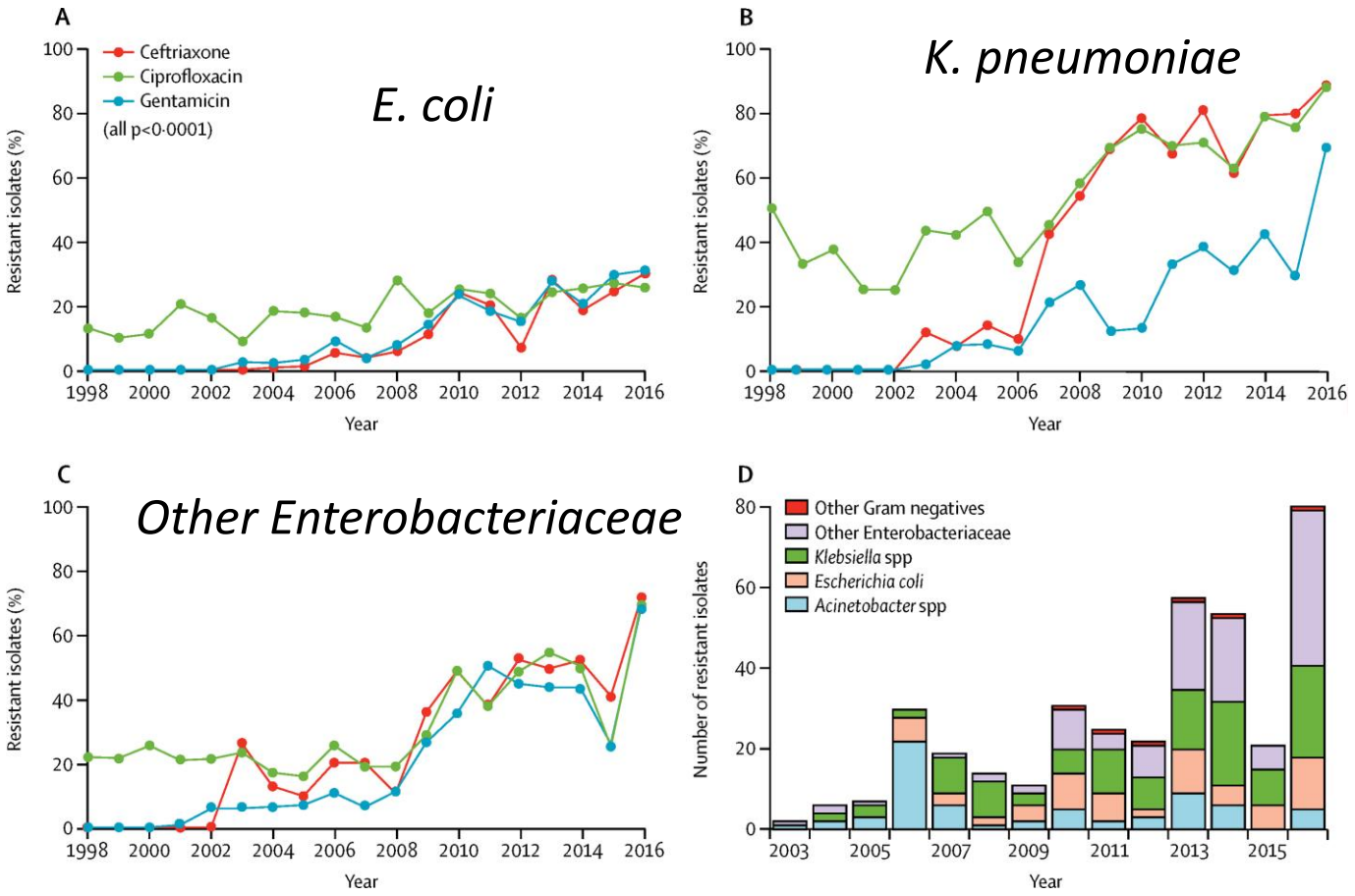
ESBL producing Enterobacteriaceae in Malawi



Musicha, *et al.*
Lancet Infec Dis. 2017

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Questions we asked

- What are the genetic determinants of ESBL production?
- Are there specific clones of *E. coli* and *K. pneumonaie* responsible for the spread of ESBL genes?

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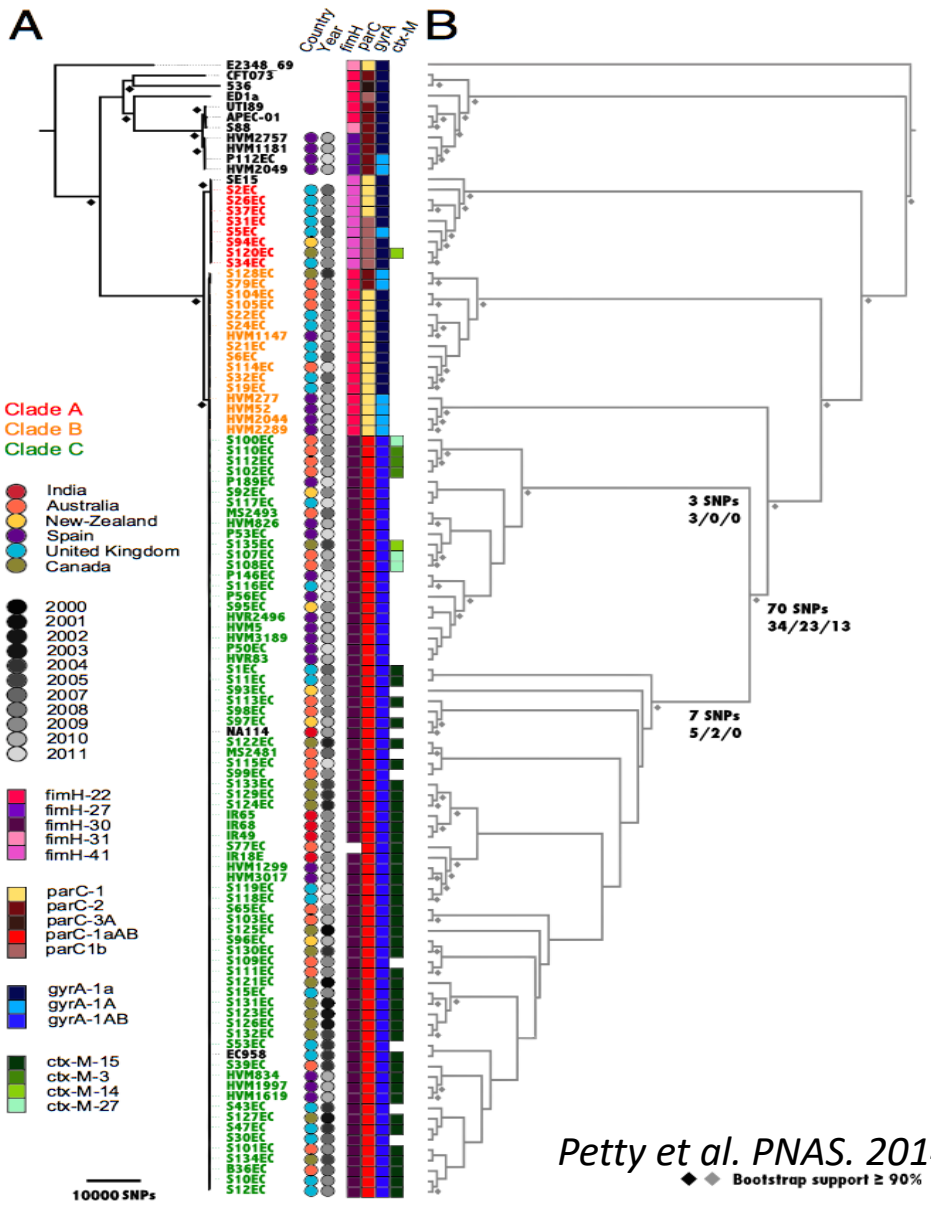
E. coli ST131 responsible for global spread of $bla_{CTX\text{-}M\text{-}15}$

- E. coli-A genetically very diverse species
- ESBL resistance is associated with specific clones
  - ❑ In particular $bla_{CTX\text{-}M\text{-}15}$ is associated with ST131



Petty et al. PNAS. 2014

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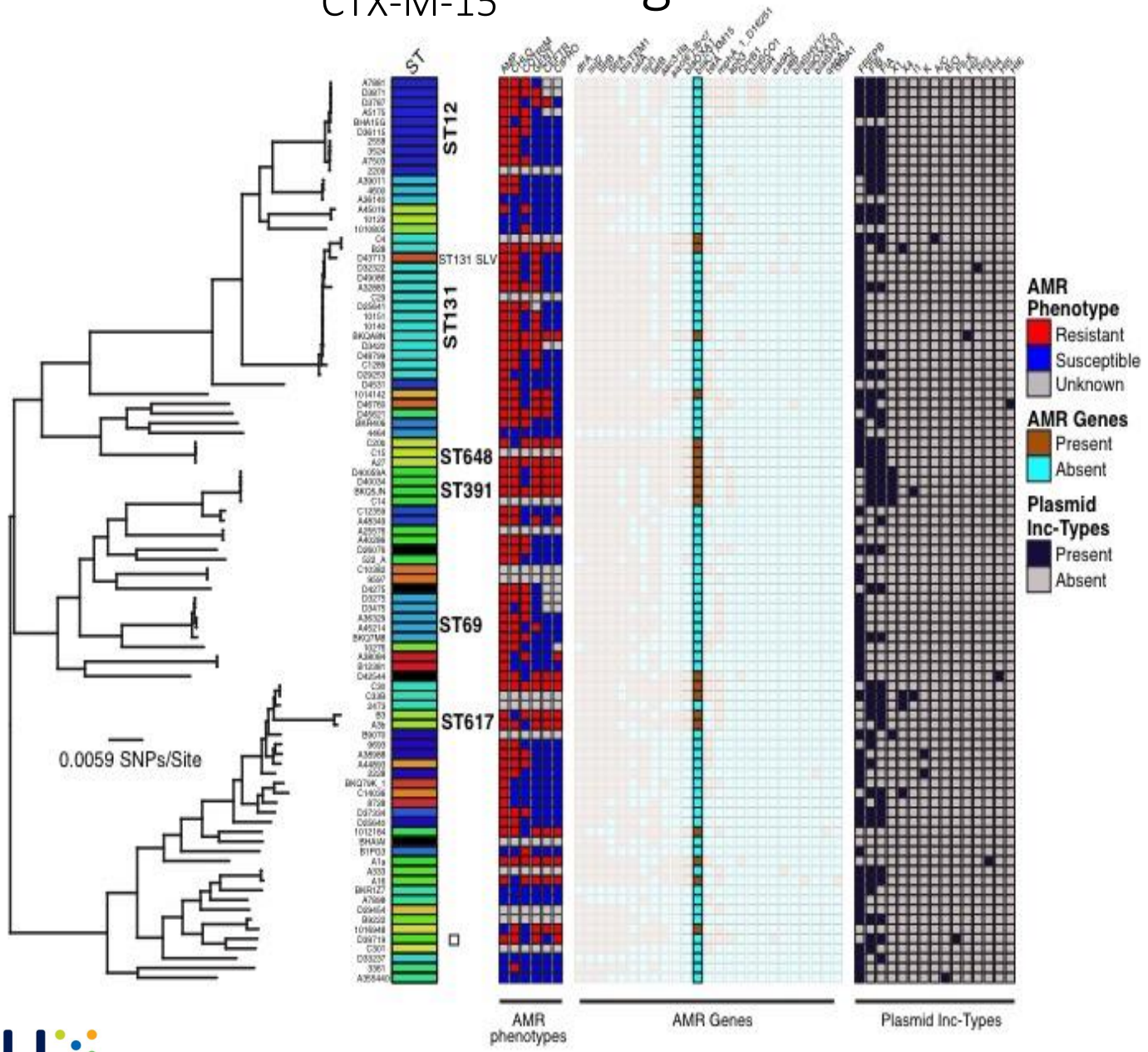
No dominant *bla*$_{\text{CTX-M-15}}$ lineage in Malawian isolates



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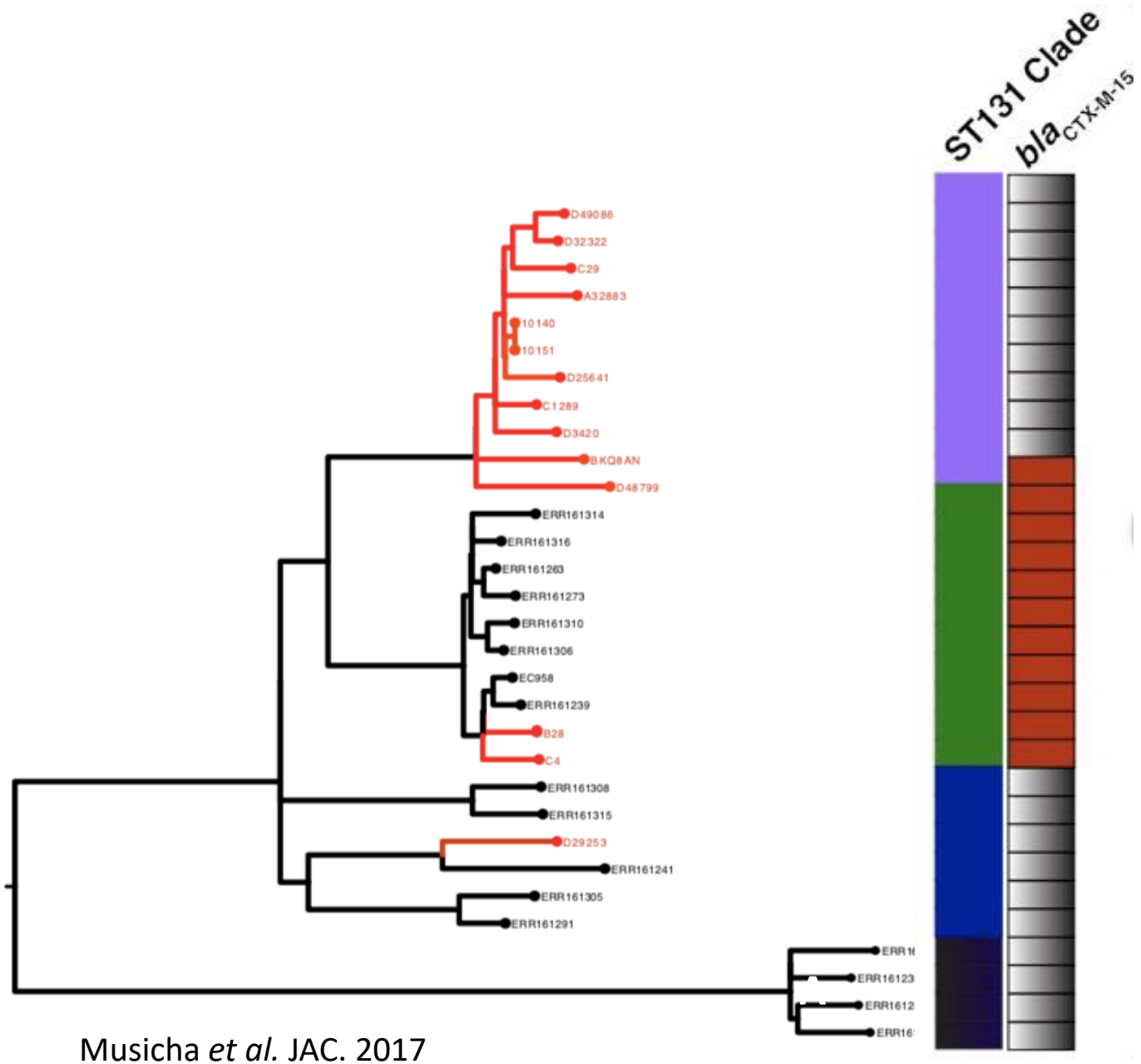
Musicha *et al.* JAC. 2017

A new *E. coli* ST131 clade with CTX-M-15 potential



Musicha *et al.* JAC. 2017

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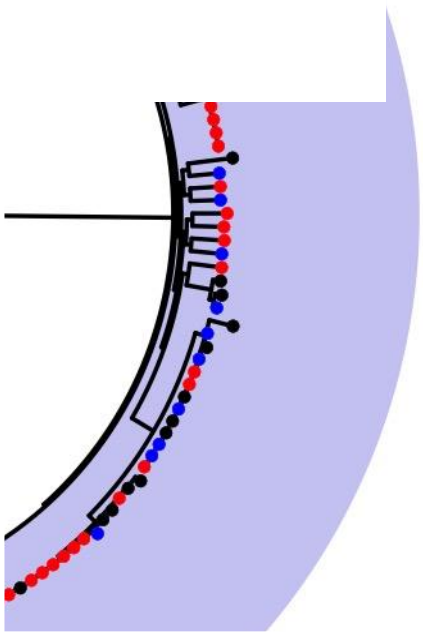
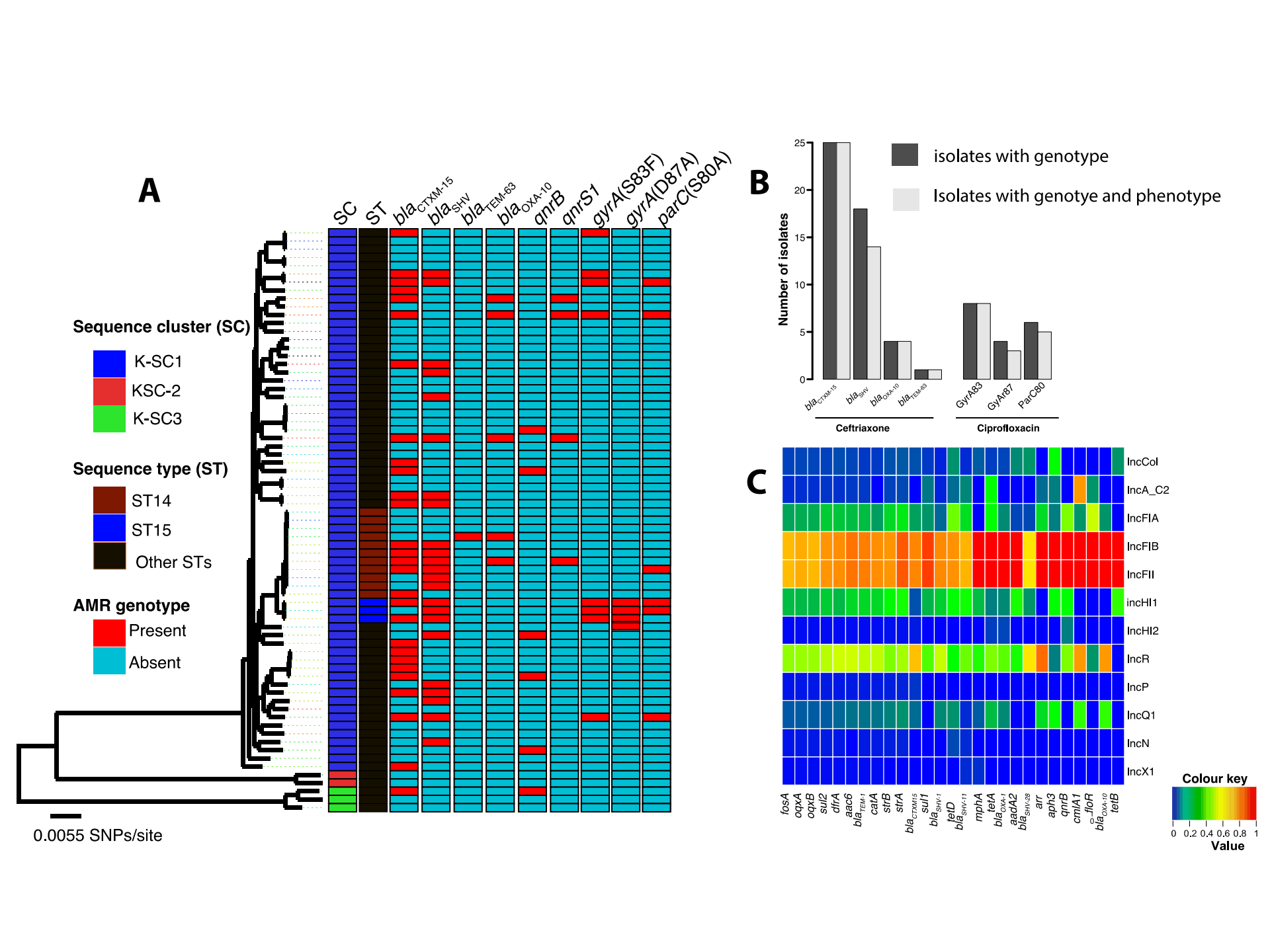
Diversity of ESBL producing K. ɛumoniae in Malawi




A
SC
ST
bla CTXM-15
bla SHV
bla TEM-63
bla OXA-10
qnrB
qnrS1
gyrA(S83F)
gyrA(D87A)
parC(S80A)
Sequence cluster (SC)
K-SC1
KSC-2
K-SC3
Sequence type (ST)
ST14
ST15
Other STs
AMR genotype
Present
Absent
0.0055 SNPs/site
B
isolates with genotype
Isolates with genotye and phenotype
Number of isolates
25
20
15
10
5
0
bla CTXM-15
bla SHV
bla OXA-10
bla TEM-63
GyrA83
GyrA87
ParC80
Ceftriaxone
Ciprofloxacin
C
IncCol
IncA_C2
IncFIA
IncFIB
IncFII
incHI1
IncHI2
IncR
IncP
IncQ1
IncN
IncX1
fosA
oqxA
oqxB
sul2
dfrA
aac6
bla TEM-1
catA
strB
strA
bla CTXM15
sul1
bla SHV-1
tetD
bla SHV-11
mphA
tetA
bla OXA-1
aadA2
bla SHV-28
arr
aph3
qnrB
cmlA1
floR
bla OXA-10
tetB
Colour key
0 0.2 0.4 0.6 0.8 1
Value

Conclusions

- CTX-M-15 is produced by diverse lineages/STs of *E. coli and K.* pneumoniae, with no clear dominant producing ST
- HGT rather than clonal expansion, could be the main mechanism for dissemination of CTX-M15.
- The epidemiology of ESBL producing *E. coli* in SSA is different from what has been observed globally where a *bla*CTXM-15 is associated with a single clone of *E. coli* ST131.
- Findimg raise the hypoethesis that there is community-hospital transmission, but direction of transmission remains unclear

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Modelling acquisition and carriage dynamics of FQR-E in Europe

- Prospective cohort study at three Euaropean sites: Antwerp, Geneva, Lodz.
- Estimate rates of acquisition and duration of carriage of FQR-E
- Quantify the impact of ciprofloxacin and nitrofurantoin on rate of acquisition of FQR-E
- Identify other baseline covariates associated with risk of acquisition of FQR-E.

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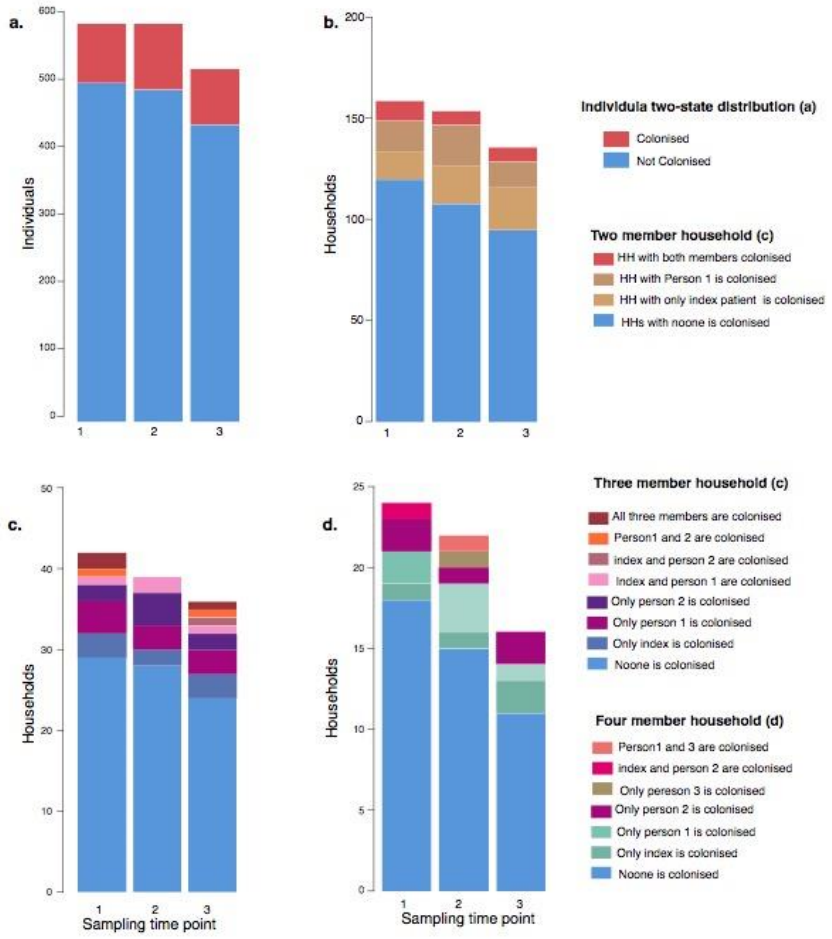
Data

- Feacal samples at baseline, 7-10 days after first sample and 28 days after the second sample.
- Covariates:

  antibiotic exposure, location, travel, and use of antibiotics in prior 12 months



Musicha *et al. (In preparation)*

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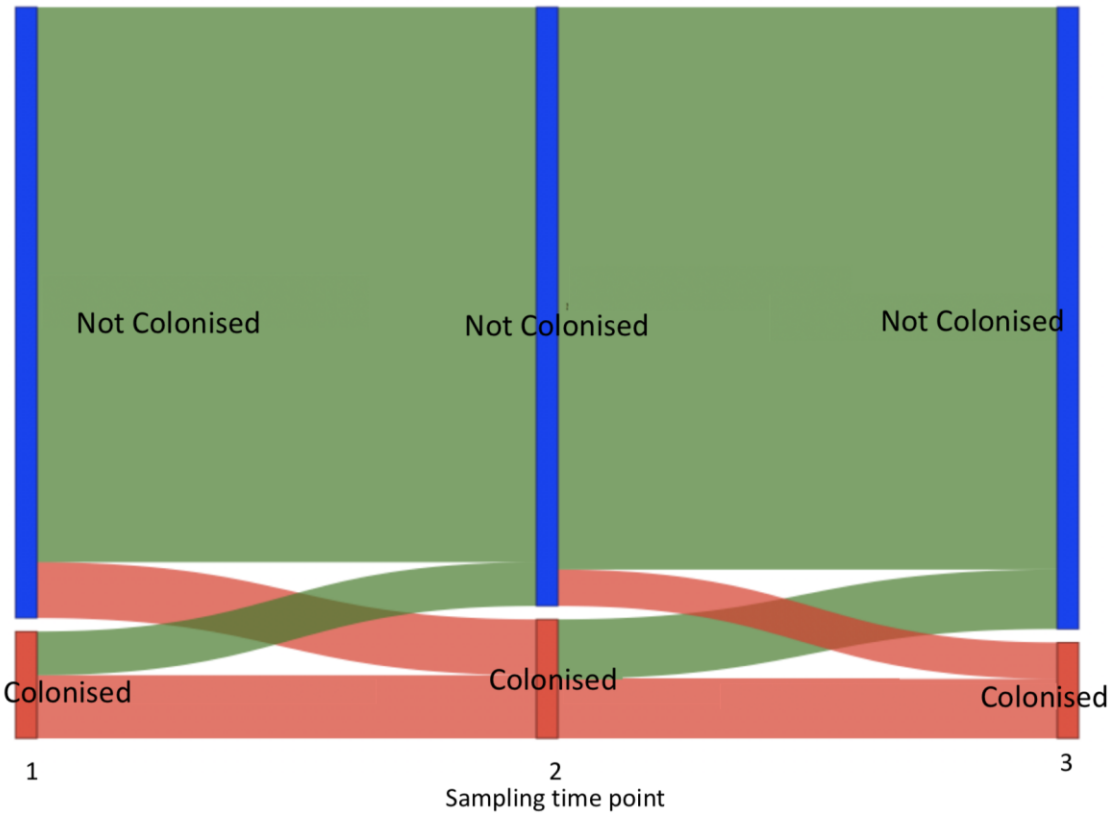
Summary of colonization events

- 590 participants with ≥ 2 samples:
- 144(24.4%) from Antwerp, 233(39.5%) from Geneva and 213(36.1%) from Lodz.



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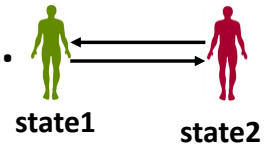
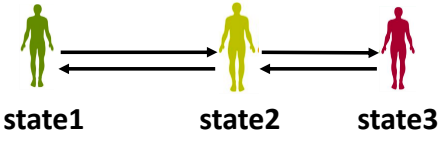
Multistate Markov models

A.



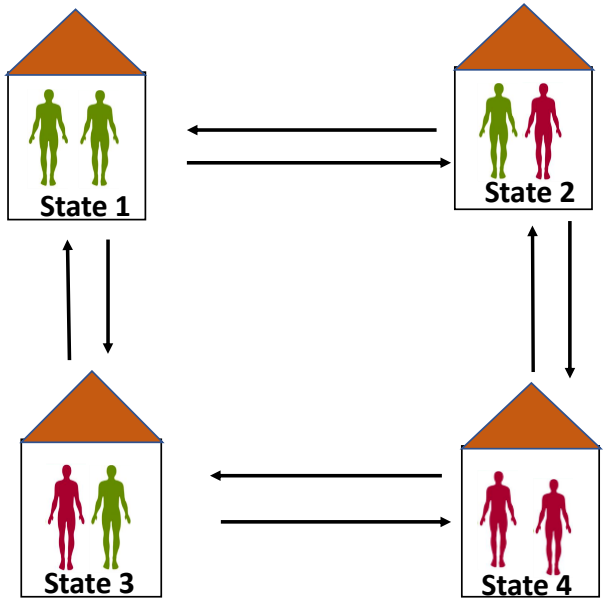
$$Q_1 = \begin{bmatrix} \lambda_{11} & \lambda_{12} \\ \lambda_{21} & \lambda_{22} \end{bmatrix}$$

B.



$$Q_2 = \begin{bmatrix} \lambda_{11} & \lambda_{12} & 0 \\ \lambda_{21} & \lambda_{22} & \lambda_{23} \\ 0 & \lambda_{32} & \lambda_{33} \end{bmatrix}$$

C.



$$Q_3 = \begin{bmatrix} \lambda_{11} & \lambda_{12} & \lambda_{13} & 0 \\ \lambda_{21} & \lambda_{22} & 0 & \lambda_{24} \\ \lambda_{31} & 0 & \lambda_{33} & \lambda_{34} \\ 0 & \lambda_{42} & \lambda_{43} & \lambda_{44} \end{bmatrix}$$

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Models

- Given covariates {X_1, X_2, …,X_D}, the transition rate from state r to state s ($r \neq\neq s$) was modelled by:

$$log(\lambda_{rs}) = \alpha + \sum_{d=1}^{D} \beta_d * X_d$$

When $r = s$:

$$\lambda_{rr} = -\sum_{s \neq r}^{K} \lambda_{rs}$$

And the likelihood function of observation y for individual i at time t:

$$y_{it} \sim categorical(P_{y[i,t-1]})$$

$P = e^{tQ}$ is a $K \times K$ probability matrix such that

$$P[r, S] = \Pr(y_{it} = s \mid y_{it-1} = r)$$

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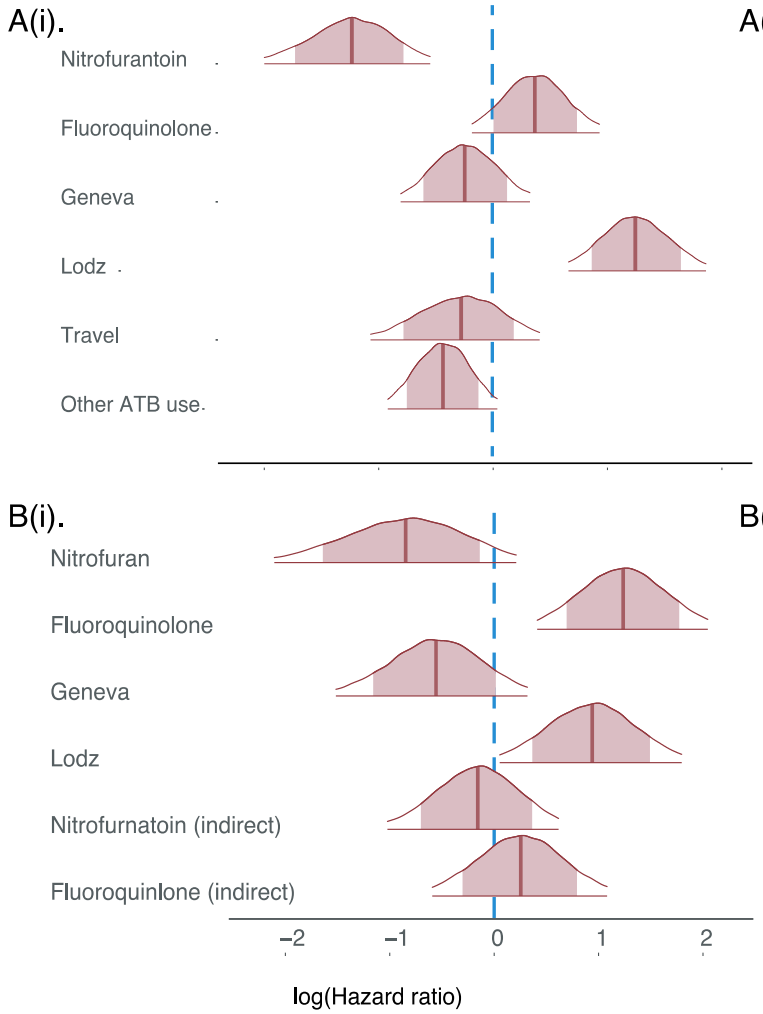
FQR-E acquisition rates

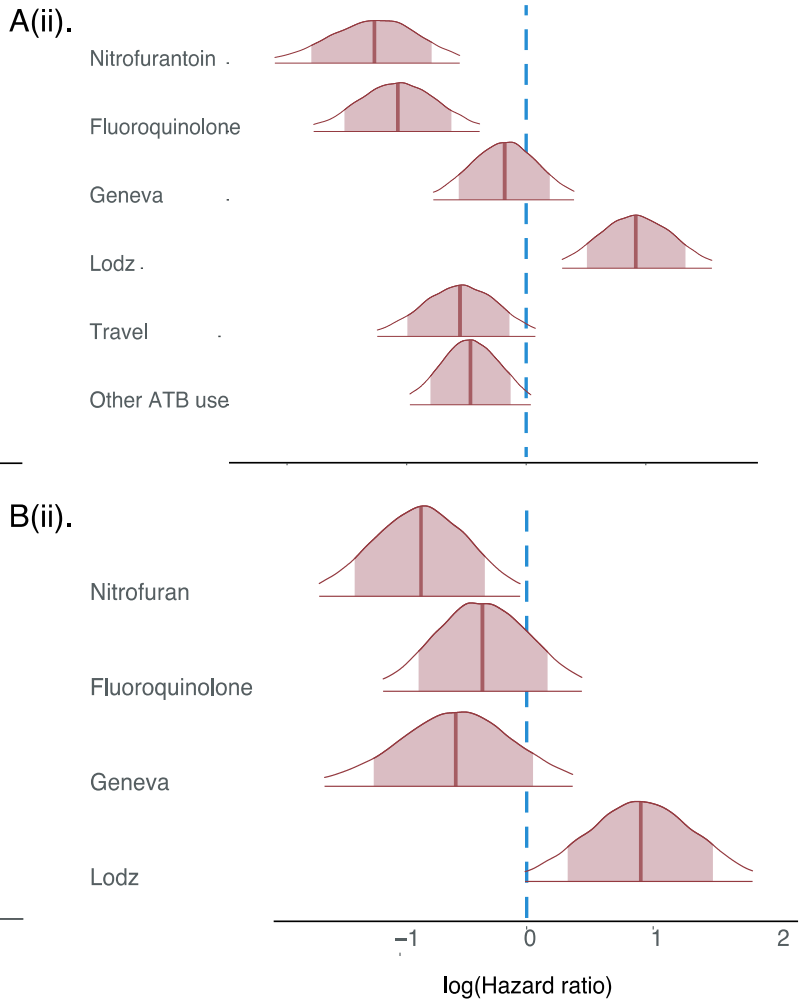
- Daily rate of colonization was 0.006 (95%CrI=[0.006, 0.010])
- Mean carriage duration of 24.6 days (95%CrI=[20.6,34.4])
- With no prior colonization, daily acquisition rates was 0.024 (95%CrI=[0.008, 0.072]) in a two member HH and 0.13 (95%CrI=[0.002, 14.54]) in a three-member HH
- Rates were 2.4(95%CrI=[2.8,3.4]) and 3.0 (95%CrI=[2.9,4.0]) times higher if at least one member was already colonised

Covariate effect on individual level model

Colonisation



Decolonisation



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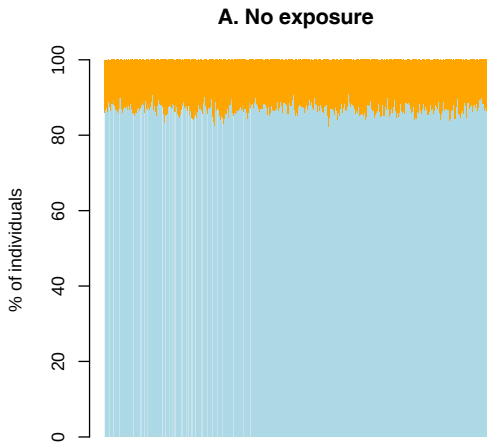
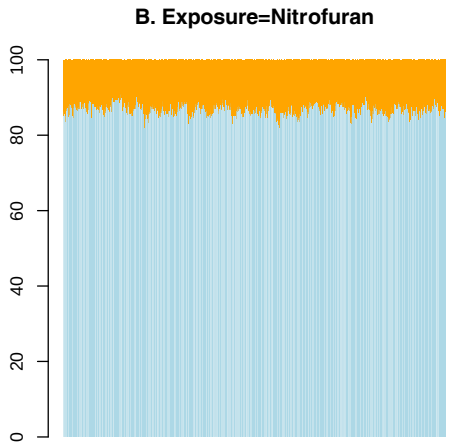
Would Nitrofuran use reduce FQR-E colonization rates?

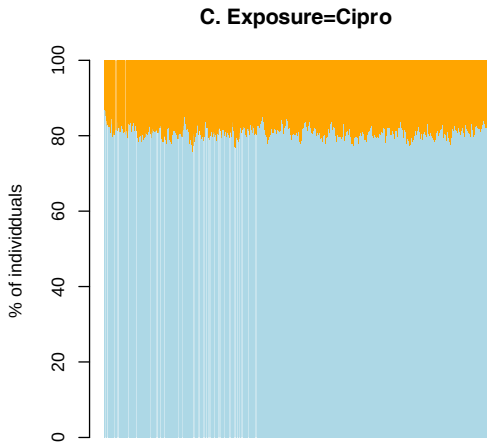
Colonisation: 12.7%

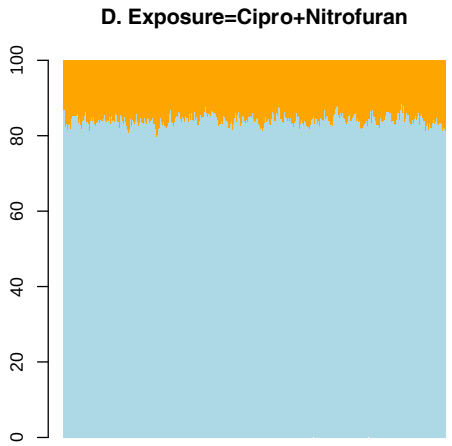




Colonisation: 13.0%

Colonisation: 19.1%





Colonisation: 15.9%

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Carriage duration of carbapenemases producing Enterobacteriaceae (Singapore)

- A prospective cohort study involving CPE carriers from October 2016 to February 2018.
- Study participants were recruited from two tertiary referral Hospitals with over 1600 beds in Singapore.
- All admitted patients above 21 years with prior hospitalization within 12 months were screened for CPE carriage.

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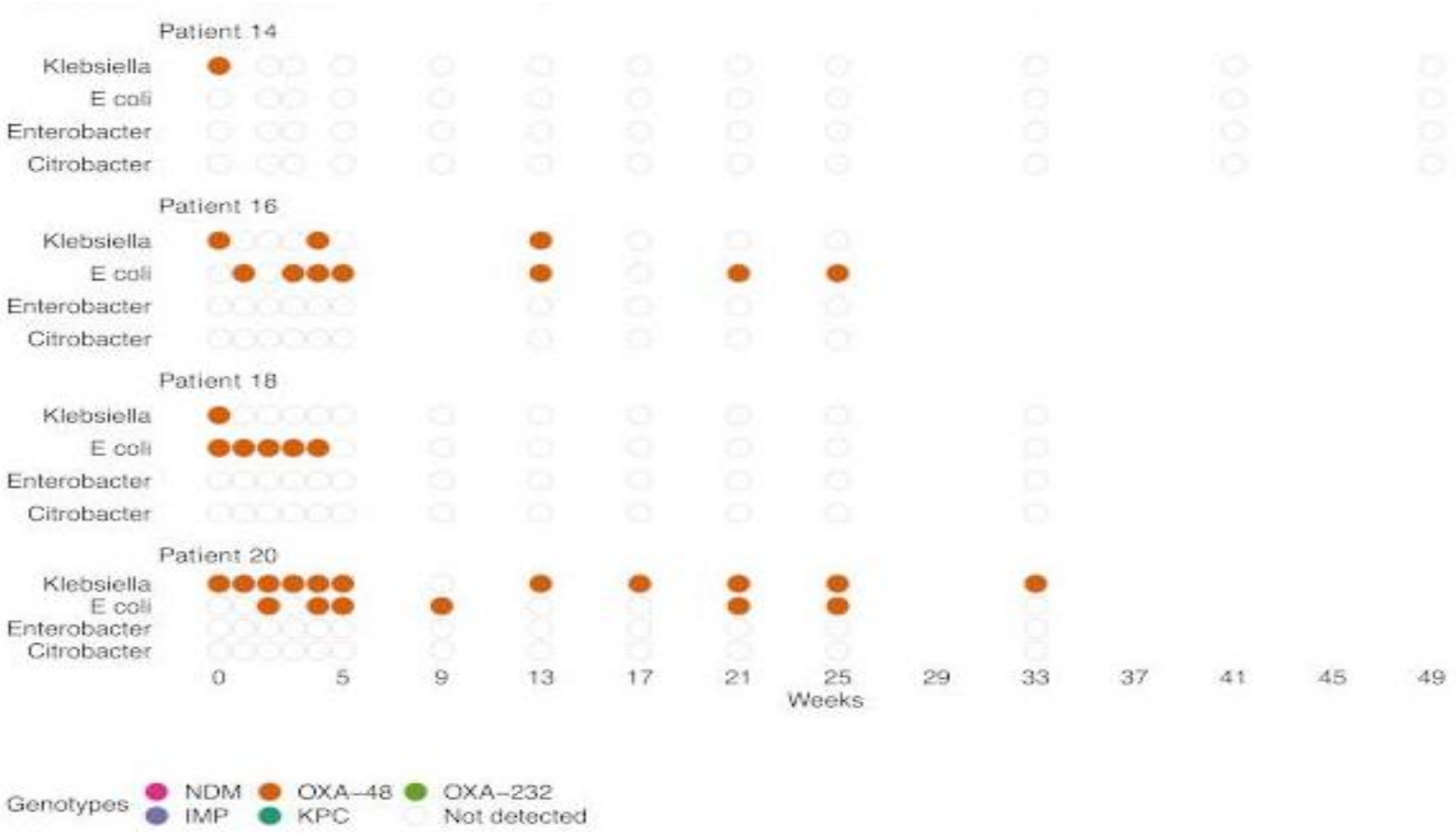

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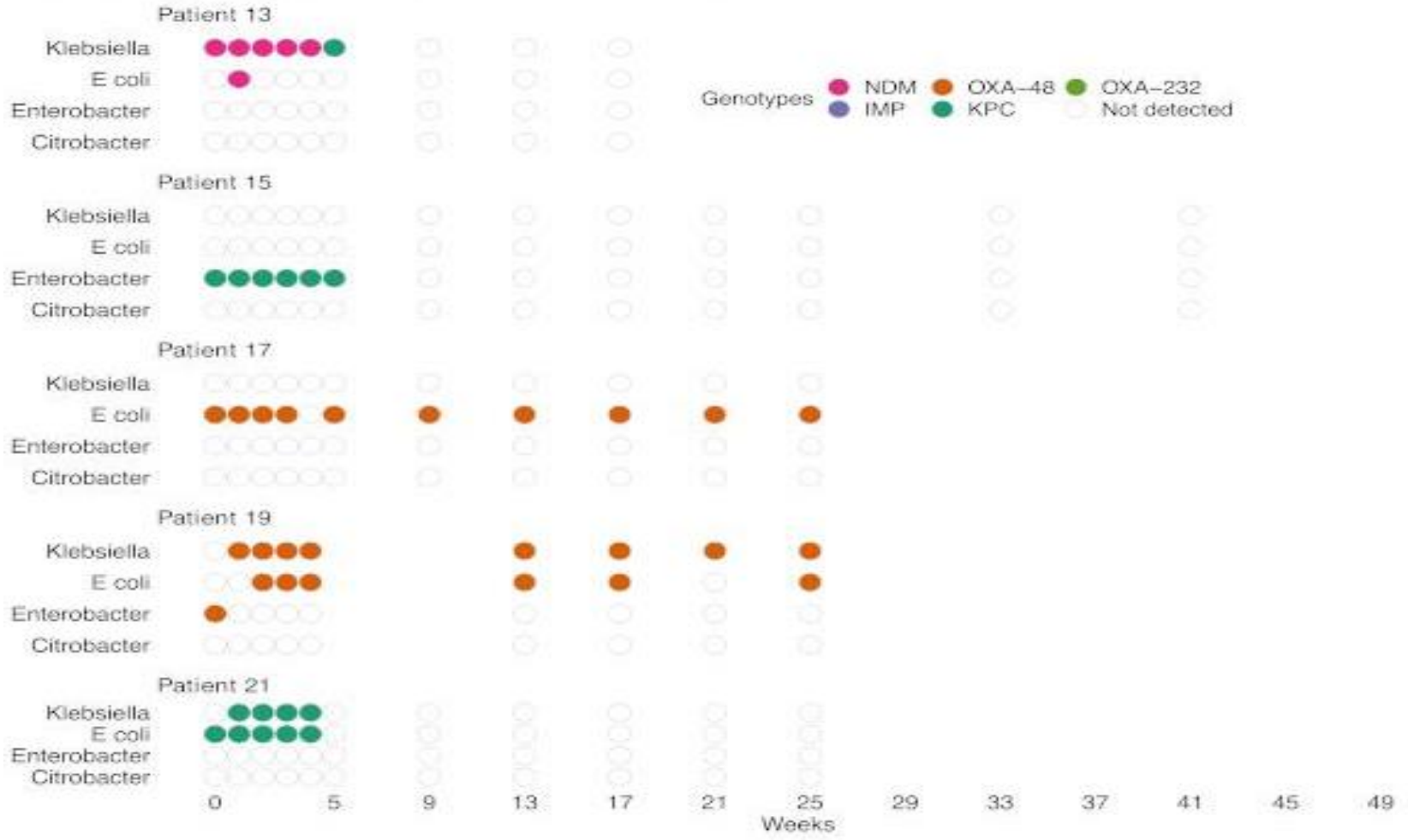
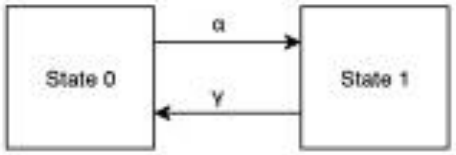
Mo, *et al. (under review at Emerg. Infect Dis.)*


Patient 13
Klebsiella
E coli
Enterobacter
Citrobacter
Patient 15
Klebsiella
E coli
Enterobacter
Citrobacter
Patient 17
Klebsiella
E coli
Enterobacter
Citrobacter
Patient 19
Klebsiella
E coli
Enterobacter
Citrobacter
Patient 21
Klebsiella
E coli
Enterobacter
Citrobacter
Genotypes
NDM
OXA–48
OXA–232
IMP
KPC
Not detected
0
5
9
13
17
21
25
29
33
37
41
45
49
Weeks

CPE carriage dynamics

Multistate Model 1:
Two states with carbapenamase-producing Enterobacteriaceae (CPE) carrying state and CPE non-carrying state

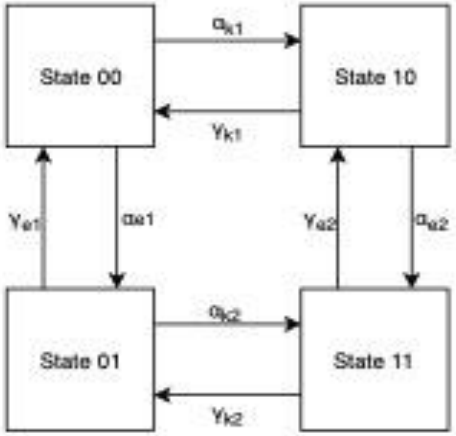


Legend

State 0: Not colonized with CPE
State 1: Colonized with CPE

α: Colonization rate
γ: Decolonization rate

Multistate Model 2:
Four states with CP-E coli and CP-Klebsiella carrying states and CPE non-carrying state



Legend

State 00: Not colonized with CPE
State 01: Colonized with CP- E. coli
State 10: Colonized with CP- Klebsiella
State 11: Colonized with CP- E.coli and CP--Klebsiella

α_k: Colonization rate of CP-Klebsiella
γ_k: Decolonization rate of CP-Klebsiella
α_e: Colonization rate of CP-E. coli
γ_e: Decolonization rate of CP-E. coli

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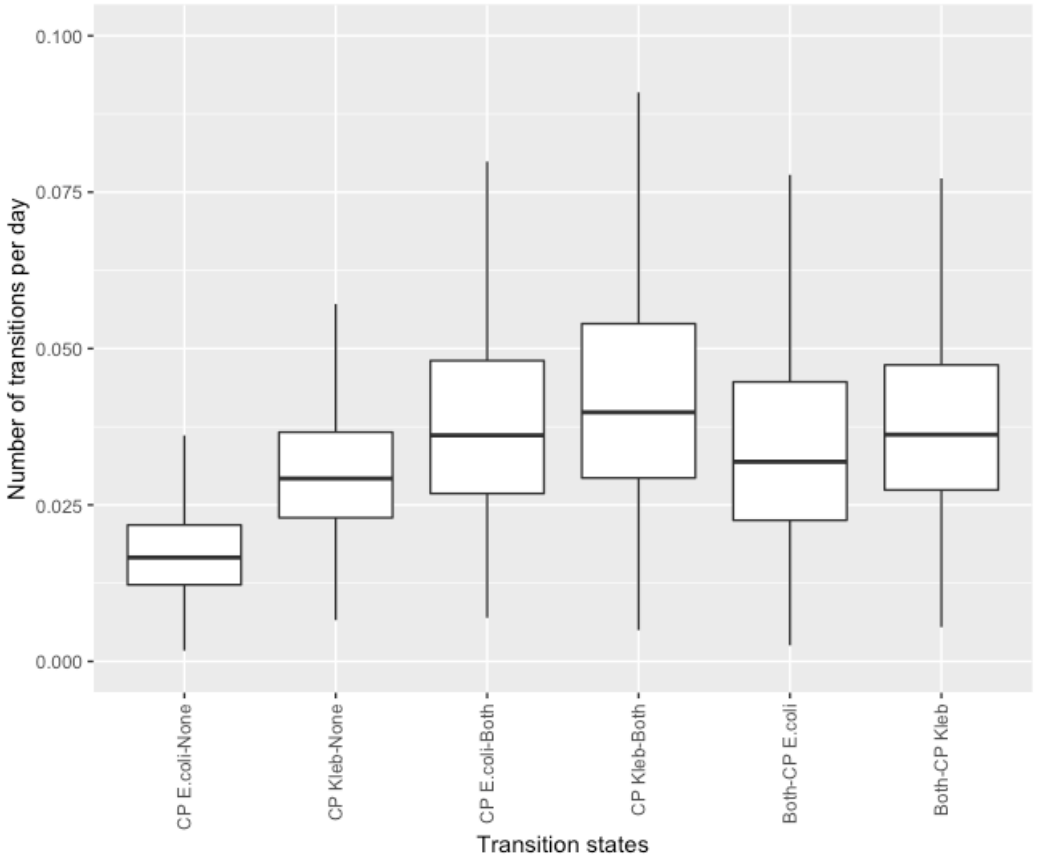
Mo, *et al. (Emerg. Infect Dis. Under review)*

Daily decolonisation rates



- Mean duration of carriage 86 (95%CrI= [60, 122]) days

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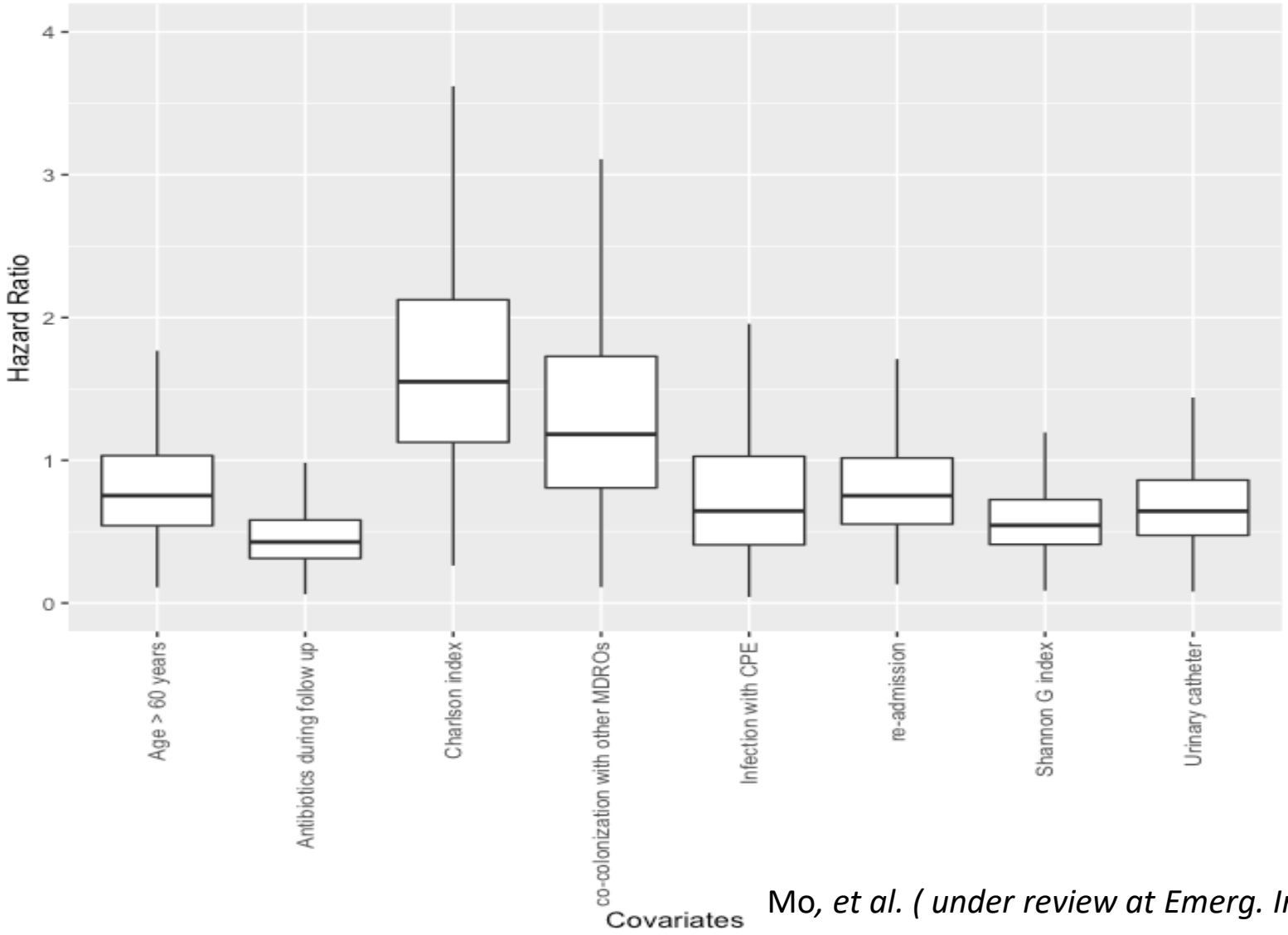
Mo, *et al. (under review at Emerg. Infect Dis)*

Decolonisation covariate effects



Mo, *et al. (under review at Emerg. Infect Dis)*

Summary

- Both genomics and epidemiological models can help to understand spread of AMR
- Integrating genomic information and epidemiological models would help improve estimates and refine our understanding of AMR spread

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SATURN WP1&3