Modelling the Nosocomial Transmission of Multi-drug Resistant Enterobacteriaceae

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Postdoctoral Researcher

Transmission and epidemiology of MDR bacteria

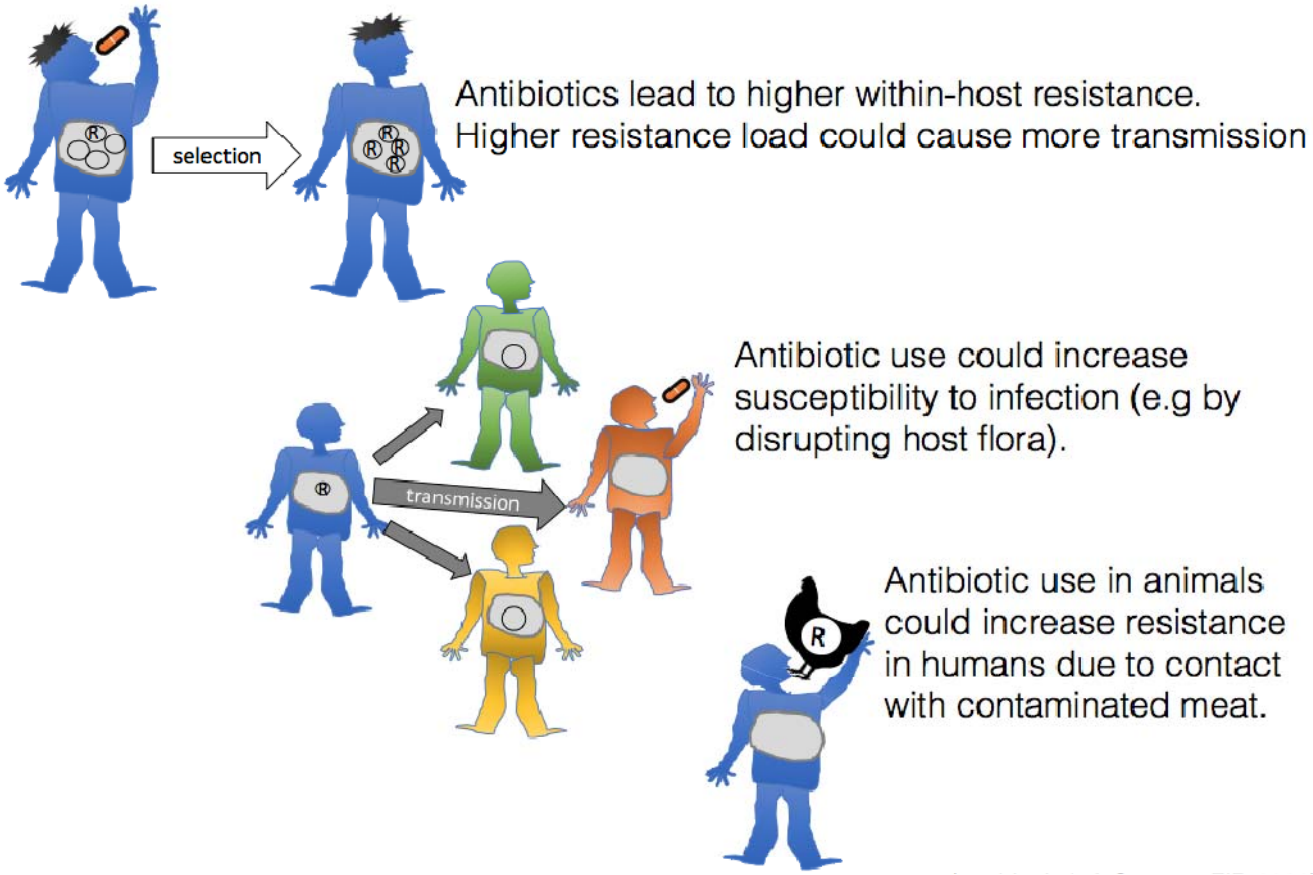


Figure by Ben Cooper

Reference: Lipsitch, M. and Samore, M.H., 2002. Antimicrobial use and antimicrobial resistance: a population perspective. *EID*, *8*(4), p.347.

High risk populations for multi-drug resistant bacteria

- Hospital settings where antibiotic consumption is high and patients are in close proximity
- Transmission can be enhanced by a lack of cleanliness, absence of hand washing and invasive devices
- Neonates are at a higher risk as their immune systems / microbiomes are undeveloped. Along with immunosuppressed or older patients with multiple conditions
- Intensive care units in LMICs have a combination of factors that create a ‘perfect storm’ for transmission of MDR bacteria

Image from: Dondorp, A.M., Limmathurotsakul, D. and Ashley, E.A., 2018. What’s wrong in the control of antimicrobial resistance in critically ill patients from low-and middle-income countries?. *Intensive care medicine*, *44*(1), pp.79-82.

Cambodian neonates carriage study

Prof. Paul Turner, COMRU

- Prospectively followed neonates admitted to a neonatal unit (NU) from the ward's opening 11/09/13 until 10/09/14

- 333 infants admitted over this period. Median length of stay was 5 (range 0, 65) days and median age at admission was 10 days (0, 43).

- Aimed to perform rectal swabs on infants within 24 hours of admission and then twice weekly until discharge (more variable in practice). Cultured on selective MacConkey agar.

- High prevalence of third generation cephalosporin resistance: 286 infants colonised with a 3GC resistant organism either at entry or during admission (85.6%). Mainly *K. pneumoniae* and *E. coli*.

- Lower prevalence of carbapenem resistance; 25 patient colonised by an imipenem-resistant organism (7.5%). Predominantly *Acinetobacter baumannii* and these organisms were mainly acquired outside the ward

See Turner *et al.* Ped. Infect. Dis. J. 2016 for details.

Angkor Hospital for Children
Siem Reap, Cambodia

Carriage of MRD Bacteria among neonates

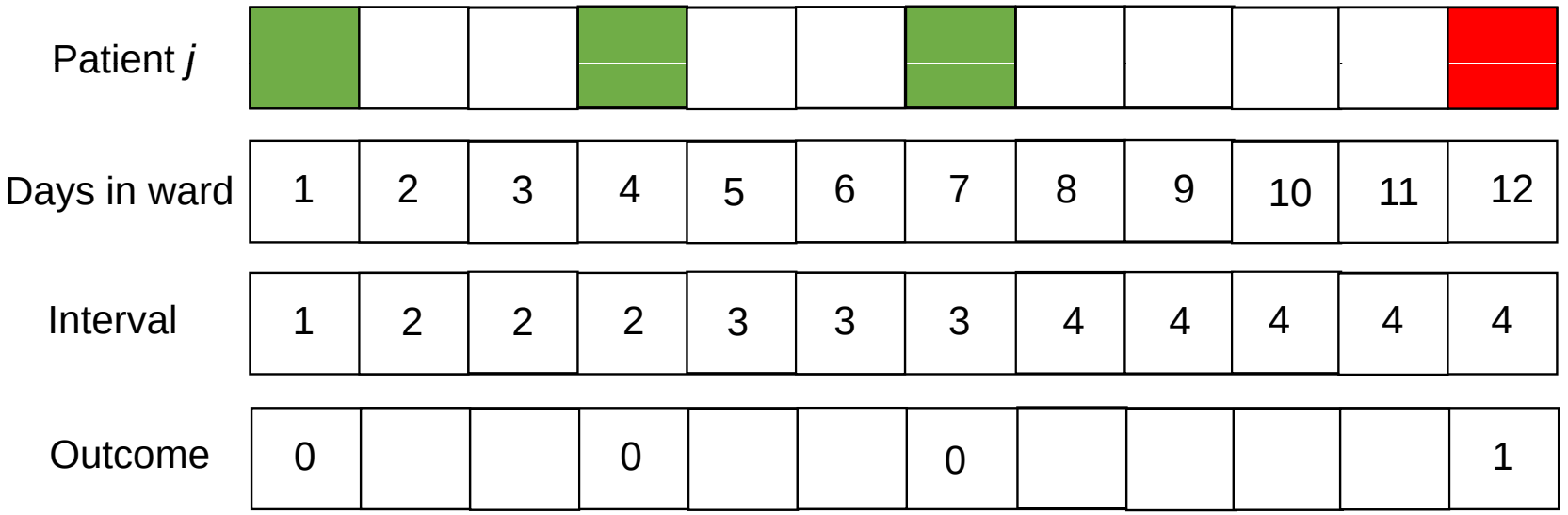
3GC *K. pneumoniae:*
121 infants colonised on first admission (36%)
109 colonised during their stay (33%)
21 colonised at an unknown timepoint (6%)
82 remained uncolonised (25%)

3GC *E. coli:*
97 infants colonised on first admission (29%)
72 colonised during their stay (22%)
14 colonised at an unknown timepoint (4%)
150 remained uncolonised (45%)

Research Aims

- Can we identify the main routes of transmission?
- What are effective interventions?
- Which antibiotics should be prioritised?
- How can models or simulations improve our decision making?

Likelihood function for interval censored data

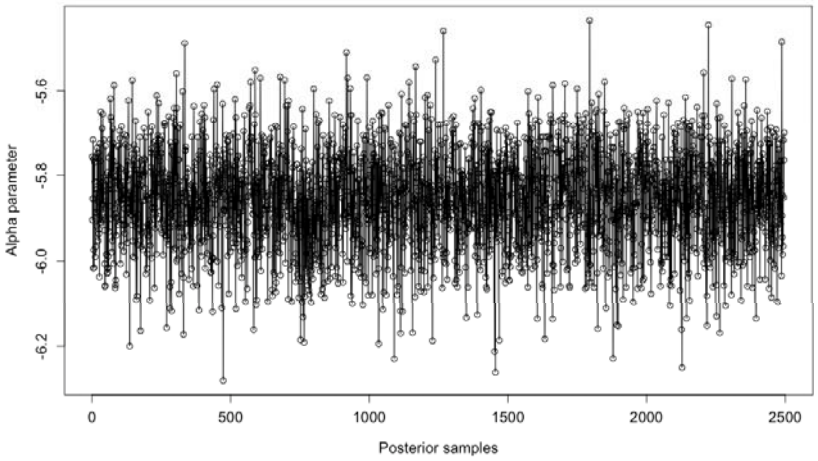


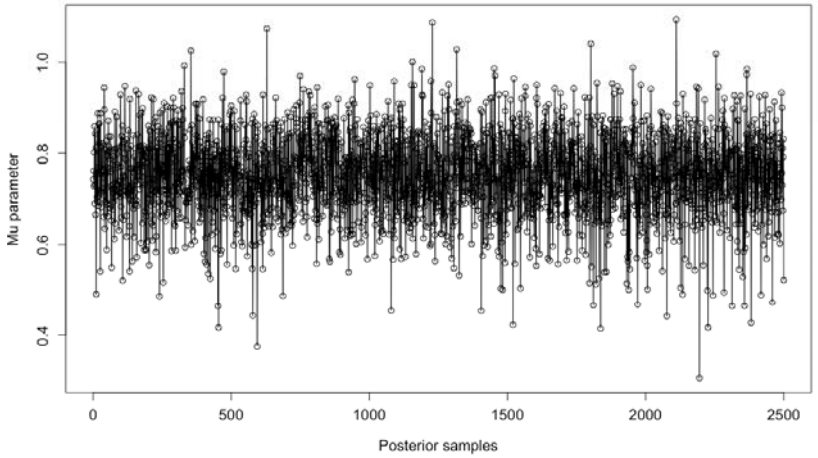
= Rectal swab taken, no MDR bacteria cultured (outcome = 0)

= Rectal swab taken, MDR bacteria cultured (outcome =1)

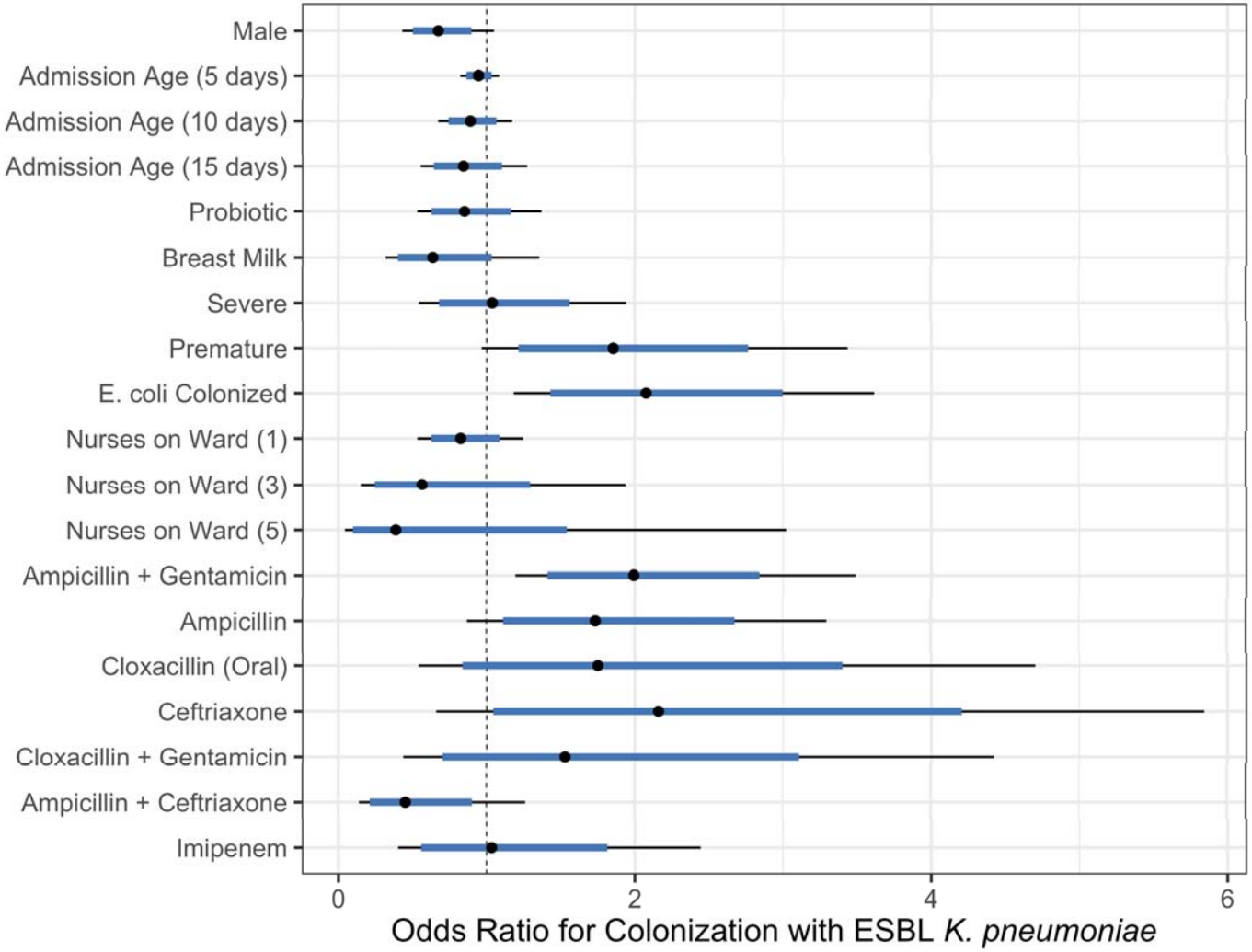
Model Fitting

- We calculated the probability of patient *j* acquiring an MDRO on day *i* (p_{ij}) as a logit transformed linear function of intercept and covariates
- Over a swab interval of *N* days, the likelihood of becoming colonised is given by: $1 - \prod_{i=1}^{N}(1 - p_{ij})$
- The model was fit to data using a Bayesian framework for parameter estimation
- Prior distributions were vaguely informative normal distributions and we obtained posterior distributions for all parameters. We also allowed intercepts or parameters to vary by ‘cluster’ (hierarchical model)





Risk factors for ESBL *K. pneumoniae* acquisition

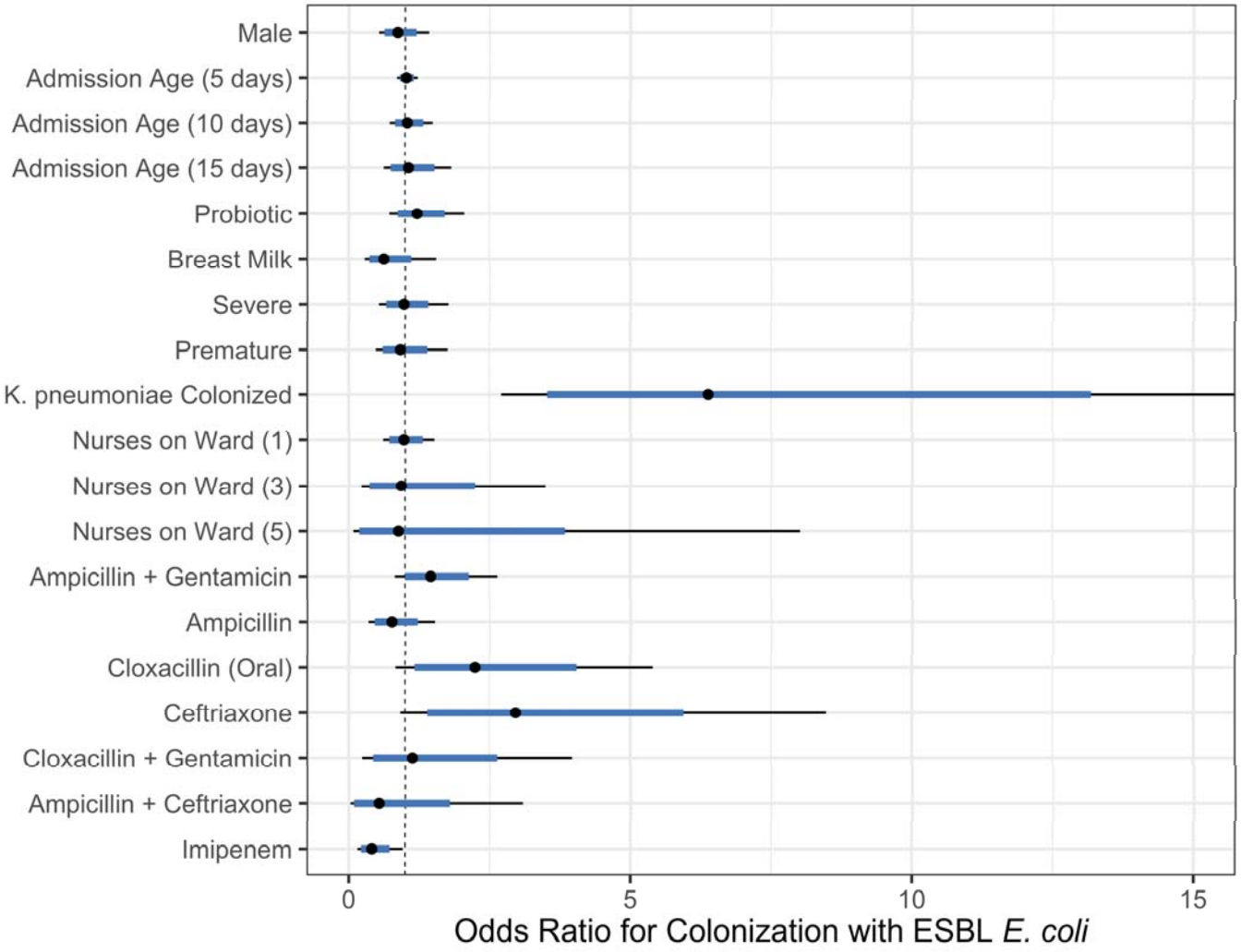


Data
871 patient days
402 swabbing interval
191 infants

109/191 (57%) of susceptible infants acquired ESBL *K. pneumoniae*

Most risk factors show only modest odds ratios

Risk factors for ESBL *E. coli* acquisition



Data
1728 patient days
689 swabbing interval
222 infants

77/222 (35%) of susceptible infants acquired ESBL *E. coli*

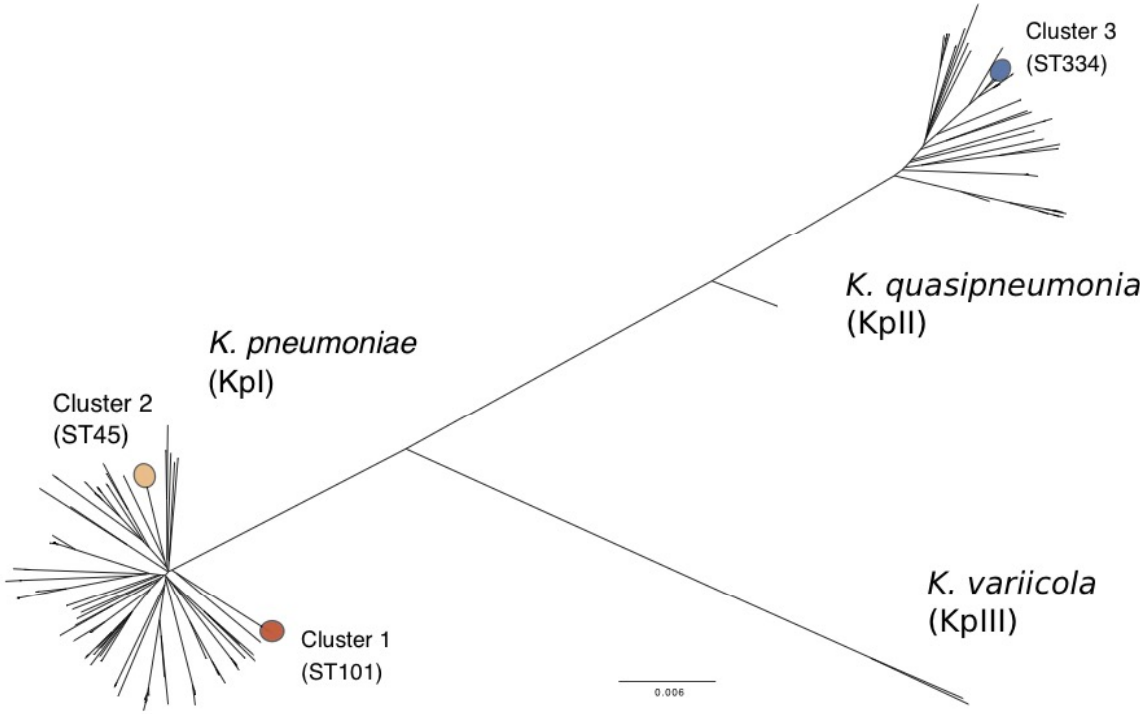
Major risk factor:
Prior colonization with resistant *K. pneumoniae* (6.4 odds ratio)

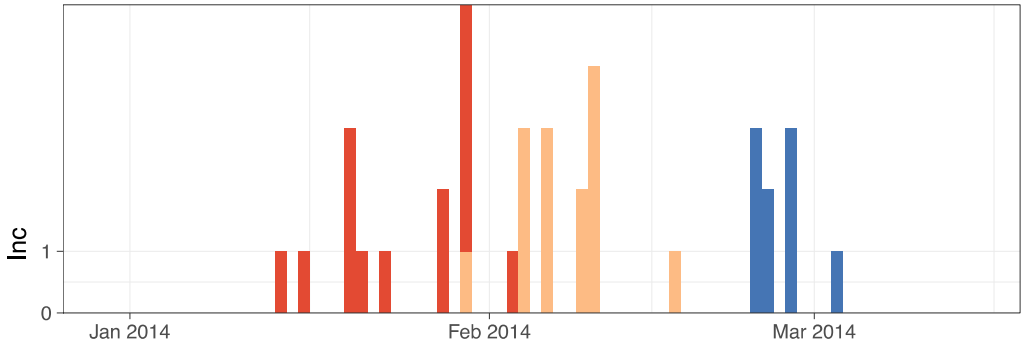
Alters daily probability of acquisition from baseline of 0.015 to 0.09

Aim 2: Inferring route of transmission

- We used 317 whole-genome sequences of *K. pneumoniae* collected over 4 months to investigate the population structure of the pathogen and infer transmission parameters within closely related clusters

- After adaptor trimming, reads were assembled *de-novo*. Distances between assemblies are shown as an unrooted phylogenetic tree below





Models for cluster transmission (1)

- We can test different assumptions on the routes of transmission with different models, and then compare the models using information criterion (measure of how well the models fits the data)

- Each model is examining the risk of a patient newly acquiring a specific cluster of *K. pneumoniae* on a certain day

$$logit(p_{ijc}) = \alpha \qquad \text{(Transmission Model 1)}$$

This model includes an intercept (α) and no transmission term, consistent with within-host selection or background contamination

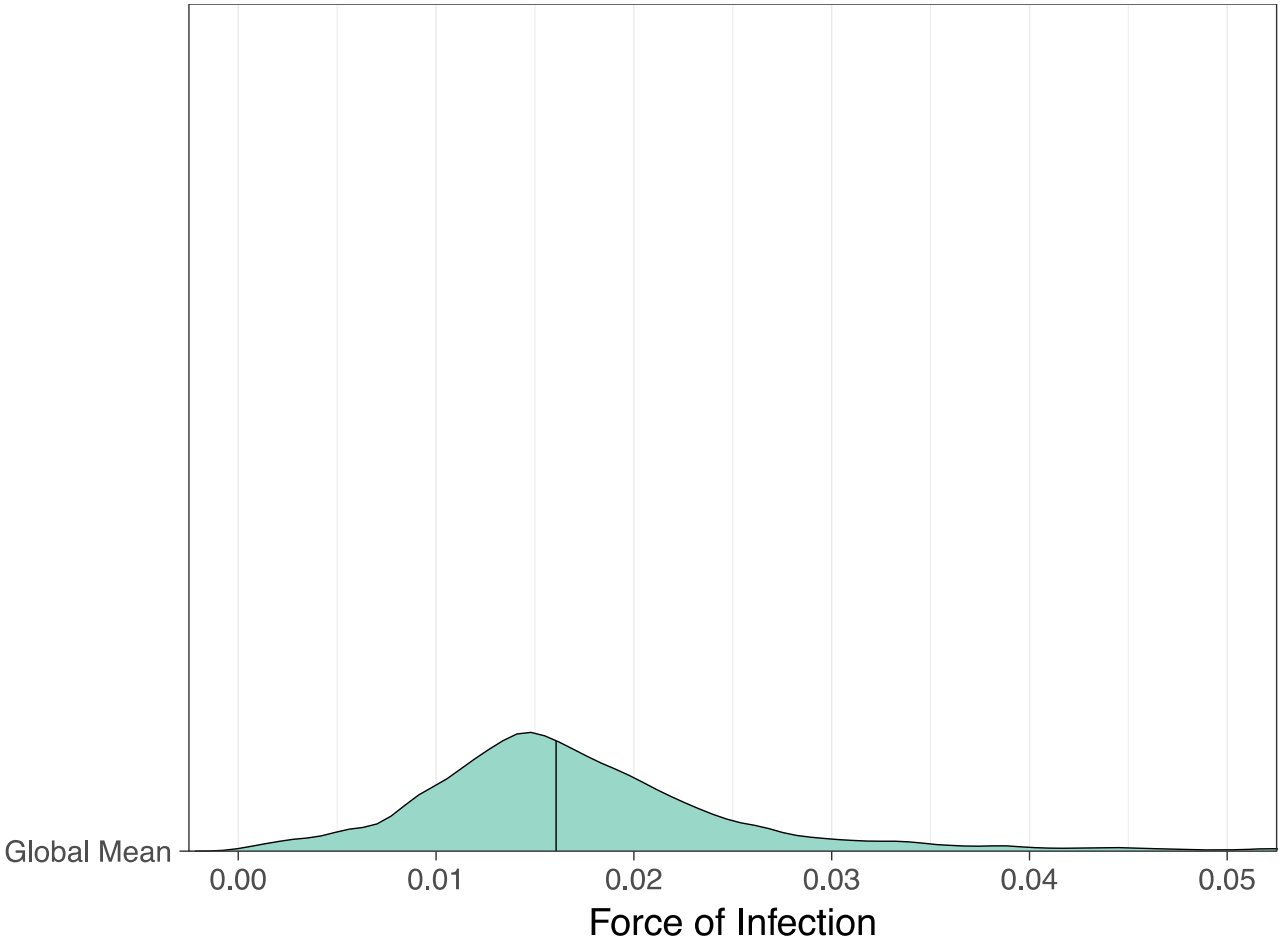
$$logit(p_{ijc}) = \alpha + \beta_1 n_{ic} \qquad \text{(Transmission Model 2)}$$

This model includes a transmission term (β) which allows for person-to-person transmission. Other routes of transmission are captured by the intercept (α)

$$logit(p_{ijc}) = \beta_1 n_{ic} \qquad \text{(Transmission Model 3)}$$

This model consists only of a transmission term (β) which allows for person-to-person transmission but no other routes

Models for cluster transmission (2)



- Model comparison strongly favoured **model 2** (intercept and transmission parameter)
- Posterior parameter distributions of the transmission parameter from model 2, fitted as a hierarchical model which can vary by transmission cluster
- The value gives the probability of acquisition per colonised patient per day

Summary: What have we learned?

- Patient to patient transmission (likely mediated by healthcare workers) seems to be an important factor in the spread of 3GC resistant *K. pneumoniae*
- *E. coli* appear to acquire resistance through horizontal gene transfer within patients from *K. pneumoniae* (we lack *E. coli* genomic data to infer the role of person-to-person transmission)
- Most antibiotics increase the risk of acquisition of a MRD bacteria, imipenem is protective against acquisition of 3GC resistant *E. coli*, likely reflecting the low levels of carbapenem resistance in this cohort
- Breast feeding was protective against acquisition of either 3GC resistant organism, links to what we know about the role of maternal antibodies
- Oral probiotic did not appear to have a substantial protective effect against colonisation with either 3GC resistant organism
- **Future plans: forward simulate the impact of interventions using an agent-based model and parameter estimates**

Pre-print out now on BioRxiv

Transmission dynamics and between-species interactions of multidrug-resistant Enterobacteriaceae

Thomas Crellen[1,2*], Paul Turner[1,2,3], Sreymom Pol[1,3], Stephen Baker[2,4], To Nguyen Thi Nguyen[4], Nicole Stoesser[2], Nicholas P.J. Day[1,2], and Ben S. Cooper[1,2*]

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Acknowledgements

Cohort study in Angkor Hospital for Children

Paul Turner
Claudia Turner
Sreymon Pol
Hospital Staff and Patients

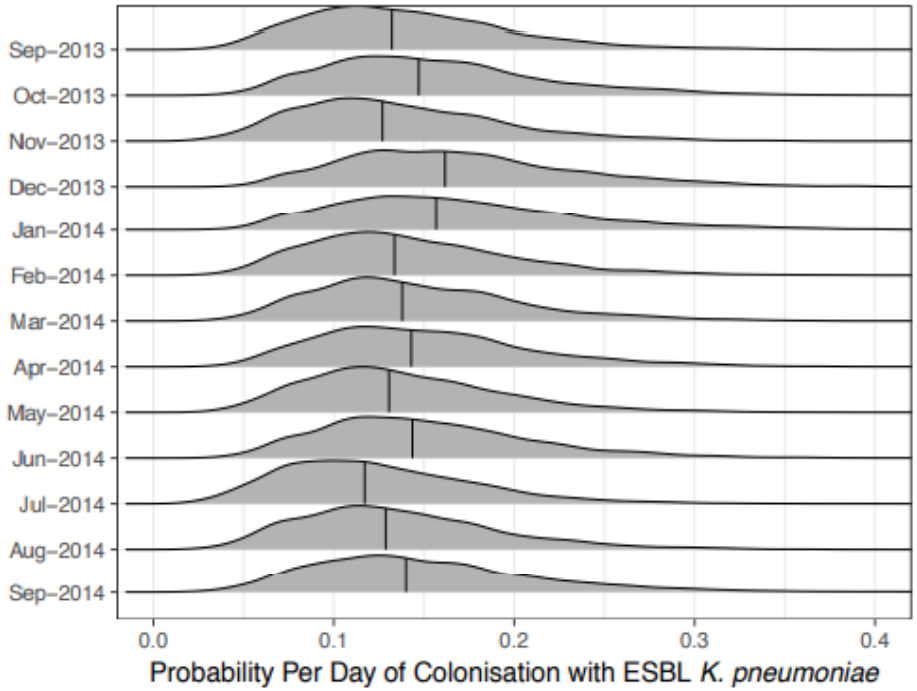
MORU Bangkok

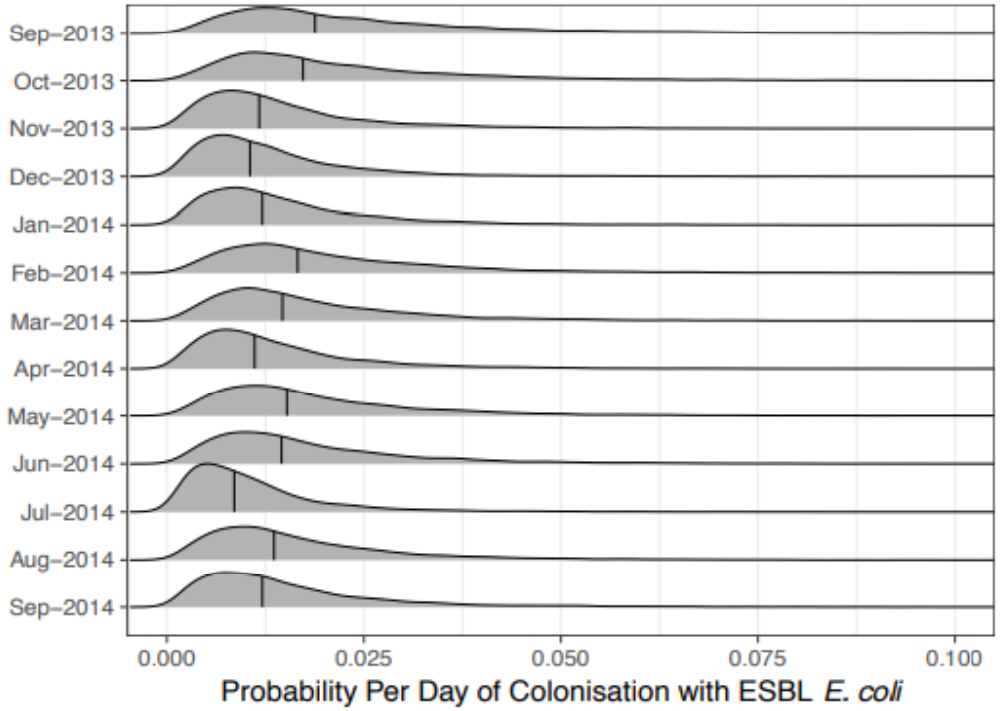
Ben S. Cooper
Pieter Smit
Liz Batty
Nicholas P.J. Day

Sequencing support from OUCRU and NDM Oxford

Nicole Stoesser
Stephen Baker
To Nguyen Thi Nguyen

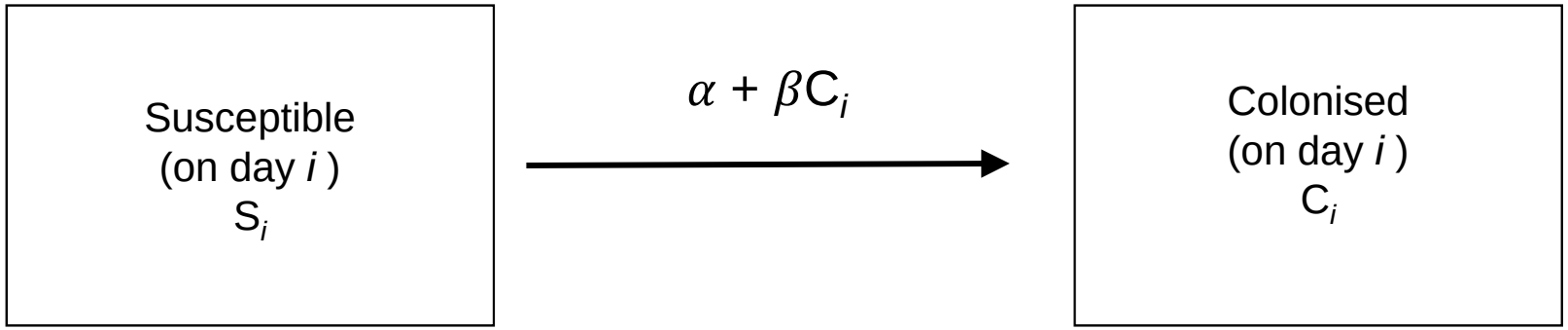
Varying intercept by month (hierarchical model)



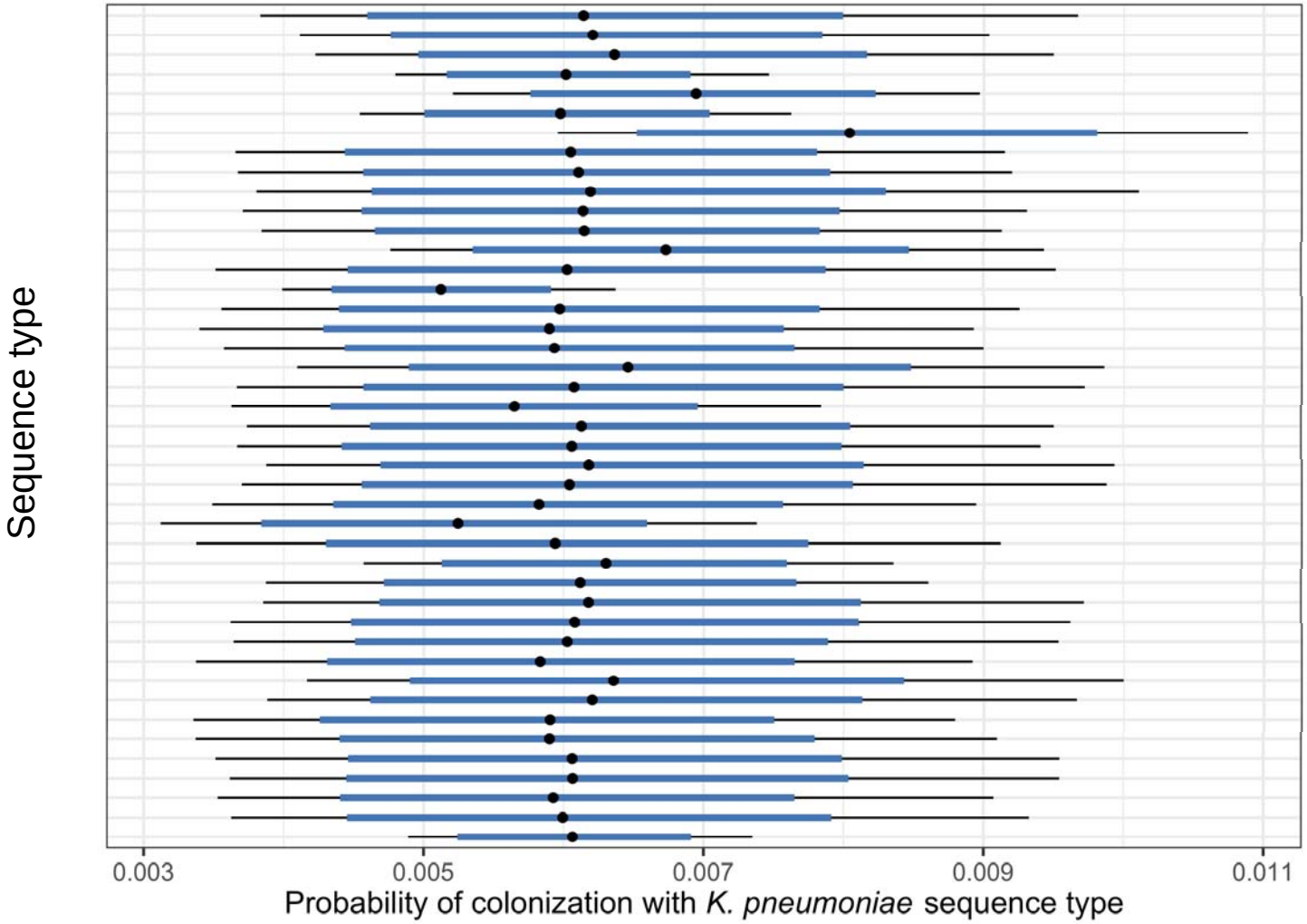


Models for cluster transmission (3)

- Transmission models are analogous to fitting a stochastic compartmental model with two states (susceptible and colonised)
- Given our parameter estimates for α and β, we can simulate the transmission process given per-day numbers of susceptible patients



Extending transmission models to sequence types



Using software that analyses whole genome assemblies of *Klebsiella*, we have identifed the sequence type for each of our 317 samples.

Here we shown transmission parameter estimates for 42 sequence types (all samples sequenced from January 2014-March 2014)