**Modeling Interventions and Contact Networks to Reduce the Spread of Carbapenem-Resistant Organisms Between Individuals in the ICU**

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**Supplement: Mathematical Model, Extension of Main Results, and Robustness of Main Results**

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# **MATHEMATICAL MODEL**

## **Formulation**

In network analysis, the terms *ego* and *alter* are used to identify subjects of interest.[[18]](https://www.zotero.org/google-docs/?nVCjcV) Ego is the patient of interest (susceptible patient), and everyone to whom the ego is directly connected to is considered an alter (exposed or unexposed colonized patients). Each alter can also be an ego in their own ego network, and the interconnected ego networks form a longitudinal social network. In this analysis, egos of interest were patients who were not colonized at unit admission and thus were susceptible to the outcome of interest. Namely, incident *CROk* colonization by a microorganism of type *k* are termed ego. All other patients who were co-located in the same hospital unit at the same day as the indexed patient are termed alters. The alters, specifically colonized patients' contact precaution status, represented the exposure of interest. The egos are censored after their first incidence of CRO colonization because they were no longer considered susceptible. Even if they were treated with antibiotics, colonized egos remained in the model as *CROk*-positive alters that can interact with other patients. Patients who were found to be colonized at unit admission were similarly censored as egos, because it was not possible to determine whether their colonization was nosocomial or what their network connections were at the time of colonization. Patients who were found to be colonized with CRO were assumed to be colonized for all subsequent times in which they remained hospitalized. This *once positive, always positive* approach was used because we assume that once a colonized, patients remain colonized for several months consistent with studies,[1,2] and thus extending beyond our study timeframe. Any bias attributable to falsely treating CRO-uncolonized alters as colonized would be toward the null hypothesis. If CRO colonization in an alter was associated with an ego becoming colonized, then assuming that *CROk*-negative alters were colonized would lessen the association, because that *CROk*-positive alter would decrease the odds of an ego becoming colonized.

Egocentric patient interaction data of susceptible patients with CRO-positive patients were used to model a patient's probability of acquiring CRO during unit admission as

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|  | , | (1) |

Where the Boolean variable, *yikt*, is equal to 1 if patient *i* was incidentally colonized by the end of interval *t* with strain *k*; *Zijk*is the number of hours in time interval *t* in which patient could have been infected by patient *j* with strain *k;* *βijkt* is the probability of transmission during time interval *t* calculated as a function of covariates as discussed below; *δijk* is equal to 1 if patient *i* and patient *j* were colonized with strain *k* during hospital unit encounter; and, *αit* is the probability of patient *i* being infected by a source other than another patient in time interval . Equation (1) is informed by the probability of *likely transmission-mediated* acquisition risk as

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|  | , ∀ | (2) |

Where *βijkt* is the log-odds that patient was colonized by patient *j* with microorganism *k* during time interval *t*; *Contactjt*is an indicator of whether patient *j* was on contact precautions during time interval *t*; *Abxit*is an indicator of carbapenem exposure by patient *i* during time *t*, as carbapenem exposures may impact susceptibility to transmission-mediated acquisition; *Envt* is an indicator of whether the percentage of hospital unit adherence environmental cleaning compliance at time *t* is higher than 95%; *HHt* is the percentage of hospital unit hand hygiene compliance in time interval *t* is higher than 95%; and, *HCWijt* is the number of healthcare worker-mediated connections between patients *i* and *j* in time interval *t*. In addition, Equation (1) is further informed by the probability of *likely non-transmission-mediated* acquisition risk as

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|  | , | (3) |

where *αit* is the log-odds that a patient *i* was colonized in time interval *t*, and *Abxit* is an indicator of carbapenem exposure by patient *i* during time *t*, as carbapenem exposure might exert selective pressure that can promote de novo acquisition of resistance.[3]

## **Parameter Estimation**

Markov chain Monte Carlo (MCMC) methods and Metropolis-Hastings algorithm with delayed rejection were used to estimate the unknown model parameters (s and s) and their 95% credible intervals.[4] Eight weakly informative priors *N*(0,1.5) with truncated bounds from -1,000 to 1,000 were sampled for the eight MCMC chains, which were started from a randomly selected number from the -5 to 5 range. Model convergence was checked by trace plots of MCMC chains, comparison of the posterior distributions estimated from different chains, and Gelman-Rubin statistic.[5] Five chains were run for 100,000 iterations, but the posterior distributions were estimated from the last 50,000. Reported parameter estimates are the medians of the samples from the posterior distributions, and 95% credible intervals were calculated using 2.5th and 97.5th percentiles of the posterior samples. All statistical analyses were performed in R version 3.5.1, using the freely distributed statistical package *BayesianTools* version 0.1.6.[6]

# **EXTENSION OF MAIN RESULTS**

## **Determinants of Incident CRO Acquisition by Carbapenemase-Producing Status**

Our main results (Table S1, Model A) are based on incident CRO acquisition. As part of our research protocol, CROs were also analyzed for the presence of carbapenemase. Carbapenemase genes can be shared between bacteria, leading to a more rapid spread of resistance. Therefore, carbapenemase-producing (CP)-CROs are considered the greater threat. [24,27] Here, we analyzed the acquisition dynamics of CP- versus non-CP-CRO in separate models.

For CP-CRO (Table S1, Model B), we found the primary protective factor continued to be the placement of CRO-positive patients on contact precautions (Adj OR=0.03, 95% CrI 0.01-0.17). However, the exposure of the susceptible patient to carbapenems did not reach statistical significance (Bayesian significance) (Adj OR=2.19, 95% CrI 0.96-4.56). For non-CP-CRO (Table S1, Model C), we found the primary driver of incident acquisition of CRO was carbapenem use (Adj OR=2.01, 95% CrI 1.33-2.95), while the primary protective factor was placing CRO colonized patients in the unit on contact precautions (Adj OR=0.03, 95% CrI 0.01-0.16). The results of this sensitivity analysis suggest that our main findings are similar for the incident acquisition of non-CP-CRO, but there are different acquisition dynamics for CP-CRO that deserve further study.

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| **Table S1. CRO Acquisition Dynamics by Carbapenemase-Producing Status.** | | | | | |
|  | **Adj OR (95% CrI)** | | | | |
| ***Acquisition Mechanism*** | **Model A** |  | **Model B** |  | **Model C** |
| **Variable** | **All CRO** |  | **CP-CRO** |  | **Non-CP-CRO** |
| *Level-2: Acquisition from sources other than a known infection* |  |  |  |  |  |
| Carbapenems exposure last 7 days | 2.38 (1.70-3.29)a |  | 2.19 (0.96-4.56) |  | 2.01 (1.33-2.95)a |
| *Level-1: Potential for transmission* |  |  |  |  |  |
| HCW-mediated connection to CRO patients | 0.9 (0.05-18.58) |  | 0.81 (0.05-13.69) |  | 0.93 (0.05-17.05) |
| Contact isolation on CRO patients | 0.03 (0.01-0.17)a |  | 0.04 (0.01-0.19)a |  | 0.03 (0.01-0.16)a |
| Environmental cleaning compliance >95% | 0.41 (0.03-3.27) |  | 0.62 (0.04-6.59) |  | 0.4 (0.03-3.25) |
| Carbapenems exposure last 7 days | 0.39 (0.03-2.97) |  | 0.66 (0.04-5.03) |  | 0.4 (0.03-2.94) |
| HCW hand hygiene compliance >95% | 0.33 (0.03-2.47) |  | 0.32 (0.03-2.28) |  | 0.34 (0.03-2.51) |
| Abbreviations: CRO, carbapenem-resistant organism; HCW, healthcare worker; OR, odds ratio; CrI, credible interval; Adj, adjusted.  a Statistically significant (Bayesian significance) | | | | | |

## **Determinants of Incident CRO Acquisition with Randomized Colonization Date**

The exact moment at which a patient acquires a new CRO is impossible to observe or measure. These unobservable events might be responsible for the associations we report in the main manuscript. Table S2 reports if randomization of the actual acquisition date, between the dates of the last known CRO-negative culture and the last CRO-positive culture, significantly impacted our Bayesian estimations. Five models with random dates are compared with the model reported in our main manuscript. Each of the five models shows that the primary driver of the incident acquisition of CRO was exposing susceptible patients to carbapenems. Similarly, the primary protective factor was placing CRO colonized patients in the unit on contact precautions. The results of this sensitivity analysis suggest that our main results are robust to variations in the colonization date between the last negative and the last positive CRO culture.

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| **Table S2. Determinants of Incident CRO Acquisition with Randomized Colonization Date.** | | | | | | | | | | | |
| ***Acquisition Mechanism*** | **Adj OR (95% CrI)** | | | | | | | | | | |
| **Variable** | **CRO colonization date is the swab date of** |  | **CRO colonization date randomized between the last known CRO-negative culture and the CRO-positive culture** | | | | | | | | |
|  | **the CRO-positive culture** |  |  | | | | | | | | |
| *Level-2: Acquisition from sources other than a known infection* |  |  |  |  |  |  |  |  |  |  |  |
| Carbapenems exposure last 7 days | 2.38 (1.70-3.29)a |  | 2.54 (1.76-6.44) a |  | 2.34 (1.65-3.28)a |  | 2.49 (1.77-3.45)a |  | 2.36 (1.67-3.28 a |  | 2.51 (1.79-3.47)a |
| *Level-1: Potential for transmission* |  |  |  |  |  |  |  |  |  |  |  |
| HCW-mediated connection to CRO patients | 0.9 (0.05-18.58) |  | 0.94 (0.05-18.12) |  | 0.91 (0.05-16.68) |  | 0.87 (0.05-17.83) |  | 0.93 (0.05-18.75) |  | 0.94 (0.05-18.14) |
| Contact isolation on CRO patients | 0.03 (0.01-0.17)a |  | 0.05 (0.01-0.64)a |  | 0.05 (0.01-0.23)a |  | 0.05 (0.01-0.23)a |  | 0.05 (0.01-0.24)a |  | 0.05 (0.01-0.23)a |
| Environmental cleaning compliance >95% | 0.41 (0.03-3.27) |  | 0.52 (0.04-3.38) |  | 0.42 (0.03-3.3) |  | 0.43 (0.03-3.53) |  | 0.43 (0.03-3.72) |  | 0.4 (0.03-3.67) |
| Carbapenems exposure last 7 days | 0.39 (0.03-2.97) |  | 0.35 (0.02-2.98) |  | 0.42 (0.04-2.88) |  | 0.39 (0.03-3.07) |  | 0.41 (0.04-2.96) |  | 0.41 (0.03-3.15) |
| HCW hand hygiene compliance >95% | 0.33 (0.03-2.47) |  | 0.39 (0.03-2.21) |  | 0.31 (0.03-2.18) |  | 0.31 (0.03-2.28) |  | 0.33 (0.03-2.42) |  | 0.32 (0.03-2.33) |
| Abbreviations: CRO, carbapenem-resistant organism; HCW, healthcare worker; OR, odds ratio; CrI, credible interval; Adj, adjusted.  a Statistically significant (Bayesian significance) | | | | | | | | | | | |

## **Positive Culture Tests by Acquisition Mechanism and by Carbapenemase-Producing Status**

Table S3 presents the number of positive culture test results for CRO, which were stratified by the likely acquisition mechanism and the carbapenemase-producing status. In the 'likely transmission mediated' CRO acquisitions, the most prevalent CRO types were *Enterobacter asburiae* and *Hafnia alvei*. On the other hand, 'likely non-transmission-mediated' CRO acquisitions were predominantly *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

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| **Table S3. Number of positive culture test results for carbapenemase-resistant organism** | | | | | | |
| **Organism** |  | **No. first positive** | | | | |
|  | **Potentially transmission-mediated** | |  | **Not potentially transmission mediated** | |
|  | **CP-CRO** | **Non-CP-CRO** |  | **CP-CRO** | **Non-CP-CRO** |
| Klebsiella pneumoniae |  | 11 | 3 |  | 13 | 20 |
| Pseudomonas aeruginosa |  | 3 | 2 |  | 3 | 36 |
| Enterobacter asburiae |  | 0 | 36 |  | 0 | 2 |
| Enterobacter Cloacae Complex |  | 6 | 0 |  | 8 | 15 |
| Hafnia alvei |  | 0 | 20 |  | 1 | 5 |
| Escherichia coli |  | 2 | 5 |  | 3 | 12 |
| Other |  | 2 | 16 |  | 4 | 18 |

# **ROBUSTNESS OF MAIN RESULTS**

## **Determinants of Incident CRO Acquisition with Varying Healthcare Worker-Mediated Social Network**

Our main results (Table Sf, Model A) assume that connections between patients were defined as contacts with two different patients by the same healthcare worker within 60 minutes (i.e., social network). Here, we conducted sensitivity analyses on this 60-minute window, variating from 15 minutes (Table Sf, Model B) to 12 hours (Table Sf, Model G), consistent with the typical length of a nurse's shift. Models B to G shows that the primary driver of the incident acquisition of CRO was exposing susceptible patients to carbapenems. Also, the main protective factor was placing CRO colonized patients in the unit on contact precautions. The results of this sensitivity analysis suggest that our main findings are robust to variations in the social network definition.

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| **Table S4. CRO Acquisition Dynamics with Varying HCW-mediated Social Networks.** | | | | | | | | | | | | | |
|  | **Adj OR (95% CrI)** | | | | | | | | | | | | |
| ***Acquisition Mechanism*** | **Model A** |  | **Model B** |  | **Model C** |  | **Model D** |  | **Model E** |  | **Model F** |  | **Model G** |
| **Variable** | **Same HCW within 60 min** |  | **Same HCW within 15 min** |  | **Same HCW within 30 min** |  | **Same HCW within 2 hours** |  | **Same HCW within 4 hours** |  | **Same HCW within 8 hours** |  | **Same HCW within 12 hours** |
| *Level-2: Acquisition from sources other than a known infection* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carbapenems exposure last 7 days | 2.38 (1.70-3.29)a |  | 2.38 (1.7-3.28)a |  | 2.38 (1.71-3.3)a |  | 2.39 (1.69-3.29)a |  | 2.39 (1.71-3.3)a |  | 2.39 (1.71-3.27)a |  | 2.38 (1.7-3.27)a |
| *Level-1: Potential for transmission* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HCW-mediated connection to CRO patients | 0.9 (0.05-18.58) |  | 0.89 (0.05-16.64) |  | 0.87 (0.04-15.36) |  | 0.87 (0.05-21.69) |  | 0.81 (0.04-16.14) |  | 0.78 (0.04-13.37) |  | 0.80 (0.05-15.09) |
| Contact isolation on CRO patients | 0.03 (0.01-0.17)a |  | 0.03 (0.01-0.16)a |  | 0.04 (0.01-0.17)a |  | 0.03 (0.01-0.16)a |  | 0.03 (0.01-0.16)a |  | 0.04 (0.01-0.17)a |  | 0.03 (0.01-0.17)a |
| Environmental cleaning compliance >95% | 0.41 (0.03-3.27) |  | 0.41 (0.03-3.23) |  | 0.4 (0.04-3.4) |  | 0.43 (0.03-3.28) |  | 0.43 (0.03-3.58) |  | 0.41 (0.03-3.29) |  | 0.42 (0.04-3.25) |
| Carbapenems exposure last 7 days | 0.39 (0.03-2.97) |  | 0.4 (0.03-2.88) |  | 0.39 (0.03-2.95) |  | 0.43 (0.04-3.11) |  | 0.39 (0.03-2.81) |  | 0.39 (0.03-2.86) |  | 0.38 (0.03-2.81) |
| HCW hand hygiene compliance >95% | 0.33 (0.03-2.47) |  | 0.33 (0.03-2.33) |  | 0.32 (0.03-2.33) |  | 0.34 (0.03-2.54) |  | 0.36 (0.03-2.59) |  | 0.33 (0.03-2.25) |  | 0.33 (0.03-2.36) |
| Abbreviations: CRO, carbapenem-resistant organism; HCW, healthcare worker; OR, odds ratio; CrI, credible interval; Adj, adjusted.  a Statistically significant (Bayesian significance) | | | | | | | | | | | | | |

## **Determinants of Incident CRO Acquisition by Unit**

Our main results (Table S5, Model A) are based on acquisition dynamics at both units, the CTU and the MICU. Here, we studied each hospital unit by fitting separate models for each unit. Model B and Model C show that at each unit, the primary driver of the incident acquisition of CRO was exposing susceptible patients to carbapenems. Also, the main protective factor was placing CRO colonized patients in the unit on contact precautions. The results of this sensitivity analysis suggest that our main findings are consistent in both settings.

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| **Table S5. CRO Acquisition Dynamics by Carbapenemase-Producing Status.** | | | | | |
|  | **Adj OR (95% CrI)** | | | | |
| ***Acquisition Mechanism*** | **Model A** |  | **Model B** |  | **Model C** |
| **Variable** | **CTU and MICU** |  | **CTU** |  | **MICU** |
| *Level-2: Acquisition from sources other than a known infection* |  |  |  |  |  |
| Carbapenems exposure last 7 days | 2.38 (1.70-3.29)a |  | 2.09 (1.28-3.33)a |  | 2.58 (1.57-4.09)a |
| *Level-1: Potential for transmission* |  |  |  |  |  |
| HCW-mediated connection to CRO patients | 0.9 (0.05-18.58) |  | 0.87 (0.05-16.1) |  | 0.85 (0.05-16.23) |
| Contact isolation on CRO patients | 0.03 (0.01-0.17)a |  | 0.03 (0.01-0.13)a |  | 0.05 (0.01-0.28)a |
| Environmental cleaning compliance >95% | 0.41 (0.03-3.27) |  | 0.51 (0.04-5.97) |  | 0.37 (0.03-2.75) |
| Carbapenems exposure last 7 days | 0.39 (0.03-2.97) |  | 0.4 (0.03-3.06) |  | 0.41 (0.03-3.1) |
| HCW hand hygiene compliance >95% | 0.33 (0.03-2.47) |  | 0.31 (0.03-2.59) |  | 0.32 (0.03-2.33) |
| Abbreviations: CRO, carbapenem-resistant organism; HCW, healthcare worker; OR, odds ratio; CrI, credible interval; Adj, adjusted.  a Statistically significant (Bayesian significance) | | | | | |

# **REFERENCES**

1. Sanford MD, Widmer AF, Bale MJ, Jones RN, Wenzel RP. Efficient detection and long-term persistence of the carriage of methicillin-resistant Staphylococcus aureus. Clin Infect Dis Off Publ Infect Dis Soc Am 1994; 19:1123–1128.

2. Bonten MJ, Hayden MK, Nathan C, Rice TW, Weinstein RA. Stability of vancomycin-resistant enterococcal genotypes isolated from long-term-colonized patients. J Infect Dis 1998; 177:378–382.

3. Treviño M, Moldes L, Martínez-Lamas L, Varón C, Regueiro BJ. Carbapenem-resistant Enterobacter cloacae and the emergence of metallo-beta-lactamase-producing strains in a third-level hospital (Santiago de Compostela, NW Spain). Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 2009; 28:1253–1258.

4. Green PJ, Mira A. Delayed rejection in reversible jump Metropolis–Hastings. Biometrika 2001; 88:1035–1053.

5. Gelman A, Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. Stat Sci 1992; 7:457–472.

6. Hartig F, Minunno F, Paul S. BayesianTools: General-purpose MCMC and SMC samplers and tools for Bayesian statistics. R Package Version 016 2019; Available at: https://github.com/florianhartig/BayesianTools.