# Modelling interventions and contact networks to reduce the spread of carbapenem-resistant organisms between individuals in the ICU

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SUMMARY

***Background:*** Contact precautions are widely used to prevent the transmission of carbapenem-resistant organisms (CROs) in hospital wards. However, evidence for their effectiveness in natural hospital environments is limited.
***Objective:*** To determine which contact precautions, healthcare worker (HCW)—patient interactions, and patient and ward characteristics are associated with greater risk of CRO infection or colonization.
***Design, setting and participants:*** CRO clinical and surveillance cultures from two high-acuity wards were assessed through probabilistic modelling to characterize a susceptible patient's risk of CRO infection or colonization during a ward stay. User- and time-stamped electronic health records were used to build HCW-mediated contact networks between patients. Probabilistic models were adjusted for patient (e.g. antibiotic administration) and ward (e.g. hand hygiene compliance, environmental cleaning) characteristics. The effects of risk factors were assessed by adjusted odds ratio (aOR) and 95% Bayesian credible intervals (CrI).
***Exposures:*** The degree of interaction with CRO-positive patients, stratified by whether CRO-positive patients were on contact precautions.

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***Main outcomes and measures:*** The prevalence of CROs and number of new carriers (i.e. incident CRO aquisition).
***Results:*** Among 2193 ward visits, 126 (5.8%) patients became colonized or infected with CROs. Susceptible patients had 4.8 daily interactions with CRO-positive individuals on contact precautions (vs 1.9 interactions with those not on contact precautions). The use of contact precautions for CRO-positive patients was associated with a reduced rate (7.4 vs 93.5 per 1000 patient-days at risk) and odds (aOR 0.03, 95% CrI 0.01—0.17) of CRO acquisition among susceptible patients, resulting in an estimated absolute risk reduction of 9.0% (95% CrI 7.6—9.2%). Also, carbapenem administration to susceptible patients was associated with increased odds of CRO acquisition (aOR 2.38, 95% CrI 1.70—3.29).
***Conclusions and relevance:*** In this population-based cohort study, the use of contact precautions for patients colonized or infected with CROs was associated with lower risk of CRO acquisition among susceptible patients, even after adjusting for antibiotic exposure. Further studies that include organism genotyping are needed to confirm these findings.


## Introduction

Carbapenem-resistant organisms (CROs) are a significant and growing source of healthcare-associated infections with high morbidity and mortality [1—8]. CRO colonization or infection (acquisition) in the hospital setting is driven by transmission from contaminated healthcare workers (HCWs) or equipment [9—11]. However, these sources are complemented by endogenous patient factors, such as selective pressure exerted by antibiotics [9—11]. Infection control measures for CROs include interventions such as the use of contact precautions, environmental cleaning, hand hygiene and antibiotic stewardship. Contact precautions are assumed to reduce the likelihood that HCWs become contaminated and transmit organisms horizontally to patients. However, contact precautions are typically included as part of a bundle of interventions, and this has challenged studies to demonstrate their effectiveness [12—15].

The majority of studies investigating interventions to control the spread of CROs have been cross-sectional [9—11,16]. The difficulty with this design is that it can be challenging to differentiate the effect of interventions, such as contact precautions, from other factors mediating incident acquisition [17]. Evidence limited to vancomycin-resistant enterococci (VRE) and *Pseudomonas aeruginosa*, for example, highlights the importance of understanding dominant acquisition routes for tailored infection control — cross-transmission was the dominant acquisition route for VRE and endogenous colonization was the dominant acquisition route for *P. aeruginosa* [18]. Thus, most studies, including many of longitudinal design [18—22], have been restricted to the conclusion that contact precautions are associated with lower prevalence of CROs in a hospital population. However, the extent to which contact precautions are associated with a lower risk of incident CRO acquisition at patient level, and how exogenous sources and endogenous patient characteristics modulate this risk, remain unknown. A better understanding of CRO acquisition dynamics is important for developing evidence-based CRO control interventions and programmes. As such, this retrospective longitudinal study assessed whether contact precautions protect susceptible patients from CRO acquisition from other colonized patients.

## Methods

Probabilistic models and CRO clinical and surveillance cultures were used to describe the risk of CRO infection or colonization of a susceptible patient during hospitalization. This was done by measuring and comparing patient exposure to other colonized patients with and without contact precautions. As part of a research protocol [23], all patients were screened for CRO colonization (or infection) in a non-outbreak setting where these screening results were not available in real-time, and therefore did not guide antibiotic management or the use of contact precautions. The effectiveness of contact precautions was studied using probabilistic models to isolate the relative contributions of individual characteristics (e.g. antibiotic administration, contact precautions), sources of potential transmission (e.g. HCW hand hygiene) and unit characteristics (e.g. environmental cleaning). The Johns Hopkins Medicine institutional review board (IRB00074840) approved this study, with a waiver of informed consent.

### *Study design and setting*

A retrospective cohort study of patients admitted to a medical intensive care unit (MICU) and a comprehensive transplant unit (CTU) from 1$^{st}$ July 2016 to 30$^{th}$ June 2017 was conducted. Although the CTU is not considered an intensive care unit (ICU), it delivers ICU-level care and, along with the MICU, has private patient rooms and uses contact precautions (gown and gloves) for those with a history of multi-drug-resistant organisms or recent (<6 months) international hospitalization [23]. All patients admitted to the MICU or CTU had perirectal ESwabs (Copan Diagnostics, Inc., Murrieta, CA, USA) collected at unit admission and weekly thereafter as part of a longstanding VRE surveillance programme. As part of a research protocol (described elsewhere [24]), residual media from this surveillance programme, in addition to those cultures resulting from clinical care, were analysed for the presence of

CROs: Enterobacterales resistant to ertapenem, meropenem and/or imipenem, which were classified as carbapenem-resistant Enterobacterales; and glucose non-fermenting Gram-negative bacilli resistant to meropenem and/or imipenem. CROs were further identified as carbapenemase-producing (CP) CROs or non-CP CROs by the phenotypic modified carbapenem inactivation method [25,26].

### *Outcomes*

The main outcome under study was incident acquisition of CROs, which was defined as: (i) a patient that had a negative clinical or surveillance culture at unit admission; and (ii) a clinical or surveillance culture that was obtained more than 2 days after unit admission and grew a CRO. Each positive culture was classified as either potentially transmission-mediated or not potentially transmission mediated [18]. Potentially transmission-mediated CRO acquisition was assumed when a patient grew a CRO of the same species as another patient on the same unit where there were overlapping days of care. Not potentially transmission mediated CRO acquisition was assumed when no other patient with the same CRO species was on the unit. Patients could be incident cases more than once if they acquired a CRO of a different species and met the above criteria. Once a patient became incidentally colonized or infected for a given CRO species, he or she was no longer included in the analysis of risk of incident acquisition, but remained in the study as contributing to the risk of transmission to others.

### *Exposure, covariates and contact data*

Trained research staff rounded on each unit during weekdays to determine whether patients were on contact precautions for any indications (e.g. meticillin-resistant *Staphylococcus aureus*, *Clostridioides difficile*, influenza virus). Staff from the Department of Hospital Epidemiology and Infection Control measured HCW hand hygiene and

**Table I**
Study participant characteristics at study entry by carbapenem-resistant organism (CRO) acquisition during observation in a longitudinal study of two tertiary high acuity units in Baltimore, Maryland, July 2016–June 2017 (*N*=2193)

| Variable | Non-incident[a] | Incident CRO[b] |
|---|---|---|
| Cohort size, *count of unit admissions* | 2067 | 126 |
| Predicted outcomes, *count of incident CRO acquisitions* | | |
| Potentially transmission-mediated | - | 120 |
| Not potentially transmission mediated | - | 126 |
| Demographics and arrival mode, *% of unit admissions* | | |
| Age (years) | | |
| 15–29 | 7.0 | 6.0 |
| 30–44 | 15.0 | 11.0 |
| 45–59 | 35.0 | 38.0 |
| 60–74 | 33.0 | 38.0 |
| 75–89 | 9.0 | 6.0 |
| ≥90 | 1.0 | 1.0 |
| Sex, male | 51.4 | 54.0 |
| Race, White | 43.8 | 46.0 |
| Race, Black | 49.8 | 44.4 |
| Ethnicity, non-Latino | 95.6 | 96.8 |
| Patient residence, Maryland | 86.5 | 83.3 |
| Patient residence, another state within the USA | 13.3 | 15.9 |
| Patient residence, foreign | 0.2 | 0.8 |
| Admission type, emergency | 88.6 | 95.2 |
| Admission type, elective | 8.5 | 4.0 |
| Admission source, home | 71.3 | 65.1 |
| HCW-mediated connections to CRO-positive patients, *daily median (IQR)* | 2 (0–6.0) | 3 (1–7.5) |
| Clinical variables, *% of unit admissions* | | |
| Contact precaution order | 87.4 | 88.9 |
| Environmental cleaning compliance | 88.9 | 87.4 |
| Hand hygiene compliance | 93.6 | 92.9 |
| Carbapenem administration in last 7 days | 10.0 | 47.6 |

HCW, healthcare worker; IQR, interquartile range.
[a]Distinguishing between patients who became incidentally colonized with CROs vs those who did not become incidentally colonized with CROs.
[b]Patients could be incident cases more than once if they acquired a CRO of a different species and met the following criteria: an incident acquisition of CRO was defined as (i) a patient that had a negative clinical or surveillance culture at unit admission; and (ii) a clinical or surveillance culture that was obtained more than 2 days after unit admission and grew a CRO. Each positive culture was classified as either potentially transmission-mediated CRO acquisition or not potentially transmission-mediated CRO acquisition. Potentially transmission-mediated CRO acquisition was assumed when a patient grew a CRO of the same species as another patient on the same unit with overlapping days of care. Not potentially transmission-mediated CRO acquisition was assumed when no other patient with the same CRO species was on the unit.

environmental cleaning compliance of the units. The method used to monitor unit cleaning practice was based on fluorescent markers [27].

Patient encounter data were collected retrospectively using bulk extraction methods from the hospital's electronic health records (EHR) system. Patient data included demographic information, laboratory test results, medication administration and room assignment.

Details of time-stamped in-room visits by HCWs were extracted from the EHR system to estimate a patient's social network (i.e. HCW-mediated connections with other patients on the hospital ward). Two patients, say Patients A and B, were considered to be epidemiologically linked if the same HCW visited their rooms within a 60-min period. HCW interactions with patients were estimated through time-stamps of in-room medication administrations, laboratory specimen collections, assessments and other in-room routine care tasks based on the methodology developed by the study team and presented elsewhere [16].

### *Statistical analysis*

The primary statistical analysis involved the specification of a probabilistic model describing the risk of a susceptible patient becoming colonized or infected as a function of measured attributes of the individual, surrounding patients, and the unit environmental cleaning levels. A Bayesian hierarchical logistic regression model was fitted with the Markov Chain Monte Carlo method (see 'Parameter estimation' in the online supplementary material). Outputs from the model were adjusted odds ratios (aOR) and 95% credible intervals (CrI). The OR and CrI estimates were reported and used to estimate the absolute risk reduction in susceptible individuals. All statistical analyses were performed in R Version 3.5.1 using the freely distributed statistical package BayesianTools Version 0.1.6 [28].

The probabilistic model had two levels, with information about transmission-mediated sources at level 1 and other sources at level 2 (see 'Formulation' in the online supplementary material). The risk of CRO acquisition per day was modelled to control for varying length of stay among patients. All model levels were assessed simultaneously to disentangle spatiotemporal patterns of each outcome, manifesting across each acquisition mechanism with respect to the individuals' characteristics, their HCW-mediated social network, and the broader unit characteristics.

As carbapenemase-producing (CP) CROs were considered the highest threat due to their resistance to multiple antibiotic classes and potential for plasmid transmission [24,29], the acquisition dynamics of CP CROs vs non-CP CROs were analysed independently. The clinical and surveillance data did not allow the authors to ascertain the exact moment when a patient acquires a new CRO (unobservable clinical event). To evaluate the possibility that unobserved events may explain associations, the authors also examined whether randomization of the actual acquisition date, between the dates of the last known CRO-negative culture and the CRO-positive culture, impacted the direction and size of the estimated effects substantially (see 'Extension of main results' in the online supplementary material).

The robustness of the results was evaluated by varying the time window of 60 min that established a patient's HCW-mediated social network from 15 min to 12 h; the latter was included as this is consistent with the maximum length of most HCWs' shifts. Acquisition dynamics on each hospital ward were also studied in separate models (see 'Robustness of main results' in the online supplementary material).

## Results

### *Study sample and demographic characteristics*

The study cohort included 2193 unit admissions (1715 unique patients) to the MICU and the CTU (Table I). Patients were predominantly adults aged 45–59 years old (724/2193, 35%), male (1131/2193, 52%), Black (1085/2193, 50%), non-Latino (2098/2193, 96%) and Maryland residents (1893/2193, 86%) who were typically admitted as emergency or urgent cases (1951/2193, 89%). Patients in the cohort were connected through 216,069 distinct HCW-mediated connections, representing a daily average of 591 HCW-mediated contacts between patients. Most patients in the cohort were on contact precautions for CROs or other antibiotic-resistant organisms (87.4% and 88.9% amongst non-incident and incident CRO admissions, respectively). Susceptible patients had, on average, 4.8 daily connections through HCWs with CRO-positive patients on contact precautions and 1.9 daily connections with CRO-positive patients not on contact precautions.

**Table II**
Risk factors for incident carbapenem-resistant organism (CRO) acquisition among patients hospitalized in a medical intensive care unit and a solid organ transplantation unit of a tertiary hospital by mode of acquisition

| Variable | Adjusted odds ratio (95% CrI) |
|---|---|
| Level 1: Potential for transmission | |
| HCW-mediated connection to patients with CROs | 0.90 (0.05–18.58) |
| Contact precautions on CRO-positive patients on the unit | 0.03 (0.01–0.17)[a] |
| Environmental cleaning compliance >95%[b] | 0.41 (0.03–3.27) |
| Carbapenem exposure in the preceding 7 days | 0.39 (0.03–2.97) |
| HCW hand hygiene compliance >95%[b] | 0.33 (0.03–2.47) |
| Level 2: Acquisition from sources other than a known infection | |
| Carbapenem exposure in the preceding 7 days | 2.38 (1.70–3.29)[a] |

HCW, healthcare worker; CrI, credible interval.
[a] Significant (Bayesian significance).
[b] Hospital wards with environmental cleaning compliance >95% and HCW hand hygiene compliance >95% represented the top-quartile performers in the study sample.

### *Colonization and infection*

In total, 126 of 2193 (5.8%) unit visits had a negative swab on admission and at least one positive swab more than 2 days after admission, and were classified as incident for CRO acquisition (Table I) [30]. Amongst the 126 visits, 120 (93.0%) were linked with potentially transmission-mediated CRO acquisition events because the patient grew a CRO of the same species as another patient on the hospital ward, while all of the 126 visits (100%) were detected to have at least one CRO acquisition event with no evidence of transmission. Patients could be incident cases more than once if they acquired a CRO of a different species and met the outcome definition criteria. Non-incident and incident CRO patients had similar baseline demographics at unit entry. However, incident CRO individuals were more likely to have HCW-mediated contacts with CRO-positive individuals who were not on contact precautions {median 1 [interquartile range (IQR) 1—2] vs 2 [IQR 1—2]}. Compared with non-incident CRO patients, incident CRO patients were more likely to receive carbapenems (10.0% vs 47.6%, respectively).

### *Modelling results*

The use of contact precautions for CRO-positive patients was associated with reduced rate and odds of CRO acquisition among susceptible individuals (7.4 vs 93.5 per 1000 patient-days at risk; aOR 0.03, 95% CrI 0.01—0.17). The estimated absolute risk reduction of contact precautions for CRO-positive patients, compared with CRO-positive individuals without contact precautions, was 9.0% (95% CrI 7.6—9.2%), corresponding to three events prevented per 1000 patient-days at risk. For susceptible individuals, recent exposure to carbapenems (last 7 days) was the primary driver of CRO acquisition (aOR 2.38, 95% CrI 1.70—3.29) (Table II).

The mechanism of resistance appeared to be important. When the cohort was restricted to the acquisition of CP CRO (vs non-CP CRO), recent carbapenem exposure in susceptible patients had no statistically meaningful (i.e. Bayesian significance) relationship with incident CP CRO acquisition (aOR 2.19, 95% CrI 0.96—4.56), whereas carbapenem exposure was significantly asscociated with non-CP CRO acquisitions (aOR 2.01, 95% CrI 1.33—2.95). The use of contact precautions for CRO-positive patients, however, was linked with reduced rate and odds of CP CRO acquisition (48.0 vs 417.6 per 1000 patient-days at risk; aOR 0.04, 95% CrI 0.01—0.19) and non-CP CRO acquisition (12.1 vs 157.8 per 1000 patient-days at risk; aOR 0.03, 95% CrI 0.01—0.16) among susceptible patients (Table S1, see online supplementary material).

The robustness of the results to unobservable clinical events was evaluated [i.e. the authors' inability to determine the actual CRO acquisition date precisely during the patient stay (Table S2, see online supplementary material)]. The CRO acquisition date in the models within a reasonable time interval, from the last known CRO-negative culture to the CRO-positive culture, was randomized. As presented in Table S2 (see online supplementary material), the direction and magnitude of effects shown in Table II remained similar.

The robustness of the results to the definition of a patient's social network (i.e. HCW-mediated contacts with other patients on the ward) was also investigated. When modifying the time lapse of 60 min from 15 min to 12 h, the magnitude and direction of the effect of contact precautions were virtually unchanged (aOR 0.03—0.04). However, much uncertainty (95% CrI 0.01—0.17) was found in estimation of the posterior coefficient (Table S4, see online supplementary material), signalling potential workflow differences between wards. Separate models were fitted for each ward to determine whether workflow differences explained some of the variability in the effect of contact precautions. No significant differences in the effect of contact precautions between the MICU (aOR 0.03, 95% CrI 0.01—0.13) and the CTU (aOR 0.05, 95% CrI 0.01—0.28) were found.

## Discussion

Contact precautions are a common intervention used to prevent transmission from patients colonized or infected with multi-drug-resistant organisms. However, evidence for the effectiveness of contact precautions in natural hospital environments for meticillin-resistant *S. aureus* and VRE is limited [13], and is restricted to theoretical models and aggregate secondary analyses of clinical trial data for CROs [21,31]. This uncertainty is due, in part, to the low frequency of CRO acquisition events in the hospital setting, and the challenge of observing these events in the absence of robust surveillance. Furthermore, there is rapid turnover in the patient population, large numbers of HCWs and staff that attend each patient or room, and sharing of equipment among units that make it challenging to assign causal factors to acquisition events [32]. Disaggregate (patient-level) probabilistic models can overcome some of these challenges. By decomposing distinct longitudinal patient and environmental factors of CRO acquisition explicitly, it seems that contact precautions may reduce the risk of CRO acquisition, even after adjusting for carbapenem exposure.

This patient-level probabilistic modelling approach contributes to recent aggregate (hospital ward level) data suggesting that the use of contact precautions in intensive care environments is associated with a non-significant decrease in CRO acquisitions [21,31]. As they quantify acquisition dynamics with observable (covariates) and unobservable (outcome) clinical events, these disaggregate models are sensitive to the uncertainty of the epidemic process (e.g. endogenous vs exogenous acquisition mechanism), and include longitudinally dynamic parameters of particular interest (e.g. contact precautions). The use of Bayesian hierarchical logistic regression allows for more mechanistic insights on acquisition risk factors, which is advantageous over machine-learning models that lack interpretability [33]. However, contrary to a recent study suggesting that increased HCW-mediated connections were significantly associated with transmission of enteric pathogens [16], the present results were not significant for HCWs (95% CrI 0.05—18.58). There are multiple reasons for this difference. The disaggregated models used in the present study included contemporaneous overlap on the hospital ward as a prerequisite to link two patients epidemiologically, which challenges the ability to disentangle overlap in the department from strength of connection on a day-to-day basis. Alternatively, the HCW connectivity data are based on EHR entries which may miss important connections that are not well documented. Also, surface contamination may result in indirect transmission that is not specific to direct

patient—HCW—patient connectivity. Thus, further analysis of these network connections and the relative importance of HCWs to acquisition are needed.

This study found that the primary driver of CRO acquisition was exposure to carbapenems, highlighting the opportunity for CRO-targeted antibiotic stewardship programmes. Carbapenems may exert selective pressure that induces endogenous flora to evolve to become CROs, or enriches existing CROs below the limit of detection of culture methods [34]. Alternatively, they can disrupt flora and make the patient more susceptible to colonization upon exogenous exposure. Either way emphasizes the potential role of antibiotic stewardship [35].

A limitation of any effort to capture transmission of a pathogen in a hospital with so many potential opportunities for transmission is that the actual date of acquisition is typically unknown (i.e. unobservable clinical event). This somewhat inconclusive direct evidence fed into the models produced estimates of effect with wide CrIs, signalling considerable uncertainty about the true value of the effect size. The parameters for the model were estimated assuming a random acquisition date to account for the uncertainty in the colonization date. That is, if a patient is known to be CRO negative in Week 1, and is known to be CRO positive in Week 2, the model was evaluated assuming that CRO acquisition event took place at some random time period between these two surveillance tests. The results of randomizing the acquisition date did not impact the direction and size of the estimated effects qualitatively, suggesting that the use of contact precautions in patients with CROs is still better than no intervention.

While the authors attempted to collect detailed data on patient hospitalizations and infections, limitations remain regarding the estimated transmission parameters. One limitation is the observation scope of transmission-mediated acquisitions being limited to departments offering ICU-level care in a tertiary research hospital, which means the results may not be generalizable to other hospitals given patient diversity, varying clinical guidelines and protocols, and location-specific transmission pathways. Still, the process by which the CRO data were collected and analysed should be suitable in analogous situations where HCW interactions, contact precautions and carbapenem exposure are risks. Second, clinical risk factors that impact acquisition dynamics, such as history of previous overseas hospitalization, were not incorporated explicitly into the assessment. Third, some activities and contacts may not be logged on the EHR system by individuals. Still, contact networks between patients and providers built with data collected regularly in most EHRs are surrogates for understanding the extent of connectivity between individuals. This facilitates the translation of this research to operational infection control practices scalable across institutions with an EHR system. Fourth, not all patients in the study cohort were screened at discharge, which may have resulted in ascertainment bias. Post-hoc analyses showed that 97.5% of patients were screened within 8.3 days of discharge and 99% were screened within 11.6 days of discharge. Therefore, it is believed that ascertainment bias was minimal and did not have a significant impact on the study results. Finally, the classification of CRO types may benefit from better diagnostic methods of microbial genotyping, which can distinguish cross- and environmental transmission events more precisely. It was assumed that all colonized patients with the same CRO type could be a transmission source, which was considered a reasonable assumption.

In conclusion, the analysis of extensive longitudinal clinical and surveillance data from two tertiary high-acuity hospital wards demonstrated that the use of contact precautions may be an effective intervention for preventing CRO acquisition among susceptible patients, even after adjusting for antibiotic exposure.

**Author contributions**

Dr. Martinez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Martinez, Lessler, Milstone, Klein.

Acquisition, analysis, and interpretation of data: All authors.

Drafting of the manuscript: Martinez, Lin, Paul, Milstone, Klein.

Critical revision of the manuscript for important intellectual content: All authors.

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**Conflict of interest statement**

Dr. Martinez reported receiving grants from the National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ), and personal fees from the Johns Hopkins Health System during the conduct of the study. Drs. Hinson and Levin reported receiving grants from AHRQ during the conduct of the study. Dr. Klein reported receiving grants from the Centers for Disease Control and Prevention (CDC) during the conduct of the study. Drs. Lessler and Milstone reported receiving grants from NIH during the conduct of the study. No other disclosures were reported.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2023.02.016.

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