**Main Manuscript for**

Estimating importation and nosocomial transmission of micro-organisms in hospital settings using patient records and culture data

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**Author Contributions:** J.C.V., S.P. and J.S. conceived the study and managed the project. J.C.V. performed the analysis. L.W. and J.Z. curated the data, J.C.V., T.R., A.C.U., S.P. and J.S. analyzed the results. J.C.V drafted the manuscript. All authors revised and reviewed the manuscript.

**Competing Interest Statement:** J.S. and Columbia University disclose partial ownership of SK Analytics. J.S. discloses consulting for BNI. ACU discloses research support from Merck. All other authors declare no competing interests.

**Classification:** Major: Biological Sciences. Minor: Biophysics and Computational Biology.

**Keywords:** epidemiology, microorganisms, antimicrobial resistance, Bayesian inference, individual-based model.

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Main Text

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**Abstract (244/250 words)**

Antimicrobial-resistant organisms (AMROs) are a major threat to public health. These organisms increase mortality, hospital length of stay, and healthcare-associated costs. Many AMROs are present in both hospitals and the broader community; however, information on AMRO transmission in both settings is limited. In this work, we leverage electronic health records from a major New York City hospital system collected during 2020-2021 to support simulation-based inference of detection and transmission quantities for eight pathogens. We develop an agent-based model to simulate the admission, transfer, and discharge of patients at the ward facility level in the hospital system, AMRO importation from the community, and patient-to-patient transmission of AMROs. The model is coupled with a Bayesian inference data assimilation algorithm to estimate effective sensitivity and nosocomial transmission rates. We evaluate parameter identifiability for this model-inference system and then apply the framework to estimate both quantities for seven prevalent organisms: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* (both sensitive, MSSA, and resistant, MRSA, phenotypes), *Staphylococcus epidermidis*, *Enterococcus faecium* and *Enterococcus faecalis*. We discern whether bias in the inference is caused by the structural identifiability of the system or by the inherent stochasticity of the model.

The parameter estimates reveal substantially higher community prevalence (i.e., importation rate) for *E. coli* and *K. pneumoniae* than the other six organisms. Nosocomial transmission rates are found to be highest for *P. aeruginosa* and MSSA. This work highlights how fine-scale patient data can support dynamic modeling and estimation of epidemiological properties of microorganisms. Evaluation of the community prevalence and transmission potential for different pathogens could ultimately support the development of in-hospital control measures that limit the spread of these pathogens.

**Main Text**

**Introduction**

Antimicrobial resistance (AMR) is a major threat to human health worldwide and has emerged as one of the leading public threats of the 21st century 1. An estimated 4.95 million deaths were associated with bacterial AMR in 2019 globally, and mortality caused by AMR is projected to reach 10 million by 2050 2. Hospital-acquired (nosocomial) infections by AMROs are a major contributor to mortality, length of stay in hospital and health-care associated costs 2. Understanding the burden and spread of AMROs, and microorganisms in general, within hospital settings, as well as the effects of potential interventions, is critical for effective control planning; however, quantification of these characteristics remains challenging due to limited observation of AMRO carriage, difficulty assessing interventions in real-world settings, and incomplete understanding of the mechanisms shaping the coexistence of antibiotic-resistant and antibiotic sensitive microorganism in hospitals 33,4.

To circumvent these difficulties, mathematical models have been applied to study AMROs in hospital settings. For instance, mathematical models have been used to understand the emergence of resistance and its interplay with community-acquired infection 5, to evaluate antibiotic treatment protocols 6, and to assess control measures to reduce nosocomial transmission 7–11. However, most existing modeling studies focus on either general theoretical frameworks of AMR 5–7,12–14 or single AMROs of interest such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *K. pneumoniae*. Studies on the epidemiological characteristics of multiple co-circulating organisms supported by real-world data are rare.

The epidemiology and transmission dynamics of healthcare-associated infections (HAI) differ from community-acquired infections in a number of important ways.

First, hospitals are open systems with significant variations in the daily influx and outflux of patients at finer spatial scales, ranging from 10% to 30% of the average number of hospitalized patients (See Figure 1 B-C and Supplementary Information Figure S1-S2).

In contrast, communities are more closed systems with individuals moving in or out at much lower rates. Second, the capacity of many bacterial species to persist as commensals on human hosts makes the detection of colonization both difficult and differential by body site. Indeed, patients with infections of the bloodstream or lower respiratory tract are more likely to be detected in hospital than those colonized at other sites 5,15. Third, facilities within a single hospital system (e.g., infusion, pediatric, emergency wards, among others) may differ substantially in their control and detection of AMROs, a complication compounded by transfers between wards and hospitals 16,17. Fourth, a lack of observational data for multiple microorganisms in the same hospital system often imposes further challenges in comparing the epidemiological features of co-circulating organisms.

In this study, we use an agent-based model (ABM) and detailed observational data for eight prevalent organisms collected in a major New York City (NYC) hospital system to address these challenges. The agent-based model is informed by real-world patient movement in the hospital system and incorporates importation of microorganisms from the community, patient-to-patient transmission, and patient transfer across hospital wards. To account for the heterogeneity of testing frequency and microorganism prevalence among facilities, we use clinical testing records to design an observational model that mimics the detection of microorganisms in hospitals. We couple the ABM with a Bayesian inference algorithm, validate the system against simulated outbreaks and estimate importation rates and nosocomial transmission rates for the eight organisms, which cause substantial mortality associated with AMR worldwide 2.

**Results**

### *Empirical patterns and heterogeneity of microorganism burden*

In Figure 1A, we plot monthly incidence by body site for *E. coli* (total positives cultures, n=2,829), *K. pneumoniae* (n=1149), *P. aeruginosa* (n=837), MSSA (n=810), *C. albicans* (n=631), MRSA (n=576), *S. epidermidis* (n=512), and *E. faecalis* (n=502). During the study period, the daily number of patients present in the hospital system fluctuated between 1,000 and 2,500. Daily numbers of new admissions ranged between 100 and 1,000, including outpatients. Both quantities exhibited a strong weekly oscillation (Fig. 1B) principally explained by a substantial drop in numbers on Saturday and Sunday. During the first COVID-19 wave in New York City, the numbers of in-patients and admissions were generally lower; after June 2020, patient traffic was higher and relatively stationary. Ward size, defined as the average occupancy per day during the study period, was heterogeneous (Fig. S1) with the majority of wards experiencing an occupancy below 10 patients. However, a few wards (e.g., emergency rooms) could admit over 100 patients each day. Figure S2 displays the ward size per ward category; larger wards are in the 'emergency', 'laboratory' and 'infusion' categories, whereas ICUs have ward sizes from 1 to 10. To visualize patient traffic within each ward, we investigated temporal occupancy. Fig 1C shows the daily number of patients relative to average occupancy for each ward and highlights the 10 most and least populated wards. The least populated wards were empty most of the time, whereas patient numbers in the most populated wards were relatively stable during the study period. The relationship between newly admitted and in-hospital patients (Figures 1D and 1E) was linear and depended on ward size (Figure S3) and the category of the ward (Figures S2-3). AMRO testing numbers were also heterogeneous across wards. Most cultures were sampled from a small subset of wards, as shown by the weekly number of cultures collected in each (Fig. 1D). We found that certain species were predominantly discovered in specific body sites: urine for *E. coli*, *K. pneumoniae*, *C. albicans*, and *E. faecalis*; blood for *S. epidermidis*; and respiratory for *P. aeruginosa*.

We aggregated wards into several clusters based on the number of transfers between wards. The total number of patient transfers between all pairs of wards during the study period was used to perform the ward clustering (Fig. 2A). Note that the diagonal entries of the patient transfer matrix (Fig. 2A) are non-zero as we assume patients that stay in the same ward for consecutive days are transferred to the same ward. Based on this patient transfer matrix, we used a community detection method, the InfoMap algorithm 18, to partition all wards into six clusters containing dense within-cluster transfers (Fig. 2B). Monthly incidence and cumulative numbers of positive cultures for each of these ward clusters are shown in Fig. 2C. We subsequently used these six ward cluster times series to infer model parameters. Testing and new admissions exhibit significant variability among the six clusters of wards (Fig. 2D).

### *Identifiability: synthetic simulations and inference*

To investigate the identifiability of the model-inference system, we generated ten synthetic scenarios by running the model with assigned parameters and initial conditions in free simulation. We then applied the full model-inference framework to the output of these stochastic simulations to determine if the system could reliably estimate the imposed parameters (See Methods section). The posterior parameter estimates of the inference generally capture the true parameter values, particularly for the importation rate, (Figure 3A). Posterior estimates for the nosocomial transmission rate, , are not as consistently accurate and, in particular, are at times biased low (Figure 3B); however, the mean posterior estimates of do find the true value within an error of ±0.01. We ran free simulations using the estimated parameters to generate imported and nosocomial-derived colonization at both hospital and cluster levels (Fig. 3C-D and Figure S4). These simulations generally agree with the synthetic truth time series at the hospital and ward cluster levels (Figure S5), even though the estimated parameters do not exactly match the true parameters. This suggests that there may exist a structural identifiability limitation in which only one parameter can be reliably estimated 19–21. We further examined simulations at the ward level (the finest spatial scale) and found that, overall, the medians of simulations reconstruct the observations in the most populated wards (Fig. 3E); however, the model does not fully capture observed incidence in smaller wards due to the stochastic nature of transmission. In summary, the findings from these synthetic tests indicate strong identifiability for the importation rate and gross discrimination of the nosocomial transmission rate.

### *Inference using real data*

We applied the model-inference system to estimate the epidemiological quantities of interest for eight different microbial species. Posterior estimates of the importation rate and nosocomial transmission rate are compared in Figure 4A. Species are sorted from the most abundant (*E. coli)* to the least (*E. faecalis).* We found *E. coli* importation was the highest with an estimated 64.18% of patients entering the hospital system colonized. This high importation likely reflects high community prevalence, which is in line with empirical findings22. *E. coli* was followed by *K. pneumoniae* with an importation rate of 25.61%, and MSSA at 14.48% (Figure 4A). We found similar importation rates for MRSA, *C. albicans* and *S. epidermidis* of around 10.5%. *P. aeruginosa* and *E. faecalis* had slightly lower estimated importation rates of 9.9%. While the estimates for importation rates across organisms match the frequency of detection across the hospital network, nosocomial transmission rates differ. We estimated *P. aeruginosa* had the highest nosocomial transmission rate, followed by *C. albicans* and MSSA. We found nosocomial transmission rates for *E. coli* and *E. faecalis* were the lowest with rates less than 0.005 per capita per day. Table 2 shows all the posterior estimates for importation and nosocomial contact rates.

To assess the goodness-of-fit of the model to the data, we simulated the dynamics using the posterior estimates of parameters and found that simulated detected positive cases span the observed numbers at the hospital and ward cluster level (Figure 4B-C right column and Figure S6). We also produced reliability plots to examine whether the uncertainty in the observed data can be reproduced by model simulations. Specifically, we computed the percentage of observations falling within a given credible interval (CI) of the quantity obtained from model simulations. For a perfectly calibrated simulation, X% of observed values should fall within the X% CI generated by model simulations, producing a diagonal line (y=x) in the reliability plot. We found that the coverage of simulated CIs is slightly below expected values (under the diagonal line), indicating an uncertainty level biased low (Fig. 5D), possibly due to stochastic processes not represented in the model. The model simulations allow estimation of the relative contributions of importation and nosocomial transmission to the overall burden of different species. We found that importation plays a more important role than nosocomial transmission for all species examined (Fig. 5).

To assess the robustness of the parameters estimates to specimens collected from specific body sites, we repeated the previous analyses using subsets of the data that excluded observations from one of the 5 body sites (See Methods sections). We found, excepting one instance, that the estimates remain similar. The exception corresponds to the instance in which the body site with the most observed positive cultures of each species was excluded (See Figures S7-S8). For example, the estimates of both importation and nosocomial transmission rates changed when urine observations were dropped for *E. coli, C. albicans, K. pneumoniae*, and *E. faecalis*, leaving only a small fraction of observations for use in the inference. Finally, we found the parameter estimates were unchanged when excluding outpatient wards (See Figures S9-S10).

**Discussion**

The epidemiological properties of microorganisms present in hospitals are difficult to quantify. Estimating these epidemiological properties can distinguish the roles of different mechanisms of transmission, such as community importation and nosocomial transmission, and help support improved AMR control in healthcare systems. In this paper, we used an agent-based model informed by patient hospitalization records and culture testing results from a large hospital system in New York City to study eight co-circulating microbial species. We coupled this model with an inference algorithm to estimate importation and nosocomial transmission rates for these organisms and found substantial variation in community prevalence and within-hospital transmission.

Our findings echo several previous observations about the transmission of different microorganisms. The difference in nosocomial transmission rates among resistant and sensitive strains of *S. aureus* is potentially explained by the relative fitness of the two strains. It has been reported that resistance generates a decrease in fitness with respect to the sensitive strain, making it less transmissible 1,7,12 consistent with our findings here. Our model-inference system estimated *P. aeruginosa* to be the most transmissible microbial species, consistent with reports that classify this organism as an opportunistic pathogen able to easily colonize non-healthy patients more likely to experience lengthy stays in hospital 4,23,24. We also found that while *E. coli* has the highest importation rate, it has the lowest nosocomial transmission rate suggesting that most carriage can be associated with infections of host commensal strains that do not contribute to transmission, which has been reported empirically 25. These results remained unchanged in response to the underlying observational network across body sites and to exclusion of outpatient wards (See Figures S7-S10).

Here, the goal of using detailed mathematical models to infer transmission properties is to provide quantitative evidence disentangling the force of transmission, which might be used to inform interventions in hospital networks. We show that importation and nosocomial transmission play different roles across organisms. This information itself could potentially help with the design of screening strategies in hospitals. Species with importation considerably greater than nosocomial transmission (e.g. *E. coli*) could be actively screened upon admission to reduce subsequent transmission within the hospital. On the other hand, further research to understand the sources of nosocomial transmission should be undertaken. Our model considers a ward level force of infection that might be due to not only patient-to-patient transmission but also transmission vectored by healthcare workers or environmental contamination 4,26. It might be possible to test interventions in the first days of admission that potentially disrupt transmission chains (e.g. improved sanitation, vaccines) for pathogens with high nosocomial transmission rates (e.g. *P. aeuruginosa*)4,23,24. Finally, our model-inference sensitivity analysis, in which we dropped observations from specific body sites, showed that, for quantifying importation and nosocomial rates, it might be enough to consider only a portion of body sites. The selection of body sites could be investigated more rigorously to prevent possible biases in detection and further inform differential testing strategies across body sites.

Mathematical models of infectious diseases are simplifications of real-world transmission dynamics. The ABM used here is not an exception. While the ABM captures multiple sources of heterogeneity (e.g., length of stay, contact patterns, observations, etc.) that otherwise cannot be represented by compartmental models, it has several limitations. First, we used an abstract nosocomial transmission rate to represent the collective effects of several processes that may contribute to the dissemination of microbial species, including direct patient-to-patient contact, healthcare worker-mediated contact, environment-mediated contact, etc. Other mechanisms potentially occurring within host (such as horizontal gene transfer) were also not represented in the current model form. The inferred transmission rate therefore cannot distinguish the relative contributions of these processes.

Second, we treated species with resistant and sensitive phenotypes separately, as we were limited by the classification available from the culture data used to detect carriage; however, it has been suggested that resistant and sensitive strains could compete (although it is possible that for some species this is not true). Further research is needed to test this competition hypothesis for species for which data from both resistant and sensitive strains are available. In addition, bacterial species do not simply compete with their own species. As many species are commensals with the human host, a variety of ecological interactions may occur. It may be possible to extend the proposed model to study these interactions. Other limitations of the current framework include the absence of information on demographics and age profiles of patients admitted to the hospital network, which we therefore do not model. Finally, we estimated the effective sensitivity of testing using empirical data on community prevalence for *S. aureus* and validated these estimates with *E. coli* community prevalence (see Methods); however, this approach assumes a 100% specificity and that the effective sensitivity of the clinical culture does not vary across hospital or microbial species. Further clinical and empirical information on these issues should be used to better inform the observational model in the future.

The implications of these findings for disease control are linked to the spatial resolution of the analysis. Previous research has highlighted the important contribution of community prevalence to hospital prevalence, a direct effect of host population exchange between healthcare systems and the community at various rates 44–47. However, as shown in Figures 1 D-E and Figure S3, patient admissions are heterogeneous and have linear relationships with in-hospital patients that are dictated by ward size, and ward category (Figure S2); therefore, community importation should be assessed differently across wards. The use of antibiotics and different schemes for using them (e.g. cycling, mixing at ward level, alternating antibiotics) have been tested using mathematical models and found less effective in model simulations 5. However, those conclusions were mostly drawn from research performed using compartmental models with assumed rates of movement within hospital networks and at the hospital level. Analyses using data-driven agent-based models, such as the one developed here, should also be used to study different antibiotic usage schema and the introduction of new antibiotics. These analyses might be performed at the ward level to study how different scenarios of interventions affect prevalence at both ward and hospital levels.Further, the current work exploits the availability of individual-level patient records to estimate the transmission properties of pathogenic microorganisms. Individual-level data and models can be employed in future research to understand the impact of individual-level interventions on disease control. An example might be to test counterfactual scenarios of individual-level interventions that replace infections caused by resistant strains with infections caused by sensitive strains in order to quantify the impact of resistance at the hospital level 1.

**Materials and Methods**

### *Overview*

To estimate key epidemiological characteristics of AMROs, we developed an ABM to simulate the dynamics of these organisms in hospital settings. The model was informed by patient hospitalization and culture data from electronic healthcare records collected between February 1 2020 and February 28 2021. We coupled the ABM with a Bayesian inference algorithm and, using simulated outbreaks, validated the ability of this ABM-inference system to identify importation and nosocomial transmission rates. We then assimilated the real-world lab-confirmed positive case data and estimated the importation and nosocomial transmission rates for eight co-circulating organisms. Using these estimated parameters and the ABM, we were able to reproduce the time series of positive cases for six clusters of wards in the hospital system. The estimated importation rates and nosocomial transmission rates were compared for the eight organisms.

### *Data*

Data for this study derives from 3 hospitals of a Northern Manhattan Hospital System, including a quaternary care center, pediatric hospital, and community hospital. The hospitals contain 224 wards of different types including emergency, infusion, cardiology, pediatrics, etc. Hospitalization and microorganism testing data were collected during the study period from February 1 2020 to February 28 2021. The hospitalization data include admission, discharge, and transfer of patients within the hospital system (see Figure 6 for schematic). The dates and wards in which each patient stayed during hospitalization were used to construct a time-evolving contact network. Laboratory test results were available for the eight most prevalent organisms in the hospital system: *Eschericia coli*, *K. pneumoniae* *Pseudomonas aeruginosa*, methicillin-susceptible *S. aureus* (MSSA), *Candida albicans*, MRSA, *Staphylococcus epidermidis* and *Enterococcus faecalis*. Clinical cultures were taken from four major body sites for all eight species: urine (number of cultures, n=26,599), blood (n=26,960), respiratory tract (n=2,734) and cerebral spinal fluid (CSF) (n=251). Cultures taken from other sites were labelled as Other (n=3,746). The date and patient associated with each test were used to inform the observation model (see Methods below). We plotted the number of tests across the 3 hospitals (Figure S11) and in the wards in each hospital (Figure S12), which show a similar order in cultures across the hospital but substantial heterogeneity inside the hospital at the ward scale.

### *The transmission models*

We used an ABM to simulate transmission in the study hospital system8. For the ABM, the patient-to-patient contact network was constructed using hospitalization records. Two patients staying in the same ward on the same day were connected in the contact network as they are expected to have close contact and care from the same hospital workers who might facilitate transmission of microbial species. Due to patient movement (admission, discharge, and transfer), the contact network is time-varying and was updated daily. We assumed each patient is either susceptible (S) or colonized (C). Patients in contact on a given day (those who shared the same ward) can be infected in proportion to the number of patients in the ward carrying a particular microorganism. We model the force of infection in ward , , following the law of mass action, as described below. We assumed colonized patients can spontaneously decolonize and become susceptible after a decolonization period, sampled from a uniform distribution days 10. Colonization in hospital can be attributed to two mechanisms: importation from the community and nosocomial transmission. Specifically, we defined these two processes as follows:

1. **Importation from the community:** Using hospital admission records, we assumed a newly admitted patient is colonized with a particular pathogen with an importation probability . The number of patients admitted from the community is shown in Figure 2B. We treated all admissions independently and did not track changes in importation rates due to re-admission. As a consequence, the number of admitted, colonized patients on day , , among all admitted patients on day , , can be computed as:
2. **Nosocomial contact transmission:** We defined a force of infection for each ward as . The force of infection is proportional to the number of individuals carrying the pathogen in a given ward on day , denoted by . We defined a frequency-dependent transmission rate per ward as , where is the average ward daily occupancy (Density distribution shown in Supplementary Information Figure S1). The force of infection per ward is computed as:

Thus, the force of infection per ward, or probability of colonization for susceptible individuals staying in ward at time , is given by , and the transition equations governing the change of state for a patient, , residing in ward during time are given by:

where is the decolonization period of patient and is a random variable with uniform distribution as indicated previously.

### *Individual Observational model*

Colonized patients may develop clinical infections due to invasion of typically sterile body sites such as blood. At other body sites (i.e. respiratory and urinary tract) the presence of pathogens may indicate both infection or colonization, depending on additional clinical variables1,7. Other individuals carrying pathogens may be discovered through routine screening or cultures ordered discretionarily by clinicians for patients without clinical manifestations. In the ABM, we did not explicitly distinguish between colonized and clinically infected patients. Instead, we applied an observational model to detect carriers. This observational model represents the detection probability for clinical cultures taken from individuals in the hospital network during the study period; it captures the heterogeneous observation of microorganisms across wards and body sites. Weekly number of cultures across hospital wards and weekly number of admitted patients have a strong positive correlation (cultures are proportional to admissions) (Figure 1D-E). Ward size distribution is shown in Supplementary Information Figure S1, and we further stratified by ward type, based on the procedure conducted in each ward (Figure S2). The proportional relationship between the number of admissions, in-hospital days, and ward size is shown in Figure S3.

A key challenge in colonization detection is that cultures collected from one body site may miss colonization of other sites even though the patient carries the bacterium or fungus. For instance, blood cultures of a patient colonized by *E. coli* in the urinary tract will likely test negative. To define our observational model, we therefore estimated the ‘effective sensitivity’ of detecting colonization, i.e. the probability of identifying carriage given that the patient is carrying a particular microorganism. This effective sensitivity not only represents culture test sensitivity, in the strict sense, but also the likelihood a specimen will be taken from a colonized site (and capture bacteria) given colonization or infection exists anywhere on a patient.

To estimate this effective sensitivity, denoted by , we used the empirical estimate of *S. aureus* prevalence (30%) in the community of northern Manhattan, site of the study hospital network 27,28, as a proxy for the community importation rate. This empirical estimate indicates that 30% of new admissions from the community carry *S. aureus* (both sensitive and resistant phenotypes). We then performed a grid search for the nosocomial transmission rate and the effective sensitivity that best fit the observed *S. aureus* carriage in the hospital system (see Supplementary Information Figure S13 - Estimating culture sensitivity for further details). We used the resulting estimate, , as the observational model across all other microbial species. For instance, using , we estimated the community prevalence of *E. coli* is around 70% (see Results section), which generally agrees with the prevalence of *E. coli* in the human population and provides cross-validation of the observational model 22. We also performed additional sensitivity analysis using alternative values of , and the findings remain qualitatively similar.

The defined observational model indicates the likelihood that a colonized patient is detected given the effective sensitivity is . Assuming 100% specificity for the cultures (i.e., no false positives), the number of false negatives is , where TP is the number of true positives (observed positives). Combining the observational model and the observed positives, we can estimate the total positives in hospital, , by summing the observed positives and false negatives, . This estimate of total positives adjusts for the under-detection of microorganism carriage and was used for parameter inference with the ABM.

### *Hospital-level Observational model*

Due to substantial testing heterogeneity, observations of positive cultures were dominated by a few wards with a disproportionately large number of tests. To facilitate use of more granular observations at the sub-hospital level while avoiding excessive noise, we partitioned all wards (n=224) into six clusters and used the aggregated number of positive tests in those clusters to perform inference. The clusters were defined based on patient movement across wards within the hospital system and were identified using a network community detection algorithm 18. The number of transfers between wards is shown in Figure 2A. Wards within each identified cluster have more frequent within-cluster transfers than cross-cluster transfers.

### *Inference*

Inference for dynamic and latent variables and parameters is often treated as a filtering problem, in which the state space is sequentially estimated as observations become available 29,30. This framework has been applied to many infectious diseases, including influenza, dengue, malaria, cholera, Ebola, enterovirus D68, and COVID-19 31–40, using compartmental models that represent transmission dynamics with a set of ordinary differential equations (ODEs). However, there are fewer instances in which filters have been used in conjunction with ABMs, possibly due to the considerably higher dimension of the state space for these models 8. For this ABM system, we simplify the inference problem and only estimate two parameters, i.e., the importation rate and the nosocomial contact rate .

We use the ensemble adjustment Kalman filter (EAKF), which assumes both the prior and the observations are normally distributed. Compared to other data assimilation techniques, the EAKF is amenable for use with high-dimensional models such as numerical weather models. We assimilated weekly observations of total numbers positive for microorganisms 29 using an iterated filtering framework (IF) 41,42, substituting the usual ODE model form with the ABM. The implementation of the IF-EAKF in python was made using the packages NumPy and SciPy 43,44. Further details and hyperparameters for this implementation are available in the Supplementary Information.

### *Identifiability: Synthetic simulations and inference*

To verify that the model-inference system is able to accurately estimate the two key epidemiological parameters, we first investigated the identifiability of the system using simulated outbreaks (i.e., the ability of the framework to infer the parameters when they are known). We generated synthetic observations of incident microorganism colonization using the ABM and assigned importation and nosocomial transmission rates. The synthetic observations were then assimilated into the full model-inference system to assess system ability to accurately estimate the parameters. In total, ten synthetic time series of observations were generated with parameters spanning a broad range of values (see Table 1 for the parameter combinations). We chose these scenarios such that different combinations of importation and nosocomial transmission rates could be tested.

### *Inference using real-world data*

We next used actual weekly observations for the six ward clusters to infer community importation and nosocomial transmission rates for all eight microbial species. The model-inference framework was applied to each species separately with the assumption that no ecological interaction exists among species. The primary observational model uses culture data from all body sites; however, we also performed sensitivity analyses in which we restricted the observation of positives to particular body sites. Specifically, we estimated parameters using positive observations excluding one body site at a time. A detailed description of the number of specimens used and the number of cultures across ward clusters is shown in the Supplementary Information. We also performed sensitivity analysis on the Observational Error Variance (OEV) used in the IF-EAKF to investigate its impact on inferred parameter outcomes (See Figure S14). Finally, we performed a sensitivity analysis that excluded wards only receiving outpatients (See SI for further details, Figures S9-S10).

**Acknowledgments**

This study was supported by funding from the Centers for Disease Control and Prevention U01CK000592 and 75D30122C14289. We thank Matteo Perini and the CDC Modeling Infectious Diseases in Healthcare Network (MInD – Healthcare) for comments and discussions. We also thank Rami Yaari for partially reproducing the results.

**References**

1. de Kraker, M. E. A. & Lipsitch, M. Burden of Antimicrobial Resistance: Compared to What? *Epidemiologic Reviews* **43**, 53–64 (2022).

2. Murray, C. J. *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* **399**, 629–655 (2022).

3. Lehtinen, S. Co-colonisation and coexistence. *Nat Ecol Evol* **3**, 334–335 (2019).

4. Pham, T. M., Kretzschmar, M., Bertrand, X., Bootsma, M., & on behalf of COMBACTE-MAGNET Consortium. Tracking Pseudomonas aeruginosa transmissions due to environmental contamination after discharge in ICUs using mathematical models. *PLoS Comput Biol* **15**, e1006697 (2019).

5. Bergstrom, C. T., Lo, M. & Lipsitch, M. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proc Natl Acad Sci U S A* **101**, 13285 (2004).

6. Bonhoeffer, S., Lipsitch, M. & Levin, B. R. Evaluating treatment protocols to prevent antibiotic resistance. *Proc Natl Acad Sci USA* **94**, 12106 (1997).

7. Lipsitch, M., Bergstrom, C. T. & Levin, B. R. The epidemiology of antibiotic resistance in hospitals: Paradoxes and prescriptions. *Proc Natl Acad Sci USA* **97**, 1938 (2000).

8. Pei, S., Morone, F., Liljeros, F., Makse, H. & Shaman, J. L. Inference and control of the nosocomial transmission of methicillin-resistant Staphylococcus aureus. *eLife* **7**, e40977 (2018).

9. Paul, P., Slayton, R. B., Kallen, A. J., Walters, M. S. & Jernigan, J. A. Modeling Regional Transmission and Containment of a Healthcare-associated Multidrug-resistant Organism. *Clin Infect Dis* **70**, 388–394 (2020).

10. Cooper, B. S. *et al.* Methicillin-resistant Staphylococcus aureus in hospitals and the community: Stealth dynamics and control catastrophes. *Proceedings of the National Academy of Sciences* **101**, 10223–10228 (2004).

11. Pei, S., Liljeros, F. & Shaman, J. Identifying asymptomatic spreaders of antimicrobial-resistant pathogens in hospital settings. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2111190118 (2021).

12. Lipsitch, M. & Samore, M. H. Antimicrobial Use and Antimicrobial Resistance: A Population Perspective. *Emerg. Infect. Dis.* **8**, 347–354 (2002).

13. Austin, D. J., Kristinsson, K. G. & Anderson, R. M. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proceedings of the National Academy of Sciences* **96**, 1152–1156 (1999).

14. Austin, D. J., Bonten, M. J. M., Weinstein, R. A., Slaughter, S. & Anderson, R. M. Vancomycin-resistant enterococci in intensive-care hospital settings: Transmission dynamics, persistence, and the impact of infection control programs. *Proceedings of the National Academy of Sciences* **96**, 6908–6913 (1999).

15. Uhlemann, A.-C., Otto, M., Lowy, F. D. & DeLeo, F. R. Evolution of community- and healthcare-associated methicillin-resistant Staphylococcus aureus. *Infection, Genetics and Evolution* **21**, 563–574 (2014).

16. Smith, D. L., Levin, S. A. & Laxminarayan, R. Strategic interactions in multi-institutional epidemics of antibiotic resistance. *Proc Natl Acad Sci U S A* **102**, 3153 (2005).

17. the EuSCAPE Working Group *et al.* Epidemic of carbapenem-resistant Klebsiella pneumoniae in Europe is driven by nosocomial spread. *Nat Microbiol* **4**, 1919–1929 (2019).

18. Rosvall, M. & Bergstrom, C. T. Maps of random walks on complex networks reveal community structure. *Proceedings of the National Academy of Sciences* **105**, 1118–1123 (2008).

19. Gelman, A., Simpson, D. & Betancourt, M. The Prior Can Often Only Be Understood in the Context of the Likelihood. *Entropy* **19**, 555 (2017).

20. Kennedy, L., Simpson, D. & Gelman, A. The experiment is just as important as the likelihood in understanding the prior: A cautionary note on robust cognitive modelling. 12.

21. Wieland, F.-G., Hauber, A. L., Rosenblatt, M., Tönsing, C. & Timmer, J. On structural and practical identifiability. *Current Opinion in Systems Biology* **25**, 60–69 (2021).

22. Larramendy, S. *et al.* Risk Factors of Extended-Spectrum Beta-Lactamases-Producing Escherichia coli Community Acquired Urinary Tract Infections: A Systematic Review. *IDR* **Volume 13**, 3945–3955 (2020).

23. Diggle, S. P. & Whiteley, M. Microbe Profile: Pseudomonas aeruginosa: opportunistic pathogen and lab rat: This article is part of the Microbe Profiles collection. *Microbiology* **166**, 30–33 (2020).

24. Reuter, S., Sigge, A., Wiedeck, H. & Trautmann, M. Analysis of transmission pathways of Pseudomonas aeruginosa between patients and tap water outlets\*: *Critical Care Medicine* **30**, 2222–2228 (2002).

25. Harris, A. D. *et al.* How important is patient-to-patient transmission in extended-spectrum β-lactamase Escherichia coli acquisition. *American Journal of Infection Control* **35**, 97–101 (2007).

26. Lu, D., Aleta, A. & Moreno, Y. Assessing the Risk of Spatial Spreading of Diseases in Hospitals. *Front. Phys.* **10**, 882314 (2022).

27. Miller, M. *et al.* Staphylococcus aureus in the Community: Colonization Versus Infection. *PLoS ONE* **4**, e6708 (2009).

28. Sakr, A., Brégeon, F., Mège, J.-L., Rolain, J.-M. & Blin, O. Staphylococcus aureus Nasal Colonization: An Update on Mechanisms, Epidemiology, Risk Factors, and Subsequent Infections. *Front. Microbiol.* **9**, 2419 (2018).

29. Anderson, J. L. An Ensemble Adjustment Kalman Filter for Data Assimilation. *Mon. Wea. Rev.* **129**, 2884–2903 (2001).

30. Arulampalam, M. S., Maskell, S., Gordon, N. & Clapp, T. A tutorial on particle filters for online nonlinear/non-Gaussian Bayesian tracking. *IEEE Trans. Signal Process.* **50**, 174–188 (2002).

31. Subramanian, R., He, Q. & Pascual, M. Quantifying asymptomatic infection and transmission of COVID-19 in New York City using observed cases, serology, and testing capacity. *PNAS* **118**, (2021).

32. Romeo-Aznar, V., Picinini Freitas, L., Gonçalves Cruz, O., King, A. A. & Pascual, M. Fine-scale heterogeneity in population density predicts wave dynamics in dengue epidemics. *Nat Commun* **13**, 996 (2022).

33. Santos-Vega, M. *et al.* The neglected role of relative humidity in the interannual variability of urban malaria in Indian cities. *Nat Commun* **13**, 533 (2022).

34. Li, R. *et al.* Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science* **368**, 489–493 (2020).

35. Pei, S. & Shaman, J. Aggregating forecasts of multiple respiratory pathogens supports more accurate forecasting of influenza-like illness. *PLoS Comput Biol* **16**, e1008301 (2020).

36. Pei, S., Teng, X., Lewis, P. & Shaman, J. Optimizing respiratory virus surveillance networks using uncertainty propagation. *Nat Commun* **12**, 222 (2021).

37. Pei, S., Cane, M. A. & Shaman, J. Predictability in process-based ensemble forecast of influenza. *PLoS Comput Biol* **15**, e1006783 (2019).

38. Park, S. W. *et al.* Epidemiological dynamics of enterovirus D68 in the United States and implications for acute flaccid myelitis. *Sci. Transl. Med.* **13**, eabd2400 (2021).

39. Yang, W. *et al.* Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis. *The Lancet Infectious Diseases* **21**, 203–212 (2021).

40. Ukawuba, I. & Shaman, J. Inference and dynamic simulation of malaria using a simple climate-driven entomological model of malaria transmission. *PLoS Comput Biol* **18**, e1010161 (2022).

41. Ionides, E. L., Breto, C. & King, A. A. Inference for nonlinear dynamical systems. *Proceedings of the National Academy of Sciences* **103**, 18438–18443 (2006).

42. Ionides, E. L., Nguyen, D., Atchadé, Y., Stoev, S. & King, A. A. Inference for dynamic and latent variable models via iterated, perturbed Bayes maps. *Proc Natl Acad Sci USA* **112**, 719–724 (2015).

43. Harris, C. R. *et al.* Array programming with NumPy. *Nature* **585**, 357–362 (2020).

44. Virtanen, P. *et al.* SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods* **17**, 261–272 (2020).

**Figures and Tables**Calendar

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**Figure 1. Empirical colonization of microbial organisms, hospital admissions and testing.** **A)** Incident observations for microorganisms of interest, from left to right and top to bottom: *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *MSSA*, *S. epidermis*, *Candida albicans*, *MRSA*, *E. faecalis*. **B)** Numbers of in-hospital patients (red) and admitted patients (blue) during the study period at daily resolution (weekly variability is evident). **C)** Numbers of in-hospital patients normalized by ward size (average occupancy per day during the study period); blue lines show the 10 most populated wards, green lines the 10 least populated, and the remaining wards are shown in gray in the background **D)** Heatmap showing the number of weekly cultures in each ward during the study period. **E)** Heatmap plot showing the number of patients admitted weekly to each ward during the study period.

Graphical user interface

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**Figure 2. A)** Adjacency matrix of transfers between wards during the study period. **B)** Adjacency matrix of transfers between clusters (aggregation of wards) during the study period. Color bar is in Log10 scale; darker colors indicate greater movement of individuals between each pair of wards or ward clusters. **C)** Incident colonization for the 8 study species; line color designates the cluster. **D)** Heatmap plot showing the number of weekly cultures identified in each ward cluster during the study period. **E)** Heatmap showing the number of patients admitted weekly to each ward cluster during the study period.

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**Figure 3. Posterior parameter estimates.** Estimates for the **A)** importation rate and **B)** nosocomial transmission rate. Violin plots show the posterior distribution an estimates for the last iteration of the IF-EAKF (see Methods section) for 3 different runs of the model-inference system. Red dots show the value used in the synthetic simulation (i.e. the truth).Hospital-level simulations ofthe number of **C)** imported, **D)** nosocomial, and **E)** detected colonizations. Each column represents one scenario used for studying the identifiability of the system. Light and dark ribbons show the 95% and 50% uncertainty, respectively, constructed from 300 simulations of the posterior, and dots show the hospital-level observation of the synthetic simulation. Note, hospital level data were not used to optimize the model.

A picture containing diagram

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**Figure 4. Posterior parameter estimates (A-B):** Violin plots show the posterior distribution and point estimates from the last iteration of the IF-EAKF (Methods section) for each of the microbial species (Data section). **C)** Hospital level fit: Light and dark ribbons show the 95% and 50% quantiles, respectively, constructed from 300 simulations with the posterior estimates of parameters. Observed carriage is plotted with dots at weekly time scale. D) Calibration plot. Hospital-level fit with 4 different confidence intervals (25%, 50, 75%, 95%). The black dotted line is the reference perfect calibration.

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**Figure 5. Importation and nosocomial contribution.** Weekly incident colonization of microbial species. Light and dark ribbons show the 95% and 50% quantiles, respectively, constructed from 300 simulations with the posterior estimates of parameters. Salmon/red color shows importation; light blue shows nosocomial transmission (left and right axis, respectively).

Diagram

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**Figure 6. A)** Schematic of agent states, S: susceptible to colonization and C: colonized. **B)** Model diagram showing the colonization process for a single ward facility; is the force of Infection for ward i, . **C)** Schematic of a hospital with 2 wards of different size; arrows show the movement process within the hospital at the ward level: admission to the hospital network, transfer between wards, and discharge from the hospital network.

**Table 1.** Parameters used for synthetic scenarios and investigation of ABM identifiability.

|  |  |  |
| --- | --- | --- |
|  | **Importation probability** | **Nosocomial contact transmission rate** |
| Scenario 1 | 0.10 | 0.04 |
| Scenario 2 | 0.05 | 0.04 |
| Scenario 3 | 0.07 | 0.04 |
| Scenario 4 | 0.10 | 0.01 |
| Scenario 5 | 0.03 | 0.02 |
| Scenario 6 | 0.03 | 0.025 |
| Scenario 7 | 0.015 | 0.02 |
| Scenario 8 | 0.15 | 0.04 |
| Scenario 9 | 0.20 | 0.03 |
| Scenario 10 | 0.30 | 0.035 |

**Table 2.** **Posterior estimates**. Mean posterior estimates for the eight species studied; both

importation and nosocomial transmission rates, γ and β, are presented as rates per day.

|  |  |  |
| --- | --- | --- |
| **Organism** | **Importation probability** | **Nosocomial transmission rate** |
| *E. coli* | 0.64 | 0.0022 |
| *K. pneumoniae* | 0.26 | 0.00875 |
| *MSSA* | 0.145 | 0.020 |
| *MRSA* | 0.11 | 0.0148 |
| *C. albicans* | 0.11 | 0.0244 |
| *S. epidermis* | 0.10 | 0.011 |
| *P. aeruginosa* | 0.09 | 0.055 |
| *E.faecalis* | 0.09 | 0.0052 |