**Title 1:** Quantifying nosocomial transmission of pathogenic bacteria in hospital settings using patient records and culture data

**Title 2:** Hospital traffic and surveillance determine nosocomial transmission and detection of pathogenic bacteria in hospital settings in New York City

**Authors:** Jaime Cascante Vega1, Rami Yaari1, Tal Robin1, Lingsheng Wen2, Jason Zucker2, Anne-Catrin Uhlemann2, Sen Pei1,\*, Jeffrey Shaman1,3,\*

**Affiliations:**

1. Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA.

2. Division of Infectious Diseases, Department of Medicine, Columbia University, College of Physicians and Surgeons, New York, New York, USA.

3. Columbia Climate School, Columbia University, New York, NY, USA.

\* Corresponding authors: Sen Pei, Jeffrey Shaman

\*Corresponding authors. Email: sp3449@cumc.columbia.edu, jls106@cumc.columbia.edu

**One Sentence Summary:**

**Abstract (261/250 words)**

Pathogenic bacteria are a major threat to patients' health in hospitals. In this work, we leverage electronic health records from a major New York City hospital system collected during 2020-2021 to support the simulation-based inference of nosocomial transmission for eight pathogens. We develop an agent-based model informed by patient hospitalization records to simulate importation from the community, nosocomial transmission, and patient spontaneous decolonization of bacteria. The model is coupled with a Bayesian inference algorithm to estimate the likelihood of detection upon testing and nosocomial transmission rates. We evaluate parameter identifiability for this simulation-based inference system and find that it is able to discriminate nosocomial transmission and effective sensitivity. We apply the framework to estimate both quantities for eight prevalent bacterial pathogens: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* (both sensitive, MSSA, and resistant, MRSA, phenotypes), *Staphylococcus epidermidis*, *Enterococcus faecium* and *Enterococcus faecalis*. We find that nosocomial transmission for *E. coli* is negligible, and *MSSA* has a lower nosocomial transmission rate than *MRSA.* We show that while bacterial pathogens have different levels of importation rates, nosocomial transmission rates were similar suggesting similar levels of transmission for all, except *E. coli*. We also find that estimated likelihoods of detection are similar for all pathogens and it's ordering is proportional to their abundance. This work highlights how fine-scale patient data can support inference of epidemiological properties of micro-organisms and how hospital traffic, patient contact and surveillance determine epidemiological features. Evaluation of the surveillance and transmission potential for different pathogens could ultimately support the development of in-hospital control measures as well as design of surveillance strategies.

**Main Text:**

**Introduction**

Antimicrobial resistance micro-organisms (AMRO) are 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 bacterial pathogens including those resistant to antibiotics are a major contributor to mortality, length of stay in hospital and health-care-associated costs *(2)*.

Understanding the burden, spread and detection of AMR pathogens, and micro-organisms in general, within hospital settings, is critical for effective control planning and design of testing/culture protocols. Quantification of these characteristics remains challenging due to limited observation of micro-organisms carriage, difficulty assessing interventions in real-world hospital settings and incomplete understanding of the underlying data generation processes *(3–5)*.

To circumvent these difficulties, mathematical models have been applied to study pathogen transmission in hospital settings, to quantify and understand the relative roles of different routes of transmission *(4)*, and to characterize the condition of the hospital settings to sustain transmission of both resistant and sensitive strains *(6)*. In the context of AMRO, theory has been used to understand the emergence of resistance and its interplay with community-acquired infections *(7, 8)*, to evaluate antibiotic treatment protocols *(9)*, to assess control measures to reduce nosocomial transmission *(6, 10–13)*. More recently, models have been used in pair with empirical observations to assess the role of competition of different strains at the between-host level and the role of within-host microbiome pathogen interactions *(14)*.

Most existing modeling studies focus on general theoretical frameworks of AMR organisms *(6–9, 14–18)* providing insights on possible mechanisms behind transmission, co-existence and other processes in the hospital settings. Process-based models need to be interrogated with data before being used as reliable tools for public health *(19)*. Investigations using simulation-based inference *(20)* tools usually focused on a single pathogen of interest such as (MRSA) *(10, 13, 21, 22)*, *P. aeuruginosa (4), C. difficil (23),* and *Vancomycin-resistant enterococci* (VRE) *(24)* using carriage detection *(10, 13, 22, 24)*, intensive care unit (ICU) clinical culture data *(4, 22)* or sequencing data *(23)*. Studies on the epidemiological characteristics of multiple co-circulating organisms in a single hospital network supported by real-world data are absent.

Understanding the transmission dynamics of healthcare-associated (HA) infections is challenging. The epidemiology and transmission HA infections differ from community-acquired (CA) infections in a number of important ways. First, hospital networks are open systems with significant variations in the daily and weekly admission rate ranging from 23% to 52% (See Figure 1A). Variations are explained by heterogeneous patient traffic at the building and ward scale (Results). In contrast, communities are relatively closed systems with individuals moving in or out at much lower rates. Second, as many bacterial species exist as commensals on the human hosts, detection of colonization is difficult and differential by body site. Indeed, patients with infections of the bloodstream or lower respiratory tract are more likely to be detected in hospitals than those colonized at other sites *(7, 25)*. Third, facilities within a single hospital system (e.g., infusion, pediatric, emergency wards, surgical, among others) may differ substantially in their control and surveillance of micro-organisms as well as in the hospital traffic features, a complication compounded by patient transfers between wards and hospital buildings (see SM Figure S1 for the patient transfer matrix at both spatial scales) *(26, 27)*. Fourth, a lack of observational data for communities of micro-organisms spreading among patients and the environment in the same hospital system often imposes further challenges in comparing its epidemiological features. Lastly, the emergence of strains with different genetic backgrounds that were once confined to hospital circulation such as CA-MRSA clone-USA300 in the United States with enhanced features compared to HA-MRSA makes epidemiology in communities and healthcare settings different *(8, 25)*.

In this study, we use a process agent-based model (ABM) and patient clinical culture data for seven prevalent pathogenic bacterial species collected in a major New York City (NYC) hospital system to address these challenges. The ABM is informed by real-world patient movement in the hospital system and incorporates importation of micro-organisms from the community, nosocomial transmission, decolonization via host clearance and patient transfer across hospital wards. To account for the heterogeneity of testing frequency and micro-organism prevalence among facilities, we used clinical testing records to design a patient-level observational model that mimics the detection of micro-organisms in hospitals. We fix the importation rates by surveying the literature and estimate nosocomial transmission and the likelihood of detection given carriage upon testing. We couple the ABM with a Bayesian inference algorithm and explore the identifiability of the system against simulated data. We estimate the two epidemiological features for eight pathogenic bacteria, which cause substantial mortality associated with AMR worldwide *(2)*. The ABM captures multiple sources of heterogeneity (e.g., patient length of stay, contact patterns, individual observational model, etc.) that otherwise cannot be represented by compartmental models. To simulate and quantify the transmission and detection of different micro-organisms using the same modeling-inference framework, we simplify the underlying biological details that are unique to each microparasitic infection. Our aim is, in consequence, to understand the general similarities and quantify epidemiological properties of communities of circulating bacteria among patients in hospitals. We show that while bacterial pathogens have different levels of importation rates, nosocomial transmission rates were similar suggesting similar levels of transmission for all. We also found the likelihood of detection is similar for all pathogens and its ordering is proportional to the reported abundance of bacteria.

**Results**

### *Empirical patterns of hospital traffic and heterogeneity of nosocomial infections burden*

In Figure 1A, we plotted weekly and monthly incidence using faded and solid lines respectively for *E. coli* (total positives cultures, n=2890), *K. pneumoniae* (n=1139), *P. aeruginosa* (n=809), MSSA (n=773), MRSA (n=486), *S. epidermidis* (n=694), *E. faecalis* (n=596) and *E. faecium (n=*263*)*. We deduplicated multiple positive clinical culture results during a patient visit, and consistently deduplicated them in the observational model. During the study period, the daily number of hospitalized patients fluctuated between 1,000 and 2,500 with most of the variation explained by differences in the day of the week (See solid line for daily and dashed line for weekly in Figure 1B). Daily numbers of new admissions ranged between 100 and 1,000, including outpatients. 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 ward occupancy per day during the study period, was heterogeneous (SM Figure S2A) 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. Average ward size was 9 considering all the wards and 20 excluding wards with ward size equal to 1.

Hospital-level variation in hospital traffic, admission and discharge rate, is explained mostly by the heterogeneity at the building scale in the hospital network with some ranging from 0-50% (See building traffic for Allen, Harkness Pavilion and Milstein hospitals in Supplementary Material Figure S1), and others with faster patient replacement between 80% to 150%, a consequence of admitting and discharching mostly outpatients (See Presbyterian hospital and Rest in SM Figure S3). This heterogeneity at the building scale is in turn explained by the variation across the ward traffic composing each building (See SM Figure S4 ward traffic). Discharges or outflux of patients at ward facility scale follows similar patterns as admissions with a few wards per building admitting the majority of patients per week and with stable patient traffic (See Figure 1C and SM Figure S4). This heterogeneity in admissions and hospitalizations is principally dictated by ward size that was also variable at the building scale (See SM Figure S2B for ward size distribution and SM Figure S5 for the linear relationship). To visualize patient traffic within each ward, we investigated temporal occupancy. Figure 1C shows the weekly number of patients relative to average occupancy for each ward and highlights the 5 most and least populated wards (see red and blue lines respectively); we only included wards with sizes greater than one for better visualization. The least populated wards were empty most of the time with irregular occupancy during the study period, whereas hospitalizations in the most populated wards were relatively stable. The relationship between newly admitted and hospitalized patients (Figures 1D and 1E) was linear and depended on ward size (see SM Figure S5). Clinical culture 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 (see Figure 1D). In SM Figure S6A we plotted the distribution of discharge rates at hospital and building level and in SM Figure S6B the distribution of time in hospital obtained from the patient hospitalization records, in average a person spent 3.85 days in the hospital, and 3.17, 4.18, 6.22, 5.05, 1.25 and 1.85 days in Allen Hospital, Harkness Pavilion, Milstein Hospital, Mschony, Presbyterian Hospital and a fictitious unit 'Rest' with all the other wards respectively.

### *Model framework and setting: micro-organism prevalence and effective sensitivity*

We assumed community-acquired carriage was at a steady state and in consequence parametrized the probability of importing a micro-organism from the community. Studies for the pathogens considered in the setting of the study, northern Manhattan, are limited. However, epidemiological observational studies show consistency in the range of human prevalence reported for each bacterial micro-organism worldwide. Other studies have also pointed at this stability in prevalence for resistant strains of *S. pneumoniae*, and *S. aureus (28)*. We searched the literature to inform the importation rate of each micro-organism as a proxy of the community prevalence. Our search terms include 'prevalence', 'colonization', 'carriage rate', and used reviews for some of the microparasites that report pooled estimates across different geographical locations. In the Supplementary Material section *Prevalence estimates* we include the different values, sources, and a brief description of the study, with the geographical location and population of interest. We reported the values used for the analysis in Table 1. In the following analyses, we fixed importation rates or of micro-organisms using the estimated community prevalence. We designed an individual-level observational model to quantify the likelihood of detection upon testing given an effective sensitivity or .

### *Identifiability: synthetic simulations and inference*

To investigate the identifiability of the model-inference system, we explored inferences on simulated trajectories with known parameters. We investigated if the model inference is capable of recovering parameters for a variety of parameter combinations: we fixed the importation rate to 25% and 50% and varied the effective sensitivity and the nosocomial transmission rate . The parameter estimates of the inference consistently captured the true parameter values for both detection rates and nosocomial transmission rates (See Figure 2A and 2B for equal to 25% and 50% respectively). In Figure 2 we show first how the model inference was able to explore different regions of the prior range (range of each axis), and second how the posterior captures the true parameter values. Inferences with were more biased but resulted in a broader distribution than inferences with . Estimates with both importation rates generally captured the truth, with only two instances that were substantially biased, see scenarios 2 and 4 in Figure 2. We visually inspect if the marginal posterior asymptotically converged to the true parameter values in the inference algorithm (see SM Figure S7A and S7B).

We investigated how statistical uncertainty and Monte Carlo error impact the inference (see *Making sense of bias* in Methods). Guided by numerical results, SM Figure S8A shows the goodness-of-fit can be linearly predicted by the oddness of the stochastic realization and SM Figure S8B shows the relation when controlling both by the statistical and Monte Carlo error.

We ran model simulations using parameters drawn from posterior distributions and compared them with simulations generated using the true parameters. We highlight the observation used to conduct inference and the mean trajectory across the simulations based on true parameters, defined as the true ensemble simulations (See SM Figure S9A.1 and S9B.1, for respectively). We find that, qualitatively, even biased inferences (scenarios 2 and 4 in Figure 2) reproduce well both the true ensemble simulations and the assimilated data. We quantified the calibration to study if observed uncertainty is replayed by the model displaying the reliability plot (see *Calibration of inference* in Methods) of both the inferred posterior and truth ensemble simulations (see SM Figure S9A.2 and S9B.2, for respectively). We found that the coverage of confidence intervals for both the posterior inference and true ensemble simulations were usually over the expected values (above the diagonal line), indicating the uncertainty in these simulations is typically higher than that in the observation data. Calibration of the inference and true ensemble simulations are similar, but is better for the true ensemble simulations, as expected. We found it depends on the magnitude of the nosocomial data: lower values of weekly incident simulated data (low and low ) resulted in less calibrated ensembles.

The last approach showed the performance of the model inference to solve the inverse problem in different regions of the parameter range. We studied its ability in parameter combination, pairs, whose simulated data reproduce the observed data aggregated at the hospital level (aggregation of buildings time series shown in Figure 1A) for each pathogenic bacteria. We used the middle prevalence of each bacterial micro-organism (see Table 1). We find the model-inference system was able to discriminate between the scenarios. This analysis covers a broad range of prevalences from 'low' to 'high' importation rates ; 4% and 16% for MRSA and *K. pneumoniae* to 50% and 70% for *E. faecium* and *E. coli* respectively.

### *Inference using real data*

We applied the model-inference system to estimate the epidemiological quantities of interest for eight different microbial bacterial pathogens. We compared joint posterior estimates of the effective sensitivity and nosocomial transmission rate in Figure 3. Posterior for the different values of are color-coded and indicated in the legend of each subplot. Species are sorted from the most abundant (*E. coli*) to the least (*E. faecium*) from left to right (see previous section *Empirical patterns and heterogeneity of micro-organism burden* for the total numbers). In Figure 3 we plotted the posterior joint estimates in the main plot to show how for most species (except MRSA) the system is able to localize the posterior in the same region of the prior range (range of each axis). We also plotted a zoomed version inside each subplot to highlight that the posterior inferences were sensitive to , i.e. both the mean (intersection of dashed lines) and the posterior estimate change (note that zoomed plots have different ranges in each axis). We find *E. coli* has the lowestestimated mean nosocomial transmission rate across the bacterium and the highest mean likelihoods of detection of 18.53%, 18.63%, and 17.31% for community prevalence of 55%, 63% and 70% respectively (see Table 2 for confidence intervals). *E. coli* is followed by *MSSA* with mean nosocomial transmission rates of 0.141, 0.121, and 0.0994 and likelihoods of detection of 1.63%, 1.65%, and 1.58% for prevalence of 25%, 29% and 35% respectively (Table 2 for 95% CI). For the rest of the micro-organisms, except MRSA and *E. faecalis*, we found that mean nosocomial transmission rate estimates are consistently between 0.17 and 0.19, and likelihoods of detection upon testing between 0.5% (*E. faecium)* to 2.5% (*K. pneumoniae*). Effective sensitivity was similar for all pathogens, except *E. coli*, and its ordering was proportional to the reported abundance of bacteria (see SM Figure S10B for marginal estimates for ). Mean nosocomial transmission estimates ordering did not follow the abundance of bacteria but were consistently between 0.15 and 0.2, except for *E. coli* and MSSA (see SM Figure S10A for marginal estimates for ). MSSA nosocomial transmission rate estimates were the second lowest with mean values between 0.099 and 0.14. For MRSA*,* we found that the model inference system found two solutions as a function of the value of . For equal to 5% and 10%, inference estimated high equal to 0.17 and 0.18 and low equal to 1.96 and 1.38 (See Table 2 for 95% CI); for the lowest community prevalence of 3.9%, inference estimated that the nosocomial transmission rate was 0.0017 and likelihood of detection upon testing was 17.15%. We compiled the mean posterior estimates and 95% CI for the different values of in Table 2.

To assess the goodness-of-fit of the modeled detected nosocomial infection to the observed, we simulated the dynamics using the posterior estimates of parameters and found that simulated detected nosocomial infections span the observed numbers at the hospital and building level for all micro-organisms (Figure 4A and SM Figure S11 for each spatial scale respectively). We produced reliability plots to examine whether the uncertainty in the observed data can be reproduced by model simulations (Methods). We found that the coverage of simulated CIs is slightly below expected values (under the diagonal line), indicating an uncertainty level biased low (Figure 4B). The model simulations allow estimation of the relative contributions of importation and nosocomial transmission to the overall burden of different bacterial pathogens as well as the prevalence in the hospital.

**Discussion**

Transmission is a fundamental property that governs epidemiological dynamics and is also a step in the life cycle of bacterial pathogens *(29)*. It is also one of the most challenging processes to understand and quantify. Estimating this property could improve understanding of the mechanism behind the risk of contagion and ultimately support improved control in healthcare systems. Nosocomial infection data have been the usual measure used to approximate and infer transmission; however it represents multiple factors of the surveillance system. Surveillance of micro-organism circulation in clinics is a product of patients who are being screened at the discretion of the clinicians and diagnostic of patients who present symptoms due to infection. Without additional data or knowledge on these factors, quantification of individual probabilities of detection is important. Quantifying it could help contextualize the design of better surveillance strategies in the hospital and understand trade-offs between screening and diagnosis to better detect carriers in hospitals.

We assumed the decolonization rate was constant for all micro-organisms. However, it is known for example that *S. pneumoniae* bacterial clearances are strain dependent *(28)*. Host clearance rates for the bacteria studied in this work are reported between 5 months to 2 years *(10, 24)*. In SM section *The ordinary differential equation* we show the basic reproductive number is non-sensitive to clearance rate given the fast replacement of patients in the hospital network. This plus the stochastic nature of the ABM and the desegregation of the transmission rate by building a time-varying contact network will make the inference robust to changes in the bacterial decolonization period (Methods).

The record of observed nosocomial infection (Figure 1A) is a stochastic realization among an ensemble of possible outcomes of an underlying stochastic process. In order to evaluate the ability of the system to infer key epidemiological parameters, we studied how the oddness of a stochastic realization impacts the estimate. We demonstrated the method is able to recover the parameters reliably across different levels of importation rates, nosocomial transmission rates and detection levels.

We used an individual-based computational model to enrich the dynamical representation of patient movement across the hospital network using patient records in a major New York City hospital network. We were able to accurately reproduce the observed data across the hospital and building levels. Our model absorbs both direct and indirect modes of transmission in the same parameter . Fast dynamics of patient traffic, from daily to weekly timescales, points to transmission possibly dominated by indirect modes of transmission, that do not depend on host-to-host contact, especially environmental or fomite as well as HCW-mediated transmission *(4, 30–35)*. In fact, the Center for Disease Control and Prevention (CDC) healthcare infection control webpage *(36, 37)* highlights the environment, surfaces and devices, as a common reservoir of germs in healthcare places. How does environmental transmission impact the force of infection? (linearly or non-linearly) and the timescales of bacterial clearance rates (survival times) in the environment will also be relevant questions for future research. Other limitations of the current study include the absence of information on the demographics, age profiles and co-morbidities of patients in the hospital network that are known to have differential susceptibility to bacterial acquisition and infection *(1)*(cite), which we therefore do not model.

Our observational model was designed to quantify in one parameter individual-level probabilities of testing, which absorbs imperfect sensitivity of the clinical cultures, probabilities of testing depending on the patient status and imperfect observation across body sites. All these factors contribute to the uncertainty in detecting carriage. In the SM section *Understanding the effective sensitivity* guided by a theoretical transmission model, we show that is in fact the result of interactions of 4 main mechanisms. We show it is a function of **i)** the biology of the infection of host-pathogen interaction, **ii)** properties of the clinical culture, that also compact heterogeneities across body sites, **iii)** hospital traffic and **iv)** hospital surveillance settings. Most of these factors are variables that cannot be controlled. Factors are intrinsic to the hospital dynamics or the clinical culture except hospital surveillance settings, screening and diagnostic, and by treating patients' infections the biology of host-pathogen interaction. Our mean estimates of except for *E. coli* (whose mean estimates were between 17.3% and 18.53%), were 'low' ranging from 0.5% to 2.5%. We show that there is a range of non-linear parameter combinations of the factors described above that could result in the estimated values of (see SM Figure S12 and SM section *Understanding the effective sensitivity* ). Research that clarifies the biology of the host-pathogen interaction in the hospital, specifically understanding the mechanism behind the transition from asymptomatic carriage to symptomatic infections as well as data availability about surveillance in the clinics, will permit further understanding of the estimated values. Ultimately, models that embed in their parameters probabilities of testing across a range of states of the host and model those states, such as asymptomatic carriage and symptomatic infection, will also help to have a quantitative framework to design better surveillance strategies.

We found that while *E. coli* has the highest likelihood of detection, it has the lowest nosocomial transmission rate, which is almost negligible, suggesting that most nosocomial infections can be associated with infections with host commensal strains that are not transmitted, as was reported empirically *(38)*. We found nosocomial transmission rates of *S. aureus* phenotypes were different, suggesting a difference in the fitness of the two strains. We found MSSAhas a lower nosocomial transmission rate than MRSA. The enormous known diversity of *S. aureus* hampers our understanding and discussion of the possible source of the difference. From differences in fitness and dynamical interactions of CA-MRSA and HA-MRSA *(8, 25)* to different levels of resistance in different strains *(39)* and within-host dynamics *(5, 14, 39, 40)*. As well as between-species interactions *(41)*. Further research that represents in the same framework dynamics of MSSA and MRSA in hospital settings could improve understanding of the sources of the estimated differences.

The current work exploits the availability of individual-level patient records to estimate the transmission properties and detection of pathogenic bacteria in hospital settings. Individual-level data and models can be employed in future research to understand the impact of individual-level interventions on disease control, such as the disinfection of shared medical devices to diminish the risk of contagion (CDC recommendations). Additionally, using an ABM allows to test counterfactual scenarios of individual-level interventions that replace infections caused by resistant strains with infections caused by sensitive strains to quantify the impact of resistance at the hospital level and its broader implications to resistance emergence *(1)*.

**Materials and Methods**

### *Overview*

To estimate key epidemiological characteristics of bacterial pathogens, we developed an ABM to simulate the dynamics of these organisms in hospital settings. The model was informed by patient hospitalization and clinical 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 nosocomial infection data, validated the ability of this ABM inference system to identify likelihood of detection and nosocomial transmission rates. The process model, as is an ABM, tracks the state of patients at daily time scales. Patients were either susceptible to colonization or carriers with a micro-organism (See *The transmission model* in Methods). The observational model designed at the individual level allows us to map from the carriers to detected individuals via a simulated clinical culture (See *The individual observational model* in Methods). We parametrize the patient observational model with a likelihood of detection given carriage upon testing given the effective sensitivity or . Data assimilation is conducted at the building level therefore we consistently aggregate simulated patient detections at this scale (See *Hospital-level observational model* in Methods). We then assimilated the clinical culture data and estimated the effective sensitivity and nosocomial transmission rates for eight co-circulating bacterial pathogens. Using these estimated parameters and the ABM, we were able to reproduce the time series of positive cases for five major buildings in the hospital network and the aggregation of all the other wards in a fictitious unit 'Rest'. The estimated effective sensitivity and nosocomial transmission rates were compared for the eight pathogens.

### *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 221 wards of different types including emergency, infusion, cardiology, pediatrics, etc. Hospitalization and clinical culture 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. The dates and wards in which each patient stayed during hospitalization were used to construct a time-evolving contact network. Clinical culture records to confirm nosocomial infection were available for the eight most prevalent organisms in the hospital system: *E. coli*, *K. pneumoniae,* *P. aeruginosa*, methicillin-susceptible *S. aureus* (MSSA), MRSA, *S. epidermidis*, *E. faecalis* and *E. faecium*. 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 and it's buildings (SM Figure S13) and in the wards in each hospital (SM Figure S14), which show a similar order in cultures across the hospital but substantial heterogeneity inside the hospital at the ward scale.

### *The transmission model*

We use a process ABM to simulate transmission in the study hospital system *(10)*. For the ABM, the patient-to-patient daily contact networks were 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 pathogens and share the same environment. 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 converted to carriers proportional to the number of patients in the ward carrying a particular micro-organism. 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 days *(12)*. Colonization in hospitals is 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 but keep track of patient states on consecutive days and assumed their colonization status did not change. 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 define a frequency-dependent transmission rate per ward as , where is the average ward daily occupancy (See *Empirical patterns of hospital traffic and heterogeneity of nosocomial infections burden* in Results). 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 shown below by, where is the decolonization period of patient .

### *The individual observational model*

Colonized patients may develop clinical infections due to the 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 variables *(1, 6)*. Other individuals carrying pathogens may be discovered through routine screening or cultures ordered discretionarily by clinicians for patients without clinical manifestations. In the process ABM, we did not explicitly distinguish between colonized and clinically infected patients. Instead, we apply an observational to encapsulate detection of 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 micro-organisms across wards. 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).

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. For instance, blood cultures of a patient colonized by *E. coli* in the urinary tract will likely test negative, and this patient may not necessarily present symptoms. This compounded with differential detection of screening and diagnosis makes the parametrization challenging. To define our observational model, we therefore estimated the ‘effective sensitivity’ of detecting colonization upon testing defined by the culture data, i.e. the probability of identifying carriage given that the patient is carrying a particular micro-organism. 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 that colonization or infection exists anywhere on a patient as well as probability of detection depending on the state of the patient (colonization, and infection). The defined observational model indicates the likelihood that a colonized patient is detected given the effective sensitivity or .

### *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 used the building aggregation to sum the number of nosocomial infection data and perform inference. SM Figure S12 shows the number of clinical cultures per building, we merge buildings composed mostly by outpatients and with few clinical cultures into a fictitious unit presented as 'Rest'. The number of transfers between wards is shown in SM Figure S1. Wards within each identified building have more frequent within-building 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 *(42, 43)*. This framework has been applied to many infectious diseases, including influenza, dengue, malaria, cholera, Ebola, enterovirus D68, and COVID-19 *(44–53)*, typically 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 17. For this ABM system, we solve the inverse problem without solving the filtering problem and therefore only estimate parameters, i.e., infer the effective sensitivity and the nosocomial transmission rate , without re-adjusting the state space.

We use the ensemble adjustment Kalman filter (EAKF *(42)*), 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 (cite). We assimilated weekly observations of nosocomial infection detections for micro-organisms using an iterated filtering framework (IF). Iterated filtering for dynamical systems was proposed in the context of epidemiology using particle filters or sequential Monte Carlo *(54, 55)*, but has also been proposed in the context of inverse problems using Kalman filters *(56, 57)*. We base most of our implementation in the algorithms proposed in the epidemiological context but grab some ideas from the algorithms using Kalman filters. The implementation of the IF-EAKF in Python was made using the packages NumPy and SciPy *(58, 59)*. Further details and hyperparameters for this implementation are available in the Supplementary Material section Simulation-based inference framework.

### *Identifiability: Synthetic simulations and inference*

To verify that the simulation-based inference system is able to accurately estimate the two key epidemiological parameters, we first investigated the identifiability of the system using simulated data (i.e., the ability of the framework to infer the parameters when they are known). We generate synthetic observations of incident micro-organism colonization using the ABM and assigned effective sensitivity and nosocomial transmission rates . The synthetic observations were then assimilated into the full model-inference system to assess the system ability to accurately estimate the parameters.

*Identifiability: Making sense of the bias*

In the synthetic inferences the true parameters **P** are known and the simulator allows repetition of the experiment. We define the oddness of a stochastic realization as the average Continuous Ranked Probability Score (CRPS) over data assimilation times between an ensemble and a single stochastic realization. Additionally, the parameters of the simulator are known to impact the spread of the simulated data (statistical uncertainty) *(50, 60)* (Bolker and Grenfell). In consequence, we define the ensemble spread using the CRPS of ensemble simulations and its mean. Ensemble spread is a common measure in weather forecasting but is usually computed as the average deviation of an ensemble of trajectories from the mean. The CRPS is defined as shown below, F is the cumulative density distribution computed from the ensembles and y is a trajectory *(61, 62)*. is the indicator function where if or otherwise. The CRPS is in fact a standard proper score to evaluate epidemic forecasts *(61)*.

In synthetic tests, inferences about the mean trajectory could be made. The resulting inferred parameter density provides a benchmark of the method given the noise-less signal possible. Quality of inferred parameter densities conducted on single stochastic realizations can be weighted by the goodness-of-fit of the benchmark . We measure the goodness-of-fit of a posterior density given **P** as proposed in *(57)*. Specifically, the inferred posterior can be parametrized with a vector of means , and a covariance matrix and the goodness-of-fit assessed with the L2 norm scaled by , as shown below.

We first studied how the oddness of the observation explain the goodness-of-fit of the inferred parameters (SM Figure S7A). In this controlled experiment the true parameters and the ensemble spread are known. Monte Carlo errors *(63)* are controlled by normalizing by and removing statistical uncertainty . In SM Figure S7B we show the controlled goodness-of-fit of against the normalized oddness (Figure S7B).

### *Inference using real-world data*

We next used actual weekly observations for the six buildings to infer the epidemiological parameters for all eight bacterial pathogens. The model-inference framework was applied to each bacteria separately. To account for uncertainty in the reported estimates for community prevalence for the pathogens (See Result section *Model framework and setting: micro-organism prevalence and effective sensitivity* and Table 1) we conducted inferences on 3 values for the importation rate . We, therefore, studied the sensitivity of the simulation-based inference to this parameter. The values are related to high, middle and low importation rate values based on the literature review, also providing a picture of the uncertainty obtained for the estimates for and not only capture by the uncertainty in the process model.

### *Calibration of inferences*

We measure the consistency of the modeled nosocomial detection and the observed ones statistically. We produced reliability plots *(64)*. 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.

**List of Supplementary Materials**

### *Supplementary Materials and Methods*

* Prevalence estimates.
* The ordinary differential equation.
* Understanding the effective sensitivity .
* Simulation-based inference framework.

### *Supplementary Material Figures*

* Figure S1. Transfer matrices at the ward and building levels (done).
* Figure S2. Ward size distribution (done).
* Figure S3. Hospital traffic at the building level (done).
* Figure S4. Hospital traffic at the ward level (done).
* Figure S5. Relationship between hospitalizations-admissions (done).
* Figure S6. Length of stay distributions at hospital and building levels (done).
* Figure S7. Convergence plots of inferences for synthetic data (done).
* Figure S8. Goodness-of-fit of posterior inferences on synthetic data, Monte Carlo and statistical uncertainty analysis (done).
* Figure S9. Hospital-level simulation of synthetic tests and calibration (done).
* Figure S10. Marginal posterior parameter estimates for each pathogen (done).
* Figure S11. Simulation with posterior parameter estimates at the building level and calibration for each pathogen.
* Figure S12. Understanding the effective sensitivity (done).
* Figure S13. Total clinical cultures in each hospital and its buildings.
* Figure S14. Clinical cultures per ward.

**Acknowledgments**

This study was supported by funding from the Centers for Disease Control and Prevention U01CK000592 and 75D30122C14289. We thank Matteo Perini, the Shaman lab and the CDC Modeling Infectious Diseases in Healthcare Network (MInD – Healthcare) for comments and discussions.

**Author Contributions:**

Conceptualization: J.C.V., A.C.U., S.P. and J.S.

Data curation: J.Z. and L.W.

Data processing: J.C.V. and R.Y.

Methodology: J.C.V., T.R., S.P. and J.S.

Investigation: J.C.V., R.Y., A.C.U., J.Z., S.P. and J.S.

Visualization: J.C.V.

Funding acquisition: S.P. and J.S.

Project administration: J.C.V., S.P. and J.S.

Supervision: S.P. and J.S.

Writing - original draft: J.C.V.

Writing - review & editing: 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.

**Data and materials availability:** All data, code, and materials used in the analysis must be available in some form to any researcher for purposes of reproducing or extending the analysis. Include a note explaining any restrictions on materials, such as materials transfer agreements (MTAs). Note accession numbers to any data relating to the paper and deposited in a public database; include a brief description of the data set or model with the number. If all data are in the paper and supplementary materials, include the sentence “All data are available in the main text or the supplementary materials.”

**Keywords:** epidemiology, microorganisms, antimicrobial resistance, Bayesian inference, individual-based model, agent-based model, inverse problems

**Figures and Tables:**

Main Text

Figures 1 to 6

Figure 1. Data figure. A) observed data. B) Timeseries for hospitalizations, admissions and discharges. C) Ward level weekly occupancy (hospitalizations normalized by ward size). D) Heatmap with ward-level number of tests. E) Heatmap with ward-level number of admissions.

Figure 2. Posterior joint inferences on simulated data. A) \gamma=25%, B) \gamma=50%.

Figure 3. Posterior joint inferences on observed data.

Figure 4. Simulation with parameter estimates to assess fit at the hospital. A) Hospital level fit. B) Reliability plots.

Tables 1 to 2

             Table 1. Values of \gamma used for sensitivity - ranges reported.

             Table 2. Posterior parameters estimates and 95% CI for all micro-organisms

**A picture containing text, line, plot, font

Description automatically generated**

**Figure 1. Data: empirical colonization of microbial organisms, hospital admissions and number of clinical cultures.** **A)** Nosocomial infection data for pathogenic bacteria studied, faded dots are the weekly incident and solid lines the monthly incident detections, from left to right and upper to lower plots: *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *MSSA*, *MRSA*, *S. epidermis,* *E. faecalis* and *E. faecium*. **B)** Numbers of hospitalized (green), admitted patients (salmon) and discharged 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); red lines show the 5 most populated wards, blue lines the 5 least populated, and the remaining wards are shown in gray in the background. We remove wards with ward size equal to 1 for better visualisation. **D)** Heatmap showing the number of weekly cultures in each ward during the study period. **E)** Heatmap showing the number of patients admitted weekly to each ward during the study period.

**A picture containing text, screenshot, line, number

Description automatically generated**

**Figure 2. Identifiability, posterior estimates.** Joint posterior estimates for **A)** importation rate =25% and **B)** =50%. The posterior estimate is highlighted with a density plot (darker means more probable), and posterior ensemble members are shown as purple dots. In each subplot the true value used for simulating the stochastic trajectory to infer is highlighted in the title of each scenario, with a yellow cross and the intersection of the two black dashed lines. x-axis shows the effective sensitivity (%) and y-axis the nosocomial transmission rate . Note that in both **A)** and **B)** the prior range is the limits of each axis, increments from left to right and from upper to lower plots.

**A picture containing screenshot

Description automatically generated**

**Figure 3. Posterior parameter estimates.** Joint estimates for the effective sensitivity (%) (x-axis) and the nosocomial transmission rate (y-axis). Importation rate values for sensitvity analysis are color-coded with high, medium and low prevalences, and indicated in each subplot. Color-coded dashed lines show the mean estimates, and posterior is shown with both a density plot (darker indicates more probable) and with the posterior ensemble members plotted as dots.

**A collage of graphs

Description automatically generated with low confidence**

**Figure 4. Hospital level fit (not used for data assimilation):** **A)** Ensemble simulation of modeled nosocomial data with estimated parameters, solid lines show the mean and ribbons the 95% CI. Importation rate is highlighted in the legend and color-coded for high, medium and low prevalences in all plots. Weekly nosocomial infection data is displayed with red dots. **B)** Reliability plot (Methods). Hospital-level fit with 4 different confidence intervals (25%, 50%, 75%, 95%). Importation rate is color-coded. The black dotted line is the reference perfect calibration.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| *E. coli* |  |  |  |
| *K. pneumoniae* |  |  |  |
| *P. aeruginosa* |  |  |  |
| MSSA |  |  |  |
| MRSA |  |  |  |
| *S. epidermis* |  |  |  |
| *E. faecalis* |  |  |  |

**Table 1.** Human prevalence range from the literature, we present the 3 values used in the inferences (SI *Prevalence estimates)*.

**Table 2.** **Parameter estimates**. Posterior estimates for the eight bacterial pathogens; the value for the importation rate γ is shown in the second column. Nosocomial transmission rates β is presented as rate per day in the third column and likelihoods of detection upon testing in the fourth column.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Importation rate, (%)** | **Nosocomial transmission rate**  **Mean (95% CI)** | **Effective sensitivity (%)**  **Mean (95% CI)** |
| *E. coli* | 55 | 2.54E-03 (1.72E-03, 3.58E-03) | 18.53 (17.30, 19.43) |
|  | 63 | 8.66E-04 (3.78E-04, 1.58E-03) | 18.63 (17.85, 19.23) |
|  | 70 | 9.62E-04 (4.06E-04, 1.73E-03) | 17.31 (16.33, 18.02) |
| *K. pneumoniae* | 15 | 0.187 (0.180, 0.194) | 2.51 (2.36, 2.65) |
|  | 23 | 0.189 (0.180, 0.195) | 2.14 (1.98, 2.29) |
|  | 35 | 0.181 (0.165, 0.193) | 2.05 (1.92, 2.17) |
| *P. aeruginosa* | 11.6 | 0.189 (0.183, 0.194) | 1.93 (1.78, 2.07) |
|  | 18.8 | 0.190 (0.182, 0.195) | 1.61 (1.47, 1.75) |
|  | 25 | 0.187 (0.178, 0.194) | 1.55 (1.43, 1.67) |
| *MSSA* | 25 | 0.141 (0.122, 0.164) | 1.63 (1.47, 1.79) |
|  | 29 | 0.121 (0.103, 0.140) | 1.65 (1.49, 1.81) |
|  | 35 | 9.94E-02 (8.43E-02, 0.116) | 1.58 (1.40, 1.73) |
| *MRSA* | 10 | 0.170 (0.136, 0.184) | 1.38 (1.21, 1.60) |
|  | 3.9 | 1.70E-02 (9.16E-03, 2.74E-02) | 17.15 (12.48, 18.96) |
|  | 5 | 0.182 (0.168, 0.190) | 1.96 (1.72, 2.19) |
| *S. epidermidis* | 58 | 0.171 (0.117, 0.190) | 1.24 (1.12, 1.35) |
|  | 75 | 0.174 (0.134, 0.190) | 1.21 (1.10, 1.33) |
|  | 90 | 0.173 (0.107, 0.189) | 1.23 (1.12, 1.36) |
| *E. faecalis* | 36 | 0.167 (0.121, 0.186) | 1.05 (0.96, 1.17) |
|  | 47.6 | 0.149 (9.69E-02, 0.182) | 1.07 (0.96, 1.19) |
|  | 55.0 | 0.159 (0.101, 0.185) | 1.09 (0.96, 1.21) |
| *E. faecium* | 36.8 | 0.182 (0.163, 0.192) | 0.58 (0.54, 0.63) |
|  | 40.6 | 0.179 (0.147, 0.191) | 0.57 (0.54, 0.65) |
|  | 50.0 | 0.178 (0.123, 0.193) | 0.58 (0.54, 0.66) |

**References**

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

2. C. J. Murray, K. S. Ikuta, F. Sharara, L. Swetschinski, G. Robles Aguilar, A. Gray, C. Han, C. Bisignano, P. Rao, E. Wool, S. C. Johnson, A. J. Browne, M. G. Chipeta, F. Fell, S. Hackett, G. Haines-Woodhouse, B. H. Kashef Hamadani, E. A. P. Kumaran, B. McManigal, R. Agarwal, S. Akech, S. Albertson, J. Amuasi, J. Andrews, A. Aravkin, E. Ashley, F. Bailey, S. Baker, B. Basnyat, A. Bekker, R. Bender, A. Bethou, J. Bielicki, S. Boonkasidecha, J. Bukosia, C. Carvalheiro, C. Castañeda-Orjuela, V. Chansamouth, S. Chaurasia, S. Chiurchiù, F. Chowdhury, A. J. Cook, B. Cooper, T. R. Cressey, E. Criollo-Mora, M. Cunningham, S. Darboe, N. P. J. Day, M. De Luca, K. Dokova, A. Dramowski, S. J. Dunachie, T. Eckmanns, D. Eibach, A. Emami, N. Feasey, N. Fisher-Pearson, K. Forrest, D. Garrett, P. Gastmeier, A. Z. Giref, R. C. Greer, V. Gupta, S. Haller, A. Haselbeck, S. I. Hay, M. Holm, S. Hopkins, K. C. Iregbu, J. Jacobs, D. Jarovsky, F. Javanmardi, M. Khorana, N. Kissoon, E. Kobeissi, T. Kostyanev, F. Krapp, R. Krumkamp, A. Kumar, H. H. Kyu, C. Lim, D. Limmathurotsakul, M. J. Loftus, M. Lunn, J. Ma, N. Mturi, T. Munera-Huertas, P. Musicha, M. M. Mussi-Pinhata, T. Nakamura, R. Nanavati, S. Nangia, P. Newton, C. Ngoun, A. Novotney, D. Nwakanma, C. W. Obiero, A. Olivas-Martinez, P. Olliaro, E. Ooko, E. Ortiz-Brizuela, A. Y. Peleg, C. Perrone, N. Plakkal, A. Ponce-de-Leon, M. Raad, T. Ramdin, A. Riddell, T. Roberts, J. V. Robotham, A. Roca, K. E. Rudd, N. Russell, J. Schnall, J. A. G. Scott, M. Shivamallappa, J. Sifuentes-Osornio, N. Steenkeste, A. J. Stewardson, T. Stoeva, N. Tasak, A. Thaiprakong, G. Thwaites, C. Turner, P. Turner, H. R. van Doorn, S. Velaphi, A. Vongpradith, H. Vu, T. Walsh, S. Waner, T. Wangrangsimakul, T. Wozniak, P. Zheng, B. Sartorius, A. D. Lopez, A. Stergachis, C. Moore, C. Dolecek, M. Naghavi, Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* **399**, 629–655 (2022).

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

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

5. N. G. Davies, S. Flasche, M. Jit, K. E. Atkins, Within-host dynamics shape antibiotic resistance in commensal bacteria. *Nat Ecol Evol* **3**, 440–449 (2019).

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

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

8. R. Kouyos, E. Klein, B. Grenfell, B. R. Levin, Ed. Hospital-Community Interactions Foster Coexistence between Methicillin-Resistant Strains of Staphylococcus aureus. *PLoS Pathog* **9**, e1003134 (2013).

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

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

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

12. B. S. Cooper, G. F. Medley, S. P. Stone, C. C. Kibbler, B. D. Cookson, J. A. Roberts, G. Duckworth, R. Lai, S. Ebrahim, 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).

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

14. D. R. Smith, L. Temime, L. Opatowski, Microbiome-pathogen interactions drive epidemiological dynamics of antibiotic resistance: A modeling study applied to nosocomial pathogen control. *eLife* **10**, e68764 (2021).

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

16. D. J. Austin, K. G. Kristinsson, R. M. Anderson, 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).

17. S. E. Drohan, S. A. Levin, B. T. Grenfell, R. Laxminarayan, Incentivizing hospital infection control. *Proc Natl Acad Sci USA* **116**, 6221–6225 (2019).

18. S. Lehtinen, F. Blanquart, M. Lipsitch, C. Fraser, Mechanisms that maintain coexistence of antibiotic sensitivity and resistance also promote high frequencies of multidrug resistance. .

19. G. M. Knight, N. G. Davies, C. Colijn, F. Coll, T. Donker, D. R. Gifford, R. E. Glover, M. Jit, E. Klemm, S. Lehtinen, J. A. Lindsay, M. Lipsitch, M. J. Llewelyn, A. L. P. Mateus, J. V. Robotham, M. Sharland, D. Stekel, L. Yakob, K. E. Atkins, Mathematical modelling for antibiotic resistance control policy: do we know enough? *BMC Infect Dis* **19**, 1011 (2019).

20. K. Cranmer, J. Brehmer, G. Louppe, The frontier of simulation-based inference. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 30055–30062 (2020).

21. A. S. de Vos, S. J. de Vlas, J. A. Lindsay, M. E. E. Kretzschmar, G. M. Knight, Understanding MRSA clonal competition within a UK hospital; the possible importance of density dependence. *Epidemics* **37**, 100511 (2021).

22. M. Forrester, A. Pettitt, G. Gibson, Bayesian inference of hospital-acquired infectious diseases and control measures given imperfect surveillance data. *Biostatistics* **8**, 383–401 (2007).

23. D. W. Eyre, M. Laager, A. S. Walker, B. S. Cooper, D. J. Wilson, on behalf of the CDC Modeling Infectious Diseases in Healthcare Program (MInD-Healthcare), R. D. Kouyos, Ed. Probabilistic transmission models incorporating sequencing data for healthcare-associated Clostridioides difficile outperform heuristic rules and identify strain-specific differences in transmission. *PLoS Comput Biol* **17**, e1008417 (2021).

24. B. S. Cooper, G. F. Medley, S. J. Bradley, G. M. Scott, An Augmented Data Method for the Analysis of Nosocomial Infection Data. *American Journal of Epidemiology* **168**, 548–557 (2008).

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

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

27. the EuSCAPE Working Group, the ESGEM Study Group, S. David, S. Reuter, S. R. Harris, C. Glasner, T. Feltwell, S. Argimon, K. Abudahab, R. Goater, T. Giani, G. Errico, M. Aspbury, S. Sjunnebo, E. J. Feil, G. M. Rossolini, D. M. Aanensen, H. Grundmann, Epidemic of carbapenem-resistant Klebsiella pneumoniae in Europe is driven by nosocomial spread. *Nat Microbiol* **4**, 1919–1929 (2019).

28. S. Lehtinen, F. Blanquart, N. J. Croucher, P. Turner, M. Lipsitch, C. Fraser, Evolution of antibiotic resistance is linked to any genetic mechanism affecting bacterial duration of carriage. *Proc. Natl. Acad. Sci. U.S.A.* **114**, 1075–1080 (2017).

29. R. M. Anderson, R. M. May, Population biology of infectious diseases: Part I. *Nature* **280**, 361–367 (1979).

30. D. J. Weber, D. Anderson, W. A. Rutala, The role of the surface environment in healthcare-associated infections: *Current Opinion in Infectious Diseases* **26**, 338–344 (2013).

31. E. Tajeddin, M. Rashidan, M. Razaghi, S. S. S. Javadi, S. J. Sherafat, M. Alebouyeh, M. R. Sarbazi, N. Mansouri, M. R. Zali, The role of the intensive care unit environment and health-care workers in the transmission of bacteria associated with hospital acquired infections. *Journal of Infection and Public Health* **9**, 13–23 (2016).

32. R. W. Loftus, J. R. Brown, M. D. Koff, S. Reddy, S. O. Heard, H. M. Patel, P. G. Fernandez, M. L. Beach, H. L. Corwin, J. T. Jensen, D. Kispert, B. Huysman, T. M. Dodds, K. L. Ruoff, M. P. Yeager, Multiple Reservoirs Contribute to Intraoperative Bacterial Transmission. *Anesthesia & Analgesia* **114**, 1236–1248 (2012).

33. L. Chaoui, R. Mhand, F. Mellouki, N. Rhallabi, Contamination of the Surfaces of a Health Care Environment by Multidrug-Resistant (MDR) Bacteria. *International Journal of Microbiology* **2019**, 1–7 (2019).

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

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

36. Center for Disease Control and Prevention, Learn About Infection Control in Health Care (available at https://www.cdc.gov/infectioncontrol/projectfirstline/healthcare.html).

37. Center for Disease Control and Prevention, Learn Where Germs Live in Health Care (available at https://www.cdc.gov/infectioncontrol/projectfirstline/healthcare/where-germs-live.html).

38. A. D. Harris, M. Kotetishvili, S. Shurland, J. A. Johnson, J. G. Morris, L. L. Nemoy, J. K. Johnson, How important is patient-to-patient transmission in extended-spectrum β-lactamase Escherichia coli acquisition. *American Journal of Infection Control* **35**, 97–101 (2007).

39. Q. Leclerc, A. Clements, H. Dunn, J. Hatcher, J. A. Lindsay, L. Grandjean, G. M. Knight, *Quantifying patient- and hospital-level antimicrobial resistance dynamics in* Staphylococcus aureus *from routinely collected data* (Epidemiology, 2023; http://medrxiv.org/lookup/doi/10.1101/2023.02.15.23285946).

40. B. J. Arnold, I.-T. Huang, W. P. Hanage, Horizontal gene transfer and adaptive evolution in bacteria. *Nat Rev Microbiol* **20**, 206–218 (2022).

41. M. E. Schoen, M. A. Jahne, J. Garland, L. Ramirez, A. J. Lopatkin, K. A. Hamilton, Quantitative Microbial Risk Assessment of Antimicrobial Resistant and Susceptible *Staphylococcus aureus* in Reclaimed Wastewaters. *Environ. Sci. Technol.* **55**, 15246–15255 (2021).

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

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

44. R. Subramanian, Q. He, M. Pascual, Quantifying asymptomatic infection and transmission of COVID-19 in New York City using observed cases, serology, and testing capacity. *PNAS* **118** (2021), doi:10.1073/pnas.2019716118.

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

46. M. Santos-Vega, P. P. Martinez, K. G. Vaishnav, V. Kohli, V. Desai, M. J. Bouma, M. Pascual, The neglected role of relative humidity in the interannual variability of urban malaria in Indian cities. *Nat Commun* **13**, 533 (2022).

47. R. Li, S. Pei, B. Chen, Y. Song, T. Zhang, W. Yang, J. Shaman, Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science* **368**, 489–493 (2020).

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

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

50. S. Pei, M. A. Cane, J. Shaman, V. E. Pitzer, Ed. Predictability in process-based ensemble forecast of influenza. *PLoS Comput Biol* **15**, e1006783 (2019).

51. S. W. Park, M. Pons-Salort, K. Messacar, C. Cook, L. Meyers, J. Farrar, B. T. Grenfell, Epidemiological dynamics of enterovirus D68 in the United States and implications for acute flaccid myelitis. *Sci. Transl. Med.* **13**, eabd2400 (2021).

52. W. Yang, S. Kandula, M. Huynh, S. K. Greene, G. V. Wye, W. Li, H. T. Chan, E. McGibbon, A. Yeung, D. Olson, A. Fine, J. Shaman, 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).

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

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

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

56. D. Sanz-Alonso, A. M. Stuart, A. Taeb, Inverse Problems and Data Assimilation (2023) (available at http://arxiv.org/abs/1810.06191).

57. D. Z. Huang, T. Schneider, A. M. Stuart, Iterated Kalman Methodology For Inverse Problems (2022) (available at http://arxiv.org/abs/2102.01580).

58. C. R. Harris, K. J. Millman, S. J. van der Walt, R. Gommers, P. Virtanen, D. Cournapeau, E. Wieser, J. Taylor, S. Berg, N. J. Smith, R. Kern, M. Picus, S. Hoyer, M. H. van Kerkwijk, M. Brett, A. Haldane, J. F. del Río, M. Wiebe, P. Peterson, P. Gérard-Marchant, K. Sheppard, T. Reddy, W. Weckesser, H. Abbasi, C. Gohlke, T. E. Oliphant, Array programming with NumPy. *Nature* **585**, 357–362 (2020).

59. P. Virtanen, R. Gommers, T. E. Oliphant, M. Haberland, T. Reddy, D. Cournapeau, E. Burovski, P. Peterson, W. Weckesser, J. Bright, S. J. van der Walt, M. Brett, J. Wilson, K. J. Millman, N. Mayorov, A. R. J. Nelson, E. Jones, R. Kern, E. Larson, C. J. Carey, İ. Polat, Y. Feng, E. W. Moore, J. VanderPlas, D. Laxalde, J. Perktold, R. Cimrman, I. Henriksen, E. A. Quintero, C. R. Harris, A. M. Archibald, A. H. Ribeiro, F. Pedregosa, P. van Mulbregt, SciPy 1.0 Contributors, A. Vijaykumar, A. P. Bardelli, A. Rothberg, A. Hilboll, A. Kloeckner, A. Scopatz, A. Lee, A. Rokem, C. N. Woods, C. Fulton, C. Masson, C. Häggström, C. Fitzgerald, D. A. Nicholson, D. R. Hagen, D. V. Pasechnik, E. Olivetti, E. Martin, E. Wieser, F. Silva, F. Lenders, F. Wilhelm, G. Young, G. A. Price, G.-L. Ingold, G. E. Allen, G. R. Lee, H. Audren, I. Probst, J. P. Dietrich, J. Silterra, J. T. Webber, J. Slavič, J. Nothman, J. Buchner, J. Kulick, J. L. Schönberger, J. V. de Miranda Cardoso, J. Reimer, J. Harrington, J. L. C. Rodríguez, J. Nunez-Iglesias, J. Kuczynski, K. Tritz, M. Thoma, M. Newville, M. Kümmerer, M. Bolingbroke, M. Tartre, M. Pak, N. J. Smith, N. Nowaczyk, N. Shebanov, O. Pavlyk, P. A. Brodtkorb, P. Lee, R. T. McGibbon, R. Feldbauer, S. Lewis, S. Tygier, S. Sievert, S. Vigna, S. Peterson, S. More, T. Pudlik, T. Oshima, T. J. Pingel, T. P. Robitaille, T. Spura, T. R. Jones, T. Cera, T. Leslie, T. Zito, T. Krauss, U. Upadhyay, Y. O. Halchenko, Y. Vázquez-Baeza, SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods* **17**, 261–272 (2020).

60. D. Alonso, A. J. McKane, M. Pascual, Stochastic amplification in epidemics. *J. R. Soc. Interface.* **4**, 575–582 (2007).

61. J. Bracher, E. L. Ray, T. Gneiting, N. G. Reich, V. E. Pitzer, Ed. Evaluating epidemic forecasts in an interval format. *PLoS Comput Biol* **17**, e1008618 (2021).

62. T. Gneiting, F. Balabdaoui, A. E. Raftery, Probabilistic Forecasts, Calibration and Sharpness. *Journal of the Royal Statistical Society Series B: Statistical Methodology* **69**, 243–268 (2007).

63. E. L. Ionides, C. Breto, J. Park, R. A. Smith, A. A. King, Monte Carlo profile confidence intervals for dynamic systems. *J. R. Soc. Interface.* **14**, 20170126 (2017).

64. The International Research Institute for Climate and Society, Description of the IRI Climate Forecast Verification Scores (available at https://journals.plos.org/ploscompbiol/article/file?id=10.1371/journal.pcbi.1006783&type=printable).