**Supplementary material**

Manuscript: Trends in Infection Incidence and Antimicrobial Resistance in the US Veterans Affairs Healthcare System: A Nationwide Retrospective Cohort Study (2007-2022)

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# S1 Data

## S1.1 Databases

The main source for the data used in this study was the Veterans Affairs Corporate Data Warehouse (CDW), which is a national repository that includes clinical and administrative data from the VHA. These data are updated on a continual basis and additional information can be found here: <https://www.hsrd.research.va.gov/for_researchers/cdw.cfm>

Two large datasets were generated from the Veterans Health administration’s (VHA’s) electronic health records with over 15 years of data from all patients admitted to acute care wards (either medical/surgical wards or ICUs) from Veterans Affairs Medical Centers (VAMCs) between 1st January 2007 and 31st March 2022 for the analyses of this study. We excluded facilities from the study if they did not provide acute care or if they did not report data to the VA’s facility complexity assessment1,2 (e.g., level and type of care provided) in all eligible years during the study period. In total, we included data from 138 VAMCs .

The first dataset represents a hospital-day level dataset for all acute care hospitalizations and any administered antibiotics on those days and contains over 50,000,000 hospital days. It includes information on patient demographics, comorbidities, mortality, readmission information, risk factors, and primary diagnosis categories. We used days of therapy divided by occupied bed days (bed days of care) as the primary measure of antibiotic use, in concordance with National Health Safety Network (NHSN) guidelines for electronic reporting of antibiotic utilization data.3

The second dataset includes all microbiology cultures of the nine target organisms (*Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* *cloacae*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter sp*.), and their antibiotic susceptibility patterns. For our analysis, we considered only positive clinical cultures and removed any surveillance cultures. These clinical cultures were obtained only when infection is suspected in symptomatic individuals. The systemic antibiotics were broken out by specific antibiotics (Table S1) and antibiotic (sub)class, and by Standardized Antimicrobial Administration Ratio (SAAR) antimicrobial category.4 The antibiotic susceptibility test (AST) results for the key antibiotics/antibiotic classes (methicillin, fluoroquinolone, 3rd generation cephalosporins, carbapenem, vancomycin) were determined by reported minimum inhibitory concentrations (MIC) for specific antibiotics or by tests of specific genetic determinants (Table S1). Interpretation of AST results adhered to breakpoint revisions by the Clinical and Laboratory Standards Institute.

The microbiology-level dataset contains identification for clinical cultures that are classified as community-onset (within 72 hours after admission), hospital-onset (after 72 hours post hospital admission), or 30-day post discharge onset. In our analysis, we considered clinical cultures that were classified as hospital-onset or post-discharge as hospital-associated. Under the assumption that clinical cultures taken at least 30 days apart belong to different clinical infections, we defined a (30-day) incident isolate as a clinical culture where no other clinical culture of the same species was identified in the prior 30 days and used it as a proxy measure for clinical infection incidence. We defined bloodstream infections as positive cultures for a target organism from blood samples. Nonblood infections were defined as isolation from any other sample type, excluding those obtained for surveillance purposes and those obtained within 14 days following a positive blood culture. When multiple species were recovered from the same sample or from different samples collected during the same hospitalization, each incident isolate was separately counted in the analysis of a given species.

**Table S1. Overview of specific antibiotics and other genetic determinants to determine antibiotic susceptibility test results in key antibiotic classes.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methicillin** | **Fluoroquinolones** | **3rd generation cephalosporins** | **Carbapenems** |
| Cefazolin | Ciprofloxacin | Cefoperazone | bla(KPC) gene (test for presence using molecular method) |
| Cefoxitin | Gatifloxacin | Cefotaxime | Carbapenemase gene (by nucleic acid amplification with probe detection) |
| mecA gene | Gemifloxacin | Cefpodoxime | Hodge test |
| Methicillin | Levofloxacin | Ceftazidime | Imipenem |
| Nafcillin | Lomefloxacin | Ceftizoxime | Meropenem |
| Oxacillin | Moxifloxacin | Ceftriaxone | Doripenem |
|  | Norfloxacin | Moxalactam | Ertapenem |
|  | Ofloxacin |  |  |

## S1.2 VA facility complexity model

Each VAMC facility is characterized by various variables that may be influential in the context of analytical modeling. The Facility Complexity Model is a VHA method to define clinical complexity at each medical center.1,2 It designates VHA facilities into three categories. These designations are based on a score involving the number of patients seen, patient risk, number of physician specialists, teaching status, research dollars, and intensive care unit capability (Table S2). The model is reviewed and updated every three years across the VA on behalf of the VHA National Leadership Council.1

Table S2. Facility Complexity definitions based on Broskey (2018)1.

|  |  |
| --- | --- |
| **Complexity level** | **Facility description** |
| 1a (highest complexity) | Facility with high volume, high-risk patients, most complex clinical programs, and large research and teaching programs |
| 1b (highest complexity) | Facilities with medium-high volume, high-risk patients, many complex clinical programs, and medium-large research and teaching programs |
| 1c (mid-high complexity) | Facilities with medium-high volume, medium-risk patients, some complex clinical programs, and medium sized research and teaching programs |
| 2 (medium complexity) | Facilities with medium volume, low-risk patients, few complex clinical programs, and small or no research and teaching programs |
| 3 (low complexity) | Facilities with low volume, low-risk patients, few or no complex clinical programs, and small or no research and teaching programs |

Most 30-day incident isolates in our study (86%, Figure S1) were collected at facilities designated with the highest complexity (1a-1c).



Figure S1. Proportion of 30-day incident isolates across facilities with different complexity levels. The facility complexity level was based on the VHA complexity model.1

## S1.3 Data on geography

In addition to the beforementioned facility information, our database comprises geographic information for each facility, including the US state, census division and census region.

## S1.4 Data on patient demographics

Information on patient demographics (age, race, ethnicity) were available in the hospital-level data set. The patient age was determined from the patient’s date of birth. Biological sex of patients was determined from their birth certificates. Race and ethnicity were collected by self-report. An overview of patient demographics (race and ethnicity) can be found in Table S3 and Table S4.

Table S3. Summary statistics of race information of patients associated with 30-day incident isolates per organism. The total number and percentages (per organism) are reported. Race information of patients was collected by self-report.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Organism** | **White** | **Black or African American** | **American Indian or Alaska native** | **Asian** | **native Hawaiian or other Pacific islander** | **Mixed** | **Missing** |
| Staphylococcus aureus | 188,964 (76.4%) | 42,986 (17.4%) | 1,861 (0.8%) | 853 (0.3%) | 1,605 (0.6%) | 1,978 (0.8%) | 9,082 (3.7%) |
| Enterococcus faecalis | 97,755 (72.9%) | 27,999 (20.9%) | 835 (0.6%) | 438 (0.3%) | 848 (0.6%) | 1,094 (0.8%) | 5,122 (3.8%) |
| Enterococcus faecium | 27,310 (72%) | 8,109 (21.4%) | 240 (0.6%) | 154 (0.4%) | 199 (0.5%) | 302 (0.8%) | 1,592 (4.2%) |
| Escherichia coli | 156,882 (70.6%) | 50,674 (22.8%) | 1,530 (0.7%) | 859 (0.4%) | 1,543 (0.7%) | 1,851 (0.8%) | 8,759 (3.9%) |
| Klebsiella pneumoniae | 96,760 (70.2%) | 32,511 (23.6%) | 856 (0.6%) | 553 (0.4%) | 878 (0.6%) | 1,129 (0.8%) | 5,236 (3.8%) |
| Enterobacter cloacae | 31,635 (73.2%) | 9,094 (21%) | 272 (0.6%) | 135 (0.3%) | 252 (0.6%) | 300 (0.7%) | 1,530 (3.5%) |
| Serratia marcescens | 16,688 (73.9%) | 4,546 (20.1%) | 138 (0.6%) | 94 (0.4%) | 136 (0.6%) | 171 (0.8%) | 795 (3.5%) |
| Pseudomonas aeruginosa | 95,636 (73.3%) | 26,771 (20.5%) | 796 (0.6%) | 448 (0.3%) | 834 (0.6%) | 982 (0.8%) | 5,029 (3.9%) |
| Acinetobacter Sp. | 10,852 (68.3%) | 4,146 (26.1%) | 84 (0.5%) | 48 (0.3%) | 98 (0.6%) | 126 (0.8%) | 544 (3.4%) |

Table S4. Summary statistics of ethnicity information of patients associated with 30-day incident isolates per organism. The total number and percentages (per organism) are reported. Ethnicity information of patients was collected by self-report.

|  |  |  |  |
| --- | --- | --- | --- |
| **Organism** | **Not Hispanic or Latino** | **Hispanic or Latino** | **Missing** |
| Staphylococcus aureus | 226803 (89.6%) | 14644 (5.8%) | 11764 (4.6%) |
| Enterococcus faecalis | 123102 (89.6%) | 7645 (5.6%) | 6688 (4.9%) |
| Enterococcus faecium | 34663 (89%) | 2219 (5.7%) | 2048 (5.3%) |
| Escherichia coli | 199892 (87.9%) | 16800 (7.4%) | 10812 (4.8%) |
| Klebsiella pneumoniae | 123902 (87.7%) | 10700 (7.6%) | 6642 (4.7%) |
| Enterobacter cloacae | 39626 (89.6%) | 2574 (5.8%) | 2036 (4.6%) |
| Serratia marcescens | 20435 (88.5%) | 1615 (7%) | 1036 (4.5%) |
| Pseudomonas aeruginosa | 118105 (88.4%) | 9218 (6.9%) | 6346 (4.7%) |
| Acinetobacter Sp. | 14252 (87.7%) | 1292 (7.9%) | 708 (4.4%) |

## S2 VA Hospital infection control measures

In 2007, Veterans Affairs Hospitals throughout the United States introduced a multifaceted methicillin-resistant *Staphylococcus aureus* prevention strategy (“MRSA bundle”), including universal nasal surveillance for MRSA, contact precautions for patients colonized or infected with MRSA, hand hygiene, and a change in the institutional culture whereby infection control would become the responsibility of everyone involved in patient care.5 As such, the bundle included one vertical intervention (screening and contact precautions) and two horizontal interventions (hand hygiene and culture change). Each month, personnel at each facility entered into a central database aggregate data on adherence to surveillance practice, the prevalence of MRSA colonization or infection, and health care–associated transmissions of and infections with MRSA.6 In addition, the VA launched a national *Clostridium difficile* (C difficile) Prevention Initiative in July 2012 with the goal of reducing *Clostridium difficile* infections (CDIs) in VA acute care medical centers.7 Infection prevention practices targeted at CDIs included contact precautions, isolation or cohorting of patients infected with C difficile, hand hygiene, terminal disinfecting of rooms or equipment of patients, and daily cleaning of high-touch surfaces in rooms.8

In 2011, The Veterans Health Administration (VHA) created the Antimicrobial Stewardship Task Force to develop a national strategic plan to improve antibiotic use.9 In 2014, the VHA Directive 1031 established a policy for implementation and maintenance of antimicrobial stewardship programs at all VHA medical facilities.

# S3 Measures of antimicrobial resistance

In this paper, we used two measures of antimicrobial resistance (AMR). In what follows, we give more detailed explanations and examples as to why we believe that these two measures are most informative for reporting AMR.

The resistance proportion represents a prevalence-type measure that provides an estimate of the probability a given isolate is resistant to an antibiotic or not. As such, it is useful for a clinician who must choose antimicrobial agents for treatment of the infection at a specific point in time at a specific location. The following formulas represent the calculation of resistance proportions: if represents the number of resistant isolates, and the number of susceptible isolates, then the percentage of resistant isolates, , is represented as

(assuming no missing test results) or

where is the number of isolates with missing susceptibility test results.

The use of resistance proportion can be misleading for assessing trends of resistance over time. For example, if the introduction of an antibiotic into a patient population reduces the number of susceptible isolates in that population, it will lead to a rise in the percentage of resistant isolates. Analyses that are based on comparisons of proportions can therefore be misleading as they can be interpreted as indicating an increase in resistance when the percentage of resistant isolates has increased, while the number of resistant isolates may have remained unchanged. The phenotypic incidence metrics are the preferred way to quantify population burden where the term “phenotypic incidence” or “incidence rate” refers to the absolute number of phenotypes (resistant, susceptible, or missing) in a given population per unit of time. Another way to characterize the relationship between these two measures is that the resistance proportion represents the ratio of resistant infection incidence to total infection incidence.

# S4 Statistical analysis

## S4.1 Generalized Estimating Equation approach

To model incidence rate trends, we employed robust Poisson regression with the Generalized Estimating Equation approach (GEE)10 where we accounted for the clustering by the VAMC with an autoregressive correlation structure within a facility and used calendar year as exposure and number of admissions as offset. We adjusted for major hospital characteristics, including census region, facility rurality index, facility complexity level, patient volume, patient age, gender (female, male), race (American Indian or Alaska native, Asian, black African American, native Hawaiian or other Pacific Islander, white, mixed), and ethnicity (Hispanic, non-Hispanic) proportions. To adjust for different age distributions within hospitalization for each facility, we divided patients into the following age groups: [0-30], [31-50] [51-70], [71-90], [90+]. We estimated time trend coefficients for the pre-pandemic and pandemic period and by source of infection (Community-onset, Hospital-associated). We used a fully stratified model (with respect to onset) in the GEE approach:

where is the number of 30-day incident isolates, and represent continuous time variables (time unit = year) for the pre-pandemic and pandemic period, respectively, onset is a binary variable representing the location of infection onset (0 = community-onset, 1 = hospital-associated), is a binary variable indicating whether the time point is a pandemic year, remaining confounder variables are indicated by and is the number of admissions in the respective facility at the respective time point (used as an offset). Based on the assumption that community-onset and hospital-onset infections are approximately independent, the variable was included as an interaction term leading to a fully stratified model. The time variables and were based on the calendar year and included as follows:

and

Overall time trend coefficients were obtained by estimated marginal means for both time periods separately. We computed the average annual percentage change (AAPC) and the respective 95% confidence intervals based on estimated rates of change using the following formula:

where is the estimated marginalized time trend coefficient. As such, the AAPC represents the relative change in incidence per year (averaged over the time period) expressed as a percentage. Resistance proportions were modelled similarly but with the total number of isolates as offset. Statistical analyses were performed using the *geeasy* and *emmeans* package in R version 4.3.1.11

A detailed list of variables that were used in the GEE analysis can be found below. The covariates were included because they are known to be correlated with the exposure and the outcome(s) of interest.

* Calendar year for pre-pandemic period (exposure)
* Calendar year for pandemic period (exposure)
* Onset of infection (community-onset, hospital-associated)
* Census region (adjustment for spatial variation)
* Facility rurality (adjustment for access to healthcare services, population density and demographics, ..)
* Facility complexity (adjustment for patient case mix, quality of care, operational capabilities, resource availability, …)
* The following variables were rolled up per calendar year and were included to adjust for the patient composition in the facility:
  + Median length of stay
  + Percentage of female/male patients
  + Percentage of patients classified as white/non-white
  + Percentage of patients classified as non-Hispanic
  + Percentage of patients in the following age categories: Under 30, 30-49, 50-69, 70-89, 90+
  + Number of hospitalizations with an ICU as their admitting ward
  + Maximum patient days that occur at the facility
  + Number of hospitalizations with a history of myocardial infarction in the 365 days prior to admission date
  + Number of hospitalizations with a history of congestive heart failure in the 365 days prior to admission date
  + Number of hospitalizations with a history of cerebrovascular disease in the 365 days prior to admission date
  + Number of hospitalizations with a history of chronic pulmonary disease in the 365 days prior to admission date
  + Number of hospitalizations with a history of rheumatologic disease in the 365 days prior to admission date
  + Number of hospitalizations with a history of dementia in the 365 days prior to admission date
  + Number of hospitalizations with a history of peptic ulcer disease in the 365 days prior to admission date
  + Number of hospitalizations with a history of mild liver disease in the 365 days prior to admission date
  + Number of hospitalizations with a history of diabetes without complications in the 365 days prior to admission date
  + Number of hospitalizations with a history of diabetes with complications in the 365 days prior to admission date
  + Number of hospitalizations with a history of hemiplegia or paraplegia in the 365 days prior to admission date
  + Number of hospitalizations with a history of renal disease in the 365 days prior to admission date
  + Number of hospitalizations with a history malignancy including leukemia lymphona in the 365 days prior to admission date
  + Number of hospitalizations with a history of moderate severe liver disease in the 365 days prior to admission date
  + Number of hospitalizations with a history of metastatic solid tumor cancer in the 365 days prior to admission date
  + Number of hospitalizations with a history of aids in the 365 days prior to admission date
  + Total number of admissions

## S4.2 Assumptions of the Generalized Estimating Equation approach

We used an autoregressive correlation structure within a facility when deploying the GEE approach. This assumes an exponential decay. In Figure S2, we the autocorrelation for one example: *S. aureus* hospital-associated infection incidence. We observed a decline in the

autocorrelation over time confirming that an autoregressive correlation structure is suitable. Additionally, we checked the estimated working correlation from the GEE model, which indicated a positive correlation (Table S3). Given the large number of facilities and a substantial number of data points for each facility, the GEE approach remains robust regardless of the working correlation structure chosen. Even if the selected structure deviates from the actual structure, the resulting estimates maintain statistical consistency. This robustness is even more apparent in our data setting where each facility has approximately the same number of observations and few missing data.



Figure S2. Autocorrelation plot for *Staphylococcus aureus* hospital-associated infection incidence for a subset of facilities for 2007-2019.

Table S5. Estimated working correlation parameters from the autoregressive correlation structure in the generalized estimating equation analysis for infection incidence time trend analyses.

|  |  |
| --- | --- |
| **Organism** | **Estimated correlation parameter** |
| *S. aureus* | 0.28 |
| *E. faecalis* | 0.27 |
| *E. faecium* | 0.785 |
| *E. coli* | 0.51 |
| *K. pneumoniae* | 0.33 |
| *E. cloacae* | 0.35 |
| *S. marcescens* | 0.37 |
| *P. aeruginosa* | 0.2 |
| *Acinetobacter sp.* | 0.41 |

## S4.3 Relative contribution in time trend analyses

We computed the relative contribution of the time trend of community-onset () and hospital-associated infections () to the overall trend based on the estimated time trend coefficients using the following formula:

where is the overall time trend coefficient estimated by the marginalized means method, is the estimated time trend coefficient with respect to the reference category (in this case: community-onset).

# S5 Supplementary results

## S5.1 Temporal trends in infection incidence for each pathogen

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**Figure S3. Infection incidence trends for nine organisms from February 2007 till March 2022. Points represent the number of 30-day incident isolates per quarter.** Lines and grey bands are smoothing curves using the *locally estimated scatterplot*

*smoothing (loess)* method and corresponding 95% confidence intervals. Dashed vertical lines indicate the start of the COVID-19 pandemic.

## S5.2 Infection incidence stratified by source of infection and pathogen



Figure S4. Infection incidence trends for nine organisms stratified by infection category from February 2007 till March 2022. Points represent the number of 30-day incident isolates per quarter. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Dashed vertical lines indicate the start of the COVID-19 pandemic. Colors represent different sources of infection.



Figure S5. Time trend analysis for community-onset infection incidence for nine target pathogens and for pre-pandemic (2007-2019) and pandemic period (2020-2022). Average annual percentage changes (AAPC) were obtained from generalized estimating equations analysis. AAPC larger than zero indicate an increasing trend, coefficients smaller than zero a declining trend in infection incidence.



Figure S6. Time trend analysis for hospital-associated infection incidence for nine target pathogens and for pre-pandemic (2007-2019) and pandemic period (2020-2022). Average annual percentage changes (AAPC) were obtained from generalized estimating equations analysis. AAPC larger than zero indicate an increasing trend, coefficients smaller than zero a declining trend in infection incidence.

Table S6. Change in infection incidence for all nine organisms for pre-pandemic (2007-2019) and pandemic (2020-2022) period. The overall absolute change was calculated by the absolute difference between the start and end year of the respective time period. Average annual percentage change (AAPC) estimates were obtained from time trend coefficients using generalized estimating equations. 95% confidence intervals are reported in brackets. White rows represent results for the pre-pandemic (2007-2019), grey shaded rows for the pandemic (2020-2022) period. Upward or downward pointing arrows indicate statistically significant increasing or decreasing incidence trends. P-values are given for statistically significant time trends if p-value is larger or equal than 0.0001.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Organism** | **Overall absolute change (%)**  2007-2019  2020-2022 | **AAPC (time trend estimates)**  Point estimate (95% confidence interval) | | | | | |
| *Overall*  2007-2019  2020-2022 | | *Community-onset*  2007-2019  2020-2022 | | *Hospital-associated*  2007-2019  2020-2022 | |
| *S. aureus* | -18.5 | **↓** | -3.8% ( -4.7, -2.9)\* | **↓** | -1.8% ( -2.9, -0.6)  p-value = 0.0029 | **↓** | -5.8% (-6.8, -4.7)\* |
| -4.6 |  | -2.9% (-5.9, 0.2) | **↓** | -10.5% (-13.8, -7.1)\* | **↑** | 5.3% (0.6, 10.1)  p-value = 0.025 |
| *E. faecalis* | -38.9 |  | -0.1% (-1.8, 1.7) |  | 1.1% ( -0.9, 3.1) |  | -1.2% (-2.9, 0.5) |
| -7.75 |  | 1.3% (-3.8, 6.7) |  | -3.4% ( -8.8, 2.2) |  | 6.3% (-0.4, 13.5) |
| *E. faecium* | +6.5 | **↓** | -7.5% (-10.2, -4.7)\* | **↓** | -7.1% (-10.5, -3.7)  p-value = 0.0001 | **↓** | -7.8% (-10.7, -4.9)\* |
| +2.0 | **↑** | 23.8% (10.4, 38.8)  p-value = 0.0002 | **↑** | 15.5% (1.0, 32.0)  p-value = 0.0358 | **↑** | 32.8% (16.1, 51.7)\* |
| *E. coli* | -60.4 | **↓** | -1.5% (-2.2, -0.7)  p-value = 0.0001 |  | -0.6% ( -1.4, 0.3) | **↓** | -2.3% (-3.2, -1.5)\* |
| +26.5 |  | -1.1% (-4.3, 2.2) | **↓** | -6.5% (-10.1, -2.8)  p-value = 0.0007 |  | 4.6% (-0.1, 9.5) |
| *K. pneumoniae* | -5.0 |  | -0.5% (-1.6, 0.5) |  | 1.0% ( -0.2, 2.3) | **↓** | -2.0% (-3.3, -0.8)  p-value = 0.0017 |
| -6.1 |  | -2.2% (-5.8, 1.6) | **↓** | -5.5% ( -9.7, -1.1)  p-value = 0.014 |  | 1.3% (-3.8, 6.7) |
| *E. cloacae* | +0.03 |  | -1.2% (-2.6, 0.1) |  | 0.8% ( -0.9, 2.5) | **↓** | -3.2% (-4.7, -1.7)\* |
| -5.5 |  | 2.6% (-3.0, 8.4) |  | 0.5% ( -6.3, 7.9) |  | 4.7% (-3.1, 13.0) |
| *S. marcescens* | -2.85 |  | 0.0% (-1.3, 1.4) | **↑** | 1.9% (0.2, 3.6)  p-value = -0.0268 | **↓** | -1.8% (-3.6, 0.0)\* |
| -12.8 |  | 3.4% (-2.9, 10.2) |  | 1.9% (-5.8, 10.1) |  | 5.0% (-5.0, 16.1) |
| *P. aeruginosa* | -16.2 | **↓** | -2.3% (-3.4, -1.2)\* |  | -0.8% (-2.2, 0.6) | **↓** | -3.8% (-5.0, -2.6)\* |
| -4.7 |  | -1.2% (-5.1, 2.9) | **↓** | -8.8% (-13.6, -3.8)  p-value = 0.0007 | **↑** | 7.1% (1.6, 12.9)  p-value = 0.0108 |
| *Acinetobacter sp.* | -17.1 |  | -2.2% (-4.7, 0.5) |  | 0.0% (-3.3, 3.4) | **↓** | -4.2% (-7.3, -1.1)  p-value = 0.0092 |
| -3.9 | **↑** | 11.5% (0.9, 23.3)  p-value = 0.0335 |  | 9.2% (-3.2, 23.2) |  | 13.9% (-2.0, 32.4) |

\* p-value < 0.0001

Table S7. Change in methicillin and vancomycin phenotypic incidence, and resistance proportion for gram-positive organisms during the pre-pandemic (2007-2019) and and pandemic (2020-2022) period. Average annual percentage change (AAPC) estimates were obtained from time trend coefficients using generalized estimating equations. 95% confidence intervals are reported in brackets. White rows represent results for the pre-pandemic (2007-2019), grey shaded rows for the pandemic (2020-2022) period. Upward or downward pointing arrows indicate statistically significant increasing or decreasing incidence trends. P-values are given for statistically significant time trends if p-value is larger or equal than 0.0001.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Organism** | **Source of infection** | **Methicillin** | | | | | |
| Incidence of resistant infections  2007-2019  2020-2022 | |  | Incidence of susceptible infections  2007-2019  2020-2022 | Resistance proportion  2007-2019  2020-2022 | |
| *S. aureus* | Overall | **↓** | -5.5% (-6.7, -4.3)\* | **↓** | -1.5% (-2.4, -0.5)  p-value = 0.0036 | **↓** | -1.8% (-2.4, -1.2)\* |
|  | -4.5% (-9.0, 0.2) |  | 0.0% (-3.7, 3.9) |  | -2.7% (-5.5, 0.1) |
| Community-onset | **↓** | -3.7% (-5.1, -2.2)\* |  | 0.3% (-0.9, 1.5) | **↓** | -1.9% (-2.6, -1.2)\* |
| **↓** | -10.2% (-15.2, -5.0)  p-value = 2e-04 | **↓** | -10.3% (-14.2, -6.3)\* | **↓** | -1.7% (-2.3, -1.1)\* |
| Hospital-associated |  | -7.3% (-8.6, -6.1) | **↓** | -3.2% (-4.3, -2.1)\* |  | -0.6% (-3.7, 2.5) |
|  | 1.6% (-4.9, 8.6) | **↑** | 11.5% (5.6, 17.8)  p-value = 1e-04 | **↓** | -4.8% (-8.5, -0.9)  p-value = 0.0175 |
|  | | **Vancomycin** | | | | | |
| *E. faecalis* | Overall |  | -1.3% (-4.9, 2.5) |  | 0.2% (-1.7, 2.2) |  | -1.5% (-5.6, 2.8) |
|  | -4.0% (-18.7, 13.3) |  | 1.5% (-4.0, 7.3) |  | -11.3% (-28.9, 10.6) |
| Community-onset |  | -0.3% (-4.0, 3.5) |  | 1.4% (-0.8, 3.7) |  | -2.1% (-6.6, 2.7) |
|  | -6.1% (-21.8, 12.8) |  | -3.9% (-9.7, 2.2) |  | -16.3% (-32.5, 3.8) |
| Hospital-associated |  | -2.2% (-6.3, 2.1) |  | -0.9% (-2.9, 1.0) |  | -0.9% (-5.3, 3.6) |
|  | -1.9% (-19.8, 19.9) | **↑** | 7.1% (0.0, 14.8)\* |  | -6.1% (-29.7, 25.4) |
| *E. faecium* | Overall | **↓** | -9.9% (-12.8, -6.9)\* |  | -1.3% (-4.1, 1.7) |  | -1.2% (-2.5, 0.0) |
| **↑** | 26.3% (10.8, 43.9)  p-value = 5e-04 | **↑** | 26.0% (13.7, 39.7)\* |  | 0.2% (-5.0, 5.7) |
| Community-onset | **↓** | -10.4% (-14.3, -6.3)\* |  | -0.6% (-3.3, 2.2) | **↓** | -2.0% (-3.4, -0.5)\*  p-value = 0.01 |
| **↑** | 18.7% ( 1.3, 39.0)  p-value = 0.0335 | **↑** | 21.6% (8.2, 36.7)  p-value = 0.001 |  | 0.2% (-7.1, 8.0) |
| Hospital-associated | **↓** | -9.4% (-12.2, -6.5)\* |  | -1.9% (-5.5, 1.8) |  | -0.5% (-1.7, 0.7) |
| **↑** | 34.4% (12.6, 60.4)  p-value = 0.0011 | **↑** | 30.5% (14.1, 49.3)  p-value = 0.0001 |  | 0.2% (-6.4, 7.2) |

\* p-value < 0.0001

Table S8. Change in fluoroquinolone phenotypic incidence and resistance proportion for the pre-pandemic (2007-2019) and pandemic (2020-2022) period. Average annual percentage change (AAPC) estimates were obtained from time trend coefficients using generalized estimating equations. 95% confidence intervals are reported in brackets. White rows represent results for the pre-pandemic (2007-2019), grey shaded rows for the pandemic (2020-2022) period. Upward or downward pointing arrows indicate statistically significant increasing or decreasing incidence trends. P-values are given for statistically significant time trends if p-value is larger or equal than 0.0001.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Organism** | **Source of infection** | **Fluoroquinolones**  AAPC point estimates (95% confidence interval) | | | | | |
| Incidence of resistant infections  2007-2019  2020-2022 | | Incidence of susceptible infections  2007-2019  2020-2022 | | Resistance proportion  2007-2019  2020-2022 | |
| *S. aureus* | Overall | **↓** | -6.2% ( -7.9, -4.5)\* |  | -1.2% ( -3.0, 0.7) | **↓** | -2.6% (-4.6, -0.5)  p-value = 0.0163 |
|  | -8.1% (-16.5, 1.2) |  | -2.6% (-10.4, 5.9) | **↓** | -11.6% (-19.0, -3.6)  p-value = 0.0055 |
| Community-onset | **↓** | -3.8% ( -5.8, -1.8)  p-value = 3e-04 |  | 0.4% ( -1.7, 2.4) | **↓** | -2.6% (-4.8, -0.5)  p-value = 0.017 |
| **↓** | -16.9% (-25.2, -7.8)  p-value = 5e-04 | **↓** | -15.1% (-21.3, -8.3)\* | **↓** | -8.5% (-16.0, -0.3)  p-value = 0.0421 |
| Hospital-associated | **↓** | -8.5% (-10.4, -6.6)\* | **↓** | -2.7% ( -4.7, -0.6)  p-value = 0.0114 | **↓** | -2.5% (-4.7, -0.3)  p-value = 0.0286 |
|  | 1.7% (-11.1, 16.2) |  | 11.7% ( -1.2, 26.1) | **↓** | -14.6% (-23.4, -4.9)  p-value = 0.004 |
| *E. faecalis* | Overall | **↓** | -5.7% ( -9.4, -1.9)  p-value = 0.0035 |  | 0.7% ( -2.2, 3.7) | **↓** | -6.4% (-9.2, -3.6)\* |
|  | 0.1% (-11.3, 13.0) |  | 6.5% ( -4.0, 18.2) |  | -9.9% (-20.9, 2.6) |
| Community-onset | **↓** | -5.1% ( -9.3, -0.7)  p-value = 0.0229 |  | 1.4% ( -1.8, 4.7) | **↓** | -7.1% (-10.1, -4.0)\* |
| **↓** | -7.1% (-19.1, 6.8) |  | -4.4% (-14.1, 6.4) |  | -9.9% (-21.3, 3.1) |
| Hospital-associated | **↓** | -6.3% ( -9.9, -2.6)  p-value = 0.001 |  | 0.1% ( -2.9, 3.1) | **↓** | -5.7% (-8.5, -2.9)  p-value = 1e-04 |
|  | 7.8% ( -6.2, 23.9) | **↑** | 18.7% ( 4.3, 35.0)  p-value = 0.0094 |  | -9.9% (-22.4, 4.6) |
| *E. faecium* | Overall | **↓** | -9.3% (-14.2, -4.0)  p-value = 7e-04 |  | 2.4% ( -0.7, 5.7) |  | -4.5% (-8.6, -0.2)  p-value = 0.0418 |
|  | 12.6% ( -4.5, 32.6) | **↑** | 33.3% ( 11.4, 59.4)  p-value = 0.0017 |  | -4.2% (-18.2, 12.1) |
| Community-onset | **↓** | -8.8% (-15.4, -1.7)  p-value = 0.0162 |  | 2.0% ( -1.8, 6.0) |  | -4.4% (-8.8, 0.2) |
|  | 5.4% (-13.2, 28.2) |  | 13.1% (-15.8, 51.9) |  | -3.0% (-19.3, 16.8) |
| Hospital-associated | **↓** | -9.7% (-14.3, -4.9)\*  p-value = 1e-04 |  | 2.9% ( -1.2, 7.1) |  | -4.6% (-8.8, -0.2)  p-value = 0.0406 |
|  | 20.2% ( -3.6, 49.9) |  | 57.0% ( 29.5, 90.3)\* |  | -5.5% (-20.7, 12.6) |
| *E. coli* | Overall | **↓** | -1.4% ( -2.6, -0.1)\*  p-value = 0.0319 |  | -1.0% ( -1.9, 0.0) |  | -0.1% (-1.1, 1.0) |
|  | -2.8% ( -8.9, 3.7) |  | -1.6% ( -5.3, 2.3) |  | -4.5% (-8.8, 0.1) |
| Community-onset |  | 0.0% ( -1.3, 1.4) |  | -0.4% ( -1.4, 0.6) |  | 0.5% (-0.6, 1.6) |
| **↓** | -7.5% (-13.6, -0.9)  p-value = 0.0256 | **↓** | -6.7% (-10.7, -2.4)  p-value = 0.0024 |  | -4.5% (-9.7, 0.9) |
| Hospital-associated | **↓** | -2.8% ( -4.1, -1.4)  p-value = 1e-04 | **↓** | -1.5% ( -2.7, -0.3)  p-value = 0.012 |  | -0.6% (-1.8, 0.6) |
|  | 2.1% ( -6.1, 10.9) |  | 3.8% ( -1.5, 9.4) |  | -4.4% (-9.6, 1.1) |
| *K. pneumoniae* | Overall |  | -1.4% ( -4.5, 1.8) |  | 0.0% ( -1.1, 1.1) |  | -1.6% (-4.0, 0.9) |
|  | 12.4% ( -0.3, 26.6) | **↓** | -4.1% ( -7.9, -0.1)  p-value = 0.0457 |  | 7.6% (-3.7, 20.3) |
| Community-onset |  | 0.5% ( -2.7, 3.7) | **↑** | 1.3% ( 0.1, 2.6)  p-value = 0.0353 |  | -0.8% (-3.3, 1.7) |
|  | 7.6% ( -5.3, 22.3) | **↓** | -7.2% (-11.5, -2.6)  p-value = 0.0025 |  | 8.2% (-3.4, 21.1) |
| Hospital-associated |  | -3.2% ( -6.7, 0.4) |  | -1.4% ( -2.8, 0.0) |  | -2.3% (-5.0, 0.4) |
| **↑** | 17.3% ( 1.0, 36.3)  p-value = 0.0372 |  | -0.8% ( -6.6, 5.3) |  | 7.1% (-7.7, 24.3) |
| *Enterobacter cl.* | Overall |  | -1.5% ( -4.4, 1.5) |  | -0.4% ( -1.9, 1.0) | **↓** | -6.5% (-9.2, -3.7)\* |
|  | 22.8% ( 7.9, 39.8)  p-value = 0.0019 |  | 1.8% ( -3.9, 7.8) |  | 12.4% (-7.2, 36.1) |
| Community-onset |  | 1.2% ( -2.2, 4.7) |  | 1.4% ( -0.5, 3.3) | **↓** | -5.7% (-8.9, -2.3)  p-value = 0.0011 |
|  | 15.5% ( -3.6, 38.3) |  | -1.2% ( -8.2, 6.4) |  | 14.1% (-10.9, 46.1) |
| Hospital-associated | **↓** | -4.1% ( -6.7, -1.4)\*  p-value = 0.0032 | **↓** | -2.2% ( -3.9, -0.6)  p-value = 0.0082 | **↓** | -7.3% (-10.8, -3.6)  p-value = 1e-04 |
| **↑** | 30.6% ( 14.7, 48.7)\*  p-value = 1e-04 |  | 4.9% ( -3.2, 13.7) |  | 10.6% (-13.7, 41.8) |
| *Serratia m.* | Overall |  | 1.6% ( -1.4, 4.7) |  | 0.7% ( -0.8, 2.1) | **↓** | -7.2% (-10.9, -3.4)  p-value = 3e-04 |
|  | 10.8% ( -3.6, 27.2) |  | 2.3% ( -4.4, 9.4) | **↑** | 27.9% ( 0.2, 63.2)  p-value = 0.0478 |
| Community-onset | **↑** | 4.1% ( 0.4, 7.9)\*  p-value = 0.0277 | **↑** | 2.4% ( 0.6, 4.2)  p-value = 0.0076 | **↓** | -7.2% (-11.7, -2.6)  p-value = 0.0026 |
|  | 1.1% (-18.4, 25.3) |  | 3.0% ( -5.2, 12.0) |  | 4.6% (-22.8, 41.7) |
| Hospital-associated |  | -0.9% ( -3.7, 2.0) |  | -1.1% ( -2.9, 0.8) | **↓** | -7.2% (-11.9, -2.4)  p-value = 0.0039 |
| **↑** | 21.3% ( 4.1, 41.4)\*  p-value = 0.0135 |  | 1.5% (-9.1, 13.4) | **↑** | 56.3% (6.4, 129.8)  p-value = 0.0229 |
| *P. aeruginosa* | Overall |  | -5.0% ( -6.9, -3.1)\* |  | -1.0% (-2.3, 0.4) | **↓** | -3.3% (-4.9, -1.7)  p-value = 1e-04 |
|  | 0.7% ( -8.5, 10.9) |  | 0.3% (-4.5, 5.4) |  | -3.4% (-11.8, 5.8) |
| Community-onset | **↓** | -2.6% ( -4.6, -0.6)\*  p-value = 0.0127 |  | 0.3% ( -1.2, 1.9) | **↓** | -2.4% (-4.0, -0.8)  p-value = 0.0029 |
|  | -6.9% (-15.9, 3.1) | **↓** | -7.6% (-12.7, -2.2)  p-value = 0.006 |  | -4.5% (-12.3, 4.1) |
| Hospital-associated |  | -7.3% ( -9.4, -5.1)\* | **↓** | -2.3% (-3.8, -0.7)  p-value = 0.0043 | **↓** | -4.1% (-5.9, -2.3)\* |
|  | 9.0% ( -4.2, 24.0) | **↑** | 8.9% (1.9, 16.4)  p-value = 0.0115 |  | -2.3% (-14.1, 11.0) |
| *Acinetobacter sp.* | Overall |  | -3.4% ( -7.1, 0.6) |  | 2.1% ( -0.2, 4.4) | **↓** | -6.9% (-9.2, -4.5)\* |
| **↑** | 29.9% ( 1.7, 65.8)\*  p-value = 0.0359 |  | -1.8% (-10.6, 7.9) | **↑** | 22.3% ( 0.8, 48.3)  p-value = 0.0414 |
| Community-onset |  | -0.4% ( -4.5, 3.8) |  | 3.0% ( -0.1, 6.2) | **↓** | -6.9% (-9.7, -4.1)\* |
| **↑** | 36.4% ( 12.0, 66.1)\*  p-value = 0.002 |  | 2.5% (-10.0, 16.7) |  | 23.6% (-0.3, 53.1) |
| Hospital-associated | **↓** | -6.2% (-11.1, -1.0)\*  p-value = 0.0212 |  | 1.2% ( -1.3, 3.6) | **↓** | -6.8% (-9.5, -4.1)\* |
|  | 23.7% (-15.4, 81.1) |  | -5.9% (-18.2, 8.2) |  | 21.0% (-10.2, 62.9) |

\* p-value < 0.0001

**Table S9. Change in 3rd generation cephalosporin phenotypic incidence and resistance proportion for the pre-pandemic (2007-2019) and pandemic (2020-2022) period.** White rows represent average annual percentage change estimates based on generalized estimating equations for 2007-2019, grey shaded rows for 2020-2022. Upward or downward pointing arrows indicate statistically significant increasing or decreasing time trends. P-values are given for statistically significant time trends if p-value is larger or equal than 0.0001.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Organism** | **Source of infection** | **3rd generation cephalosporins**  AAPC point estimates (95% confidence interval) | | | | | |
| Incidence of resistant infections  2007-2019  2020-2022 | | Incidence of susceptible infections  2007-2019  2020-2022 | | Resistance proportion  2007-2019  2020-2022 | |
| *E. coli* | Overall | **↑** | 6.1% ( 3.9, 8.2)\* | **↓** | -2.0% (-3.2, -0.8)  p-value = 0.0016 | **↑** | 8.5% ( 6.2, 10.7)\* |
|  | -0.2% (-8.8, 9.3) |  | -1.6% (-6.7, 3.8) |  | -1.7% (-9.4, 6.8) |
| Community-onset | **↑** | 6.5% ( 4.0, 9.0)\* |  | -1.0% (-2.4, 0.4) | **↑** | 8.2% ( 5.8, 10.7)\* |
|  | -10.6% (-19.7, -0.3)  p-value = 0.0431 | **↓** | -6.0% (-11.2, -0.6)  p-value = 0.0303 |  | -7.4% (-16.3, 2.5) |
| Hospital-associated | **↑** | 5.6% ( 3.5, 7.9)\* | **↓** | -2.9% (-4.1, -1.7)\* | **↑** | 8.7% ( 6.3, 11.2)\* |
|  | 11.4% ( 1.0, 22.9)  p-value = 0.0302 |  | 3.0% (-3.7, 10.2) |  | 4.5% (-4.5, 14.2) |
| *K. pneumoniae* | Overall |  | 1.6% (-1.6, 4.9) |  | -0.5% (-1.9, 0.9) |  | 2.1% (-0.6, 4.8) |
|  | 6.2% (-4.3, 17.8) |  | -1.3% (-6.7, 4.4) |  | 0.3% (-9.1, 10.5) |
| Community-onset |  | 2.8% (-0.8, 6.5) |  | 1.0% (-0.7, 2.7) |  | 2.2% (-0.6, 5.1) |
|  | 0.1% (-11.0, 12.6) |  | -5.1% (-10.9, 1.0) |  | -2.5% (-12.9, 9.0) |
| Hospital-associated |  | 0.4% (-3.1, 3.9) | **↓** | -2.0% (-3.5, -0.5)  p-value = 0.0085 |  | 1.9% (-0.9, 4.8) |
|  | 12.7% (-0.7, 27.9) |  | 2.7% (-4.2, 10.1) |  | 3.1% (-8.6, 16.4) |
| *Enterobacter cl.* | Overall |  | -1.2% (-3.3, 0.9) |  | -0.9% (-2.7, 0.8) |  | -0.2% (-2.5, 2.1) |
|  | 0.8% (-7.9, 10.4) | **↑** | 9.6% ( 2.7, 17.0)  p-value = 0.0056 | **↓** | -11.8% (-19.6, -3.1)  p-value = 0.0085 |
| Community-onset |  | 0.3% (-2.5, 3.3) |  | 0.8% (-1.4, 2.9) |  | -0.6% (-3.5, 2.4) |
|  | 5.8% (-8.3, 22.0) |  | 2.7% (-6.1, 12.3) |  | -8.8% (-20.7, 4.9) |
| Hospital-associated | **↓** | -2.7% (-4.8, -0.5)  p-value = 0.0166 | **↓** | -2.6% (-4.5, -0.7)  p-value = 0.0079 |  | 0.2% (-1.9, 2.3) |
|  | -3.8% (-13.7, 7.1) |  | 17.0% (7.2, 27.8)  p-value = 4e-04 | **↓** | -14.6% (-22.4, -6.1)  p-value = 0.0011 |
| *Serratia m.* | Overall |  | 1.8% (-2.3, 6.0) |  | 0.5% (-1.1, 2.2) |  | -0.5% (-5.3, 4.6) |
| **↑** | 25.7% ( 6.7, 48.1)  p-value = 0.0062 |  | 1.5% (-6.2, 9.7) |  | 15.9% (-7.1, 44.5) |
| Community-onset |  | 2.3% (-2.5, 7.3) | **↑** | 2.0% ( 0.2, 3.9)  p-value = 0.0313 |  | -0.9% (-6.2, 4.6) |
|  | 16.0% (-6.1, 43.3) |  | 0.8% (-7.9, 10.3) |  | -6.6% (-28.7, 22.3) |
| Hospital-associated |  | 1.3% (-2.9, 5.6) |  | -1.0% (-3.0, 1.1) |  | 0.0% (-5.3, 5.6) |
| **↑** | 36.3% ( 7.0, 73.6)  p-value = 0.0122 |  | 2.1% (-9.5, 15.1) | **↑** | 43.7% (10.1, 87.6)  p-value = 0.0076 |
| *P. aeruginosa* | Overall | **↓** | -11.8% (-15.0, -8.4)\* |  | 2.1% (-0.4, 4.7) | **↓** | -10.1% (-12.9, -7.1)\* |
|  | -9.2% (-25.3, 10.4) |  | -0.2% (-6.9, 7.0) |  | -13.0% (-27.6, 4.6) |
| Community-onset |  | -10.9% (-14.7, -7.0) | **↑** | 3.9% ( 1.2, 6.7)  p-value = 0.0044 | **↓** | -10.5% (-13.7, -7.1)\* |
|  | -17.2% (-35.9, 6.9) |  | -6.8% (-13.4, 0.2) |  | -13.1% (-29.9, 7.9) |
| Hospital-associated | **↓** | -12.6% (-15.7, -9.4)\* |  | 0.4% (-2.4, 3.3) | **↓** | -9.7% (-12.3, -6.9)\* |
|  | -0.4% (-15.6, 17.4) |  | 7.0% (-2.2, 17.1) |  | -12.9% (-27.2, 4.2) |
| *Acinetobacter sp.* | Overall |  | -3.4% (-7.0, 0.3) |  | 1.8% (-1.2, 4.8) |  | -1.7% (-4.3, 1.0) |
|  | 10.1% (-8.1, 31.9) |  | 1.3% (-11.2, 15.6) |  | -3.7% (-16.6, 11.1) |
| Community-onset |  | -1.3% (-5.9, 3.4) | **↑** | 3.6% ( 0.2, 7.2)  p-value = 0.0392 |  | -1.8% (-4.7, 1.2) |
|  | 11.3% (-8.2, 34.9) |  | 14.0% (-3.7, 34.8) |  | 1.5% (-13.1, 18.7) |
| Hospital-associated | **↓** | -5.4% (-9.6, -1.0)  p-value = 0.0157 |  | -0.1% (-3.5, 3.5) |  | -1.6% (-4.3, 1.2) |
|  | 8.9% (-14.5, 38.8) |  | -10.0% (-25.8, 9.1) |  | -8.7% (-24.1, 9.7) |

\* p-value < 0.0001

Table S10. Change in carbapenem phenotypic incidence and resistance proportion for the pre-pandemic (2007-2019) and pandemic (2020-2022) period. Average annual percentage change (AAPC) estimates were obtained from time trend coefficients using generalized estimating equations. 95% confidence intervals are reported in brackets. White rows represent results for the pre-pandemic (2007-2019), grey shaded rows for the pandemic (2020-2022) period. Upward or downward pointing arrows indicate statistically significant increasing or decreasing incidence trends. P-values are given for statistically significant time trends if p-value is larger or equal than 0.0001.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Organism** | **Source of infection** | **Carbapenems**  AAPC point estimates (95% confidence interval) | | | | | |
| 2007-2019 | | | | | |
| 2020-2022 | | | | | |
| Incidence of resistant infections | | Incidence of susceptible infections | |  | Resistance proportion |
| *K. pneumoniae* | Overall |  | -0.3% (-4.3, 3.9) |  | -0.9% (-2.6, 0.8) |  | -0.1% (-6.7, 6.9) |
|  | -6.1% (-20.6, 11.0) |  | -1.0% (-6.7, 5.2) |  | 14.9% (-11.5, 49.3) |
| Community-onset |  | 3.6% (-1.5, 9.0) |  | 0.7% (-1.2, 2.6) |  | -2.6% (-9.7, 5.1) |
|  | -5.7% (-22.1, 14.1) |  | -4.1% (-10.1, 2.3) |  | -10.5% (-32.0, 17.9) |
| Hospital-associated | **↓** | -4.1% (-7.4, -0.7)  p-value = 0.0182 | **↓** | -2.4% (-4.3, -0.5)  p-value = 0.0122 |  | 2.4% (-4.3, 9.6) |
|  | -6.5% (-22.5, 12.9) |  | 2.3% (-5.3, 10.4) | **↑** | 47.6% (4.4, 108.6)  p-value = 0.0274 |
| *Enterobacter cl.* | Overall | **↑** | 5.0% (1.9, 8.2)  p-value = 0.0012 |  | -1.8% (-3.7, 0.2) | **↑** | 19.8% (13.7, 26.2)\* |
|  | 11.0% (-1.7, 25.2) |  | 7.0% (-0.9, 15.5) |  | 6.0% (-14.1, 30.7) |
| Community-onset |  | 4.3% (-0.3, 9.0) |  | 0.6% (-1.7, 2.9) | **↑** | 18.4% (10.7, 26.6)\* |
|  | 13.6% (-7.7, 39.6) |  | 4.4% (-4.6, 14.2) |  | 4.4% (-19.9, 36.2) |
| Hospital-associated | **↑** | 5.8% (2.9, 8.7)  p-value = 1e-04 | **↓** | -4.0% (-6.1, -1.9)  p-value = 2e-04 | **↑** | 21.1% (15.0, 27.6)\* |
|  | 8.4% (-11.0, 32.1) |  | 9.7% (-0.8, 21.3) |  | 7.5% (-19.8, 44.2) |
| *Serratia m.* | Overall |  | 4.5% (-0.4, 9.6) |  | -1.0% (-2.7, 0.7) | **↑** | 19.9% ( 8.6, 32.3)  p-value = 3e-04 |
|  | 1.3% (-16.6, 23.2) | **↑** | 11.0% ( 2.3, 20.5)  p-value = 0.0176 |  | -4.4% (-41.1, 55.2) |
| Community-onset |  | 3.8% (-2.9, 10.9) |  | 0.0% (-2.0, 2.0) | **↑** | 15.9% ( 3.3, 29.9)  p-value = 0.0117 |
|  | 4.4% (-24.6, 44.4) |  | 5.3% (-4.9, 16.6) |  | -1.1% (-45.9, 80.8) |
| Hospital-associated |  | 5.3% (-0.6, 11.5) |  | -2.0% (-4.3, 0.2) | **↑** | 24.0% (11.1, 38.4)  p-value = 1e-04 |
|  | -1.6% (-25.1, 29.2) | **↑** | 17.0% ( 3.6, 32.2)  p-value = 0.0463 |  | -7.6% (-49.5, 69.2) |
| *P. aeruginosa* | Overall |  | -1.1% (-3.6, 1.5) | **↓** | -2.3% (-3.8, -0.9)  p-value = 0.0019 |  | 1.8% (-1.0, 4.6) |
|  | 7.1% (-4.7, 20.4) |  | 0.0% (-6.2, 6.5) |  | 4.8% (-7.1, 18.3) |
| Community-onset |  | 1.7% (-1.3, 4.7) |  | -0.9% (-2.6, 0.9) |  | 3.0% (-0.1, 6.2) |
|  | -2.3% (-16.1, 13.8) | **↓** | -7.8% (-14.7, -0.5)  p-value = 0.0369 |  | -0.2% (-14.2, 16.1) |
| Hospital-associated | **↓** | -3.7% (-6.4, -1.0)  p-value = 0.0083 |  | -3.8% (-5.4, -2.1)\* |  | 0.5% (-2.3, 3.4) |
| **↑** | 17.4% (2.3, 34.8)  p-value = 0.0228 | **↑** | 8.4% (0.4, 17.0)\*  p-value = 0.0382 |  | 10.2% (-3.6, 25.9) |
| *Acinetobacter sp.* | Overall |  | -2.8% (-6.0, 0.5) |  | -2.6% (-5.2, 0.0) |  | -3.7% (-8.6, 1.5) |
|  | 16.2% (-12.8, 54.9) |  | 8.4% (-4.0, 22.5) |  | 18.5% (-16.2, 67.7) |
| Community-onset |  | -0.3% (-4.4, 3.9) |  | -2.2% (-5.7, 1.4) |  | -3.9% (-9.5, 2.1) |
|  | 18.0% (-10.7, 55.9) |  | 5.0% (-10.0, 22.5) |  | 32.6% (-6.9, 88.7) |
| Hospital-associated | **↓** | -5.1% (-8.9, -1.2)  p-value = 0.0176 |  | -3.0% (-6.1, 0.2) |  | -3.5% (-8.6, 1.9) |
|  | 14.5% (-25.9, 77.1) |  | 12.0% (-4.2, 30.9) |  | 6.0% (-32.7, 66.9) |

\* p-value < 0.0001

**S5.2 Resistance stratified by location of infection onset**

Figure S7. Third-generation cephalosporin resistance levels for *K. pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Acinetobacter* Sp. stratified by location of infection onset. Points represent the incidence in infections with susceptible (turquoise), resistant (red), and missing (grey) susceptibility test results. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Bar plots (orange) show respective resistance proportions. Dashed vertical lines denote the start of the COVID-19 pandemic era.



Figure S8. Carbapenem resistance levels for *K. pneumoniae, Enterobacter cloacae, Serratia marcescens, Pseudomonas aeruginosa,* and *Acinetobacter Sp.* stratified by location of infection onset. Points represent the incidence in infections with susceptible (turquoise), resistant (red), and missing (grey) susceptibility test results. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Bar plots (orange) show respective resistance proportions. Dashed vertical lines denote the start of the COVID-19 pandemic era.

## S5.3 Infection incidence stratified by US census region

For most pathogens, infection incidence trends were similar across the four major US census regions (Midwest, northeast, south, west).



Figure S9. Infection incidence for nine species stratified by four major US census region from February 2007 to March 2020. Points represent the number of 30-day incident isolates per quarter. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Dashed vertical lines indicate the start of the COVID-19 pandemic. Colors represent different US census regions (Midwest, Northeast, South, West).

# S6 Sensitivity analyses

## S6.1 Changes in incidence during COVID-19 pandemic

During the COVID-19 pandemic, significant reductions in hospital admissions were observed.12 There are multiple reasons for such a change, including a reduced access to healthcare, in particular at the beginning of the pandemic. Outpatient clinics were closed or offered only limited appointments, many hospitals cancelled elective surgeries, and healthcare seeking behavior changed during this period. These factors (among others) have likely contributed to a change in patient case-mix in hospitals with a higher proportion of patients with more severe diseases and comorbidities. As a sensitivity analysis, we estimated trends in the absolute number of incident isolates, without dividing by number of admissions, to assess whether changes in the pandemic era might be caused by changing admission patterns. Trends in hospital-associated incidence largely persist under this alternative approach. However, for community-onset infection, we observed an increase in the infection incidence rate per hospital admission but not in the absolute number of infections when comparing infections in 2019 and during the pandemic years (Figure S10), suggesting that the increased incidence rate may be attributable to a drop in admissions for non-infectious causes. Consistent with this explanation, the absolute number of hospital admissions dropped drastically in March 2020 (Figure S11), suggesting a change in the patient case mix during the pandemic years.

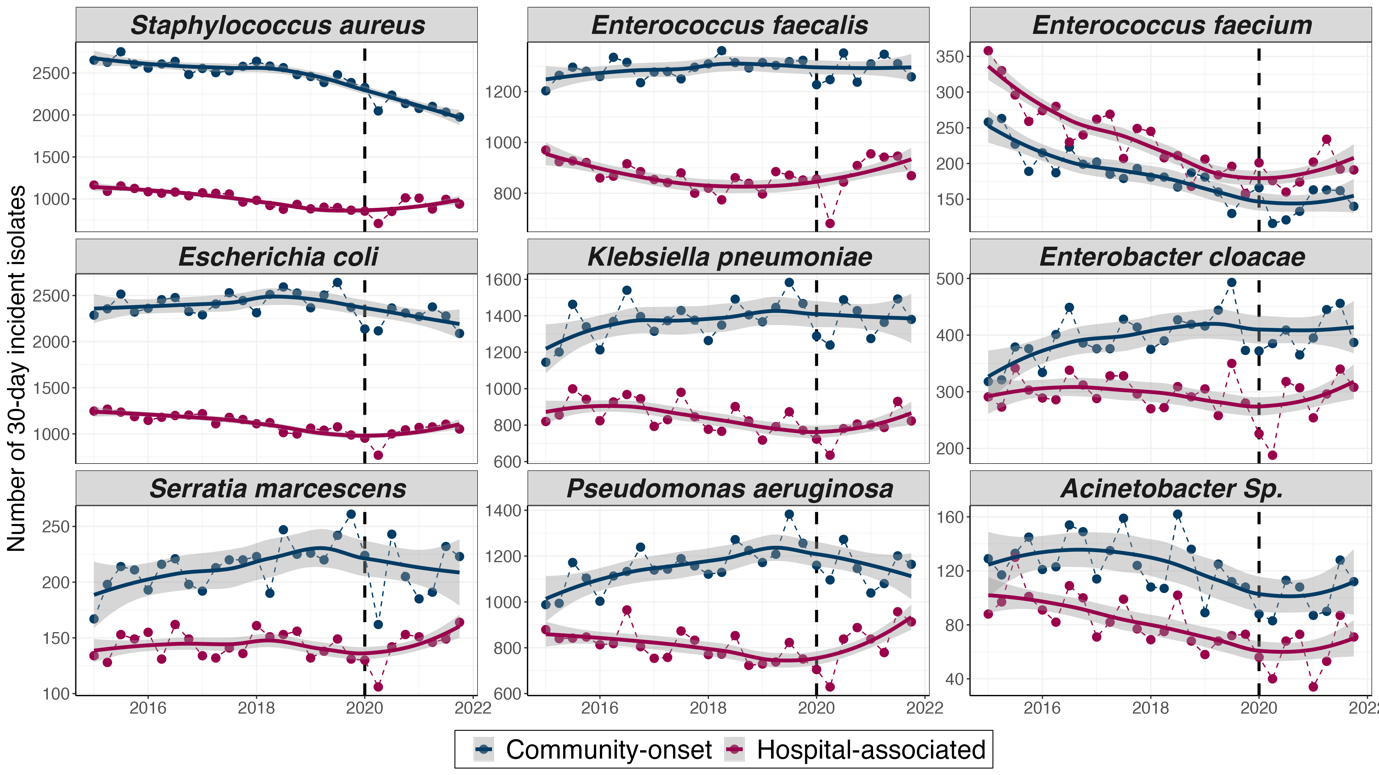


Figure S10. Number of incident isolates for nine organisms stratified by infection category from January 2015 till December 2021. Points represent the number of 30-day incident isolates per quarter. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Dashed vertical lines indicate the start of the COVID-19 pandemic. Colors represent different sources of infection.



Figure S11. Number of hospital admission from February 2007 till March 2022 across 138 Veteran Affairs Medical Centers. Points represent the number of admissions and dashed lines are linear interpolations between the points.

## S6.2 Different denominator for incidence rate calculation

There are different possibilities for denominators when calculating incidence rates. In our main analysis, we used the number of hospital admissions both calculating the incidence of infections as the denominator. The rationale behind that choice is that all clinical cultures used in our analyses were obtained from inpatients and are therefore hospital-based. However, community-onset infections may serve as proxy for community-acquired infections and thus, ideally, the size of the VA community population would be used as the denominator. In absence of these numbers, we obtained obtained information on the number of patients hat have received either outpatient or inpatient care at a given facility defined as the number of patients who had at least one outpatient or inpatient visit during that year (Figure S12). As such it includes more patients than covered by the number of inpatient hospital admissions and may be a better approximation of the community VA population. However, it is still a reflection of the population utilizing Veterans health care services and may be impacted by changes in these (as it can be seen in the drop in numbers in 2020, Figure S12). We performed the GEE analysis for the incidence of community-onset infections using these numbers as a sensitivity analysis and compared to our results in the main analysis (Figure S13). Generally, estimates for the time trend of community-onset infections remained similar.



Figure S12. Temporal trends of the number of outpatient or inpatients that received care by Veterans Healthcare Services. Patients who received care were defined by patients who had at least one outpatient or inpatient visit in a given year.



Figure S13. Time trend analyses for the incidence of community-onset infections for the main analysis and sensitivity analysis. In the Covered lives analysis, the number of patients that had at least one outpatient or inpatient visit in a given year was used as the offset (instead of the number of hospital admissions). Average annual percentage changes (AAPC) were obtained from generalized estimating equations analysis for each pathogen and for pre-pandemic (2007-2019) and pandemic period (2020-2022). AAPC larger than zero indicate an increasing trend, AAPC smaller than zero a declining trend in infection incidence.

## S6.3 Approaches to handle missing values in antibiotic susceptibility data

The interpretation of resistance data with missing susceptibility test results is a complex problem. It remains crucial to assess whether missing test results may have biased the main conclusions of our time trend analyses as presented in the main text. We performed several sensitivity analyses to investigate this.

### S6.3.1 Resistance proportion under various assumptions

In the main analysis, we calculated the resistance proportion as the number of 30-day incident isolates divided by the total number of 30-day incident isolates, including the isolates without reported susceptibility test results. This implicitly assumes that all missing test results are susceptible results. For sensitivity analyses, we considered two scenarios based an average weighted approach to calculate resistance proportions. We use the following formula:

where and are the resistance proportion and number of the isolates with known susceptibility test results, and are the resistance proportion and number of the isolates with unknown susceptibility test results, and is the total number of isolates.

In the main text, we implicitly assumed , i.e., no resistance among isolates with unknown susceptibility test results. In a first sensitivity analysis, we assumed , i.e., the resistance proportion among isolates with known is equal to the one with unknown test results. The overall resistance proportion was then weighted by their sample size, resulting in . This is equivalent with excluding the missing test results in the denominator of the resistance proportion.

In a second sensitivity analysis, we assumed . This scenario has no biological explanation but only serves as a hypothetical scenario between the other two scenarios that we considered.



Figure S14. Proportion of incident isolates resistant to Carbapenems for *K. pneumoniae, E., cloacae, P. aeruginosa*, and *Acinetobacter Sp.* under three different scenarios. The first scenario (left) represents the assumptions in the main text where missing test results are assumed to be susceptible (). The second scenario (middle) represents the assumption that the resistance proportion among isolates with known is equal to the one with unknown test results (). The third scenario (right) represents the assumption that the resistance proportion among isolates with unknown test results are half of the resistance proportion among isolates with known test results . This scenario serves as a hypothetical scenario between the other two scenarios that we considered.

### S6.3.2 Sensitivity analyses for time trend estimates

We performed various sensitivity analyses to explore the impact of different assumptions on missing test results on our main conclusions of our time trend analyses. For each of the assumptions, we performed our time trend analysis using generalized estimating equations (GEE) as described in the Methods section and in the supplement and calculated the average annual percentage change for the pre-pandemic and pandemic time trend for the resistance proportion, the incidence of resistant as well as the incidence of susceptible infections. Here, we describe two pathogen-drug combinations with a high incidence of infections with missing susceptibility test results and large temporal variability.

***Staphylococcus aureus* and fluoroquinolone resistance**

We used the following scenarios for our sensitivity analyses:

1. Methicillin resistance as a proxy for fluoroquinolone resistance: We imputed the missing test results according to known methicillin susceptibility test results, assuming that there's a perfect correlation between methicillin and fluoroquinolone resistance.
2. All missing test results are susceptible test results: We assumed that all missing test results are susceptible. This scenario represents our suspicion that generally missing test results are more likely to be susceptible.

For both sensitivity analyses, the downward trend of the overall incidence of susceptible infections slows down from 2016. In particular, for the second sensitivity analysis, where we assumed that all missing test results are susceptible, we observed an increase in the incidence of susceptible infections from 2016 (Figure S13B-C). However, these changes are not reflected in the GEE time trend estimates (Figure S13D). Given the change in trend in 2016, the GEE analysis could be by extended by introducing

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Description automatically generated with medium confidence a third time variable and performing a segmented time trend analysis. Similar to the pandemic time period, this may result in high uncertainty of estimates due to a low number of time points. When assuming that all MRSA are fluoroquinolone resistant, the resistance proportion and incidence in resistant infections increase but it does not affect its pre-pandemic trend analysis. When all missing test results are assumed to be susceptible, the trends in resistance proportion and incidence remain unaltered. Thus, our main conclusions regarding the declining trend in fluoroquinolone resistance (both in proportion and incidence) remain the unchanged and are thus robust with respect to these sensitivity analyses.

Figure S15. Sensitivity analyses for temporal trends of fluoroquinolone resistance for S. aureus infections. (A-C) Temporal trends in resistance proportion and phenotypic incidence from 2007-2022 for the main and sensitivity analyses. Two sensitivity analyses were considered: (1) Methicillin resistance as a proxy for fluoroquinolone resistance where missing test results are imputed according to known methicillin susceptibility test results, assuming that there is a perfect correlation between methicillin and fluoroquinolone resistance, (2) All missing test results are susceptible test results where all missing test results are imputed with susceptible test results. Bar plots (orange) show respective resistance proportions. Points represent the incidence in infections with susceptible (turquoise), resistant (red), and missing (grey) susceptibility test results. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Dashed vertical lines denote the start of the COVID-19 pandemic era. (D) Average annual percentage change (AAPC) obtained from generalized estimating equations analysis for resistance proportion, and the phenotypic incidence of resistant and susceptible infections and for the main and sensitivity analyses. Points represent point estimates, lines the 95% confidence intervals of the GEE estimates. AAPC larger than zero indicate an increasing trend, coefficients smaller than zero a declining trend in infection incidence.

***Pseudomonas aeruginosa* and 3rd generation cephalosporin resistance**

For this example, we performed the sensitivity analysis where *All missing test results are susceptible test results* (see description above). Similar to the previous example, we observe an increase in the overall incidence susceptible infections from 2016 but the overall trends remain the same (Figure S14). Thus, our main conclusions regarding the declining trend in 3rd generation cephalosporin resistance (both in proportion and incidence) for *P. aeruginosa* remain the unchanged and are thus robust with respect to this sensitivity analysis.

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Figure S16. Sensitivity analyses for temporal trends of 3rd generation cephalosporin resistance for *P. aeruginosa* infections. (A-B) Temporal trends in resistance proportion and phenotypic incidence from 2007-2022 for the main and sensitivity analysis. In the sensitivity analysis all missing test results are susceptible test results (all missing test results are imputed with susceptible test results). Bar plots (orange) show respective resistance proportions. Points represent the incidence in infections with susceptible (turquoise), resistant (red), and missing (grey) susceptibility test results. Lines and grey bands are smoothing curves using the *locally estimated scatterplot smoothing (loess)* method and corresponding 95% confidence intervals. Dashed vertical lines denote the start of the COVID-19 pandemic era. (C) Average annual percentage change (AAPC) obtained from generalized estimating equations analysis for resistance proportion, and the phenotypic incidence of resistant and susceptible infections and for the main and sensitivity analyses. Points represent point estimates, lines the 95% confidence intervals of the GEE estimates. AAPC larger than zero indicate an increasing trend, coefficients smaller than zero a declining trend in infection incidence.

### S6.3.3 Distribution of missing susceptibility test results across different complexity levels

Individual VA Medical Centers are allowed to develop and implement their own policies for reporting antimicrobial susceptibility results. However, the Veterans Health Administration Pathology and Laboratory Medicine Service provides overall guidance to VA facilities and supports adherence to the interpretive criteria established by the Clinical and Laboratory Standards Institute (CLSI). Hence, we expect that practices are more similar among VA hospitals compared to a random sample of US hospitals. We do not have information on the exact policies and reasons for missing susceptibility test results for each facility and expect that these may vary by the complexity level of the facility. We explored the proportion of missing susceptibility test results for fluoroquinolones, 3rd generation cephalosporins, and carbapenems stratified by facility complexity level (Figures S15-17). Generally, the missingness proportion and its distribution across facility complexity levels varies across different pathogens. For gram-negative organisms, the missingness proportion for these three drug classes tends to be higher in facilities with low complexities compared to with high complexities. In contrast, the proportion of missing fluoroquinolone susceptibility test results are lower in facilities with lower complexities than for those with higher complexities for *S. aureus* and *E. faecium*. Thus, there are differences in reporting practices among facilities with different complexity levels. In our time trend analyses, we included facility complexity level as a covariate to adjust for these differences.

**Figure S17. Missing fluoroquinolone susceptibility test results for all nine target organisms stratified by facility complexity level.** The missingness proportion was calculated as the percentage of 30-day incidence isolates with missing susceptibility test results per year and is depicted as a bar plot. 95% confidence intervals were calculated using the normal approximation of binomial proportion confidence intervals.



Figure S18. Missing 3rd generation cephalosporin susceptibility test results for *E. coli, K. pneumoniae, E. cloacae, Serratia marcescens, P. aeruginosa*, and *Acinetobacter s*p. stratified by facility complexity level. The missingness proportion was calculated as the percentage of 30-day incidence isolates with missing susceptibility test results per year and is depicted as a bar plot. 95% confidence intervals were calculated using the normal approximation of binomial proportion confidence intervals.



Figure S19. Missing carbapenem susceptibility test results for *E. coli, K. pneumoniae, E. cloacae, Serratia marcescens, P. aeruginosa*, and *Acinetobacter sp.* stratified by facility complexity level. The missingness proportion was calculated as the percentage of 30-day incidence isolates with missing susceptibility test results per year and is depicted as a bar plot. 95% confidence intervals were calculated using the normal approximation of binomial proportion confidence intervals.

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