**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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**Summary**

**Background:** Antimicrobial resistance (AMR) poses a major threat to public health. Comprehensive nationwide studies that quantify long-term trends in infection incidence and AMR for multiple pathogens are scarce. This study aims to fill this gap by analyzing trends in inpatient infection incidence and AMR for nine pathogens over the past 15 years across the United States (US).

**Methods:** We analyzed clinical microbiology data from electronic health records from all patients admitted to all 138 Veterans Affairs (VA) Medical Centers with acute-care wards across the US from February 1, 2007 through March 1, 2022. We quantified inpatient antibiotic use as days of therapy (DOT) per 1,000 patient-days and AMR by: (1) resistance proportion (percentage of incident isolates identified as resistant); (2) phenotypic incidence (incidence of infections per 1,000 admissions classified as resistant, susceptible, or missing). To analyze pre-pandemic and pandemic trends, we used generalized estimating equation models and report average annual percentage changes (AAPC).

**Findings:** Between 2007 and 2019,infection incidence and AMR declined for many pathogens and pathogen-drug combinations. The proportion of methicillin resistance in *S. aureus* (MRSA) dropped from 58%(11876/20584) to 44.7%(5916/13257) over these 13 years (AAPC: -1.8%, 95%CI:[-2.4, -1.2]; p-value<0.0001), while vancomycin-resistant *E. faecium* (VRE) infections decreased from 77.8%(2555/3285) to 65.1%(893/1371) (AAPC: -1.2%, 95%CI:[-2.5, 0.0]; p-value = 0.052). Fluoroquinolone resistance declined in both proportion and incidence for most pathogens. These trends correlated with substantial reductions in fluoroquinolone use, from 125 to 20 DOT/1,000 patient-days. Third generation cephalosporin resistance increased steeply in *E. coli* infections (6.7%(942/14042) to 15.3%(2153/14053); AAPC: +8.5%, 95%CI:[6.2, 10.7]; p-value<0.0001). Carbapenem resistance proportion increased in *E. cloacae* infections (1%(30/2852) in 2007 to 7.3%(212/2919) in 2019; AAPC: 19.8%, 95%CI:[13.7, 26.2]; p-value<0.0001), but remained low for *K. pneumoniae* and *E. coli*. Since the emergence of SARS-CoV-2 in 2020, several pathogen-drug combinations increased in both incidence and resistance for hospital-associated infections (HAI). For some pathogen-drug combinations, trends in incidence of resistant and susceptible infections were divergent, whereas for other combinations, these trends were in the same direction.

**Interpretation:** Significant reductions in MRSA, VRE, and fluoroquinolone resistance across multiple pathogens suggest that control efforts have had an impact. The rise in extended-spectrum beta-lactamases producing Enterobacterales and recent surge in HAI emphasize the need for ongoing surveillance and interventions. Our study highlights how coupling the analysis of phenotypic incidence with resistance proportion can enhance interpretation of AMR data.

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**Research in context**

**Evidence before this study**

Long-term surveillance data describing trends in clinical infection incidence and antimicrobial resistance (AMR) across multiple pathogens and locations are scarce. We searched PubMed for publications in English from January 1, 1990 till March 1, 2022 with the terms (trends OR epidemiology OR dynamics OR incidence OR prevalence) AND (infection OR 'antimicrobial resistance' OR resistance OR 'antibiotic susceptibility') and reviewed titles to identify relevant articles and reference lists from relevant articles. Most studies of temporal infection incidence and AMR trends focus on bloodstream infections, target specific pathogen-drug combinations, were performed in a single center, span only a few years, or were performed over a decade ago. Most studies do not report antibiotic use data. Only one study reports temporal trends for infection incidence, AMR, and antibiotic consumption for both pre-pandemic and pandemic period for *S. aureus* in a UK pediatric hospital between 2000–2021. One study estimated AMR proportions for thirteen pathogen-drug combinations in 51 countries from 2009 to 2019 based on the Antimicrobial Testing Leadership and Surveillance (ATLAS) database. For the US, the most comprehensive estimates on AMR are reported in CDC’s 2019 Antibiotic Resistance Threats report for 18 antimicrobial-resistant bacteria and fungi from 2012 to 2016. AMR proportions (percentage of isolates with a resistant test result) declined in the U.S. during this period for multiple pathogens, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, multi-drug resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter*. An increase in resistance proportions was reported for several organisms including ESBL-producing Enterobacteriaceae. The impact of COVID-19 on AMR in the U.S. was highlighted in CDC’s 2022 special report reporting an increase in AMR proportion of at least 15% from 2019 to 2020 among seven pathogens. The databases from these studies rely on voluntarily participating hospitals in countries around the world (ATLAS) and in selected states in the US (CDC) and include only a subset of bacterial isolates within each hospital. It is unclear whether the selected samples reflect a random sample of all healthcare-associated infections. In addition, these studies exclusively report AMR proportions. However, temporal trends of AMR proportions alone give an incomplete picture, as they do not reveal the change in the incidence of infection by AMR phenotypes (incidence of infections per 1,000 admissions classified as resistant or susceptible, or for which susceptibility data are missing).

**Added value of this study**

We highlight the value of routinely collected microbiology data and delineate trends of infection incidence and AMR for nine major pathogens causing both community-acquired and hospital-associated infections. Our study provides data for 13 years prior to the COVID-19 pandemic and 2 years during the pandemic and covers over 138 facilities with varying complexities and over all census regions in the US. Whereas previous studies solely reported AMR proportions, we coupled two measures of AMR by simultaneously reporting and visualizing both AMR proportions and AMR phenotypes (incidence per 1,000 admissions for isolates that are resistant, susceptible, or with missing susceptibility test results). We showed that trends in susceptible infections may be inverse to trends in resistance proportions. For instance, for hospital-associated infections in *E. coli* and third generation cephalosporins, resistance proportion increased while the incidence of susceptible infection declined. Our visualization method also offers a crucial perspective on potential biases in reported resistance levels by explicitly providing incidence rates of missing susceptibility test results. We observed high rates of missing carbapenem test results, with high variability over time indicating selective reporting of antibiotic susceptibilities. Using antibiotic prescribing data in VA facilities, we were able to show that the decline in fluoroquinolone resistance was associated with a substantial decline in fluoroquinolone use in the VA during the same period.

**Implications of all available evidence**

Substantial reductions in hospital-associated infections imply that hospital infection control measures may have been effective and should be continued. This success may now be challenged with the rise of ESBL-producing and carbapenem-resistant Enterobacterales and the increase in hospital-associated infections across several pathogen-drug combinations. Surveillance programs should focus on reporting both AMR proportions and phenotypic incidence to understand the underlying dynamics causing AMR and to devise effective infection control strategies.

**Introduction**

Antimicrobial resistance (AMR) is a critical global health concern. Antibiotic resistant pathogens in healthcare settings have significantly complicated the management of infections, increasing morbidity, mortality, and healthcare costs.(1) An estimated 4.95 million deaths were associated with and 1.27 million deaths were attributable to AMR worldwide in 2019.(2)

Most studies of temporal AMR trends target specific pathogen-drug combinations, were performed either in a single center, span only a few years, cover only a specific geographic region within a country, or were performed over a decade ago.(3–9) Few studies provide estimates for multiple pathogen-drug combinations over an extended period.(10) Rahbe and colleagues estimated AMR rates for thirteen pathogen-drug combinations in 51 countries from 2009 to 2019 based on the Antimicrobial Testing Leadership and Surveillance (ATLAS) database.(10,11) Emons and colleagues provide an overview of temporal patterns of antibiotic resistance rates in Europe for 1998-2019.(12) For the US, the latest AMR estimates were provided by the CDC in the AMR threat report, covering 2013 to 2019(1) and in a special report highlighting the impact of the first year of the COVID-19 pandemic on AMR(13). All four studies suffer from limitations on data quality and consistency within and across countries. The databases from these studies rely on participating hospitals in countries around the world (ATLAS), in Europe (ECDC) and in selected states in the US (CDC) and include only a subset of bacterial isolates within each hospital. It is unclear whether the selected samples reflect a random sample of healthcare-associated infections. In addition, these studies focus on reporting AMR proportions (percentage of isolates with a resistant test result). While local data on AMR proportion can be helpful for guiding clinicians in the selection of the best antibiotic therapy, temporal trends of AMR proportions alone can be misleading to public health professionals as they do not reveal the change in the incidence of infection by AMR phenotypes. For example, an increase in AMR proportion may suggest an increase in the incidence rate of resistant infections. However, it may be due to a decrease in the incidence of susceptible infections combined with a stable incidence of resistant infections.(14) Reporting both AMR proportions and the phenotypic incidence is, therefore, crucial for a holistic view of the changing AMR landscape.

In this study, we used all clinical microbiology data from patients admitted to acute care wards of the US Veterans Affairs (VA) Healthcare System from 2007 to 2022. As the largest integrated healthcare network in the US, the VA database includes detailed clinical and microbiology data, and linked information on hospitalizations and inpatient antibiotic consumption. We focused on nine pathogens: *Staphylococcus aureus, Enterococcus faecium, Enterococcus faecalis, Acinetobacter sp., Pseudomonas aeruginosa, Serratia marcescens, Enterobacter cloacae, Escherichia coli,* and *Klebsiella pneumoniae*; representing a range of pathogens commonly associated with healthcare-associated and community-acquired infections, and multidrug-resistance.(1) We calculated the incidence of infection by species, and assessed trends in AMR using both the proportion resistant and the phenotypic incidence (rate of susceptible, resistant and missing susceptibility test results) over time. Our aim is to describe the landscape of infection incidence and AMR within the US VA Healthcare System over the last 15 years.

**Methods**

*Data*

We analyzed clinical data from all patients admitted to all VA medical centers (VAMC) with acute care wards (either medical/surgical wards or intensive care units) in the US from February 1, 2007 through March 1, 2022. 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 assessment (e.g., level and type of care provided, Appendix S1.2) in all eligible years during the study period. In total, 138 VAMCs were included in the analysis. Information on patient demographics (age, race, ethnicity) were available and reported in Table 1 and in the appendix (S1.4 page 5). 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.

Clinical diagnostic cultures were extracted from electronic health records as previously described.(15) Our analysis only included results from clinically-directed cultures, ordered to evaluate suspected infection. 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 cultures grown 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. Infections were classified as community-onset (COI) when the specimen was obtained ≤3 days after admission and as hospital-associated (HAI) if the specimen was obtained >3 days after admission or within 30 days after discharge. We defined infection incidence as the number of incident isolates per 1,000 admissions.

Antimicrobial susceptibility test (AST) results were used to determine whether a culture was resistant to a specific antibiotic. Interpretation of ASTs was based on the reported minimum inhibitory concentrations (MIC) and categorized into susceptible, intermediate, and resistant. We grouped intermediate and resistant in our analyses. Resistance to an antibiotic class was defined as resistance to at least one antibiotic in that class. Interpretation of AST results adhered to breakpoint revisions by the Clinical and Laboratory Standards Institute. We assessed AMR using two measures: (1) resistance proportion, i.e., the percentage of all 30-day incident isolates with a resistant or intermediate susceptibility test result divided by the total number of isolates (including missing results); (2) phenotypic incidence rate, i.e., the absolute number of incident isolates with susceptible, resistant, and missing test result per 1,000 admissions. Inpatient antibiotic use was calculated as days of therapy (DOT) per 1,000 patient days. We report changes in resistance proportion by reporting both the absolute difference in resistance proportion between the start and end of a period and by reporting trend analyses estimates (see below).

This study received approval from the University of Utah Institutional Review Board and the VA Salt Lake City Health Care System Research and Development Office which waived patient consent because the project relied on retrospective analysis of existing patient records.

*Statistical Analysis*

To model incidence rate and resistance proportion trends, we employed robust Poisson regression with the Generalized Estimating Equation (GEE) approach.(16)Clustering by VAMC was modeled with an autoregressive correlation structure within a facility, used calendar year as a continuous variable as exposure, and number of admissions (for incidence rates) or the total number of isolates (for resistance proportion) as offset. We adjusted for major hospital characteristics including patient demographics, census region, facility complexity level, and patient volume and thereby accounted for spatial variation and population density (Appendix S1.4, S4.1). In addition, we estimated the multiplicative average annual percentage change (AAPC) based on the estimated marginalized time trend coefficient from our GEE analysis and calculated it as follows:

i.e., as the relative rate of change in incidence per year (averaged over the time period), expressed as a percentage. We computed the relative contribution of COI and HAI to the overall time trend based on estimated time trend coefficients (Appendix S4.2). Separate time trend coefficients were obtained for the pre-pandemic and the pandemic period. Statistical analyses used R version 4.3.1.(17) The code and results of our analyses can be found online: <https://github.com/tm-pham/mind_aim2-1_descriptive_paper.git>

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Role of the Funding Source

Funding resources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Results**

Between Feb 1, 2007 and March 1, 2022, 991,527 clinical 30-day incident isolates were collected from 507,760 patients in 138 VA medical centers and 50 states in the US. The most commonly isolated organisms were *S. aureus*, *E. coli*, and *K. pneumoniae* (Table 1)*.* Most cultures were collected from non-blood culture sites, with proportions ranging from 86.1% for *S. aureus* to 95.4% for *P. aeruginosa*.

The overall infection incidence across all nine pathogens declined (Figure 1A, Appendix page 12, Table S6) during the pre-pandemic period (2007-2019), with an AAPC of -2.2% (95%CI: [-3.2, -1.2]; p-value < 0.0001). For individual pathogens, overall infection trends declined or remained stable (Figure 1C and S2, Appendix page 12, Table S6). The largest pre-pandemic decline was observed for *E. faecium* and *S. aureus,* with an AAPC of -7.5% (95%CI: [-10.2, -4.7]; p-value<0.0001) and -3.8% (95%CI: [-4.7, -2.9]; p-value<0.0001), respectively. A decline in HAI accounted for 82.4% of the pre-pandemic decline in the overall infection burden. Each pathogen had a downward trend in HAI (Appendix Figure S4 and S6, Table S6). The overall burden of COI across all pathogens remained stable (AAPC: 0.4%, 95%CI: [-0.6, 1.4], Figure 1C).

Overall proportions of infections resistant to one or more key antibiotic classes declined from 57.9% in 2007 to 47.0% in 2019. The proportion resistant to a single key antibiotic class remained stable while the proportion resistant to multiple drug classes declined from 39.5% in 2007 to 29.5% in 2019 (Figure 1C).

From 2007 to 2019, the proportion of *S. aureus* infections that were methicillin resistant declined from 57.7% (11876/20584) to 44.6% (5916/13257) over these 13 years (AAPC: -1.8%, 95%CI: [-2.4, -1.2]; p-value < 0.0001 ) (Figure 2, Appendix page 13, Table S7), and the proportion of *E. faecium* infections resistant to vancomycin declined from 77.8% (2555/3285) to 65.1% (893/1371; AAPC: -1.2%, 95%CI: [-2.5, 0.0]; p-value= 0.052). The decline in the fraction of infections that were resistant was proportional to the decreasing incidence of resistant infection. These trends were primarily driven by decreases in resistant HAI (relative contribution of 65.7% and 70.1% for MRSA and VRE, respectively). Compared to *E. faecium, E. faecalis* infections were much less likely to be vancomycin resistantbut also demonstrated a decreasing secular trend, from5.8% (447/7721) in 2007 to 3.3% (285/8663) in 2019 (AAPC: -1.5%, 95%CI: [-5.6, 2.8]; p-value= 0.4913)

Fluoroquinolone resistance declined from 2007 to 2019 both in proportion and in incidence for most pathogens (Figure 3A,B, Table S8), most notably for *E. faecium*, *E. faecalis*, and *S. aureus* for which the AAPC in the incidence of fluoroquinolone-resistant infections was -9.3% (95%CI: [-14.2, -4]; p-value = 0.0007), -5.7% (95%CI: [-9.4, -1.9]; p-value = 0.0035), and -6.2% (95%CI: [-7.9, -4.5]; p-value < 0.0001), respectively. For *S. aureus*, *E. coli*, and *P. aeruginosa*, we estimated a declining trend for fluoroquinolone-susceptible infections as well, but the confidence intervals for the change included zero (Appendix page 14-15, Table S8). Overall inpatient administrations of fluoroquinolones declined from 125 DOT to 20 DOT per 1,000 patient days from 2007 to 2022 (Figure 3B).

For aerobic Gram-negative non-fermenters (*P. aeruginosa, Acinetobacter Sp.*), the proportion of infections resistant to 3rd generation cephalosporins (CPH-03) declined due to a decline in the incidence of resistant infections (Figure 4A, Appendix page 16, Table S9). We estimated a steeper decline for *P. aeruginosa* (AAPC: -10.1%, 95%CI: [-12.9, -7.1]; p-value < 0.0001) than for *Acinetobacter sp.* (-1.7%, 95%CI: [-4.3, 1.0]; p-value= 0.2086).

Within the order of Enterobacterales, resistance patterns did not follow a consistent trend. CPH-03 resistance proportions stayed stable for *E. cloacae* (AAPC: -0.2%, 95%CI: [-2.5, 2.1]; p-value=0.8615) and *S. marcescens* (AAPC: -0.5%, 95%CI: [-5.3, 4.6]). For *K. pneumoniae*, overall CPH-03 resistance proportion had an increasing trend (AAPC: 2.1%, 95%CI: [ -0.6, 4.8]; p-value= 0.1258) with increasing trends for both COI (AAPC: 2.2%, 95%CI: [-0.6, 5.1]; p-value= 0.126) and HAI (AAPC: 1.9%, 95%CI: [-0.9, 4.8]; p-value= 0.1754).

For *E. coli*, the CPH-03 resistance proportion increased steeply from 6.7% (942/14042) in 2007 to 15.3% (1945/12696) in 2019 (AAPC: +8.5% (95%CI: [6.2, 10.7]; p-value < 0.0001). While CPH-03 resistance proportion increased both for COI and HAI in *E. coli* infections, phenotypic incidence dynamics differed (Figure 4B). For COI, the incidence in resistant *E. coli* infections increased (AAPC: 6.5%, 95%CI: [4.0, 9.0]; p-value < 0.0001) whereas CPH-03 susceptible COI infection incidence stayed stable. In contrast, for HAI, while the incidence of resistant *E. coli* infections increased, the incidence of susceptible infections decreased (Figure 4B, Appendix page 16, Table S9). For *P. aeruginosa*, the CPH-03 resistance proportion declined, in parallel to a decrease in the incidence of resistant infections. However, the incidence of CPH-03 susceptible *P. aeruginosa* infections showed an increasing trend (AAPC: 2.1%, 95%CI: [-0.4, 4.7]; p-value=0.0968). The overall inpatient administrations of 3rd generation cephalosporins increased from 47.1 to 77.1 DOT per 1,000 patient days from 2007 to 2022 (Figure 4D).

Overall, carbapenem resistance was infrequent among Enterobacterales (Figure 5, Appendix page 18, Table S10). Carbapenem resistance proportion in *E. cloacae* increased from 1% (30/2852) in 2007 to 7.3% (212/2919) in 2019. This increase was largely caused by an increase in the carbapenem-resistant infection incidence for which we estimated an AAPC of 5.0% (95%CI: [1.9, 8.2]; p-value=0.0012). For *K. pneumoniae* infections, carbapenem resistance proportions stayed stable with a maximum of 2.6% (222/8557) in 2007. For *E. coli*, it remained less than 0.5% throughout the period.

The highest proportion of carbapenem resistance was observed in infections caused by *Acinetobacter sp.* with 19.4% (257/1322) in 2007, a maximum of 31.2% (475/1521) in 2009, and declining to 15.7% (111/705) in 2019 (AAPC: -3.7%, 95%CI: [-8.6, 1.5]; p-value= 0.16). The incidence of susceptible infections declined at a similar rate (AAPC: -2.6%, 95%CI: [-5.2, 0.0]) to the incidence of resistant infections (AAPC: -2.8%, 95%CI [-6.0, 0.5]; p-value= 0.131). The overall inpatient administrations of carbapenems increased from 22.1 to 26.6 DOT per 1,000 patient days from 2007 to 2012 and subsequently declined to 20.4 DOT per 1,000 patient days (Figure 4D).

Carbapenems had one of the highest rates of non-reported susceptibility test results (Figure 5) among the key antibiotic classes we evaluated, indicating selective reporting of susceptibility test results. We performed sensitivity analyses by using an average weighted approach to calculate resistance proportions under different assumptions than in the main analysis (Appendix 5.3). General time trends remained unaffected by these assumptions (Figure S14). However, resistance proportions could be higher under different assumptions. For example, for *Acinetobacter sp.*, carbapenem resistance proportions reached values up to 42% (compared to 32% in the main analysis) if isolates with known and unknown susceptibility test results are assumed to have the same resistance proportions.

Since the start of the COVID-19 pandemic, infection incidence trends have reversed for HAI in many pathogen-drug combinations (Appendix Figure S6, Table S7-10). While the incidence of vancomycin resistant HAI increased for *E. faecium*, we also estimated increases in the incidence of susceptible infections (Table S7). Thus, resistance proportions remained stable for *E. faecium* (AAPC: 0.2%, 95%CI: [ -5.0, 5.7]; p-value= 0.9489). We estimated a larger downward trend for MRSA resistance proportions (AAPC: -4.8% (95%CI: [-8.5, -0.9]; p-value=0.0175) in HAI during the pandemic years than prior to the pandemic. However, the decline was primarily due to a steep increase in the incidence of MSSA (AAPC: 11.5%, (95%CI: [5.6, 17.8]; p-value=0.0001) rather than due to a decline in MRSA. As a sensitivity analysis, we assessed trends in the absolute number of incident isolates, without normalizing by number of admissions, to evaluate if shifts during the pandemic era could be attributed to variations in admission patterns. Trends in HAI largely persist under this alternative approach. However, for COI, we did not observe an increase in the absolute number when comparing infections in 2019 and during pandemic years (Figure S10). 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 and that the increase in incidence of COI may be attributable to a drop in admissions for non-infectious causes.

**Discussion**

We presented a US national study analyzing trends in infection incidence and AMR across nine pathogens and 28 pathogen-drug combinations over 13 years before and two years during the COVID-19 pandemic. To examine AMR dynamics, we developed a visualization method that presents information on both resistance proportion and phenotypic incidence.

For each pathogen, we observed a trend of declining incidence of HAI from 2007 to 2019. In contrast, trends in incidence of COI varied across pathogens. The decrease in HAI accounted for an overall reduction of infection incidence from 2007 to 2019. In 2020, coincident with the COVID-19 pandemic, incidence rose, particularly for HAI.

Resistance proportions between 2007 and 2019 declined for many but not all pathogen-drug combinations. A consistent finding for all nine species was a decrease in fluoroquinolone resistance proportion between 2007 and 2019. Similar to the CDC AMR threats report from 2019, infections caused by ESBL-producing and by carbapenem-resistant Enterobacterales increased in our study. We provide more species-level details: these increases were caused by an increase in the incidence of ESBL-producing *E. coli* infections and in carbapenem-resistant *E. cloacae* infections from 2007 to 2019. During the pandemic years (2020-2022), we observed a rise in resistance proportions of HAI for several pathogen-drug combinations, reversing some previously declining trends.

While proportion-based analyses can be helpful for guiding empiric therapy, they can lead to biased assessments of AMR trends.(14) To address this, we coupled our analysis of resistance proportion to an examination of phenotypic incidence. We observed that trends in resistance proportion generally correlated with trends in incidence of resistant infection. In contrast, the relationship between resistance proportion and incidence of susceptible infection was more variable. For HAI in *E. coli* and CPH-03, resistance proportion increased while the incidence of susceptible infection declined. In other cases, trends in resistance proportions were the inverse to both the incidence of resistant and susceptible infections. For example, the percentage of *S. aureus* isolates resistant to fluoroquinolones decreased during the pandemic period (2020-2022). Although this suggests a reduction in the incidence of resistant infections, our data indicate a minor increase and an even sharper increase in the incidence of susceptible infections.

It is useful to consider potential explanations for the observed trends. The decline in fluoroquinolone resistance paralleled a substantial decline in fluoroquinolone use in the VA during the same period. In addition, the Food and Drug Administration has issued six safety warnings related to fluoroquinolones since 2008,(18) and the declining antibiotic prescribing trends might reflect a broader shift within the VA and elsewhere toward more cautious fluoroquinolone prescribing practices.(19)The VHA launched infection control and stewardship initiatives between 2007 and 2014(20–22) that may have affected rates of transmission between hospitalized patients as well as the risk of clinical infection among colonized individuals.(23) Interventions vary in their expected effects on trends in incidence of susceptible and resistant pathogens. For instance, we would expect that preventive measures that reduce the risk of clinical infection but not colonization, such as the central line-associated infection (CLABSI) bundle, are likely to affect both the incidence of resistant and susceptible infections. In practice, patients with central lines are often in intensive care units and therefore more likely to be exposed to resistant bacteria. The CLABSI bundle might, therefore, have a differentially greater impact on resistant than on susceptible infections. Similarly, interventions aimed at decreasing transmission are expected to disproportionately reduce rates of resistant infections.(24) Given the observed increase in the use of CPH-03 across VA facilities, one might have expected a corresponding consistent rise in resistance across pathogens. However, the impact of changes in antibiotic use on AMR likely depends on the magnitude of change.(25,26) Fluoroquinolone use declined more than 6-fold during the study period while for CPH-03 use we observed an increase by only 1.6-fold. In addition, while we have reported inpatient antibiotic use in this study, other settings may play an important role for antibiotic selection pressure. McFadden and colleagues showed that community antibiotic use was the dominant factor governing the prevalence of ESBL-producing *E. coli* colonization.(27) Our observed trends are likely a combination of the complex pathogen-drug interactions, direct and indirect consequences of infection control measures at the VA, and characteristics of the underlying population.(19,28) Teasing apart the distinct effects for each of these factors would require additional data on putative exposures and confounders and warrants detailed explorations in future studies.

Our work highlights potential biases in resistance reporting by showcasing the incidence rates of missing susceptibility test results. We observed high rates of missing carbapenem test results, with high variability over time. This observation is in line with empirical evidence suggesting concern about the emerging threat of carbapenem resistance and that selective reporting of antibiotic susceptibilities can influence physicians' prescribing decisions and therefore help reducing inappropriate and unnecessary antibiotic prescriptions(29). However, these missing test results hinder our ability in accurately assessing current levels of and changes in carbapenem resistance. Thus, AMR data with high rates of missing test results have to be interpreted with caution. While we cannot fully address this issue without understanding the reasons for their absence, we introduced a crucial dimension for representing uncertainty and provide a holistic view for making informed interpretations of the results. In addition, we performed sensitivity analyses (appendix S6.3 page 25ff) to assess the impact of different assumptions about missingness on our estimates of trends in resistance proportion and infection incidence and showed that our main conclusions remained unchanged. Ongoing and improved surveillance remains vital for comprehensively tracking changes in AMR trends.

These results have several limitations. First, the patient population is limited to enrolled veterans in the US with access to the VA Healthcare System. The veteran population differs from the general population in their health characteristics, including their demographics, underlying health conditions, exposures, and healthcare utilization patterns. However, our study included data from 138 medical facilities with varying complexity level, from different geographic regions in the US, and over 15 years. Second, while we assessed many pathogen-drug combinations, we only assessed one antibiotic class for each pathogen at a time. To accurately assess multidrug resistance, it remains crucial to evaluate full susceptibility profiles.(30) Third, we used the incidence of 30-day incident clinical isolates as a proxy for the incidence of clinical infections. These will include episodes of colonization as well as infection and may therefore overestimate the true incidence of clinical infections. Fourth, time trend analysis estimates for the pandemic period show large uncertainties due to a small number of three time points. Fifth, for calculating infection incidence, we used the number of hospital admissions as the denominator. For community incidence, alternative denominators that represent the true VA population at risk may be more appropriate. Changes in community incidence (such as observed during the COVID-19 pandemic) may be attributable to changes in the admitted patient population. In absence of the true number of the population at risk, we performed sensitivity analyses using the number of patients who had at least one outpatient or inpatient visit during that year as the denominator. This is a more accurate indicator of the community VA population at risk; however, it is still influenced by disruptions in use of VA health care services. In the appendix (S6.2 page 23), we showed that estimates for the time trend of community-onset infections remained similar when using this alternative denominator. Lastly, we do not have sufficient information about infection control practices, strain characteristics, or colonization data to assess the impact of the COVID-19 pandemic on AMR. Although we cannot determine causes for the observed trends, we have identified potential explanations for some. These hypotheses may serve as targets for further investigations.

The findings of this study have implications for policy, clinical practice, and antimicrobial stewardship within the US VA Healthcare System and beyond. The significant reductions in MRSA, VRE and hospital-associated infections underscore the importance of system-wide infection prevention and antimicrobial stewardship programs such as those implemented in the VA. Amidst these promising developments, the surges in ESBL-producing and carbapenem-resistant Enterobacterales and in resistance of hospital-associated infections during the COVID-19 pandemic call for enhanced surveillance and action to counteract these rising trends.

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The views expressed in this article are those of the authors and do not necessarily represent the position or policy of the Department of Veterans Affairs, the United States government, or any of the affiliated institutions.

**Contributors**

MS, TMP, ML, YG conceptualized the study. MS, ML, and YG obtained funding for the study. YZ, TMP, and ML developed the methodology. MN, TMP, HL, YZ curated the data. TMP, YZ, HL performed the formal analysis. TMP visualized the data. YZ, HL, and MN accessed and verified the data for the analysis. TMP prepared the first draft of the manuscript. MS, ML, YG, YZ, KK, MN, and HL commented on the data and its interpretation. All authors revised the content of the manuscript critically and approved the final version. All authors had final responsibility for the decision to submit for publication.

**Declarations of Interest**

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**Data Sharing Statement**

Individual-level patient data cannot be provided due to VA Privacy Practices. Artificial data that represents the original data will be provided along with a data dictionary that defines each field in the data set, and supporting documentation (statistical/analytic code) is published on Github: <https://github.com/tm-pham/mind_aim2-1_descriptive_paper.git>

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Table 1. Descriptive statistics of clinical cultures by organism, Feb 2007 - March 2022. 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. Only the most common groups are displayed in this table. A more detailed table on patient demographics can be found in the appendix.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Organism** | **No. of incident isolates** | **Perc. male (%)** | **Median age (IQR)** | **Race and ethnicity** | | | **Perc. HAI\*** | **Culture sites (n, %)** | | | |
| **White**  **(n, %)** | **Black or African American (n, %)** | **Hispanic or Latino (n, %)** | **blood** | **respiratory** | **urine** | **other** |
| **Gram-positive cocci** | *Staphylococcus aureus* | 247,329 | 96.6 | 66 (59, 75) | 188,964 (76.4%) | 42,986 (17.4%) | 14,644 (5.9%) | 32.2% | 34,496 (13.9%) | 48,954 (19.8%) | 28,145 (11.4%) | 135,734 (54.9%) |
| *Enterococcus faecalis* | 134,091 | 96.4 | 71 (63, 80) | 97,755 (72.9%) | 27,999 (20.9%) | 7,645 (5.7%) | 44.8% | 2,205 (9.8%) | 6,370 (28.2%) | 7,584 (33.6%) | 6,409 (28.4%) |
| *Enterococcus faecium* | 37,906 | 95.6 | 69 (62, 78) | 27,310 (72%) | 8,109 (21.4%) | 2,219 (5.9%) | 45.3% | 6,068 (4.6%) | 34,172 (26.2%) | 56,488 (43.3%) | 33,768 (25.9%) |
| **Enterobacterales** | *Escherichia coli* | 222,098 | 92 | 71 (63, 81) | 156,882 (70.6%) | 50,674 (22.8%) | 16,800 (7.6%) | 42.2% | 15,212 (11%) | 20,171 (14.6%) | 78,072 (56.6%) | 24,468 (17.7%) |
| *Klebsiella pneumoniae* | 137,923 | 95.1 | 70 (63, 79) | 96,760 (70.2%) | 32,511 (23.6%) | 10,700 (7.8%) | 34.9% | 24,491 (11%) | 12,780 (5.8%) | 148,361 (66.8%) | 36,466 (16.4%) |
| *Enterobacter cloacae* | 43,218 | 96.9 | 69 (62, 77) | 31,635 (73.2%) | 9,094  (21%) | 2,574  (6%) | 62.8% | 5,246 (13.8%) | 1,099 (2.9%) | 15,359 (40.5%) | 16,202 (42.7%) |
| *Serratia marcescens* | 22,568 | 97.9 | 69 (62, 77) | 16,688 (73.9%) | 4,546 (20.1%) | 1,615 (7.2%) | 43.1% | 10,855 (8.1%) | 1,717 (1.3%) | 83,696 (62.4%) | 37,823 (28.2%) |
| **Gram-negative non-fermenters** | *Pseudomonas aeruginosa* | 130,496 | 97.4 | 71 (63, 80) | 95,636 (73.3%) | 26,771 (20.5%) | 9,218 (7.1%) | 47% | 3,725 (8.6%) | 6,403 (14.8%) | 17,754 (41.1%) | 15,336 (35.5%) |
| *Acinetobacter sp.* | 15,898 | 97.3 | 67 (60, 76) | 10,852 (68.3%) | 4,146 (26.1%) | 1,292 (8.1%) | 47.6% | 1,967 (12.4%) | 3,638 (22.9%) | 4,734 (29.8%) | 5,559 (35%) |

**Figures**

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**Figure 1.** **Burden of infections and antimicrobial resistance from 2007 till 2022 for nine pathogens.** (A) Total number of 30-day incident isolates across nine pathogens. Colors of the bars represent the individual pathogen. (B) Average annual percentage change (AAPC) obtained from infection incidence time trend analyses using generalized estimating equations for pre-pandemic (2007-2019) and pandemic period (2020-2022). AAPC larger than zero indicates an increasing trend, AAPC smaller than zero a declining trend in infection incidence. (C) Number of 30-day incident isolates across nine pathogens stratified by infection source. Colors of the bars represent the different infection sources.



**Figure 2.** **Methicillin and vancomycin resistance in infections caused by *S. aureus, E. faecalis, and* *E. faecium*, stratified by location of infection onset.**

(A) 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 the respective resistance proportion. Dashed vertical lines denote the start of the COVID-19 pandemic era. (B) Average annual percentage change (AAPC) obtained from time trend analyses using generalized estimating equations for overall methicillin resistance in *S. aureus*, vancomycin resistance in *E. faecalis* and in *E. faecium* for the pre-pandemic (2007-2019) and pandemic period (2020-2022). AAPC larger than zero indicate an increasing trend, AAPC smaller than zero a declining trend. Estimates were obtained separately for resistance proportion, the incidence of resistant infections (resistant phenotype) and the incidence of susceptible infections (susceptible phenotype).

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**Figure 3.** **Temporal trends in fluoroquinolone resistance in infections caused by nine organisms of interest and fluoroquinolone inpatient utilization in VA facilities from 2007 to 2022.**

(A) Fluoroquinolone resistance in infections caused by nine organisms of interest. Points represent the incidence in infections with susceptible (green), resistant (red), and missing (grey) susceptibility test results (left axis). 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. Bar plots represent yearly resistance proportion (right axis), defined as the number of resistant incident isolates divided by the total number of incident isolates (including isolates with missing susceptibility test results). (B) Average annual percentage change (AAPC) obtained from tim trend analysis using generalized estimating equations 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. Estimates were obtained separately for resistance proportion, the incidence of resistant infections (resistant phenotype) and the incidence of susceptible infections (susceptible phenotype). (C) Fluoroquinolone antibiotic utilization in the Veterans Affairs inpatient setting, defined as number of inpatient administration days of antibiotics classified as fluoroquinolones (ciprofloxacin, delafloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin) per 1,000 patient days.

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**Fig 4. Temporal trends for 3rd generation cephalosporin resistance of infections caused by *E. coli, K. pneumoniae, E. cloacae, S. marcescens, P. aeruginosa, Acinetobacter sp.*** (A) Resistance proportion and phenotypic incidence from 2007 to 2022 for 3rd generation cephalosporins of infections caused by (A) *E. coli, K. pneumoniae, E. cloacae, S. marcescens, P. aeruginosa, Acinetobacter sp. (B) E. coli*, stratified by location of infection onset.(C)Average annual percentage change (AAPC) 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. Estimates were obtained separately for resistance proportion, the incidence of resistant infections (resistant phenotype) and the incidence of susceptible infections (susceptible phenotype). (D) 3rd generation cephalosporin antibiotic utilization in the Veterans Affairs inpatient setting, defined as number of inpatient administration days of antibiotics classified as 3rd generation cephalosporins (cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftizoxime, ceftriaxone, Moxalactam) per 1,000 patient days.

**Fig 5**. **Temporal trends of carbapenem resistance from 2007 to 2022 *E. coli, K. pneumoniae, E. cloacae, S. marcescens, P. aeruginosa, and Acinetobacter sp.***

(A)Carbapenem resistance proportion and phenotypic incidence from 2007 to 2022 for *E. coli, K. pneumoniae, E. cloacae, S. marcescens, P. aeruginosa, and Acinetobacter sp.* Bar plots represent yearly resistance proportion, defined as the number of resistant incident isolates divided by the total number of incident isolates (including isolates with missing susceptibility test results) per year. Points represent the incidence in infections with susceptible (green), 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. (B) Average annual percentage change (AAPC) obtained from generalized estimating equations analysis for each pathogen (except *E. coli* due to small numbers of resistant isolates) and for pre-pandemic (2007-2019) and pandemic period (2020-2022). AAPC larger than zero indicate an increasing trend, coefficients smaller than zero a declining trend. Estimates were obtained separately for resistance proportion, the incidence of resistant infections (resistant phenotype) and the incidence of susceptible infections (susceptible phenotype). (C) Carbapenem antibiotic utilization in the Veterans Affairs inpatient setting, defined as number of inpatient administration days of antibiotics classified as carbapenems (imipenem, meropenem, doripenem, ertapenem) per 1,000 patient days.