Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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Methods

Data Sources

Three electronic health databases were used to create these estimates: Premier Healthcare Database (1), Cerner Health Facts (2) and BD Insights Research Database (3-6). Data from any inpatient visit in participating acute care hospitals that took place between January 1, 2012-December 31, 2017 were included in the analysis. This differs from methods used in the 2013 CDC Antibiotic Resistance Threats report. Use of these electronic health databases has a number of advantages including the ability to estimate the burden of infection involving both non-sterile and sterile body sites, the inclusion of both hospital-onset and community-onset infections (among hospitalized patients), better precision in estimates due to increased sample size, and the ability to readily create serial annual estimates and trends.

Data in Cerner Health Facts were extracted directly from the electronic medical records (EMR) system from hospitals with which Cerner has a data use agreement. The number of participating hospitals varied between 178-217 hospitals depending on year. Inpatient visit records for all admissions to participating hospitals included clinical and microbiology laboratory results (including antimicrobial sensitivity testing results), admission and discharge dates, and billing information from affiliated patient care locations. All admissions, laboratory orders and specimens were date and time stamped, allowing for the timing of treatment patterns and clinical information to be reviewed. Cerner Corporation previously established Health Insurance Portability and Accountability Act – compliant operating policies, which ensure that Health Facts data are de-identified to protect privacy (2).

The Premier Healthcare Database contains hospital records for all patients discharged from participating acute care, general, and non-federal, U.S. hospitals. Inpatient visit records included diagnostic and procedure codes, demographic information, admission and discharge dates, and facility characteristics. Microbiology data were available for all admissions for a subset of participating hospitals, which varied between 158 to 191 hospitals annually. These data included detailed information such as genus and species of bacterial isolates, day and time

stamp of specimen, and associated antimicrobial sensitivity testing results(1). Data from the Premier Healthcare Database is de-identified.

The BD Insights Research Database, previously called the CareFusion Clinical Research Database, is both an electronic based surveillance system and a clinical research database (3-6). Data used in this analysis included information on any isolates of the bacteria of interest, day and time stamp of specimen, associated antimicrobial sensitivity testing results, certain patient demographics, monthly facility denominators (admissions), and facility characteristics. The number of participating hospitals from which data were available varied from 188 to 355 annually. Data received from BD were de-identified.

Hospital Cohort

A dynamic cohort of short-term acute care hospitals was included from each of the databases from 2012-2017. This dynamic cohort is not limited to hospitals who are reporting in all months or years, but evolves monthly. A hospital's data was included in the cohort for any month during which it reported at least one positive result from a microbiology culture (growth of any bacterial organism) with its associated antimicrobial susceptibility testing results. For each hospital in the cohort, facility level characteristics such as bed size category, geographic region (U.S. census division), urban/rural designation and teaching status were documented. All participating hospitals were de-identified prior to data being shared with CDC.

In order to avoid duplication of data, we performed an analysis to identify hospitals that may be represented in more than one of the three databases. Potential duplicates were identified by comparing hospitalizations among hospitals from the different databases in 32 strata defined by bed size (<300, ≥300), U.S. census division, urban/rural designation, and teaching status. Strata were defined using data from the Centers for Medicare & Medicaid Services Healthcare Cost Report Information System (HCRIS), which includes data from all Medicare certified non-federal, U.S. hospitals (7). When two databases were compared, we examined every possible pair of hospitals within each stratum (each pair comprising one hospital from each database), and flagged any pair having similar numbers of hospitalizations as potential duplicates. The threshold used for flagging a hospital pair

was a difference in hospitalizations less than the 25th percentile of the distribution of differences for every possible pair of U.S. hospitals within each stratum (per HCRIS data). When potential duplicate pairs were identified, only one hospital was chosen from the pair to be used in the analysis. Hospitals in the BD database were always removed first, and when there were potential duplicates identified between Cerner and Premier, Premier hospitals were removed. In 2017, 20 hospitals from the BD database and 6 hospitals from Premier data were removed as potential duplicates. Similar numbers of potential duplicate hospitals were removed in other years (10-17 hospitals from BD and 4-10 hospitals from Premier).

Detailed demographics for all included hospitals, stratified by data source, compared with the distribution of U.S. hospitals as provided by the American Hospital Association (AHA) are shown for 2017 data in Table S1.

Case Cohort Definition

From the hospital cohort, we identified a cohort of patients who had any clinical culture that yielded an isolate of the organisms of interest, and had accompanying susceptibility testing results sufficient for determining whether that isolate had the resistance phenotype of interest (Table S2). Our starting sample size for our analysis was comprised of any microbiologic culture that yielded an organism of interest, and antimicrobial susceptibility testing for that organism. We removed specimens that were categorized as surveillance (i.e., cultures labeled as rectal, perirectal, or nasal), were not obtained during hospitalization (i.e., specimen collection date culture was not in the window from 3 days before admission until 3 days after discharge), were collected outside of study dates, had uninterpretable susceptibility testing results, or were not incident cases. . We categorized clinical cultures as either sterile, non-sterile, or surveillance depending on the specimen site. Sterile sites included clinical specimens, such as blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, synovial fluid, and lymph nodes. Non-sterile sites included clinical specimens, such as urine, sputum, and wounds. Among clinical isolates with sufficient susceptibility testing results, those with the resistance phenotype of interest were eligible to be considered as an incident case. Only isolates from patients having no culture yielding the same resistance phenotype of interest in the previous 14 days were counted as an incident case. For

patients with isolates with the resistance phenotype of interest from both a sterile and non-sterile positive culture taken within 14 days of each other, only the sterile culture was counted as an incident case. For both CRE and ESBL reporting, denominator definitions account for potential antimicrobial susceptibility cascade reporting by hospitals (Table S2).

To calculate a combined total of cases for multiple threats, we summed the number of incident cases for all organisms of interest. CRE and ESBL organisms and phenotypes were not mutually exclusive, such that the same isolate could be potentially considered a case for both phenotypes. If a specimen was determined to be a case for both CRE and ESBL, we only counted that specimen once. Because of this nuance, the total estimated cases reported does not exactly match the simple sum of reported cases by pathogen. Confidence intervals for total cases were calculated using these de-duplicated numbers and a combined standard error estimate. To calculate standard error for the combined estimates, the standard errors from each individual estimate were combined such that the square of the standard error equals the sum of the square of the standard error for each of the estimates.

Cases were defined as community-onset when the culture was obtained immediately preceding admission or within the first three days of hospitalization, and hospital-onset when the culture was obtained on day four or later. Due to the limited epidemiologic information, further classification of community-onset infections into those with and without previous health care exposures was not possible.

For the purposes of this report, we use the term “infection” to describe incident cases defined by isolates from either sterile body or non-sterile body sites. We did not attempt to make a clinical determination of whether an isolate from a non-sterile site represented a true infection. While some subset of such isolates may not represent true infection, they do represent an important epidemiologic burden in that they serve as potential reservoirs for transmission, potentially put carriers at risk for progressing to infection in the future, and may impact decisions regarding antibiotic treatment. We therefore elected to include them in our burden estimates

Estimated Number of Cases

For each year, we used a raking-procedure to determine weights to extrapolate the number of hospitalizations included in our sample, which included facilities from all three databases, to match the distribution of discharges for all hospitals from the American Hospital Association survey for that respective year(8). This raking method, proportional iterative fitting, is often used in public health studies to combine individual datasets to build a single weighted dataset for national estimation(9-15). Weights were based on the following hospital characteristics: bed size, U.S. census division, urban/rural designation, and teaching status. Using these weights, we extrapolated our findings to calculate a national burden estimate of cases and associated 95% confidence intervals for each pathogen using a weighted means survey procedure separately for each year from 2012-2017.

We also conducted a sensitivity analysis in which we determined the weights for each of the three electronic databases separately using the same method as the combined cohort. We then combined the three database hospital cohorts by multiplying the weight for each database by one-third. Our results were similar using this methodology.

Rates and Trends

Pooled rates were calculated using the weighted number of cases and weighted number of hospitalizations in each month. The number of cases per 10,000 hospitalizations for each pathogen in our three data systems is reported in Table S3a, and the weighted extrapolations in Table S3b. Results were further stratified by HO and CO trends.

To examine trends in the rates over time, we used a multivariable logistic model incorporating a survey design with the corresponding weights described above and hospital designation as the specific cluster (9, 10). Using monthly hospital level data from 2012- 2017, we modeled cases per hospitalization controlling for hospital characteristics including bed size, U.S. census division, urban/rural designation, teaching status, month of hospitalization, proportion of patients in specific age groups (0-17, 18-54, 55-64, 65-74, ≥75), and database. The parameter year, representing the trend, was modelled in two ways: as a log-linear trend (i.e., continuous

variable) and as linear combination of five independent parameters representing each year (i.e., as a categorical variable). Results from the linear model are provided in Table 3 in the manuscript, and results from the categorical model are given in Table S3c. Results stratified by onset (community, hospital) and specimen source (sterile, non-sterile) are shown in Table S3d.

Strengths and Limitations of Approach

Using three electronic health databases uniquely positions this analysis to determine burden and assess trends of these antimicrobial resistant threats among hospitalized patients in the U.S. We were able to use a weighting methodology to extrapolate to national burden estimates of several antimicrobial resistant threats in the U.S. However, as these data are collected for billing and clinical purposes and are adapted for research, they have certain limitations.

There is potential for misclassification in clinical and facility information; however, this bias is most likely non-differential. Because this is a convenience (not random) sample, there is over and under-representation of hospital characteristics, including geographic regions. There also may be variability in clinical or data capture practices across different hospitals that may affect the validity of the data and trends. For 20 hospitals, teaching status was missing for hospitals in the Cerner database. We imputed teaching status as non-teaching to match the distributions of teaching status reported among the other two hospital systems, AHA data, and HCRIS data. In rare instances, a culture drawn date was not reported in the Cerner data system. For those cases with missing data we imputed culture date using date of result report and the distribution of time to result from the 99.9% of cases for which the data were available. We sought to overcome these limitations through inclusion of three different data sources for microbiology data, and adjustment of estimates using nationally representative data from AHA. To ensure this, we compared the results for burden and trends between each dataset to assure internal consistency. The incidence rate ratios, measuring trends in incidence for each pathogen from 2012 – 2017, were calculated for each data system using the multivariable logistic model incorporating a survey design used in the main analysis and found similar results and conclusions (Figure S2).

Our extrapolations were limited to acute care hospitals in the U.S. and do not adequately represent children's hospital (<1% of included hospitals). In aggregate, our national estimates appear consistent with estimates for invasive MRSA cultures (16) and prevalence estimates for resistant gram negatives (17) and other unpublished internal data sources (e.g., National Healthcare Safety Network).

Because hospitals remained de-identified, it is possible a hospital could contribute data in more than one system despite our efforts to remove likely duplicates. We examined the impact of including potentially duplicate hospitals through a sensitivity analysis, which determined the hospital-weights for each data system independently and then counted each system equally towards the final extrapolations. We observed similar results to our primary analysis, suggesting potential duplication of hospitals have minimal impact on our findings.

We included a dynamic cohort that ranged from 532 – 722 hospitals annually. Non-continuous reporters may impact trends due to unmeasured confounding. Among hospitals who submitted data to two of the three systems (Cerner and Premier), we found some differences in months with microbiology data reported versus not. For example, excluded months were associated with rural, non-teaching, and small hospitals. However, the two groups were largely similar, and our extrapolation and trend models adjusted for differences in hospital characteristics, likely minimizing the impact any differences may have had on the results. To further ensure the dynamic nature of the cohort was not impacting our trends, we performed two different sub-analyses for each of our microbiologic outcomes that was restricted to hospitals the consistently reported over the course of the study period. First, we defined consistent reporters as those reporting at least 60 out of a possible 72 months in the study period (410 hospitals met this definition). Second, we defined consistent reporters as those reporting in all 72 months of the study period (265 hospitals met this definition). To measure trends in incidence in these sub-populations, we used mixed-effects regression models that adjusted for the same covariates as the primary analysis and for hospital-level clustering using a random intercept. We then compared the marginal estimates from these models with those from the primary analysis. For both sub-analyses, the results yielded very minor changes in the slope of the trends for each pathogen, and similar over-lapping confidence intervals (Figure S3). Therefore, these consistent reporter sub-analyses do not substantially change our original findings or conclusions, suggesting that there was no bias introduced by including data from hospitals not reporting for the entire (or the majority of) the study period.

It is possible that changes in culturing practice and microbiologic detection may have influenced our findings. However, for two of the three databases (Cerner and Premier), the overall rate of clinical cultures (cultures per 1,000 patient discharges) did not change significantly during the study period. To address potential concern that changes in urine culture practices may have influenced ESBL rates, we also examined trends in urine culture rates, and found no change over the study period. The data supplied to us by BD included culture data for positive cultures only, therefore we could not perform a similar analysis on that database. However, given that our findings and conclusions were the same when we performed our analyses separately for each of the three datasets, it seems unlikely that any change in culture practice unique to BD hospitals could explain the trends we observed.

We do not have data that details specific techniques or equipment (such as automated antimicrobial susceptibility testing devices) used to process clinical cultures in individual hospitals. Because we found similar trends for each data system and with independent CDC surveillance efforts, it seems unlikely that changes in such practices over time would account for the observed trends in resistant pathogens. If the trends we observed were due primarily to an artifact introduced by testing technique, one would expect to see similar trends across all pathogens and epidemiologic categories. However, we observed divergent incidence trends across the six pathogens we studied (e.g. four pathogens decreased, one increased, and one remained unchanged), and across epidemiologic categories within pathogens (e.g. incidence of hospital-onset ESBL-producing *Enterobacteriaceae* remained unchanged, but community-onset ESBL infections increased).

Increasing use of MALDI-TOF (matrix-assisted laser desorption/ionization time of flight) by clinical laboratories for organism identification would also have minimal effects on trends as results from MALDI-TOF show very high concordance with other commonly used systems (>90-95% depending on pathogen, 18).

Culture-independent diagnostic tests (CIDT) for respiratory, cerebrospinal and stool specimens do not detect the bacterial pathogens in this report and should not impact our findings. Although CIDT may be used for blood specimens, these systems were not available during the study period and/or the Food and Drug Administration (FDA) recommended that these systems were used in conjunction with traditional culture and antimicrobial

susceptibility testing. Further, data from CDC's Emerging Infections Program annual survey of all clinical microbiology laboratories within the ten surveillance catchment areas (containing all hospitals serving a population base of over 15 million people) have not identified significant changes in antimicrobial susceptibility testing systems during the study period (unpublished data).

Clinical and Laboratory Standards Institute (CLSI) lowered MIC breakpoints in 2010 for many beta-lactam antibiotics, including carbapenems, to enhance detection of known resistance among *Enterobacteriaceae*. Because these breakpoint changes increase the likelihood of finding resistance, a lag in incorporating these interpretive changes would have introduced an upward bias in trends for CRE, CRASP and MDR *Pseudomonas* that we did not observe. The upward trends in ESBL are unlikely due to a lag in implementation of these breakpoints given the apparent acceleration of increase in more recent years between 2014-2017. Further, the difference in trends for hospital- and community-onset ESBL infections could not be explained by this change, since the effect would have been to bias both trends in the same direction. In 2014, CLSI also changed cefepime breakpoints for *Enterobacteriaceae.* The potential impact of these changes has been examined in peer-reviewed publications, and the magnitude of potential changes is lower in comparison to the magnitude of the changes we observed (19).

Due to data availability, previous estimates for these threats focused solely on healthcare-associated infections, which represent a fraction of all relevant antimicrobial resistance. This analysis was able to include all clinical cultures among hospitalized patients; however, it was limited in differentiating epidemiological classifications. We were only able to categorize community-onset and hospital-onset cases by timing of culture relative to admission, and were not able to account for previous healthcare exposures (i.e., identify healthcare-associated community onset cases).

Using positive clinical cultures to measure the burden is a more accurate measure of the number of cases compared to other methods. Administrative diagnosis codes likely under-represent the true burden of cases, suffer from misclassification for determining drug resistant organisms, and can be impacted by reimbursement

policies (20-22). Death certificate codes have also shown to be a poor measure of infection related mortality (23). Alternatively, infection-related conditions (i.e., sepsis) show clinical criteria from electronic health data (that includes but is not limited to microbiology results) are immune to large temporal variations in incidence and mortality rates due to changes in administrative coding practices (24). Therefore, using clinical cultures to identify the burden of antimicrobial resistance allows for more robust and comprehensive estimation of burden than analyses focused on healthcare-associated infection surveillance, and with a lower potential for misclassification than analyses using administrative diagnosis codes.

Supplementary Tables and Figures

Figure S1. Accounting of sample size among all positive cultures

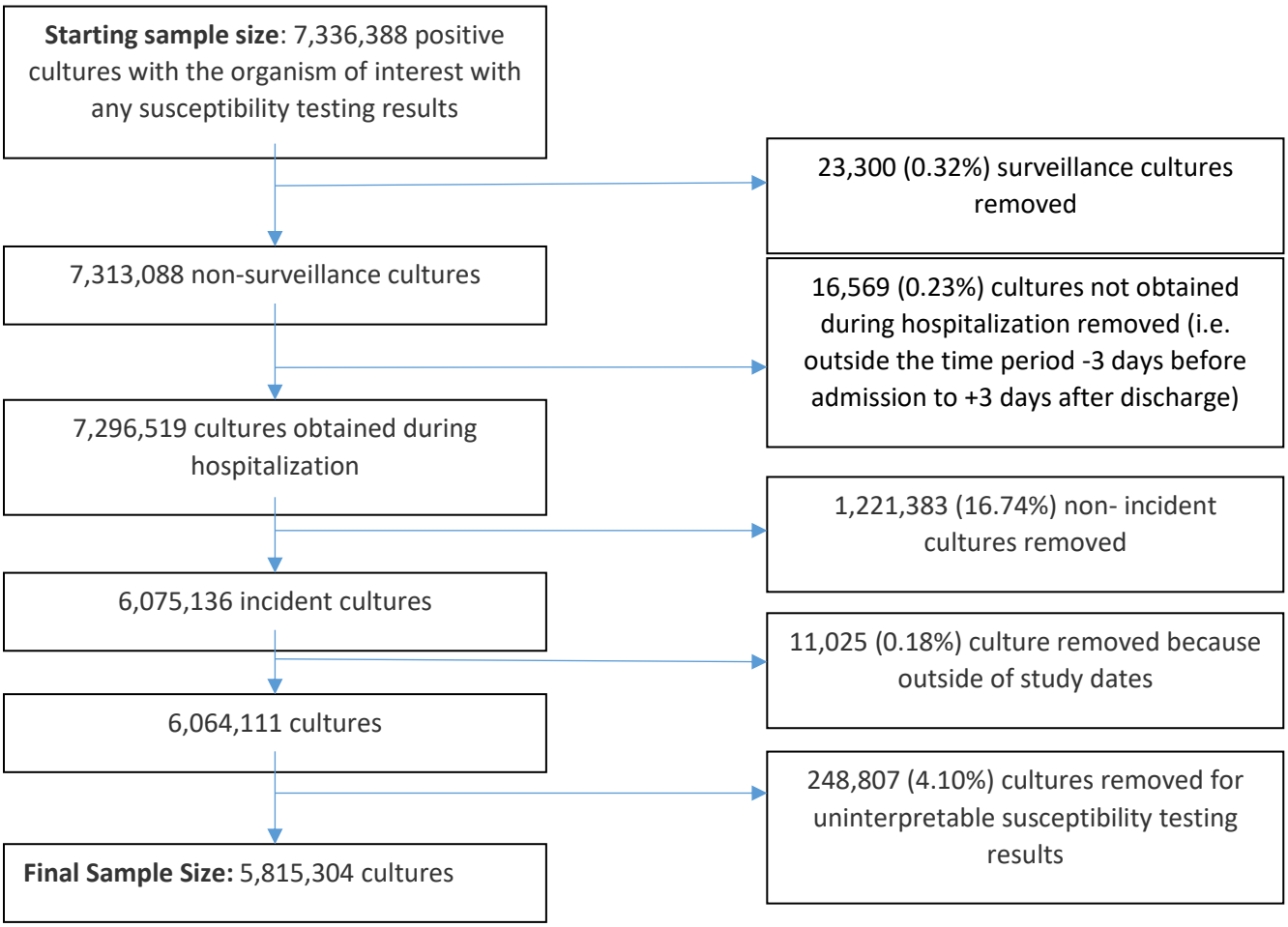

Figure S2. Annual Incidence Rate Ratios and corresponding 95% confidence intervals for continuous trend estimates by pathogen and contributing data system, 2012-2017.

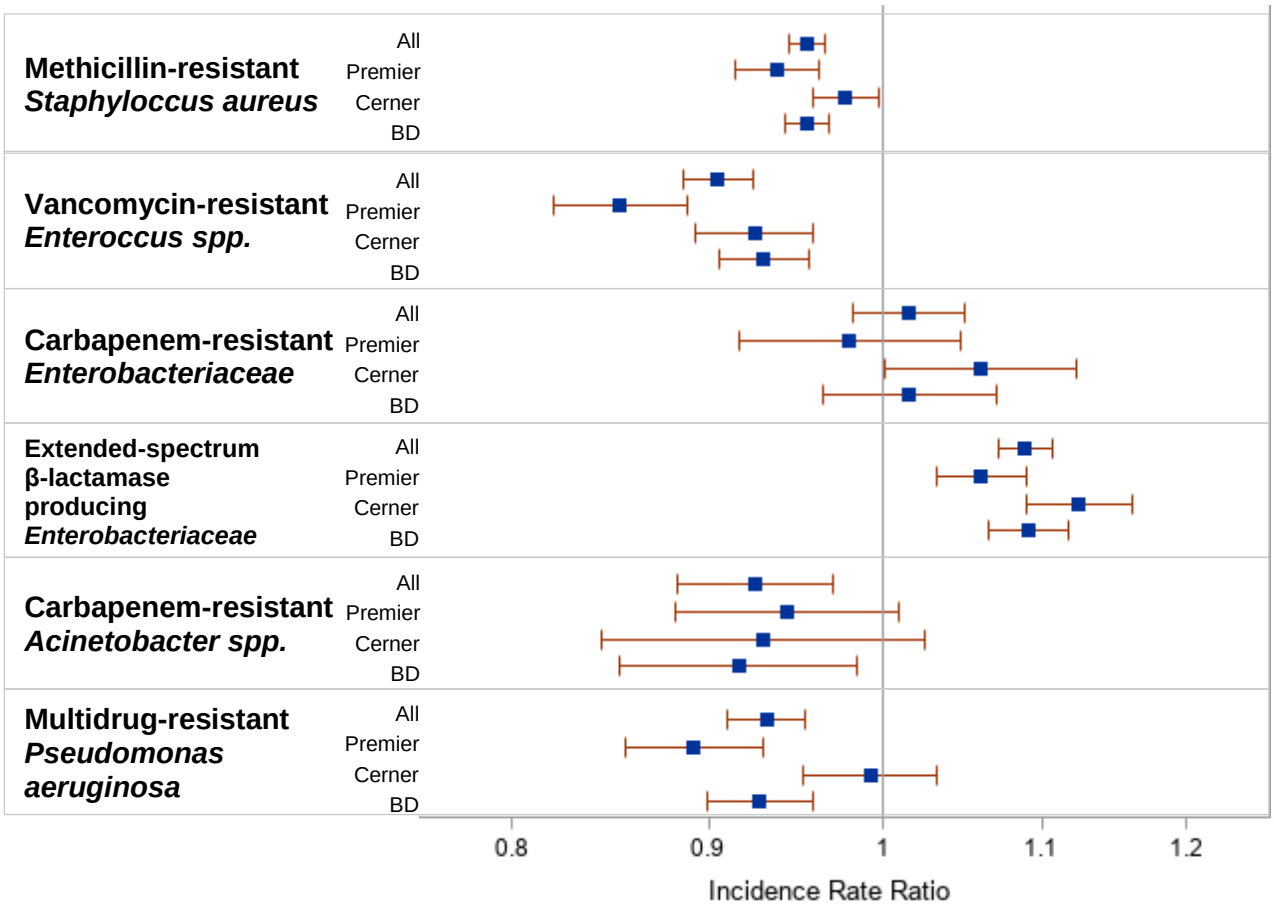

Figure S3. Annual Incidence Rate Ratios and corresponding 95% confidence intervals for continuous trend estimates by pathogen and consistent reporting status, 2012-2017.

All=primary analysis including all 890 cohort hospitals, Consistent (60+months)= analysis restricted to hospitals contributing at least 60 out of possible 72 months of data (n=410 hospitals), Consistent (72 months)= analysis restricted to hospitals contributing data for all possible 72 months of data (n=265 hospitals)

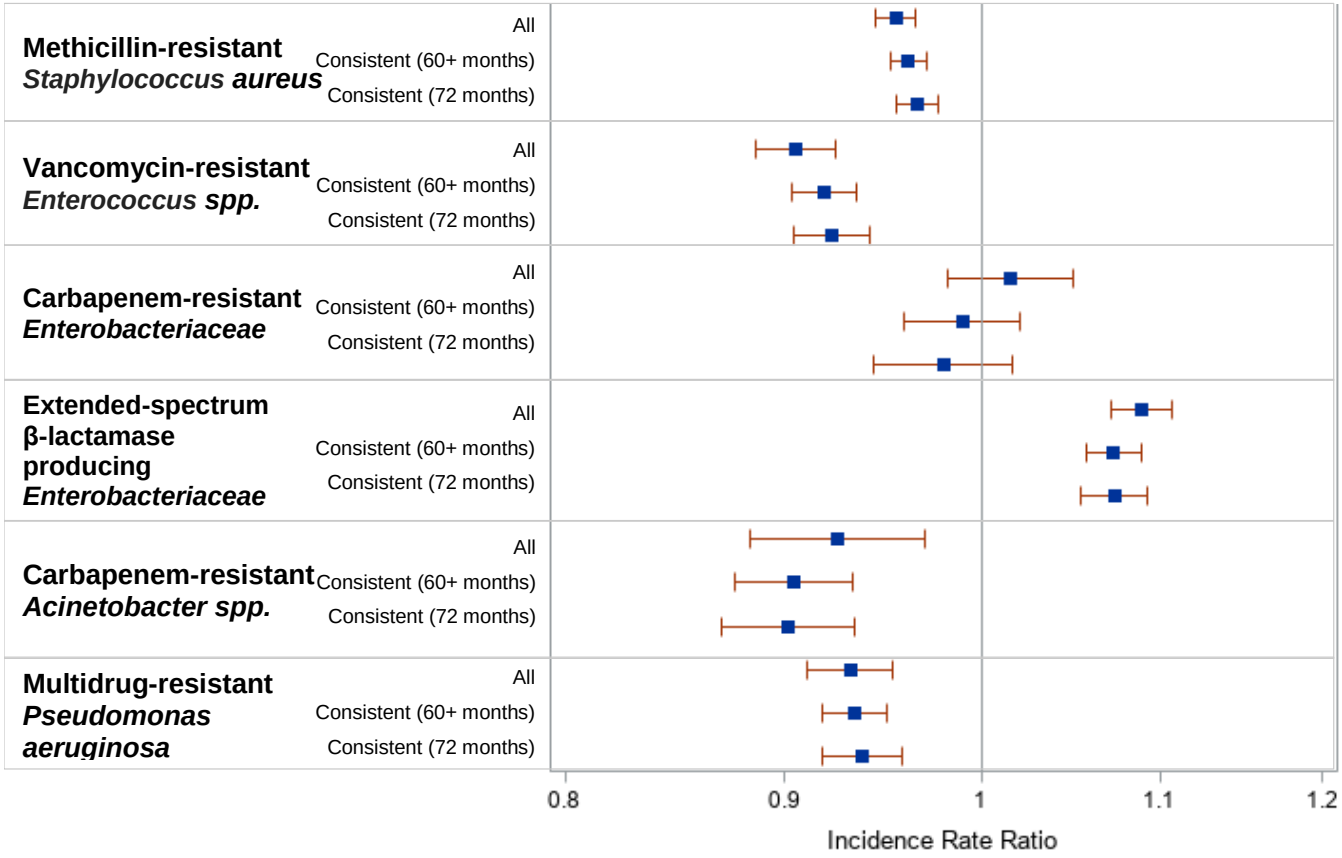

Table S1. Demographics for all included hospitals, stratified by data source, compared with the distribution of U.S. hospitals as provided by the American Hospital Association (AHA), 2017

	All Data Sources Combined		All US Hospitals*		Cerner		Premier		BD	
Characteristics	Hospitals	Percent	Hospitals	Percent	Hospitals	Percent	Hospitals	Percent	Hospitals	Percent
Total	722		4847		178		189		355	
Urban	528	73.1%	2965	61.2%	127	71.3%	135	71.4%	266	74.9%
Rural	194	26.9%	1882	38.8%	51	28.7%	54	28.6%	89	25.1%
Teaching	233	32.3%	1768	36.5%	55	30.9%	50	26.5%	128	36.1%
Non-Teaching**	489	67.7%	3079	63.5%	123	69.1%	139	73.5%	227	63.9%
No. of beds, <300	498	69.0%	4025	83.0%	144	80.9%	127	67.2%	227	63.9%
No. of beds, ≥300	224	31.0%	822	17.0%	34	19.1%	62	32.8%	128	36.1%
U.S. Census Division										
1-New England	23	3.2%	181	3.7%	7	3.9%	9	4.8%	7	2.0%
2-Mid-Atlantic	77	10.7%	412	8.5%	7	3.9%	22	11.6%	48	13.5%
3-South Atlantic	133	18.4%	714	14.7%	37	20.8%	53	28.0%	43	12.1%
4-Northeast Central	154	21.3%	735	15.2%	19	10.7%	51	27.0%	84	23.7%
5-Southeast Central	69	9.6%	392	8.1%	14	7.9%	9	4.8%	46	13.0%
6-Northwest Central	37	5.1%	700	14.4%	18	10.1%	6	3.2%	13	3.7%
7-Southwest Central	101	14.0%	738	15.2%	19	10.7%	21	11.1%	61	17.2%
8-Mountain	44	6.1%	418	8.6%	26	14.6%	1	0.5%	17	4.8%
9-Pacific	84	11.6%	557	11.5%	31	17.4%	17	9.0%	36	10.1%
Annual Hospitalizations	7,389,022	21.4%	34,554,279		1,727,265	5.0%	1,153,040	3.3%	4,508,717	13.1%

*All US hospitals (short-term, acute care) per the American Hospital Association

**20 hospitals in the Cerner database were missing values for teaching status. In these cases, we imputed teaching status as non-teaching to match the distributions reported among the other two hospital systems, AHA data, and HCRIS data.

Table S2. Detailed Pathogen Phenotype Definitions

Pathogen	Organisms Included in Definition	Antibiotics Included in Definition	Definition of Resistance Phenotype	Denominator for Calculating Proportion of Isolates with Resistant Phenotype
Methicillin-resistant *Staphylococcus aureus* (MRSA)	*Staphylococcus aureus*	methicillin, oxacillin, cefoxitin	Any isolate that tested (R) to at least 1 of these: methicillin, oxacillin, cefoxitin	Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to: methicillin, oxacillin, cefoxitin
Vancomycin-resistant *Enterococcus* (VRE)	*Enterococcus* spp.	vancomycin	Any isolate that tested (R) to vancomycin	Any isolate that tested (S, I, R) to vancomycin
Carbapenem-resistant *Enterobacteriaceae* (CRE)	*E. coli, Klebsiella* spp., *Enterobacter* spp.	imipenem, meropenem, doripenem, ertapenem, ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan	Any isolate with at least 1 resistant result (R) to imipenem, meropenem, doripenem, ertapnem	*Any isolate with at least 1 non-susceptible or susceptible result (S, I, R) to imipenem, meropenem, doripenem, ertapnem **OR** same isolate with at least 2 reported susceptible (S) results to: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, cefotetan
Extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*	*E. coli, Klebsiella* spp. *(not Klebsiella aerogenes)*	cefotaxime, ceftriaxone, ceftazidime, cefepime, ampicillin, piperacillin, aztreonam, cefazolin	Any isolate with at least 1 non-susceptible, result (I or R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime	**Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to: cefotaxime, ceftriaxone, ceftazidime, cefepime OR same isolate with at least 2 reported susceptible (S) results to: ampicillin, piperacillin, aztreonam, or cefazolin
Carbapenem-resistant *Acinetobacter* (CRAsp)	*Acinetobacter* spp.	imipenem, meropenem, doripenem	Any isolate with at least 1 non-susceptible result (I or R) to: imipenem, meropenem, doripenem	Any isolate with at least 1 susceptible or non-susceptible result (S, I, R) to at least 1 drug in the medication categories
Multidrug-resistant (MDR) *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	1. Extended-spectrum cephalosporins (cefepime, ceftazidime), 2. Fluoroquinolones (ciprofloaxacin, levofloxacin), 3. Aminoglycosides (amikacin, gentamicin, tobramycin), 4. Carbapenems (imipenem, meropenem, doripenem), 5. Piperacillin Group (piperacillin, piperacillin/tazobactam)	Any isolate that tested either (I) or (R) to at least 1 drug in at least 3 of the medication categories	Any with at least 1 susceptible or non-susceptible result (S, I, R) to at least 1 drug in the medication categories

* we accounted for cascade reporting by assuming isolates of Enterobacteriaceae to be carbapenem-susceptible if no carbapenem susceptibility result was reported but the isolate was reported to be susceptible to >1 of the following: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefoxitin, or cefotetan

** we accounted for cascade reporting by assuming isolates of *Enterobacteriaceae* to be susceptible to third and fourth generation cephalosporins if no susceptibility test results to these agents were reported but the isolate was reported to be susceptible to >1 of the following: ampicillin, piperacillin, aztreonam, or cefazolin.

Table S3a. Incidence rates[ǂ] for three electronic data systems without extrapolation, by year and pathogen, 2012 - 2017

	MRSA^			VRE^			CRE^			ESBL^			CRAsp^			MDR Pseudomonas^		
	Overall	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**
2012	119.01	23.21	95.79	30.84	13.87	16.97	4.94	2.00	2.94	41.17	9.65	31.52	5.18	2.45	2.73	15.71	6.29	9.42
2013	119.70	22.48	97.23	28.02	12.17	15.84	5.06	2.00	3.06	45.35	9.42	35.92	4.60	1.92	2.68	15.87	6.14	9.73
2014	110.23	20.33	89.90	25.09	10.55	14.54	4.70	1.79	2.91	45.40	9.06	36.34	3.84	1.52	2.32	13.73	5.02	8.72
2015	110.25	20.40	89.85	24.69	10.17	14.51	4.65	1.68	2.97	54.51	10.15	44.36	3.83	1.67	2.17	13.59	5.11	8.48
2016	105.74	18.42	87.32	22.40	8.89	13.51	4.71	1.68	3.02	59.89	10.68	49.21	3.58	1.41	2.17	12.50	4.28	8.22
2017	99.51	17.08	82.43	20.33	7.60	12.73	4.58	1.50	3.08	60.17	10.19	49.98	3.22	1.15	2.07	11.27	3.74	7.53

ǂ: Unweighted number of cases per 10,000 hospitalizations

†HO: Hospital-Onset, defined as a positive culture ≥4 days from the time of admission

‡CO: Community-Onset, defined as a positive culture <4 days from the time of admission

^methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum cephalosporin resistance in *Enterobacteriaceae* suggestive of extended-spectrum β-lactamase (ESBL)-production, carbapenem-resistant *Acinetobacter* species (CRAsp), and multidrug-resistant (MDR) *Pseudomonas aeruginosa*

Table S3b. National estimates of incidence rates[ǂ], by year and pathogen, 2012 - 2017

		MRSA^			VRE^			CRE^			ESBL^			CRAsp^			MDR Pseudomonas^		
		Overall	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**
2012	Estimate	114.18	18.72	95.45	24.15	9.43	14.72	3.36	1.03	2.32	37.55	6.90	30.65	3.33	1.36	1.97	13.10	4.17	8.92
	95% CI*	98.32 to 130.04	15.99 to 21.46	82.12 to 108.79	19.98 to 28.33	7.78 to 11.07	12.08 to 17.37	2.54 to 4.17	0.76 to 1.30	1.68 to 2.97	31.82 to 43.29	5.66 to 8.15	25.93 to 35.36	2.53 to 4.13	0.97 to 1.75	1.50 to 2.43	10.88 to 15.31	3.36 to 4.99	7.39 to 10.46
2013	Estimate	113.67	17.92	95.75	21.46	8.14	13.32	3.46	1.19	2.27	42.46	6.88	35.58	3.00	1.21	1.79	13.37	4.53	8.84
	95% CI*	99.33 to 128.01	15.45 to 20.39	83.69 to 107.81	18.45 to 24.48	6.95 to 9.32	11.38 to 15.27	2.87 to 4.05	0.94 to 1.44	1.87 to 2.67	36.60 to 48.32	5.79 to 7.97	30.64 to 40.52	2.40 to 3.61	0.91 to 1.51	1.45 to 2.14	11.32 to 15.41	3.69 to 5.36	7.49 to 10.18
2014	Estimate	108.00	16.44	91.56	19.61	7.35	12.26	3.38	1.14	2.25	43.35	6.73	36.62	2.60	0.92	1.68	11.11	3.43	7.69
	95% CI*	94.19 to 121.80	14.15 to 18.73	79.83 to 103.28	16.94 to 22.29	6.29 to 8.41	10.53 to 14.00	2.73 to 4.03	0.88 to 1.39	1.79 to 2.70	37.74 to 48.97	5.69 to 7.78	31.87 to 41.37	2.07 to 3.14	0.65 to 1.20	1.34 to 2.02	9.42 to 12.80	2.82 to 4.03	6.51 to 8.86
2015	Estimate	105.39	15.82	89.57	18.69	6.79	11.89	3.38	0.97	2.41	51.34	7.15	44.19	2.88	1.15	1.73	10.85	3.33	7.52
	95% CI*	92.88 to 117.90	13.83 to 17.82	78.90 to 100.24	16.24 to 21.13	5.78 to 7.80	10.34 to 13.45	2.78 to 3.98	0.73 to 1.20	1.99 to 2.84	44.75 to 57.92	6.10 to 8.20	38.47 to 49.91	2.26 to 3.51	0.85 to 1.46	1.36 to 2.10	9.28 to 12.42	2.76 to 3.89	6.44 to 8.60
2016	Estimate	100.02	14.52	85.50	17.80	6.35	11.45	3.82	1.13	2.69	55.89	7.97	47.92	2.67	0.95	1.72	10.55	3.10	7.45
	95% CI*	88.97 to 111.06	12.71 to 16.32	76.11 to 94.89	15.28 to 20.31	5.22 to 7.48	9.91 to 12.99	3.16 to 4.48	0.85 to 1.40	2.24 to 3.14	49.26 to 62.53	6.75 to 9.20	42.26 to 53.58	2.15 to 3.18	0.73 to 1.17	1.38 to 2.05	8.87 to 12.23	2.46 to 3.75	6.34 to 8.55
2017	Estimate	93.68	13.44	80.25	15.76	5.29	10.47	3.79	1.01	2.78	57.12	7.46	49.66	2.47	0.80	1.67	9.43	2.76	6.66
	95% CI*	83.34 to 104.03	11.82 to 15.06	71.39 to 89.10	13.70 to 17.82	4.54 to 6.05	9.09 to 11.84	3.22 to 4.36	0.82 to 1.21	2.36 to 3.20	50.33 to 63.91	6.44 to 8.47	43.72 to 55.61	1.95 to 2.99	0.59 to 1.01	1.32 to 2.01	8.12 to 10.74	2.22 to 3.31	5.77 to 7.56

ǂ: Weighted number of cases per 10,000 hospitalizations

†HO: Hospital-Onset, defined as a positive culture ≥4 days from the time of admission

‡CO: Community-Onset, defined as a positive culture <4 days from the time of admission

^methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum cephalosporin resistance in *Enterobacteriaceae* suggestive of extended-spectrum β-lactamase (ESBL)-production, carbapenem-resistant *Acinetobacter* species (CRAsp), and multidrug-resistant (MDR) *Pseudomonas aeruginosa*

Table S3c. Adjusted* national incidence trends, by pathogen, using categorical parameters, 2012 - 2017

	MRSA^			VRE^			CRE^			ESBL^			CRAsp^			MDR Pseudomonas^		
	Overall	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**	**Overall**	**HO†**	**CO‡**
Parameter estimate 2012 vs 2017	-0.231	-0.397	-0.200	-0.526	-0.714	-0.419	0.068	-0.109	0.140	0.409	-0.010	0.485	-0.404	-0.640	-0.269	-0.341	-0.477	-0.282
95% Confidence Interval	-0.288 to -0.173	-0.478 to -0.316	-0.259 to -0.142	-0.637 to -0.416	-0.846 to -0.581	-0.531 to -0.306	-0.125 to 0.262^^	-0.327 to 0.109^^	-0.101 to 0.380^^	0.328 to 0.49	-0.146 to 0.127^^	0.403 to 0.567	-0.643 to -0.166	-0.964 to -0.315	-0.498 to -0.040	-0.454 to -0.229	-0.688 to -0.267	-0.389 to -0.175
Percent change** 2012 vs 2017	-20.6%	-32.8%	-18.1%	-40.9%	-51.0%	-34.2%	7.0%	-10.3%	15.0%	50.5%	-1.0%	62.5%	-33.3%	-47.2%	-23.6%	-28.9%	-37.9%	-24.6%
95% Confidence Interval	-25.0% to -15.9%	-38.0% to -27.1%	-22.8% to -13.2%	-47.1% to -34.0%	-57.1% to -44.1%	-41.2% to -26.3%	-11.8% to 30.0%^^	-27.9% to 11.5%^^	-9.6% to 46.2%^^	38.9% to 63.2%	-13.6% to 13.5%^^	49.7% to 76.4%	-47.4% to -15.3%	-61.9% to -27.0%	-39.2% to -3.9%	-36.5% to -20.4%	-23.4% to -49.7%	-32.2% to -16.1%

*Adjusted for hospital characteristics including bed size, U.S. census division, urban/rural designation, teaching status, month of hospitalization, age distributions, and data source

**Percent change is calculated as (e^p-1)*100%, where p is the modeled parameter estimate for the variable year.

†HO: Hospital-Onset, defined as a positive culture ≥4 days from the time of admission

‡CO: Community-Onset, defined as a positive culture <4 days from the time of admission

^methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum cephalosporin resistance in *Enterobacteriaceae* suggestive of extended-spectrum β-lactamase (ESBL)-production, carbapenem-resistant *Acinetobacter* species (CRAsp), and multidrug-resistant (MDR) *Pseudomonas aeruginosa*

^^Confidence Intervals cross null value

Table S3d. Adjusted* national incidence trends, by pathogen, using continuous parameters and stratified by hospital-onset, community-onset, and sterile vs. non-sterile infection sources, 2012-2017

	MRSA^		VRE^		CRE^		ESBL^		CRAsp^		MDR Pseudomonas^	
Hospital-Onset†												
	Sterile	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**
Parameter Estimate	-0.073	-0.079	-0.149	-0.131	-0.043	-0.028	0.007	0.008	-0.187	-0.111	-0.156	-0.101
95% Confidence Interval	-0.097 to -0.048	-0.095 to -0.064	-0.185 to -0.113	-0.156 to -0.106	-0.107 to 0.020^^	-0.070 to 0.013^^	-0.040 to 0.053^^	-0.017 to 0.033^^	-0.264 to -0.109	-0.175 to -0.047	-0.230 to -0.082	-0.142 to -0.061
Annual percent change**	-7.0%	-7.6%	-13.8%	-12.3%	-4.2%	-2.8%	0.7%	0.8%	-17.0%	-10.5%	-14.4%	-9.6%
95% Confidence Interval	-9.3% to -4.6%	-9.0% to -6.2%	-16.9% to -10.7%	-14.4% to -10.0%	-10.1% to 2.0%^^	-6.7% to 1.3%^^	-3.9% to 5.5%^^	-1.7% to 3.3%^^	-23.2% to -10.3%	-16.1% to -4.6	-20.6 to -7.9%	-13.2 to -5.9%
Community-Onset‡												
	Sterile	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**	**Sterile**	**Non-Sterile**
Parameter Estimate	-0.016	-0.045	-0.052	-0.083	0.049	0.033	0.153	0.091	-0.060	-0.051	-0.072	-0.054
95% Confidence Interval	-0.031 to -0.001	-0.057 to -0.034	-0.081 to -0.023	-0.108 to -0.059	-0.015 to 0.112^^	-0.012 to 0.078^^	0.127 to 0.179	0.075 to 0.107	-0.131 to 0.011	-0.098 to -0.004	-0.134 to -0.010	-0.076 to -0.033
Annual percent change**	-1.6%	-4.4%	-5.1%	-8.0%	5.0%	3.4%	16.5%	9.6%	-5.8%	-5.0%	-6.9%	-5.3%
95% Confidence Interval	-3.0% to -0.1%	-5.5% to -3.4%	-7.8% to -2.3%	-10.2% to -5.7%	-1.5% to 11.9%^^	-1.1% to 8.1%^^	13.6% to 19.6%	7.8% to 11.3%	-12.3% to 1.1%	-9.3% to -0.4%	-12.5% to -1.0%	-7.3% to -3.2%

*Adjusted for hospital characteristics including bed size, U.S. census division, urban/rural designation, teaching status, month of hospitalization, age distributions, and data source

**Annual percent change is calculated as $(e^{p}-1)*100\%$, where p is the modeled parameter estimate for the variable year.

†HO: Hospital-Onset, defined as a positive culture ≥4 days from the time of admission

‡CO: Community-Onset, defined as a positive culture <4 days from the time of admission

^methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum cephalosporin resistance in *Enterobacteriaceae* suggestive of extended-spectrum β-lactamase (ESBL)-production, carbapenem-resistant *Acinetobacter* species (CRAsp), and multidrug-resistant (MDR) *Pseudomonas aeruginosa*

^^Confidence Intervals cross null value

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