

CDC Antimicrobial Resistance Threats Report

Carbapenem-resistant Enterobacterales Data Methods

National estimates of the total number of carbapenem-resistant Enterobacterales (CRE) cases in hospitalized patients, attributable deaths, and healthcare costs were determined for 2023 using multiple data sources.

Definitions

- **Carbapenem-resistant Enterobacterales (CRE):** An isolate of *Citrobacter amalonaticus*, *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter* spp., *Escherichia coli* (*E. coli*), *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, or *Serratia marcescens* (*S. marcescens*) that tested resistant to at least one of the following: imipenem, meropenem, doripenem, or ertapenem; or an isolate of *Proteus mirabilis*, *Proteus penneri*, *Proteus vulgaris*, or *Morganella morganii* (*M. morganii*) that tested resistant to at least one of the following: meropenem, doripenem, or ertapenem.
- **Hospital-onset CRE case:** A case was defined as hospital-onset (HO) when the specimen for culture was collected on hospital day four or later (where the day of admission was considered day one).
- **Community-onset CRE case:** A case was defined as community-onset (CO) when the specimen for culture was obtained in the Emergency Department (ED), Pediatric ED, or 24-hour Observation Area before hospital admission or within the first three days of the hospitalization (where the day of admission was considered day one). CO cases include cases in patients with recent healthcare exposures (e.g., stays in hospitals or nursing homes) as well as cases in patients without prior healthcare exposure.
- **Invasive CRE case:** A case was defined as invasive when CRE was isolated from specimens taken from parts of the body that are normally sterile (free from germs), such as blood, cerebrospinal fluid, or bone.
- **Non-invasive CRE case:** A case was defined as non-invasive when CRE was isolated from specimens taken from parts of the body that are not normally sterile. Non-invasive specimens include the following specimen types: urine, lower respiratory, soft tissue, wound, and specimens from other body sites that are not normally sterile. Because these parts of the body can be colonized with bacteria, some non-invasive cases may not represent clinical infections.

National case estimates

Description of the National Healthcare Safety Network Antimicrobial Use and Resistance Module – AR Option

Data submitted to the National Healthcare Safety Network (NHSN) Antimicrobial Resistance (AR) Option of the Antimicrobial Use and Resistance (AUR) module were used to estimate the total number of CRE cases in hospitalized patients in the United States in 2023.

Hospitals participating in the AR Option are required to submit isolate-based reports to CDC electronically in Health Level 7 (HL7) Clinical Document Architecture (CDA) format from patients in all NHSN-defined inpatient locations, EDs, Pediatric EDs, and 24-hour Observation Areas [2,3]. Isolate-based reports from other outpatient location types, such as outpatient clinics, are not accepted.

An isolate-based report is a report of a single organism, regardless of antimicrobial susceptibility, isolated from a culture of a specimen source included in the AR Option protocol. Isolate-based reports include antimicrobial susceptibility testing data available from the hospital's clinical laboratory.

The AR Option requires reporting of selected organisms isolated from certain invasive and non-invasive specimen sources [2,3]. The list of organisms and specimen sources has changed over time. Organisms reported to the AR Option in 2023 included but were not limited to all *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Klebsiella* spp., and *Proteus* spp., plus *E. coli*, *M. morganii*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *S. marcescens*, and *Staphylococcus aureus* (*S. aureus*). In 2023, invasive specimens were blood and cerebrospinal fluid, and non-invasive specimens were urine and lower respiratory.

For isolates from invasive sources, only one positive culture from the same patient for the same organism (genus and species, unless only genus was identified) per 14-day period, even across calendar months, was submitted. For isolates from non-invasive sources, only the first organism per patient per month was submitted [3].

NHSN AR Option data included in the national case estimate analysis

To be included in the analysis, hospitals participating in the AR Option had to meet all of the following criteria:

1. Be one of the following hospital types: general acute care, critical access, children's, oncology, orthopedic, surgical, women's, and women's or children's hospitals;
2. Have submitted at least nine months of AR Option data to NHSN in 2023;
3. Have self-reported that their clinical laboratories had adopted the 2023 Clinical and Laboratory Standards Institute (CLSI) Performance Standards for Antimicrobial Susceptibility Testing (M100) [4];
4. Have reported antimicrobial susceptibility results within the permissible interpretive categories stipulated by CLSI [4].

Isolate-based reports were eligible for inclusion in the analysis if the culture was collected in 2023 from a patient in an inpatient location or from a patient in an ED, Pediatric ED, or 24-hour Observation Area who was subsequently admitted to an inpatient location.

Hospitals were excluded from this individual pathogen analysis if antimicrobial susceptibility test results to identify CRE were available for less than 90% of Enterobacterales isolates. To account for cascade reporting or suppression of results, isolates of Enterobacterales were assumed to be carbapenem-susceptible if no carbapenem susceptibility result was reported but the isolate was reported to be susceptible to at least two of the following drugs: ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin/tazobactam (susceptible or susceptible-dose dependent), cefazolin, cefoxitin, or cefotetan.

In addition, hospitals were excluded from all NHSN pathogen analyses if:

1. Data quality or completeness issues were identified for the AR Option variable that indicated whether cases reported from ED, Pediatric ED, or 24-hour Observation Areas were subsequently admitted to the hospital, or
2. Antimicrobial susceptibility test results to identify the resistant phenotype were available for less than 90% of isolates for three or more of the following pathogens: carbapenem-resistant *Acinetobacter*, CRE, extended-spectrum cephalosporin-resistant Enterobacterales, methicillin-resistant *S. aureus*, multidrug-resistant *P. aeruginosa*, and vancomycin-resistant *Enterococcus*.

The AR Option cohort for this analysis included 726 hospitals; 7,215,773 hospitalizations; and 2,592 isolate-based reports.

Statistical analysis for weighted national case estimates

Because not all U.S. hospitals reported data to the AR Option, we used methods of previous studies to weight the observed CRE cases in hospitals reporting data to the AR Option to represent the total burden of CRE in all U.S. hospitals in 2023 [5-7]. To calculate sample weights, annual national NHSN hospital census data and the subset of hospitals reporting to the AR Option in 2023 were stratified by the following hospital characteristics: intensive care unit bed size, U.S. Census division, urban-rural classification defined by the National Center for Health Statistics [8], and average length of stay. A sample weight was calculated only for strata with at least one hospital in the NHSN hospital census and at least one hospital reporting to the AR Option.

Iterative proportional fitting (IPF) was applied to derive hospital-specific weights for the AR Option data such that the weighted distribution of hospitalizations matched the distribution in all hospitals reporting to NHSN across these hospital characteristics. Using the IPF-derived weights, we extrapolated facility-specific case counts to estimate the national burden of CRE cases and corresponding 95% confidence intervals, the range of values likely to include the true value. Estimates were calculated with a weighted survey procedure incorporating finite population correction and were further stratified by case onset location (HO vs. CO) and by specimen source (invasive vs. non-invasive).

Multipliers to account for additional specimen sources not included in the NHSN AR Option

Previous AR Threats Report analyses included additional specimen sources, such as skin, soft tissue, wound, and musculoskeletal, that were not included in the 2023 AR Option protocol. Data from the Premier Healthcare Database (PHD) [9] were used to generate multipliers to account for those additional specimen sources. Clinical cultures in PHD were identified and categorized using methods like those in previously presented analyses [5-7].

PHD data from hospitalizations with discharge dates in 2022 and 2023 were included. Using the same pathogen and case onset location definitions applied to the AR Option data, positive cultures for CRE were identified and categorized as invasive or non-invasive and HO or CO. For each stratum (HO-invasive, HO-non-invasive, CO-invasive, CO-non-invasive), the ratio of all specimen sources in PHD data to AR Option specimen sources was determined. This ratio was

used as a multiplier for the weighted national case estimates from AR Option data in each stratum to adjust for specimen sources not included in the AR Option. Variances for the multipliers were determined through the delta method [10]. After applying the multipliers, estimates in each stratum were summed to obtain the total national case estimate.

Attributable mortality estimates

Estimates of 90-day attributable mortality, including in-hospital and post-discharge deaths, were reported previously [7]. Methods were described in the AR Threats Report published in 2019 [7]. Due to sample size limitations, carbapenem-resistant *Acinetobacter*, CRE, and multidrug-resistant *P. aeruginosa* were combined to create a pooled attributable mortality estimate for multidrug-resistant gram-negative pathogens. Estimates of attributable mortality for these multidrug-resistant gram-negative pathogens were multiplied by the estimates of the total number of CRE cases within the HO and CO strata to calculate the total number of deaths due to hospitalized CRE cases.

Attributable healthcare cost estimates

Estimates of attributable costs for CRE cases generated using methods described in the AR Threats Report published in 2019 were converted to 2023 U.S. dollars using the Personal Consumption Expenditures – Health Price Index [7,11-12]. These attributable costs were applied to the corresponding number of CRE cases within each stratum (HO-invasive, HO-non-invasive, CO-invasive, CO-non-invasive) to calculate the total estimated attributable healthcare costs for CRE cases.

Uncertainty and credible intervals

Uncertainty and credible intervals, or the range of values likely to include the true value, for the total burden, attributable mortality, and attributable healthcare cost estimates were quantified and propagated using Monte Carlo simulations.

Additional methods for CRE

Trends in carbapenemase-producing CRE (CP-CRE) were described based on clinical isolates reported to the CDC's Antimicrobial Resistance Laboratory Network. Detailed methods and findings were described previously [1]. An open cohort of 29 U.S. states with mandated submission of all carbapenem-resistant *Klebsiella* spp., *E. coli*, and *Enterobacter* spp. isolates was established to examine temporal trends of the incidence of CP-CRE overall and by identified carbapenemase [1].

Data methods references

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Additional references

The following additional references were used for the development of the AR Threats Report content for CRE not already included in the data methods.

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