

CDC Antimicrobial Resistance Threats Report

Drug-resistant *Candida* Data Methods

National estimates of the total number of hospitalized drug-resistant *Candida* cases and their attributable mortality were reported for the years 2019-2023.

The national estimates of the number of *Candida* bloodstream cases (candidemia) were calculated using data submitted to CDC's Emerging Infections Program (EIP) [1]. CDC conducts population-based active surveillance for culture-confirmed candidemia through EIP in specific counties in 10 U.S. states: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. A culture-confirmed candidemia case was defined as a positive blood culture for any *Candida* species from a resident in the surveillance catchment area. A positive *Candida* culture within the 30-day period after the initial blood culture in the same person was considered part of the same case; a positive *Candida* culture after the 30-day period in the same person was considered a new case [1]. *Candida* isolates associated with candidemia cases were obtained and sent by EIP sites to CDC to confirm species identification and perform antifungal susceptibility testing (AFST). AFST was performed using prepared microdilution plates for fluconazole, voriconazole, anidulafungin, caspofungin, and micafungin according to guidelines in the Clinical and Laboratory Standards Institute (CLSI) M27 standard [2]. Amphotericin B susceptibility was performed using gradient diffusion. For cases where multiple isolates were available, only one isolate per case (the first one submitted) was included in this analysis. The percentage of isolates with any resistance was calculated by dividing the number of resistant isolates from the five most common *Candida* species by the total number of isolates from those species that underwent AFST. The calculation only includes isolates from the top five *Candida* species (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) because breakpoints for many other *Candida* species do not exist. *Candida krusei* has intrinsic resistance to fluconazole [1].

Multiple imputation analysis was performed for missing race based on the distribution of known values stratified by age, sex, and year. The population estimates from the U.S. Census Bureau, stratified by age, sex, and race distribution of the United States and EIP population, were used to calculate the sampled weights to estimate the 2019 to 2023 national burden of all candidemia [3]. Estimates of national drug-resistant candidemia cases were calculated by multiplying the estimated number of national cases by the percentage of cases with resistance from EIP.

Estimates of total drug-resistant *Candida* were determined by multiplying the number of drug-resistant candidemia cases by a ratio of all other specimen sources to blood specimen sources for *Candida* specimens identified during a hospitalization in the Premier Healthcare Database (PHD) [4]. The PHD was used to identify any cultures (i.e., any specimen type) with "*Candida*" listed as a final result during hospitalizations with discharge dates from 2019-2023. Specimens were categorized as blood or non-blood, consistent with prior methods [5,6]. For each calendar year, the ratio of all other specimen sources to blood specimen

sources was determined for *Candida* specimens. Variance for the multiplier was determined through the delta method. The West region is substantially under-represented in the PHD, potentially affecting the representativeness of the data.

Estimates of total attributable mortality were determined by multiplying the attributable mortality for invasive *Candida* specimens and non-invasive *Candida* specimens by their respective burden estimates from above and summing. Attributable mortality for *Candida*-positive cultures was estimated for both invasive and non-invasive cases using the PHD [6]. Invasive specimens included those collected from blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, synovial fluid, and lymph nodes, and non-invasive specimens included those collected from urine, sputum, and wounds. Specimens that were categorized as surveillance (i.e., cultures labeled as rectal, perirectal, or nasal) were excluded. Adjusted risk differences from logistic regression models comparing *Candida*-positive cases with matched controls were calculated using an outcome of in-hospital deaths or discharge to hospice. Up to five matched controls were selected from the same hospital using exposure density sampling by day of an inpatient stay (i.e., the selected control must have been in the hospital with no positive *Candida* culture on the day of hospitalization that the matched case had a positive culture). Models were adjusted for patient and hospitalization characteristics.

Uncertainty and credible intervals (range of values likely to include the true value) for all burden and mortality estimates were quantified and propagated using Monte Carlo simulations.

References

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