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# Prevalence, incidence burden, and clinical impact of healthcare-associated infections and antimicrobial resistance: a national prevalent cohort study in acute care hospitals in Greece

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**Background:** Assessing the overall burden of healthcare-associated infections (HAIs) is challenging, but imperative in evaluating the cost-effectiveness of infection control programs. This study aimed to estimate the point prevalence and annual incidence of HAIs in Greece and assess the excess length of stay (LOS) and mortality attributable to HAIs, overall and for main infection sites and tracer antimicrobial resistance (AMR) phenotypes and pathogens.

**Patients and methods:** This prevalent cohort study used a nationally representative cross-section of 8,247 inpatients in 37 acute care hospitals to record active HAIs of all types at baseline and overall LOS and in-hospital mortality up to 90 days following hospital admission. HAI incidence was estimated using prevalence-to-incidence conversion methods. Excess mortality and LOS were assessed by Cox regression and multistate models correcting for confounding and time-dependent biases.

**Results:** HAIs were encountered with daily prevalence of 9.1% (95% confidence interval [CI] 7.8%–10.6%). The estimated annual HAI incidence was 5.2% (95% CI 4.4%–5.3%), corresponding to approximately 121,000 (95% CI 103,500–123,700) affected patients each year in the country. Ninety-day mortality risk was increased by 80% in patients with HAI compared to those without HAI (adjusted hazard ratio 1.8; 95% CI 1.3–2.6). Lower respiratory tract infections, bloodstream infections, and multiple concurrent HAIs doubled the risk of death, whereas surgical site and urinary tract infections were not associated with increased mortality. AMR had significant impact on the daily risk of 90-day mortality, which was increased by 90%–110% in patients infected by carbapenem-resistant gram-negative pathogens. HAIs increased LOS for an average of 4.3 (95% CI 2.4–6.2) additional days. Mean excess LOS exceeded 20 days in infections caused by major carbapenem-resistant gram-negative pathogens.

**Conclusion:** HAIs, alongside with increasing AMR, pose significant burden to the hospital system. Burden estimates obtained in this study will be valuable in future evaluations of infection prevention programs.

**Keywords:** nosocomial infections, antibiotic resistance, length of stay, mortality, prevalence, incidence

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## Introduction

Healthcare-associated infections (HAIs) represent a major issue for healthcare providers, infection control specialists, public health authorities, and the patients. The most recent estimate of the average daily prevalence of HAIs in acute care hospitals in Europe is 6%, involving approximately 3.2 million affected patients each year.[1]

The dramatic increase of antimicrobial resistance (AMR) in pathogenic bacteria seen in hospital settings worldwide[2] has resulted in more complications to treat HAIs, and associated treatment failure and deaths have risen.[3]

Even with optimal care, the extent to which HAIs are preventable depends on the setting, type of infection, and baseline infection rates. Systematic reviews of interventions to reduce HAIs have suggested that at least 20% of all HAIs are probably avoidable.[4] Preventability proportions may exceed 50% for surgical site and device-associated infections with current evidence-based strategies.[5] However, infection prevention programs have an associated cost, which should be compared with the expected benefits to ensure that the most cost-effective measures are implemented.[6,7] This requires accurate assessment of the overall burden of HAIs in terms of excess deaths, length of hospitalization, and costs.[6,7]

The resources and effort required have rarely allowed multicenter studies of the global burden of all types of HAIs to be carried out. Consequently, only a handful of epidemiological studies have attempted to assess the impact of all HAIs on prolongation of length of stay (LOS) and/or mortality in hospital-wide settings.[7–11] Moreover, studies attempting to provide this information face considerable challenges. Patients with HAIs are older, suffer from more chronic diseases, and are generally more ill than patients without HAIs;[12] consequently, patients with HAIs experience long exposure to the hospital environment before becoming infected. Such confounding effects and time-dependent biases may have been inadequately addressed in previous studies.[6,13]

The aim of this study was to obtain the first national estimates of the current prevalence and incidence burden of HAIs in acute care hospitals in Greece and assess the excess mortality and LOS attributable to HAIs, overall and separately for main sites of infection and tracer AMR phenotypes and pathogens.

# Patients and methods

## Study design and setting

This prevalent cohort study was based on a baseline survey of 8,247 inpatients in 37 hospitals in Greece. The sample was a nationally representative cross-section of all patients hospitalized in acute care hospitals in a single day and was formed as part of the country's participation in the first pan-European point prevalence survey of HAIs in June 2012.[14] Mortality and LOS were ascertained at the time of hospital discharge and up to 90 days after the baseline survey.

The study was approved by the Review Board of Hellenic Center for Disease Control and Prevention. As data collection originated from routine care activities and was included in monitoring activities mandated by national legislation (Ministerial Decisions Y1/4234/13.6.2001 and Y1.114971/18.02.2014), separate approvals by the institutional ethics committees in participating hospitals and patient informed consent were not required. Data were anonymous, kept confidential, and not linked to individuals. Study results are reported according to the STROBE guidelines.

## Hospital selection criteria and sample size

We calculated that a total of 40 hospitals (10,506 patients) would be required to estimate an anticipated HAI point prevalence of 7%,[12] with precision of ±1% at the national level, based on an average hospital size of 260 beds and a total number of 35,120 beds. We used an estimated design effect of 4.5 to account for clustering at the hospital level.[14]

We recruited hospitals on a voluntary basis using a purposive sampling method. Three criteria were used to frame the sample: 1) inclusion of at least one district-referral hospital from each of the seven Regional Health Districts in the country, 2) inclusion of at least four general hospitals from each district, and 3) all included hospitals have a fully operational infection control team with prior experience in HAI surveillance. We identified 39 hospitals satisfying the selection criteria, which we invited to participate; two hospitals refused to participate.

The 37 sampled hospitals comprised 27% of all public hospitals in Greece, had 16,164 beds (46% of the country's total), and had completed 1,068,311 discharges and 4,127,210 patient-days in 2011 (46% and 44% of country's total, respectively).

## Patient selection criteria

All patients admitted to an acute care ward before 8:00 AM and not discharged from the ward at the time of the baseline survey were included in the study cohort. Day-case patients undergoing same-day treatment or surgery, seen in the emergency room or at outpatient departments, and dialysis outpatients were excluded.

## Data collection and processing

Data were collected by 115 infection control practitioners across the country who had attended a 2-day online training course based on standardized European Centre for Disease Prevention and Control (ECDC) and national training materials. A help-desk service was provided during data collection by the Infection Control Unit of University Hospital of

Heraklion, which served as the coordinating center for this study. All raw data were submitted to the coordinating center through a web-based data entry system and underwent central data management, including data checking for obvious errors and omissions, corrective queries, and statistical analysis.

Data were extracted from review of nursing and medical records and on the basis of information provided by the physicians and nurses in charge of the patients. Data collected for all patients included demographic characteristics, comorbid conditions determined by use of the weighted Charlson comorbidity index,[15] severity of underlying disease determined in accordance with the McCabe classification,[14] patient specialty, exposure to invasive devices at baseline, and prior surgery in the 30 days preceding the baseline survey. Comorbidities were evaluated at the time of hospital admission. Disease severity was determined in accordance to ECDC guidelines,[14] and assessed before infection for patients with an active HAI and at the day of survey for uninfected patients.

Active HAIs at baseline were identified using the ECDC case definitions.[14] Data collected for each HAI included date of onset, site, microorganisms, and AMR status. For purposes of data analysis, HAIs were categorized into lower respiratory tract infections (LRTIs) including pneumonias, bloodstream infections (BSIs) including catheter-related infections, urinary tract infections (UTIs), surgical site infections (SSIs), systemic infections including clinical sepsis, and other infections. Patients with multiple concurrent HAIs were analyzed as a separate group. AMR was assessed based on antibiotic susceptibility data that were available at the time of the baseline survey. Selected tracer phenotypes were recorded, including methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant *Enterococcus* species (VRE); third-generation cephalosporins and carbapenems for Enterobacteriaceae; and carbapenems for *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Intermediate sensitive strains were recorded as resistant.

Baseline data collection was completed in a single day at the ward/unit level and within a period of 3–4 weeks at the hospital level. Patient outcome was recorded as in-hospital death, discharge alive, or hospital stay 3 months following the baseline survey. Six hospitals did not provide outcome data as patient follow-up was an optional part of the study protocol.

## Statistical analysis

HAI point prevalence was calculated as the number of infected patients divided by the total number of patients, overall and separately for each site of infection, resistance phenotype, and pathogen. Population estimates of prevalence proportions were calculated with 95% confidence intervals (CI) and were compared across different patient groups using chi-square tests accounting for the stratified clustered design (by region and hospital) of the baseline survey.

The annual incidence burden of HAIs was quantified by estimating the number of patients expected to acquire a HAI in a year in acute care hospitals in the country, overall and separately by type of HAI and AMR phenotype. This was calculated by multiplying the point prevalence estimate by the national total of acute care patient-days in the country (9,312,024 patient-days in 2011) and dividing the product by the average duration of infection. The calculation has been described by Freeman and Hutchison,[16] and forms the basis of the Rhame and Sudderth prevalence-to-incidence conversion.[17] The estimated number of patients acquiring a HAI in a year was divided by the national total of discharges (2,344,999 discharges in 2011) to obtain annual cumulative incidence proportions for each type of HAI and resistance phenotype. Duration of infection was estimated as the interval between date of onset of infection and date of baseline survey, excluding HAIs present at admission.[1,18] Median values were used to account for the high degree of right skewness in the distribution of infection durations, and associated CIs were calculated using bootstrapping.

Multivariable Cox proportional hazards models were used to compare the daily risk (hazard) of death between patients with HAIs and uninfected patients in terms of adjusted hazard ratios (HRs) and associated 95% CIs. The day of admission was used as the time variable, and times to death within 30 and 90 days of hospital admission were the outcome variables in the models. Occurrence of HAI was treated as a time-dependent exposure to account for the indirect effect on mortality of a potentially extended LOS due to HAI. Main infection types and AMR phenotypes were examined separately. Baseline covariates were adjusted for in the models with the assumption that patient characteristics at admission remained unaltered throughout a patient's stay. The models accounted for clustering at the hospital level and stratification at the regional level.

Differences in hospital LOS between patients with HAI and those without were estimated by a multistate model using the "Empirical Transition Matrix" package (version 0.6–2) in R, version 3.3.0.[19] The model comprised two transient states (hospital admission and HAI) and two absorbing states (discharge alive and in-hospital death). HAI was considered an intermediate state between admission and discharge or death in order to mitigate the potential for time-dependent bias, which has been shown to overestimate the extra LOS.[13,20] This time-adjusted

estimate of excess LOS cannot be adjusted for other confounders. Associated CIs were calculated using bootstrapping.

# Results

## Studied population

The study cohort consisted of 8,247 inpatients at baseline, who had a median age of 63 years (interquartile range [IQR], 38–76 years) and 54.4% were males. Most patients had an emergency admission (74.7%) and were located in tertiary care hospitals (63.6%). The median Charlson comorbidity index was 1 (IQR, 0–2), and 26.8% of the patients had a rapidly or ultimately fatal underlying disease. At the time of the baseline survey, 80.8% were exposed to one or more invasive devices and 28.4% had undergone recent surgery. Outcome data were obtained for 7,147/8,247 (87%) patients in 31/37 (84%) hospitals (Figure 1). Any-cause mortality was 3.3% at 30 days and 6.1% at 90 days following hospital admission. The median LOS was 11 (IQR, 6–23) days.

## Characteristics of HAIs

A total of 746 patients with an active HAI were identified, of whom 71 (9.5%) patients had two concurrent infections and

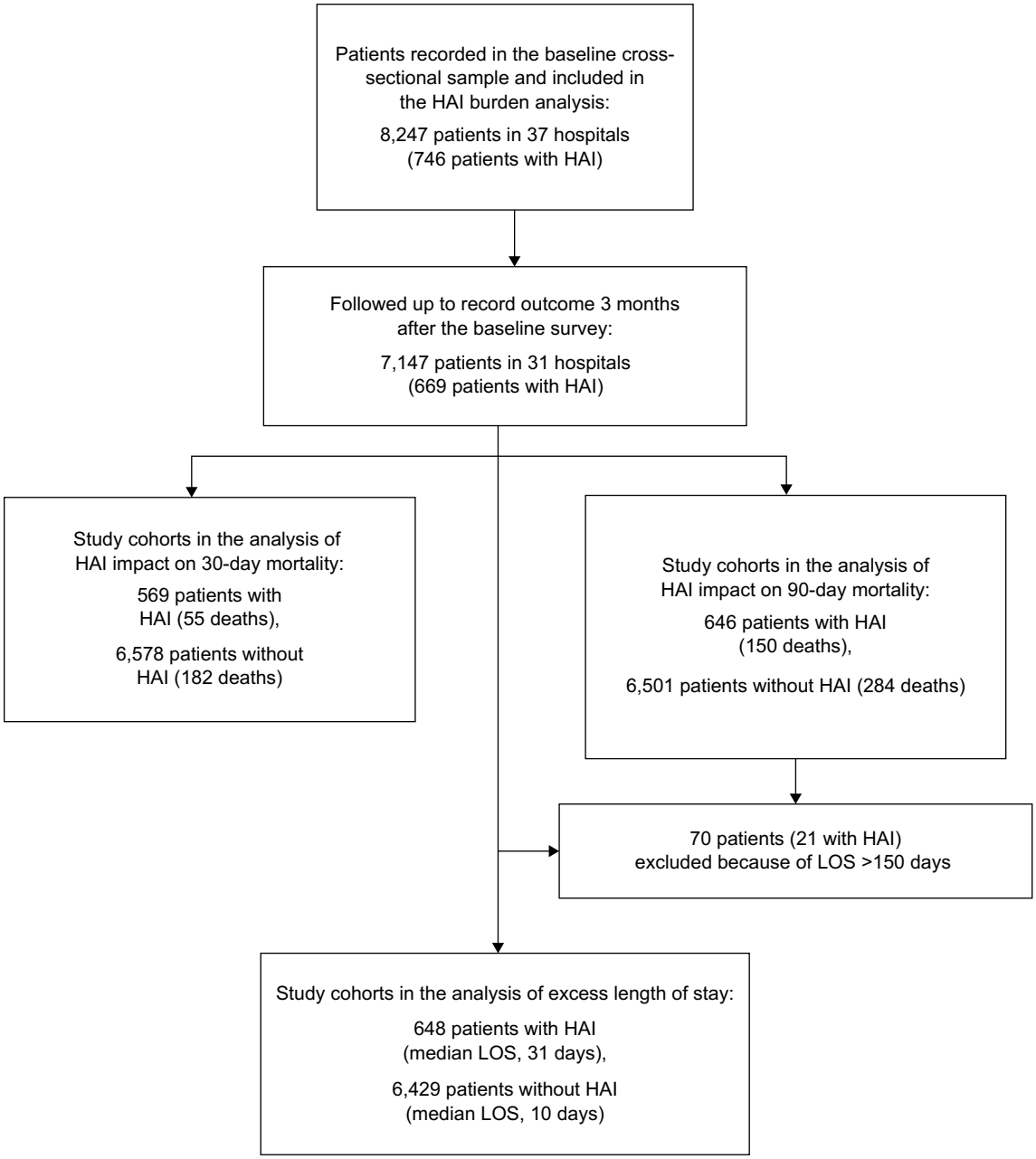


**Figure 1** Flow chart showing patient inclusion and follow-up in the study and the sample sizes in the analyses of the burden and impact of HAI.
**Abbreviations:** HAI, healthcare-associated infection; LOS, length of hospital stay.

three (0.4%) patients had three infections. Among the 820 recorded episodes of HAI, the most frequent type was LRTI (2.7 infections per 100 patients; 26.7% of all infections), followed by BSIs (2.1 infections per 100 patients, 20.7% of infections), UTIs (1.7 infections per 100 patients; 17.0% of infections), SSIs (3.8 infections per 100 operated patients; 10.9% of infections), and systemic infections (0.7 infections per 100 patients; 6.7% of infections). The "other" category accounted for an additional 18.0% of HAIs (1.8 infections per 100 patients). A total of 222 (27.1%) HAIs were present at hospital admission, originating from the same or other hospital. The median time from hospital admission to onset of infection was 11 (IQR, 6–25) days. The median duration of infection was 7.0 (95% CI, 7.0–8.0) days.

A total of 564 microorganisms were recorded in 449 (54.8%) of 820 episodes of HAI. The pathogens isolated most frequently included *Klebsiella* species (17.6%), *P. aeruginosa* (16.8%), *Acinetobacter* species (16.8%), *Staphylococcus* species (9.2%, including 2.7% *S. aureus*), *Enterococcus* species (8.9%), and *Escherichia coli* (8.3%). Of the 424 isolates with available antibiogram data, 204 (48.1%) had a tracer AMR phenotype. Fifty percent (8/16) of *S. aureus* isolates were MRSA; 12.5% (6/48) of enterococci were VRE; and 39.9% (48/183) of Enterobacteriaceae, 83% (73/88) of *A. baumannii*, and 49.4% (44/89) of *P. aeruginosa* were resistant to carbapenems.

## HAI prevalence and incidence burden

The overall point prevalence of patients with HAI was 9.1% (95% CI 7.8–10.6). Table 1 shows HAI prevalence according to baseline patient characteristics. HAI prevalence was higher in males than in females, varied by patient specialty and increased with age, severity of underlying disease, comorbidity index, and number of invasive devices. Higher HAI prevalence was also observed for patients who had undergone recent surgery and those with an emergency admission. The highest overall prevalence proportions were observed in intensive care patients (32.7%, 95% CI 27.4–38.4), patients admitted with a rapidly fatal disease (30.5%, 95% CI 25.0–36.7), and those exposed to 3–4 invasive devices (47.9%, 95% CI 42.3–53.5).

The total number of patients with at least one HAI on any given day in the country was estimated at 2,323 patients (95% CI 1,985–2,712). The estimated annual incidence of patients acquiring at least one HAI in a year was 5.2% (95% CI 4.4%–5.3%), corresponding to an absolute number of 121,142 patients (95% CI 103,522–123,738) acquiring a HAI per year in the country. National estimates of prevalence and incidence burden according to type of infection and AMR phenotype are shown in Table 2.

## Impact of HAI on inpatient mortality

Table 3 shows cumulative proportions and HRs for 30-day and 90-day mortality according to patient characteristics. No major difference in mortality was observed according to sex and hospital type. Patients in internal medicine wards and intensive care units had significantly higher mortality compared to surgical patients, whereas no deaths were recorded in pediatric, gynecology, and obstetrics departments. Patients with emergency admission had higher mortality than those with elective admission. Mortality increased with age, underlying disease severity, comorbidity index, and exposure to invasive devices. Mortality was substantially higher for patients with HAI at baseline (9.7% and 23.2% at 30 and 90 days, respectively) than those without HAI (2.8% and 4.4% at 30 and 90 days, respectively).

Following adjustment for confounding and time-dependent bias in Cox regression, presence of HAI continued to show elevated risk of mortality at 30 days (HR=1.3, 95% CI 0.7–2.4, $p$=0.363) and 90 days (HR=1.8, 95% CI 1.3–2.6, $p$=0.001). Table 4 shows case-fatality rates and adjusted HRs according to type of infection, resistance phenotype, and pathogen. Compared to uninfected patients, increased mortality risk was observed for patients with LRTIs, BSIs, and multiple concurrent infections. By contrast, no increase in the risk of death was observed in patients with UTIs, SSIs, systemic infections, or other infections. Mortality risk was also increased in patients infected by third-generation cephalosporin-resistant Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and carbapenem-resistant *A. baumannii*. No significant impact on mortality was seen in patients infected with MRSA or VRE.

## Excess length of hospital stay associated with HAI

Using a multistate model, presence of HAI was found to significantly increase LOS for a mean of 4.3 (95% CI 2.4–6.2) additional days. The time-adjusted mean difference in LOS between patients with HAI and those without HAI varied substantially according to the type of infection and ranged from −2.8 (95% CI −6.6–1.0) days in UTIs to 10.5 (95% CI 5.3–15.8) days in BSIs. High excess LOS estimates were obtained in patients with multiple concurrent infections (16.6 days; 95% CI 8.9–24.3) and those infected

**Table 1** Comparison of patients with and without HAI and population estimates of HAI prevalence according to baseline patient characteristics

| Patient characteristics | Group | No. (%) of patients | | HAI prevalence % (95% CI)[a] | *P*-value |
|---|---|---|---|---|---|
| | | With HAI | Without HAI | | |
| All | All | 746 (100) | 7,501 (100) | 9.1 (7.8–10.6) | – |
| Sex | Male | 439 (58.8) | 4,048 (54.0) | 9.8 (8.3–11.5) | 0.005 |
| | Female | 307 (41.2) | 3,453 (46.0) | 8.3 (7.0–9.8) | |
| Age (years) | 0–14 | 52 (7.0) | 941 (12.5) | 5.0 (3.0–8.0) | <0.001 |
| | 15–34 | 47 (6.3) | 774 (10.3) | 5.7 (4.1–7.8) | |
| | 35–54 | 124 (16.6) | 1,267 (16.9) | 8.9 (7.3–10.8) | |
| | 55–74 | 262 (35.1) | 2,359 (31.5) | 10.0 (8.7–11.5) | |
| | 75+ | 261 (35.0) | 2,158 (28.8) | 11.1 (9.1–13.3) | |
| Hospital type | Tertiary-care | 532 (71.3) | 4,716 (62.9) | 10.1 (8.6–11.8) | 0.118 |
| | Other | 214 (28.7) | 2,785 (37.1) | 7.4 (5.2–10.5) | |
| Admission type | Emergency | 616 (82.6) | 5,542 (73.9) | 10.0 (8.6–11.7) | <0.001 |
| | Elective | 130 (17.4) | 1,959 (26.1) | 6.4 (5.1–8.0) | |
| Patient specialty | Surgery | 193 (25.9) | 2,822 (37.6) | 6.4 (5.1–8.0) | <0.001 |
| | Medicine | 343 (46.0) | 3,067 (40.9) | 10.1 (8.7–11.7) | |
| | Pediatrics | 9 (1.2) | 465 (6.2) | 2.0 (0.6–6.6) | |
| | Gynecology, obstetrics | 10 (1.3) | 441 (5.9) | 1.7 (0.9–3.3) | |
| | Intensive care | 186 (24.9) | 415 (5.5) | 32.7 (27.4–38.4) | |
| | Other | 5 (0.7) | 291 (3.9) | 1.9 (0.9–4.0) | |
| Underlying disease severity (McCabe) | Nonfatal | 349 (46.8) | 5,548 (74.0) | 5.8 (4.8–6.9) | <0.001 |
| | Ultimately fatal | 242 (32.4) | 1,477 (19.7) | 14.4 (12.1–16.9) | |
| | Rapidly fatal | 140 (18.8) | 357 (4.8) | 30.5 (25.0–36.7) | |
| | Unknown | 15 (2.0) | 119 (1.6) | 10.6 (7.0–15.8) | |
| Comorbidity index (Charlson) | 0 | 187 (25.1) | 3,734 (49.8) | 4.8 (3.7–6.1) | <0.001 |
| | 1 | 101 (13.5) | 1,030 (13.7) | 9.0 (7.5–10.8) | |
| | 2–3 | 261 (35.0) | 1,615 (21.5) | 14.0 (11.7–16.7) | |
| | 4+ | 197 (26.4) | 1,122 (15.0) | 15.2 (13.4–17.2) | |
| Recent major surgery | No | 494 (66.2) | 5,414 (72.2) | 8.4 (7.1–9.9) | 0.002 |
| | Yes | 252 (33.8) | 2,087 (27.8) | 10.9 (9.1–13.0) | |
| Number of invasive, devices at baseline[b] | 0 | 30 (4.0) | 1,555 (20.7) | 2.0 (1.4–2.9) | <0.001 |
| | 1 | 242 (32.4) | 3,977 (53.0) | 5.5 (4.4–6.8) | |
| | 2 | 287 (38.5) | 1,764 (23.5) | 14.1 (11.5–17.1) | |
| | 3–4 | 187 (25.1) | 205 (2.7) | 47.9 (42.3–53.5) | |
| | Yes | 736 (98.7) | 3,778 (50.4) | 16.5 (14.1–19.1) | |
| Overall LOS (days)[c] | Median (IQR) | 32 (17–56) | 10 (5–19) | – | – |
| Inpatient mortality[c] | At 30 days[d] | 55 (8.2) | 182 (2.8) | – | |
| | At 90 days[e] | 150 (22.4) | 284 (4.4) | – | |
| | At follow-up end | 168 (25.1) | 296 (4.6) | – | |

**Notes:** [a]Population prevalence estimate, accounting for the stratified cluster sampling design of the study. [b]Recorded invasive devices included urinary, central vascular, and peripheral vascular catheters and intubation. [c]Provided for background information only, as this analysis suffers from length-time bias.[13,20] [d]Death occurring within 30 days of hospital admission. Patients with infection onset after the 30th day were included in the "without HAI" group. [e]Death occurring within 90 days of hospital admission. Patients with infection onset after the 90th day were included in the "without HAI" group.

**Abbreviations:** HAI, healthcare-associated infection; CI, confidence interval; LOS, length of stay; IQR, interquartile range.

by an antimicrobial-resistant pathogen (16.9 days; 95% CI 12.9–20.9). Mean excess LOS peaked in patients infected by carbapenem-resistant Enterobacteriaceae, *P. aeruginosa*, or *A. baumannii* (Table 4).

## Discussion

In this first attempt to assess the overall burden of HAIs at the national level in Greece, we estimated that HAIs are encountered with an average daily prevalence of 9.1% (95% CI 7.8%–10.6%) in acute care hospitals in the country, and at an annual incidence rate of 5.2% (95% CI 4.4%–5.3%) involving approximately 121,000 affected patients each year in the country. We found that the daily risk of hospital death within 90 days of admission was increased by 80% in patients with a HAI compared to those without HAI (HR 1.8, 95% CI 1.3–2.6). Presence of HAI was seen to significantly increase hospital LOS for an average of 4.3 (95% CI 2.4–6.2) additional days. Our site-specific results suggested

**Table 2** National estimates of prevalence and incidence burden according to type of HAI and antimicrobial resistance status in Greek acute care hospitals

| | Duration of HAI, days | | Point prevalence | | Patients with a HAI, per day[a] | | Annual incidence | | Patients with a HAI, per year[b] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Median | 95% CI | % | 95% CI | N | 95% CI | % | 95% CI | N | 95% CI |
| Type of infection | | | | | | | | | | |
| Lower respiratory | 7.0 | 7.0–8.0 | 2.6 | 2.0–3.3 | 660 | 520–840 | 1.5 | 1.2–1.6 | 34,600 | 27,200–38,500 |
| Bloodstream | 9.0 | 9.0–10.0 | 2.0 | 1.7–2.5 | 520 | 420–640 | 0.9 | 0.7–1.0 | 21,200 | 17,200–23,500 |
| Urinary tract | 6.0 | 5.0–7.0 | 1.7 | 1.4–2.1 | 440 | 350–540 | 1.1 | 1.1–1.2 | 26,700 | 25,700–28,400 |
| Surgical site | 9.0 | 7.0–12.0 | 1.0 | 0.8–1.3 | 260 | 200–340 | 0.4 | 0.4–0.4 | 10,500 | 10,300–10,300 |
| Systemic | 6.0 | 5.0–7.0 | 0.7 | 0.4–1.1 | 180 | 110–290 | 0.5 | 0.3–0.6 | 10,900 | 8,100–15,100 |
| Other infections | 7.0 | 6.0–7.0 | 1.8 | 1.3–2.5 | 460 | 330–640 | 1.0 | 0.9–1.4 | 24,200 | 20,300–33,600 |
| Any HAI | 7.0 | 7.0–8.0 | 9.1 | 7.8–10.6 | 2,320 | 1,990–2,710 | 5.2 | 4.4–5.3 | 121,100 | 103,500–123,700 |
| Resistance phenotype[c] | | | | | | | | | | |
| Sensitive | 9.0 | 7.0–10.0 | 1.3 | 1.1–1.7 | 340 | 270–420 | 0.6 | 0.6–0.7 | 13,700 | 14,100–15,400 |
| Resistant | 10.0 | 10.0–11.0 | 2.7 | 2.1–3.5 | 690 | 530–900 | 1.1 | 0.8–1.3 | 25,100 | 19,200–29,800 |
| Resistant pathogens | | | | | | | | | | |
| MRSA or VRE | 11.0 | 8.0–16.7 | 0.1 | 0.1–0.3 | 40 | 20–70 | 0.1 | 0.0–0.1 | 1,300 | 900–1,500 |
| 3GCR Enterobacteriaceae | 11.0 | 8.0–14.9 | 0.5 | 0.4–0.8 | 140 | 100–200 | 0.2 | 0.2–0.2 | 4,600 | 4,600–4,800 |
| CR Enterobacteriaceae | 12.0 | 10.0–12.0 | 0.9 | 0.7–1.2 | 240 | 180–310 | 0.3 | 0.3–0.4 | 7,300 | 6,600–9,600 |
| CR *P. aeruginosa* | 9.0 | 8.0–12.0 | 0.5 | 0.3–0.7 | 120 | 80–180 | 0.2 | 0.2–0.2 | 4,800 | 3,600–5,400 |
| CR *A. baumannii* | 9.0 | 9.0–10.0 | 1.0 | 0.7–1.4 | 250 | 170–370 | 0.4 | 0.3–0.6 | 10,100 | 6,900–13,300 |

**Notes:** [a]Numbers have been rounded to the nearest tenth. [b]Numbers have been rounded to the nearest hundredth. [c]The "resistant" category includes patients infected with MRSA, VRE, 3GCR or CR Enterobacteriaceae, CR *P. aeruginosa*, or CR *A. baumannii*. All other infections with known antibiotic susceptibility data were categorized as "sensitive".

**Abbreviations:** HAI, healthcare-associated infection; CI, confidence interval; N, number of patients; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus* species; 3GCR, third-generation cephalosporin resistant; CR, carbapenem resistant; *P. aeruginosa*, *Pseudomonas aeruginosa*; *A. baumannii*, *Acinetobacter baumannii*.



that LRTIs, BSIs, and multiple concurrent HAIs double the risk of death in hospitalized patients, whereas SSIs and UTIs are not associated with increased mortality. AMR was shown to have a significant effect on the risk of in-hospital mortality, which was particularly high in patients infected by carbapenem-resistant gram-negative pathogens. Infections caused by pathogens with tracer AMR phenotypes were shown to independently increase hospitalization by more than 2 weeks (mean excess of 16.9 days, 95% CI 12.9–20.9 days).

Few comparable studies of the global burden of HAIs have been performed to date, mostly at the regional or single-center level,[8,9,11,12] and even fewer at the national level.[7,10] Most multicenter studies assessing the impact of HAIs have been primarily conducted in intensive care units,[21,22] or have focused on a single type of HAI and/or resistance phenotype.[23,24] This is not surprising given the amount of resources and effort required to conduct multicenter hospital-wide studies of all types of HAI. As in other national-level studies,[7,10] we attempted to make best use of available data from a national point prevalence study of HAIs that was combined with patient follow-up and linkage to national registry data to make projections at the national level.

Comparison of results between different studies remains difficult mainly because of differences in patient case mix and methodology.[12] Compared to ECDC data from 33 countries,[1] the overall HAI prevalence and incidence rates reported in this study rank Greece as 4th and 8th highest in Europe, respectively, affirming a significant burden to the Greek hospital system. The 30-day case-fatality rate in patients with HAI in this study appears to be lower than that reported in hospital-wide studies in Finland and Norway (8.2% vs 9.8% and 10.8%, respectively),[10,11] but the longer term case-fatality appears similar to that reported in France and previously in Greece and Cyprus (25.1% vs 21.6% and 27.9%, respectively).[8,12] As shown in other studies,[7,8,11] we also found that patients with BSI or LRTI had increased risk of dying during the follow-up period, even after adjusting for the effects of age, comorbidity, underlying disease severity, and other important risk factors for death. SSIs and UTIs were not associated with increased mortality risk, which has also been seen by others.[7,8,11,25]

The present study is unique, however, in showing the significant independent impact of AMR in patient mortality, even outside the critical care setting. Indeed, hospital-wide

**Table 3** Univariate comparisons of all-cause in-hospital mortality within 30 and 90 days following hospital admission according to baseline patient characteristics in 7,147 acute care patients

| Patient characteristics | Group | 30-day mortality | | 90-day mortality | |
|---|---|---|---|---|---|
| | | N (%) | HR (95% CI)[a] | N (%) | HR (95% CI)[a] |
| All | All | 237 (3.3) | – | 434 (6.1) | – |
| Sex | Male | 136 (3.5) | 1.0 (0.8–1.3) | 249 (6.4) | 0.9 (0.8–1.1) |
| | Female | 101 (3.1) | Ref. | 185 (5.7) | Ref. |
| Age (years) | 0–14 | 1 (0.1) | Ref. | 4 (0.5) | Ref. |
| | 15–34 | 4 (0.6) | 5.2 (1.5–17.8) | 5 (0.7) | 1.8 (0.6–5.6) |
| | 35–54 | 17 (1.4) | 10.2 (4.5–23.6) | 36 (3.0) | 6.1 (2.8–12.9) |
| | 55–74 | 67 (2.9) | 20.5 (8.9–47.4) | 156 (6.8) | 15.2 (7.3–31.9) |
| | 75+ | 148 (7.2) | 48.4 (21.6–108.8) | 233 (11.3) | 32.4 (15.0–70.4) |
| Hospital type | Tertiary care | 140 (3.1) | 0.6 (0.4–1.0) | 276 (6.2) | 0.8 (0.5–1.4) |
| | Other | 97 (3.6) | Ref. | 158 (5.9) | Ref. |
| Admission type | Emergency | 214 (4.0) | 2.6 (1.6–4.2) | 370 (6.9) | 1.5 (1.0–2.3) |
| | Elective | 23 (1.3) | Ref. | 64 (3.6) | Ref. |
| Patient specialty | Surgery | 39 (1.5) | Ref. | 75 (2.9) | Ref. |
| | Medicine | 157 (5.2) | 3.1 (2.2–4.4) | 242 (8.0) | 2.3 (1.6–3.3) |
| | Pediatrics | 0 (0.0) | – | 0 (0.0) | – |
| | Gynecology, obstetrics | 0 (0.0) | – | 0 (0.0) | – |
| | Intensive care | 41 (8.4) | 2.7 (1.8–4.2) | 116 (23.6) | 2.6 (1.7–4.0) |
| | Other | 0 (0.0) | – | 1 (0.4) | – |
| Underlying disease severity (McCabe) | Nonfatal | 56 (1.1) | Ref. | 108 (2.1) | Ref. |
| | Ultimately fatal | 95 (6.1) | 3.7 (2.6–5.2) | 169 (10.9) | 3.5 (2.5–4.9) |
| | Rapidly fatal | 84 (18.3) | 8.6 (5.9–12.4) | 151 (32.9) | 7.1 (5.2–9.9) |
| | Unknown | 2 (1.9) | 1.1 (0.3–3.6) | 6 (5.6) | 1.9 (1.1–3.2) |
| Comorbidity index (Charlson) | 0 | 19 (0.6) | Ref. | 48 (1.5) | Ref. |
| | 1 | 35 (3.5) | 4.5 (2.7–7.6) | 65 (6.4) | 4.3 (3.2–5.9) |
| | 2–3 | 66 (4.0) | 4.4 (2.7–7.1) | 133 (8.0) | 3.8 (2.9–5.0) |
| | 4+ | 117 (9.9) | 8.8 (4.7–16.7) | 188 (15.9) | 7.4 (4.8–11.6) |
| Recent major surgery | No | 202 (3.9) | Ref. | 343 (6.6) | Ref. |
| | Yes | 35 (1.8) | 0.5 (0.3–0.9) | 91 (4.6) | 1.0 (0.7–1.3) |
| Number of invasive devices at baseline[b] | 0–1 | 55 (1.1) | Ref. | 106 (2.1) | Ref. |
| | 2 | 139 (8.1) | 5.8 (4.2–8.1) | 208 (12.2) | 4.8 (3.8–6.2) |
| | 3–4 | 43 (12.8) | 4.5 (3.1–6.3) | 120 (35.7) | 4.4 (3.0–6.2) |
| Healthcare-associated infection | No | 182 (2.8) | Ref. | 284 (4.4) | Ref. |
| | Yes | 55 (9.7) | 2.3 (1.2–4.1) | 150 (23.2) | 3.0 (2.3–4.0) |

**Notes:** [a]Hazard ratios were estimated using univariate Cox proportional hazards regression and accounting for the stratified cluster design of the baseline survey. Healthcare-associated infection was treated as a time-dependent risk factor for death. [b]Recorded invasive devices included urinary, central vascular, and peripheral vascular catheters and intubation.

**Abbreviations:** N, number of deaths; HR, hazard ratio; CI, confidence interval; Ref., reference category.



case-fatality rates at 90 days in this study reached 37% in patients infected by third-generation cephalosporin-resistant Enterobacteriaceae, 33% in patients infected by carbapenem-resistant Enterobacteriaceae, and 35% in those infected by carbapenem-resistant *A. baumannii*. Correcting for the effects of other important risk factors for death, the daily risk of dying within 90 days of admission was shown to increase by 90%–110% in patients infected by these resistant pathogens compared to uninfected patients.

Our overall estimate of the excess LOS due to HAIs (4.3 days) is almost identical to the estimate of 4 days from the seminal 1981 study of Haley et al,[26] which used direct attribution by expert reviewers to assess the prolongation of LOS due to HAI. By contrast, our excess LOS estimate is considerably lower than those given in comparative attribution studies in Belgium (7.3 days), Greece and Cyprus (10.1 days), and England (14.1 days).[7,12,27] The latter were based on time-invariant methods that cannot fully account for the timing of infection and thereby have most likely overestimated the effect of HAI on excess LOS.[13,20] In agreement with the site-specific estimates of excess LOS obtained in this study, a cohort study of hospitalized patients in Australia controlling for a comprehensive set of confounders found that UTIs were not associated with prolongation of LOS, while LRTIs had an excess LOS of 2.6 (95% CI 1.8–3.7) days.[6] The latter also illustrated that many factors, other than HAI, are associated

**Table 4** Clinical impact of HAIs according to infection type and antimicrobial resistance status

| | Excess LOS[a] | | | 30-day in-hospital mortality[a] | | | | 90-day in-hospital mortality[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of infections | Mean (days)[b] | 95% CI (days) | No. of deaths / patients (%) | aHR[c] | 95% CI | *P*-value | No. of deaths / patients (%) | aHR[c] | 95% CI | *P*-value |
| Type of infection | | | | | | | | | | | |
| Lower respiratory | 153 | 2.9 | −0.4 to 6.2 | 22/137 (16.1) | 1.7 | 0.9–3.2 | 0.073 | 54/149 (36.2) | 2.2 | 1.4–3.4 | 0.001 |
| Bloodstream | 111 | 10.5 | 5.3 to 15.8 | 13/87 (14.9) | 2.0 | 1.0–3.7 | 0.037 | 36/110 (32.7) | 2.1 | 1.3–3.5 | 0.005 |
| Urinary tract | 109 | −2.8 | −6.6 to 1.0 | 7/100 (7.0) | 1.3 | 0.5–3.2 | 0.517 | 11/109 (10.1) | 1.1 | 0.6–2.3 | 0.683 |
| Surgical site | 69 | 3.1 | −1.7 to 7.8 | 0/65 (0.0) | 0.0 | – | – | 7/70 (10.0) | 0.9 | 0.5–1.7 | 0.664 |
| Systemic | 48 | 4.9 | −1.3 to 11.0 | 4/43 (9.3) | 0.7 | 0.2–2.3 | 0.508 | 12/47 (25.5) | 1.2 | 0.5–2.5 | 0.686 |
| Other | 104 | 9.3 | 5.1 to 13.6 | 3/93 (3.2) | 0.3 | 0.1–1.0 | 0.051 | 12/104 (1.5) | 1.0 | 0.5–2.0 | 0.929 |
| Multiple infections | 54 | 16.6 | 8.9 to 24.3 | 6/44 (13.6) | 1.5 | 0.6–3.9 | 0.359 | 18/57 (31.6) | 2.0 | 1.3–3.3 | 0.005 |
| Any HAI | 648 | 4.3 | 2.4 to 6.2 | 55/569 (9.7) | 1.3 | 0.7–2.4 | 0.363 | 150/646 (23.2) | 1.8 | 1.3–2.6 | 0.001 |
| Resistance phenotype[d] | | | | | | | | | | | |
| Sensitive | 104 | 5.0 | 0.7 to 9.3 | 7/92 (7.6) | 0.7 | 0.3–1.6 | 0.341 | 23/103 (22.3) | 1.3 | 0.9–1.9 | 0.240 |
| Resistant | 172 | 16.9 | 12.9 to 20.9 | 14/134 (10.4) | 1.5 | 0.7–3.3 | 0.275 | 52/176 (29.5) | 1.8 | 1.2–2.7 | 0.006 |
| Unknown | 372 | 0.6 | −1.4 to 2.7 | 34/343 (9.9) | 1.3 | 0.7–2.5 | 0.361 | 75/367 (20.4) | 1.8 | 1.2–2.6 | 0.006 |
| Resistant pathogen | | | | | | | | | | | |
| MRSA or VRE | 14 | 9.6 | 0.6 to 18.5 | 0/12 (0.0) | 0.0 | – | – | 2/14 (14.3) | 1.0 | 0.4–2.1 | 0.901 |
| 3GCR Enterobacteriaceae | 42 | 16.6 | 7.6 to 25.6 | 4/34 (11.8) | 1.5 | 0.6–3.6 | 0.393 | 14/38 (36.8) | 2.1 | 1.1–3.7 | 0.020 |
| CR Enterobacteriaceae | 70 | 20.3 | 12.3 to 28.2 | 6/45 (13.3) | 2.2 | 0.7–6.7 | 0.147 | 20/61 (32.8) | 1.9 | 1.1–3.2 | 0.021 |
| CR *P. aeruginosa* | 40 | 23.2 | 12.1 to 34.3 | 1/16 (6.3) | 1.8 | 0.3–10.7 | 0.517 | 7/29 (24.1) | 1.5 | 0.4–5.0 | 0.537 |
| CR *A. baumannii* | 73 | 18.6 | 11.9 to 25.3 | 5/40 (12.5) | 1.7 | 0.6–5.1 | 0.316 | 21/60 (35.0) | 1.9 | 1.1–3.0 | 0.014 |

**Notes:** [a]All comparisons are with respect to the common control group of uninfected patients at baseline. [b]Mean excess LOS has been adjusted for time dependence of infection using multistate modeling. [c]Hazard ratios have been adjusted for the effect of age, type of admission, McCabe classification of underlying disease severity, Charlson weighted index of comorbidity, admission to an ICU, and exposure to invasive devices. Occurrence of infection was treated as a time-dependent exposure. [d]The "resistant" category includes patients infected with MRSA, VRE, 3GCR or CR Enterobacteriaceae, CR *P. aeruginosa*, or CR *A. baumannii*. All other infections with known antibiotic susceptibility data were categorized as "sensitive".

**Abbreviations:** HAI, healthcare-associated infection; LOS, length of hospital stay; CI, confidence interval; aHR, adjusted hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococcus species; 3GCR, third-generation cephalosporin resistant; CR, carbapenem resistant; *P. aeruginosa*, *Pseudomonas aeruginosa*; *A. baumannii*, *Acinetobacter baumannii*.

with increased LOS, and omitting these confounders from analysis leads to inflated estimates of excess LOS due to HAI.[6] The multistate modeling used in the current study provided estimates of excess LOS that were time adjusted but not fully adjusted for other confounders. Time adjustment is probably more important than adjustment for confounders as was illustrated by Beyersmann et al who reported that accounting for a large number of potential confounders did not redeem the overestimation of excess LOS.[28]

UTI was the single type of HAI that was associated with decreased LOS in this study. This contradicts with the findings of other time-adjusted estimates of excess LOS due to UTI obtained from multicenter studies in Spain (4.6 days) and Australia (4.0 days). [7,24] Both of the latter seem high and might be the result of rather complicated cases of UTIs, mainly in elderly patients surviving a prolonged hospitalization.[7] Indeed, UTIs in intensive care units in 10 developing countries were seen to prolong LOS by only 1.6 (95% CI 0.6–2.6) extra days.[29] It is possible, however, that accurately estimating excess LOS requires further adjusting for patient case mix in addition to accounting for time-dependent bias, which is a gap in available statistical methods.

Controlling for time-dependent bias, we found that AMR is a major contributing factor in prolonging hospital LOS, with the mean excess LOS ranging from 9.6 days in MRSA or VRE infections to more than 20 days in infections caused by major carbapenem-resistant gram-negative pathogens. Using similar statistical methods, a cohort study at a Swiss university hospital found that excess LOS attributable to MRSA infection was 11.5 (95% CI 7.9–15) days,[23] which resembles our findings. To the best of our knowledge, no other study has assessed the excess LOS due to infections caused by carbapenem-resistant gram-negative pathogens in hospital-wide settings to date.

Particular limitations in this study should be acknowledged when interpreting our findings. The first relates to the absence of global national surveillance data in Greece, which compelled us to rely entirely on data from the only existing national point prevalence survey to assess the global burden of HAIs. It is well known that cohorts of patients gathered through sampling prevalent cases tend to have longer survival times than those obtained in an incident cohort study. Our approach to estimating excess mortality assumes that the composition of the two patient groups (with HAI and without HAI at the time of the baseline survey) and their underlying conditions remained constant during follow-up. We cannot exclude the possibility that some subjects without HAI at baseline may have developed a HAI at a later time; depending on the extent of this misclassification, we might have underestimated the effect of HAI on mortality. The incidence-to-prevalence conversion used in this study also requires data from an incidence series of HAIs; we used median values to estimate the average duration of HAI correcting for the skewness towards patients with longer duration of infection in our sample. Simulations based on Europe-wide surveillance data in intensive care units have confirmed that incidence-to-prevalence conversion performs well using this method,[1] although the use of antibiotic treatment as a proxy for infection has been reported to improve the method.[30] Nevertheless, we must acknowledge that incident sampling, although logistically difficult and more expensive, remains the gold standard for estimating HAI incidence and impact on LOS and mortality.

Another limitation relates to the fact that we relied on antibiotic susceptibility tests available at the day of the baseline survey and thereby were able to assess resistance phenotypes for about half of the HAIs recorded in this study. This led to reduced sample sizes and thereby wide CIs for excess LOS and mortality associated with specific resistance phenotypes. Previous experience has shown that extending the period of recording microbiology data to a week following the detection of an active HAI in a prevalent cohort study may increase culture and antibiogram availability to about 70% of detected infections,[12] thereby improving pathogen-specific burden estimation. Moreover, we did not account for treatment factors in our analysis because our objective was to assess the real-life effect of AMR. Whether this effect was due to intrinsic pathogen factors or treatment failure was beyond the scope of this study.

## Conclusion

This assessment of the burden of HAIs from a public health-care provider's perspective showed that the incidence of HAIs, alongside their associated impact on LOS and mortality, presents a significant burden to the Greek hospital system. These findings, together with the increasing AMR in hospital settings, suggest that it is time to consider systematic interventions to reduce HAI incidence, including the potential of developing a global national surveillance system. Burden estimates obtained in this study will be valuable in future evaluations of the cost-effectiveness of infection prevention programs.

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## Author contributions

Study conception: EIK, AG; study design: EIK, EA, MR, EI, AG; data acquisition: EIK, FK, EA, MR, EI, AG; data management and statistical analysis: EIK; drafting of the manuscript: EIK; data interpretation and critical revision of the manuscript: EIK, FK, EA, MR, EI, AG. All authors approved the final manuscript and are accountable for all aspects of this work.

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