


Original Article

Association between antibiotic resistance in intensive care unit (ICU)–acquired infections and excess resource utilization: Evidence from Spain, Italy, and Portugal

Miquel Serra-Burriel PhD^{1,2} , Carlos Campillo-Artero MD, PhD^{3,1}, Antonella Agodi MD, PhD^{4,5}, Martina Barchitta PhD^{4,5} and Guillem López-Casasnovas PhD¹

¹Centre for Research in Health and Economics, Pompeu Fabra University, Barcelona, Spain, ²Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland, ³Balearic Islands Health Service, Palma de Mallorca, Balearic Islands, Spain, ⁴Department of Medical and Surgical Sciences and Advanced Technologies “GF Ingrassia,” University of Catania, Catania, Italy and ⁵GISIO-SItI: Italian Study Group of Hospital Hygiene—Italian Society of Hygiene, Preventive Medicine and Public Health, Rome, Italy

Abstract

Background: Intensive care unit (ICU)–acquired infections with antibiotic-resistant bacteria have been associated with substantial health and economic costs. Moreover, southern Europe has historically reported high levels of antimicrobial resistance.

Objectives: We estimated the attributable economic burden of ICU-acquired infections due to resistant bacteria based upon hospital excess length of stay (LOS) in a selected sample of southern European countries.

Methods: We studied a cohort of adult patients admitted to the ICU who developed an ICU-acquired infection related to an invasive procedure in a sample of Spanish, Italian, and Portuguese hospitals between 2008 and 2016, using data from The European Surveillance System (TESSy) released by the European Centers for Disease Control (ECDC). We analyzed the association between infections with selected antibiotic-resistant bacteria of public health importance and excess LOS using regression, matching, and time-to-event methods. We controlled for several confounding factors as well as time-dependent biases. We also computed the associated economic burden of excess resource utilization for each selected country.

Results: In total, 13,441 patients with at least 1 ICU-acquired infection were included in the analysis: 4,106 patients (30.5%) were infected with antimicrobial-resistant bacteria, whereas 9,335 patients (69.5%) were infected with susceptible bacteria. The unadjusted association between resistance status and excess LOS was 7 days (95% CI, 6.13–7.87; $P < .001$). Fully adjusted models yielded significantly lower estimates: 2.76 days (95% CI, 1.98–3.54; $P < .001$) in the regression model, 2.60 days (95% CI, 1.66–3.55; $P < .001$) in the genetic matching model, and a hazard ratio of 1.15 (95% CI, 1.11–1.19; $P < .001$) in the adjusted Cox regression model. These estimates, alongside the prevalence of resistance, translated into direct hospitalization attributable costs per ICU-acquired infection of 5,224€ (95% CI, 3,691–6,757) for Spain, 4,461€ (95% CI, 1,948–6,974) for Portugal, and 4,320€ (95% CI, 1,662–6,977) for Italy.

Conclusions: ICU-acquired infections associated with antibiotic-resistant bacteria are substantially associated with a 15% increase in excess LOS and resource utilization in 3 southern European countries. However, failure to appropriately control for significant confounders inflates estimates by ~2.5-fold.

(Received 17 May 2021; accepted 1 September 2021; electronically published 18 October 2021)

Healthcare-associated infections (HAIs) represent major patient safety problems, especially in intensive care units (ICUs). The use of invasive procedures, such as intubation or the placement of central venous catheters, always involves some risk of infection.¹ Although a wide range of strategies is available to minimize this risk,^{2,3} once an infection by antibiotic-resistant bacteria occurs, difficulties in adequately treating it can have a significant impact on both patient and economic outcomes.^{4–10}

Multiple studies have investigated the association between ICU-acquired infections and mortality or excess length of stay (LOS) of patients.^{7,11–13} Given that ICU LOS is the best predictor of resource utilization and cost of care, special attention has been given to this outcome.^{14–16}

However, estimating the attributable LOS of patients with resistant versus susceptible strains of ICU-acquired infections presents several methodological¹⁷ and logistic challenges.¹⁸ Several well-known biases arise when analyzing the association between multidrug resistance and prolonged LOS outcomes.^{19–22}

The time-dependent bias of infection has been suggested to inflate estimates around when time to occurrence is not considered. Furthermore, significant confounding in the form of

Author for correspondence: Miquel Serra-Burriel, E-mail: miquel.serraburriel@uzh.ch

Cite this article: Serra-Burriel M, et al. (2022). Association between antibiotic resistance in intensive care unit (ICU)–acquired infections and excess resource utilization: Evidence from Spain, Italy, and Portugal. *Infection Control & Hospital Epidemiology*, 43: 1360–1367, <https://doi.org/10.1017/ice.2021.429>

differential observable and unobservable baseline prognostic factors between patients infected with susceptible and resistant organisms have been reported, which poses a threat to the correct assessment of attributable effects.

The objective of the present study was to estimate the effect of multidrug resistance on excess LOS of ICU-acquired bacterial infections. We emulated an unfeasible target trial^{23,24} in a sample of southern European ICUs to measure the attributable economic burden associated with an excess of resource utilisation. To overcome the aforementioned biases, we made use of complementary analytical approaches, multivariable regressions, and matching methods.^{25,26}

Methods

The present study is a multicentric retrospective cohort study of ICU-admitted patients that developed an HAI, combined with economic modelling. Our main hypothesis was that patients infected with resistant organisms have an associated longer LOS thereafter, which often entails increased utilization of resources. Our study also compared different analytical strategies of estimating this association as means to approximate the causal effect of antimicrobial resistance and to explore the potential biases inherent to each model.¹⁹ This manuscript was prepared in accordance with the STROBE guidelines for reporting observational studies. The study was approved by the Ethics Committee “Catania 1”, Catania, Italy (protocol nos. 111/2018/PO and 295/2019/EMPO).

Patient population and data source

A cohort based on data from The European Surveillance System (TESSy), provided by Spain, Italy (SPIN-UTI network^{27–29}), and Portugal and released by European Centre for Disease Prevention and Control (ECDC), was used.³⁰ The cohort consisted of adult patients admitted to ICUs who developed a HAI during the surveillance period between 2008 and 2016.

Our patient population included adult patients with at least 1 confirmed HAI (ie, bloodstream, catheter-related infection, pneumonia, or urinary tract infection) diagnosed at least 48 hours after ICU admission and with at least 1 of 4 potential invasive procedures performed: central venous catheter (CVC), intubation (INT), parenteral nutrition (PNUT) or a urinary catheter (UC). Only adult patients with confirmed susceptibility testing to selected antimicrobial agents and microorganisms were included in the analysis.

Microbiology and susceptibility definitions

The antibiotic-resistant condition of bacteria was drawn from a 2019 study by Cassini et al,¹⁷ which selects specific microorganisms and antibiotic resistance profiles based on public health importance. The microorganism–antibiotic resistance pairings were as follows: third-generation cephalosporin-resistant *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Pseudomonas aeruginosa*, third-generation cephalosporin-resistant *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter* spp, carbapenem-resistant *K. pneumoniae*, colistin-resistant *K. pneumoniae*, vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*, colistin-resistant *E. coli*, penicillin-resistant *Streptococcus pneumoniae*, penicillin-resistant and macrolide-resistant *Streptococcus pneumoniae*, carbapenem-resistant *E. coli*,

colistin-resistant *Acinetobacter* spp, and colistin-resistant *P. aeruginosa*.

Patients infected by >1 microorganism were classified as resistant if at least 1 of the isolated microorganisms was deemed resistant to at least 1 of the selected antibiotics.

Statistical and economic analyses

Balance across baseline patient characteristics of susceptible and resistant infections was analyzed using unadjusted univariate comparisons. For that purpose, *t* tests for continuous variables and Fisher exact tests were used with a 2-tailed design, and a statistical significance level of 0.05 was prespecified.

We followed 3 complementary multivariable estimation strategies with (1) an unadjusted linear specification,³¹ (2) adjusted linear specification,³² (3) genetic 1:1 matching³³ as well as adjusted Cox regression.³⁴ Genetic 1:1 matching automates a combination of propensity scores and Mahalanobis distance matching for each covariate such that the a version of optimal balance is achieved after matching.³⁵ The selection of control variables was driven by availability of data regarding patient, procedure, and contextual characteristics associated with both resistance and LOS. Variables included in the matching process included: age, sex, time to infection, procedures, and infection site. Each other estimation strategy was replicated with an incremental set of control variables (ie, age, sex, bacteria fixed effects, ICU fixed effects, and time to infection) to assess coefficient stability to assess unobservable selection to resistance.³⁶ Our study included deidentified fixed effects, country, hospital, and ICU. Relevant patient parameters included age, sex, type of exposure, type of infection, and type of microorganism. Moreover, to assess the magnitude of time-dependent bias,³⁷ all estimation strategies included at least 1 model specification controlling or matching for time to infection. Uncertainty of estimates was constructed with Huber-White robust standard errors clustered at the ICU level.³⁸ To assess the robustness of the estimates to resistance unobservable selection, we performed a quantitative bias analysis.³⁶ We also estimated the linear model for the number of antimicrobial-resistant organisms present at the time of infection.

To approximate the attributable economic burden of ICU-acquired resistant infections, we developed a simple economic model relating the excess LOS estimates to direct hospitalization costs. Direct costs were obtained from national price lists and standardized costing methods for ICU stays.^{39–41} Costs were adjusted to 2019 euros with country-specific healthcare price indices.⁴² All analyses were performed in R version 3.6.2 software (2019).⁴³

The study was approved by the Ethics Committee “Catania 1”, Catania, Italy (protocol nos. 111/2018/PO and 295/2019/EMPO).

Results

In total, 18,773 patients with ICU-acquired bacterial infections were assessed for eligibility, and 13,441 were included in the analysis after meeting eligibility criteria: 9,335 patients (69.5%) were infected with antimicrobial-susceptible microorganisms and 4,106 patients (30.5%) were infected with resistant ones. Figure 1 depicts the patient selection flow chart.

The mean age of the patients was 62 years (SD ±15.6). Moreover, 65% of patients were from Spanish ICUs, 20% were from Italian ICUs, and 15% were from Portuguese ICUs. In total, 66% of patients were male, and most patients (84%) stayed in mixed ICUs. The most prevalent invasive procedures involved

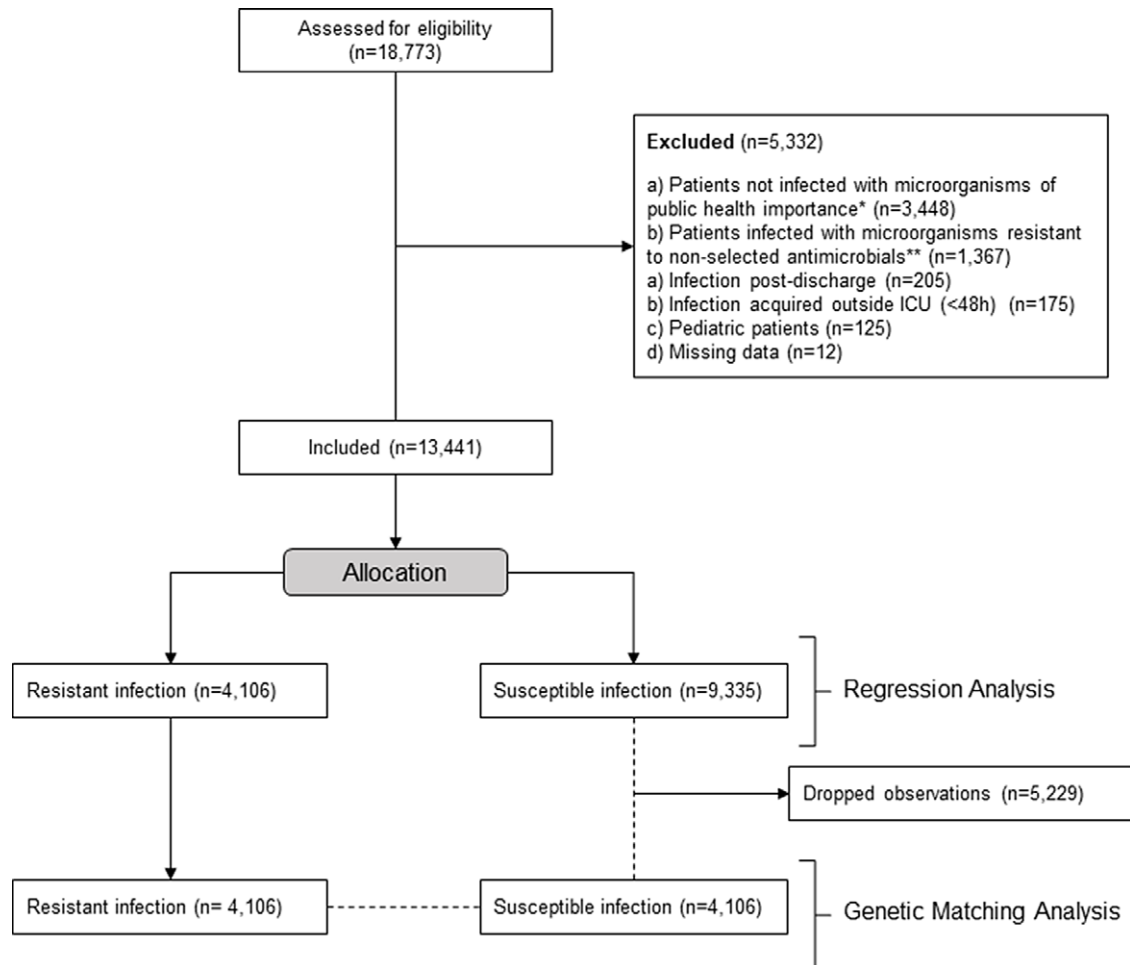


Fig. 1. Patient flowchart diagram. *Included microorganisms: *Acinetobacter baumannii*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. **Included antimicrobial agents: third-generation cephalosporins (cefotaxim, ceftriaxone, ceftazidim), carbapenems (imipenem, meropenem, doripenem), methicillin, and vancomycin.

were central venous catheter (97.5% of patients) and intubation (94% of patients). Table 1 shows patient characteristics by the resistance status of bacteria isolated from ICU-acquired infections. On average, patient characteristics, including the type of infection and invasive procedures performed, were different regarding their susceptibility classification. Supplementary Table S1 (online) presents the empirical propensity distribution of organisms by type of infection and antibiotic resistance level in kernel density estimates. After genetic 1:1 matching, 4,106 susceptible patients were included, whereas 5,229 were dropped from the matched analysis. Balance across baseline prognostic factors greatly improved, and only 3 baseline variables were statistically significant different across groups. The right panel of Table 1 presents the distribution of variables after matching. Supplementary Figures S1 and S2 (online) present the propensity score distributions and the standardized bias plots before and after matching.

The association between resistance status and excess LOS of unadjusted models was 6.998 days (95% CI, 6.130–7.866; $P < .001$) in the linear regression model, it was 4.076 days (95% CI, 3.001–5.151; $P < .001$) in the matched analysis, and the hazard ratio (HR) was 1.278 (95% CI, 1.232–1.308; $P < .001$) in the Cox regression model. Table 2 presents all 3 model estimates. The inclusion of additional control variables (specifications b to d: age, gender, bacteria fixed-effects, hospital-ICU fixed effects,

infection site, invasive procedures, and time to infection) yielded a decrease in the association between resistance and excess LOS by 30% for the linear regression model, 20% in the matched model, and 9% in the Cox model. However, the greatest estimate change resulted from the inclusion of time to infection confounding control. Fully adjusted estimates were 2.756 days (95% CI, 1.977–3.535; $P < .001$) in the linear model and 2.604 days (95% CI, 1.661–3.548; $P < .001$) in the matched model, and HR was 1.146 (95% CI, 1.101–1.178; $P < .001$) in the Cox model. Thus, the inclusion of time-to-infection controls reduced the estimates by 61% in the linear model, 35% in the matched model, and 11% in the Cox model.

In terms of time to discharge or death, Figure 2 displays the Kaplan-Meier estimates of cumulative incidence. During the first 5 days after ICU admission, no significant differences between resistant and susceptible infection groups were detected. After day 6, the estimates started to diverge, leading to a difference of 2.7 days at median cumulative incidence.

Figure 3 presents the fully adjusted country-specific cumulative incidence estimates of the Cox regression models in the upper panel, while the lower panel illustrates the unadjusted and adjusted cost estimates by country. Adjusting the estimates reduces the attributable burden in all included countries. Unadjusted direct cost estimates (2019) per resistant infection for Spain are 13,855€

Table 1. Patient Characteristics by Resistance Status of Bacteria Isolated From ICU-Acquired Infections, Full and Matched Samples

Variable	Full Sample		P Value	Matched Sample		P Value
	Susceptible (N = 9,335)	Resistant (N = 4,106)		Susceptible (N = 4,106)	Resistant (N = 4,106)	
Country			<.001			<.001
Spain	6,572 (70.4)	2,404 (58.5)		2,894 (70.5)	2,404 (58.5)	
Italy	1,538 (16.5)	944 (23.0)		613 (14.9)	944 (23.0)	
Portugal	1,225 (13.1)	758 (18.5)		599 (14.6)	758 (18.5)	
Age, mean y (SD)	62.0 (15.6)	62.1 (15.9)	.732	62.3 (15.3)	62.1 (15.9)	.599
Sex			.003			.813
Female	3237 (34.7)	1314 (32.0)		1,325 (32.3)	1,314 (32.0)	
Male	6,098 (65.3)	2,792 (68.0)		2,781 (67.7)	2,792 (68.0)	
Type of ICU			<.001			.003
Burned	27 (0.33)	11 (0.29)		10 (0.27)	11 (0.29)	
Coronary	25 (0.30%)	10 (0.27)		12 (0.32)	10 (0.27)	
Medical	202 (2.45)	103 (2.75)		96 (2.58)	103 (2.75)	
Mixed	6,864 (83.3)	3,194 (85.1)		3,106 (83.4)	3,194 (85.1)	
Neuro-trauma	197 (2.39)	21 (0.56)		58 (1.56)	21 (0.56)	
Other	418 (5.08)	189 (5.04)		211 (5.67)	189 (5.04)	
Surgical	503 (6.11)	224 (5.97)		229 (6.15)	224 (5.97)	
Invasive procedure						
Central venous catheter			.025			1
No	246 (2.64)	81 (1.97)		81 (1.97)	81 (1.97)	
Yes	9,089 (97.4)	4,025 (98.0)		4,025 (98.0)	4,025 (98.0)	
Intubation			<.001			1
No	693 (7.42)	125 (3.04)		124 (3.02%)	125 (3.04)	
Yes	8,642 (92.6)	3,981 (97.0)		3,982 (97.0)	3,981 (97.0)	
Parenteral nutrition			<.001			.883
No	7,212 (77.3)	2,941 (71.6)		2,948 (71.8)	2,941 (71.6)	
Yes	2,123 (22.7)	1,165 (28.4)		1,158 (28.2)	1,165 (28.4)	
Urinary catheter			<.001			1
No	1,316 (14.1)	419 (10.2)		419 (10.2)	419 (10.2)	
Yes	8,019 (85.9)	3,687 (89.8)		3,687 (89.8)	3,687 (89.8)	
Infection site						
Bloodstream			.001			<.001
No	5,654 (60.6)	2,362 (57.5)		2,598 (63.3)	2,362 (57.5)	
Yes	3,681 (39.4)	1,744 (42.5)		1,508 (36.7)	1,744 (42.5)	
Cather-related			<.001			.716
No	8,730 (93.5)	3,769 (91.8)		3,779 (92.0)	3,769 (91.8)	
Yes	605 (6.48)	337 (8.21)		327 (7.96)	337 (8.21)	
Pneumonia			<.001			.009
No	5,778 (61.9)	1,754 (42.7)		1,873 (45.6)	1,754 (42.7)	
Yes	3,557 (38.1)	2,352 (57.3)		2,233 (54.4)	2,352 (57.3)	
Urinary tract			<.001			.685
No	6,563 (70.3)	3,060 (74.5)		3,077 (74.9)	3,060 (74.5)	
Yes	2,772 (29.7)	1,046 (25.5)		1,029 (25.1)	1,046 (25.5)	

Note. ICU, intensive care unit; SD, standard deviation. To calculate P value, the Fisher exact test was used for categorical variables and the Student t test was used for continuous variables.

Table 2. Regression, Matching and Time-to-Event Results

Regression model	a) Unadjusted	b) Age-sex adjusted	c) Hospital-ICU fixed-effects	d) Infection site and procedure adjusted	e) Full control specification
Linear regression model					
Resistance	6.998***	7.001***	6.942***	4.983***	2.756***
95% CI	(6.130–7.866)	(6.132–7.869)	(5.960–7.923)	(3.990–5.977)	(1.977–3.535)
Matched					
Resistance	4.076***	4.065***	4.235***	3.270***	2.604***
95% CI	(3.001–5.151)	(2.990–5.140)	(3.046–5.424)	(2.073–4.468)	(1.661–3.548)
Mean days LOS in outcome	29.32				
Cox proportional hazards model					
Resistance, hazard ratio	1.278***	1.276***	1.268***	1.168***	1.146***
95% CI	(1.232–1.308)	(1.231–1.309)	(1.222–1.298)	(1.121–1.198)	(1.101, 1.178)
Included Control variables					
Age		●	●	●	●
Sex		●	●	●	●
Bacteria fixed effects			●	●	●
Hospital-ICU fixed effects				●	●
Infection site				●	●
Procedures				●	●
Time to infection					●

Note. CI, confidence interval, LOS, length of stay; ICU, intensive care unit. Significance: *** 0.01; ** 0.05; *0.10.

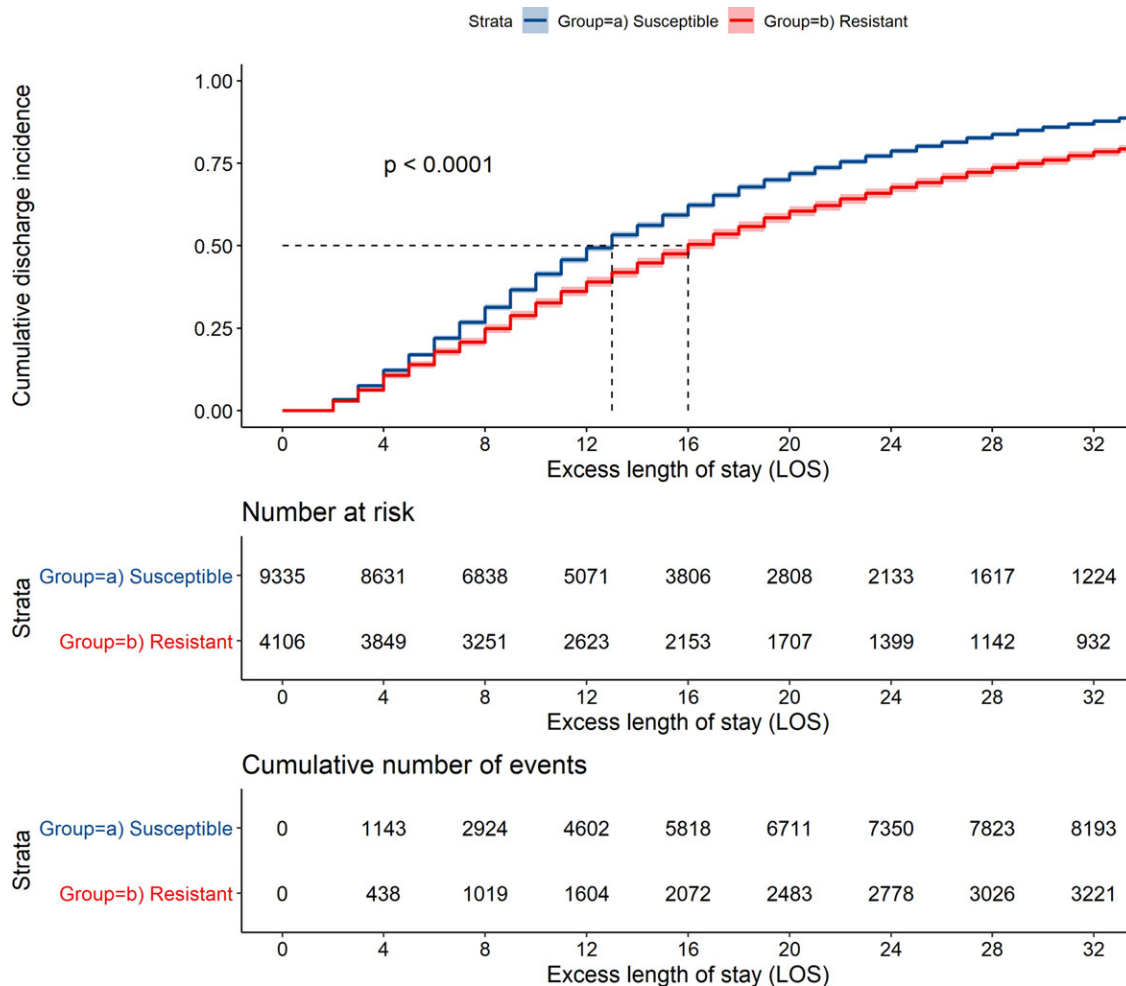


Fig. 2. Kaplan-Meier estimates cumulative time to discharge.

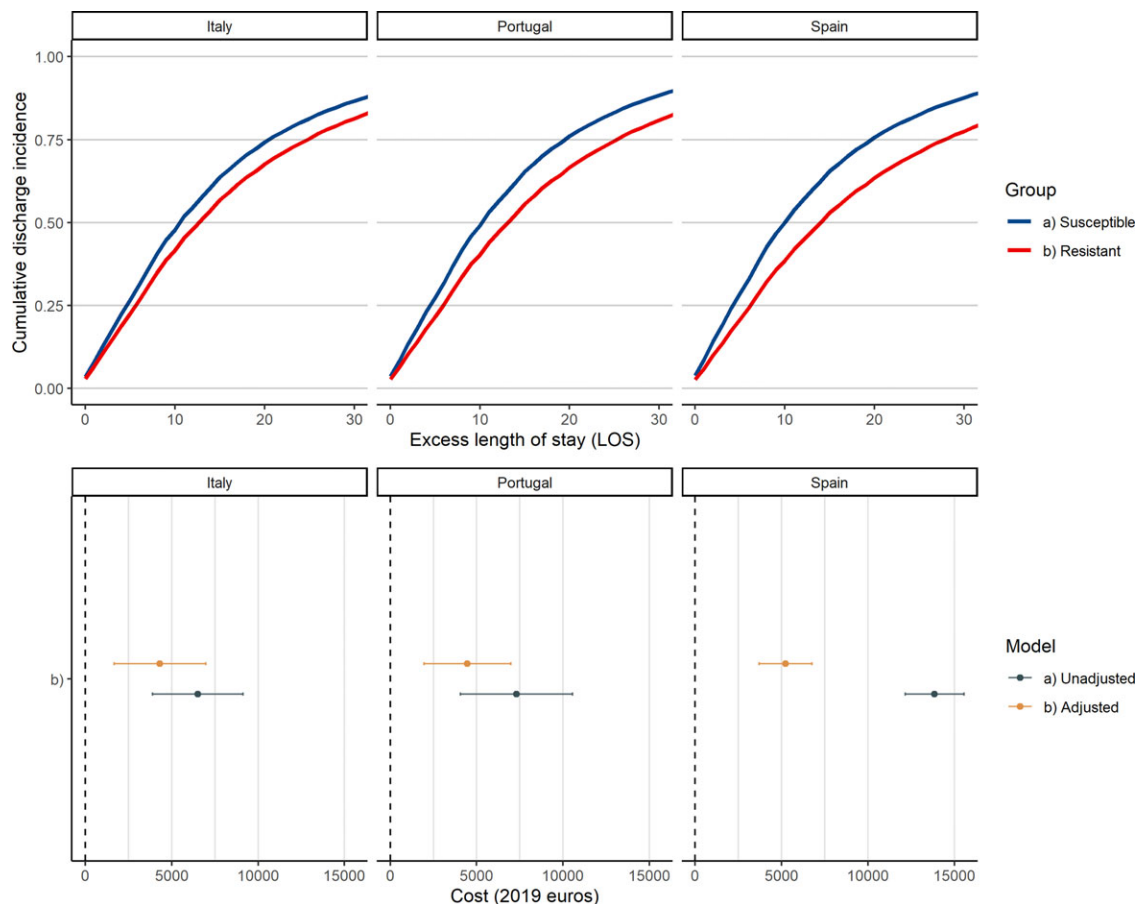


Fig. 3. Adjusted cumulative discharge incidence Cox estimates and cost estimates by resistance status and country.

[16,008USD] (95% CI, 12,148–15,562), 6,518€ [7,531USD] (95% CI, 3,903–9,133) for Italy, and 7,301€ [8,435USD] (95% CI, 4,053–10,548) for Portugal. However, when fully adjusted for all baseline characteristics, all estimates are reduced, with 5,224€ [6,036USD] per resistant infection (95% CI, 3,691–6,756) for Spain, 4,461€ [5,154USD] (95% CI, 1,948–6,973) for Portugal, and 4,320€ [4,991USD] (95% CI, 1,662–6,977) for Italy.

The estimates from the quantitative bias analysis show a 30% increase in R^2 alongside a $\delta = 1$, meaning equal importance of unobservable to current specification to drive resistance estimates to 0 (Supplementary Fig. S3 online). Furthermore, the results of the sensitivity analysis breaking down the estimate of the number of resistant organisms at the time of infection showed that having 2 resistant organisms at the time of infection was associated with an increase in LOS of 5.787 days (95% CI, 4.548–7.025; $P < .001$) and that having 3 or more resistant organisms at the time of infection is associated with an increase in LOS of 15.249 days (95% CI, 12.911–17.587; $P < .001$).

Discussion

In this study, we approximated the causal effect of antimicrobial resistance on excess LOS and direct in-hospital economic cost in the ICU setting. We approached the research question using complementary methodologies alongside variations in confounding control.⁴⁴ Moreover, we estimated a significant burden of resistance ranging from 2 to 3.5 extra days, resulting in a plausible economic effect ranging from 1,600€ to 7,000€ per

resistant infection. These results contribute significantly to the antimicrobial resistance literature that explores the consequences of resistance on health and economic outcomes.

Notably, given that all patients in the sample had a relatively long mean and median LOS (29–23 days), the relative size of estimated effects ranges from 10% to 20% of the total LOS. Considering that each invasive procedure increases the patient's chances of HAI by itself, the inclusion of confounding controls did not substantially change the estimates except for time-to-infection adjustments, which shrunk estimates between one-third and one-half. Our findings are consistent with previous studies that have explored the magnitude of time-dependent bias.^{19,20,22} However, we report an even larger reduction in the attributable association, up to 60% compared to the 33% previously reported upward bias. Our results suggest that within southern European ICU settings, the extent of this bias could be magnified. There are several potential explanations: an older population on average, a historically higher level of antimicrobial resistance, and a relatively lower economic endowment in all areas of healthcare compared to the overall European average. Compared to other international settings, in our study, antimicrobial resistance levels fall below those of South America and Asia/Middle East (45% and 44%, respectively).⁴⁵ However, when compared to North America and Australasia (19% and 21%, respectively), prevalence is much higher in our setting, representing a relative increase of ~50%. Our results should be interpreted within high prevalence contexts in developed countries.

The strengths of the analyses performed here relate to (1) the validity of our analysis for southern European countries, and by

extension, to developed countries with a high level of antimicrobial resistance, (2) the extensive use of complementary methodological approaches including multivariate and matching strategies alongside differential confounding control strategies, and (3) the use of a large and potentially representative sample of patients with ICU-acquired infections.

This study also had several limitations. We were not able to meet international definitions of antimicrobial resistance due to limited antimicrobial reporting (although this likely reflects clinical practice). The lack of observability in the use of inappropriate antimicrobial therapy, could have had an independent effect over LOS, alongside its independent economic effect. Potential unmeasured confounding could represent a bias that moved our estimates upward. We lacked information regarding severity of illness upon initial presentation, comorbidities, and immune status. Finally, no follow-up data were available after ICU discharge.

In conclusion, ICU-acquired HAI has been associated with clinically important outcomes and significant healthcare costs. Consequently, the prevention of HAI, particularly regarding those associated with invasive procedures, is essential to reduce the burden of HAI,⁴⁶ including those caused by antibiotic-resistant microorganisms. Overall, we observed a significant overall excess LOS and a substantial economic burden of resistant ICU-acquired infections compared to their susceptible counterparts. A relative increase of ~14% in excess LOS was estimated when time to infection was introduced in the models. Failure to account for or match for HAI timing rendered an upward bias in the estimates between 10% to 60%, slightly alleviated by the inclusion of other confounding factors in line with Nelson *et al.*¹⁹ Further studies estimating the attributable burden of antimicrobial-resistant infections in the ICU should be aware of the timing of infection.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2021.429>

Acknowledgments. The authors thank all colleagues, physicians and nurses in the participating hospitals, ICUs and networks for providing surveillance data. We acknowledge Victor Paradis for his assistance with language editing. The views and opinions of the authors expressed herein do not necessarily state or reflect those of the ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of the ECDC. The ECDC is not responsible for conclusions or opinions are drawn from the data provided. The ECDC is not responsible for the correctness of the data and data management, data merging, and data collation after the provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

Financial support. This study was funded by an unrestricted grant for the study of the consequences of antimicrobial resistance by Angelini SpA. The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest. M.S.B. acknowledges research grants from Horizon2020, EIT Health and ISCIII programs outside the submitted work. All other authors report no conflicts of interest relevant to this article.

References

1. Edwardson S, Cairns C. Nosocomial infections in the ICU. *Anaesth Intensive Care Med* 2019;20:14–18.
2. Li Y, Cao X, Ge H, Jiang Y, Zhou H, Zheng W. Targeted surveillance of nosocomial infection in intensive care units of 176 hospitals in Jiangsu Province, China. *J Hosp Infect* 2018;99:36–41.
3. Ramsamy Y, Hardcastle TC, Muckart DJJ. Surviving sepsis in the intensive care unit: the challenge of antimicrobial resistance and the trauma patient. *World J Surg* 2017;41:1165–1169.
4. Roberts RR, Hota B, Ahmad I, *et al.* Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis* 2009;49:1175–1184.
5. Micek ST, Wunderink RG, Kollef MH, *et al.* An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. *Crit Care* 2015;19:219.
6. Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multidrug-resistant *Acinetobacter baumannii*. *Int J Infect Dis* 2015;38:32–35.
7. Fernández-Barat L, Ferrer M, De Rosa F, *et al.* Intensive care unit-acquired pneumonia due to *Pseudomonas aeruginosa* with and without multidrug resistance. *J Infect* 2017;74:142–152.
8. Engler-Hüsch S, Heister T, Mutters NT, Wolff J, Kaier K. In-hospital costs of community-acquired colonization with multidrug-resistant organisms at a German teaching hospital. *BMC Health Serv Res* 2018;18:737.
9. Adrie C, Ibn W, Schwebel C, *et al.* Attributable mortality of ICU-acquired bloodstream infections: impact of the source, causative micro-organism, resistance profile and antimicrobial therapy. *J Infect* 2017;74:131–141.
10. Lambert ML, Suetens C, Savey A, *et al.* Clinical outcomes of healthcare-associated infections and antimicrobial resistance in patients admitted to European intensive care units: a cohort study. *Lancet Infect Dis* 2011;11:30–38.
11. Martin-Loeches I, Torres A, Rinaudo M, *et al.* Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug-resistant organisms. *J Infect* 2015;70:213–222.
12. Pelz RK, Lipsett PA, Swoboda SM, *et al.* Vancomycin-sensitive and vancomycin-resistant enterococcal infections in the ICU: attributable costs and outcomes. *Intensive Care Med* 2002;28:692–697.
13. Magira EE, Islam S, Niederman MS. Multidrug-resistant organism infections in a medical ICU: association to clinical features and impact upon. *Med Intensiva (English Ed)* 2018;42:225–234.
14. Vrijens F, Hulstaert F, Devriese S, Van de Sande S. Hospital-acquired infections in Belgian acute-care hospitals: an estimation of their global impact on mortality, length of stay and healthcare costs. *Epidemiol Infect* 2012;140:126–136.
15. Glance LG, Stone PW, Mukamel DB, Dick AW. Increases in mortality, length of stay, and cost associated with hospital-acquired infections in trauma patients. *Arch Surg* 2011;146:794–801.
16. Graves N, Weinhold D, Tong E, *et al.* Effect of healthcare-acquired infection on length of hospital stay and cost. *Infect Control Hosp Epidemiol* 2007;28:280–292.
17. Cassini A, Högberg LD, Plachouras D, *et al.* Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
18. Serra-Burriel M, Keys M, Campillo-Artero C, *et al.* Impact of multidrug-resistant bacteria on economic and clinical outcomes of healthcare-associated infections in adults: systematic review and meta-analysis. *PLoS One* 2020;15(1):e0227139.
19. Nelson RE, Samore MH, Jones M, *et al.* Reducing time-dependent bias in estimates of the attributable cost of healthcare-associated methicillin-resistant *Staphylococcus aureus* infections: a comparison of three estimation strategies. *Med Care* 2015;53:827–834.
20. Nelson RE, Schweizer ML, Perencevich EN, *et al.* Costs and mortality associated with multidrug-resistant healthcare-associated *Acinetobacter* infections. *Infect Control Hosp Epidemiol* 2016;37:1212–1218.
21. Nelson RE, Stevens VW, Jones M, *et al.* Attributable cost and length of stay associated with nosocomial gram-negative bacterial cultures. *Antimicrob Agents Chemother* 2018;62(11):e00462–18.
22. Nelson RE, Slayton RB, Stevens VW, *et al.* Attributable mortality of healthcare-associated infections due to multidrug-resistant gram-negative bacteria and methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol* 2017;38:848–856.
23. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med* 2019;25:1601–1606.

24. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016;183:758–764.
25. Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–387.
26. Dodd S, Bassi A, Bodger K, Williamson P. A comparison of multivariable regression models to analyse cost data. *J Eval Clin Pract* 2006;12:76–86.
27. Agodi A, Auxilia F, Barchitta M, et al. Building a benchmark through active surveillance of intensive care unit-acquired infections: the Italian network SPIN-UTI. *J Hosp Infect* 2010;74:258–265.
28. Masia MD, Barchitta M, Liperi G, et al. Validation of intensive care unit-acquired infection surveillance in the Italian SPIN-UTI network. *J Hosp Infect* 2010;76:139–142.
29. Agodi A, Auxilia F, Barchitta M, et al. Trends, risk factors and outcomes of healthcare-associated infections within the Italian network SPIN-UTI. *J Hosp Infect* 2013;84:52–58.
30. Monnet DL. Trends in antimicrobial resistance in Europe. *Int J Infect Dis* 2016;53:22.
31. Hahn PR, Carvalho CM, Puelz D, He J. Regularization and confounding in linear regression for treatment effect estimation. *Bayesian Anal* 2018;13:163–182.
32. Bithell JF, Dutton SJ, Neary NM, Vincent TJ. Controlling for socioeconomic confounding using regression methods. *J Epidemiol Community Health* 1995;49 suppl 2:S15–S19.
33. Diamond A, Sekhon JS. Genetic matching for estimating causal effects: a general multivariate matching method for achieving balance in observational studies. *Rev Econ Stat* 2013;95:932–945.
34. Lin DY, Ying Z. Cox regression with incomplete covariate measurements. *J Am Stat Assoc* 1993;88:1341–1349.
35. Abadie A, Imbens GW. Bias-corrected matching estimators for average treatment effects. *J Bus Econ Stat* 2011;29:1–11.
36. Oster E. Unobservable selection and coefficient stability: theory and evidence. *J Bus Econ Stat* 2019;37:187–204.
37. van Walraven C, Davis D, Forster AJ, Wells GA. Time-dependent bias was common in survival analyses published in leading clinical journals. *J Clin Epidemiol* 2004;57:672–682.
38. Freedman DA. On the so-called “Huber Sandwich Estimator” and “robust standard errors.” *Am Stat* 2006;60:299–302.
39. Rodrigues J, Sousa P. Economic and clinical impact of ventilator-associated pneumonia in intensive care units of a university hospital center. In: Cotrim T, et al, editors. *Health and Social Care Systems of the Future: Demographic Changes, Digital Age and Human Factors*. Advances in Intelligent Systems and Computing, vol 1012. New York: Springer; 2019.
40. Precios públicos SMS según BORM 28-febrero-2017. Formación y la Investigación Sanitaria website. http://www.ffis.es/investigacion/precios_pruebas.php. Published 2017. Accessed September 30, 2021.
41. Tan SS, Bakker J, Hoogendoorn ME, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. *Value Heal* 2012;15:81–86.
42. Organisation for Economic Co-operation and Development. Healthcare prices. *Health Care Financ Trends* 2020;2:15–20.
43. Team RC. R: A Language and Environment for *Statistical Computing*. Vienna, Austria; 2019.
44. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006;163:262–270.
45. Vincent J-L, Sakr Y, Singer M, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA* 2020;323:1478–1487.
46. Agodi A, Barchitta M, Quattrocchi A, et al. Preventable proportion of intubation-associated pneumonia: role of adherence to a care bundle. *PLoS One* 2017;12(9):e0181170.