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Time-dependent analysis of extra length of stay and mortality due to ventilator-associated pneumonia in intensive-care units of ten limited-resources countries: findings of the International Nosocomial Infection Control Consortium (INICC)

V. D. ROSENTHAL[1]*, F. E. UDWADIA[2], H. J. MUÑOZ[3], N. ERBEN[4], F. HIGUERA[5], K. ABIDI[6], E. A. MEDEIROS[7], E. FERNÁNDEZ MALDONADO[8], S. S. KANJ[9], A. GIKAS[10], A. G. BARNETT[11], N. GRAVES[11] and the International Nosocomial Infection Control Consortium (INICC)†

[1] *International Nosocomial Infection Control Consortium, Buenos Aires, Argentina;* [2] *Breach Candy Hospital Trust, Mumbai, India;* [3] *Clínica Reina Sofía, Bogotá, Colombia;* [4] *Eskisehir Osmangazi University, Eskisehir, Turkey;* [5] *Hospital General de México, Mexico City, Mexico;* [6] *Ibn-Sina Hospital, Medical ICU, Rabat, Morocco;* [7] *Hospital São Paulo, São Paulo, Brazil;* [8] *Clínica San Pablo, Lima, Peru;* [9] *American University of Beirut Medical Center, Beirut, Lebanon;* [10] *University Hospital of Heraklion, Heraklion, Greece;* [11] *School of Public Health, Queensland University of Technology*

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SUMMARY

Ventilator-associated pneumonias (VAPs) are a worldwide problem that significantly increases patient morbidity, mortality, and length of stay (LoS), and their effects should be estimated to account for the timing of infection. The purpose of the study was to estimate extra LoS and mortality in an intensive-care unit (ICU) due to a VAP in a cohort of 69 248 admissions followed for 283 069 days in ICUs from 10 countries. Data were arranged according to the multi-state format. Extra LoS and increased risk of death were estimated independently in each country, and their results were combined using a random-effects meta-analysis. VAP prolonged LoS by an average of 2·03 days (95% CI 1·52–2·54 days), and increased the risk of death by 14% (95% CI 2–27). The increased risk of death due to VAP was explained by confounding with patient morbidity.

Key words: Bacterial infections, hospital-acquired (noscomial) infections, hygiene and hospital infections, pneumonia, surveillance.

INTRODUCTION

Healthcare-associated infections (HAIs) are associated with an increase in morbidity, mortality, length of hospital stay, and healthcare costs that would normally not be associated with the underlying disease [1–3]. Many cases can be avoided by the application of careful infection prevention activities as described in 'Strategies to prevent ventilator-associated pneumonia in acute care hospitals' published in 2008 by the Society for Health Epidemiology of America [4]. These programmes are costly to implement, but building a strong economic argument about the cost savings from prevention is important to influence policy makers and budget managers in health. Health benefits are also enjoyed as mortality

* Author for correspondence: V. D. Rosenthal, M.D., M.Sc., C.I.C., International Nosocomial Infection Control Consortium (INICC), Corrientes Ave no. 4580, Floor 12, Apt D, ZIP 1195, Buenos Aires. Argentina.
(Email: victor_rosenthal@inicc.org)
† Members of the INICC are listed in the Appendix.

risk is reduced and infection-related morbidity avoided among patients. Effective infection prevention will incur a cost but lead to cost savings and will also generate health benefits [5, 6].

Ventilator-associated pneumonia (VAP) is a common problem in hospitals and the consequences are often serious. The economic arguments for prevention are more important when competition for scarce resources is high and this is the case in lower- and middle-income settings [7, 8]. The aim of this study is to determine values for two important parameters in the economic decision-making process, excess length of stay (LoS) and mortality risk. This does not complete the full economic argument for investing in prevention activities, but instead provides valuable information for that argument. Data collected from intensive-care units (ICUs) in lower- and middle-income countries were used for this analysis. The research literature is sparse in these settings and this work is novel.

METHODS

We aimed to estimate the impact of infection on both LoS and risk of death. Infection is a time-dependent variable, and it is therefore essential to use statistical methods that correctly account for this, otherwise estimates are inevitably biased [9–11]. To avoid any biases when estimating the extra LoS due to infection we used the methods described in Allignol *et al*. [12], and to estimate the unbiased risk of mortality due to infection we used the sub-distribution hazards approach described in Beyersmann & Schumacher [13].

Both methods arrange the data according to the multi-state format shown in Figure 1. A patient enters the ICU and becomes susceptible to infection after being ventilated. If the time to ventilation is not modelled then the estimated effects of infection are prone to 'length bias', which tends to underestimate the effects of infection (although the effects on the relative risk of death are more difficult to predict) [14]. Once a patient has been ventilated they may either be discharged or die, or they may first become infected. If the time to infection is not modelled then this leads to time-dependent bias, which tends to overestimate the effects of infection [9].

We censored patients when it was not known whether they died or were discharged, using a censoring date of their last day in ICU. We also censored patients who contracted another unrelated infection (e.g. an unrelated bloodstream infection) using the date of the unrelated infection. This censoring was

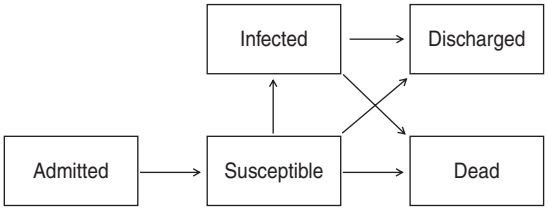

Fig. 1. Multi-state model used to estimate the time-dependent effect of nosocomial infection on length of stay and risk of death. Patients become susceptible to infection after they have been ventilated.

used to ensure that we estimated the independent effect of VAP, and not the combined effects of multiple infections. This censoring meant we assumed partial transition probabilities for the multi-state model [15].

We estimated the extra LoS and increased risk of death independently in each country. We then combined the results using a random-effects meta-analysis using a random intercept for each study. As a sensitivity analysis we re-ran the meta-analysis leaving out each country in turn. This assessed whether any particular country had a strong influence on the estimated mean effect. As another sensitivity analysis we first stratified admissions according to the Average Severity Illness Score (ASIS) score. We estimated the extra LoS and risk of death for admissions in the lower three ASIS categories ('healthier' group), and in the upper two categories ('sicker' group). ASIS was not collected in Greece or Lebanon, so these countries were excluded from this sensitivity analysis.

For all analyses R 2.11.0 software was used (R Foundation, Austria), using the 'etm' library to estimate the extra LoS due to infection [16], and the 'rmeta' library for meta-analysis [17].

RESULTS

Table 1 shows the summary statistics by country. Across all ten countries there were 283 069 ICU days observed after the patient had been ventilated. On average 11 % of admissions with ventilation ended in death.

Table 2 shows the estimated extra LoS and risk of death due to infection by country and the meta-analysis summary. On average a VAP infection led to 2·03 extra days in the ICU [95 % confidence interval (CI) 1·52–2·54 days] and a 14 % increase in the risk of death (95 % CI 2–27). For both estimates there was no evidence of heterogeneity between countries.

Table 1. *Cohort characteristics by country*

Country	Admissions	Admissions with a ventilator (%)	Length of stay, days	Mean age, years	Men (%)	Dead (%)
Argentina	17 910	4628 (26)	43855	68	2525 (14)	1724 (10)
Brazil	2452	1359 (55)	21 456	56	770 (31)	499 (20)
Colombia	8155	3731 (46)	39 546	47	2088 (26)	1041 (13)
Greece	105	89 (85)	918	66	57 (54)	22 (21)
India	24 583	11 164 (45)	76 307	54	8241 (34)	1650 (7)
Lebanon	383	244 (64)	2756	62	171 (45)	71 (19)
Mexico	3423	1629 (48)	15 608	38	806 (24)	443 (13)
Morocco	2584	796 (31)	7633	45	473 (18)	542 (21)
Peru	1970	861 (44)	7038	54	464 (24)	254 (13)
Turkey	7683	4269 (56)	67 952	49	2679 (35)	1661 (22)
Total	**69 248**	**28 770 (42)**	**283 069**	**54**	**18 274 (26)**	**7907 (11)**

All statistics are for admissions with a mechanical ventilator, except the 'Admissions' column.

Table 2. *Estimated extra length of stay (LoS) and relative risk of death due to a ventilator-acquired pneumonia*

Country	Admissions	Total extra LoS, days	Relative risk of death
Argentina	3532	1·93 (0·57 to 3·28)	0·92 (0·78 to 1·08)
Brazil	1350	−3·45 (−10·61 to 3·70)	1·24 (0·96 to 1·61)
Colombia	3651	1·92 (−0·05 to 3·89)	0·99 (0·74 to 1·34)
Greece	89	−0·45 (−4·44 to 3·53)	1·29 (0·31 to 5·45)
India	11130	2·85 (1·58 to 4·12)	1·31 (1·03 to 1·65)
Lebanon	241	−0·17 (−3·31 to 2·96)	0·74 (0·21 to 2·59)
Mexico	1622	1·69 (0·14 to 3·24)	1·21 (0·89 to 1·65)
Morocco	796	2·94 (0·74 to 5·14)	1·18 (0·88 to 1·58)
Peru	854	1·73 (0·74 to 2·73)	1·05 (0·75 to 1·49)
Turkey	4234	2·52 (1·31 to 3·73)	1·30 (1·13 to 1·49)
Meta-analysis	27499	2·03 (1·52 to 2·54)	1·14 (1·02 to 1·27)
Heterogeneity test, τ^2 (P value)		0·006 (0·43)	0·009 (0·13)
Leave-one-out meta-analysis, mean (country)			
Smallest		1·88 (India)	1·09 (Turkey)
Largest		2·11 (Peru)	1·22 (Argentina)

Values are means (95% confidence intervals).

Figure 2 plots the mean relative risk of death in each country and the meta-analysis. The most unusual result was from Lebanon, where an infection reduced the relative risk to 0·74, although this reduction was far from statistically significant (95% CI 0·21–2·59). Argentina also showed a non-significant reduction in the risk of death after infection. Without Argentina the mean relative risk of death rose slightly from 1·14 to 1·22 (14–22%).

Figure 3 plots the mean extra LoS in each country and the meta-analysis. The extra LoS was shortest in Brazil (3·45 fewer days after infection), but this decrease was not statistically significant (95% CI −10·61 to 3·70).

Table 3 shows the results after stratifying on ASIS. The mean relative risk of death was close to 1 and not statistically significant in either group. The estimated extra LoS were similar to the unstratified estimate for both ASIS groups.

DISCUSSION

We used the best available statistical methods to estimate the extra LoS and risk of death due to nosocomial VAP. These methods treat both the day of ventilation and the day of infection as time-dependent variables (Fig. 1). This means the results are not prone to length bias (which would underestimate the risks of

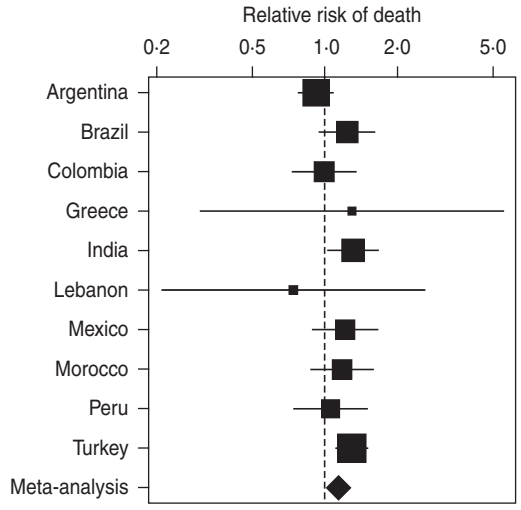

Fig. 2. Relative risk of death due to a nosocomial ventilator-associated pneumonia in each country and the overall relative risk from a meta-analysis. The relative risk axis is on a log scale. The squares are the mean estimates and the horizontal lines the 95% confidence intervals. The size of the squares is inversely proportional to the standard error of the estimate.

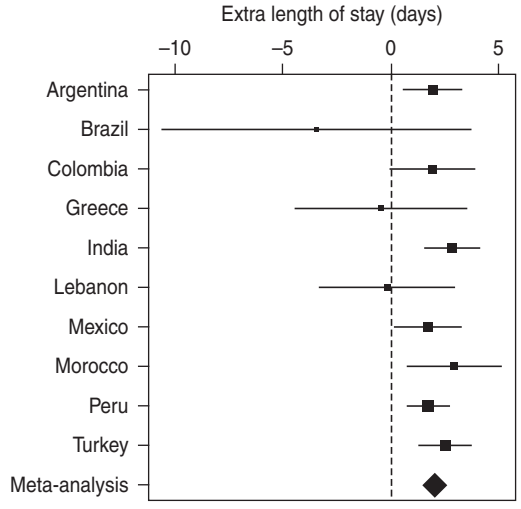

Fig. 3. Extra length of stay in days due to a nosocomial ventilator-associated pneumonia in each country and the overall extra length of stay from a meta-analysis. The squares are the mean estimates and the horizontal lines the 95% confidence intervals. The size of the squares is inversely proportional to the standard error of the estimate.

infection), or time-dependent bias (which would overestimate the risks of infection).

The results were consistent between countries and showed a modest increase in the extra LoS due to infection as, on average, there were 2·03 extra days. This increase was strongly statistically significant,

Table 3. *Estimated extra length of stay* (*LoS*) *and relative risk of death due to a ventilator-acquired pneumonia stratified by Average Severity Illness Score* (*ASIS*)

ASIS	Admissions	Total extra LoS, days	Relative risk of death
'Healthier' (1–3)	9249	1·94 (0·27–3·62)	0·95 (0·78–1·15)
'Sicker' (4–5)	11 361	1·46 (0·88–2·05)	0·99 (0·86–1·14)
Total	20 610		

Values are means (95% confidence intervals).
The higher the ASIS score the sicker the patient.

and this small increase still represents an important and potentially costly consequence of infection. Moreover, the increase remained after stratifying on ASIS score, so the extra LoS is independent of patient morbidity. A recent study in Europe found an excess LoS for pneumonia of 7·2 days for sensitive microorganisms and 6·3 days for resistant microorganisms [18].

If an infection hastens the time to death then acquiring an infection appears to be a cost-saving event; this might be occurring in Brazil and Greece (Table 2). A good economic analysis will account for this by including changes to both costs and health benefits from a decision to adopt an intervention that reduces risk [5, 6]. The extra benefit from saving lives is likely to be valued far more than a few extra days bed day. Ideally bed days and lives are saved at the same time with extra infection control.

The relative risk for mortality was 1·14 on average, and again this increase was strongly statistically significant and reasonably consistent across countries. However, the risk disappeared after stratifying on ASIS score. This suggests that the original increased risk was due to confounding by ASIS. We know that sicker patients have an increased risk of death; the confounding would be complete if sicker patients were also more likely to get ventilator-associated infections.

The method we used to estimate the extra LoS and risk of death due to infection cannot adjust for important covariates such as age. However, a recent study by Beyersmann *et al.* demonstrated that adjusting for the timing of infection is likely to be more important than adjusting for confounders, as they found that adjusting for 20 potential confounders did not redeem the time-dependent bias [19].

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DECLARATION OF INTEREST

None.

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APPENDIX

International Nosocomial Infection Control Consortium (countries listed alphabetically)

Argentina: Sandra Guzman (Centro Médico Bernal, Buenos Aires); Luis Pedro Flynn, Diego Rausch, Alejandro Spagnolo (Sanatorio Británico, Rosario); Guillermo Benchetrit, Claudio Bonaventura, María de los Ángeles Caridi, Adriana Messina, Beatriz Ricci (Centro Gallego de Buenos Aires, Buenos Aires); María Laura Frías, Griselda Churruarín (Clínica Modelo de Lanús, Lanús); Daniel Sztokhamer (Clínica Estrada, Buenos Aires); Luisa C. Soroka (Hospital Interzonal General de Agudos Evita, Lanús); Silvia Forciniti, Marta Blasco, Carmen B. Lezcano (Hospital Interzonal General de Agudos Pedro Fiorito, Avellaneda); Carlos Esteban Lastra (Hospital Narciso López, Lanús); Mónica Viegas, Beatriz Marta Alicia Di Núbila, Diana Lanzetta, Leonardo J. Fernández, María Adelaida Rossetti, Adriana Romani, Claudia Migazzi, Clarisa Barolin, Estela Martínez (Hospital Interzonal General de Agudos Presidente Perón, Avellaneda) Alicia Kobylarz (Hospital Materno Infantil Eduardo Oller Solano)

Brazil: Gorki Grinberg, Iselde Buchner Ferreira, Raquel Bauer Cechinel (Hospital General Porto Alegre, Porto Alegre); Daniela Bicudo Angelieri (Hospital São Paulo, São Paulo); Simone Nouer, Rosa Vianna, Ana Lucia Machado, Elaine Gama, Doris Blanquet (Hospital Universitario Clementino Fraga Filho (HUCFF), Rio de Janeiro); Bruna Boaria Zanandrea, Carolina Rohnkohl, Marcos Regalin (Hospital São Miguel, Joaçaba); Reinaldo Salomao, Maria Ângela Maretti da Silva, Clélia Heloísa de Jesus Silva, Margarete Vilins, Sergio Blecher (Hospital Santa Marcelina, São Paulo); Jamile Leda Spessatto, Ricardo Scopel Pasini, Shaline Ferla (Hospital Universitario Santa Terezinha, Joaçaba); Gorki Grinberg (Maternidade e Hospital Día Santa Luíza, Balneario Camboriú)

Colombia: Otto Sussmann, Beatriz Eugenia Mojica (Clínica Nueva, Bogotá); Wilmer Villamil Gómez, Guillermo Ruiz Vergara, Patrick Arrieta (Clínica Santa María, Sucre); Catherine Rojas, Humberto Beltran, Jerson Paez (Centro Policlínico del Olaya, Bogotá); Otto Sussmann, María del Pilar Torres Navarrete (Clínica Palermo, Bogotá); Wilmer Villamil Gómez, Luis Dajud, Mariela Mendoza, Patrick Arrieta (Clínica de la Sabana, Sucre); Carlos Álvarez Moreno, Claudia Linares (Hospital Universitario San Ignacio, Universidad Pontificia Javeriana, Bogotá); Carlos Álvarez Moreno, Laline Osorio (Hospital Simón Bolívar ESE, Bogotá); Nayide Barahona Guzmán, Marena Rodríguez Ferrer, Guillermo Sarmiento Villa, Alfredo Lagares Guzmán (Universidad Simón Bolivar, Barranquilla); Narda Olarte, Alberto Valderrama (Hospital El Tunal ESE, Bogotá); Julio Garzón Agudelo (Hospital Videlmédica, Bogotá), María Eugenia Rodríguez Calderón (Hospital La Victoria, Bogotá)

Greece: Kalliopi Chaniotaki, Constantinos Tsioutis, Dimitris Bampalis (University Hospital of Heraklion, Heraklion)

India: Subhash Kumar Todi, Arpita Bhakta, Mahuya Bhattacharjee (AMRI Hospitals, Kolkata); R. Krishna Kumar, Kavitha Radhakrishnan (Amrita Institute of Medical Sciences & Research Center, Kochi); Reshma Ansari, Aruna Poojary, Geeta Koppikar, Lata Bhandarkar, Shital Jadhav (Breach Candy Hospital Trust, Mumbai); Nagamani Sen, Kandasamy Subramani (Christian Medical College, Vellore); Anil Karlekar (Escorts Heart Institute & Research Centre, New Delhi); Camilla Rodrigues, Ashit Hegd, Farahad Kapadia (PD Hinduja National Hospital & Medical Research Centre, Mumbai); Samir Sahu (Kalinga Hospital, Bhubaneswar); Ramachadran Gopinath, Nallagonda Ravindra (Nizam's Institute of Medical Sciences, Hyderabad); Sheila Nainan Myatra, J. V. Divatia, Rohini Kelkar, Sanjay Biswas, Sandhya Raut, Sulochana Sampat, Rishi Kumar (Tata Memorial Hospital, Mumbai); Murali Chakravarthy, B.N.Gokul, Sukanya R., Leema Pushparaj (Wockhardt Hospitals, Bangalore), Arpita Dwivedy, Suvin Shetty, Sheena Binu (Dr L. H. Hiranandani Hospital, Mumbai)

Lebanon: Nada Zahreddine, Nisreen Sidani, Lamia Alamaddni Jurdi, Zeina Kanafani (American University of Beirut Medical Center, Beirut)

Mexico: Martha Sánchez López (Hospital General de la Celaya, Celaya); Héctor Torres Hernández, Amalia Chávez Gómez, Jaime Rivera Morales, Julián Enrique Valero Rodríguez (Hospital General de Irapuato, Irapuato); Martha Sobreyra Oropeza (Hospital de La Mujer, Mexico City); Manuel Sigfrido Rangel-Frausto (Specialties IMSS Hospital, Mexico City); José Martínez Soto (Gabriel Mancera IMSS Hospital, Mexico City), Alberto Armas Ruiz, Roberto Campuzano, Jorge Mena Brito (Centro Médico la Raza, Mexico)

Morocco: Rédouane Abouqal, Naoufel Madani, Amine Ali Zeggwagh, Tarek Dendane (Ibn-Sina Hospital, Medical ICU, Rabat), Amina Barkat, Naima Lamdouar Bouazzaoui, Kabiri Meryem (Children Hôspital of Rabat, Rabat)

Peru: Luis Cuellar, Rosa Rosales, Luis Isidro Castillo Bravo, María Linares Cáceres (Instituto Nacional de Enfermedades Neoplásicas (INEN), Lima); Teodora Atencio Espinoza, Favio Sarmiento López (Hospital Regional de Pucallpa, Pucallpa); Manuel Jesús Mayorga Espichan, Liliana Echenique (Clínica San Pablo, Lima); Alex Castañeda Sabogal, Iliana Paredes Goicochea, Abel Arroyo Sánchez, Guillermo Ríos Alva, Jorge García Ventura, Miguel Ramírez Aguilar, Niler Segura Plasencia, Teófilo Rodríguez (Hospital Víctor Lazarte Echegaray, Trujillo)

Turkey: A. Nevzat Yalcin, Ozge Turhan, Sevim Keskin, Eylul Gumus, Oguz Dursun (Akdeniz University, Antalya); Davut Ozdemir, Ertugrul Guclu, Selvi Erdogan (Duzce Medical School, Duzce); Sercan Ulusoy, Bilgin Arda, Feza Bacakoglu (Ege University Medical Faculty, Izmir); Emine Alp, Bilgehan Aygen (Erciyes University, Faculty of Medicine, Kayseri); Dilek Arman, Kenan Hizel, Kesver Özdemir (Gazi University Medical School, Ankara); Cengiz Uzun (German Hospital, Istanbul); Yesim Cetinkaya Sardan, Gonul Yildirim, Arzu Topeli (Hacettepe University School of Medicine, Ankara); Fatma Sirmatel, Mustafa Cengiz, Leyla Yilmaz (Harran University, Faculty of Medicine, Sanliurfa); Asu Özgültekin,

Güldem Turan, Nur Akgün (Haydarpasa Hospital, Istanbul); Recep Öztürk, Yalim Dikmen, Gökhan Aygún (Istanbul University Cerrahpasa Medical School, Istanbul); Özay Arıkan Akan, Melek Tulunay, Mehmet Oral, Necmettin Ünal (Ankara University School of Medicine Ibni-Sina Hospital, Ankara); Iftíhar Koksal, Gürdal Yýlmaz, AC Senel, Ebru Emel Sözen (Karadeniz Technical University School of Medicine, Trabzon); Gulden Ersoz, Ali Kaya, Ozlem Kandemir (Mersin University, Faculty of Medicine, Mersin); Hakan Leblebicioglu, Saban Esen, Fatma Ulger, Ahmet Dilek, Canan Aygun, Sukru Küçüködük (Ondokuz Mayis University Medical School, Samsun); Ilhan Ozgunes, Gaye Usluer (Eskisehir Osmangazi University, Eskisehir); Huseyin Turgut, Suzan Sacar, Hülya Sungurtekin, Doğaç Uğurcan (Pamukkale University, Denizli)