Attributable Mortality of Ventilator-associated Pneumonia: Replicating Findings, Revisiting Methods

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Abstract

Rationale: Estimating the impact of ventilator-associated pneumonia (VAP) from routinely collected ICU data is methodologically challenging.

Objectives: We aim to replicate earlier findings of limited VAP-attributable ICU mortality in an independent cohort. By refining statistical analyses, we gradually tackle different sources of bias.

Methods: Records of 2,720 adult patients admitted to Ghent University Hospital ICUs (2013—2017) and receiving mechanical ventilation within 48 hours following admission were extracted from linked ICIS and COSARA databases. The VAP-attributable fraction of ICU mortality was estimated using a competing risk analysis that is restricted to VAP-free patients (approach 1), accounts for VAP onset by treating it as either a competing (approach 2) or censoring event (approach 3), or additionally adjusts for time-dependent confounding via inverse probability weighting (approach 4).

Results: Two hundred ten patients (7.7%) acquired VAP. Based on benchmark approach 4, we estimated that (compared to current preventive measures) hypothetical eradication of VAP would lead to a relative ICU mortality reduction of 1.7% (95% confidence interval: -1.3—4.6) by day 10 and of 3.6% (95% confidence interval: 0.7—6.5) by day 60. Approaches 1—3 produced estimates ranging from -0.7 to 2.5% by day 10, and from 5.2 to 5.5% at day 60.

Conclusions: In line with previous studies using appropriate methodology, we found limited VAP-attributable ICU mortality given current state-of-the-art VAP prevention measures. Our study illustrates that inappropriate accounting of the time-dependency of exposure and
confounding of its effects may misleadingly suggest protective effects of early-onset VAP and systematically overestimate attributable mortality.

**Abstract Word Count:** 250
Hospital-acquired infections (HAIs) form a major public health problem in developed countries as they are associated with increased morbidity, mortality and health-related costs (1–3). Given their critical illness and exposure to invasive treatments, intensive care unit (ICU) patients are particularly prone to acquire HAIs, especially ventilator-associated pneumonia (VAP).

Appropriate quantification of the impact and burden of unprevented VAP is imperative to understanding its severity and the importance of additional preventive measures and timely treatment. Although its occurrence is reported to be associated with increased ICU mortality, the well-known mantra ‘correlation does not imply causation’ dictates that a considerable number of intubated patients dies with but not necessarily from VAP. Estimation of the causal impact of HAIs, however, remains subtle and controversial because such assessments are either based on observational data or randomized trials with varying levels of prevention effectiveness (4). Given the multitude of potential sources of variation, past observational studies produced highly variable findings with excess risk estimates ranging from 0 up to 50% (5).

Multi-state model (MSM) approaches for estimating mortality and prolonged stay due to HAIs have been widely advocated in recent years as they aid in avoiding common types of bias (5–7). Their focus on a specific effect measure, the time-dependent population-attributable fraction (PAF), may moreover reduce variability in findings due to various definitions of excess risk. Even so, widely used MSM approaches (8) produce results that cannot be causally interpreted, even in the absence of confounding (9,10). Moreover, MSM approaches are ill-equipped to tackle bias due to group imbalances in prognostic factors that may accrue over the course of time. They may therefore misinform clinical practice. This latter
shortcoming, although repeatedly highlighted in the literature (5,11,12), remains underappreciated.

The aim of this article is twofold. First, we aim to replicate earlier findings from Bekaert and colleagues (13), who provided the first and (to our knowledge) only study to appropriately address time-dependent confounding in estimation of VAP-attributable ICU mortality. We assess whether their findings of limited VAP-attributable ICU mortality, based on the French multicenter Outcomerea database (n = 4,479) (1997—2008), generalize to an independent cohort of 2,720 mechanically ventilated patients. To maximally reduce bias and ensure between-study comparability, we use identical estimation approaches for causal inference. Second, we illustrate the importance of appropriately accounting for the time-dependent nature of events under study and of their confounding factors by comparing results to those produced by MSM approaches. In doing so, we gradually refine our analysis to demonstrate, in each subsequent step, how different types of bias can be eliminated or reduced.

Methods

Study Population
VAP-attributable ICU mortality was estimated based on records of a cohort of adult patients (aged 18 or older) admitted to the Ghent University Hospital (medical and surgical) ICUs between January 2013 and November 2017, who stayed at the ICU for at least 48 hours and received mechanical ventilation within 48 hours following admission. In case of ICU re-admissions, only the first episode was included.
Data Collection

Admission characteristics were extracted from the Intensive Care Information System (ICIS) database (GE Healthcare Centricity Critical Care®) and consisted of demographic data (sex, age and weight), admission category (medicine, emergency surgery or scheduled surgery) and severity of illness and comorbidities as captured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the updated Charlson comorbidity index (14), respectively. In addition, ICU admission and discharge dates, ICU survival, and data on daily interventions and treatments were extracted: enteral feeding, corticosteroids (>0.5 mg/kg), mechanical ventilation, use of vasoactive agents, hemodialysis, tracheotomy tube, and treatment limitation decisions (code 0—4). Measurements on daily disease severity and organ function, as captured by the Sequential Organ Failure Assessment (SOFA) score, were extracted from the Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU (COSARA) (15–17) database.

Following (18), VAP was defined as ‘hospital-acquired pneumonia diagnosed in patients under mechanical ventilation for 48 hours or longer, or in patients who had been extubated for less than 48 hours after mechanical ventilation for at least 2 days’ to exclude community-acquired pneumonia or other types of hospital-acquired pneumonia unrelated to mechanical ventilation. Daily indicators of acquisition of VAP and other infections (fungal infections and bacterial infections, including abdominal, catheter-related, respiratory, and urinary tract infections), and administered antibiotic treatments were extracted from COSARA. A more detailed list of extracted variables, their definitions and (re)coding are included as Online Supplement.
The Ghent University Hospital Ethics Committee approved the study (registration number B670201732106) and waived informed consent since all analyses were performed retrospectively on pseudonymized records. Unique patient and ICU admission identifiers allowed to link extracted records.

**Statistical Analysis**

In this paper, we focus on estimation of the time-dependent PAF of ICU mortality due to VAP, which expresses the proportion of preventable death cases in the ICU in the absence of VAP as a function of time since admission. This (inherently causal) effect measure involves a comparison of the observed cumulative incidence of ICU death, which can readily be estimated using a standard competing risk (CR) analysis (that treats ICU discharge as a competing event), with the non-observable *counterfactual* cumulative incidence of ICU death that would have been observed if, *counter to the fact*, VAP had been avoided for all considered patients. Due to its hypothetical nature, estimation of this second quantity is more challenging. We revisit and compare four proposed approaches for estimating the time-dependent PAF (within the first 60 days following ICU admission) which differ only in estimation of this counterfactual (VAP-free) cumulative incidence. Each of these approaches apportions weights to VAP-free events that are inversely proportional to the amount of selection of VAP-free patients in the analysis to ‘reconstruct’ the original cohort in the absence of VAP. However, their respective weighting schemes differ in terms of how well they respect the temporal ordering of events and take into account differential selection of VAP-free patients over time. In a methodological companion paper (19), we illustrate how each approach involves a refinement with respect to another,
thereby enabling to gradually tackle and assess different sources of bias. In the discussion (and in the Online Supplement), we provide more intuition into these refinements.

Approach 1 approximates this quantity by the cumulative incidence of ICU death in patients who remained VAP-free until death or discharge, as estimated by a standard CR analysis (using the Aalen-Johansen estimator), treating ICU discharge as a competing event. This approach ignores VAP onset time or, equivalently, VAP-free patient-time of infected patients.

Approach 2 is based on a CR analysis that treats VAP-free ICU discharge and VAP onset as competing events for VAP-free ICU death. The counterfactual cumulative incidence of ICU death is estimated as a function of the respective cumulative incidences of these competing events that takes into account VAP onset. This approach corresponds to estimation of the PAF by a particular MSM, i.e. the progressive disability model, originally proposed in (8).

Approach 3, also based on a CR analysis, accounts for VAP onset by treating it as a censoring rather than a competing event for both ICU discharge and death. By censoring infected patients as soon as they acquire VAP, this approach aims to recover the cumulative incidence of ICU death had all patients remained VAP-free. This alternative MSM-based approach (20) was originally proposed in another setting and corresponds to an inverse probability (IP) of censoring weighted Aalen-Johansen estimator of VAP-free ICU mortality, which weighs each VAP-free event by the probability of having remained VAP-free while hospitalized (21).

Approach 4 is an extension of approach 3 in which informative censoring of infected patients (or, equivalently, time-dependent confounding of the effect of VAP) is accounted for
by additionally incorporating patient (covariate) history into calculation of the IP weights. This approach is identical to previously suggested causal inference techniques based on IP weighting (13,22–25) and involves a more elaborate modelling component (due to adjustment for time-dependent covariates). In particular, a Cox proportional hazards model was fitted for the daily probability of acquiring VAP in function of the available covariate history, including admission characteristics and time-dependent factors as listed in the section ‘Data Collection’. For each VAP-free patient-day at the ICU, weights were calculated from the fitted probabilities from the final Cox model. These time-dependent patient-specific weights express the reciprocal of the probability of having remained VAP-free while hospitalized and the patient’s observed covariate profile up to that day (for more details on causal and modeling assumptions, the set of adjusted covariates, obtained balance across these covariates, and the distribution of the IP weights, see Online Supplement and Figures E1—E5).

We used nonparametric bootstrapping based on 1,000 samples to calculate percentile-based 95% CIs for the time-dependent PAF, as estimated by each of the four approaches. All analyses were conducted in R (26) (version 4.0.2) using the ipw (27) and survival (28) R packages.

The STROBE (29) and RECORD (30) guidelines for reporting of observational studies and studies conducted using observational routinely collected health data were followed.
Results

Descriptives

For 2,729 patients the first ICU episode was included that fulfilled the inclusion criteria (see flow diagram in Figure 1). Nine were excluded from final analyses because either ICU survival (1 episode) or APACHE II score (8 episodes) was missing. During the 32,526 patient days of follow-up in the remaining 2,720 patients, 210 patients (7.7%) developed VAP, resulting in 29,091 VAP-free patient days and 3,471 VAP-infected patient days. Half of VAP-infected patients were diagnosed with VAP within 5 days following admission. Patients who acquired VAP had a median ICU stay of 21 days and received mechanical ventilation for a median duration of 15 days. In contrast, patients who did not acquire VAP had a median length of ICU stay of only 7 days and received mechanical ventilation for a median duration of 3 days. Patient characteristics on admission and crude mortality rates are summarized in Table 1.

Population-attributable Fraction of ICU Mortality Due to VAP

Figure 2 and Table 2 provide a comprehensive comparison of the results obtained from the different estimation approaches under study. The observed 10-day, 30-day and 60-day ICU mortality risk in mechanically ventilated patients was 12.5% (340 ICU deaths out of 2,720 patients), 18.9% (513/2720), and 19.9% (540/2720), respectively (t-day ICU mortality risk corresponds to the proportion of all admitted patients that died in the ICU within t days following admission).
Among patients who did not acquire VAP by the end of follow-up (approach 1), the 10-day ICU mortality risk was 12.6% (316/2510). Extrapolated to the original population, it was estimated that, if all patients had remained without VAP, about 342 patients would have died in the ICU by day 10. In other words, approach 1 estimated an excess of 2 deaths by day 10 in the absence of VAP (PAF = -0.7%, 95% confidence interval (CI): -3.6—0.2%). In contrast, it was estimated that 23 ICU deaths could have been prevented by day 30 (PAF = 4.5%, 95% CI: 1.8—7.4%) and about 30 by day 60 (PAF = 5.5%, 95% CI: 2.9—8.2%) if all patients had remained without VAP.

Approach 2 produced a highly similar estimate as approach 1 at day 30, an identical one at day 60 (because no patients acquired VAP after day 60), but a positive estimate of the counterfactual risk at day 10. Among patients who remained without VAP (at least) up to day 10, the 10-day ICU mortality risk was 12.3% (316/2560). This approach thus suggests that, had all patients remained without VAP (at least) up to day 10, nearly 336 would have died at the ICU by day 10, corresponding to 4 prevented deaths by day 10 (PAF = 1.3%, 95% CI: -1.5—3.7%).

Approach 3 estimated that almost 8 deaths could have been prevented by day 10 (PAF = 2.5, 95% CI: -0.3—5.1%). At day 30 and 60, approach 3 produced similar estimates as approaches 1 and 2.

Finally, according to approach 4, the 10-day, 30-day and 60-day ICU mortality risk had all patients remained without VAP was estimated to be 12.3%, 18.2% and 19.1%, respectively. These estimated risks correspond with considerably lower estimates of preventable cases at longer follow-up as compared to the other approaches: 6.2 by day 10 (PAF = 1.8%, 95% CI: -
1.1—4.8), 16.8 by day 30 (PAF = 3.3%, 95% CI: 0.2—6.3) and 19.9 by day 60 (PAF = 3.7%, 95% CI: 0.8—6.6).

In sum, the favored benchmark approach 4 demonstrates that ICU mortality attributable to VAP is very limited: about 3-4% by day 60. Shortly after ICU admission (within the first two weeks) approach 1 indicates a modest but non-negligible protective effect of VAP, which is not corroborated by more refined analyses 2—4. When considering larger time windows, approach 4 indicates that the attributable ICU mortality due to VAP may be even smaller as compared to estimates obtained from less refined analyses 1—3.

**Discussion**

In this study, we aimed to replicate earlier findings of limited VAP-attributable ICU mortality (13) and, in doing so, illustrate the importance of appropriately accounting for the time-dependent nature of the events under study and their confounding factors.

**Main Findings**

We estimated that, by day 30, 3.3% of deaths in ventilated patients could have been avoided by successful VAP prevention. By day 60, the proportion of preventable cases increased to 3.7%. Although largely in line with the modest impact reported by Bekaert and colleagues (13) (4.4% on day 30 and 5.9% on day 60), we found an even more limited impact. Between-study variability in estimates may be related to a host of factors, such as differences in patient case-mix, diagnostic procedures and definitions, characteristics of infection, timeliness and
appropriateness of treatment, application of different (and often suboptimal) statistical methods and use of various definitions of excess risk (5,13). In keeping with (13), we have chosen to focus on the PAF because of its intuitively appealing interpretation and its central role as a target of inference of predominant MSM-based approaches (8). Unlike other effect measures, such as the absolute risk reduction, it implicitly captures VAP incidence because not only lower incidences of ICU mortality but also higher incidences of infection translate into larger PAFs. A differential incidence ratio may explain discrepancies between our findings, based on a cohort in which 7.7% of patients acquired VAP and 19.9% died in the ICU by day 60 (incidence ratio = 0.39) and those of (13) where the incidences were reported to be 15.3% and 25.6% respectively (incidence ratio = 0.60). Remarkably, despite lower incidences, our cohort had worse prognosis at ICU admission (SAPS II score interquartile range, 59 to 80 vs 28 to 53). Our smaller estimates may also in part reflect a smaller excess risk of death in patients with a poorer prognosis (13,31,32).

Comparison with Findings from Conventional Statistical Approaches

Our focus on the time-dependent PAF facilitated both between-study comparisons and within-study comparisons of alternative estimation approaches targeting the same effect measure. Along with a recent study by von Cube and colleagues (9), our study is among the first to compare different MSM approaches for estimating the time-dependent PAF of ICU mortality due to VAP. While their comparison did not include an analysis that adjusts for time-dependent confounding (approach 4) nor a naive CR analysis (approach 1), we chose to additionally include these for two reasons. First, we believe that proper adjustment for available time-dependent
factors may considerably reduce confounding bias and therefore produces the most reliable benchmark. Second, the PAF can be interpreted as the relative mortality reduction in an RCT that randomly assigns eligible patients to receive either a fully effective bundle of preventive measures or standard of care (for more details, see the Online Supplement). A recent characterization reveals that the compared approaches can be organized hierarchically with respect to how well they emulate this hypothetical prevention trial using observational data (19). To the best of our knowledge, this is the first study to directly compare these four approaches in a hierarchical fashion.

Approach 1 compares the original population with patients who remained VAP-free until death or discharge. This comparison is known to produce immortal time bias because, unlike patients who eventually acquired VAP, these patients may not have survived long enough to acquire VAP and accordingly, did not get apportioned protective ‘immortal time’. This time-dependent bias is apparent during the first two weeks and gradually attenuates, being practically non-existent at four weeks (after which only few patients acquire VAP) (Figure 2A).

Approach 2 accounts for the time-dependent nature of VAP onset by comparing the original population with patients who had remained VAP-free by each consecutive time wave, which eliminates immortal time bias (8). Yet, it fails to fully respect the temporal ordering of events because deceased patients receive weights that incorporate information on future events while ignoring information on past events (for more details, see the Online Supplement). The (modest) protective negative ‘bump’ during the first 10 days (Figure 2B) may partly be explained by this residual, more subtle form of time-dependent bias. In contrast to earlier
reports (8), results obtained by this approach can therefore not be causally interpreted, even given sufficient confounding adjustment (9).

Approach 3 (Figure 2C), a less familiar MSM-based approach closer in spirit to causal inference methods for longitudinal data (10,20,33–35) fully eliminates all forms of time-dependent bias because it apportions weights that do not incorporate information on future events and exploit additional available information on past events. Residual time-dependent bias produced by approach 2, which can be readily quantified by comparing results of approaches 2 and 3, is clearest within the first days to weeks. Although it seems to become negligible towards the end of follow-up, bias may remain more pronounced in settings with different temporal dynamics of the considered events (9). In general, residual time-dependent bias is expected to be relatively small whenever exposure prevalence is low, as in our study (although see (19) for an example with higher exposure prevalence).

Finally, approach 4 assigns weights to deceased patients that not only depend on their time of death (as approach 3), but also on their individual characteristics and ( evolution of) disease severity. As approach 3, this approach compares the original population with the same population in a hypothetical world where VAP is eradicated, but no longer naively assumes that, on any given day, incident VAP cases are exchangeable with hospitalized VAP-free patients. Comparing results from the third and the last (benchmark) analysis (Figure 2C,D) indicates that, once measured imbalances over time are adjusted for, the estimated counterfactual cumulative incidence curve more closely matches the observed cumulative incidence curve or, in other words, that a considerable share of patients who die with VAP do not die from VAP. In line with recent findings (9), adjusting only for baseline confounders
produces results that are almost identical to an unadjusted analysis (approach 3) (see Figure E5). This suggests that, in acute settings such as the ICU, imbalances at baseline may often be negligible, but rather accrue over time. Although observational studies based on MSMs have similarly indicated a relatively modest excess risk of ICU death due to VAP (9,31,32), these estimates may still have been upwardly biased due to failure to adjust for time-dependent confounding.

Limitations

Although our final estimates may be considered more reliable than those obtained by other approaches, they are also prone to bias. First, residual confounding bias cannot be ruled out because certain confounders may either have been unknown or simply missing from available databases, or because of potential misspecification of the Cox model fitted to calculate IP weights. However, these concerns may be rather limited compared to other studies as, in accordance with (13), our analysis adjusted for a much richer set of available time-varying confounders. Second, measurement error in VAP diagnosis as well as timing of its onset (due to an incubation effect) may have affected our analysis. Missed VAP cases may have resulted in underestimation of VAP incidence and, consequently, also the VAP-attributable fraction. Underestimation may also be likely in case of ascertainment bias, e.g. when missed VAP cases would be more common among severely ill patients with a treatment limitation decision (although see Online supplement for details on how we attempted to tackle this). Finally, as pointed out elsewhere (13), we emphasize that our analysis estimated the fraction of ICU mortality attributable to diagnosed and treated VAP that could not be prevented by current
state-of-the-art prevention efforts. As such, we caution against interpreting our findings as an indication to minimize the importance of prevention measures (as current measures may likely have prevented VAP and considerably shortened hospitalization in many patients), accurate diagnosis or adequate treatment, because these are inherently captured by our estimates.

**Conclusions**

In conclusion, this study replicates earlier findings of limited ICU mortality attributable to treated VAP given current state-of-the-art VAP prevention measures (13) in an independent cohort using the same causal modelling techniques for estimation. In addition, it provides a compelling illustration that (i) failure to (properly) account for the time-dependent nature of events may misleadingly indicate survival advantages of infected patients shortly after ICU admission and that (ii) failure to account for the time-dependent nature of confounding leads to systematic overestimation of the PAF, mostly towards end of follow-up.

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Figure Legends

**Figure 1.** Study flow diagram.

**Figure 2.** Results of the four different competing risk (CR) analysis approaches for estimating the time-dependent population-attributable fraction (PAF) of intensive care unit (ICU) mortality due to ventilator-associated pneumonia (VAP). Upper panels: observed cumulative incidence of ICU mortality (*black curves*) and estimated counterfactual VAP-free cumulative incidence of ICU mortality (*grey curves*). Lower panels: estimated PAF of ICU death due to VAP (*solid lines*) and 95% pointwise confidence intervals (*shaded areas*).
|                         | Patients with VAP (n = 210) | Patients without VAP (n = 2,510) | All patients (n = 2,720) |
|-------------------------|-----------------------------|----------------------------------|--------------------------|
| Male sex, n (%)         | 146 (69.5)                  | 1,569 (62.5)                     | 1,715 (63.1)             |
| Age, mean (SD)          | 56.1 (16.7)                 | 60.5 (15.7)                      | 60.2 (15.9)              |
| ICU length of stay, median (Q1, Q3) | 21 (12, 31) | 7 (5, 13)                         | 8 (5, 15)                |
| Ventilation days, median (Q1, Q3) | 15 (9, 23) | 3 (2, 8)                          | 4 (2, 9)                 |
| APACHE II score, mean (SD) | 27.1 (6.8) | 27.1 (6.7)                       | 27.1 (6.7)               |
| SOFA score on admission, mean (SD) | 9.5 (3.7) | 9.1 (3.7)                        | 9.1 (3.7)                |
| Respiratory, mean (SD)  | 2.2 (1.3)                   | 2.1 (1.2)                        | 2.1 (1.2)                |
| Coagulation, mean (SD)  | 0.7 (1.1)                   | 0.6 (1.0)                        | 0.6 (1.0)                |
| Liver, mean (SD)        | 0.3 (0.7)                   | 0.4 (0.9)                        | 0.4 (0.9)                |
| Cardio, mean (SD)       | 3.1 (1.5)                   | 2.7 (1.6)                        | 2.8 (1.6)                |
| Central nervous system, mean (SD) | 2.6 (1.8) | 2.8 (1.7)                        | 2.8 (1.7)                |
| Renal, mean (SD)        | 0.5 (0.9)                   | 0.5 (0.9)                        | 0.5 (0.9)                |
| Admission category      |                             |                                  |                          |
| Medicine, n (%)         | 70 (33.3)                   | 956 (38.1)                       | 1,026 (37.7)             |
| Emergency surgery, n (%)| 111 (52.9)                  | 1,023 (40.8)                     | 1,134 (41.7)             |
| Scheduled surgery, n (%)| 29 (13.8)                   | 531 (21.2)                       | 560 (20.6)               |
| Charlson comorbidity index (updated), mean (SD) | 1.2 (1.7) | 2.1 (2.4) | 2.0 (2.3) |
| Myocardial infarction, n (%) | 9 (4.3) | 126 (5.0) | 135 (5.0) |
| Congestive heart failure, n (%) | 33 (15.7) | 486 (19.4) | 519 (19.1) |
| Peripheral vascular disease, n (%) | 28 (13.3) | 324 (12.9) | 352 (12.9) |
| Cerebrovascular disease, n (%) | 12 (5.7) | 141 (5.6) | 153 (5.6) |
| Dementia, n (%)          | 1 (0.5)                     | 30 (1.2)                         | 31 (1.1)                 |
| Chronic pulmonary disease, n (%) | 26 (12.4) | 373 (14.9) | 399 (14.7) |
| Mild liver disease, n (%) | 8 (3.8) | 38 (1.5) | 46 (1.7) |
| Diabetes without chronic complications, n (%) | 20 (9.5) | 364 (14.5) | 384 (14.1) |
| Diabetes with chronic complications, n (%) | 5 (2.4) | 54 (2.2) | 59 (2.2) |
| Hemiplegia or paraplegia, n (%) | 5 (2.4) | 67 (2.7) | 72 (2.6) |
| Renal disease, n (%)     | 21 (10.0)                   | 423 (16.9)                       | 444 (16.3)               |
| Any malignancy, incl leukemia and lymphoma, n (%) | 23 (11.0) | 418 (16.7) | 441 (16.2) |
| Moderate or severe liver disease, n (%) | 10 (4.8) | 259 (10.3) | 269 (9.9) |
| Metastatic solid tumor, n (%) | 2 (1.0) | 187 (7.5) | 189 (6.9) |
| AIDS/HIV, n (%)          | 3 (1.4)                     | 13 (0.5)                         | 16 (0.6)                 |
| Crude mortality rates    |                             |                                  |                          |
| 30-day ICU mortality, n (%) | 60 (28.6) | 451 (18.0) | 511 (18.8) |
| 60-day ICU mortality, n (%) | 69 (32.9) | 470 (18.7) | 539 (19.8) |
| Global ICU mortality, n (%) | 69 (32.9) | 473 (18.8) | 542 (19.9) |

Q1 = first quartile or 25th percentile; Q3 = third quartile or 75th percentile; APACHE = Acute Physiology And Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment
Table 2. Comparison of estimates of the population-attributable fraction of ICU death due to ventilator-associated pneumonia as obtained by four different competing risk analyses.

|                                | 10 days since ICU admission | 30 days since ICU admission | 60 days since ICU admission |
|--------------------------------|----------------------------|----------------------------|---------------------------|
| VAP-infected patients, n (%)  | 160 (5.9)                  | 208 (7.6)                  | 210 (7.7)                 |
| VAP-free ICU deaths, n (%)    | 316 (11.6)                 | 452 (16.6)                 | 471 (17.3)                |
| ICU deaths, n (%)             | 340 (12.5)                 | 513 (18.9)                 | 540 (19.9)                |

**Approach 1: Competing risk analysis restricted to patients who remain VAP-free until end of follow-up**

Estimated deaths had VAP been eradicated (%)

- 342.4 (12.6) for 10 days
- 489.8 (18.0) for 30 days
- 510.4 (18.8) for 60 days

Estimated PAF (95% CI)

- -0.7% (-3.6, 0.2) for 10 days
- 4.5% (1.8, 7.4) for 30 days
- 5.5% (2.9, 8.2) for 60 days

**Approach 2: Competing risk analysis that treats VAP acquisition as a competing event**

Estimated deaths had VAP been eradicated (%)

- 335.8 (12.3) for 10 days
- 489.4 (18.0) for 30 days
- 510.4 (18.8) for 60 days

Estimated PAF (95% CI)

- 1.3% (-1.5, 3.7) for 10 days
- 4.6% (1.9, 7.4) for 30 days
- 5.5% (2.9, 8.2) for 60 days

**Approach 3: Competing risk analysis that treats VAP acquisition as a censoring event**

Estimated deaths had VAP been eradicated (%)

- 331.6 (12.2) for 10 days
- 488.6 (18.0) for 30 days
- 512.2 (18.8) for 60 days

Estimated PAF (95% CI)

- 2.5% (-0.3, 5.1) for 10 days
- 4.8% (2.0, 7.7) for 30 days
- 5.2% (2.6, 7.8) for 60 days

**Approach 4: Competing risk analysis that additionally adjusts for time-dependent confounding by IP weighting**

Estimated deaths had VAP been eradicated (%)

- 333.8 (12.3) for 10 days
- 496.2 (18.2) for 30 days
- 520.1 (19.1) for 60 days

Estimated PAF (95% CI)

- 1.8% (-1.1, 4.8) for 10 days
- 3.3% (0.2, 6.3) for 30 days
- 3.7% (0.8, 6.6) for 60 days

*The counterfactual risk of ICU death by day t had VAP been prevented for all is estimated by weighing each VAP-free ICU death before or at day t by a factor that captures the degree of depletion of VAP-infected patients by the end of study follow-up (approach 1); by day t (approach 2); by the corresponding time of ICU death (approach 3); with a similar observed covariate history by the corresponding time of ICU death (approach 4). See the Online Supplement for more details.
15,943 ICU episodes 
(Jan 1st 2013 - Nov 8th 2017)

8,752 episodes of <48 hours excluded

7,191 ICU episodes of ≥48 hours

3,918 episodes without mechanical ventilation excluded

2,988 first ICU episode of ≥48 hours with mechanical ventilation in the study period

285 re-admissions (with mechanical ventilation) excluded

2,970 ... in patients ≥18 years old

18 admissions of patients <18 years old

2,729 ... receiving mechanical ventilation within first 48 hrs after ICU admission

40 episodes in which mechanical ventilation was initiated more than 48 hrs after admission excluded

1 episode with incorrect admission time excluded

2,728 ... with recorded ICU mortality status

1 episode with unknown ICU mortality status excluded

2,720 ... with known APACHE II score at admission

8 episodes with unknown APACHE II score at admission excluded

2,510 did not acquire VAP during ICU stay

210 acquired VAP during ICU stay

473 died during ICU stay

69 died during ICU stay
Approach 1: CR analysis restricted to VAP-free patients

Approach 2: CR analysis that treats VAP as a competing event

Approach 3: CR analysis that treats VAP as a censoring event

Approach 4: CR analysis adjusted for time-dependent confounding
Attributable mortality of ventilator-associated pneumonia: replicating findings, revisiting methods

Johan Steen, Stijn Vansteelandt, Liesbet De Bus, Pieter Depuydt, Bram Gadeyne, Dominique D. Benoit, Johan Decruyenaere

Online data supplement
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Detailed list of variables and definitions

Main time-varying exposures and primary outcomes

Mechanical ventilation

A patient’s daily mechanical ventilation (MV) status was derived from patient-specific MV episodes. Daily MV status was coded 1 if the MV episode covered the corresponding calendar date, and 0 otherwise. An MV episode was defined as an uninterrupted time window in which at least 2 ventilation parameters (including but not restricted to PEEP, tidal volume, FiO₂, SpO₂, respiratory rate, I:E ratio, pressure support, mean airway pressure) were registered. A time window is considered uninterrupted if there were no gaps of more than 24 hours with less than 2 registered ventilation parameters. Ventilation parameters (set and measured values) were either routinely entered by nursing staff every 30 minutes to 2 hours (depending on the parameter) or automatically registered through a connected monitoring device (such as respiratory rate and SpO₂) and validated by nursing staff every 30 minutes. Internal code was used to calculate MV episodes from time-dependent ventilator parameters.

Ventilator-associated pneumonia (VAP)

Hospital-acquired pneumonia diagnosed in patients under mechanical ventilation for 48 hours or longer, or in patients who had been extubated for less than 48 hours after mechanical ventilation for at least 2 days (1). Following (2), we included only pneumonia with high and moderate probability. Pneumonia was considered to be highly probable in the case of presence of a new or worsening infiltrate on chest X-ray, together with clinical signs of sepsis and new respiratory symptoms (increased sputum, increased purulence of sputum, worsening oxygenation), and a semi-quantitative score of 1+ growth or more of a pathogen in a good-
quality respiratory sample. Pneumonia was considered to be moderately probable in the case of all previous criteria but in the absence of respiratory pathogens or growth below the threshold of 1+. This is a clinically pragmatic definition that closely matches reality and has high concordance with the CDC definition (2).

Suspected VAP diagnosis was entered by the treating intensive care physician in the Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU (COSARA) system.

Two hundred ninety-five (295) patients were registered with suspected VAP. Forty (40) of these were not microbiologically confirmed and had low probability on clinical re-evaluation after 48-72h of empirical antibiotic therapy. Of the remaining 255, 44 patients were coded with a VAP diagnosis within 48 hours after ICU admission and within 48 hours after the start of the first episode of mechanical ventilation (as defined above). Assuming correct ICU admission times, correct coding/registration of mechanical ventilation episodes at the ICU, we considered these patients as either misdiagnosed by the treating physician (because failure to adhere to the aforementioned definition of VAP) or as correctly diagnosed, but not ICU-acquired (possibly due to mechanical ventilation prior to ICU admission). These ‘ambiguous’ VAP cases were recoded as non-VAP, and remaining VAP cases were considered as ‘incident VAP cases’, i.e. ICU-acquired VAP due to mechanical ventilation administered at the ICU. One of the remaining 211 VAP cases was excluded from the final analysis due to a missing APACHE II score (cf. flow diagram in Figure 1 in the main manuscript).

VAP diagnosis may have been susceptible to differential misclassification bias in patients with treatment limitation decisions (cf. below), i.e. VAP cases could have been missed relatively more often (false negatives) in patients with DNR codes because accurate diagnosis may not have been as pressing for considering adequate therapy options as for patients without a DNR code. However, in estimating the population-attributable fraction (using approach 4), we aimed
to correct for such potential detection bias by adjusting for time-varying DNR code as a potential confounder in the Cox proportional hazards model to calculate inverse probability weights (see section ‘Cox proportional hazards model for the daily probability of acquiring VAP’). There is, however, no guarantee that this may have completely eliminated potential detection bias.

Daily VAP acquisition status was coded 1 from the first calendar date of VAP diagnosis and 0 otherwise. Following (3), we coded daily VAP status as ‘having acquired VAP on the current calendar date or earlier’ (i.e. VAP status was coded 1 even if clinical cure from VAP had occurred). Clinical cure after VAP acquisition was considered irrelevant as we aimed to estimate attributable ICU mortality due to VAP acquisition rather than that of time-varying VAP.

**ICU death/discharge status and time**

Time of death at the ICU and discharge from the ICU were entered by nursing staff in the Intensive Care Information System (ICIS), along with event status (ICU death/discharge). No information bias was expected because these involved hard endpoints. Nonetheless, one patient had a missing event status and was therefore discarded from the analysis, under the assumption of missing completely at random (MCAR) (see flow diagram; Figure 1 in the main text).
Baseline covariates

Admission category

Admission category was extracted from the ICIS and indicated whether a patient was admitted at the Medical ICU (MICU) or Surgical ICU (SICU), and whether admission to the SICU was considered for emergency or scheduled surgery.

Demographic data

Gender and date of birth was extracted from the ICIS, which retrieves this information through the Admission Discharge Transfer (ADT) feed at ICU admission. Age at ICU admission was derived from ICU admission date, which was entered manually at ICU admission, and the patient’s date of birth. In addition, weight (kg) was either measured and retrieved from external hospital records, estimated by nursing staff or reported by the patient or their relatives, and entered in the ICIS by nursing staff. For 9 patients, weight was missing.

Charlson comorbidity index (updated)

The updated Charlson comorbidity index was calculated from patient admission data in the ICIS using weights as described in (4), using internal code (mapping and code available upon request). Data on rheumatologic disease was missing for all patients. The corresponding weight of 1 was therefore replaced by 0. The same principle was applied whenever information on other conditions was missing for certain patients.

Acute Physiology and Chronic Health Evaluation (APACHE) II score

APACHE II score (5) was calculated using proprietary code of GE Centricity Critical Care 8.1 and incorporated in the ICIS. Eight cases with missing APACHE score were deleted and a
complete case analysis was performed under the assumption of missing completely at random (MCAR) (see flow diagram; Figure 1 in the main text).

Time-varying covariates

Antibiotic therapy

Daily binary indicators of antibiotic (AB) therapy (1 if AB received; or 0 otherwise) were derived from time windows in which a specific AB was administered, as entered by physicians in the COSARA database. A detailed list of included AB can be found in (6).

Vasoactive agent use

Daily binary indicators of vasoactive agent (VA) use (1 if VA received; or 0 otherwise) were derived from registered infusion rates of vasoactive agents (including dobutamine, dopamine, epinephrine, milrinone, norepinephrine and vasopressin) in the ICIS database.

Enteral feeding

Daily binary indicators of enteral feeding (EF) were derived from registered doses in the ICIS database.

Corticosteroids

Daily binary indicators of administration of corticosteroids (1 if total day-specific dose >0.5 mg/kg; or 0 otherwise) were derived from estimated/measured weight at admission (cf supra) and corticosteroid doses as entered by nursing staff (in case of oral administration or intravenous (IV) injection) or registered through IV infusion pumps in the ICIS (aggregated per patient per day). For 2 patients who received corticosteroids, weight was missing, such that
dose/kg could not be calculated. Each of these patients had only one recorded dose. Based on
other non-missing demographic characteristics (gender and age), it was assumed that these
doses exceeded 0.5mg/kg (i.e. under the assumption that the weight of these patients did not
exceed the maximum weight at which the respective doses >0.5mg/kg).

Hemodialysis

Timestamps on hemodialysis episodes were missing from the ICIS and COSARA databases.
This information was therefore derived from recorded ultrafiltration rates. Daily binary
indicators of the presence of ultrafiltration rate records (1 if present; 0 otherwise) were
calculated from the ICIS database.

Tracheotomy tube

Daily binary indicators of the presence of a tracheotomy tube (1 if present; 0 otherwise) were
derived from time windows from placement to removal of tracheotomy tube, as entered by
nursing staff in the ICIS database. In case no timestamp for removal of tracheotomy tube was
registered, tracheotomy tube was assumed to be present until ICU death or discharge.

Treatment limitation decisions (TLDs)

Daily TLD codes (code 0-4) were derived from registered do-not-resuscitate (DNR) codes, as
entered by physicians in the ICIS database, and their timestamps. In case a DNR code was
changed on a particular day, only the last registered DNR code by the end of that day was with
held as the day-specific DNR code. The last registered DNR code of a patient was assumed
to hold until time of ICU death or discharge. The following progressive coding scheme was
used (also see (7)):

- Code 0 = full therapy (no therapy restrictions);
- Code 1 = no cardiopulmonary resuscitation, no defibrillation;
- Code 2 = withholding of therapy (therapy restrictions that may include no referral to the ICU, no dialysis, no upgrading of antibiotics, no vasopressors or inotropes, no colloids or cristalloids in case of hypotension, no intubation and mechanical ventilation, no blood transfusions or blood cultures, no metabolic correction, no surgical procedures);
- Code 3 = withdrawal of life-sustaining therapy (only comfort care; may include pain relief and symptom control, discontinuation of vasopressors/inotropes, discontinuation of mechanical ventilation);
- Code 4 = withdrawal of all active and supportive therapy, mechanical ventilation

Due to data sparsity codes 2, 3 and 4 were collapsed into one category.

Other hospital-acquired infections

Daily binary indicators of suspected or confirmed bacterial and fungal infections (1 if suspected or confirmed; 0 otherwise) were derived from infection diagnosis as entered in the COSARA database by treating physicians. More specifically, separate daily indicators were calculated for

- bacterial abdominal infections
- bacterial catheter-related infections
- bacterial respiratory infections
- bacterial urinary tract infections
- all other bacterial infections (including endocarditis, meningitis, encephalitis, neutropenic sepsis, other neurological infections, skin infection)
- fungal infections (including yeast infections and other fungal infections)
Sequential Organ Failure Assessment (SOFA) score

Daily SOFA scores (8) were extracted from the COSARA database. These were calculated as the sum of six SOFA subscores, each of which are scored from 0 to 4 and are calculated in real-time in the ICIS for each 24h interval from 5am of the current calendar day to 5am the next calendar day, based on available lab results imported in the ICIS, physiological parameters and administered drugs and interventions (as detailed in (9)). The six SOFA subscores reflect

- coagulation function
- renal function
- cardiovascular system function
- central nervous system function
- hepatic system function
- respiratory function

Higher scores reflect increasing levels of organ dysfunction. However, this score may in part reflect the subjective appraisal of a patient’s condition by intensive care physicians because when a patient is not suspected to have a particular organ dysfunction no tests are ordered beyond routine test and measurement procedures. Corresponding subscores that therefore may be missing are scored 0.

Standard of care VAP prevention

The following measures to prevent VAP are applied in our ICU: 1) use of short acting sedatives and analgetics and thrice daily assessment of sedation goals (morning, noon and evening rounds) 2) application of early mobilization and twice daily assessment of weaning readiness (morning and noon rounds) 3) use of oral chlorhexidine 4) 30% semi-recumbent positioning. Continuous subglottic aspiration is not systematically used.
Comparison of statistical approaches with respect to emulation of a randomized controlled prevention trial

The (time-dependent) population-attributable fraction (PAF) of ICU mortality due to VAP expresses the percentage of preventable cases in the ICU in the absence of VAP as a function of time since ICU admission. Under certain assumptions, its estimate can be interpreted as the relative mortality reduction that would be found in the ICU in a hypothetical RCT in which eligible patients are randomly assigned to receive either a fully effective bundle of preventive measures or standard of care (see ‘Detailed list of variables and definitions’). Due to randomization, the cumulative incidence in the latter arm of this target prevention trial is expected to correspond to the observed cumulative incidence in an observational study (where all patients receive standard of care). This quantity can directly be estimated from a competing risk analysis (treating ICU discharge as a competing event for ICU death).

The cumulative incidence in the preventive bundle arm, on the other hand, corresponds to the ‘counterfactual’ VAP-free cumulative incidence. This quantity cannot readily be estimated from observational data. However, explicit description of the hypothetical target trial provides

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The sufficient set of assumptions entails consistency, no unmeasured confounding, positivity and no misspecification of the nuisance models (e.g. to estimate IP weights). A key component of consistency is that of ‘well-defined interventions’. In particular, in our study, we aim to compare outcomes under ‘standard-of-care’ and ‘a fully effective bundle of VAP prevention’. The latter intervention may not be sufficiently well-defined because, as of yet, such a bundle is unavailable. Note that this inherent vagueness may hinder an unambiguous interpretation of the PAF estimates in our study, because the definition in itself determines how ‘counterfactual’ interventions may be linked to the data (another key component of consistency) and may guide expert opinion on sufficient adjustment sets that suffice for confounding control. For instance, due to the inherent vagueness of the prevention bundle, we may have adjusted away preventive effects via manipulable confounders that may be effective targets for VAP prevention. For more details on this discussion, see (22,23).
a roadmap for statistical analysis (10,11) and offers a general framework for comparing existing analytical approaches. In particular, estimation of the ‘counterfactual’ VAP-free cumulative incidence poses additional challenges as it necessarily relies on causal assumptions that cannot be verified from the data at hand. Although proposed estimation approaches for ‘emulating’ this hypothetical trial arm (or counterfactual scenario) differ in the extent to which such causal assumptions are made explicit, each approach involves some form of up-weighting VAP-free events from observational data.

The (often implicit) rationale behind weighting events is as follows. As patients acquire VAP, they are no longer compatible with receiving a fully effective preventive bundle in the target prevention trial (or with the counterfactual scenario) we aim to emulate. As their subsequent events are therefore discarded from further statistical analysis, they should transfer their weight to patients who have remained VAP-free, thereby accounting for the selection of the latter group of ‘compatible’ patients. By receiving additional weight in the analysis, VAP-free patients substitute for VAP-infected patients being excluded from the original population for which we aim to estimate the hypothetical CI had no one acquired VAP. As illustrated in more technical detail in (12), it turns out that all proposed methods under comparison apportion weights to VAP-free events that are inversely proportional to the overall amount of selection, so as to ‘reconstruct’ the original patient population. However, their respective weighting schemes differ largely in terms of how well they respect the temporal ordering of events and how well they take into account the (possibly) selective nature of ‘compatible’ patients over time. Consequently, proposed approaches are successful at tackling different sources of bias to varying degrees. Successful emulation of the cumulative incidence in this hypothetical trial arm critically hinges on the following guiding principles.

First, the total amount of transferred weight at any given time wave should be inversely proportional to the likelihood of being VAP-free (i.e. degree of selection of VAP-free patients)
until (at least) that time wave. Deviations from this principle produce immortal time bias, because they fail to respect the temporal ordering of events. Such bias typically occurs when the analysis is restricted to never infected patients (i.e. patients who remained without VAP until the end of study follow-up) as in approach 1 (though not approaches 2—4). Indeed, such analysis implicitly weighs VAP-free events at each time wave according to the likelihood of remaining VAP-free until the end of study follow-up, which is only known at the ultimate VAP onset in the sample population.

Second, at any given time wave, weight transferred from newly VAP-infected patients should only be distributed among VAP-free patients that are still hospitalized at the ICU at that time wave. Deviations from this principle likewise fail to fully respect the timing of events. They often yield a more subtle form of time-dependent bias, which has only been documented recently (12,13). One widely advocated multi state modelling approach for estimating the PAF (14) (approach 2, along with approach 1, though not approaches 3—4) violates this second principle because it (implicitly) distributes the (correct) total amount of transferred weight at a given time wave evenly among all patients who did not acquire VAP by that time, including patients that already experienced a VAP-free event (i.e. patients that have died or been discharged by that time without VAP). This implies that a deceased VAP-free patient is not only weighed in the analysis at her time of death, to compensate for the depletion of VAP-infected patients by that time wave, but gets re-weighted after her death to compensate for further depletion of VAP-infected patients in the future.

Third, at any given time wave, VAP-infected patients should transfer weight to VAP-free patients with the same patient profile in terms of admission characteristics and evolution of disease severity up to that time wave. This is required to ensure comparability of patients in each of the arms of our target prevention trial, or in other words, to emulate randomized assignment of eligible patients to the preventive bundle arm. For instance, susceptible patients...
who acquire VAP generally tend to be more severely ill than those who do not acquire VAP. Accordingly, the weight received by a VAP-free ICU patient who is severely ill at a particular time wave should be proportional to the degree of depletion of comparable VAP-infected patients with the same severity of illness up to that time. Deviations from this principle fail to account for the selective nature of VAP-free ICU patient profiles over time and may result in estimates of the counterfactual VAP-free cumulative incidence that are systematically biased downward. Approach 3 (15–18), which has rarely been applied for estimation of time-dependent PAFs, violates this third principle (along with approaches 1 and 2). This is because, in their current form, multi state modelling approaches only allow to accommodate the selective nature of VAP-free patients insofar as this is captured by admission characteristics, but not to the extent that this is driven by time-dependent confounding factors that evolve since admission. This is a less well understood but important shortcoming because, for instance, prior to acquiring VAP, patients may deteriorate further and may therefore be at increased risk of VAP, even if, at ICU admission, their prognosis is similar to that of patients who eventually do not acquire VAP. Consequently, adjustment for time-dependent confounding (or equivalently, adjustment for the ensuing differential selection of VAP-free patients / informative censoring of VAP-infected patients) should not only be made at baseline, e.g. for severity of illness indicators recorded at time of admission, but also for the evolution of such indicators over time. Generalized methods, abbreviated g-methods (19,20), comprise a class of methods, some of which, in particular inverse probability (IP) weighting (approach 4), can be characterized as a natural generalization of approach 3 that enables additionally respecting this third principle by tackling issues related to the time-dependent nature of confounding and selection of VAP-free patients (12). In contrast to the first two principles, one’s ability to correctly adhere to this third principle necessarily relies on subject matter knowledge of the selective nature of VAP-free...
patients, especially in relation with the patient outcome under study, i.e. ICU mortality, and the availability of data on relevant characteristics that sufficiently capture this selective nature.
Cox proportional hazards model for the daily probability of acquiring VAP

Causal assumptions encoded in a causal diagram

Figure E1 (A) displays a simplified causal diagram that depicts the time-dependent setting (restricted to VAP acquisition at time waves $t-1$ and $t$) along with the causal assumptions with respect to measured baseline and time-varying covariates. Specifically, the red nodes capture a set of covariates, as listed below (heading ‘Adjustment set and simplifying model and causal assumptions’), that were deemed sufficient to adjust for confounding (i.e. assumption of no unmeasured confounding). The temporal ordering of the variables is explicitly displayed in the causal diagram by representing earlier measurements and events to the left and later measurements and events to the right. Pink pathways indicate biasing pathways of the effect of time-dependent VAP on ICU mortality.

Rationale behind inverse probability weighting

Inverse probability (IP) weighting aims to resolve this confounding bias by constructing a pseudo-population that consists of the original study population under the hypothetical scenario that all patients had remained without VAP until the end of hospitalization (i.e. until ICU death or discharge). It does so in a way that aims to render VAP acquisition at time $t$ among hospitalized patients that have remained without VAP up until time $t-1$ independent of the measured covariate history up until time $t-1$ or, in other words, in a way that aims to restore covariate balance (up until time $t-1$) between incident VAP cases and VAP-free patients at time $t$ among hospitalized patients that have remained without VAP up until time $t-1$. In graphical terms, IP weighting removes all incoming edges into time-varying VAP such that biasing pathways are resolved, as displayed in the modified causal diagram in Figure E1 (B).
Adjustment set and simplifying model and causal assumptions

In order to calculate IP weights, a time-dependent Cox proportional hazards model was fitted for time-to-VAP (or, equivalently, the daily probability of acquiring VAP) in function of the available covariate history, including admission characteristics and time-dependent factors, as detailed below.

At each time wave, the history of daily measures of interventions and treatments was summarized in terms of their presence or absence on the day before possible VAP acquisition and by the total number of previous days exposed to each of these interventions and treatments. It was assumed that this summary coding of the covariate history was sufficient for confounding adjustment. To acknowledge that SOFA scores and antibiotic treatment the day before possible VAP diagnosis may be surrogate markers for an incubating infection, and hence potentially be affected by VAP, in accordance with (3), we adjusted for SOFA score and antibiotic treatment (and total number of treated days up to) two days before each considered time wave of possible occurrence of VAP.

The model included a flexible functional form of all continuous covariates (a restricted cubic spline with 3 knots (***)) whenever feasible, or 2 knots (**) otherwise) and additional time-transformed functions of covariates (the product of log(time-1) and the covariate) for which a smoothed function of the scaled Schoenfeld residuals over time indicated clear violations of the proportional hazards assumption (indicated with a single asterisk (*) in the list below).

Baseline and admission characteristics

- Gender
- Age at ICU admission (***)
- Admission category (medical, emergency surgery or scheduled surgery)
- Admission year (2013, 2014, 2015, 2016, 2017)
• APACHE II score (***)

• Updated Charlson comorbidity index (**) 

• Antibiotic therapy at baseline (i.e. during the first two days at the ICU)

• Total SOFA score at baseline (i.e. at day 1 = the second calendar day at the ICU) (***)

Time-varying covariates including daily updated disease severity and interventions

• Daily total SOFA score two days before possible occurrence of VAP (***)

• Daily evolution in total SOFA score (i.e. difference in total SOFA score two vs three days before possible occurrence of VAP) (***) 

• Daily updated treatment limitation decisions (TLDs) (code 0, 1, 2 or higher) 

• Daily indicator of antibiotic therapy two days before possible occurrence of VAP

• Daily indicator of
  
  o mechanical ventilation (*)
  
  o administration of vasoactive agents 
  
  o enteral feeding 
  
  o administration of corticosteroids (>0.5 ml/kg)
  
  o hemodialysis 
  
  o presence of a tracheotomy tube 
  
  o suspected or confirmed bacterial abdominal infection 
  
  o suspected or confirmed bacterial catheter-related infection 
  
  o suspected or confirmed bacterial respiratory infection (*)
  
  o suspected or confirmed bacterial urinary tract infection
  
  o suspected or confirmed other bacterial infections
  
  o suspected or confirmed fungal infection 

1 day before possible occurrence of VAP
• Daily updated cumulative number of days exposed to antibiotic therapy up to two days before possible occurrence of VAP

• Daily updated cumulative number of days exposed to
  o mechanical ventilation
  o administration of vasoactive agents
  o enteral feeding
  o administration of corticosteroids (>0.5 ml/kg)
  o hemodialysis
  o presence of a tracheotomy tube
  o suspected or confirmed bacterial abdominal infection
  o suspected or confirmed bacterial catheter-related infection
  o suspected or confirmed bacterial respiratory infection
  o suspected or confirmed bacterial urinary tract infection
  o suspected or confirmed other bacterial infections
  o suspected or confirmed fungal infection

  up to 1 day before possible occurrence of VAP

Figure E2 and Figure E3 display the results of the final time-dependent Cox model. Figure E4 displays the distribution of IP weights assigned to VAP-free patients as a function of day since ICU admission.
Assessment of covariate balance

At every time wave, time-dependent IP weights ideally restore covariate balance across future exposures, conditional on the past exposure history. Because we aim to compare the counterfactual VAP-free cumulative incidence curve with the observed cumulative incidence curve (rather than another counterfactual curve), we focused on covariate balance between patients that were at risk of VAP at the beginning of each day (i.e. had remained hospitalized and without VAP (at least) up until the previous day) and a subgroup of those patients who died or were discharged without VAP or remained hospitalized without VAP until the end of that day (i.e. those patients whose weighted deaths that day contributed to the ‘counterfactual’ cumulative incidence curve).

Figure E5 displays covariate balance at days 2, 4, 8, 12 and 24, before and after IP weighting. These plots allow to assess extent to which IP weighting succeeded to accommodate covariate imbalances (summarized by standardized mean differences for continuous covariates or raw mean differences for binary covariates) due to selection of the latter from the former group of hospitalized patients on each day.

In theory, covariate balance should be checked at every single time window at which we considered incident VAP cases (i.e. daily, up to day 60 from ICU admission). However, this becomes quite cumbersome with an increasing number of time waves. We have therefore chosen to restrict assessment of covariate balance to a limited number of time waves.
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Figure legends

Figure E1.
Simplified causal diagram (A) (also available as an interactive DAGitty diagram from this webpage: http://dagitty.net/mdJm-Ys) and modified causal diagram after IP weighting (B) (also available from this webpage: http://dagitty.net/dags.html?id=ebuxWi).

Figure E2.
Point and 95% confidence interval estimates of adjusted hazard ratios of all categorical variables in the final time-dependent Cox model for daily risk of acquiring VAP.

Figure E3.
Point and 95% confidence interval estimates of adjusted hazard ratios of all continuous variables in the final time-dependent Cox model for daily risk of acquiring VAP.

Figure E4.
Distribution of inverse probability (IP) weights assigned to VAP-free patients as a function of day since ICU admission.

Figure E5.
Covariate balance before and after IP weighting at days 2, 4, 8, 12 and 24 between patients at risk of VAP at the beginning of each day (i.e. had remained hospitalized and without VAP (at least) up until the previous day) and a subgroup of those patients who died or were discharged without VAP or remained hospitalized without VAP until the end of that day.
Figure E6.

Comparison of results for estimating the time-dependent population-attributable fraction (PAF) of intensive care unit (ICU) mortality due to ventilator-associated pneumonia (VAP) based on an unadjusted competing risk (CR) analysis (approach 3 in the main text; A), a CR analysis that adjusts for gender, age and SOFA score at ICU admission (B), a CR analysis that adjusts for an extended set of admission characteristics including admission year, admission category, updated Charlson comorbidity index, APACHE II score and antibiotic treatment at ICU admission (C), and a CR analysis that additionally adjusts for time-dependent confounding (approach 4 in the main text; D). Upper panels: observed cumulative incidence of ICU mortality (black curves) and estimated counterfactual VAP-free cumulative incidence of ICU mortality (grey curves). Lower panels: estimated PAF of ICU death due to VAP (solid lines) and 95% pointwise confidence intervals (shaded areas).
Figure E1.

(A)
Figure E2.

| variable                          | Estimate (CI95)            | variable                          | Estimate (CI95) |
|-----------------------------------|---------------------------|-----------------------------------|-----------------|
| gender                            |                           | respiratory infection             |                 |
| Male                              | 1.00 (1.00–1.00)          | 1d lag                            |                 |
| Female                            | 1.46 (1.07–1.97)          | respiratory infection             |                 |
|                                   |                           | for each log(day) shift from day 2|                 |
| admission category                |                           | urinary tract infection           |                 |
| Medicine                          | 1.00 (1.00–1.00)          | 1d lag                            | 0.04 (0.01–0.13)|
| Emergency surgery                 | 1.58 (1.09–2.16)          | other bacterial infection         | 2.46 (1.36–4.65)|
| Scheduled surgery                 | 1.70 (1.06–2.74)          | 1d lag                            | 0.23 (0.02–3.22)|
| admission year                    |                           | ndays on antibiotic treatment    |                 |
| 2013                              | 1.00 (1.00–1.00)          | 1d lag                            |                 |
| 2014                              | 0.75 (0.49–1.59)          | ndays on enteral feeding          | 0.99 (0.92–1.06)|
| 2015                              | 0.89 (0.25–3.62)          | ndays on corticosteroids          |                 |
| 2016                              | 0.86 (0.59–1.23)          | ndays on mechanical ventilation   |                 |
| 2017                              | 0.28 (0.14–0.55)          | ndays on vasoactive agents        |                 |
| antibiotic treatment at baseline  |                           | ndays on hemodialysis            |                 |
| antibiotic treatment              | 0.66 (0.62–1.18)          | 1d lag                            |                 |
| 2d lag                            |                           | ndays on tracheostomy tube        |                 |
| enteral feeding                   | 0.57 (0.39–0.84)          | 1d lag                            |                 |
| 1d lag                            |                           | ndays fungal infection            |                 |
| corticosteroids treatment         | 1.53 (1.03–2.29)          | 1d lag                            | 0.98 (0.92–1.04)|
| 1d lag                            |                           | ndays abdominal infection         |                 |
| mechanical ventilation            | 0.66 (0.44–0.98)          | 1d lag                            |                 |
| 1d lag                            |                           | ndays respiratory infection       |                 |
| mechanical ventilation for each  | 10.08 (3.01–33.75)        | 1d lag                            | 1.12 (1.03–1.22)|
| log(day) shift from day 2         |                           | ndays urinary tract infection     |                 |
| vasoactive agents                 |                           | 1d lag                            |                 |
| 1d lag                            | 0.52 (0.28–0.96)          | ndays other bacterial infection   |                 |
| hemodialysis                      |                           | 1d lag                            | 0.98 (0.91–1.05)|
| 1d lag                            | 1.20 (0.82–1.75)          | ndays abdominal infection         |                 |
| tracheostomy tube                 |                           | 1d lag                            | 1.02 (0.92–1.13)|
| 1d lag                            | 0.63 (0.31–1.30)          | ndays catheter–related infection  |                 |
| DNR code (1d lag)                 |                           | 1d lag                            | 1.25 (0.97–1.60)|
| Code 0                            | 1.00 (1.00–1.00)          | ndays respiratory infection       |                 |
| Code 1                            | 0.67 (0.21–2.13)          | 1d lag                            | 1.01 (0.94–1.09)|
| Code >=2                          | 0.44 (0.20–0.97)          | ndays urinary tract infection     |                 |
| fungal infection                  | 1.41 (0.77–2.57)          | 1d lag                            | 0.88 (0.63–1.21)|
| 1d lag                            |                           | ndays other bacterial infection   |                 |
| abdominal infection               | 0.18 (0.07–0.46)          | 1d lag                            | 1.04 (0.95–1.13)|
| 1d lag                            |                           |                                   |                 |
| catheter–related infection        | 0.47 (0.08–2.88)          |                                   |                 |
| 1d lag                            |                           |                                   |                 |
Figure E3.
Figure E4.
Figure E5.

covariate balance on day 2

Gender: Male
Age
Adm category: medicine
Adm category: emergency surgery
Adm category: scheduled surgery
Adm year: 2017
Adm year: 2016
Adm year: 2015
Adm year: 2014
APACHE II score
Charlson comorbidity index
AB therapy (baseline)
total SOFA score (baseline)
total SOFA score (2d lag)
SOFA difference score (2d lag)

Standardized Mean Differences
Sample  Weighted  Unweighted
-0.001 -0.000 0.001 0.002

covariate balance on day 6

Gender: Male
Age
Adm category: medicine
Adm category: emergency surgery
Adm category: scheduled surgery
Adm year: 2017
Adm year: 2016
Adm year: 2015
Adm year: 2014
APACHE II score
Charlson comorbidity index
AB therapy (baseline)
total SOFA score (baseline)
total SOFA score (24 lag)
SOFA difference score (24 lag)

Standardized Mean Differences
Sample  Weighted  Unweighted
-0.005 0.000 0.0025 0.004

covariate balance on day 12

Gender: Male
Age
Adm category: medicine
Adm category: emergency surgery
Adm category: scheduled surgery
Adm year: 2017
Adm year: 2016
Adm year: 2015
Adm year: 2014
APACHE II score
Charlson comorbidity index
AB therapy (baseline)
total SOFA score (baseline)
total SOFA score (2d lag)
SOFA difference score (2d lag)

Standardized Mean Differences
Sample  Weighted  Unweighted
-0.015 -0.010 -0.005 0.000 0.005

covariate balance on day 24

Gender: Male
Age
Adm category: medicine
Adm category: emergency surgery
Adm category: scheduled surgery
Adm year: 2017
Adm year: 2016
Adm year: 2015
Adm year: 2014
APACHE II score
Charlson comorbidity index
AB therapy (baseline)
total SOFA score (baseline)
total SOFA score (24 lag)
SOFA difference score (24 lag)

Standardized Mean Differences
Sample  Weighted  Unweighted
-0.002 0.000 0.002 0.004

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| Covariate Balance | Day 2   |
|------------------|--------|
| Weighted Mean    | Unweighted Mean |
| Other bacterial infx (1d lag) | -0.002 | -0.001 |
| Urinary tract infx (1d lag) | -0.003 |
| Respiratory infx (1d lag) | -0.005 |
| Catheter-related infx (1d lag) | -0.006 |
| Abdominal infx (1d lag) | 0.000 |
| Fungal infx (1d lag) | 0.000 |
| Other bacterial infx (1d lag) | 0.000 |
| Urinary tract infx (1d lag) | 0.000 |
| Respiratory infx (1d lag) | 0.000 |
| Catheter-related infx (1d lag) | 0.000 |
| Abdominal infx (1d lag) | 0.000 |
| Fungal infx (1d lag) | 0.000 |

| Covariate Balance | Day 6   |
|------------------|--------|
| Weighted Mean    | Unweighted Mean |
| Other bacterial infx (1d lag) | -0.004 |
| Urinary tract infx (1d lag) | -0.005 |
| Respiratory infx (1d lag) | -0.006 |
| Catheter-related infx (1d lag) | -0.007 |
| Abdominal infx (1d lag) | 0.000 |
| Fungal infx (1d lag) | 0.000 |
| Other bacterial infx (1d lag) | 0.000 |
| Urinary tract infx (1d lag) | 0.000 |
| Respiratory infx (1d lag) | 0.000 |
| Catheter-related infx (1d lag) | 0.000 |
| Abdominal infx (1d lag) | 0.000 |
| Fungal infx (1d lag) | 0.000 |

| Covariate Balance | Day 12  |
|------------------|--------|
| Weighted Mean    | Unweighted Mean |
| Other bacterial infx (1d lag) | -0.008 |
| Urinary tract infx (1d lag) | -0.009 |
| Respiratory infx (1d lag) | -0.010 |
| Catheter-related infx (1d lag) | -0.011 |
| Abdominal infx (1d lag) | 0.000 |
| Fungal infx (1d lag) | 0.000 |
| Other bacterial infx (1d lag) | 0.000 |
| Urinary tract infx (1d lag) | 0.000 |
| Respiratory infx (1d lag) | 0.000 |
| Catheter-related infx (1d lag) | 0.000 |
| Abdominal infx (1d lag) | 0.000 |
| Fungal infx (1d lag) | 0.000 |
Figure E6.