ORIGINAL ARTICLE

Descriptive Epidemiology and Attributable Morbidity of Ventilator-Associated Events

Michael Klompas, MD, MPH;[1,2] Ken Kleinman, ScD;[1] Michael V. Murphy, BA[1]
for the CDC Prevention Epicenters Program

OBJECTIVE. The Centers for Disease Control and Prevention implemented new surveillance definitions for ventilator-associated events (VAEs) in January 2013. We describe the epidemiology, attributable morbidity, and attributable mortality of VAEs.

DESIGN. Retrospective cohort study.

SETTING. Academic tertiary care center.

PATIENTS. All patients initiated on mechanical ventilation between January 1, 2006, and December 31, 2011.

METHODS. We calculated and compared VAE hazard ratios, antibiotic exposures, microbiology, attributable morbidity, and attributable mortality for all VAE tiers.

RESULTS. Among 20,356 episodes of mechanical ventilation, there were 1,141 (5.6%) ventilator-associated condition (VAC) events, 431 (2.1%) infection-related ventilator-associated complications (IVACs), 139 (0.7%) possible pneumonias, and 127 (0.6%) probable pneumonias. VAC hazard rates were highest in medical, surgical, and thoracic units and lowest in cardiac and neuroscience units. The median number of days to VAC onset was 6 (interquartile range, 4–11). The proportion of IVACs to VACs ranged from 29% in medical units to 42% in surgical units. Patients with probable pneumonia were more likely to be prescribed nafcillin, ceftazidime, and fluroquinolones compared with patients with possible pneumonia or IVAC-alone. The most frequently isolated organisms were *Staphylococcus aureus* (29%), *Pseudomonas aeruginosa* (14%), and *Enterobacter* species (7.9%). Compared with matched controls, VAEs were associated with more days to extubation (relative rate, 3.12 [95% confidence interval (CI), 2.96–3.29]), more days to hospital discharge (relative rate, 1.46 [95% CI, 1.37–1.55]), and higher hospital mortality risk (odds ratio, 1.98 [95% CI, 1.60–2.44]).

CONCLUSIONS. VAEs are common and morbid. Prevention strategies targeting VAEs are needed.

Infect Control Hosp Epidemiol 2014;35(5):502-510

The Centers for Disease Control and Prevention (CDC) replaced their long-standing ventilator-associated pneumonia (VAP) definitions with ventilator-associated event (VAE) definitions on January 1, 2013.[1] The CDC shifted to VAE definitions in order to enhance the efficiency, objectivity, and reproducibility of surveillance.[2] VAE definitions intentionally broaden the focus of surveillance from pneumonia alone to include additional physiologically significant complications of mechanical ventilation.[3] The new definitions are based on quantitative clinical criteria and are amenable to automated electronic detection. VAE surveillance is currently optional in most states, but VAEs were designed to support the possibility of benchmarking and pay-for-performance measurements. Despite the potential importance of VAE surveillance to both hospital and national quality improvement programs, very little is known about VAE epidemiology.

The VAE paradigm includes a nested hierarchy of 3 types of events (Figure 1). The first tier flags respiratory complications in general, defined solely by sustained increases in ventilator settings after 2 or more days of stable or decreasing ventilator settings. These events are termed ventilator-associated conditions (VACs). This tier deliberately flags all complications of mechanical ventilation, including both infectious and noninfectious complications as well as pulmonary and nonpulmonary events sufficiently severe to require sustained increases in ventilator support.

The second VAE tier, called infection-related ventilator-associated complications (IVACs), flags the subset of VACs that may be due to infection, as suggested by inflammatory signs and the initiation of 4 or more days of new antibiotics within 2 days before or after the rise in ventilator settings. As with VAC, this tier is also intentionally broad and designed

Affiliations: 1. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; 2. Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Received September 11, 2013; accepted December 22, 2013; electronically published March 14, 2014.

 0899-823X/2014/3505-0006$15.00. DOI: 10.1086/675834

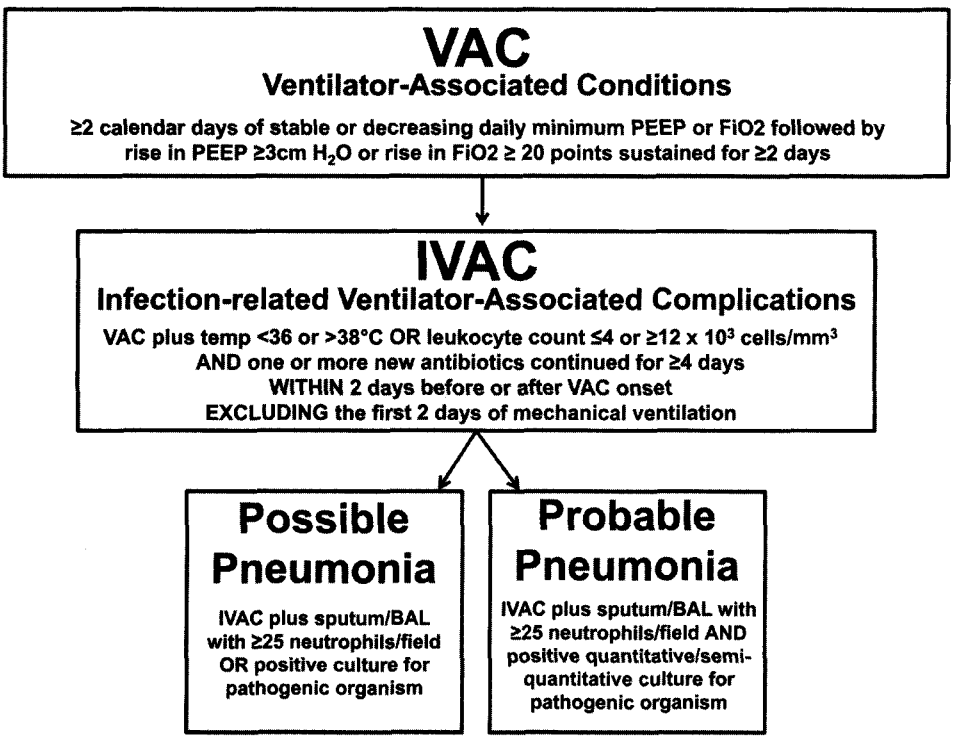

FIGURE 1. Centers for Disease Control and Prevention's ventilator-associated event definitions. Reprinted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.[26] BAL, bronchoalveolar lavage; PEEP, positive end expiratory pressure.

to capture both pulmonary and nonpulmonary infectious complications severe enough to compromise respiratory function.

The third tier flags the subset of IVACs that may indeed be pneumonias. It is divided into 2 categories. Patients with IVAC and more than 25 neutrophils per low-power field on Gram stain of respiratory secretions or positive respiratory cultures for pathogenic organisms have possible pneumonia. Those with IVAC and 25 or more neutrophils per low-power field on Gram stain and positive quantitative or semiquantitative cultures for pathogenic organisms have probable pneumonia. Suggestive histology, diagnostic tests for *Legionella*, and laboratory evidence of respiratory viruses can also establish a case of probable pneumonia.

The new definitions are based on exploratory work demonstrating that screening patients' daily ventilator settings for trajectory changes is feasible and efficient and strongly predicts adverse outcomes.[4-8] Qualitative analyses suggest that most VAEs are triggered by pneumonia, pulmonary edema, acute respiratory distress syndrome, and/or atelectasis.[5,9] Multiple studies have shown strong associations between VACs and prolonged mechanical ventilation, length of stay, and mortality.[5,7-10] Very little is known, however, about the epidemiology of VAEs using the CDC's complete new definition set, including IVAC, possible pneumonia, and probable pneumonia. We therefore undertook a comprehensive evaluation of VAE epidemiology, focusing specifically on relative rates, timing, microbiology, antibiotic prescribing, attributable morbidity, and attributable mortality for each tier of the VAE definition set.

METHODS

We retrospectively applied the CDC's VAE definitions to all adult patients initiated on mechanical ventilation at Brigham and Women's Hospital between January 1, 2006, and December 31, 2011. Brigham and Women's Hospital is an academic, urban, tertiary care center located in Boston. We extracted data on ventilator exposures and daily ventilator settings from the hospital's respiratory therapy database; demographics, laboratory values, and medication orders from the hospital's clinical data repository; and endotracheal aspirate and bronchoalveolar lavage Gram stains and culture results from the hospital's microbiology database. We merged these data using medical record numbers and dates of mechanical ventilation. We assessed patients' comorbidities and calculated a comorbidity index, using the *International Classification of Disease, Ninth Revision, Clinical Modification* codes and diagnosis-related group codes, using the methods of Elixhauser and Charlson.[11,12]

We applied the CDC's VAE criteria, using SAS (ver. 9.3; SAS Institute).[1] VAC was defined as 2 or more days of stable

https://doi.org/10.1086/675834 Published online by Cambridge University Press

TABLE 1. Characteristics of Patients with and without Ventilator-Associated Events (VAEs)

	No VAE (N = 19,300)	VAC-plus (N = 1,056)	IVAC-plus (N = 420)	Possible pneumonia (N = 139)	Probable pneumonia (N = 126)
Age, mean ± SD, years	62.3 ± 16.0	58.0 ± 16.6	56.3 ± 17.3	58.0 ± 16.7	53.6 ± 17.2
Sex, male	11,534 (60)	650 (62)	270 (64)	90 (65)	89 (71)
Race/ethnicity					
White	15,555 (81)	836 (79)	335 (80)	112 (81)	102 (81)
Black	1,259 (6.5)	64 (6.1)	26 (6.2)	9 (6.5)	9 (7.1)
Hispanic	611 (3.2)	31 (2.9)	8 (1.9)	3 (2.2)	1 (0.8)
Asian	365 (1.9)	27 (2.6)	11 (2.6)	4 (2.9)	2 (1.6)
Other (including unknown)	1,510 (7.8)	98 (9.3)	40 (9.5)	11 (7.9)	12 (9.5)
Unit type					
Medical	3,053 (16)	321 (30)	98 (23)	33 (24)	18 (14)
Cardiac medicine	1,165 (6.1)	89 (8.4)	35 (8.3)	13 (9.4)	9 (7.1)
General surgery	3,732 (19)	321 (30)	144 (34)	47 (34)	50 (40)
Cardiac surgery	7,464 (39)	98 (9.3)	44 (10.5)	14 (10)	16 (13)
Thoracic surgery	1,607 (8.4)	120 (11.4)	55 (13)	15 (11)	16 (13)
Neuroscience	2,151 (11)	106 (10)	44 (10)	17 (12)	17 (13)
Comorbidities					
Myocardial infarction	4,533 (23)	199 (19)	64 (15)	18 (13)	23 (18)
Congestive heart failure	5,949 (31)	284 (27)	96 (23)	34 (25)	26 (21)
Peripheral vascular disease	2,588 (13)	105 (9.9)	35 (8.3)	5 (3.6)	14 (11)
Cerebrovascular disease	3,178 (16)	164 (16)	55 (13)	19 (14)	16 (13)
Chronic lung disease	3,598 (19)	253 (24)	99 (24)	28 (20)	27 (21)
Diabetes	4,102 (21)	204 (19)	71 (17)	23 (17)	22 (17)
Renal failure	2,696 (14)	159 (15)	49 (12)	13 (9.4)	19 (15)
Liver disease	458 (2.4)	43 (4.1)	10 (2.4)	3 (2.2)	3 (2.4)
Cancer	4,545 (24)	323 (31)	108 (26)	36 (26)	24 (19)
Rheumatologic disease	486 (2.5)	30 (2.8)	9 (2.1)	2 (1.4)	3 (2.4)
Charlson score, mean ± SD	2.9 ± 2.6	3.5 ± 2.7	3.2 ± 2.7	3.2 ± 2.7	3.0 ± 2.9
Pressors at intubation	12,280 (64)	731 (69)	278 (66)	89 (64)	85 (67)
Days to event onset, median (IQR)	...	6.0 (4.0–11)	6.0 (4.0–10)	6.0 (4.0–9.0)	6.0 (4.0–11)
Outcomes					
Ventilator-days					
Median (IQR)	2 (1–4)	16 (10–26)	17.5 (11.5–28.5)	18 (12–27)	17 (12–32)
Mean ± SD	3.7 ± 5.1	20.3 ± 17.3	23.4 ± 20.7	21.6 ± 19.0	25.3 ± 23.2
Hospital-days					
Median (IQR)	12 (8–20)	28 (18–43)	30 (19–47)	28 (18–42)	32.5 (20–48)
Mean ± SD	17.1 ± 17.7	35.2 ± 29.5	38.4 ± 31.0	34.4 ± 27.3	39.6 ± 31.5
Hospital death	2,799 (15)	409 (39)	131 (31)	48 (35)	31 (25)
Survivors readmitted within 30 days	2,701 (16)	146 (23)	67 (23)	20 (22)	18 (19)

NOTE. Data are no. (%), unless otherwise indicated. IQR, interquartile range; IVAC, infection-related ventilator-associated complication; SD, standard deviation; VAC, ventilator-associated condition. VAC-plus includes IVACs, possible pneumonias, and probable pneumonias. IVAC-plus includes possible and probable pneumonias.

or decreasing daily minimum positive end expiratory pressure (PEEP) or fraction of inspired oxygen (FiO_2) followed by 2 or more days of increased daily minimum PEEPs of 3 cm H_2O or more or daily minimum FiO_2's of 20 or more points relative to both baseline days of stable or decreasing PEEPs and FiO_2's. We defined the first day of increased ventilator settings as the day of VAE onset. IVAC was defined as a patient with a VAC and 4 or more days of 1 or more new antibiotics and any one of the following within 2 days before or after the day of VAC onset, excluding the first 2 days of mechanical ventilation: white blood cell count of 4,000 cells/mm^3 or fewer or 12,000 cells/mm^3 or more, temperature less than 96.8°F or greater than 100.4°F. Patients that met IVAC criteria were evaluated for possible and probable pneumonias. Possible pneumonia required patients to have a positive culture (excluding *Candida* sp., *Enterococcus* sp., and coagulase-negative *Staphylococcus*) or the semiquantitative equivalent of 25 or more neutrophils and 10 or fewer epithelial cells per low-power field on Gram stain of either an endotracheal aspirate or bronchoalveolar lavage specimen taken within 2 days before or after VAC onset, excluding the first 2 days of mechanical ventilation. Probable pneumonia required both a positive semiquantitative (moderate or more) or quantitative culture (more than 10^4 colony-forming units [CFUs]/mL for

TABLE 2. Ventilator-Associated Event Rates by Intensive Care Unit Type

			VAC-plus		IVAC-plus		Possible pneumonia		Probable pneumonia		
Unit type	Episodes	Ventilator-days	Per 100 episodes	Per 1,000 ventilator-days	Per 100 episodes	Per 1,000 ventilator-days	Per 100 episodes	Per 1,000 ventilator-days	Per 100 episodes	Per 1,000 ventilator-days	Proportion of IVACs : VACs
Medical	3,374	21,904	10.2	15.7	3.0	4.6	1.0	1.5	0.5	0.8	0.31
Cardiac medicine	1,254	7,618	7.3	12.1	2.8	4.6	1.0	1.7	0.7	1.2	0.39
General surgery	4,053	21,894	8.7	16.0	3.7	6.8	1.2	2.2	1.3	2.3	0.45
Cardiac surgery	7,562	17,969	1.4	5.8	0.6	2.5	0.2	0.8	0.2	0.9	0.45
Thoracic surgery	1,727	10,817	8.1	12.9	3.3	5.3	0.9	1.4	0.9	1.5	0.46
Neuroscience	2,257	11,288	4.9	9.8	2.0	4.1	0.8	1.5	0.8	1.5	0.42

NOTE. IVAC, infection-related ventilator-associated complication; VAC, ventilator-associated condition. VAC-plus includes IVACs, possible pneumonias, and probable pneumonias. IVAC-plus includes possible and probable pneumonias.

bronchoalvolar lavage and more than 10^5 CFUs/mL for endotracheal aspirates) and 25 or more neutrophils and 10 or fewer epithelial cells per low-power field within 2 days before or after VAC onset, excluding the first 2 days of mechanical ventilation. The possible and probable pneumonia definitions are mutually exclusive. Patients were eligible for more than 1 event per episode of ventilation as long as these occurred more than 14 days apart.

Because the VAE definitions are nested (IVAC is a subset of VAC, and the pneumonias are subsets of IVAC), we defined VAC-plus as all patients with VAC, including those who also fulfilled criteria for IVAC, possible pneumonia, or probable pneumonia. We defined IVAC-plus as all patients who met IVAC criteria, including those with possible or probable pneumonia. Similarly, we defined VAC-alone as patients meeting VAC criteria but not IVAC or possible or probable pneumonia, and we defined IVAC-alone as patients meeting IVAC criteria but not possible or probable pneumonia.

We calculated event rates for VAC-plus, IVAC-plus, possible pneumonia, and probable pneumonia as both the number of events per 100 episodes of mechanical ventilation and the number of events per 1,000 ventilator-days, stratifying the results by intensive care unit (ICU) type. We plotted time to onset for each event relative to the first day of mechanical ventilation as well as the cumulative incidence of each event. We compared the probability of VAC and time to VAC using proportional hazard ratios. We compared the distribution of different antibiotics given to patients with IVAC-alone, possible pneumonia, and probable pneumonia, using Fisher exact tests. We limited this analysis to the antibiotics that fulfilled IVAC criteria, namely those initiated within the 2 days before or after VAC onset, excluding the first 2 days of mechanical ventilation. We compared the distribution of different organisms associated with possible pneumonia and probable pneumonia, using Fisher exact tests.

We assessed the impact of each VAE tier on duration of mechanical ventilation, hospital length of stay, and hospital mortality. Patients with VAEs were randomly matched to up to 5 control patients on the basis of ICU type and time to VAE onset. Controls were randomly selected from among patients ventilated for at least the number of days as matched cases' days to VAE onset plus 1 day. The additional day is because the VAE definitions require at least 2 days of increased ventilator settings. We calculated the duration of mechanical ventilation and hospital length of stay from day of VAE onset to extubation or discharge and, for controls, the time from the matched case's day of VAE onset until the control patient's extubation or hospital discharge. We then modeled the post-VAE duration of mechanical ventilation and hospital length of stay using negative binomial regression and modeled hospital mortality using logistic regression with generalized linear mixed effects to account for matching.[13,14] We compared each VAE tier to patients without any VAEs as well as to the other tiers within the framework. All comparisons were drawn from a single model in which each tier was estimated separately. We fit crude, unadjusted models as well as multivariate models adjusted for age, sex, unit type, Charlson score, use of vasopressors on the day of intubation, platelet count, total bilirubin, albumin, creatinine, and alanine aminotransferase level. We used multiple imputation to account for missing covariates in the multivariate models.[15] The study was reviewed and approved by the institutional review board of Brigham and Women's Hospital.

RESULTS

There were 20,356 episodes of mechanical ventilation and 91,830 ventilator-days. We flagged 1,141 VAC-plus events (5.6 per 100 episodes of mechanical ventilation, 12.4 per 1,000 ventilator-days), 431 IVAC-plus events (2.4 per 100 episodes of mechanical ventilation, 4.7 per 1,000 ventilator-days), 139 possible pneumonias (0.7 per 100 episodes of mechanical ventilation, 1.5 per 1,000 ventilator-days), and 127 probable pneumonias (0.6 per 100 episodes of mechanical ventilation, 1.4 per 1,000 ventilator-days). Characteristics of patients with and without VAEs are summarized in Table 1. There were no notable differences in the age, sex, race/ethnicity, and comorbidity distribution between patients with and without VAEs. Patients with VAEs had higher mean Charlson scores than patients without VAEs. The unadjusted mean and median duration of mechanical ventilation, length of hospitalization, hospital mortality rates, and 30-day readmission rates

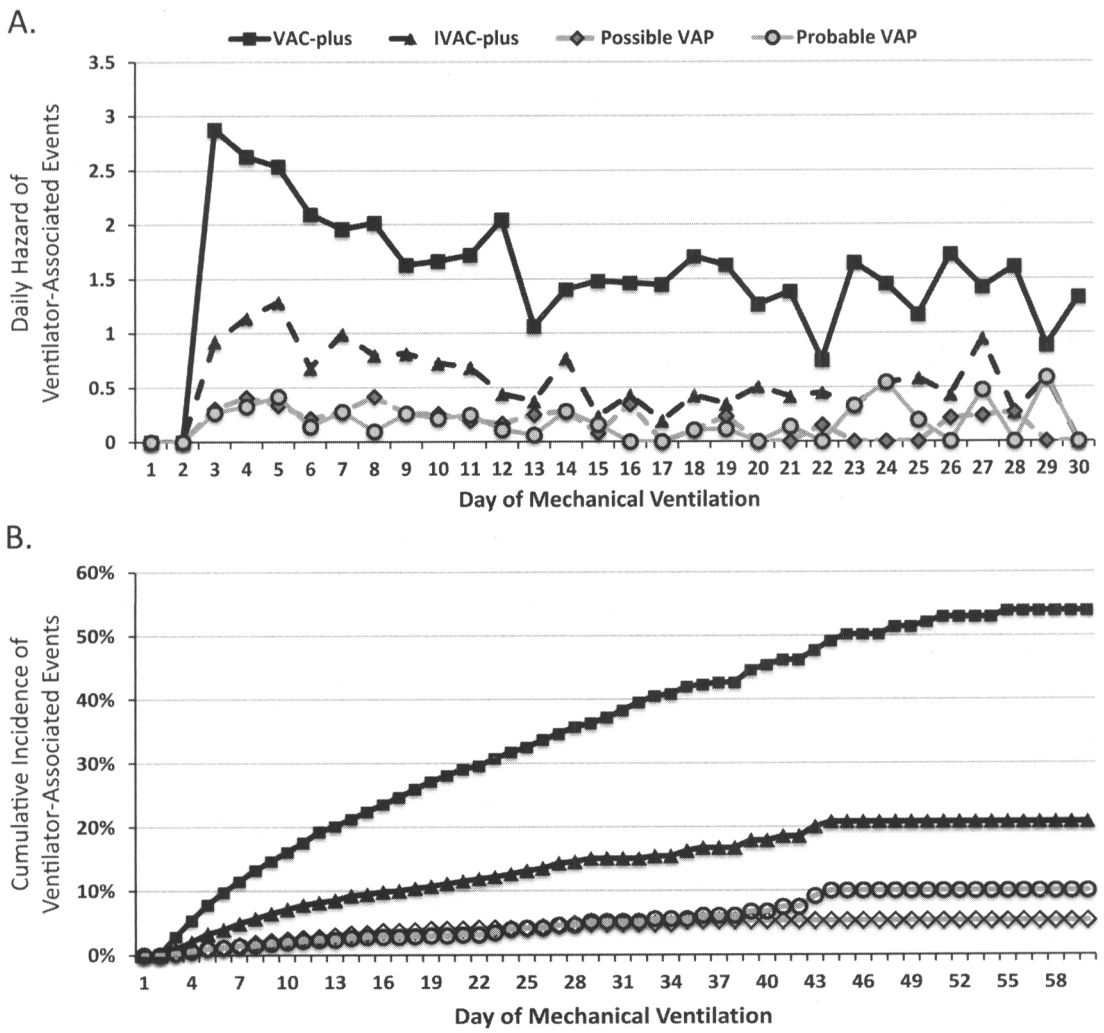

FIGURE 2. Daily hazard and cumulative incidence of ventilator-associated events (VAEs). *A*, Number of VAEs per 100 episodes of mechanical ventilation by day of mechanical ventilation. *B*, Cumulative incidence of VAEs by day of mechanical ventilation. IVAC, infection-related ventilator-associated complication; VAC, ventilator-associated condition; VAP, ventilator-associated pneumonia. VAC-plus includes IVACs, possible pneumonias, and probable pneumonias. IVAC-plus includes possible and probable pneumonias.

were higher for all VAE tiers compared with patients without VAEs.

Comparative VAE rates for different ICUs are presented in Table 2. VAE rates were highest in the general surgery, medical, and thoracic surgery units (16.0, 15.7, and 12.9 events per 1,000 ventilator-days, respectively) and lowest in the cardiac surgery unit (5.8 events per 1,000 ventilator-days). The hazard ratios for general surgery, medicine, and thoracic surgery compared with cardiac surgery were 1.77 (95% confidence interval [CI], 1.42–2.23; $P < .0001$), 1.46 (95% CI, 1.17–1.84; $P = .001$), and 1.35 (95% CI, 1.03–1.76; $P = .03$), respectively. There were no statistically significant differences in hazard ratios between the neuroscience, cardiac medicine, and cardiac surgery units. The proportion of IVAC-plus to VAC-plus ranged from 29% in the medical ICU to 42% in the general surgery and cardiac surgery ICUs (Table 2).

Daily and cumulative VAE incidence rates are depicted in Figure 2. Most VAEs occurred early in the course of mechanical ventilation. The mean daily VAC-plus rate began at 2.9 events per 100 patients on ventilator day 3, dropped to 2.0 events per 100 patients by day 7, and then tapered steadily before stabilizing at between 1.0 and 1.5 events per 100 patients from about day 14 onward. The proportion of IVAC-pluses to VAC-pluses was consistent throughout the course of mechanical ventilation, at a rate of about one-third to one-half. Likewise, the rates of possible and probable pneumonias were constant at between 0 and 0.5 events per 100 patients per day. The cumulative incidence of VAEs rose by about 1% per day. By day 30 of mechanical ventilation, the cumulative

https://doi.org/10.1086/675834 Published online by Cambridge University Press

TABLE 3. Antibiotics Associated with Infection-Related Ventilator-Associated Complication (IVAC)–Plus, IVAC-Alone, Possible Pneumonia, and Probable Pneumonia

	IVAC-plus (N = 431)	IVAC-alone (N = 165)	Possible pneumonia (N = 139)	Probable pneumonia (N = 127)	P[a]
Vancomycin	121 (28)	37 (22)	41 (30)	43 (34)	.09
Linezolid	25 (5.8)	11 (6.7)	7 (5.0)	7 (5.5)	NS
Daptomycin	2 (0.5)	1 (0.6)	0 (0.0)	1 (0.8)	NS
Nafcillin	31 (7.2)	7 (4.2)	8 (5.8)	16 (13)	.02
Cephalosporins	248 (58)	89 (49)	78 (56)	89 (70)	.01
Cefazolin	35 (8.1)	14 (8.5)	9 (6.5)	12 (9.5)	NS
Cefotaxime or ceftriaxone	38 (8.8)	16 (9.7)	11 (7.9)	11 (8.7)	NS
Ceftazidime	137 (32)	34 (21)	48 (35)	55 (43)	<.001
Cefepime	37 (8.6)	16 (9.7)	10 (7.2)	11 (8.7)	NS
Fluoroquinolone	169 (46)	53 (32)	52 (37)	64 (50)	.006
Metronidazole	116 (27)	38 (23)	48 (35)	30 (24)	.05
Carbapenem	60 (14)	24 (15)	21 (15)	15 (12)	NS
Macrolide	39 (9.1)	9 (5.5)	15 (11)	15 (12)	NS
Aminoglycosides	25 (5.8)	8 (4.9)	8 (5.8)	9 (7.1)	NS
Trimethoprim-sulfamethoxazole	25 (5.8)	11 (6.7)	6 (4.3)	8 (6.3)	NS
Colistin	8 (1.9)	2 (1.2)	1 (0.7)	5 (3.9)	NS
Piperacillin-tazobactam	7 (1.6)	1 (0.6)	4 (2.9)	2 (1.6)	NS
Clindamycin	7 (1.6)	3 (1.8)	3 (2.2)	1 (0.8)	NS
Antifungals	117 (27)	52 (32)	36 (26)	29 (23)	NS
Antibiotics, mean (SD)	2.4 (1.3)	2.1 (1.1)	2.4 (1.3)	2.7 (1.4)	<.001

NOTE. Data are no. (%), unless otherwise indicated. NS, not significant; SD, standard deviation. IVAC-plus includes possible and probable pneumonias. IVAC-alone excludes possible and probable pneumonias.

[a] IVAC-alone versus possible pneumonia versus probable pneumonia.

incidences of VAC-plus, IVAC-plus, and probable pneumonia were 37%, 15%, and 5%, respectively.

The distribution of antibiotics associated with IVAC, possible pneumonia, and probable pneumonias is summarized in Table 3. The most frequent agents for all 3 of IVAC, possible pneumonia, and probable pneumonia were cephalosporins (especially ceftazidime), fluoroquinolones, vancomycin, and antifungals. Selected agents (nafcillin, ceftazidime, fluoroquinolones, and a trend toward vancomycin) were more common among patients with probable pneumonia compared with patients with IVAC-alone or possible pneumonia. The mean number of antibiotics per patient was highest for probable pneumonia (2.7 ± 1.4), intermediate for possible pneumonia (2.4 ± 1.3), and lowest for IVAC-alone (2.1 ± 1.1).

The distribution of organisms isolated from patients with possible and probable pneumonia are arrayed in Table 4. Respiratory cultures were taken on or before the day antibiotics were started in 54% and 61% of patients with possible and probable pneumonia, respectively (P = .33). The most frequent isolates were *Staphylococcus aureus* (29%), *Pseudomonas aeruginosa* (14%), *Enterobacter* species (7.9%), and *Klebsiella* species (7.9%). Almost half (45%) of patients with possible pneumonia had negative cultures. *Pseudomonas aeruginosa* and *Haemophilus influenza* were more common among patients with probable pneumonia compared with those with possible pneumonia. Respiratory specimens were obtained in 100% of possible and probable pneumonia cases (by definition) but in only 53% of episodes of IVAC-alone.

The association between different VAEs and duration of mechanical ventilation, hospital length of stay, and hospital mortality is presented in Table 5. All tiers of the VAE framework were significantly associated with longer ventilator stays, hospital stays, and higher mortality rates compared with patients without VAEs after adjusting for potential confounders. Both IVAC-plus and IVAC-alone predicted more days to extubation and hospital discharge compared with patients with VAC-alone. Outcomes were comparable for patients with IVAC-alone, possible pneumonia, and probable pneumonia.

DISCUSSION

This is the first study to present a comprehensive overview of VAE epidemiology. Findings of note include the following: (1) the global rate of VAEs was low: only about 5% of patients met VAE criteria, and fewer than 1% met criteria for probable pneumonia; (2) rates differed depending on ICU type: hazard rates were highest in surgical, medical, and thoracic units and lowest in cardiac and neuroscience units; (3) most VAEs occurred early in the course of mechanical ventilation, with rates tapering thereafter; (4) the cumulative risk for developing a VAE rose by about 1% per day; (5) pulmonary sampling, culture results, and antibiotic prescribing patterns differed for probable pneumonia, possible pneumonia, and IVAC-alone, suggesting that these definitions identify distinct populations; (6) all tiers of the VAE framework were strongly associated with prolonged mechanical ventilation, prolonged

TABLE 4. Microorganisms Associated with Possible and Probable Pneumonia

	Possible or probable pneumonia (N = 266)	Possible pneumonia (N = 139)	Probable pneumonia (N = 127)	P[a]
Staphylococcus aureus	78 (29)	29 (21)	49 (39)	.002
Culture negative	69 (26)	69 (50)	...	...
Pseudomonas aeruginosa	38 (14)	6 (4.3)	32 (25)	<.001
Enterobacter species	21 (7.9)	12 (8.6)	9 (7.1)	NS
Klebsiella species	21 (7.9)	9 (6.5)	12 (9.5)	NS
Haemophilus influenza	18 (6.8)	3 (2.2)	15 (11.9)	.003
Escherichia coli	13 (4.9)	6 (4.3)	7 (5.6)	NS
Stenotrophomonas maltophila	12 (4.5)	4 (2.9)	8 (6.3)	NS
Acinetobacter species	10 (3.8)	4 (2.9)	6 (4.8)	NS
Serratia species	8 (3.0)	1 (0.7)	7 (5.6)	.05
Aspergillus species	6 (2.2)	5 (3.6)	1 (0.8)	NS
Other	5 (1.9)	1 (0.7)	4 (3.2)	NS
Streptococcus pneumonia	3 (1.1)	...	3 (2.4)	NS
β-hemolytic *Streptococci*	3 (1.1)	...	3 (2.4)	NS
Citrobacter species	3 (1.1)	2 (1.4)	1 (0.8)	NS
Moraxella catarrhalis	2 (0.8)	...	2 (1.6)	NS
Proteus mirabilis	2 (0.8)	2 (1.4)	...	NS

NOTE. Data are no. (%), unless otherwise indicated. NS, not significant.

[a] Possible versus probable pneumonia.

hospitalization, and increased hospital mortality; and (7) IVAC was associated with more days to extubation and hospital discharge compared with patients with VAC-alone, suggesting that the additional IVAC criteria (abnormal temperature or white blood cell count and 4 or more days of new antibiotics) do identify a subset of the VAC population prone to worse outcomes. There were no differences in attributable length of stay and mortality, however, between IVAC-alone and the pneumonias or between possible pneumonia and probable pneumonia.

Many aspects of VAE epidemiology mirror traditional VAP epidemiology. These include the pattern of rate variations by unit type and the absolute rates of probable pneumonias. VAC-plus rates were higher than traditional VAP rates, but VAC-plus intentionally captures more than just pneumonia. We found VAC-plus rates of 16.0, 5.8, and 15.7 events per 1,000 ventilator-days in general surgery, cardiac surgery, and medical units, respectively, whereas the CDC reported pooled mean VAP rates of 3.5, 1.6, and 1.4 per 1,000 ventilator-days in these units.[16] Probable pneumonia is a closer proxy for traditional VAP; rates in our cohort were 2.3, 0.9, and 0.8 per 1,000 ventilator-days, respectively. The daily hazards of VAEs also parallel prior reports on VAP documenting highest risk early in the course of mechanical ventilation that diminishes thereafter.[16-18] Patients may be more prone to VAEs early in the course of mechanical ventilation as a consequence of acute interventions taken to stabilize patient's presenting illnesses. For example, early VAEs may be due to aspiration secondary to intubation or pulmonary edema secondary to aggressive fluid repletion in hypotensive patients. Early events may also reflect the evolution of the preexisting illnesses that precipitated intubation.

The microbiology of possible and probable pneumonia was also similar to traditional VAP. The most common possible and probable pneumonia pathogens in this study were *S. aureus* (29%), *P. aeruginosa* (14%), *Klebsiella* sp. (7.9%), and *Enterobacter* sp. (7.9%). This matches the pathogen distribution among 8,474 episodes of VAP reported to the CDC from 2009 to 2010, where the most frequent pathogens were *S. aureus* (24%), *P. aeruginosa* (17%), *Klebsiella* sp. (10%), and *Enterobacter* sp. (8.6%).[19] Notably, the possible pneumonia definition allows for the possibility of detecting potential culture-negative cases of VAP. These accounted for 26% of all pneumonias in this analysis. This too mirrors prior literature documenting that tracheal aspirates and bronchoalveolar lavage cultures are negative, despite histological evidence of pneumonia in 13%–50% of patients.[20-25]

The differences in pulmonary sampling frequency, microbiology, and prescribing patterns for probable pneumonia, possible pneumonia, and IVAC-alone suggest that these criteria identify different subsets of patients. Broadly speaking, the patterns mirror what one might expect: patients with probable pneumonia were more likely to be infected with *P. aeruginosa* or *H. influenza*; to be treated with more antibiotics (mean, 2.7 agents for probable pneumonia vs 2.4 for possible pneumonia and 2.1 for IVAC-alone); and to receive nafcillin, ceftazidime, fluoroquinolones, and possibly vancomycin (these are the recommended agents for treating nosocomial pneumonias in our institution). These observations provide indirect evidence that probable pneumonia may be more specific for pneumonia than IVAC-alone or possible pneumonia.

The strong and consistent associations between different VAE tiers and prolonged mechanical ventilation, increased duration of hospitalization, and higher hospital mortality af-

TABLE 5. Attributable Morbidity and Mortality of Different Ventilator-Associated Events (Multivariate Adjusted Analyses)

		Days to extubation		Days to hospital discharge		Hospital mortality	
Outcome	Referent	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
All VAE tiers vs no VAEs							
VAC-plus	No VAE	3.12 (2.96–3.29)	<.0001	1.46 (1.37–1.55)	<.0001	1.98 (1.60–2.44)	<.0001
VAC-alone	No VAE	2.32 (2.19–2.45)	<.0001	1.29 (1.21–1.37)	<.0001	2.35 (1.91–2.90)	<.0001
IVAC-plus	No VAE	3.45 (3.23–3.68)	<.0001	1.52 (1.41–1.63)	<.0001	1.87 (1.44–2.42)	<.0001
IVAC-alone	No VAE	3.71 (3.35–4.10)	<.0001	1.69 (1.51–1.90)	<.0001	1.86 (1.27–2.73)	.002
Possible pneumonia	No VAE	3.16 (2.84–3.52)	<.0001	1.38 (1.22–1.56)	<.0001	2.15 (1.43–3.23)	.0002
Probable pneumonia	No VAE	3.50 (3.10–3.95)	<.0001	1.50 (1.31–1.70)	<.0001	1.63 (1.02–2.61)	.04
IVAC and subsets vs VAC-alone							
IVAC-plus	VAC-alone	1.49 (1.37–1.61)	<.0001	1.18 (1.08–1.29)	.0004	0.80 (0.59–1.07)	NS
IVAC-alone	VAC-alone	1.60 (1.43–1.79)	<.0001	1.32 (1.16–1.49)	<.0001	0.79 (0.52–1.20)	NS
Possible pneumonia	VAC-alone	1.36 (1.21–1.53)	<.0001	1.07 (0.93–1.22)	NS	0.91 (0.59–1.41)	NS
Probable pneumonia	VAC-alone	1.51 (1.33–1.72)	<.0001	1.16 (1.01–1.34)	.04	0.69 (0.43–1.13)	NS
Pneumonias vs IVAC-alone							
Possible pneumonia	IVAC-alone	0.85 (0.74–0.98)	.03	0.81 (0.69–0.96)	.01	1.15 (0.67–1.97)	NS
Probable pneumonia	IVAC-alone	0.94 (0.81–1.11)	NS	0.88 (0.74–1.05)	NS	0.88 (0.49–1.57)	NS
Possible or probable pneumonia	IVAC-alone	0.90 (0.79–1.02)	NS	0.84 (0.73–0.98)	.02	1.01 (0.63–1.62)	NS
Probable vs possible pneumonia							
Probable pneumonia	Possible pneumonia	1.11 (0.94–1.30)	NS	1.09 (0.91–1.30)	NS	0.76 (0.42–1.39)	NS

NOTE. CI, confidence interval; NS, not significant; OR, odds ratio.

firm the clinical significance of the events flagged by the new definitions. While it is still possible that VAEs may yet be markers for the evolution of severe illnesses rather than preventable complications, 3 lines of evidence suggest that this is not the case. (1) By definition, VAEs can be flagged only in patients who deteriorate after a period of stability or improvement on the ventilator. (2) We adjusted for a rich array of markers for severity of illness, including age, sex, comorbidities, unit type, key laboratory values, use of vasoactive medications, and duration of mechanical ventilation prior to event onset. (3) Emerging data suggest that improvements in care can decrease event rates.[10]

The findings of this investigation are tempered by important limitations. This was a single-center, retrospective evaluation that may not be generalizable to different hospitals with different kinds of patients. Different hospitals and different clinicians may vary in their preferred mechanical ventilation modes and settings, weaning strategies, decision making on when and how to obtain microbiological specimens, laboratory protocols for working up clinical cultures, prescribing patterns, and daily ventilator setting record keeping. These differences likely impact VAE rates. Comparative surveillance data from additional hospitals are needed to determine the generalizability of our observations.

This study helps establish the frequency, distribution, temporal trends, microbiology, treatment patterns, and clinical consequences of VAEs. All tiers of the VAE framework appear to be highly meaningful insofar as they increase time to extubation more than 3-fold, extend time to hospital discharge by about 50%, and double the risk of dying relative to comparable patients without VAEs. These findings bespeak the importance of developing strategies to prevent VAEs. Studies focusing on identifying modifiable risk factors and testing interventions targeting these risk factors are now needed.[26]

ACKNOWLEDGMENTS

We thank Richard Platt, MD, MSc, for thoughtful comments on an earlier version of this manuscript.

Financial support. This work was supported by the Centers for Disease Control and Prevention (grant 1U54CK000172).

Potential conflicts of interest. M.K. reports that he has received honoraria for lectures on ventilator-associated event surveillance from Premier Healthcare Alliance. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to Michael Klompas, MD, MPH, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 133 Brookline Avenue, 6th Floor, Boston, MA 02215 (mklompas@partners.org).

REFERENCES

1. Centers for Disease Control and Prevention (CDC). *Ventilator-Associated Event Protocol.* Atlanta: CDC, 2013. http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html. Accessed February 25, 2013.
2. Magill SS, Fridkin SK. Improving surveillance definitions for ventilator-associated pneumonia in an era of public reporting and performance measurement. *Clin Infect Dis* 2012;54(3):378–380.
3. Klompas M. Complications of mechanical ventilation: the CDC's new surveillance paradigm. *N Engl J Med* 2013;368(16):1472–1475.
4. Klompas M, Kleinman K, Platt R. Development of an algorithm

for surveillance of ventilator-associated pneumonia with electronic data and comparison of algorithm results with clinician diagnoses. *Infect Control Hosp Epidemiol* 2008;29(1):31–37.
5. Klompas M, Khan Y, Kleinman K, et al. Multicenter evaluation of a novel surveillance paradigm for complications of mechanical ventilation. *PLoS ONE* 2011;6(3):e18062.
6. Klompas M, Kleinman K, Khan Y, et al. Rapid and reproducible surveillance for ventilator-associated pneumonia. *Clin Infect Dis* 2012;54:370–377.
7. Klompas M, Magill S, Robicsek A, et al. Objective surveillance definitions for ventilator-associated pneumonia. *Crit Care Med* 2012;40(12):3154–3161.
8. Prospero E, Illuminati D, Marigliano A, et al. Learning from Galileo: ventilator-associated pneumonia surveillance. *Am J Respir Crit Care Med* 2012;186(12):1308–1309.
9. Hayashi Y, Morisawa K, Klompas M, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. *Clin Infect Dis* 2013;56(4):471–477.
10. Muscedere J, Sinuff T, Heyland D, et al. The clinical impact and preventability of ventilator-associated conditions in critically ill mechanically ventilated patients. *Chest* 2013:144(5)1453–1460.
11. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36(1): 8–27.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373–383.
13. Hilbe J. *Negative Binomial Regression.* 2nd ed. Cambridge: Cambridge University Press, 2011.
14. Brown AJ, Prescott C. *Applied Mixed Models in Medicine.* Chicester: Wiley, 2006.
15. Little R, Rubins D. *Statistical Analysis with Missing Data.* New York: Wiley, 1987.
16. Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. *Am J Infect Control* 2011;39(10):798–816.
17. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998;129(6):433–440.
18. Koulenti D, Lisboa T, Brun-Buisson C, et al. Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units. *Crit Care Med* 2009;37(8):2360–2368.
19. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2009–2010. *Infect Control Hosp Epidemiol* 2013;34(1):1–14.
20. Papazian L, Thomas P, Garbe L, et al. Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1995;152(6):1982–1991.
21. Torres A, el-Ebiary M, Padro L, et al. Validation of different techniques for the diagnosis of ventilator-associated pneumonia: comparison with immediate postmortem pulmonary biopsy. *Am J Respir Crit Care Med* 1994;149(2):324–331.
22. Marquette CH, Copin MC, Wallet F, et al. Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am J Respir Crit Care Med* 1995;151(6):1878–1888.
23. Kirtland SH, Corley DE, Winterbauer RH, et al. The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. *Chest* 1997;112(2):445–457.
24. Papazian L, Autillo-Touati A, Thomas P, et al. Diagnosis of ventilator-associated pneumonia: an evaluation of direct examination and presence of intracellular organisms. *Anesthesiology* 1997;87(2):268–276.
25. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax* 1999; 54(10):867–873.
26. Klompas M. Ventilator-associated events surveillance: a patient safety opportunity. *Curr Opin Crit Care* 2013;19(5):424–431.