Online supplement: (EMS1 and 3, EMS2 is provided as separate pdf-file)

Relative risk and population-attributable fraction of ICU-death caused by susceptible and resistant *Pseudomonas aeruginosa* ventilator-associated pneumonia: A competing risks approach to investigate the OUTCOMEREA database

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ESM1:

Table 2: Description of the covariate values used for adjustment in the regression analyses.

VAP Pa: Ventilator-associated pneumonia caused by Pseudomonas aeruginosa; VAP Pa sus.: Ventilator-associated pneumonia caused by the susceptible type of Pseudomonas aeruginosa; VAP Pa res.: Ventilator-associated pneumonia caused by the resistant type of Pseudomonas aeruginosa; 1st IMV: Time of first invasive mechanical ventilation. *5 missings previously excluded from dataset; ** 20 missings were assigned to the larger group “medical”; *** 49 missings were assigned SAPS score at ICU admission.

Basic descriptives of data sample:	
Number of patients	7221 patients
Summed patient-days spent in ICU without VAP *Pa*	99 004 patient-days
Summed patient-days spent in ICU with VAP *Pa*	9 935 patient-days
Length of stay in ICU (in days) Mean (SD); (min, max) Median (1st Quartile, 3rd Quartile)	 15 (17.5); (2, 238) 9 (5, 18)
Length of stay until VAP_P.a. (in days) Mean (SD); (min, max) Median (1st Quartile, 3rd Quartile)	 13.66 (12.4); (2, 110) 10 (6, 17)
Number of VAP *Pa* acquisitions	463 infected patients (136 resistant and 327 susceptible) ()
Number of discharges without VAP *Pa*	4942 uninfected patients
Number of deaths without VAP *Pa*	1816 uninfected patients
Number of discharges with VAP *Pa*	308 infected patients (79 resistant and 229 susceptible)
Number of deaths with VAP *Pa*	155 infected patients (57 resistant and 98 susceptible)
Variables:	**Descriptives for n=7221 admissions at day of first IMV (invasive mechanical ventilation)**

Number of patients with VAP (any pathogen)	1247 (at least one type of VAP)
Number of patients with VAP caused by other pathogens than *Pa* (VAP other)	784 (VAP other, no VAP *Pa*) 85 (VAP other and VAP *Pa*)
Age at 1st IMV in years* (mean, SD) median (1st quartile, 3rd quartile)	63 (16) 65 (53 – 76) min: 18; max: 111
Gender (men)	4568 (63 %)
Transfer from hospital	3449 (48 %)
Type of patient ** medical surgical	 5251 (73 %) 1970 (27 %)
SAPS score at 1st IMV *** (mean, SD) median (1st quartile, 3rd quartile)	47 (16.25) 46 (35 – 57) min: 4; max: 117
SOFA score at 1st IMV (mean, SD) median (1st quartile, 3rd quartile)	7.3 (3.8) 7 (5 – 10) min: 0; max: 23

Variables at first IMV (stratified by VAP *Pa;* VAP *Pa* sus. and *VAP Pa* res.)	**Patients without VAP *Pa* (n=6758)**	**Patients with VAP *Pa* (n=463)**	**Patients with VAP *Pa* sus. (n=327)**	**Patients with VAP *Pa* res. (n=136)**
Age at 1st IMV in years* (mean, SD) median (1st quartile, 3rd quartile)	63 (16) 65 (53 – 76) min: 18; max: 111	63 (16) 66 (53 – 76) min: 18; max: 94	64 (16) 67 (54 – 76) min: 19; max: 94	62 (15) 63 (52 – 75) min: 18; max: 89
Gender (men)	4235 (63 %)	333 (72 %)	237 (72 %)	96 (70%)
Transfer from hospital	3215 (47 %)	234 (50 %)	159 (48 %)	75 (55 %)
Type of patient ** medical surgical	 4885 (72 %) 1873 (28 %)	 366 (79 %) 97 (21 %)	 254 (78%) 73 (22 %)	 112 (82%) 24 (18 %)
SAPS score at 1st IMV *** (mean, SD) median (1st quartile, 3rd quartile)	47 (16.3) 46 (35 – 57) min: 4; max: 117	47 (15.4) 46 (35 – 56) min: 16; max: 102	46 (15.5) 45 (35 – 56) min: 17; max: 102	47 (15.2) 46 (37 – 56) min: 16; max: 93
SOFA score at 1st IMV (mean, SD) median (1st quartile, 3rd quartile)	7.3 (3.8) 7 (5 – 10) min: 0; max: 23	7.4 (3.5) 7 (5 – 10) min: 0; max: 17	7.4 (3.5) 7 (5 – 10) min: 0; max: 17	8.1 (3.7) 7 (6 – 11) min: 0; max: 17

Descriptives at VAP *Pa* acquisition	**VAP *Pa* (n=463)**	**VAP *Pa* sus. (n=327)**	**VAP *Pa* res. (n=136)**
Inadequate initial treatment	156 (106 discharged alive; 50 died)	99 (72 discharged alive; 27 died)	57 (34 discharged alive; 23 died)
SAPS score at 1st IMV *** (mean, SD) median (1st quartile, 3rd quartile)	41 (14) 39 (32 – 49) min: 6; max: 98 (13 NAs)	40 (13.5) 39 (31 – 48) min: 15; max: 91 (10 NAs)	42 (15.1) 40 (32 – 51) min: 6; max: 98 (3 NAs)
SOFA score at 1st IMV (mean, SD) median (1st quartile, 3rd quartile)	6 (3.8) 6 (3 –8.5)	5.7 (3.5) 6 (3 – 8)	6.7 (4.2) 6 (4 – 9)

Variables at first IMV (stratified by VAP *Pa;* VAP *Pa* sus. and *VAP Pa* res.)	**Patients without VAP P*a* (n=6758)**	**Patients with VAP *Pa* (n=463)**	**Patients with VAP *Pa* sus. (n=327)**	**Patients with VAP *Pa* res. (n=136)**
	min: 0; max: 18	min: 0; max: 17		min: 0; max: 18

ESM3:

Details on statistical methodology:

1. Cause specific competing risks analysis

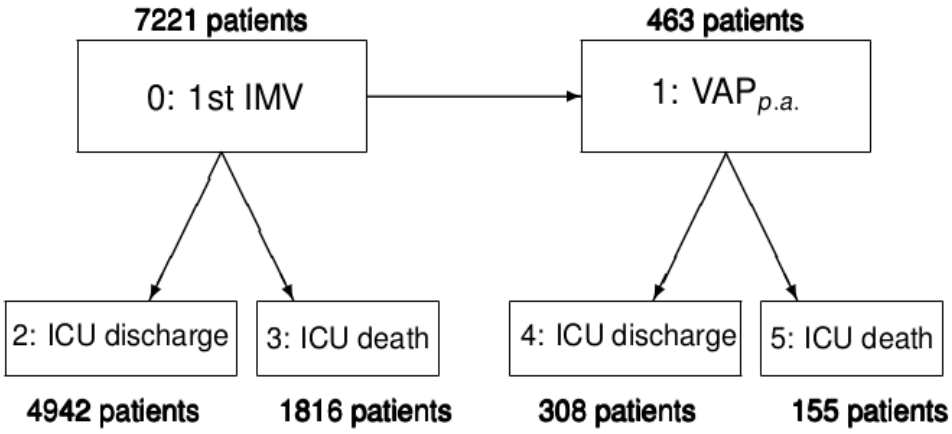

Figure 1: Extended illness-death model to study the burden of VAP pa

Burden of VAP Pa/VAP Pa resistant and susceptible

The methodology we use to analyse the data is described in detail in [4] and [7], [8]. To avoid competing risks bias and time-dependent bias ([4]) we describe the data with a multi-state model as shown in figure 1. The arrows represent possible transitions a patient can make and the boxes the possible states a patient can be in. At study entry all patients are in state 0 (ventilated without VAP Pa). Then, the patients may either die without VAP Pa (state 3) or be discharge without VAP Pa (state 2). It is also possible that the patients acquire a VAP Pa which means they move to state 1. These patients remain under observation until death or discharge after VAP Pa acquisition (states 5 and 4 resp.). The displayed multi-state model accounts for the different length of stay of the patients and the different times of onset of VAP Pa. The cause-specific hazard rates can be interpreted as the daily rate of an event [4]. For example, the infection hazard rate, which is represented by the arrow from state 0 to state 1, is the daily rate of an infection for patients being in state 0 (i.e. ventilated patients in the ICU).

To investigate the effect of VAP Pa (VAP Pa susceptible and VAP Pa resistant) we used two cause-specific Risk models (Cox regression). One for the outcome 'ICU death' (states 3 and 5) and one for 'ICU discharge' (states 2 and 4). We included baseline covariates (described in

table 2, EMS 1) and the exposure of interest VAP Pa (VAP Pa susceptible and VAP Pa resistant) as time-dependent covariate(s). The Cox proportional hazards model is the most commonly used approach to analyse cohort studies [8]. In the presence of competing risks, as in this data situation, cause-specific Cox proportional hazards models for each outcome must be used.

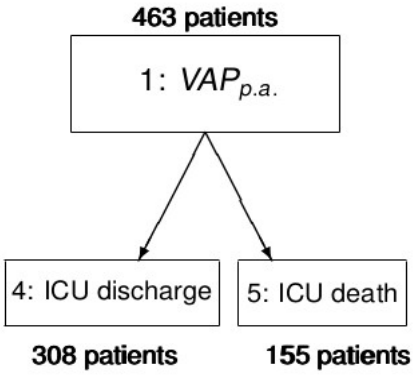

Figure 2: Competing risks model to study the burden of resistance

The burden of resistance

To study the burden of resistance we used a competing risks model (figure 2) for infected patients only. We used cause-specific Risk models (Cox regression models) for the two outcomes death in ICU and discharge in ICU after VAP Pa acquisition. To account for the different times of VAP Pa onset we used left-truncated entry times. The exposure of interest is type of VAP Pa (resistant versus susceptible). We adjusted for this time-independent covariate as well as the baseline covariates shown in table 2 EMS 1.

The competing risks approach is described in detail in references [4], [7] and [8].

2. Summary analysis

The estimates of relative-risk (RR) and population-attributable fraction (PAF) were obtained as described in [4]. Since follow-up is complete, final outcomes (death in ICU or discharge alive) were known for all patients. Then, as described in detail in [4], a basic summary analyses that ignores length of stay and time of VAP Pa onset can be performed. Relative risk (RR) of death depending on VAP Pa state and population-attributable fraction can be obtained. These analyses can be performed without sophisticated software. The time-constant incidence rates of each possible transition in the multi-state model (figure 1) can be used as plug-in values in the formulas presented in [4]. These formulas demonstrate the connection between the daily incidence rates and the quantities RR/PAF.

Adjustment for baseline covariates can be performed using standard generalized linear models (glm's).

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