**SUPPLEMENTARY MATERIAL**

**Attributable mortality of vancomycin resistance in ampicillin-resistant *Enterococcus faecium* bacteremia in Denmark and the Netherlands: A matched cohort study**

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**Matching procedure**

Study periods in hospitals in the Netherlands generally extended from January 1, 2009 to December 31, 2012, with a few exceptions due to inclusion of hospitals with vancomycin-resistant *Enterococcus faecium* (VRE) outbreaks occurring in 2013, or availability of data when the Dutch antimicrobial resistance surveillance database ISIS-AR was queried (Supplementary Table S1). Since 2011, the number of VRE outbreaks has substantially increased in the Netherlands. We decided, however, to extend the study period further backwards to January 1, 2009, firstly to increase sample size by including several sporadic VRE bacteremias occurring before 2012, and secondly to enlarge the pool of potential ARE controls, especially in smaller hospitals and on hospital wards with sporadic *E. faecium* bacteremias. January 1, 2009 was chosen as the study start date because of data availability for relevant hospitals in ISIS-AR.

In Denmark, VRE outbreaks increased in number from 2012 onwards, and the study period was set to January 1, 2012 through December 31, 2014. An extension back in time was not considered necessary to improve selection of ARE controls.

For VRE, only the first episode of bacteremia was included, and any ampicillin-resistant *E. faecium* (ARE) bacteremia before or after was not eligible as control episode. As VRE bacteremia could have been preceded by ARE bacteremia, all episodes of ARE bacteremia were eligible for selection as control episode, unless preceded by ARE bacteremia in the prior 30 days, in order to prevent inclusion of bacteremia relapses. This, however, was not an exclusion criterion for VRE bacteremias.

Matching variables were hospital, hospital ward at bacteremia onset, length of hospital stay prior to bacteremia, and age. Wards were defined as internal medicine, intensive care unit (ICU), gastro-enterology, surgery, cardiology, pulmonary medicine, urology, and orthopedics. In one Danish hospital, gastro-enterology and surgery could not be separated during the matching process and were treated as a single ward (4 VRE bacteremias affected).

The matching protocol consisted of three steps. First, for each VRE bacteremia, all episodes of ARE bacteremia occurring on the same ward, in the same hospital, during the entire hospital-specific study period were selected (potential match pool). Second, length of hospital stay prior to bacteremia was log-transformed (referred to as ln(LOS)) for all VRE and ARE bacteremia episodes, and for each VRE bacteremia episode, the definitive match pool was created by selecting controls with a ln(LOS) that fell within a 2.5% absolute difference margin of the ln(LOS) of the VRE bacteremia. If the definitive match pool did not contain at least five ARE bacteremia episodes, the absolute difference margin for ln(LOS) was increased by steps of 2.5%, until the minimum of five was reached.

Third, from the definitive match pool, the four ARE bacteremia patients with the smallest absolute difference in age were selected as controls. In case of identical absolute age differences, the elder ARE bacteremia patient was preferred, and otherwise a random selection was made. If the definitive match pool contained fewer than five ARE bacteremia episodes, all were selected as control, and a matched set of size below five emerged (2 sets of four, 4 sets of two, and 1 set of VRE only).

As analyses were always performed within sets, a single ARE bacteremia episode could serve as a control for different VRE bacteremia episodes. In fact, 26 ARE bacteremias were included twice, and 4 thrice. The distribution of ARE and VRE bacteremias over the study period is depicted in Supplementary Figure S1.

**Follow-up of patients with regard to survival status**

In Denmark, the national civil registry was consulted on June 23, 2015 for this purpose, and all patients alive on this date with a follow-up after bacteremia onset of less than 1 year, were censored on this date. In the Netherlands, survival status was based on notes in medical files, and if there was no record of survival 1 year after bacteremia onset, or the moment of file review occurred during this time period, patients were censored on the date that they were last confirmed to be alive through recorded hospitals visits, telephone calls or correspondence with other healthcare providers.

**Definitions of collected variables**

Potential confounders, for which data were collected, included sex, age; hospital ward at bacteremia onset; length of hospital and – if applicable – ICU stay prior to bacteremia; bacteremia origin; hospital admission from long-term care facility, preceding hospital admission (i.e., before the current one) of ≥2 nights within 3 months prior to bacteremia; comorbidity; immunodeficiency; treatment restriction agreed upon prior to bacteremia; any surgical procedure (i.e., in the operating room) within 30 days prior to bacteremia; mechanical ventilation and/or central venous catheter present at bacteremia onset; cultures with ARE, VRE, or methicillin-resistant *Staphylococcus aureus* (MRSA) within 1 year prior to bacteremia, and with result known at bacteremia onset; the Acute Physiology Score (APS) before bacteremia onset (see *Analysis with Acute Physiology Score* in this Supplementary Material)1; and antibiotic use within 30 days prior to bacteremia (see *Data collection* in the main text).

Bacteremia origin was defined as hospital-onset if bacteremia onset was ≥48 h after admission. Other episodes were categorized as either community-onset or healthcare-associated (in case of admission from long-term care facility; precdeing hospital admission of ≥2 nights within 3 months prior to bacteremia; or intravenous therapy, nursing at home, hemodialysis, or wound care within 1 month prior to bacteremia).2 Immunodeficiencies recorded included neutropenia at bacteremia onset (<500x106/L), high daily dose corticosteroid therapy (equivalence of ≥20mg prednisone) of ≥14 days' duration within 1 month prior to bacteremia, and other forms of immunosuppressive therapy. The Charlson index, with additional information recorded on the type of hematological or solid malignancy,3 was used to quantify comorbidity at bacteremia onset.

Infection-related variables were bacteremia source, sepsis severity at bacteremia onset, and isolation of pathogens other than *E. faecium* from the index blood culture (polymicrobial bacteremia). Bacteremia source was based on the final interpretation by treating physicians and consulting clinical microbiologists or infectious disease specialists. If patients died before consultation, the clinical working diagnosis at onset was registered. If no clear source was registered, the source was classified as primary, and when no or conflicting information was available in the medical file, the source was classified as not identifiable.

Apart from antibiotic treatment (see *Data collection* in the main text), information was gathered on source control procedures (including but not restricted to removal of vascular catheters, surgical procedures, percutaneous abscess drainage, and insertion of biliary stents) up to 7 days after bacteremia onset, including the date of the procedure. Sepsis severity on the calendar day on which the index blood culture was obtained was categorized as either severe sepsis (including septic shock) or not.4

Apart from the primary outcome (mortality before day 30 after bacteremia onset), data was collected on the following secondary outcomes: ICU admission before day 7 after bacteremia onset; length of hospital stay after bacteremia onset; and in-hospital mortality. Survival status was evaluated for each patient up to one year after bacteremia onset (see *Follow-up of patients with regard to survival status* in this Supplementary Material).

**Variable selection in multivariable analyses**

For the adjusted analysis, the first step involved *a priori* selection of a set of confounders[[1]](#footnote-1) and including them all in the so-called full model, together with the exposure evaluated (generally vancomycin resistance). It was then evaluated in a stepwise backward elimination procedure whether variables could be removed from the model while retaining approximately the same regression coefficient (β coefficient) for the exposure. This was done to increase precision of the effect estimate, reflected by a narrowing of its confidence interval (CI). Removal of variables started with removing the variable that would result in a new model with the smallest difference in β coefficient for the exposure compared to the full model. Subsequently, all variables were evaluated again, and the confounder impacting the β coefficient the least in this round, was removed, always with reference to the β coefficient of the exposure in the full model. This iterative process was continued until the β coefficient would deviate >10% from the β coefficient in the full model if one of the remaining confounding were to be removed. If the exposure consisted of multiple levels (in case of treatment variables), all β coefficient reflecting the different levels were evaluated, and if any would change >10%, the process was halted. If the resulting reduced model would be extremely overfitted (here defined as <5 events per variable), the cut-off of 10% could be increased.

As we made a selection of potential confounders on which data were collected, to include in the full model in order to prevent overfitting, a stepwise sensitivity analysis was performed in which all potential confounders[[2]](#footnote-2) were available for inclusion. The model started with the exposure only, and subsequently, for all potential confounders, it was evaluated how much the β coefficient for the exposure would be changed in case of incorporation into the model. The potential confounder with the largest resulting change in β coefficient was selected for inclusion. Taking this new model as the starting point, all remaining potential confounders were evaluated again for their effect on the β coefficient of the exposure. In each round, one variable could be incorporated into the model, as long as it would change the β coefficient >10%. To prevent overfitting, after inclusion of a new confounder, it was also evaluated whether any confounders already included could be removed again from the model. Variables were removed if the β coefficient of the exposure in the current model differed <10% from a model without the variable, starting with the variable with the smallest change in β coefficient. These cycles were repeated until no excluded variable could be found for which inclusion would change the β coefficient >10%, and no included variable had an impact <10% on the β coefficient. When cycles of exclusions and inclusions involving the same variables were detected by the algorithm, all cycling variables were included in the model. If the result of the sensitivity analysis would be extremely overfitted (<5 events per variable), the cut-off of 10% could be increased.

In the main text, only the resulting reduced models are presented. A complete overview of all adjusted model variants, including sensitivity analyses, for 30-day mortality with the baseline on the day of the index blood culture is presented in Supplementary Table S3. Sensitivity analyses for other models presented in the main text can be found in Supplementary Table S4.

**Analysis with Acute Physiology Score**

In the Netherlands, APS scores as described for APACHE III were collected for included patients (n = 166) 1. This confounding variable was supposed to represent underlying disease severity before the onset of bacteremia. In principle, all parameters were recorded on the second day before onset of bacteremia (day -2). In the case of laboratory parameters, other days prior to bacteremia could be used if unavailable on this day. In order of preference these days were -3, -1, -4, and in the case of albumin, day -5 through -9. If parameters were measured several times on the same calendar day, both the highest and lowest value were recorded, and the resulting most extreme score was used to calculate the APS.

Due to unavailability of records, in a considerable proportion of cases (n = 41, 25%) only laboratory values could be recorded, and in some cases (n = 4), there was a total absence of data on the APS. In order to perform valid analyses, an imputation procedure was used, assuming a missing at random (MAR) mechanism. Using the *multivariate imputation by chained equations* procedure as incorporated in the *mice* package (version 2.46.0) for R, 50 imputed datasets were created for the Dutch dataset.

Variables used in the imputation process were all other recorded potential confounders (indicated in Supplementary Table S2), hospital, infection-related variables (vancomycin resistance, polymicrobial bacteremia, severe sepsis at bacteremia onset, bacteremia source), treatment-related variables (source control performed before day +7, intravenous antibiotic therapy on day 0, inappropriate antibiotic therapy on day 0, day of initiation of appropriate antibiotic therapy), outcome-related variables (ICU admission before day +7, length of hospital stay after bacteremia onset, in-hospital mortality, 30-day mortality, 1-year mortality), and the APS for laboratory parameters only. Age, length of hospital/ICU stay before/after bacteremia onset, and laboratory and total APS were included as continuous predictors, while hospital (16 categories), hospital ward at bacteremia onset (internal medicine, ICU, gastro-enterology/surgery, other), bacteremia origin (hospital-onset, healthcare-associated, community-onset), bacteremia source (primary/central line/unknown, biliary, intra-abdominal, other), Charlson index (0-1, 2, 3-4, 5+), number of comorbidities (0, 1-2, 3+), and known colonization with *E. faecium* (no, ARE, VRE) were included as categorical predictors. The remainder of variables were binary predictors. No interactions were included.

Apart from imputing APS values, some other missings were imputed, namely for central venous catheter at bacteremia onset (n = 1), severe sepsis at bacteremia onset (n = 1), 1-year mortality (n = 19), and day of initiation of appropriate antibiotic therapy (n = 1).

With these 50 imputed datasets, several models were constructed, using Rubin’s rules for pooling of estimates. First, using the regularly available confounders, an optimally corrected (specifically for the Dutch dataset) model was created by combining results from the main and sensitivity analyses. The steps during creation of this model are indicated in Supplementary Table S3. Subsequently, the additional confounder APS was added to this model, while applying a restricted cubic spline function with three knots to allow for non-linearity. The effect estimates for the exposure vancomycin resistance could then be contrasted between models (Supplementary Table S3).

**References**

1. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100(6):1619-1636.

2. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137(10):791-797.

3. 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.

4. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003;29(4):530-538. doi:10.1007/s00134-003-1662-x

**Supplementary Table S1. Hospital characteristics**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Hospital** | **Country** | **Location** | **Hospital type** | **Start date** | **Stop date** | **No of****VRE****episodes** | **No of****ARE****episodes** |
| Bispebjerg Hospital | DK | Copenhagen | General | 1 Jan 2012 | 1 Jan 2015 | 10 | 36 |
| Herlev Hospital | DK | Herlev | General | 1 Jan 2012 | 1 Jan 2015 | 10 | 40 |
| Hvidovre Hospital | DK | Hvidovre | General | 1 Jan 2012 | 1 Jan 2015 | 6 | 24 |
| Rigshospitalet Glostrup | DK | Glostrup | General | 1 Jan 2012 | 1 Jan 2015 | 1 | 4 |
| St. Antonius Ziekenhuis | NL | Utrecht/Nieuwegein | General | 1 Jan 2009 | 1 Oct 2012a | 3 | 12 |
| Canisius-Wilhelmina Ziekenhuis | NL | Nijmegen | General | 1 Jan 2009 | 1 Jan 2013 | 7 | 28 |
| Catharina Ziekenhuis | NL | Eindhoven | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |
| Deventer Ziekenhuis | NL | Deventer | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |
| Flevoziekenhuis | NL | Almere | General | 1 Jan 2009 | 1 Jan 2013 | 2 | 1 |
| Isala  | NL | Zwolle | General | 1 Jan 2009 | 1 Jan 2013 | 4 | 14 |
| Jeroen Bosch Ziekenhuis | NL | ‘s-Hertogenbosch | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |
| Maasstad Ziekenhuis | NL | Rotterdam | General | 1 Jan 2009 | 1 Jan 2013 | 3 | 9 |
| Martini Ziekenhuis | NL | Groningen | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |
| Máxima Medisch Centrum | NL | Eindhoven/Veldhoven | General | 1 Jan 2009b | 1 Jan 2014b | 6 | 23 |
| Noordwest Ziekenhuisgroep | NL | Alkmaar | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |
| Onze Lieve Vrouwe Gasthuis | NL | Amsterdam | General | 1 Jan 2009 | 1 Jan 2013 | 2 | 8 |
| Radboudumc | NL | Nijmegen | University | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |
| VU medisch centrum | NL | Amsterdam | University | 1 Jan 2012c | 1 Jul 2013c | 1 | 4 |
| Zuwe Hofpoort Ziekenhuisd | NL | Woerden | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 1 |
| Zuyderland | NL | Heerlen/Sittard-Geleen | General | 1 Jan 2009 | 1 Jan 2013 | 1 | 4 |

Distribution over time of VRE and ARE bacteremia episodes is indicated in Supplementary Figure S1.

Abbreviations: DK, Denmark; NL, Netherlands.

a Earlier stop date due to data availability at the moment of querying ISIS-AR.
b Later stop date due to outbreak occurring in 2013.
c Earlier start date and later stop date due to outbreak occurring in 2013. d Hospital now merged with St. Antonius Ziekenhuis in Utrecht/Nieuwegein.

**Supplementary Table S2. Full characteristics and outcomes of VRE and matched ARE bacteremias**

|  | **Netherlands** | **Denmark** |
| --- | --- | --- |
| **ARE bacteremia,n/N with data (%)** | **VRE bacteremia,n/N with data (%)** | **ARE bacteremia,n/N with data (%)** | **VRE bacteremia,n/N with data (%)** |
| **Potential confounding variables** |  |  |  |  |
| Female sex | 47/130 (36) | 19/36 (53) | 51/104 (49) | 10/27 (37) |
| Age, median (IQR)  | 70 (62-76) | 69 (62-76) | 69 (63-77) | 71 (58-76) |
| Hospital ward at bacteremia onset |  |  |  |  |
| - Internal medicine: hematology  | 19/130 (15) | 7/36 (19) | 10/104 (10) | 6/27 (22) |
| - Internal medicine: oncology  | 19/130 (15) | 4/36 (11) | 5/104 (5) | 0/27 (0) |
| - Internal medicine: nephrology  | 4/130 (3) | 1/36 (3) | 2/104 (2) | 0/27 (0) |
| - Internal medicine: other subspecialty  | 3/130 (2) | 3/36 (8) | 11/104 (11) | 2/27 (7) |
| - Internal medicine: subspecialty unknown  | 2/130 (2) | 0/36 (0) | 3/104 (3) | 0/27 (0) |
| - ICU  | 48/130 (37) | 11/36 (31) | 25/104 (24) | 6/27 (22) |
| - Gastro-enterology  | 22/130 (17) | 7/36 (19) | 9/104 (9) | 3/27 (11) |
| - Surgery  | 12/130 (9) | 2/36 (6) | 22/104 (21) | 5/27 (19) |
| - Cardiology  | 1/130 (1) | 1/36 (3) | 4/104 (4) | 1/27 (4) |
| - Pulmonary medicine  | 0/130 (0) | 0/36 (0) | 5/104 (5) | 1/27 (4) |
| - Urology  | 0/130 (0) | 0/36 (0) | 1/104 (1) | 1/27 (4) |
| - Other surgical specialism  | 0/130 (0) | 0/36 (0) | 7/104 (7) | 2/27 (7) |
| Bacteremia origin  |  |  |  |  |
| - Hospital-onset  | 113/130 (87) | 29/36 (81) | 93/104 (89) | 24/27 (89) |
| - Healthcare-associated  | 15/130 (12) | 4/36 (11) | 10/104 (10) | 1/27 (4) |
| - Community-onset  | 2/130 (2) | 3/36 (8) | 1/104 (1) | 1/27 (4) |
| - Community-onset, unknown if healthcare-associated | 0/130 (0) | 0/36 (0) | 0/104 (0) | 1/27 (4) |
| Length of hospital stay prior to bacteremia, median (IQR)  | 17 (11-24) | 20 (14-36) | 18 (6-24) | 21 (10-29) |
| Length of ICU stay prior to bacteremia, median (IQR)  | 8 (2-17) | 10 (2-13) | 7 (1-9) | 11 (4-13) |
| Preceding hospital admission within 3 months prior to bacteremia | 58/130 (45) | 15/36 (42) | 47/103 (46) | 13/26 (50) |
| Hospital admission from long-term care facility  | 2/130 (2) | 4/36 (11) | 8/103 (8) | 1/26 (4) |
| Charlson index  |  |  |  |  |
| - 0-1  | 27/130 (21) | 12/36 (33) | 27/104 (26) | 5/27 (19) |
| - 2  | 45/130 (35) | 8/36 (22) | 20/104 (19) | 7/27 (26) |
| - 3-4  | 39/130 (30) | 12/36 (33) | 36/104 (35) | 7/27 (26) |
| - 5+  | 19/130 (15) | 4/36 (11) | 21/104 (20) | 8/27 (30) |
| Number of comorbidities  |  |  |  |  |
| - 0  | 13/130 (10) | 4/36 (11) | 13/104 (12) | 1/27 (4) |
| - 1-2  | 101/130 (78) | 24/36 (67) | 69/104 (66) | 21/27 (78) |
| - 3+  | 16/130 (12) | 8/36 (22) | 22/104 (21) | 5/27 (19) |
| Myocardial infarction  | 27/130 (21) | 1/36 (3) | 4/104 (4) | 0/27 (0) |
| Chronic pulmonary disease  | 19/130 (15) | 4/36 (11) | 23/104 (22) | 5/27 (19) |
| Diabetes mellitus  | 23/130 (18) | 9/36 (25) | 16/104 (15) | 6/27 (22) |
| Cerebrovascular disease  | 10/130 (8) | 3/36 (8) | 20/104 (19) | 5/27 (19) |
| Chronic renal disease  | 9/130 (7) | 4/36 (11) | 23/104 (22) | 2/27 (7) |
| Hematological malignancy  | 42/130 (32) | 11/36 (31) | 9/104 (9) | 6/27 (22) |
| Hematological malignancy – under treatment | 31/130 (24) | 10/36 (28) | 9/104 (9) | 6/27 (22) |
| Solid malignancy  | 41/130 (32) | 8/36 (22) | 35/104 (34) | 10/27 (37) |
| Metastasized solid malignancy  | 13/130 (10) | 1/36 (3) | 13/104 (12) | 6/27 (22) |
| Immunodeficiency  | 46/130 (35) | 11/36 (31) | 20/104 (19) | 11/27 (41) |
| Neutropenia at bacteremia onset | 32/130 (25) | 11/36 (31) | 8/104 (8) | 6/27 (22) |
| Treatment restriction in place at bacteremia onset | 26/130 (20) | 10/36 (28) | 5/102 (5) | 2/27 (7) |
| Surgical procedure within 30 days prior to bacteremia | 46/130 (35) | 9/36 (25) | 33/103 (32) | 12/27 (44) |
| Mechanical ventilation at bacteremia onset  | 34/130 (26) | 4/36 (11) | 16/104 (15) | 4/27 (15) |
| Central venous catheter at bacteremia onset  | 65/129 (50) | 19/36 (53) | 61/103 (59) | 13/27 (48) |
| Known colonization with *E. faecium*  |  |  |  |  |
| - No  | 90/130 (69) | 18/36 (50) | 88/104 (85) | 16/27 (59) |
| - Yes: ARE  | 38/130 (29) | 7/36 (19) | 16/104 (15) | 2/27 (7) |
| - Yes: VRE  | 2/130 (2) | 11/36 (31) | 0/104 (0) | 9/27 (33) |
| Known colonization with MRSA  | 0/130 (0) | 0/36 (0) | 4/104 (4) | 0/27 (0) |
| Antibiotic use within 30 days prior to bacteremia  | 122/130 (94) | 33/36 (92) | 95/104 (91) | 25/27 (93) |
|  Prior use of SOD/SDD  | 31/130 (24) | 6/36 (17) | 0/104 (0) | 0/27 (0) |
|  Prior use of β-lactams  | 113/130 (87) | 32/36 (89) | 94/104 (90) | 24/27 (89) |
|  Prior use of penicillins  | 77/130 (59) | 18/36 (50) | 80/104 (77) | 20/27 (74) |
|  Prior use of cephalosporins  | 77/130 (59) | 24/36 (67) | 38/104 (37) | 7/27 (26) |
|  Prior use of carbapenems  | 17/130 (13) | 6/36 (17) | 25/104 (24) | 11/27 (41) |
|  Prior use of fluoroquinolones  | 77/130 (59) | 18/36 (50) | 50/104 (48) | 14/27 (52) |
|  Prior use of aminoglycosides  | 27/130 (21) | 7/36 (19) | 18/104 (17) | 6/27 (22) |
|  Prior use of vancomycin  | 13/130 (10) | 15/36 (42) | 9/104 (9) | 6/27 (22) |
|  |  |  |  |  |
| **Infection-related variables** |  |  |  |  |
| Polymicrobial bacteremia  | 35/130 (27) | 8/36 (22) | 31/103 (30) | 11/27 (41) |
| Severe sepsis at bacteremia onset  | 30/129 (23) | 10/36 (28) | 20/104 (19) | 4/27 (15) |
| Bacteremia source  |  |  |  |  |
| - Primary bacteremia  | 21/130 (16) | 9/36 (25) | 23/104 (22) | 6/27 (22) |
| - Central line-associated bacteremia  | 18/130 (14) | 5/36 (14) | 15/104 (14) | 2/27 (7) |
| - Not identifiable from medical file  | 21/130 (16) | 5/36 (14) | 21/104 (20) | 3/27 (11) |
| - Biliary tract infection  | 15/130 (12) | 4/36 (11) | 10/104 (10) | 2/27 (7) |
| - Spontaneous/primary peritonitis  | 1/130 (1) | 0/36 (0) | 0/104 (0) | 0/27 (0) |
| - Other intra-abdominal infection  | 34/130 (26) | 9/36 (25) | 12/104 (12) | 7/27 (26) |
| - Urinary tract infection  | 5/130 (4) | 1/36 (3) | 11/104 (11) | 4/27 (15) |
| - Pneumonia  | 3/130 (2) | 1/36 (3) | 2/104 (2) | 1/27 (4) |
| - Skin/soft tissue infection  | 4/130 (3) | 1/36 (3) | 2/104 (2) | 0/27 (0) |
| - Wound infection  | 3/130 (2) | 0/36 (0) | 2/104 (2) | 0/27 (0) |
| - Endocarditis  | 0/130 (0) | 0/36 (0) | 1/104 (1) | 0/27 (0) |
| - Other  | 5/130 (4) | 1/36 (3) | 5/104 (5) | 2/27 (7) |
|  |  |  |  |  |
| **Treatment-related variables** |  |  |  |  |
| Intravenous antibiotic therapy on day 0a  | 95/130 (73) | 27/36 (75) | 89/104 (86) | 23/27 (85) |
| Inappropriate antibiotic therapy on day 0a  | 120/130 (92) | 35/36 (97) | 99/104 (95) | 25/27 (93) |
| Day of initiation of appropriate antibiotic therapy  |  |  |  |  |
| - Deceased/censoredb before day +4a  | 10/129 (8) | 3/36 (8) | 6/104 (6) | 4/27 (15) |
| - Day 0a  | 10/129 (8) | 1/36 (3) | 5/104 (5) | 2/27 (7) |
| - Day +1a  | 18/129 (14) | 3/36 (8) | 35/104 (34) | 4/27 (15) |
| - Day +2a  | 23/129 (18) | 4/36 (11) | 44/104 (42) | 12/27 (44) |
| - Day +3a  | 29/129 (22) | 5/36 (14) | 7/104 (7) | 2/27 (7) |
| - No appropriate antibiotic therapy before day +4a  | 39/129 (30) | 20/36 (56) | 7/104 (7) | 3/27 (11) |
| >=7 days of appropriate antibiotic therapy (if initiated before day +4a and no death during)  | 64/75 (85) | 10/11 (91) | 52/75 (69) | 15/17 (88) |
| Source control performed before day +7a (if applicable to source)  | 38/79 (48) | 8/19 (42) | 25/47 (53) | 4/13 (31) |
|  |  |  |  |  |
| **Outcome variables** |  |  |  |  |
| ICU admission before day +7a (if not yet in ICU) | 4/82 (5) | 4/25 (16) | 9/79 (11) | 1/21 (5) |
| Length of hospital stay after bacteremia onset (median, IQR)  | 22 (10-38) | 13 (8-24) | 16 (8-36) | 14 (6-30) |
| In-hospital mortality  | 34/130 (26) | 10/36 (28) | 38/104 (37) | 16/27 (59) |
| Mortality before day +30a | 35/130 (27) | 12/36 (33) | 40/104 (38) | 13/27 (48) |

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination.

a Day 0 is the day of the index blood culture of the ARE/VRE bacteremia episode.
b One Dutch patient with ARE bacteremia was censored for the assessment of antibiotic therapy (not for mortality) due to transfer to another hospital.

**Supplementary Table S3. Full overview of adjusted regression models for 30-day mortality**

|  | **Netherlands and Denmark combined** | **Netherlands only** |
| --- | --- | --- |
| **Main****analysis****- full** | **Main****analysis****- reduced** | **Sensitivity****analysis** | **Main****analysis****- full** | **Main****analysis****- reduced** | **Sensitivity****analysis****- full** | **Sensitivity****analysis****- reduceda** | **Combined****analysisb** | **With APSc** |
| *No of patients analyzed*  | *292* | *297* | *29* | *165* | *166* | *166* | *166* | *166* | *166* |
| *No of deaths* | *100* | *100* | *99* | *47* | *47* | *47* | *47* | *47* | *47* |
| *No of variables in model*  | *16* | *5* | *8* | *16* | *3* | *20* | *5* | *7* | *9* |
| *Ratio of events to variables*  | *6.2* | *20* | *12.4* | *2.9* | *15.7* | *2.4* | *9.4* | *6.7* | *5.2* |
| Vancomycin resistance | 1.49 (0.97-2.31) | 1.54 (1.06-2.25) | 1.49 (0.99-2.22) | 1.82 (0.81-4.09) | 1.81 (0.98-3.36) | 1.05 (0.46-2.43) | 1.10 (0.60-2.04) | 1.62 (0.85-3.12) | 1.17 (0.55-2.52) |
| Aged |  |  | 1.02 (0.98-1.07) |  |  | 1.03 (0.96-1.12) |  |  |  |
| Age’d |  |  | 0.99 (0.94-1.04) |  |  | 1.02 (0.94-1.11) |  |  |  |
| Number of comorbidities: 1-2 |  |  |  |  |  | 0.32 (0.17-0.60) | 0.23 (0.11-0.50) | 0.29 (0.14-0.60) | 0.19 (0.08-0.48) |
| Number of comorbidities: 3+ |  |  |  |  |  | 6.48 (2.43-17.27) | 0.64 (0.23-1.78) | 0.59 (0.20-1.75) | 0.43 (0.14-1.37) |
| Solid malignancy  | 1.16 (0.62-2.18) | 2.28 (1.47-3.53) |  | 1.25 (0.46-3.41) | 2.20 (1.17-4.13) | 0.90 (0.44-1.82) |  | 1.72 (0.77-3.81) | 2.15 (0.86-5.39) |
| Metastasized solid malignancy | 2.76 (1.39-5.46) |  | 3.45 (2.03-5.85) | 3.80 (1.18-12.24) |  | 9.48 (2.88-31.21) | 3.61 (1.54-8.51) | 2.43 (0.96-6.13) | 2.50 (0.98-6.39) |
| Myocardial infarction | 0.65 (0.30-1.38) |  |  | 0.33 (0.11-0.96) |  | 0.11 (0.04-0.34) |  |  |  |
| Diabetes mellitus | 1.87 (1.12-3.12) | 1.81 (1.11-2.96) |  | 3.05 (1.45-6.39) |  |  |  |  |  |
| Chronic renal disease | 1.57 (0.86-2.87) |  |  | 0.37 (0.13-1.06) |  |  |  |  |  |
| Chronic pulmonary disease | 1.17 (0.70-1.93) |  |  | 1.62 (0.82-3.20) |  | 0.30 (0.15-0.60) |  |  |  |
| Cerebrovascular disease | 0.54 (0.26-1.10) | 0.37 (0.16-0.83) |  | 0.07 (0.02-0.27) |  | 0.00 (0.00-0.03) |  |  |  |
| Immunodeficiency |  |  |  |  |  | 0.20 (0.03-1.34) |  |  |  |
| Neutropenia at bacteremia onset | 0.73 (0.32-1.68) |  |  | 0.15 (0.04-0.54) |  |  |  |  |  |
| Treatment restriction in place at bacteremia onset | 1.89 (1.12-3.21) |  |  | 2.59 (1.32-5.07) |  | 2.80 (1.42-5.52) |  |  |  |
| Preceding hospital admission within 3 months prior to bacteremia |  |  | 1.28 (0.86-1.92) |  |  | 0.54 (0.30-0.97) |  |  |  |
| Surgical procedure within 30 days prior to bacteremia | 1.68 (0.93-3.06) |  |  | 2.24 (0.94-5.35) |  | 0.98 (0.39-2.44) |  |  |  |
| Central venous catheter at bacteremia onset | 1.12 (0.60-2.11) |  |  | 0.42 (0.13-1.31) |  |  |  |  |  |
| Mechanical ventilation at bacteremia onset | 2.68 (1.15-6.25) | 3.44 (1.46-8.12) | 2.34 (0.96-5.69) | 23.80 (5.28-107.28) | 12.63 (3.76-42.38) | 20.82 (2.01-215.99) |  | 8.28 (2.15-31.83) | 5.66 (1.55-20.63) |
| Known colonization with ARE |  |  | 1.07 (0.61-1.87) |  |  | 0.54 (0.23-1.28) |  |  |  |
| Known colonization with VRE | 0.85 (0.36-2.00) |  | 0.93 (0.40-2.15) | 2.19 (0.81-5.96) |  | 1.83 (0.56-6.02) |  |  |  |
| β-lactam use within 30 days prior to bacteremia |  |  |  |  |  | 0.26 (0.07-0.99) |  |  |  |
| Penicillin use within 30 days prior to bacteremia |  |  |  |  |  | 1.79 (0.63-5.08) |  |  |  |
| Carbapenem use within 30 days prior to bacteremia | 0.78 (0.42-1.44) |  |  | 0.47 (0.17-1.28) |  |  |  |  |  |
| Vancomycin use within 30 days prior to bacteremia | 1.12 (0.59-2.15) |  |  | 2.29 (1.11-4.70) |  | 3.79 (1.80-7.98) | 1.79 (0.77-4.16) | 1.27 (0.51-3.14) | 1.74 (0.70-4.30) |
| Acute physiology score (APS)d |  |  |  |  |  |  |  |  | 0.98 (0.94-1.04) |
| Acute physiology score (APS)’d |  |  |  |  |  |  |  |  | 1.05 (0.99-1.11) |

This table presents risk ratios (RR, with 95% CI) for *30-day mortality* for the exposure of interest (*vancomycin resistance*) and confounders.

a As the point estimate for *vancomycin resistance* in the sensitivity analysis fluctuated near 1, it became overfitted using the standard 10% inclusion criterion. Therefore, an extra variable reduction round was added, in which the β coefficient for *vancomycin resistance* had to remain within a 200% margin of the β coefficient in the full sensitivity analysis.
b As the point estimates for *vancomycin resistance* differed considerably between the main analysis (reduced) and the sensitivity analysis (reduced), an extra model was created that combined confounding variables retained in both. This model was considered optimally corrected for confounding with regular confounders and was used as reference when including the extra confounder  *Acute Physiology Score before bacteremia onset*.
c See description in *Analysis with Acute Physiology Score* in this Supplementary Material.
d Continuous variable included in the model as a restricted cube spline with three knots.

**Supplementary Table S4. Results of sensitivity analyses for adjusted models for 1-year mortality and models evaluating appropriateness of antibiotic therapy**

|  |  |  |
| --- | --- | --- |
|  | **Main analysis** | **Sensitivity analysis** |
|  | **No of****patients****analyzed** | **No of****deaths** | **No of****variables****in model** | **Ratio of****events to****variables** | **Effect estimate of exposure of interest****(95% CI)** | **No of****patients****analyzed** | **No of****deaths** | **No of****variables****in model** | **Ratio of****events to****variables** | **Effect estimate of exposure of interest****(95% CI)** |
| **One-year follow-up for mortality** | 294 | 170 | 12 | 14.2 |  | 297 | 170 | 7 | 24.3 |  |
| Vancomycin resistance |  |  |  |  | HR 1.25 (0.80-1.98) |  |  |  |  | HR 1.46 (0.95-2.25) |
|  |  |  |  |  |  |  |  |  |  |  |
| **30-day mortality****- baseline after day 0** | 289 | 95 | 9 | 10.6 |  | 285 | 94 | 16 | 5.9 |  |
| ARE – on inappropriate therapy |  |  |  |  | Reference |  |  |  |  | Reference |
| ARE – on appropriate therapy  |  |  |  |  | RR 0.33 (0.08-1.40) |  |  |  |  | RR 0.31 (0.08-1.13) |
| VRE – on inappropriate therapy  |  |  |  |  | RR 1.69 (1.09-2.61) |  |  |  |  | RR 1.42 (0.79-2.55) |
| VRE – on appropriate therapy |  |  |  |  | NA |  |  |  |  | NA |
|  |  |  |  |  |  |  |  |  |  |  |
| **30-day mortality****- baseline after day +1** | 276 | 87 | 14 | 6.2 |  | 278 | 87 | 17 | 5.1 |  |
| ARE – on inappropriate therapy |  |  |  |  | Reference |  |  |  |  | Reference |
| ARE – on appropriate therapy  |  |  |  |  | RR 0.79 (0.43-1.45) |  |  |  |  | RR 0.69 (0.38-1.28) |
| VRE – on inappropriate therapy  |  |  |  |  | RR 2.01 (1.13-3.57) |  |  |  |  | RR 1.81 (0.99-3.31) |
| VRE – on appropriate therapy |  |  |  |  | RR 5.79 (1.43-23.40) |  |  |  |  | RR 2.60 (0.55-12.32) |
|  |  |  |  |  |  |  |  |  |  |  |
| **30-day mortality****- baseline after day +2** | 268 | 80 | 14 | 5.7 |  | 270 | 80 | 15 | 5.3 |  |
| ARE – on inappropriate therapy |  |  |  |  | Reference |  |  |  |  | Reference |
| ARE – on appropriate therapy  |  |  |  |  | RR 0.82 (0.47-1.43) |  |  |  |  | 0.88 (0.42-1.84) |
| VRE – on inappropriate therapy  |  |  |  |  | RR 2.43 (0.94-6.33) |  |  |  |  | 2.38 (0.99-5.74) |
| VRE – on appropriate therapy |  |  |  |  | RR 1.73 (0.83-3.61) |  |  |  |  | 2.12 (0.88-5.09) |

This table compares effect estimates for the exposures of interest between the main analyses and sensitivity analyses of the adjusted models presented in the main text, including Table 4.

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, risk ratio.

**Supplementary Table S5. Incidence density of mortality stratified by time to initiation of appropriate antibiotic therapy**

|  |  |  |
| --- | --- | --- |
|  | **Netherlands** | **Denmark** |
|  | **Patient days****observed** | **Deaths** | **Incidence density (per 1,000 patient days)** | **Patient days****observed** | **Deaths** | **Incidence density (per 1,000 patient days)** |
| Appropriate therapy from day 0 onwards | 276 | 2 | 7 | 183 | 1 | 6 |
|  from day +1 onwards | 470 | 8 | 17 | 873 | 13 | 15 |
|  from day +2 onwards | 680 | 5 | 7 | 1144 | 20 | 18 |
|  from day +3 onwards | 877 | 3 | 3 | 158 | 6 | 38 |
| Inappropriate therapy on days 0 through +3 | 436 | 14 | 32 | 233 | 10 | 43 |
| Inappropriate therapy at the end of day +3 | 1303 | 15 | 12 | 228 | 3 | 13 |
| **Total** | **4042** | **47** | **12** | **2818** | **53** | **19** |

This table depicts incidence densities for each level of the time-varying variable reflecting *appropriateness of antibiotic therapy*. Patients not receiving appropriate therapy on the day of the index blood culture (day 0), start off within *inappropriate therapy on days 0 through +3*. If patients within the latter group started to receive appropriate therapy on day +1, +2 or +3, they transition to the relevant appropriate therapy level on that day, and stay within that level for the remainder of follow-up. Patients not starting appropriate therapy during those days, transition to *inappropriate therapy at the end of day +3* on day +4, and remain there throughout follow-up. Follow-up lasts until day +30 or death if occurring before day +30.

**Supplementary Figure S1. Distribution of VRE and matched ARE bacteremias over study years**

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This figure indicates, separately for each study year, the proportion of bacteremia episodes from each of the four categories composed by country and vancomycin resistance.

1. This set can be found in Supplementary Table S3, in the *Main analysis – full* column. For the model for 1-year mortality, this set was expanded with sex, age (modelled as restricted cubic spline with three knots), and antibiotic use within 30 days prior to bacteremia. For models evaluating appropriateness of antibiotic therapy, myocardial infarction, carbapenem use within 30 days prior to bacteremia, and vancomycin use within 30 days prior to bacteremia were removed from the set, and length of hospital stay prior to bacteremia (restricted cubic spline with three knots), age (restricted cubic spline with three knots), cephalosporin use within 30 days prior to bacteremia, source control performed prior to baseline, severe sepsis at bacteremia onset, and bacteremia source (primary/central line/unknown, biliary, intra-abdominal, other) were added. [↑](#footnote-ref-1)
2. This set includes all variables listed underneath the header *Potential confounding variables* in Supplementary Table S2, except for hospital ward at bacteremia onset, bacteremia origin, length of ICU stay prior to bacteremia, hematological malignancy – under treatment, and SOD/SDD use within 30 days prior to bacteremia. Age and length of hospital stay prior to bacteremia were modelled as restricted cubic splines with three knots. Charlson index was modelled with two separate variables, namely Charlson index: 3+, and Charlson index: 5+. For models evaluating appropriateness of antibiotic therapy, source control performed prior to baseline, severe sepsis at bacteremia onset, and bacteremia source (primary/central line/unknown, biliary, intra-abdominal, other) were added. [↑](#footnote-ref-2)