Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial

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Summary

Background Ventilator-associated pneumonia (VAP) is associated with increased mortality, prolonged hospitalisation, excessive antibiotic use and, consequently, increased antimicrobial resistance. In this phase 4, randomised trial, we aimed to establish whether a pragmatic, individualised, short-course antibiotic treatment strategy for VAP was non-inferior to usual care.

Methods We did an individually randomised, open-label, hierarchical non-inferiority–superiority trial in 39 intensive care units in six hospitals in Nepal, Singapore, and Thailand. We enrolled adults (age ≥18 years) who met the US Centers for Disease Control and Prevention National Healthcare Safety Network criteria for VAP, had been mechanically ventilated for 48 h or longer, and were administered culture-directed antibiotics. In culture-negative cases, empirical antibiotic choices were made depending on local hospital antibiograms reported by the respective microbiology laboratories or prevailing local guidelines. Participants were assessed until fever resolution for 48 h and haemodynamic stability, then randomly assigned (1:1) to individualised short-course treatment (≤7 days and as short as 3–5 days) or usual care (≥8 days, with precise durations determined by the primary clinicians) via permuted blocks of variable sizes (8, 10, and 12), stratified by study site. Independent assessors for recurrent pneumonia and participants were masked to treatment allocation, but clinicians were not. The primary outcome was a 60-day composite endpoint of death or pneumonia recurrence. The non-inferiority margin was prespecified at 12% and had to be met by analyses based on both intention-to-treat (all study participants who were randomised) and per-protocol populations (all randomised study participants who fulfilled the eligibility criteria, met fitness criteria for antibiotic discontinuation, and who received antibiotics for the duration specified by their allocation group). This study is registered with ClinicalTrials.gov, number NCT03382548.

Findings Between May 25, 2018, and Dec 16, 2022, 461 patients were enrolled and randomly assigned to the short-course treatment group (n=232) or the usual care group (n=229). Median age was 64 years (IQR 51–74) and 181 (39%) participants were female. 460 were included in the intention-to-treat analysis after excluding one withdrawal (231 in the short-course group and 229 in the usual care group); 435 participants received the allocated treatment and fulfilled eligibility criteria, and were included in the per-protocol population. Median antibiotic treatment duration for the index episodes of VAP was 6 days (IQR 5–7) in the short-course group and 14 days (10–21) in the usual care group. 95 (41%) of 231 participants in the short-course group met the primary outcome, compared with 100 (44%) of 229 in the usual care group (risk difference –3% [one-sided 95% CI –∞ to 5%]). Results were similar in the per-protocol population. Non-inferiority of short-course antibiotic treatment was met in the analyses, although superiority compared with usual care was not established. In the per-protocol population, antibiotic side-effects occurred in 86 (38%) of 224 in the usual care group and 17 (8%) of 211 in the short-course group (risk difference –31% [95% CI –37 to –25%; p<0·0001]).

Interpretation In this study of adults with VAP, individualised shortened antibiotic duration guided by clinical response was non-inferior to longer treatment durations in terms of 60-day mortality and pneumonia recurrence, and associated with substantially reduced antibiotic use and side-effects. Individualised, short-course antibiotic treatment for VAP could help to reduce the burden of side-effects and the risk of antibiotic resistance in high-resource and resource-limited settings.

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Introduction

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection in the intensive care setting and is associated with a mortality of more than 30%.[1] Existing diagnostic criteria have low specificity,[2] and microbiology cultures of respiratory

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Research in context

Evidence before this study

We searched Embase, MEDLINE (Ovid), Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov for randomised controlled trials of antibiotic treatment duration for ventilator-associated pneumonia (VAP) published in English, from inception of the database up to May 1, 2023. The search terms used were 'ventilator-associated pneumonia', 'antibiotic', 'duration', and 'randomised controlled trial'.

We found five randomised trials, of which three achieved the target enrolment sample size; the other two were terminated prematurely because of slow accrual. All five trials showed that there was no major difference between short-course and long-course antibiotic therapy for 28-day mortality. There were trends towards increased VAP recurrence and relapses with short-course antibiotics among patients with Gram-negative non-fermenting bacilli (ie, *Pseudomonas* spp, *Acinetobacter* spp, or *Stenotrophomonas* spp) isolated from sputum cultures. All these trials adopted arbitrary fixed antibiotic treatment durations, independent of how quickly patients responded to treatment, and were restricted mainly to high-income settings. Current international guidelines recommend 7–8 days of antibiotics for VAP, and potentially shorter durations depending on the rate of improvement of the patient's clinical, radiological, and laboratory parameters. However, the approach

for identifying patients who might be suitable for shorter antibiotic treatment durations is not clearly defined.

Added value of this study

Our study showed that individualised short-course antibiotic treatment (median treatment duration 6 days [IQR 5–7]) was non-inferior to usual care (median treatment duration 14 days [IQR 10–20]) for the primary outcome of 60-day mortality or pneumonia recurrence. There was no increased risk of 60-day mortality or pneumonia recurrence for VAP associated with carbapenem-resistant Gram-negative bacilli or Gram-negative non-fermenting bacilli. There was a substantial reduction in antibiotic side-effects, from 38% in the usual care group to 8% in the individualised short-course group.

Implications of all the available evidence

These results support the use of clinical response to individualise antibiotic treatment duration for VAP associated with highly resistant Gram-negative bacilli and across various resource settings. The clinical response criteria, based on normalisation of body temperature and blood pressure, are simple and reproducible, and can be adopted by both prescribing clinicians and other health-care professionals to guide antibiotic stewardship policies, including in resource-limited settings.

samples cannot be used to differentiate between colonising bacteria and true bacterial pathogens. These factors might result in overdiagnosis and overtreatment of VAP with empirical combinations of broad-spectrum antibiotics.

Given that VAP is a major driver of antibiotic consumption in the intensive care setting, and in the absence of gold-standard diagnostics,[3] a pragmatic approach to minimise antibiotic treatment duration is needed. Critically ill patients differ in terms of their immune status and suffer infections by pathogens with various virulence and resistance profiles.[4] Clinical experience and previous studies have shown that patients with VAP have varying treatment response times and that short-course antibiotic treatment can be safe in those with early recovery.[5,6] The biomarker procalcitonin is a potential indicator for adequate response to antibiotic treatment, and its use to individualise antibiotic duration for the treatment of VAP has been investigated in randomised trials. However, a meta-analysis of trials using procalcitonin to inform decisions to stop antibiotics for VAP found that it only reduced treatment duration from 13 to 11 days,[7] which is considerably longer than the recommended 7–8 days.[8,9] There are further uncertainties for VAP associated with Gram-negative non-fermenting bacilli (ie, *Pseudomonas* spp, *Acinetobacter* spp, or *Stenotrophomonas* spp) and those with no positive sputum cultures. Increased pneumonia recurrence with

short-course antibiotics has been reported in both observational studies and randomised trials of patients with Gram-negative non-fermenting bacilli isolated from sputum cultures.[7,10]

The current major international guidelines, including those by WHO, the Infectious Disease Society of America (IDSA), and the European Society of Clinical Microbiology and Infectious Diseases, recommend a fixed 7–8 days of antibiotic treatment for VAP, and potentially shorter or longer durations depending on clinical improvement.[8,9,11] This recommendation is mainly based on three randomised trials that adopted arbitrary, fixed antibiotic durations.[12–14] Importantly, the approach for identifying patients who might be suitable for shorter-course antibiotics is not defined and has not previously been investigated in randomised trials. In addition, these three trials were done mostly in high-income settings, whereas VAP is more common in low-to-middle-income settings in which infection prevention and control and antibiotic stewardship policies are often less robust than in high-income settings.[15] There is also no evidence about optimal antibiotic duration for culture-negative VAP, which is thought to occur frequently because of previous antibiotic exposure in critically ill patients with prolonged stay in the intensive care unit.

We did the phase 4 Reducing Antibiotics Treatment Duration for Ventilator-Associated Pneumonia (REGARD-VAP) trial to assess the non-inferiority of a

pragmatic, individualised short-course treatment strategy using a set of reproducible clinical criteria to individualise antibiotic duration for the treatment of VAP.

Methods

Study design

REGARD-VAP was an individually randomised, single-blind, hierarchical non-inferiority–superiority trial to assess the clinical effect of an individualised short-duration antibiotic course versus usual care in adults with VAP in six hospitals in Nepal, Singapore, and Thailand.[10] One hospital from Brazil also participated in the study, but this site was excluded in the final analysis due to slow enrolment (only one patient was randomised) and no monitoring for data quality assurance. The individualised short-course treatment strategy considered the participants' clinical responses, defined by defervescence for 48 h and stable blood pressure without inotropic support, to discontinue antibiotics within 7 days of treatment. Antibiotic choices were culture-directed for both groups.

The overall sponsor of the study was the University of Oxford. We obtained approval from the Oxford Tropical Research Ethics Committee before applications to the respective local ethics committees were submitted (reference number OxTREC 40-17; appendix 3). The trial protocol was developed in accordance with the SPIRIT 2013 statement and CONSORT statement extension for non-inferiority and equivalence trials (appendix 3 pp 24–53). The clinical trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines.

Participants

We recruited adults (aged ≥18 years) from 39 intensive care units in the six hospitals from Nepal, Singapore, and Thailand with intensive care units and an accredited microbiology laboratory. All admissions to the intensive care units were screened according to the US Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) VAP diagnostic criteria, which included respiratory signs and symptoms compatible with pneumonia, mechanically ventilated for 48 h or longer, and new radiological changes.[16] We adopted the US CDC NHSN diagnostic criteria because they consist of clinical and radiographical criteria without the need for biomarker testing or bronchoscopy, which might not be readily available in all settings. We excluded patients who had a poor likelihood of survival as defined by a Sequential Organ Failure Assessment (SOFA) score of more than 11 points (corresponding to in-hospital mortality of more than 80%),[17] were immuno-compromised (ie, HIV with CD4 <200 cells/mm³, corticosteroids >0·5 mg/kg per day for >30 days, chemotherapy in the past 3 months, or solid organ or haematopoietic stem-cell transplant), or had other concurrent infections that required antibiotic treatment for longer than 7 days (excluding anti-tuberculosis treatment, antifungal medications, and antibiotics meant for chronic suppression of chronic infections or chronic obstructive lung disease). Details of all inclusion and exclusion criteria are available in the supplementary material (appendix 3 pp 36–37). Each participant could only be enrolled once into the trial. Written informed consent was obtained from every participant or the participant's legal representative, or the next-of-kin if the participant was sedated and did not have decision-making capacity.

Randomisation and masking

We randomly allocated participants to either the individualised short-course group (≤7 days of treatment, and as short as 3–5 days) or the usual care group (≥8 days of treatment, with precise durations determined by the primary clinicians). Randomisation was done in a 1:1 ratio, via permuted blocks of variable sizes (8, 10, and 12), and stratified by study sites. The randomisation sequence was generated with a computer program using a seed. Allocation was performed using sequentially numbered opaque envelopes. We required that fitness criteria for the discontinuation of antibiotics were met before randomisation.

To minimise observer bias by the primary clinicians and study investigators, randomisation took place after study participants met the fitness criteria for antibiotic discontinuation, ensuring that study participants did not receive differential treatment during the episode of VAP before the time when fitness criteria were met. After randomisation, investigators contacted the primary clinicians to stop antibiotics for those participants randomly assigned to the short-course group. Clinicians were not masked to treatment allocation. Independent assessors, who established pneumonia recurrence, were masked to the randomisation groups. Patients were masked as they were not informed of the treatment duration, and many were likely to be sedated and unaware of the treatment regimens.

See Online for appendix 3

Procedures

Endotracheal respiratory cultures were collected either as endotracheal tube aspiration or bronchoalveolar lavage as ordered by the primary clinicians as clinically indicated. Microbiology cultures were processed and reported in the local laboratories that had standing quality control accreditations. Antimicrobial suscepti-bility studies were reported using European Committee on Antimicrobial Susceptibility Testing or Clinical and Laboratory Standards Institute agar methods and breakpoints. We calculated the number of days of antibiotic treatment from the first day of culture-directed antibiotic coverage according to the susceptibility of at least one of the pathogens recovered from respiratory cultures taken within 48 h of screening or VAP symptom

onset, in accordance with the 2016 IDSA/American Thoracic Society VAP guideline.[9] In culture-negative cases, empirical antibiotic choices were made depending on local hospital antibiograms reported by the respective microbiology laboratories or prevailing local guidelines.

Following enrolment, we reviewed participants daily for fitness criteria to stop antibiotics. These criteria included: (1) body temperature of lower than 38·3°C (core body temperature measured orally or rectally) or lower than 38·0°C (axillary) for 48 h, and (2) haemodynamic stability (systolic blood pressure ≥90 mm Hg without inotropic support or no requirement of inotropic support to maintain systolic blood pressure above 90 mm Hg). We determined these criteria together with intensive care, respiratory, and infectious diseases clinicians from participating sites. When these fitness criteria were met, the protocol specified that all antibiotics for participants randomly assigned to the short-course group were to be stopped as early as day 3 if the respiratory culture was negative, as early as day 5 if the respiratory culture was positive and, in all cases, within 7 days of starting treatment for VAP. For participants in the usual care group, the protocol specified that antibiotic treatment should last at least 8 days with the precise duration determined by the primary clinicians.

Non-adherence, especially in non-inferiority trials, is challenging to account for in the analysis and complicates interpretation of results.[18] To ensure adherence, the study team carried out regular meetings with local investigators and health-care providers to elicit feedback on study procedures and to maintain engagement. Before enrolment and randomisation, the study team contacted the primary clinicians to confirm their intention to adhere to allocated interventions. Post-randomisation reminders were sent to the primary clinicians to ensure antibiotics were stopped in the short-course group.

We collected relevant clinical and laboratory-related information, including demographics, medical history, antibiotics administration records, chest X-ray or other imaging findings, and biochemical, microbiological, and haematological laboratory results and clinical parameters, using paper and electronic case record forms. We followed up participants daily while on antibiotics, and subsequently weekly when remaining hospitalised. Following discharge, two further follow-up visits were scheduled at day 28 and 60 after enrolment. Further details of the procedures are available in the supplementary material (appendix 3 pp 37–40).

Outcomes
The primary outcome was the composite endpoint of death or pneumonia recurrence within 60 days of enrolment. Recurrent pneumonia was defined as an additional episode of pneumonia determined by two independent intensive care, infectious disease, or respiratory medicine specialists masked to group allocation and antibiotic treatment durations. Day 60 was

chosen for the primary outcome in preference to day 30 to reduce any bias that might occur with participants in the short-course group having more antibiotic-free days, thereby leading to a differential detection of recurrences between the groups. In addition, a previous observational study suggested that mortality attributable to VAP persists to day 60.[19]

The secondary outcomes were ventilator-associated events (ie, pneumonia recurrence determined by one assessor), duration of mechanical ventilation, duration of hospitalisation (including intensive care unit stay), total duration of exposure to antibiotics during hospitalisation, readmission to an acute care hospital, bloodstream infections after randomisation (the number of cultures from other sterile sites were negligible), and acquisition of multidrug-resistant infection or colonisation during hospitalisation. We also compared so-called potential pneumonia recurrences within 60 days of follow-up between the two treatment groups (ie, as determined by at least one independent infectious disease or respiratory medicine specialist). Antibiotic side-effects were evaluated post hoc using laboratory test values after administration of appropriate antibiotics for the treatment of index VAP episodes. We defined acute kidney injury according to the Kidney Disease Improving Global Outcomes guideline[20] and drug-induced liver injury according to Aithal and colleagues.[21] All mortalities and pneumonia recurrences were reported as serious adverse events to the Data Safety and Monitoring Board, local ethics boards, and the study sponsor. As a post-hoc analysis, mortalities attributed to pneumonia for which multidrug-resistant bacteria were grown in the sputum culture during the recurrent VAP episode were compared between the allocation groups.

Statistical analysis
The primary and secondary outcomes were analysed using both the intention-to-treat and per-protocol populations.[18] The intention-to-treat population included all study participants who were randomised. The per-protocol population included all randomised study participants who fulfilled the eligibility criteria, met fitness criteria for antibiotic discontinuation, and who received 7 days or fewer of culture-directed antibiotics in the short-course group or 8 days or more in the usual care group.

We did an adjusted intention-to-treat analysis using g-computation (and bootstrapping for CIs) to estimate the absolute risk difference between the two study groups.[22] G-computation was performed firstly through a regression of the composite binary outcome on the intervention and baseline participant characteristics using a multivariable logistic regression model. We then predicted counterfactual outcomes for the short-course and usual care groups for each study participant using the estimated parameters from the model. The mean predicted value for the short-course strategy and usual

care across all study participants was calculated and used to estimate the absolute risk difference between the short-course strategy and usual care. In addition, we did an adjusted per-protocol analysis with inverse probability weighting to account for non-adherence.[23] We calculated propensity scores (ie, the conditional probabilities of receiving the allocated antibiotic treatment duration given baseline participant characteristics) using a multivariable logistic regression model. Inverse probability weights were then calculated by the inverse of the conditional probabilities, which were stabilised by multiplying by the marginal probability of receiving the actual intervention. The baseline characteristics used in the above models were study site, age, sex, comorbidities, residence before admission, type of intensive care unit admitted to, SOFA score, VAP infection with carbapenem-resistant Gram-negative bacilli, duration of intubation before developing VAP, reason for intubation, and number of days from first respiratory symptom onset to first day of appropriate antibiotics.

This trial had a hierarchical non-inferiority–superiority hypothesis. The first analysis we did was to determine non-inferiority. Only if non-inferiority was established by this primary analysis was a second analysis for superiority done.[24] Non-inferiority was to be concluded if the upper limit of the one-sided 95% CIs for absolute risk difference from both unadjusted and adjusted intention-to-treat and per-protocol analyses did not cross the non-inferiority margin. Superiority would be declared if the entire one-sided 97·5% CIs for all analyses estimates were below 0.

We expected 55% of the participants in the usual care group to experience the primary outcome (a composite binary outcome of mortality or VAP recurrence). This proportion was based on a global mortality of 14–43% associated with VAP,[25,26] 14–40% pneumonia recurrence after VAP (with increased incidence in those caused by Gram-negative non-fermenting bacilli[25,27]), and 17–50% mortality associated with VAP recurrences.[25,27] We chose an absolute non-inferiority margin of 12%, which was based on the joint recommendations from the US Food and Drug Administration, the IDSA, the ATS, the Society of Critical Care Medicine, and the American College of Chest Physicians that a 10% non-inferiority margin should be used for trials of antibacterial agents for VAP when only mortality is considered.[28] The additional 2% was to account for expected pneumonia recurrences. Using a group sequential design adopting the boundaries proposed by Fleming, Harrington, and O'Brien, a maximum of 412 participants were required to achieve a power of 80% to correctly conclude non-inferiority under the assumption of equal treatment efficacy with a one-sided α-risk of 5%.[29] As we anticipated a 10% loss to follow-up, we planned to enrol 460 participants.

Interim analyses were done after every 125 participants (25%) were randomly allocated and completed follow-up, to ensure trial safety and data quality. The Data Safety and Monitoring Board had full access to the data and

reviewed the interim analysis reports. A Trial Steering Committee was also constituted and jointly decided on termination or continuation of the trial. The trial was to be terminated prematurely if superiority of either the individualised short-course strategy or usual care was shown during interim analyses.

Two subgroup analyses were pre-specified for participants with VAP caused by Gram-negative non-fermenting bacilli and carbapenem-resistant bacilli, based on the intention-to-treat population. We did subgroup analyses with tests for interaction on both multiplicative and additive scales. We calculated multiplicative interaction effects using multivariable logistic regression models with the occurrence of the primary endpoint as the dependent variable and the allocated antibiotic treatment duration, pathogen type,
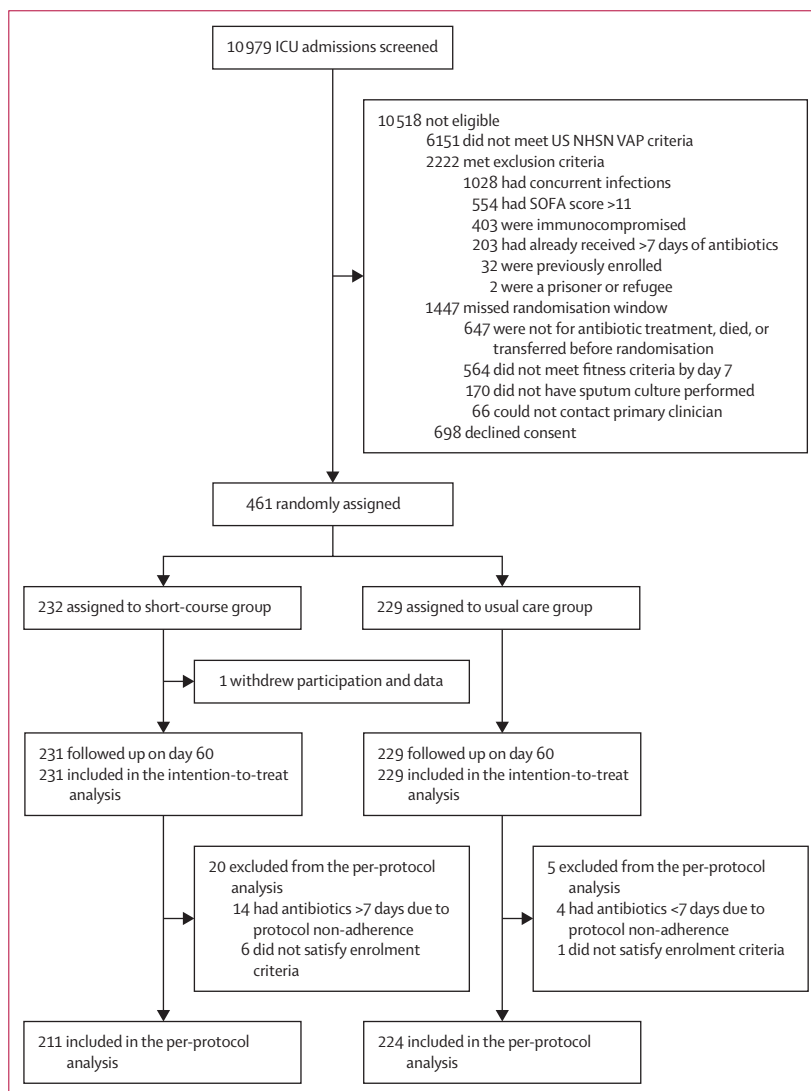

Figure 1: CONSORT diagram
ICU=intensive care unit. NHSN=National Healthcare Safety Network. SOFA=Sequential Organ Failure Assessment. VAP=ventilator-associated pneumonia.

	Short-course group (n=231)	Usual care group (n=229)
Median (IQR) age at enrolment, years	63 (50–73)	64 (52–75)
Sex		
Female	97 (42%)	84 (37%)
Male	134 (58%)	145 (63%)
Country from which patients were enrolled		
Nepal	20 (9%)	19 (8%)
Singapore	24 (10%)	26 (11%)
Thailand	187 (81%)	184 (80%)
Residence before intensive care unit admission		
Community*	76 (33%)	63 (28%)
Transfer from another health-care facility	155 (67%)	166 (72%)
Mean (SD) Charlson Comorbidity Score	3·1 (3·4)	3·2 (2·4)
Comorbidities		
Congestive heart failure	27 (12%)	14 (6%)
Coronary heart disease	12 (5%)	15 (7%)
Chronic obstructive pulmonary disease	22 (10%)	17 (7%)
Liver cirrhosis	7 (3%)	2 (1%)
Chronic kidney disease	30 (13%)	31 (14%)
Cancer	12 (5%)	11 (5%)
Diabetes	43 (19%)	63 (28%)
Median (IQR) SOFA score	6 (4–8)	6 (4–8)
Median (IQR) time between VAP symptom onset date to culture-directed antibiotics, days	0 (0–3)	0 (0–2)
Proportion of participants who received culture-directed antibiotics on the first day of symptom onset	123 (53%)	122 (53%)
Type of intensive care unit		
Medical	71 (31%)	73 (32%)
Surgical	160 (69%)	156 (68%)
Median (IQR) duration of intubation before VAP, days	15 (11–22)	14 (10–23)
Reason for intubation		
Cardiovascular failure	2 (1%)	9 (4%)
Metabolic acidosis	3 (1%)	6 (3%)
Neurological failure	60 (26%)	59 (26%)
Post-operative care	19 (8%)	23 (10%)
Respiratory failure	103 (45%)	92 (40%)
Trauma or airway obstruction	44 (19%)	40 (17%)
Carbapenem-resistant Gram-negative bacilli grown in respiratory sample during the index episode of VAP	76 (33%)	65 (28%)
Vital signs during VAP symptom onset		
Mean (SD) lowest MAP, mm Hg	72 (12)	73 (12)
Mean (SD) maximum heart rate, beats per min	120 (18)	120 (19)
Required inotropic support	40 (17%)	47 (21%)
Median (IQR) SpO₂:FiO₂ ratio	225 (192–245)	235 (196–248)
Presence of fever	176 (76%)	189 (83%)
Vital signs on day of randomisation		
Mean (SD) lowest MAP, mm Hg	83 (13)	85 (13)
Mean (SD) maximum heart rate, beats per min	100 (17)	100 (17)
Required inotropic support	11 (5%)	11 (5%)
Median (IQR) SpO₂:FiO₂ ratio	250 (231–250)	250 (233–250)

Data are n (%) unless otherwise stated. MAP=mean arterial pressure. SOFA=Sequential Organ Failure Assessment. $SpO_2:FiO_2$=ratio of peripheral arterial oxygen saturation to the inspired fraction of oxygen. VAP=ventilator-associated pneumonia. *Patient not residing in a health-care facility before admission.

Table 1: Baseline characteristics of participants

and the interaction between allocated antibiotic treatment duration and pathogen type as explanatory variables. We reported additive interaction effects as relative excess risk due to interaction, which referred to the difference between the joint relative risk and the separate contributions by the allocated antibiotic treatment duration and pathogen type.[30] We did an additional post-hoc, exploratory, subgroup analysis for culture-positive versus culture-negative VAP. The full study analysis plan is included in the appendix 3 (pp 224–253). This study is registered with ClinicalTrials.gov, number NCT03382548. All analyses were performed in R version 4.3.1.

Roles of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between May 25, 2018 and Dec 16, 2022, 461 patients were enrolled and randomly assigned to the individualised short-course group (n=232) or usual care group (n=229; figure 1). Due to the COVID-19 pandemic and local restrictions, enrolment was interrupted in various study sites at different timepoints between March, 2020 and January, 2022. None of the participants were known to have SARS-CoV-2 and the study teams were not able to screen and enrol in the COVID-19 wards for infection prevention and control reasons. All randomised participants were included in the intention-to-treat analysis, except for one who withdrew from the short-course group and did not wish for their data to be included in the final analysis.

The per-protocol analysis included 435 (95%) of 460 participants (211 in the short-course group and 224 in the usual care group). Exclusions from the per-protocol population were due to clinician non-adherence (n=18) and randomisation of participants who did not fulfil enrolment criteria (n=7). All 460 participants completed follow-up until day 60.

In the intention-to-treat population, the median age at enrolment was 64 years (IQR 51–74) and 181 (39%) were female (table 1). Most participants were enrolled from Thailand (371 [81%]). As most of the participating hospitals were referral-level or provincial-level hospitals, 321 participants (70%) were transferred from another health-care facility, and median duration of mechanical ventilation before VAP symptom onset was 14 days (10–22).

491 bacterial pathogens were isolated from 320 index episodes of VAP at enrolment in the intention-to-treat cohort (appendix 3 pp 10–12). The other 140 (30%) index VAP episodes were culture-negative. Most bacterial isolates were Gram-negative (460 [94%]); 258 (53%) were Gram-negative non-fermenting bacilli. 165 (34%) bacterial isolates (including *Acinetobacter* spp, *Pseudomonas* spp, and Enterobacterales) were carbapenem-resistant. 87 Enterobacterales isolates (18% of the total) were third-

generation cephalosporin-resistant. Of 320 index VAP episodes, six respiratory cultures were collected via bronchioalveolar lavage, whereas the rest were endotracheal aspirates.

The median antibiotic treatment duration for the index episodes of VAP was 6 days (IQR 5–7) in the short-course group and 14 days (10–21) in the usual care group (figure 2). 72 (31%) of 231 participants in the short-course group had antibiotic treatments restarted within 5 days. In terms of antibiotic choice, 215 (47%) of 460 participants had combination antibiotic treatments. The most common antibiotic regimen for carbapenem-resistant Gram-negative bacilli was colistin-based or polymyxin-B-based combinations (31 [41%] of 76 in the short-course group *vs* 32 [49%] of 65 in the usual care group; appendix 3 pp 13–14).

In the intention-to-treat population, 95 (41%) of 231 participants in the short-course group and 100 (44%) of 229 in the usual care group met the primary outcome of the composite endpoint of death or pneumonia recurrence within 60 days of enrolment (absolute risk difference –3% [one-sided 95% CI –∞ to 5%]; table 2). In the per-protocol population, 87 (41%) of 211 participants in the short-course group and 99 (44%) of 224 in the usual care group met the primary outcome (absolute risk difference –3 [one-sided 95% CI –∞ to 5%]; table 2). The adjusted intention-to-treat and per-protocol analyses showed similar effects. Non-inferiority, defined as the upper bound of the 95% CI being less than 12%, was met by all four analyses (figure 3). Superiority, defined as the upper bound of the one-sided 97·5% CI being less than 0, was not met by any of the four analyses (appendix 3 p 15). The frequency of primary outcomes between the two groups in the three countries were similar (ten [50%] of 20 in the short-course group *vs* eight [42%] of 19 in the usual care group in Nepal; five [21%] of 24 in the short-course group *vs* four [15%] of 26 in the usual care group in Singapore; 80 [43%] of 187 in the short-course group *vs* 88 [48%] of 184 in the usual care group in Thailand).

The subgroup analysis for participants with Gram-negative non-fermenting bacilli (218 in the intention-to-treat population) showed no major differences in terms of the primary outcome between the two treatment groups (multiplicative interaction effect odds ratio [OR] 1·38 [95% CI 0·65 to 2·92]; p=0·40; relative excess risk due to interaction 0·30 [–0·52 to 1·12]; p=0·24]), and neither did the subgroup analysis for participants with carbapenem-resistant Gram-negative bacilli (141 in the intention-to-treat population; 0·82 [0·37 to 1·83], p=0·62; –0·39 [–1·67 to 0·88], p=0·73); appendix 3 pp 16–18). Similarly, the exploratory subgroup analysis for culture-positive versus culture-negative VAP (n=140) did not show any difference in the primary outcome (multiplicative interaction effect OR 0·91 [0·22 to 3·82; p=0·91] and relative excess risk due to interaction –0·10 [–1·60 to 1·39; p=0·55]).

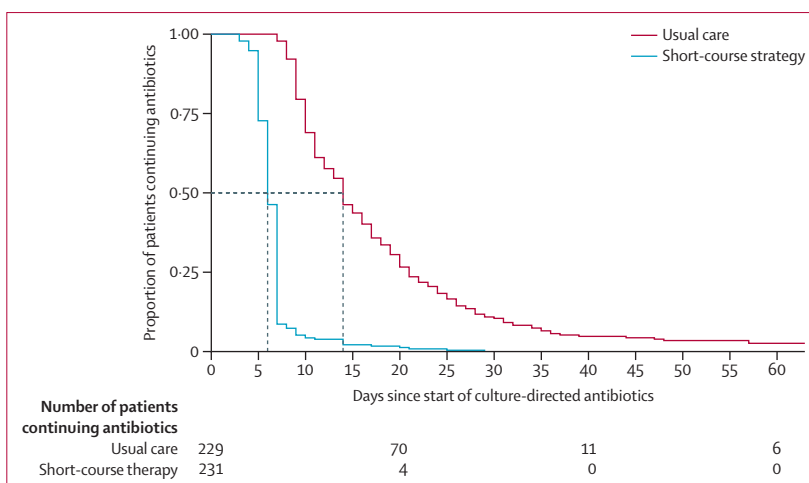During the 60-day follow-up period, 169 (37%) of

Figure 2: **Duration of antibiotics received by study participants for the index episodes of VAP by allocation groups (intention-to-treat population)**
Dotted lines represent median duration of antibiotic treatment in each group. VAP=ventilator-associated pneumonia.

	Mortality (%)	Recurrence of pneumonia (%)	Primary outcome (%)	Unadjusted absolute risk difference (one-sided 95% CI)	Adjusted absolute risk difference (one-sided 95% CI)
Intention-to-treat (n=460)	..	..	..	–3%(–∞ to 5%)	–2%(–∞ to 5%)
Short-course group (n=231)	81 (35%)	33 (14%)	95 (41%)	..	..
Usual care group (n=229)	88 (38%)	30 (13%)	100 (44%)	..	..
Per-protocol (n=435)	..	..	..	–3%(–∞ to 5%)	–2%(–∞ to 4%)
Short-course group (n=211)	76 (36%)	29 (14%)	87 (41%)	..	..
Usual care group (n=224)	87 (39%)	30 (13%)	99 (44%)	..	..

Data are n (%) unless otherwise stated.

Table 2: **Primary outcome: the composite endpoint of death or pneumonia recurrence within 60 days of enrolment**

460 participants died: 81 (35%) of 231 in the short-course group and 88 (38%) of 229 in the usual care group. As a post-hoc analysis in the intention-to-treat population, mortality was attributed to pneumonia for 27 (12%) participants in the short-course group and 28 (12%) participants in the usual care group (difference, –1·0; 95% CI –6·9 to 5·8; p=0·97). Among the 63 participants who had pneumonia recurrence, 16 (48%) of 33 in the short-course group and 17 (57%) of 30 in the usual care group had a multidrug-resistant bacteria grown in the sputum culture during the recurrent VAP episode (–1·0; –36 to 20; p=0·69). 15 (24%) of 63 patients had the same bacterial pathogen grown in the sputum cultures taken during the pneumonia recurrence episodes as the index episodes of VAP (eight in the short-course group *vs* seven in the usual care group).

The individualised short-course strategy reduced the overall mean antibiotic treatment days during hospitalisation by 5·2 days (95% CI –7·5 to –2·8; p=0·0003; table 3). A lower proportion of participants experienced antibiotic side-effects in the short-course
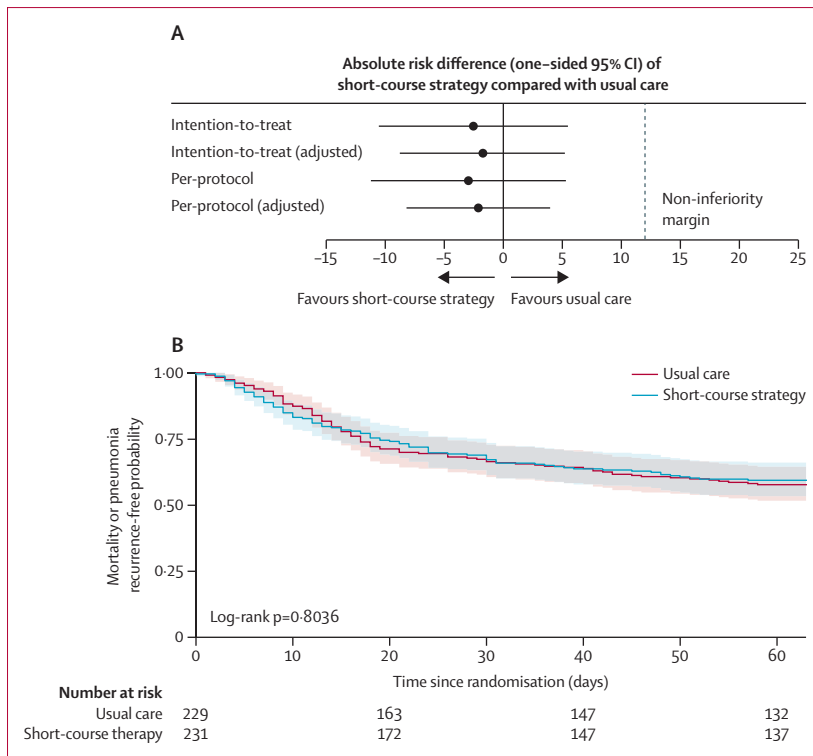
Figure 3: Primary outcome
(A) Non-inferiority of short-course strategy compared with usual care for the composite endpoint of death or pneumonia recurrence within 60 days of enrolment. (B) Unadjusted Kaplan-Meier survival estimates by intervention in the intention-to-treat population. Day 0 refers to the day of randomisation, and day 60 refers to the last day of follow-up. All participants were followed up for 60 days; there were no participants lost to follow-up.

group (17 [8%] of 211) versus the usual care group (86 [38%] of 224; absolute risk difference −31% [95% CI −37 to −25%; p<0·0001]; table 3) in the per-protocol population from randomisation to end of antibiotic treatment for VAP. The main antibiotic side-effect avoided was acute kidney injury, which occurred in 11 (5%) in the short-course group *vs* 79 (35%) in the usual care group (table 3). The lengths of hospital and intensive care unit stays were similar in the two groups. There were no major differences in the additional secondary outcome measures meant to assess the safety of the individualised short-course strategy, including readmissions and secondary bloodstream infections in both the per-protocol (table 3; appendix 3 p 19) and intention-to-treat populations (appendix 3 pp 20–23).

Discussion

In adult patients with VAP, a short-course strategy based on clinical response (ie, resolution of fever and haemodynamic stability) to individualise antibiotic treatment duration was non-inferior to usual care with respect to the primary composite outcome of 60-day mortality and pneumonia recurrences, and substantially reduced antibiotic side-effects. Among patients with VAP associated with carbapenem-resistant Gram-negative bacilli and Gram-negative non-fermenting bacilli, the

individualised short-course strategy was also similar to usual care, with no major differences in the primary outcome. In this study, the overall all-cause mortality was 37% (169 of 460) and mortality attributable to pneumonia was 12% (55 of 460). These are compatible with global estimates among critically ill patients with VAP.[31]

An important finding in this trial was that the usual care antibiotic treatment duration (median 14 days [IQR 10–21]) was longer than most current guideline recommendations of 7–8 days.[8,9,11] This observation reflects real-world practice, in which antibiotic treatment tends to be prolonged for VAP, especially those associated with Gram-negative non-fermenting and carbapenem-resistant Gram-negative bacilli. Before this trial, antibiotic treatment duration trials for VAP enrolled predominantly patients with Gram-positive or antibiotic-susceptible bacteria.[13,14] The only randomised trial that enrolled exclusively *Pseudomonas aeruginosa* VAP was terminated prematurely and did not show non-inferiority of short-course antibiotics compared with a standard 15-day course.[32] By contrast, our trial results provide evidence supporting short-course antibiotics for multidrug-resistant and Gram-negative bacterial VAP.

The key strength of this trial is the applicability of a set of simple and reproducible clinical criteria to determine antibiotic treatment duration for patients with VAP. Our study adopted this pragmatic approach given that there is currently no diagnostic test with adequate sensitivity and specificity for identifying VAP, and there is generally a low threshold to prescribe antibiotics for clinically suspected VAP in clinical practice.[1] These simple antibiotic termination criteria can be adopted by both prescribing clinicians and other health-care professionals and guide antibiotic stewardship policies across various resource settings. Although we acknowledge that other physiological parameters or biochemical thresholds might also indicate clinical response, normalisation of body temperature and blood pressure were chosen by consensus for their ease of implementation. Large observational databases with individual-level longitudinal data could potentially identify other potential markers for clinical response to tailor antibiotic treatment duration, although few would be as easily applied in low-resource settings as temperature and blood pressure measurement.

To our knowledge, this is the first randomised controlled trial of antibiotic treatment duration for VAP conducted in hospitals across low-income, middle-income, and high-income settings, with patients predominantly enrolled from low-income and middle-income countries. We found a high proportion of VAP associated with carbapenem-resistant Gram-negative bacilli and high antibiotic consumption. These VAP episodes were most commonly treated with combinations of colistin or polymyxin B, beta-lactams (including carbapenems), and amino-

	Short-course group (n=211)	Usual care group (n=224)	Unadjusted estimates (95% CI; p value)	Adjusted estimates (95% CI; p value)*
Mean (SD) duration of antibiotics during admission, days	20·5 (15·0)	25·7 (15·1)	−5·2 (−8·1 to −2·4; 0·0003)	−5·2 (−7·5 to −2·8; 0·0003)
Mean (SD) duration of mechanical ventilation during admission, days†	29·8 (27·6)	30·0 (27·1)	−0·06 (−5·2 to 5·1; 0·98)	0·14 (−4·2 to 4·5; 0·95)
Mean (SD) duration of ICU admission, days	27·0 (24·2)	28·5 (24·2)	−1·4 (−6·0 to 3·1; 0·54)	−1·3 (−5·2 to 2·5; 0·57)
Mean (SD) duration of stay in hospital, days	35·1 (23·8)	35·0 (23·0)	0·22 (−4·2 to 4·6; 0·92)	−0·15 (−3·8 to 3·5; 0·95)
Readmission to an acute care hospital	40 (19%)	40 (18%)	0·011% (−0·066 to 0·088%; 0·86)	0·014% (−0·047 to 0·074%; 0·71)
Pneumonia recurrence determined by at least one independent assessor	37 (18%)	39 (17%)	0·0013% (−0·071 to 0·074%; 1·00)	0·0010% (−0·057 to 0·059%; 0·98)
Bloodstream infection after enrolment	26 (12%)	30 (13%)	−0·011% (−0·078 to 0·056%; 0·85)	−0·013% (−0·066 to 0·040%; 0·69)
Newly colonised or infected with carbapenem-resistant Gram-negative bacilli after enrolment	37 (18%)	41 (18%)	−0·0077% (−0·084 to 0·069%; 0·93)	−0·0009% (−0·061 to 0·059%; 0·98)
Acute kidney injury‡	11 (5%)	79 (35%)	−30% (−38 to −23%; <0·0001)	−30% (−36 to −24%; <0·0001)
Drug-induced liver injury§	1 (<1%)	2 (1%)	−3% (−6 to 0; 0·093)	−3% (−5 to −1%; 0·033)
Diarrhoea	4 (2%)	5 (2%)	0 (−3 to 3%; 1·00)	−1% (−3 to 2%; 0·69)
Allergy (eg, DRESS, rash, SJS)	1 (<1%)	2 (1%)	0 (−2 to 2%; 1·00)	−1% (−2 to 1%; 0·36)
Any antibiotic side-effects	17 (8%)	86 (38%)	−30% (−38 to −23%; <0·0001)	−31% (−37 to −25%; <0·0001)

Reported estimates are absolute risk differences (ie, proportion of participants with the outcome in the short-course group minus that in the usual care group) when proportions are reported; and differences between the means (means in participants in the short-course group minus that in the usual care group) when means are reported. DRESS=drug reaction with eosinophilia and systemic symptoms. ICU=intensive care unit. KDIGO=Kidney Disease Improving Global Outcomes. SJS=Stevens-Johnson syndrome. VAP=ventilator-associated pneumonia. *Adjusted estimates were calculated using inverse probability weights, which were derived from baseline patient characteristics calculated using a logistic regression model. †The duration of mechanical ventilation during admission might be longer than the duration of ICU admission as mechanical ventilation could be carried out in intermediate care wards or the general wards in the participating hospitals. ‡Acute kidney injury was defined by the KDIGO guideline: increase in serum creatinine during antibiotic treatment for index VAP episode by ≥0·3 mg/dL (≥26·5 μmol/L), to ≥1·5 times from baseline. §Drug-induced liver injury was defined by Aithal and colleagues: (1) alanine transaminase value ≥5 × upper limit of normal, (2) alkaline phosphatase value ≥2 × upper limit of normal, or (3) alanine transaminase value ≥3 × upper limit of normal and total bilirubin ≥2 × upper limit of normal.[21]

Table 3: Secondary outcomes and side-effects in the per-protocol population

glycosides, which were frequently associated with acute kidney injury. These patterns of antibiotic prescription reflected the epidemiology of bacteria causing VAP and the sparse access to newer-generation antibiotics (eg, novel β-lactam–β-lactamase inhibitors or cefiderocol) in many regions where the study was conducted. Very few trials have been done in these settings, where rates of VAP are higher than in high-income countries. The high rates of VAP are a major driver for antibiotic prescription and are likely to contribute to the high prevalence of multidrug-resistant organisms, which suggests that the benefits of an intervention to reduce antibiotic use in such a setting are likely to have an even greater impact than in higher-income environments.

This study has several limitations. Firstly, most participants were enrolled from Thailand (81%). However, the frequency of primary outcomes between the two groups in the three countries were similar. No formal statistical testing for each country was prespecified in the analysis plan due to the small sample size expected per country. Secondly, although the trial intervention to reduce antibiotic treatment duration was ultimately aimed at reducing overall antimicrobial resistance, we did not obtain unit-level antimicrobial resistance colonisation (ie, stool or sputum samples) or infection data from other intensive care unit patients during the study. The effect of reducing antibiotic treatment duration on antimicrobial resistance overall in the intensive care unit is likely to depend on the prevailing resistance mechanism and genes, types of antibiotics used, and infection prevention and control policies limiting transmission.[33] Lastly, non-adherence to the allocated antibiotic treatment duration might increase the probability of concluding non-inferiority when the short-course strategy was actually inferior. Unbiased estimates could be derived by causal inference methods, such as instrumental variable analysis, which we did not perform due to large sample sizes required to maintain power in the presence of non-adherence.[34] However, non-adherence was kept low and we used adjusted and unadjusted analyses on both intention-to-treat and per-protocol populations to determine non-inferiority.

In conclusion, individualisation of antibiotic treatment duration for VAP based on clinical response was non-inferior to usual care and reduced antibiotic side-effects. There was no increased risk of mortality or pneumonia recurrence for VAP associated with carbapenem-resistant Gram-negative bacilli or Gram-negative non-fermenting bacilli. This strategy based on simple parameters is readily applicable in low-income and middle-income countries and could have a considerable impact on reducing overall antibiotic prescribing, potentially curbing the spread of antimicrobial resistance among the most vulnerable patients.

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