Short-course antibiotic strategies for ventilator-associated pneumonia

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Purpose of review
Evidence behind antibiotic duration while treating ventilator-associated pneumonia (VAP) remains unclear. There is a need to balance minimizing the development of antimicrobial resistance without compromising clinical outcomes given the high mortality.

Recent findings
Recent studies have suggested that shorter antibiotic courses, when individualized to clinical response, may be adequate for treating VAP without increasing the incidence of mortality or recurrence, regardless of pathogens. Moreover, shortening duration may reduce the risk of adverse events, including acute kidney injury.

Summary
Shortening the duration of antibiotic treatment for VAP, in the setting of appropriate clinical response, is a reasonable strategy to reduce costs and selective pressure driving antimicrobial resistance. This was demonstrated in the latest REGARD-VAP study, even among VAP patients with nonfermenting Gram-negative bacilli or carbapenem-resistant pathogens. Given the challenges in diagnosing VAP, such pragmatic approaches would be essential as part of overall antibiotic stewardship programmes. Further refinement to the criteria for antibiotic cessation may be possible.

Keywords
antibiotic duration, antimicrobial stewardship, ventilator-associated pneumonia

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection, affecting up to 40% of patients who have been mechanically ventilated for more than 48 h [1▪▪]. It is the leading cause of death in intensive care units (ICU), with mortality rates reaching 50% [1▪▪,2,3]. The estimated economic burden of VAP is in the excess cost of USD$40 000 per patient's episode [4], largely due to the prolonged mechanical ventilation, ICU- and hospital-length of stay (LOS) [5]. The clinical and economic burden is potentially worse among resource-limited countries, where the higher antimicrobial resistance (AMR) burden and lack of medical advancements contribute to the high mortality [6].

Current guidelines recommend an 8-day regimen of broad-spectrum antibiotics as part of VAP management. Longer duration may be considered depending on clinical response and underlying causative organism [7–9]. Multiple debates have ensued over these recommendations. Short-course regimens have been associated with higher relapse rates among VAP patients because of nonfermenting gram-negative bacilli (NFGNB). However, prolonged antibiotic courses are not without harm. Apart from increased drug toxicities [10], prolonged antibiotic duration has been associated with the development and colonization of multidrug resistant (MDR) pathogens, which contributes significantly to VAP recurrence [11]. Previous trials had demonstrated that MDR pathogens emerged more frequently among patients with pulmonary infection recurrence who had received 15 days of antibiotics as compared to 8 days [12]. This is consistent with other observational studies, where there is a direct correlation between prolonged antibiotic use and increased drug resistance [10,13,14].

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KEY POINTS

- Prolonged antibiotic exposure among patients with ventilator-associated pneumonia (VAP) may lead to the development of antibiotic-associated side effects and the development of drug-resistant pathogens in the ICU.
- Concerns remain that shortened antibiotic duration among patients with VAP may contribute to VAP recurrence and increased mortality.
- REGARD-VAP demonstrated that in the appropriate setting of clinical response, shortened antibiotic duration was noninferior in terms of a 60-day composite endpoint of death and recurrence, even among those with Gram-negative nonfermenters and carbapenem-resistant pathogens.
- Given the challenges in diagnosing VAP, appropriately shortened antibiotic duration would be an important component of antibiotic stewardship programmes.

MDR pathogens are already emerging as key pathogens among patients with VAP, with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* predominating [2,11,15,16]. Whether existing guideline recommendations on antibiotic duration apply to this subgroup of VAP patients remain unclear. The guidelines were based on clinical trials that compared arbitrary fixed durations [7–9]. This underscores the need to ascertain specific criteria of clinical response to individualize antibiotic duration.

The recently concluded REGARD-VAP study provided some illumination in this respect. In 2024, REGARD randomized 461 patients from Singapore, Nepal and Thailand to either a short-course or usual care antibiotic regimen. Out of the 320 (70%) VAP episodes with positive culture, majority were gram-negative bacterial isolates, with *Acinetobacter*, *Pseudomonas* and *Enterobacterales* predominating. In the setting of appropriate clinical response, individualized shortened antibiotic duration for VAP treatment was noninferior to longer antibiotic duration in terms of 60-day mortality and VAP recurrence [17▪▪]. However, widespread adoption of short-course antibiotic regimens has remained challenging. In this review, we aim to explore the current evidence behind short-course antibiotic strategy in the management of VAP, as well as discuss the potential approaches to tackle the challenges faced in its translation to real-world application.

EVIDENCE ON ANTIBIOTIC DURATION BEFORE 2012

In 2003, the first randomized controlled trial (RCT) comparing 8 versus 15 days of antibiotics for VAP found no difference in 28-day mortality, recurrences, mechanical ventilation-free days, organ failure-free days, and ICU LOS [8]. However, VAP patients due to NFGNB were more likely to have pneumonia recurrence with short-course antibiotic regimens (Table 1). Based on this trial, the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) published a 2005 guideline suggesting a one-week antibiotic regimen for uncomplicated VAP [18]. In the setting of *Pseudomonas* VAP, a longer two-week antibiotic regimen was still advocated [18]. Since the guidelines, three more RCTs published between 2009 and 2012 (Table 1) appeared to further reinforce the narrative of noninferiority of short-course antibiotic regimen, except among the subgroup associated with nonfermenters [19–21].

However, these studies had several limitations. The studies were underpowered. Sample sizes were small, and trials were terminated early. These studies were also at risk of increasing the chances of claiming noninferiority due to the differential time-at-risk bias in favor of longer-duration group and the lack of per-protocol analysis to address nonadherence or protocol deviations [22]. Applying the evidence from these trials to define an optimal antibiotic duration, especially those associated with NFGNB, remains challenging.

CURRENT EVIDENCE ON ANTIBIOTIC DURATION AFTER 2012 WITH CRITICAL APPRAISAL

Several meta-analyses published after these RCTs continued to support the earlier findings of comparable mortality, mechanical ventilation-free days, and ICU LOS with short-course antibiotic regimens for VAP management [23,24]. There was reinforcement of the nonsignificant higher trend of increased recurrence in the short-course treatment group, especially among the subgroup associated with nonfermenters. Based on these trials, the updated American and European guidelines recommended a one-week antibiotic regimen regardless of causative pathogen in 2016 and 2017 respectively [7,8]. However, there were several fundamental concerns with these meta-analyses.

Firstly, the Capellier's trial did not isolate any NFGNB upon enrollment [20]. Including this trial in the meta-analysis of VAP recurrence among the subgroup of NFGNB was erroneous and skewed the results in favor of short-course duration [25▪]. This was further supported by Pugh's analysis where a statistically significant higher trend of recurrence in nonfermenters was observed [odds ratio (OR) 2.07; 95% confidence interval (CI): 1.11–3.83] after

Table 1. Summary of all RCTs comparing antibiotic durations for VAP

Clinical trials	Chastre et al., 2003 (PneumA) [12]	Fekih *et al.*, 2009 [19]	Capellier *et al.*, 2012 [20]	Kollef *et al.*, 2012 [21]	Bougle *et al.*, 2022 (iDIAPASON) [26]	Mo *et al.*, 2024 (REGARD-VAP) [17▪▪]
Intervention	8 vs. 15 days	7 vs. 10 days	8 vs. 15 days	7 vs. 10 days	8 vs. 15 days	≤7 vs ≥8 days
Study setting	France	Tunisia	France	From 19 countries	France	Thailand, Nepal, and Singapore
Definition of VAP (inclusion criteria)	Clinical suspicion[a] Excluded early-onset pneumonia (first five days of mechanical ventilation and no antimicrobial therapy during the 15 days preceding infection)	Clinical suspicion defined by new or persistent radiological infiltrate	Clinical suspicion[a] Early-onset VAP defined as ventilated for more than 24 h and less than 8 days	Late-onset VAP	Clinical suspicion[a]	US CDC criteria defined by respiratory signs and symptoms compatible with pneumonia, mechanically ventilated for 48 h or longer, and new radiological changes.
Definition of VAP (microbiology)	Positive quantitative culture results from bronchoalveolar specimens	Positive quantitative culture from tracheal aspirate or protected brush specimen	Positive quantitative culture from bronchoalveolar lavage culture	Positive quantitative culture from bronchoalveolar lavage culture	Positive quantitative culture of a respiratory sample with *Pseudomonas aeruginosa*	Not an inclusion criteria
Sample size	Met	No sample size calculation	Met	Not met due to premature termination	Not met due to early termination	Met
Analysis population	ITT	ITT	ITT	ITT and mITT	ITT	ITT and PP
outcome – mortality	28-day all-cause No difference 60-day all-cause No difference	14-day all-cause No difference 28-day all-cause No difference	21- and 90-day all-cause No difference	28-day all-cause High in shorter duration group overall and in sub-group	90-day composite endpoint Higher in shorter duration group	60-day composite endpoint No difference
Outcome – recurrence/ relapse	28-day recurrence No difference overall; Higher in shorter duration group in subgroup with nonfermenting Gram-negative bacilli	28-day reinfection rate No difference	21-day pulmonary and extrapulmonary secondary infections Nonsignificant higher trend in shorter duration group	Relapse Claimed no difference but not reported		
The outcomes	28-day ventilation-free days No difference ICU length of stay No difference Acquisition of MDR pathogens in recurrence Lower in shorter duration group	28-day ventilation-free days No difference 28-day ICU length of stay No difference	21- and 90-day mechanical ventilation duration: No difference 21- and 90-day ICU length of stay No difference	Mechanical ventilation duration Claimed no difference but not reported	90-day mechanical ventilation duration No difference 90-day ICU length of stay No difference Acquisition of MDR pathogens No difference	60-day mechanical ventilation duration No difference 60-day ICU length of stay No difference Acquisition of MDR infections or colonization No difference

Table 1 (*Continued*)

Clinical trials	Chastre et al., 2003 (PneumA) [12]	Fekih et al., 2009 [19]	Capellier et al., 2012 [20]	Kollef et al., 2012 [21]	Bouglé et al., 2022 (iDIAPASON) [26]	Mo et al., 2024 (REGARD-VAP) [17▪▪]
Conclusion	Supports short course (8 days), except for those with nonfermenting Gram-negative bacilli	Supports short course (7 days)	Supports short course (8 days) for early-onset VAP	Supports short course (7 days), except those with VAP attributed to *Pseudomonas aeruginosa*	Supports long course (15 days) Lack of power limits the interpretation of the study	Supports individualized, short course (≤7 days)

[a]Clinical suspicion: At least 2 criteria (fever > 38.5, WBC >10 or <4, purulent tracheobronchial secretion, and a new or persistent infiltrate on chest radiography.
ICU, intensive care unit; ITT, intention-to-treat; MDR, multidrug-resistant; mITT, modified intention-to-treat; PP, per protocol; VAP, ventilator-associated pneumonia.

excluding Capellier's trial [24]. Secondly, these trials used a follow-up period of up to 28 days for primary outcome. This introduced differential time-at-risk bias, favoring the longer duration group because any potential recurrence may not be captured [25▪]. Notably, the Kollef's trial used the end of therapy as the point of outcome assessment, which meant that the recurrence/relapse episodes were measured for only 24 h post-therapy completion in the long-duration arm. Had the clinical outcome assessment been lengthened to a few days later, additional recurrences/relapses may have been observed in the long-arm strategy [21]. Thus, uncertainties in the guidelines pertaining to the optimal duration of antibiotics for NFGNB VAP remain.

Interestingly, these concerns are reflected in real-world practice, where physicians continue to advocate for prolonged antibiotic duration. REGARD-VAP in 2024 still observed longer median antibiotic duration [14 days; interquartile range (IQR) 10–21] despite the seven-day recommendation from IDSA and ESCMID [17▪▪]. In particular, VAP patients with NFGNB or carbapenem-resistant pathogens were subjected to prolonged antibiotic courses to reduce potential recurrences.

To address this, iDIAPASON was published in 2022 – the first trial to compare arbitrary fixed durations for *P. aeruginosa* VAP [26]. In contrast to earlier findings, the trial failed to demonstrate non-inferiority of a short-course strategy for the composite endpoint of death and recurrence within 90 days. While there was no difference in mortality between both short-course and long-course arms, patients in the short-course arm were at higher risk of recurrence as compared to those in the longer-course arm (HR 1.99, CI 90% 1.01–3.95). Unfortunately, the interpretations of these results were ultimately limited due to the lack of statistical power stemming from early termination.

Subsequently, another 2023 meta-analysis, that also included iDIAPASON, echoed earlier studies that found no difference in clinical outcomes, except for a higher recurrence rate, both overall (RR 1.34; 95% CI: 1.02–1.75; $I^2 = 2\%$) and in the subgroup associated with nonfermenters (RR 1.73; 95% CI: 1.17–2.54; $I^2 = 0\%$) [27▪,28▪]. Sensitivity analyses, though not statistically significant, still found a trend towards higher recurrence in favor of the longer-course group. This runs contrary to the existing American and European guidelines.

In 2024, REGARD-VAP, which sought to compare the efficacy of short-course and long-course antibiotic regimens in VAP, demonstrated noninferiority in terms of a composite endpoint of mortality and recurrence within 60 days, with comparable duration of mechanical ventilation and length of

ICU stay [17▪▪]. Unlike earlier studies, REGARD-VAP uniquely incorporated clinical response on top of duration as criteria for antibiotic cessation. Clinical response was defined as achieving defervescence for 48 h with no vasopressor support. In addition to the clinical outcomes, patients in the short-course regimen had statistically significant fewer antibiotic side effects, particularly acute kidney injury [29].

Together with PneumA and iDIAPASON, these three trials were the only trials that investigated the acquisition of MDR pathogens during the follow-up period [8,17▪▪,27▪]. Only PneumA observed statistically significantly lower MDR pathogen acquisition in short-course group, suggesting possible reduction in selection pressure against AMR development.

REGARD-VAP's study design attempted to address several limitations in the older studies [17▪▪]. Primary outcomes were measured on day 60 to minimize differential time-at-risk bias. This allowed sufficient time for recurrences/relapses and mortality to manifest in the long-course arm [30]. In addition, independent assessors were engaged to assess recurrences/relapses to reduce ascertainment bias, which earlier studies were more prone to [28▪]. The inclusion of clinical response in the short-course arm would help to significantly alleviate physicians' concerns of premature antibiotic cessation. This allowed the REGARD-VAP results to be more generalizable, applicable and perhaps more importantly, practically implementable within an acceptable clinical framework.

CHALLENGES IN INTERPRETING AND APPLYING CURRENT EVIDENCE INTO PRACTICE

While the existing body of evidence has provided greater clarity on the benefits and drawbacks of short-course antibiotic regimens (Fig. 1), there remains several barriers to widespread application and acceptance. The absence of a "gold standard" definition of VAP remains a challenge. The six RCTs on antibiotic durations for VAP utilized varying VAP definitions (Table 1), rendering direct comparison elusive. Without well defined VAP criteria, studies may be prone to include populations that may not accurately represent VAP patients, such as patients with ventilator-associated tracheobronchitis (VAT). VAT's clinical presentation is similar to VAP. It has been postulated that VAT is part of a continuum of colonization to VAP development. Not all VATs are treated and even if treated, may respond differently to varying durations of antibiotics [31,32]. Consequentially, including VAT patients into these trials may directly influence the results. However, given the poor sensitivity and specificity of chest radiography in differentiating VAT and VAP, it is difficult to confidently exclude this entity from existing studies. In fact, in the presence of new respiratory signs of infection (increased amount of purulent sputum in conjunction with new systemic signs of infection plus worsening oxygenation and/or increasing ventilator settings), antibiotic treatment would still be considered even in the absence of new

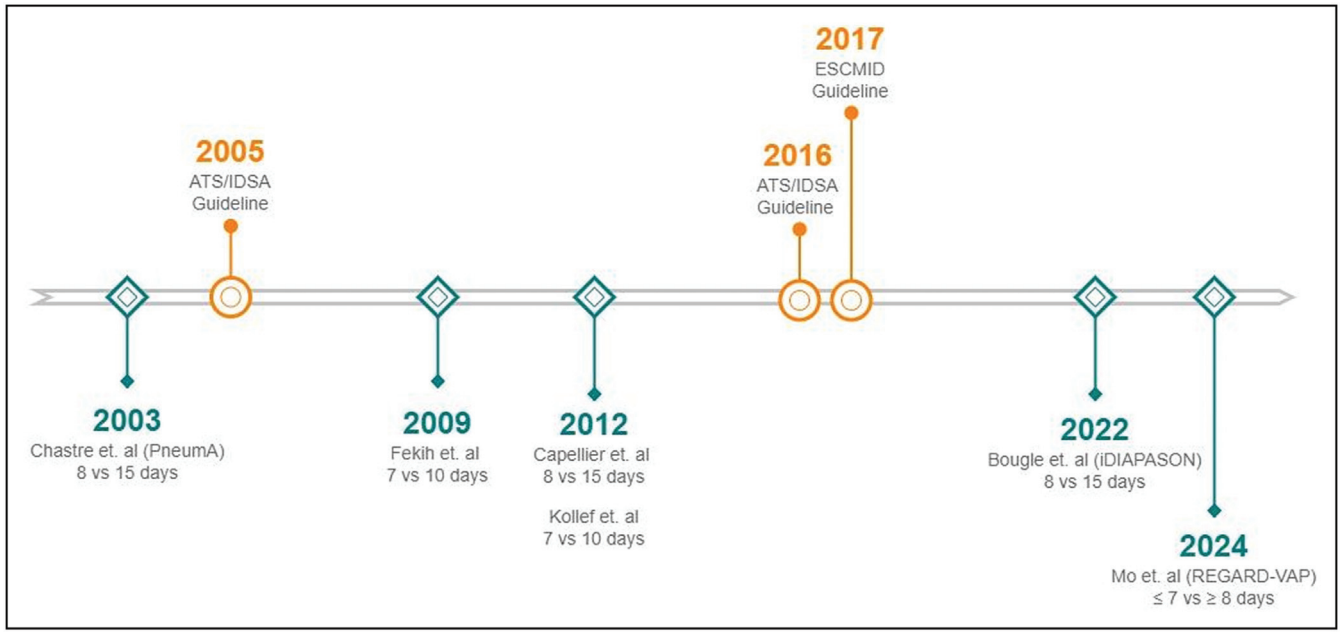

FIGURE 1. Timeline of RCTs comparing arbitrary fixed durations, and the development of international guidelines for VAP [7,8,12,17▪▪,18–21]. RCT, randomized controlled trial; VAP, ventilator-associated pneumonia.

or progressive persistent infiltrates on chest radiographs [8].

Another important population to consider would be those with culture-negative VAP. Patients treated with antibiotics before obtaining respiratory samples often have false-negative culture results. Without a microbiological confirmation, these patients potentially may not have suffered from VAP in the first place, or uncommonly, developed viral VAP instead of bacterial VAP, in which antibiotics have no role in. The absence of a well defined diagnosis and, in many cases, lack of microbiological samples due to exigencies of the clinical scenario to initiate antibiotics early, may thus inherently lead to the overprescription of antibiotics.

There is considerable heterogeneity in the diagnostic criteria employed in various RCTs (Table 1) [33]. Relying on various combinations of diagnostic criteria makes result comparison and interpretation intrinsically complex [33,34]. Each diagnostic criterion individually has poor sensitivities and specificities in diagnosing or excluding VAP (Table 2). For example, the use of clinical signs like fever or leukocytosis, or CPIS more than six are often low in specificity (53.9% and 66.4% respectively). The challenge is higher among ICU patients, where nonspecific indicators may be reflective of other ongoing pathologies instead. An example is C-reactive protein (CRP), which reflects the underlying inflammatory response nonspecifically. As such, none of the RCTs investigating antibiotic durations for VAP employed CRP as a diagnostic criterion [35]. Furthermore, microbiological diagnosis to diagnose VAP in RCTs display notable variability. Some trials mandate bronchoalveolar lavage culture while others accept endotracheal aspirate culture. Though invasive techniques have higher sensitivity and specificity, such benefits are often outweighed by the risks incurred among critically ill VAP patients [7], and thus may not be practical. Continuous efforts to standardize VAP diagnostic criteria in future clinical trials remain crucial to accurately estimate prevalence, both epidemiologically and clinically, and guide effective antimicrobial stewardship [33].

INNOVATIVE APPROACHES IN SHORTENING ANTIBIOTIC DURATION

Ultimately, the goal of VAP management is early appropriate antibiotic administration for an appropriate duration without suffering from unnecessary exposure that may lead to the emergence of MDR pathogens, VAP recurrence and drug-associated toxicities. REGARD-VAP has placed us on the path of possibly individualizing antibiotic duration and potentially shortening antibiotic regimens without compromising clinical outcomes [17▪▪]. However, further refinement of antibiotic cessation criteria can still be considered.

Many VAP studies have leveraged on biomarkers to monitor clinical responses and guide antibiotic treatments. They rely on clinical or laboratory responses based on parameters including fever, CPIS, the PaO_2/FiO_2 ratio, CRP and procalcitonin to shorten antibiotic duration [36▪]. They are deemed to reflect the inflammatory responses which often correlate to infection severity. When these biomarkers exhibit an improving trend, they should be reflecting clinical response, thus discontinuing antibiotics would logically follow suit [37]. Procalcitonin is the quintessential biomarker applied in this manner. Multiple studies have studied the use of procalcitonin to guide antibiotic duration, but success has been limited [38–40].

Table 2. Sensitivity and specificity of diagnostic criteria used in VAP diagnosis [34]

Diagnostic criteria		Sensitivity	Specificity
Clinical examination		66.4% (95% CI 40.7–85.0)	53.9% (95% CI 34.5–72.2)
Radiological	Chest XR	88.9% (95% CI 73.9–95.8)	26.1% (95% CI 15.1–41.4)
	CT	Not routinely used due to risks associated with transport and additional procedures	
	Lung ultrasound	Not currently validated as an assessment tool for VAP despite some evidence demonstrating superior diagnostic performance when used with clinical signs and symptoms	
Microbiology	Endotracheal	75.7% (95% CI 51.5–90.1)	67.9% (95% CI 40.5–86.8)
	Protected specimen brushing	61.4% (95% CI 43.7–76.5)	76.5% (95% CI 64.2–85.6)
	Bronchoalveolar lavage	71.1% (95% CI 49.9–85.9)	79.6% (95% CI 66.2–85.9)
Combination scores – Clinical Pulmonary Infection Score (CPIS) > 6		73.8% (95% CI 50.6–88.5)	66.4% (95% CI 43.9–83.3)
Biomarkers		Highly variable	Highly variable

Table 3. Pragmatic approach to overcome the current challenges faced in reducing antibiotic duration for VAP

Possible approach	Challenges that may be tackled	Current constraints
Individualizing antibiotic duration based on: (1) clinical parameters (e.g. fever, CPIS, PaO2/FiO2 ratio) (2) biomarkers (e.g. procalcitonin, C-reactive protein) (3) pathogen and associated antibiotic susceptibility (4) regional antimicrobial resistance patterns (5) prior antibiotic use	Applicable even with a lack of 'gold' standard definition for VAP diagnosis Reduce antibiotic exposure in ICU settings	Lack of longitudinal data to define specific stopping criteria to guide the tailoring of antibiotic duration Difficult to standardize antibiotic cessation criteria that can be applied across varying resource setting May require advanced techniques such as machine learning to define antibiotic cessation criteria

The ProVAP trial found a reduction in antibiotic exposure by 27% ($P = 0.038$) [40]. However, the meta-analysis looking at trials using procalcitonin to guide antibiotic cessation decisions revealed a reduction of 13 to 11 days for VAP only, which is still longer than the current 7–8 days [38]. Nevertheless, the use of such biomarkers may still be worth exploring since none of the six RCTs employed biomarkers in guiding durations. Biomarker-guided antibiotic stewardship strategy may potentially be relevant in the ICU settings, where antibiotic use is almost ubiquitous [41]. The PRORATA trial is one example, where significantly more antibiotic-free days were found in the procalcitonin-guided group in ICUs, regardless of infection sites or pathogens [42].

A 2019 meta-analysis conducted revealed higher VAP incidences in lower- and upper-middle-income countries, and lower VAP incidences in high-income countries in Asia [43]. *A. baumannii* was the most common VAP pathogen in low- and middle-income countries, as well as in tropical countries with high AMR rates [43,44]. Such high multidrug-resistant (MDR) pathogen incidence and limited antibiotic choices would lead to prolonged broad-spectrum antibiotic regimens. The biomarker-guided strategies may be challenging to implement in these resource-limited settings. In the absence of these biomarkers, REGARD-VAP has demonstrated that pragmatic, simple and reproducible antibiotic cessation criteria would suffice in resource-limited settings [17▪▪]. This is crucial especially in resource-constrained regions where access to infrastructures and biomarkers may be limited, more so when the cost-benefit for biomarker-guided regimens is not well established in VAP context [38]. This may serve as interim solutions in reducing unnecessary antibiotic use (Table 3).

Separately, machine-learning models and artificial intelligence may be another tool to further refine antibiotic cessation criteria across multiple settings [45,46]. This requires large amount of data, including local prevalence, resistance trends, patients' previous antibiotic therapy, changes in vitals and clinical markers throughout antibiotic course, among other datapoints [45]. Gathering these epidemiological data, especially in low- and middle-income countries, may pose issues due to its resource-intensive nature and the need for data-storage capabilities. This area should ideally be explored through large collaborations given the huge untapped potential.

CONCLUSION

The burden of VAP, especially those associated with NFGNB or carbapenem-resistant ones, remains high and varies across different resource settings. REGARD-VAP presented new evidence supporting an individualized, short-course antibiotic strategy, even in settings with potentially higher MDR burden. In the face of the diagnostic challenges, practical approaches for antibiotic stewardship may be essential while waiting for evidence supporting newer strategies.

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Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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