

Probiotic In The Prevention of Ventilator-Associated Pneumonia In Critically Ill Patients- Evidence From Meta-Analysis And Trial Sequential Analysis of Randomized Clinical Trials

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Research

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Abstract

Introduction: Probiotic may have a role in prevention of ventilator-associated pneumonia (VAP) among mechanically ventilated patients, but the efficacy and safety remains inconsistent. The aim of this systematic review and meta-analysis was to evaluate the efficacy and safety of probiotic (prebiotic, synbiotic) versus placebo in preventing VAP in critically ill patients undergoing mechanical ventilation.

Methods: PubMed, Embase and the Cochrane library databases were searched to 10 October 2021 without language restriction for randomized or semi-randomized controlled trials evaluating probiotic (prebiotic, synbiotic) vs. placebo in prevention of VAP in critically ill mechanically ventilated patients. The pooled relative risk (RR) along with 95% confidence intervals (CI) were combined using a random-effects model. Furthermore, the trial sequential analysis (TSA) and subgroup analyses were performed. Statistical significance was regarded as $P < 0.05$.

Results: Twenty-three trials involving 5543 patients were eligible for meta-analysis. The combined RR of decreasing the risk of VAP by probiotic was 0.67 (0.56, 0.81) for all eligible studies, 0.69 ($n = 5136$; 95% CI = 0.57 to 0.84; $P < 0.01$) for adults studies and 0.55 ($n = 407$; 95% CI = 0.31 to 0.99; $P = 0.046$) for neonates/children studies. Additionally, the above-mentioned positive finding was verified by the result of TSA, subgroup analyses and cumulative meta-analysis in adult patients. Ample evidence demonstrated the existence of a 31% decrease in RR of incidence of VAP when prophylactic probiotic therapy was administered among adult patients. Finally, there were no effects on the ICU/hospital/28-/90-day mortality, bacteremia, CRBSI, diarrhea, ICU-acquired infections, infectious complications, pneumonia, UTI and wound infection between two groups ($P = 0.05$ for all).

Conclusion: Based on the results of our study, the current evidences suggested that prophylactic administration of probiotic might be utilized as a preventive method for VAP in neonates/children and adults patients who require mechanical ventilation. However, further large, high-quality RCTs are warranted to assess the efficacy and safety of probiotic treatment in critically ill patients, especially for the neonates/children studies and the long-term consequences of this therapy.

Introduction

Ventilator-associated pneumonia (VAP), characterized as a type of nosocomial pneumonia that occurs at least 48h after the initiation of mechanical ventilation (MV) in intensive care unit (ICU), leads to prolonged the duration of MV, stay in ICU and hospital, as well as increased mortality and healthcare burden [1–3]. The latest data, conducted in 538,600 patients from 14 countries, revealed that the pooled incidence of VAP is 15.1 per 1000 ventilator-days (VD), and high-income countries (9.0 per 1000 VD) is lower than lower- and upper-middle-income countries (18.5 and 15.2, per 1000 VD, respectively) [4]. Ferrer et al., in a review of the epidemiology of ICU-acquired pneumonia, [5] have estimated that the all-cause mortality attributable to VAP ranged from 20 to 50% and the overall attributable mortality associated with VAP is approximately 13%. Furthermore, a lately data from Japan indicated that the average hospitalization costs for patients with VAP were \$ 67,080, significantly higher than that those without VAP (\$32,196) [6].

On account of the high incidence, severity and enormous burdens of VAP, ample studies have assessed various kinds of prevention strategies, including pharmacological and non-pharmacological interventions, to prevent VAP over the years [7]. Fortunately, the incidence of VAP has been steadily decreasing in recent years possibly due to the apply of the ventilator bundle, such as hand hygiene, oral care, semi-recumbent position, and subglottic secretion drainage system, daily sedation vacations as well as deep vein thrombosis prophylaxis, etc [5, 7]. For quite a long time, antibiotic use has been the cornerstone of preventing and treating various infections, especially in ICUs, but, equally, inappropriate antimicrobial therapy is linked to potential risks such as affecting the microbiota composition, bringing the problem of superinfections and the occurrence of drug-resistance bacteria [8–10].

Therefore, an emerging number of studies have assessed the non-antibiotic approaches for the prevention of VAP in the last few years. The term “probiotics”, defined as live nonpathogenic microorganisms that exert a health benefit to the host later, [11] first appeared in 1974 [12] and it may represent a novel non-antibiotic intervention [13]. The beneficial effects of probiotics in the prevention of VAP are not yet entirely elucidated, perhaps via modulating intestinal microbiota, adjusting immune response, improving gut barrier function and suppressing pathogenic bacteria overgrowth [12, 14].

There are several studies in this area over the last few years since the first study of probiotic (prebiotic and synbiotic) in preventing VAP in mechanically ventilated critically ill patients was published. A series of studies the relevant studies have shown unfavorable results with regard to the prevention of VAP by probiotics [15–18]; nonetheless, other studies [19, 20] have reported promising results, which was further confirmed by several meta-analyses [21–28].

Considering these controversial results, we therefore undertook a systematic review and meta-analysis to compare the efficacy and safety of administering probiotic (prebiotic, synbiotic) versus placebo on the prevention of VAP in critically ill ventilated patients.

Methods

This study was written following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Appendix 1) [29].

Search Strategy And Selection Criteria

The clinical questions were specified using the PICO framework listed in appendix 2. Two writers (ZL and SYC) independently searched the PubMed, Embase and the Cochrane library databases to identify randomized controlled trials (RCTs) or quasi-RCTs that addressed the efficacy of probiotic, prebiotic or symbiotic supplementation in preventing VAP among critically ill patients from the inception to 10 October 2021, without language restriction. The keywords: “probiotic”, “prebiotic”, “synbiotic”, “ventilator-associated pneumonia”, “Randomized Controlled Trial”, etc. The appendix 2 provides a full description of the search strategy. Moreover, the reference lists of relevant papers were selectively hand-searched to capture any additional studies.

We excluded studies if they were duplicate publications, case reports, letters, reviews, case-control studies, cohort studies or non-human studies. Trials eligibility were carried out by the two independent authors (ZL and SYC) through screened titles, abstracts and even read the full text.

The primary outcome was as follows: the incidence of VAP; Secondary endpoints included: ICU/hospital/28-/90-day mortality, bacteremia, catheter-related bloodstream infection (CRBSI), diarrhea, ICU-acquired infections, infectious complications, pneumonia, urinary tract infection (UTI) and wound infection.

Data Extraction

The relevant data of included articles were extracted by two separate authors (ZL and SYC) and were summarized in Table 1. We contacted original authors to ask for any relevant missing information whenever possible, for example, the Mahmoodpoor study [30].

Table 1
Core characteristics of the included studies

	Study ID	Country origin	Sample size	Mean age (years)	Female (%)	APACHE II score	Follow-up time (day)	Treatment intervention	Control intervention	Center	Setting
Adult	Spindler-Vesel 2007[34]	Slovenia	26/87	41.00	22.12	13.00	ICU stay	Synbiotic, qd	Control	S	SICU
	Forestier 2008[17]	France	102/106	58.47	29.81	44.40*	78.00	Probiotic, bid	Placebo	S	ICU
	Knight 2009[35]	England	130/129	49.75	37.84	17.00	Hospital stay	Synbiotic, bid	Placebo	S	ICU
	Giamarellos -Bourboulis 2009[36]	Greece	36/36	54.40	18.46	19.36	28.00	Synbiotic, qd	Placebo	M	SICUs
	Morrow 2010[20]	America	73/73	53.55	41.10	23.20	25.00	Probiotic, bid	Placebo	S	ICU
	Barraud 2010[37]	France	87/80	60.70	59.28	59.80*	90.00	Probiotic, qd	Placebo	S	ICU
	Tan 2011[38]	China	26/26	40.65	23.08	14.55	28.00	Probiotic, tid	Control	S	ICU
	Oudhuis 2011[39]	Netherlands	130/124	62.72	38.19	22.02	75.00	Probiotic, bid	Control	M	ICUs
	Rongrungruang 2015[40]	Thailand	75/75	71.02	58.67	19.65	90.00	Probiotic, qd	Control	S	ICU
	Zeng 2016[41]	China	118/117	52.39	41.28	15.65	14.00	Probiotic, tid	Control	M	ICUs
	Zarinfar 2016 [36]	Iran	33/33	47.80	31.67	Probiotic, tid	Control	S	ICU
	Shimizu 2018[19]	Japan	35/37	74.00	34.72	19.51	28.00	Synbiotic, qd	Control	M	ICUs
	Klarin 2018[42]	Sweden	69/68	65.75	44.53	22.99	180.00	Probiotic, bid	Control	M	ICUs
	Kooshki 2018[43]	Iran	30/30	56.95	...	23.20	84.00	Prebiotic, bid ^{&}	Control	M	ICUs
	Anandaraj 2019 [44]	India	72/74	42.51	41.78	19.49	Hospital stay	Probiotic, bid	Placebo	S	ICU, HDU
	Mahmoodpoor 2019[30]	Iran	48/54	58.25	46.08	23.41	14.00	Probiotic, bid	Placebo	M	SICUs
	Tsaousi 2019[45]	Greece	28/30	30.00	Probiotic, qd	Placebo	S	ICU
	Habib 2020[46]	Egypt	32/33	39.48	20.00	...	ICU stay	Probiotic, tid	Placebo	S	ICU
	Nazari 2020 [47]	Iran	73/74	52.60	31.29	...	Hospital stay	Probiotic, bid	Placebo	M	NICU
	Johnstone 2021[18]	multicountry	1318/1332	59.85	40.11	22.00	60	Probiotic, bid	Placebo	M	ICUs
Neonates/ Children	Li 2012[48]	China	82/83	0.61	44.24	Probiotic, qd	Control	S	PICU
	Banupriya 2015[49]	India	75/75	2.92	39.33	#11.43	Hospital stay	Probiotic, bid	Control	S	PICU
	Angurana 2018[50]	India	50/50	3.65	40.00	#16.00	ICU stay	Probiotic, bid	Placebo	S	PICU

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; HDU, high dependency unit; ICU, intensive care unit; M multi-center study; NICU neonatal intensive

care unit; PICU, pediatric intensive care unit; #PRISM score, Pediatric risk of mortality score; SICU, surgical ICU; S single-center study; *SAPS II score, Simplified physiology score II score; &Fenugreek seeds act as a prebiotic.

Assessment of risk of bias

We did a sensitivity analysis so as to appraise the stability of the pooled effect estimates. The publication bias was also examined by the two authors via the funnel plot and statistical tests (Begg's Test and Egger's Test) [31].

Statistical analysis

For each trial, the dichotomous outcomes were reported as relative risk (RR) along with 95% confidence interval (CI). The median and range/interquartile range were converted to mean and standard deviation using the formulas described by one previous study [32]. The between-study heterogeneity was determined in accordance with the Chi-square test, *P* values and the I^2 index. In view of the conservative of random-effects model, we used this model to pool all data [33]. In order to determine whether the accumulated evidence was sufficient and conclusive, a trial sequential analysis (TSA) was performed in our study. The TSA version 0.9.5.10 beta (www.ctu.dk/tsa), Stata 12.0 (StataCorp, College Station, TX, USA) and Review Manager Version 5.3.5 software (<http://tech.cochrane.org/revman/download>) were implemented to analyze data. A two-tailed *P*-value < 0.05 was considered statistically significant.

Probiotics, prebiotics and synbiotics were equal for analysis in our meta-analysis. Considering the difference in neonates/children and adults, we analyzed the data separately. In addition, we conducted subgroup analyses based on the strain types (prebiotic vs. synbiotic vs. probiotic), the risk of bias (low risk vs high risk) and the center (multi-center vs. single-center). We also applied a cumulative meta-analysis by publication year.

Results

Search results and study characteristics

The chart of the study-selection procedure is presented in Fig. 1. Up to 10 October, 2021, 222 citations through the initial search of electronic databases were identified, and only 23 remnant trials, including 20 adult and 3 neonate/child populations studies, were ultimately included in our study. The 23 literatures, including 22 full-text articles and 1 abstract, on probiotics prophylaxis were reported between 2007 and 2021 and enrolled 52 to 2650 patients with a total of 5574 participants. The ages of the patients in adult populations range from 39.48 to 74.00 years. In studies eligible for inclusion in our meta-analysis, the follow-up times varied, ranging from 14 to 180 days with the proportion of female patients from 18.46–59.28%. Of them, patients treated with placebo/control were compared to those treated with prebiotic (*n* =1), synbiotic (*n* =4) or probiotic (*n* =18), respectively. Table 1 depict the main characteristics of the 23 eligible trials.

Assessment Of Study Quality

As listed in Fig. 2, a high risk of both performance and detection bias was presented in three studies [38, 39, 41] as a result of lacking of blinding or blind inadequacy. Because of a prematurely termination of schedule [37, 39], an imbalance in several significant baseline variables [20], an unreached of predetermined sample size [17, 19] and the funding provided by parties [17, 20, 35, 40, 50], we rated these studies as having high risk of other bias.

Sensitivity Analysis And Assessment Of Reporting Bias

The sensitivity analysis across studies for the primary outcome indicated the influence of each study set to the imputed RR is nonsignificant, demonstrating the stability of pooled estimate.

The publication bias existed by inspection of the funnel plot (Fig. 3), which was further confirmed through the Egger's test (*P*<0.01). However, the Begg's test (*P*=0.81) revealed no significant publication bias for our study (Appendix 3).

Synthesis Of Primary Outcome

All 23 studies reported the main outcome of interest and the synthesized RR was 0.67 (*n*=5543; 95%CI=0.56 to 0.81; *P*<0.01), with a moderate heterogeneity among these studies ($\chi^2=53.60$, *P*<0.01; $I^2=59.00\%$, Fig. 4). Meanwhile, the combined RR was 0.69 (*n* =5136; 95% CI=0.57 to 0.84; *P*<0.05) for adults studies and 0.55 (*n*=407; 95% CI=0.31 to 0.99; *P*=0.046) for neonates/children studies.

As is shown in Fig. 5, although the accrued number of patients did not reach the required information size (RIS, 84.52%, 5136/6077), the cumulative Z-curve crossed the conventional boundary line and RIS-adjusted boundary value, thus indicating that a favorable effect of probiotic in preventing VAP is observed in adult patients. As revealed in appendix 3, however, the TSA of neonates/children patients showed that the cumulative Z-curve did not reach the adjusted boundary line and the optimal information size despite this line surpass the conventional boundary line slightly, indicating that the current evidence is inconclusive.

Synthesis Of Secondary Outcomes

Compared with the control (placebo) group, the probiotic (prebiotic, synbiotic) group had no significant effect on the ICU/hospital/28-/90-day mortality, bacteremia, CRBSI, diarrhea, ICU-acquired infections, infectious complications, pneumonia, UTI and wound infection ($P \geq 0.05$ for all, Appendix 3).

The results of subgroup analyses and cumulative meta-analysis in adult patients

From the prebiotic ($n = 60$; RR, 0.47; 95% CI = 0.22 to 0.98; $P = 0.04$), synbiotic ($n = 516$; RR, 0.57; 95% CI = 0.33 to 0.98; $P = 0.04$) and probiotic ($n = 4560$; RR, 0.74; 95% CI = 0.59 to 0.91; $P = 0.01$) analysis, the incidences of VAP in MV critically ill patients were proven to be significantly reduced by the use of this treatment. In subgroup analysis based on the risk of bias, a positive result was observed both in trials reporting low risk of bias ($n = 3610$; RR, 0.62; 95% CI = 0.45 to 0.85; $P < 0.01$) and in those reporting high risk of bias ($n = 1526$; RR, 0.76; 95% CI = 0.59 to 0.97; $P = 0.03$). This was also confirmed by another subgroup analysis of multi-center trials ($n = 3729$; RR, 0.64; 95% CI = 0.46 to 0.89; $P = 0.01$) versus single-center trials ($n = 1407$; RR, 0.73; 95% CI = 0.58 to 0.91; $P = 0.01$; Appendix 3). Details of the results of this meta-analysis are shown in Table 2.

Table 2
Summary results on the primary outcome and subgroup analyses of this meta-analysis

Results	Primary outcome			Subgroup analyses (Adults)						
	total	adults	neonates/children	prebiotic	synbiotic	probiotic	low risk	high risk	multi-center	single-center
RR	0.67	0.69	0.55	0.47	0.57	0.74	0.62	0.76	0.64	0.73
95% CI lower-bound	0.56	0.57	0.31	0.22	0.33	0.59	0.45	0.59	0.46	0.58
95% CI upper-bound	0.81	0.84	0.99	0.98	0.98	0.91	0.85	0.97	0.89	0.91
<i>P</i> -value	<0.01	<0.01	0.046	0.04	0.04	0.01	<0.01	0.03	0.01	0.01
RR relative risk, CI confidence interval.										

Our cumulative meta-analysis showed that statistical significance that prophylactic probiotic among adult patients could result in a reduction of VAP incidence is first observed in 2016 Zarinfar [36] and this promising finding tended to be relatively stable thereafter (Fig. 6).

Discussion

The present systematic review and meta-analysis of 23 studies examined the effects of probiotic versus placebo in preventing VAP among critically ill patients and concluded that prophylactic probiotic therapy impacts positively on the incidence of VAP, with a 31%, 45% reduced risk in adults and neonates/children, respectively. Furthermore, the above mentioned positive result in adults was lately confirmed by the result of TSA, subgroup analyses and cumulative meta-analysis. There was no statistical difference of ICU/hospital/28-/90-day mortality, bacteremia, CRBSI, diarrhea, ICU-acquired infections, infectious complications, pneumonia, UTI and wound infection between two groups.

Diminishing the occurrence of VAP remains a challenge. Unlike previous recognition that lung is a sterile organ [51], there exists a “lung microbiota” in our lung. In healthy lungs, a dynamic balance between immigration of microorganism from the upper respiratory tract and elimination of bacteria by host defense mechanisms [8]. Unfortunately, the balance is disrupted when people develop several certain respiratory diseases, such as asthma, cystic fibrosis and lung infections, etc. [52]. Of note, the disruption of microbial homeostasis might be associated with the occurrence of VAP. Indeed, orotracheal intubation, which might impair the natural lung defense mechanisms, is a promoter of microbiome dysbiosis [53]. Furthermore, the gut–lung–microbiome axis is one of current researching hotspots in basic research in recent years. Significantly, this axis is bidirectional—gut dysbiosis is related to lung disorders and infections, whereas, the changes in lung microbial composition can affect the intestinal flora—mainly through the circulation of soluble microbial components and metabolites (ie, peptidoglycans, lipopolysaccharide) [8]. The source of bacterial dysbiosis in the lung might be derived from the gut, thus resulting in the occurrence of VAP [54]. Hence, we suspect that as a potential benefit of inhaled antibiotics in preventing VAP, “aerosolized probiotics” [55] might emerge in the near future, which may play a role in the regulate of lung microbiome directly.

For quite a long time, probiotics are generally recognized as safe, and probiotic products are now ubiquitous in our lives, such as such as yogurts, cheeses, snacks and cosmetic products, etc [12]. Moreover, probiotics are increasingly given as accessory or therapeutic method to hospitalized patients, especially for the critically ill patients (eg. VAP, sepsis and antibiotic-associated diarrhea, etc.) [56]. Despite probiotic products and probiotics are being used widely in life and clinical practice, their safety has not been fully assessed. Recently, some of scholars have expressed their concern as regards the probiotic safety [11, 57] and Nieuwboer, et al [56] suggested that a solid evidence for the proper and safe use of probiotics still need to be established, in particular for high-risk population (eg. prematurity, immunocompromised and critically ill patients, etc.). Conversely, Cabana and colleagues [58] reported that some of probiotic strains are subject to stringent safety evaluation followed by notification of the US Food and Drug Administration for comment, and the data from many high-quality studies have tracked adverse complications and showed evidences in favor of probiotics. In our meta-analysis, 8.70% (2/23) of the eligible studies expressed a degree of uncertainty about the safety, 17.39% (4/23) of the studies are silent about the safety issues, and 69.57% (16/23) of the studies have indicated that no obvious adverse events attributed to the probiotic (prebiotic, synbiotic) are noted in these study populations. Nonetheless, a large multicenter, randomized, concealed, blinded trial of 2650 critically ill patients (4.35%, 1/23) [18], found that compared with the placebo therapy, administration of the probiotic (*Lactobacillus rhamnosus* GG) does not decrease the occurrence of VAP, and an increased risk of adverse events is noted among patients receiving this treatment.

There have been several relevant meta-analyses in this area to date, producing several conflicting outcomes [15, 16, 21–28]. Gu, et al [15] in 2012 published a meta-analysis of seven trials and failed to demonstrate a beneficial effect in reducing VAP in adult patients undergoing MV, and the result was further reinforced by a 2013 meta-analysis [16] with five trials. By contrast, an earlier meta-analysis [21] in 2010 concurred with our findings and revealed that the administration of probiotics is associated with a reduction in VAP incidence in adult patients who are mechanically ventilated, which was further proved by a subsequent 2014 Cochrane review with eight trials[22], two meta-analyses for adult and children patients [23, 24] and several meta-analyses for adult or(and) children patients[25–28]. Previous meta-analyses on this issue have focused on only adult patients or the combination analysis of both adult patients and non-adult patients.

The current meta-analysis has several strengths compared to earlier works. First, this study, to our knowledge, might be the first cumulative meta-analysis which conduct the TSA from the view of adult and neonates/children populations, resulting in a more robust, reliable and precise pooled estimate. Second, in contrast to prior meta-analyses, we analyzed the influences of probiotic to VAP from the viewpoint of neonates/children and adults populations, respectively, which is partly reflected a true effect of probiotic in the prevention of VAP in mechanically ventilated patients. Third, as the evidence accumulates and sample size increases, especially with the addition of a large new study (n=2650) [18], our study had enhanced the statistical power to examine the efficacy of protective effects of probiotics in reducing VAP incidence.

Our meta-analysis has several potential shortcomings as well. First, since the possibility of false positive result in TSA, as well as the limited numbers of the eligible articles and samples, the positive result for neonates/children patients should be interpreted with caution. Consequently, the beneficial effects of probiotics on VAP for these patients needed further study. Second, the diagnosis of VAP might be complex due to the lack of uniformly accepted diagnostic standard, which might lead to increased the heterogeneity among these included studies. Finally, another limitation of the study was that publication bias exists in our study. The following may be the possible reasons: language bias, studies with positive findings are more likely to be published than those with negative findings, and inflated effect size in smaller studies with a flawed methodologic design. Thus, further large studies, especially for the neonates/children and an objective accepted diagnostic criteria of VAP, are necessary to verify our findings in this area.

Conclusions

In conclusion, our cumulative meta-analysis strengthens the evidence that prophylactic use of probiotics can be a possible effective non-antibiotic option in reducing the incidence of VAP in critically ill ventilated patients. However, the long-run effects of probiotics safety on individuals warrant further studies, especially in special groups of critically ill patients (i.e. neonates/children, immunocompromised, severely debilitated patients, etc.).

List Of Abbreviations

CI: confidence interval; CRBSI: catheter-related bloodstream infection; HLOS: hospital length of stay; ICU: intensive care unit; MV: mechanical ventilation; RCTs: randomized controlled trials; RR: relative risk; TSA: trial sequential analysis; UTI: urinary tract infection; VAP: ventilator-associated pneumonia; VD: ventilator-days.

Declarations

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Authors' contributions

ZL and SYC conceived the study idea and designed the study. ZL performed this meta-analysis, including the literature search, data extraction, analysis and manuscript. SYC participated in these programs. SYC, WCY, WHL, YY and LJH were involved in drafting and revising the article. All authors read and approved the final manuscript.

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Availability of data and material supporting data

All data are fully available without restriction.

Ethical Approval and Consent to participate

Does not apply.

Consent for publication

Does not apply.

Competing interests

The authors declare that they have no competing interests.

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Figures

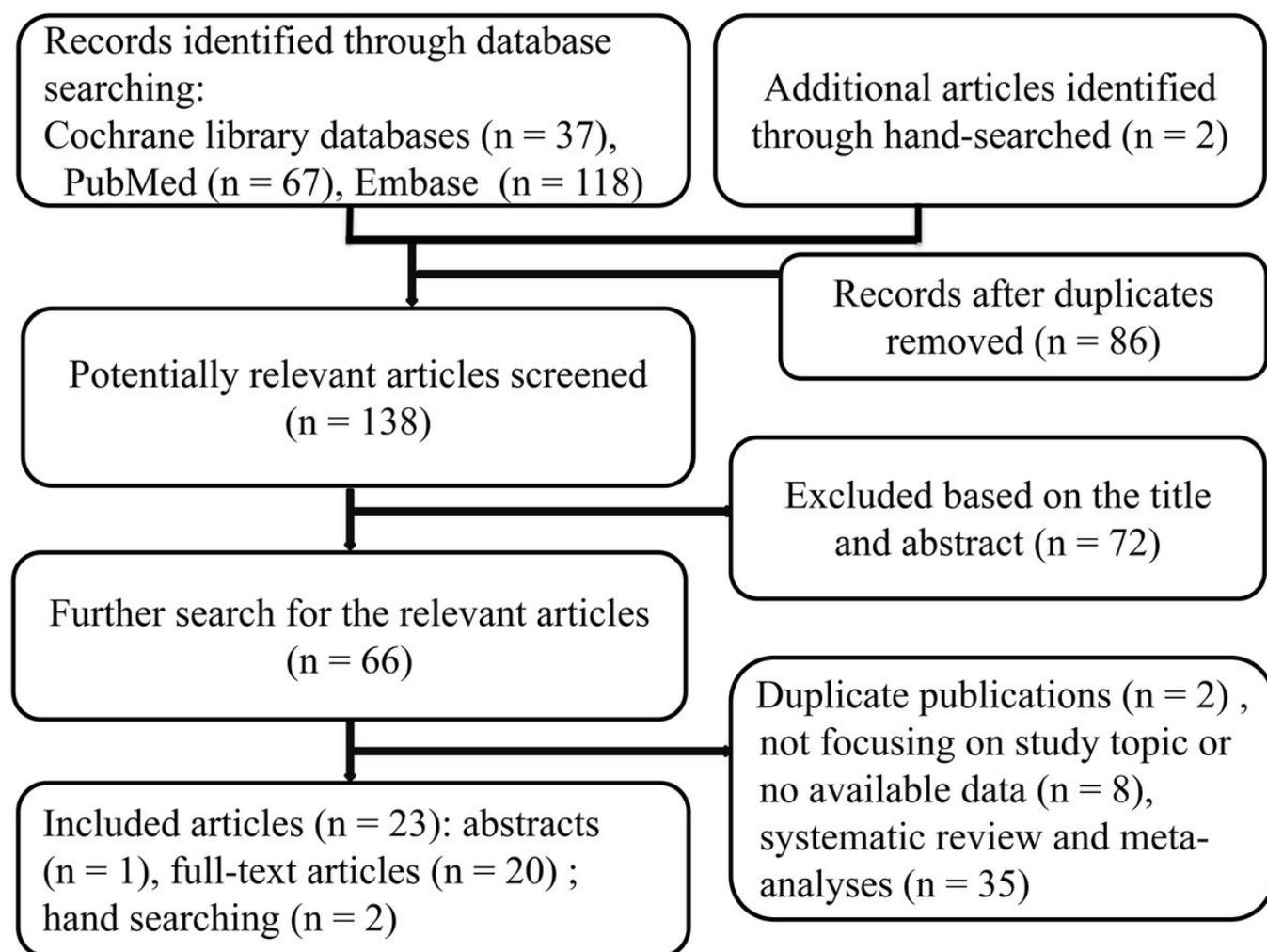


Figure 1

Flow diagram of study selection process.



Figure 2
Risk of bias assessment. a Risks of bias summary b Risks of bias graph.

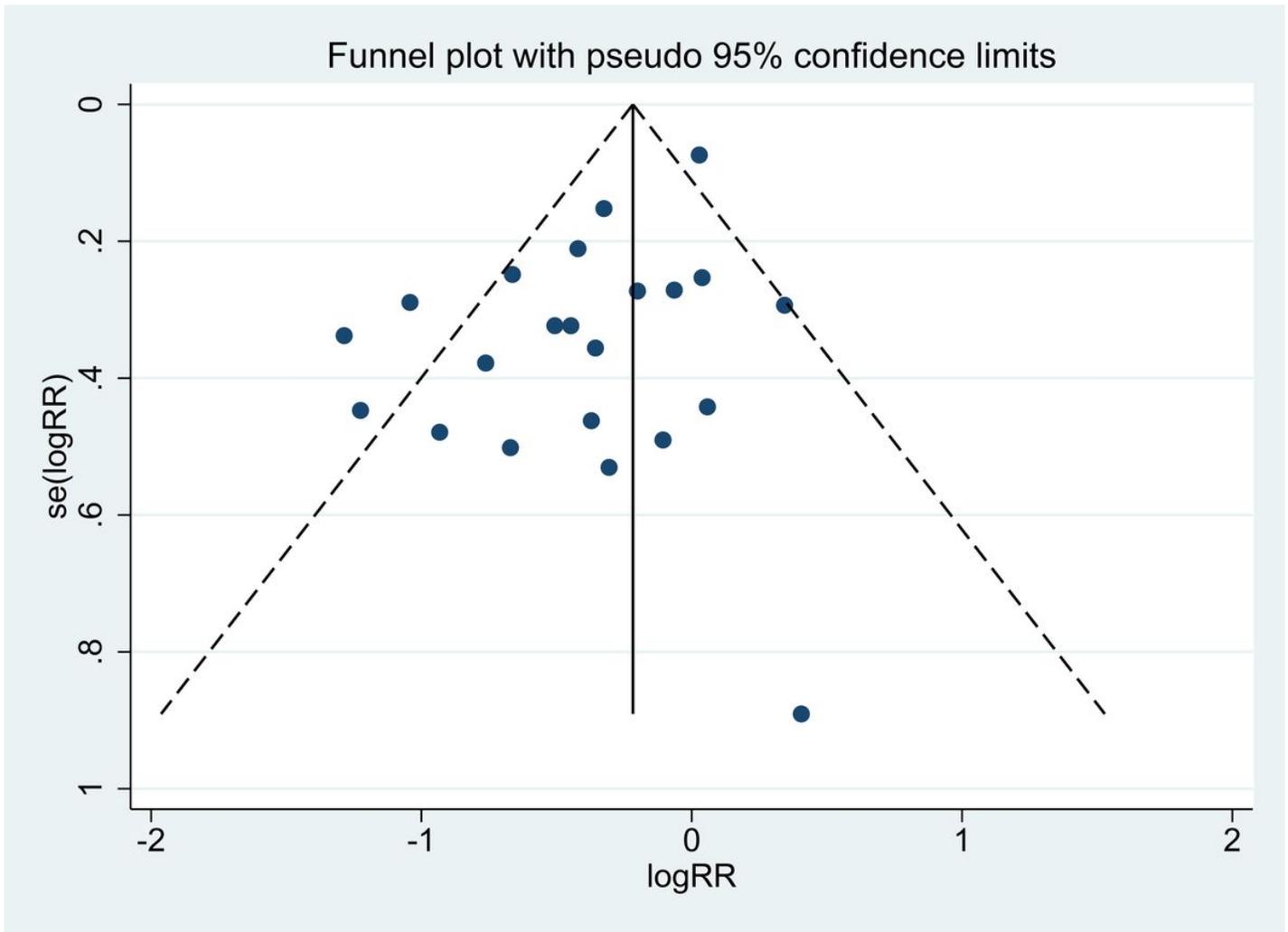


Figure 3

Funnel plot for publication bias.. The blue dots and dotted line represent one single studies and 95% confidence intervals, respectively

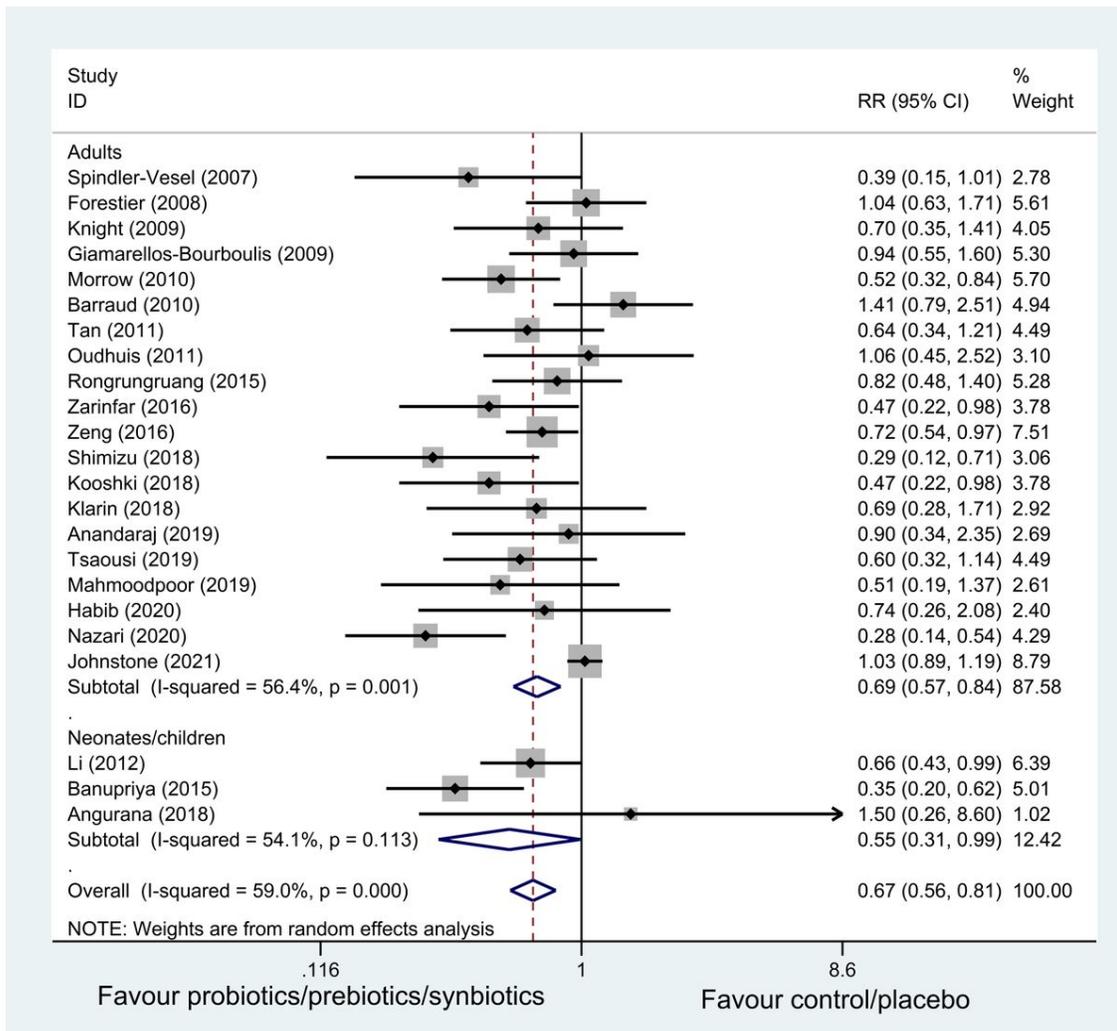


Figure 4

Forest plot of pooled data demonstrating the reduction in risk of ventilator-associated pneumonia incidence. RR relative risk, CI confidence interval

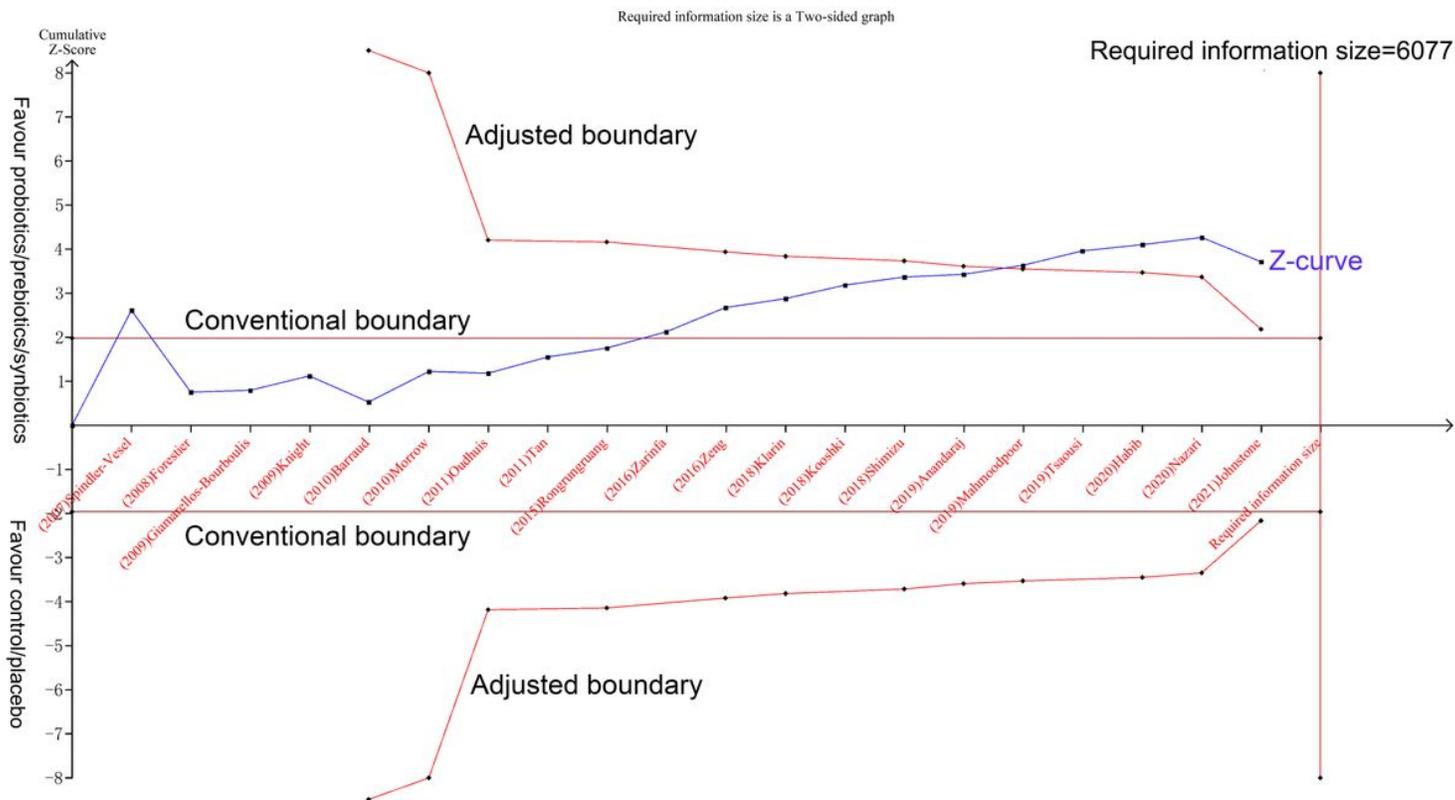


Figure 5

Trial sequential analysis for effects of probiotics on VAP incidence in adult patients. The required information size of 6077 was calculated based on the VAP incidence of 20.69, 25.27% in the probiotic and placebo group, respectively ($\alpha=5\%$, $\beta=20\%$, $I^2=56.40\%$).

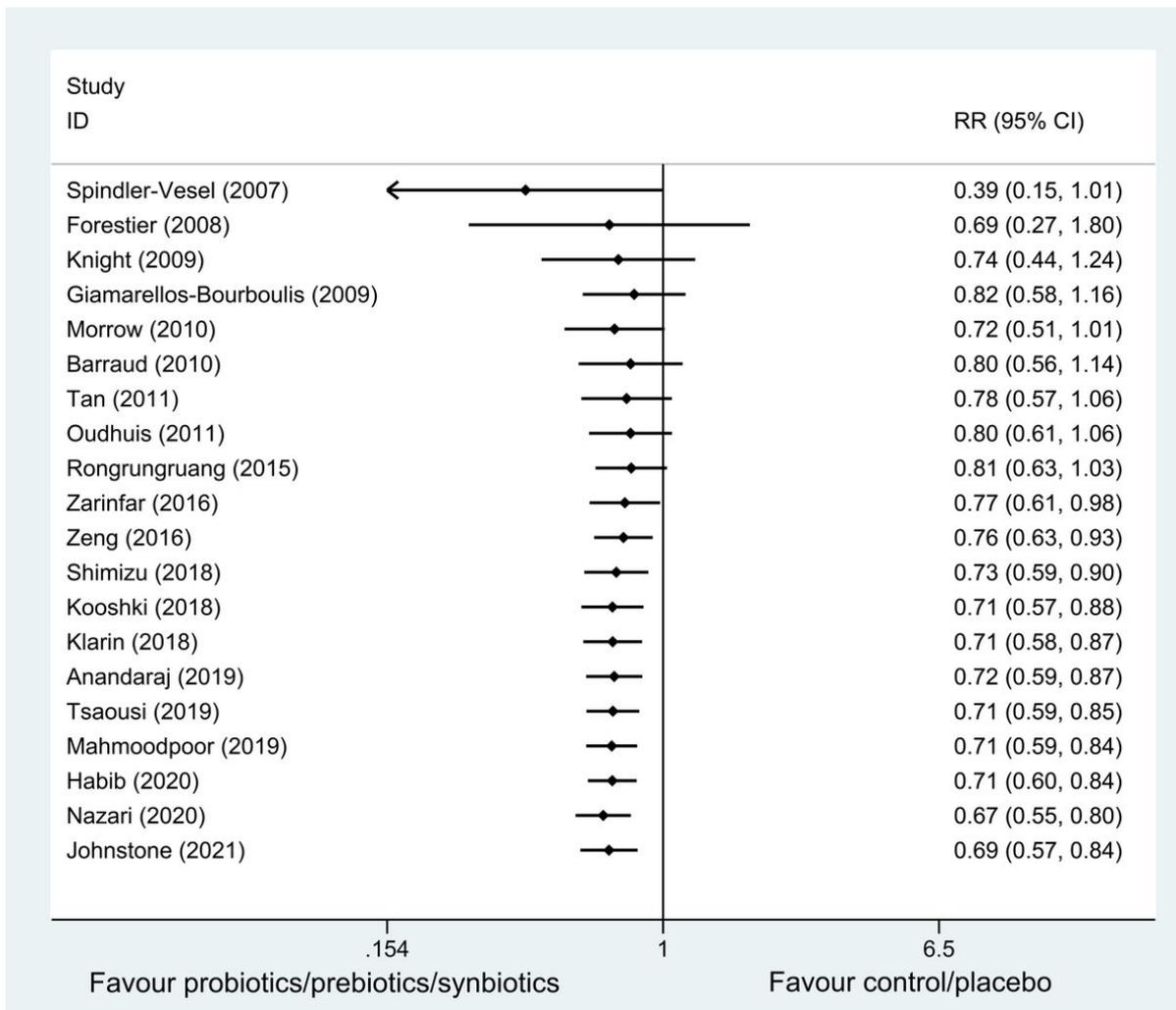


Figure 6
 Cumulative meta-analysis showing the cumulative evidence of the efficacy of probiotic in preventing VAP in adult critically ill patients undergoing MV. VAP ventilator-associated pneumonia, MV mechanical ventilation, RR relative risk, CI confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix1ThePRISMAchecklist.doc](#)
- [Appendix2ThePICOframework.docx](#)
- [Appendix3Sensitivityanalysisreportingbias.docx](#)