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Meta-Analysis

Prevention of ventilator-associated pneumonia through care bundles: A systematic review and meta-analysis

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) represents a common hospital-acquired infection among mechanically ventilated patients. We summarized evidence concerning ventilator care bundles to prevent VAP.

Methods: A systematic review and meta-analysis were performed. Randomized controlled trials and controlled observational studies of adults undergoing mechanical ventilation (MV) for at least 48 h were considered for inclusion. Outcomes of interest were the number of VAP episodes, duration of MV, hospital and intensive care unit (ICU) length of stay, and mortality. A systematic search was conducted in the MEDLINE, the Cochrane Library, and the Web of Science between 1985 and 2022. Results are reported as odds ratio (OR) or mean difference (MD) with 95% confidence intervals (CI). The PROSPERO registration number is CRD42022341780.

Results: Thirty-six studies including 116,873 MV participants met the inclusion criteria. A total of 84,031 participants underwent care bundles for VAP prevention. The most reported component of the ventilator bundle was head-of-bed elevation (n=83,146), followed by oral care (n=80,787). A reduction in the number of VAP episodes was observed among those receiving ventilator care bundles, compared with the non-care bundle group (OR=0.42, 95% CI: 0.33, 0.54). Additionally, the implementation of care bundles decreased the duration of MV (MD=−0.59, 95% CI: −1.03, −0.15) and hospital length of stay (MD=−1.24, 95% CI: −2.30, −0.18) in studies where educational activities were part of the bundle. Data regarding mortality were inconclusive.

Conclusions: The implementation of ventilator care bundles reduced the number of VAP episodes and the duration of MV in adult ICUs. Their application in combination with educational activities seemed to improve clinical outcomes.

Introduction

Ventilator-associated pneumonia (VAP) represents one of the most common intensive care unit (ICU)-acquired infections in patients requiring mechanical ventilation (MV) for at least 48 h.[1,2] Respiratory infections in intubated patients are associated with long-lasting MV and extended ICU stay, providing a rationale for initiating antibiotic treatment.[1,3–5] Additionally, the enormous effect of VAP on morbidity and mortality [1] imposes an important economic burden, adding an estimated cost of 40,000 US dollars to a typical hospital admission.[4] Variations in risk of acquisi-

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tion are related to patients' factors (including age, comorbidities, and severity), duration of hospitalization, and organizational factors. Quality of care, by adherence to a care bundle, may influence the risk of VAP and its consequences. A ventilator care bundle is a set of collectively applied interventions to reduce the risk of ventilator-associated events, including VAP. Their use constitutes a highly recommended strategy to reduce VAP incidence.[5] Although care bundles can differ in components among institutions, a core group of endorsed practices has been established and supported by different levels of evidence.[4,6]

Over the last years, several clinical practice guidelines [2,4,7,8] have discussed the most effective and quality improvement interventions to prevent VAP, because, with their promotion and implementation, VAP incidence seemed to decrease.[2] Nevertheless, although care bundles are generally considered to be beneficial in improving patient-related outcomes, recommendations across the guidelines are not consistent.

This systematic review and meta-analysis aimed to summarize the evidence concerning the role of ventilator care bundles in the prevention of VAP in adult ICUs. The secondary objective was to record the clinical outcomes of patients requiring MV who did and did not receive care bundles.

Methods

Registration and protocol

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline [9,10] was used for conducting this study. Details of the PRISMA checklist can be found in Supplementary Table S1. This systematic review and meta-analysis were previously registered in PROSPERO (CRD42022341780).

Search strategy

We performed a systematic search for studies published between 1985 and July 2022 on the MEDLINE, Cochrane Library, and Web of Science databases. No language restrictions were applied. To capture any new studies published after the initial search, alerts were created in each database. The search strategy has been detailed in Supplementary Table S2. The last search across databases was performed in June 2022.

Eligibility criteria

We considered the following inclusion criteria: (1) randomized-controlled trials (RCTs) and controlled observational studies; (2) adult (≥18 years) ICU patients undergoing MV for at least 48 h; (3) use of care bundles for VAP prevention (intervention group); and (4) the comparator group did not receive a ventilator care bundle. Isolated quality improvement interventions performed as part of standard care could be performed in the comparator group. The main outcome was VAP incidence. Duration of MV, hospital length of stay, ICU length of stay, hospital mortality, ICU mortality, and ventilator-associated respiratory infections (VARI) were reported as secondary outcomes.

Studies were excluded in the following cases: (1) studies that were not original research studies (letters, editorials, replies, comments, and conference abstracts); (2) studies that were unpublished or inaccessible to the authors; (3) inclusion of ≤10 participants; (4) no report of outcomes of interest; and (5) use of any ventilator care bundle in the control group.

Definitions

VAP definition was extracted from each study and provided in Supplementary Table S3. Furthermore, outcome definitions were considered as reported in the studies to prevent possible variations over time and across publications.

A care bundle was defined according to the Institute of Health Improvement (IHI) [11] statement as "a small, straightforward set of evidence-based practices (generally three or more) that, when performed collectively and reliably, have been proven to improve patient outcomes set of care practices" (see Supplementary Table S4 regarding care bundle recommendations by each clinical practice guideline).

Baseline measures were considered as quality improvement interventions that did not meet the minimum number of three interventions, were not applied collectively, or were not supported by scientific evidence.

Educational activities were identified when healthcare professionals received any kind of training on the application and importance of ventilator care bundles; including educational meetings, seminars, workshops, and teaching sessions.

Data collection

Two independent authors (RMR and ST) screened the references based on title and abstract using the reference software, Rayyan. Each duplicate article was identified and deleted. Selected articles underwent a full-text assessment. Disagreements were resolved by a third author (SRE). Throughout the inclusion process, a predesigned Excel spreadsheet was used to collect data about exclusion criteria, study design, participants, intervention, comparator, quality assessment, and outcomes.

When results were not reported, we attempted to contact the study's authors to obtain the relevant missing data. The number of participants and denominator were extracted for dichotomous outcomes; whereas sample size, mean±standard deviation (SD), and median [interquartile range (IQR)] were extracted for continuous outcomes.

Quality assessment

The methodological quality of included studies was assessed separately by two authors (ARS and DE). Disagreements were resolved by a third author (TV). The modified Downs and Black Checklist [12] was used for the evaluation of each study. This scale is used in the assessment of both randomized and non-randomized studies, providing an overall score for study quality and a profile of scores for quality of reporting, internal validity, external validity, and power. The modified Downs and Black questionnaire [12] consists of 27 items graded as "Yes," "No," and "Unable to determine" as per the available information. It includes five sections, which are study quality (10 items), external validity (three items), study bias (seven items), confounding and selection bias (six items), and power (one item). Each question gets a score of 1 if answered "yes," except for

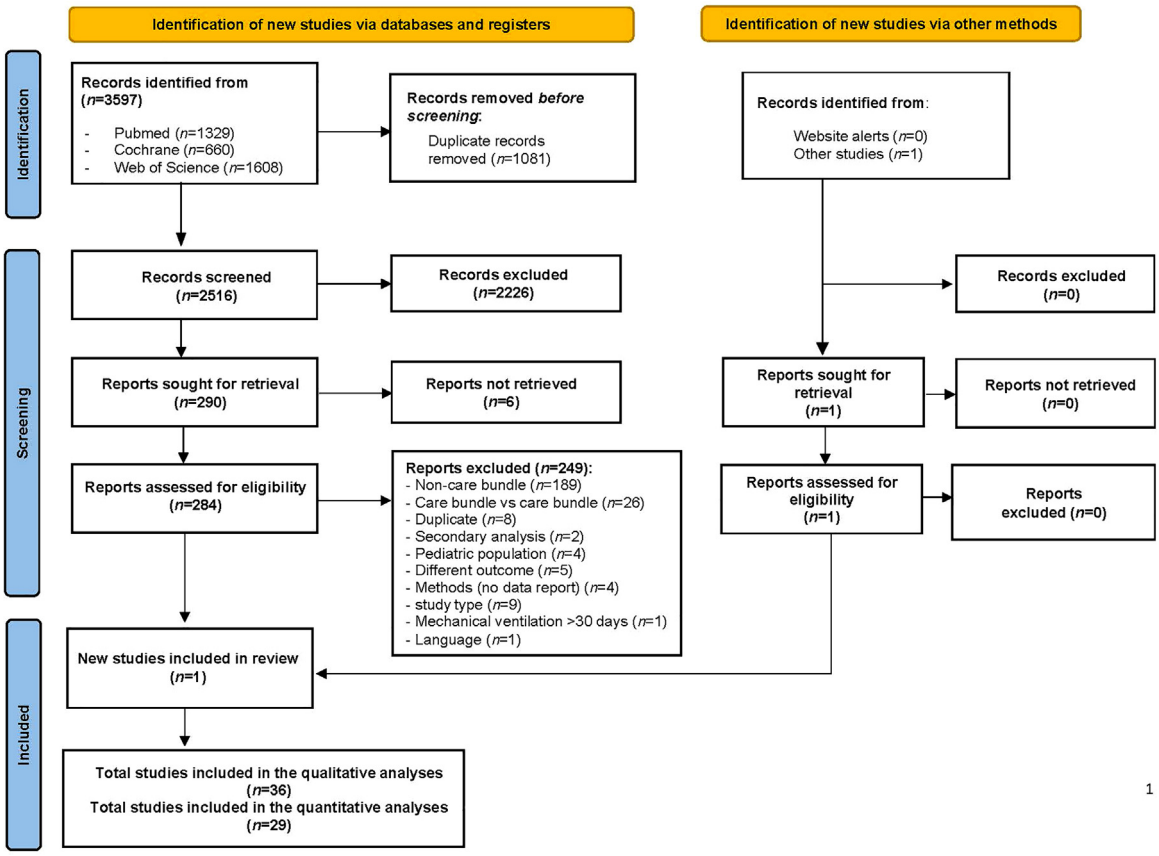

Figure 1. PRISMA flow diagram of the study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses.

the fifth question, which can get a score of 2 if answered "yes." The modified version simplifies the power question, awarding 1 point (instead of 5 points in the original article from Downs and Black) [12] if a study had adequate power to recognize a clinically significant effect. This modification has been used in several articles.[13–15] Therefore, the total score is scored out of a possible 28. In this light, each paper was assigned a rating of "excellent" (24–28 points), "good" (19–23 points), "fair" (14–18 points), and "poor" (<14 points).

Statistical analysis

If the results were not reported in a format suitable for the meta-analysis, the methods described by Luo et al.[16] and Wan et al.[17] were used. These methods used formulae for the conversion of medians to estimated mean±SD. Study authors were contacted to request unpublished data. Outcomes that did not present enough numerical results were not analyzed in the meta-analysis.

The meta-analysis was performed using RevMan version 5.3(the Nordic Cochrane Centre, Copenhagen:the Cochrane Collaboration, 2014). For dichotomous outcomes, odds ratios (ORs) were used to analyze the pooled effects, whereas mean differences were used for continuous data. All statistical measures were calculated with 95% confidence intervals (CI). The Mantel-Haenszel method was used for the random-effects model to generate pooled treatment effects across studies. The results of the meta-analysis were presented as forest plots.

Statistical heterogeneity was assessed using Higgins I^2 value.[10] Heterogeneity was considered low (I^2<30%), moderate (I^2=30–<60%), substantial (I^2=60–<75%), and considerable (I^2≥75%). When more than 10 articles were included in the meta-analysis, funnel plots together with Egger test [18] were used to assess the risk of publication bias, if present. Sensitivity analysis was performed to probe influence factor (number of included studies ≥10). When sufficient data were reported, subgroup analyses were performed on (1) health professionals receiving educational interventions, (2) baseline measures used as a standard of care, (3) overall bundle compliance exceeding 70% or not, (4) study quality, (5) study design, (6) geographical area, and (7) VAP diagnostic criteria.

Results

Study selection

The search identified 3597 potentially relevant studies. Of these, 35 [19–53] studies met inclusion criteria, and 1 additional publication [54] was found among the references from previous studies. A total of 29 studies [20–23,26–28,30,31,33–39,41–50,52–54] were suitable for the quantitative meta-analysis. The PRISMA flow diagram is shown in Figure 1.

Study and participant characteristics

Twenty-two prospective cohort studies [19,20,23,25,30–35,37–39,41,43–46,48,51,52,54], six retrospective cohort studies [26–28,36,42,50], four quasi-experimental studies [29,40,49,53], two clinical trials [21,22], one cross-sectional study [47], and one prospective plus retrospective cohort study [24] met the

Table 1
Main characteristics of 36 included studies, organized from less to more IHI recommended measures included in their care bundles.

References	Country	Study type	Age (years)		Mechanical ventilated subjects	Female
			Non-care bundles	Care bundles		
Arabnejad et al.[21]	Iran	Controlled clinical trial	38.1 ± 15.6	35.5 ± 16.1	117	17 (14.5)
Atashi et al.[22]	Iran	Randomized clinical trial	52.4 ± 14.9	45.6 ± 17.1	76	24 (31)
Baxter et al.[23]	Canada	Prospective cohort	-	-	4212	–
Omrane et al.[41]	Canada	Prospective cohort	57.4 ± 19.8	61.2 ± 18.6	709	286 (40.3)
Pérez-Granda et al.[44]	Spain	Prospective cohort	66.5 ± 12.0	67.4 ± 30.6	1935	401 (20.7)
Rello et al.[45]	Spain	Prospective cohort	59±18	66±18	1034	356 (34.4)
Sachetti et al.[47]	Brazil	Cross-sectional	–	–	433	–
Tao et al.[52]	China	Prospective cohort	–	–	3744	–
Lansford et al.[35]	USA	Prospective cohort	–	–	350	–
Liu et al.[37]	China	Prospective cohort	–	–	200	–
Ongstad et al.[42]	USA	Retrospective cohort	42.6 ± 20.1	49.2 ± 21.0	183	–
Triamvisit et al.[53]	Thailand	Quasi-experimental	53.8 ± 21.1	53.9 ± 19.7	134	47 (35.1)
Álvarez-Lerma et al.[20]	Spain	Prospective cohort	–	–	3725	–
Bukhari et al.[25]	Saudi Arabia	Prospective cohort	–	–	2747	–
Burja et al.[26]	Slovenia	Retrospective cohort	67.8 ± 14.5	64.8 ± 13.7	129	53 (41.1)
Eom et al.[29]	South Korea	Quasi-experimental	–	–	–	–
Hawe et al.[31]	UK	Prospective cohort	–	–	589	249 (42.3)
Kao et al.[32]	Taiwan	Prospective cohort	–	–	–	–
Landelle et al.[34]	Switzerland	Prospective cohort	61.9 (48.6–73.4)	60.5(49.4–71.2)	647	189 (28)
Liu et al.[38]	China	Prospective cohort	–	–	4716	2233 (47.3)
Morris et al.[39]	UK	Prospective cohort	60(47–72)	59 (48–70)	1961	776 (39.5)
Rosenthal et al.[46]	14 developing countries*	Prospective cohort	57.2 ± 19.5	57.6 ± 19.9	55,507	22,313 (40.2)
Santana et al.[49]	Brazil	Quasi-experimental	–	–	64	24 (37.5)
Cacheco and Dobkin [54]	USA	Prospective cohort	54.40±1.80	55.51±2.21	954	–
Al-Tawfiq and Abed [19]	Saudi Arabia	Prospective cohort	–	–	–	–
Bird et al.[24]	USA	Prospective/Retrospective cohort	–	–	–	–
Ding et al.[28]	USA	Retrospective cohort	66 (51–78)	63 (46–76)	350	186 (53.1)
Ferreira et al.[30]	Brazil	Prospective cohort	–	–	188	78 (41.5)
Khan et al.[33]	Saudi Arabia	Prospective cohort	53.2 ± 21.0	56.4 ± 21.0	3665	689 (18)
DeLuca et al.[27]	USA	Retrospective cohort	35 (23–55)	47 (24–63)	387	123 (31.8)
Lim et al.[36]	Taiwan	Retrospective cohort	63.2 (50.6–74.3)	62.8 (51.7–74.5)	27,125	10,896 (40.2)
Okgün et al.[40]	Turkey	Quasi-experimental	Overall: 58.3 (20.7)	128	55 (43)	
Parisi et al.[43]	Greece	Prospective cohort	59 (41–73)	58 (42–72)	362	115 (31.8)
Samra et al.[48]	Egypt	Prospective cohort	–	–	380	122 (32.1)
Sen et al.[50]	USA	Retrospective cohort	50.8 ± 18.6	46.8 ± 19.2	131	39 (29.8)
Talbot et al.[51]	UK	Prospective cohort	–	–	–	–

Data are expressed as mean±standard deviation, median (interquartile range), or *n* (%).
IHI: Institute of Health Improvement; –: Not available.
* Argentina, Brazil, China, Colombia, Costa Rica, Cuba, India, Lebanon, Macedonia, Mexico, Morocco, Panama, Peru, and Turkey.

eligibility criteria (see details in Table 1). All studies were conducted in the adult (≥18 years) population. A total of 123,829 participants were admitted to the ICU, and 39,275 (31.72%) participants were women. The current systematic review comprised 116,873 participants requiring MV. The main characteristics of the included studies are detailed in (Table 1).

A total of 84,031 participants received care bundles for the prevention of VAP, with a mean of 21.7 months (SD=24.8 months) follow-up. The most commonly reported component of the ventilator care bundle was head-of-bed elevation (*n*=83,146), followed by oral care (*n*=80,787), and daily assessment of readiness to extubate (*n*=71,408). Educational programs delivered to healthcare professionals to improve the implementation of ventilator care bundles were documented in 26 studies. Twenty-one studies reported overall compliance and 14 of these studies had high compliance (>70%). Considering all studies, 28,998 participants did not receive ventilator care bundles during their hospital stay, with a mean of 12.2 months (SD=8.9 months) follow-up. Seventeen studies reported baseline measures as the standard of care. The main characteristics of the applied ventilator care bundles are detailed in (Table 2).

Quality assessment

Methodological quality of included studies was considered good in 28 studies [19–21,23,25–28,30,31,33–36, 8–44,46,48–54] and excellent in 3 studies.[22,37,45] Four studies [24,29,32,47] were considered to be of poor methodological quality, mainly due to the issues with internal validity (confounding bias) with the inability to answer questions 22, 23, 24, and 26 of the questionnaire. Details are provided in Supplementary Table S5.

Outcomes

VAP incidence

Twenty-five studies [21–23,26,27,30,31,33–39,41–43,45–50,52,53] reported VAP incidence. The number of VAP episodes was significantly lower (OR=0.42, 95% CI: 0.33, 0.54; Figure 2) in the group receiving ventilator care bundles than the non-care bundle group. Considerable heterogeneity (I^2=82%) was found. All subgroups had significantly reduced number of VAP episodes, which included health professionals receiving educational intervention programs, baseline measures used as a standard of care, overall bundle compliance exceeding 70% or not, geographical

Table 2
Main characteristics of standard care (non-care bundles) and care bundle interventions, organized from less to more IHI recommended measures included in their care bundles.

References	Education*	Non-care bundles			CB				Nurse-patient ratio	Compliance (%)
		Length†	*n*	Baseline measures	Length‡	*n*	Guidelines of the Institute for Healthcare Improvement CB‡	Other elements		
Arabnejad et al.[21]	YES	–	71	YES	–	46	Head-of-bed elevation, daily oral care with chlorhexidine	HH, ETT cuff pressure, SSD, avoid ventilator circuits changes, sterilization	–	–
Atashi et al.[22]	YES	–	38	YES	–	38	Head-of-bed elevation, daily oral care with chlorhexidine	ETT cuff pressure, SOD	–	–
Baxter et al.[23]	YES	6	705	–	36	3507	Head-of-bed elevation, daily oral care with chlorhexidine	HH, transpyloric enteral feeding, antibiotics	–	–
Omrane et al.[41]	YES	7	349	YES	7	360	Head-of-bed elevation, stress ulcer prophylaxis	HH, nutrition, change ventilator circuit	–	–
Pérez-Granda et al.[44]	YES	9	401	–	35	1534	Head-of-bed elevation, daily oral care with chlorhexidine	SSD	–	42
Rello et al.[45]	–	3	149	–	16	885	Sedation management, daily oral care with chlorhexidine	HH; ETT cuff pressure; avoid ventilator circuit changes	–	20
Sachetti et al.[47]	YES	2	198	–	2	235	Head-of-bed elevation, daily oral care with chlorhexidine	OTT cuff pressure, clean ventilator circuits, physical therapy	–	66.7
Tao et al.[52]	YES	12	1999	YES	7	1745	Head-of-bed elevation, daily oral care with chlorhexidine	HH	–	–
Lansford et al.[35]	–	12	218	YES	12	132	Head-of-bed elevation, daily assessment of readiness to extubate, daily oral care with chlorhexidine	Nasogastric tube	–	–
Liu et al.[37]	YES	–	100	–	–	100	Head-of-bed elevation, daily assessment of readiness to extubate, daily oral care with chlorhexidine	HH, SSD, Nasogastric tube	–	–
Ongstad et al.[42]	–	24	87	–	12	96	Head-of-bed elevation, daily assessment of readiness to extubate, daily oral care with chlorhexidine	SSD, avoid ventilator circuit changes, high-frequency chest wall compressions	–	>90
Triamvisit et al.[53]	YES	12	66	YES	14	68	Head-of-bed elevation, daily assessment of readiness to extubate, daily oral care with chlorhexidine	HH, ETT cuff pressure, avoid gastric over distention	–	–
Álvarez-Lerma et al.[20]	YES	3	–	–	21	–	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	HH, ETT cuff pressure, avoid ventilator circuits changes §SOD, SSD, antibiotics	–	–
Bukhari et al.[25]	YES	12	–	YES	12	2747	Head-of-bed elevation, daily sedation vacations, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis	No	–	78.9
Burja et al.[26]	YES	4	55	YES	4	74	Head-of-bed elevation, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, daily oral care with chlorhexidine	ETT cuff pressure, SSD, tracheal aspirate	–	–
Eom et al.[29]	YES	8	–	YES	3	–	Head-of-bed elevation, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	§SSD	–	71.8
Hawe et al.[31]	YES	17	374	–	10	215	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	HH, SSD, clean ventilator circuits	–	54
Kao et al.[32]	YES	7	–	–	15	–	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	ETT cuff pressure, ventilator circuits clean	–	92.8
Landelle et al.[34]	YES	8	291	YES	11	356	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	HH, ETT cuff pressure, SSD, SOD, patient mobilization	1:2 *Nursing assistant-patient 1:4*	83.3
Liu et al.[38]	–	12	2029	YES	12	2687	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	HH, ETT cuff pressure, SSD, sterilization	–	89.8
Morris et al.[39]	YES	–	1460	–	–	501	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	No	–	70

(*continued on next page*)

Table 2 (*continued*)

References	Education*	Non-care bundles			CB				Nurse-patient ratio	Compliance (%)
		Length†	*n*	Baseline measures	Length†	*n*	Guidelines of the Institute for Healthcare Improvement CB‡	Other elements		
Rosenthal et al.[46]	YES	3	3889	YES	139	51,618	Head-of-bed elevation, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, daily oral care with chlorhexidine	HH, ETT cuff pressure, avoid gastric over distention, avoid ventilator circuit changes; clean ventilator circuits, sterilization, use of OTT	–	–
Santana et al.[49]	–	19	30	–	19	34	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	ETT cuff pressure	–	55
Cacheco and Dobkin [54]	YES	24	299	YES	36	655	Head-of-bed elevation, sedation management, daily sedation vacations, daily assessment of readiness to extubate, daily oral care with chlorhexidine	Gastrointestinal-l bleeding prophylaxis	–	91
Al-Tawfiq and Abed [19]	YES	12	–	–	24	–	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis	No	–	82
Bird et al.[24]	–	–	–	–	–	–	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis	No	–	SICU 81 TICU 91
Ding et al.[28]	–	36	213	YES	36	137	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis	No	–	97
Ferreira et al.[30]	–	12	115	–	16	73	Head-of-bed elevation, sedation management, stress ulcer prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	Nutrition, analgesia, glucose control	–	–
Khan et al.[33]	–	24	2212	–	24	1453	Head-of-bed elevation, daily sedation vacations, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	ETT cuff pressure, SSD	1:1 *RT-patient: 1:5*	94.2
DeLuca et al.[27]	YES	6	195	YES	6	192	Head-of-bed elevation, sedation management, daily sedation vacations, daily assessment of readiness to extubate, Stress Ulcer Prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	SSD	–	–
Lim et al.[36]	YES	46	12,913	YES	41	14,212	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	HH, ETT cuff pressure, sterilization	–	–
Okgün et al.[40]	YES	3	–	YES	3	–	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	HH, ETT cuff pressure	–	89.8
Parisi et al.[43]	YES	14	226	–	8.5	136	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	No	1:3 day 1:4 night	28

(*continued on next page*)

Table 2 (*continued*)

References	Education*	Non-care bundles			CB				Nurse-patient ratio	Compliance (%)
		Length†	*n*	Baseline measures	Length†	*n*	Guidelines of the Institute for Healthcare Improvement CB‡	Other elements		
Samra et al.[48]	YES	12	250	YES	24	130	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	No	1:1	94–100
Sen et al.[50]	–	33	66	–	24	65	Head-of-bed elevation, daily sedation vacations, daily assessment of readiness to extubate, stress ulcer prophylaxis, DVTP, daily oral care with chlorhexidine	No	–	–
Talbot et al.[51]	–	31	–	–	30	–	Head-of-bed elevation, sedation management, daily assessment of readiness to extubate, stress ulcer prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine	SSD (since 2009)	–	83

CB: Care bundles; DVTP: Deep venous thrombosis prophylaxis; ETT: Endotracheal tube; HH: Hand hygiene; IHI: Institute of Health Improvement; OTT: Orotracheal tube; RT: Respiratory therapist; SOD: Selective oropharyngeal decontamination; SSD: Subglottic secretion drainage; –: Not available.

* Educational activities: educational-l meetings, semi-rs, workshops, and teaching sessions.

† Months.

‡ Bundle identified by the Guidelines of the Institute for Healthcare Improvement. The key components of the IHI Ventilator Bundle are elevation of the head-of-bed, daily "sedation vacations," daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, and daily oral care with chlorhexidine.

§ Recommended but not mandatory measures.

area, and VAP diagnostic criteria (Supplementary Figure S1). Excluding three low-quality evidence studies [47,49,53], the OR of the number of VAP episodes was 0.40 (95% CI: 0.31, 0.51), but the heterogeneity remained considerable (I^2=82%).

Although the incidence of VARI was established as an outcome in the PROSPERO registry, we did not obtain enough numerical or descriptive data. Therefore, it was not analyzed in the systematic review and meta-analysis.

Duration of MV

Twenty-two studies [21,26–28,30,31,33–36,38,39,41,42,44–46,49,50,52–54] reported the duration of MV, with an estimated median of 7 days (IQR: 5–15). Sixteen [21,26–28,30,33–35,39,42,44,46,49,50,53,54] of these 22 studies were included in the pooled meta-analysis. Implementation of ventilator care bundles significantly reduced the days of MV (MD=−0.59, 95% CI: −1.03, −0.15; I^2=56%), compared to standard of care, particularly in centers conducting educational activities (MD=−0.81, 95% CI: −1.35, −0.28; Figure 3) and in those who apply baseline measures as the standard of care (MD=−0.86, 95% CI: −1.44, −0.28; Figure 4). In both cases, substantial heterogeneity was observed (I^2=62–66%). No significant differences were reported in other subgroup analyses (Supplementary Figure S2). In nine studies [21,31,35,36,45,49,50,53,54], the reduction in the duration of MV was ≥2 days. Details are reported in (Table 3).

Length of stay

Hospital length of stay was documented in 12 studies [21,26–28,30,31,39,42,46,49,50,52] with an estimated median of 16 days (IQR: 7–22 days). One of these studies [31] did not report data in a format suitable for meta-analysis. No difference was shown between both groups (MD=−0.37, 95% CI: −1.47, 0.74) with a

Table 3
Differences between studies that achieved a reduction in MV of ≥2 days and those that did not.

Reduction in MV (Δ)	≥2 days	<2 days	*P*-value
Number of studies	9 studies	13 studies	–
Number of MV patients	28,949	74,121	–
Patient characteristics			
Age (years)	53.0 ± 9.4	59.0 ± 8.3	–
MV duration(days)	14.9 ± 13.6	6.4 ± 4.9	*P* <0.05
Type of ICU admission*			
Traumatic	1584 (5.3)	269 (9.1)	*P* <0.05
Surgical	27,474 (92.3)	198 (6.7)	*P* <0.05
Medical	536 (1.8)	333 (11.3)	*P* <0.05
Neurological	134 (0.5)	131 (4.4)	*P* <0.05
Cardiothoracic	–	2025 (68.5)	*P* <0.05
Bundle elements			
HOB elevation	8 (88.9)	13 (100)	–
Oral care	9 (100)	11 (84.6)	–
Sedation management	6 (66.7)	7 (53.8)	–
Hand hygiene	5 (55.6)	5 (38.5)	–
ETT cuff pressure	5 (55.6)	5 (38.5)	–
Extubation assessment	7 (77.8)	7 (53.8)	–
SSD	2 (22.2)	7 (53.8)	–
PUP/SUP	2 (22.2)	7 (53.8)	–
DVTP	2 (22.2)	4 (30.8)	–
MV circuits no-change	2 (22.2)	2 (15.4)	–
Clean MV circuits	1 (22.2)	1 (7.7)	–
Gastric overdistention	1 (12.5)	1 (7.7)	–
SOD	–	1 (7.7)	–
Patient mobilization	–	1 (7.7)	–
Orotracheal tube	–	1 (7.7)	–
MV circuits change	–	1 (7.7)	–

Data are expressed as mean±standard deviation, median (interquartile range), or *n* (%).

DVTP: Deep venous thrombosis prophylaxis; ETT: Endotracheal tube; HOB: Head of bed; ICU: Intensive care unit; MV: Mechanical ventilation; PUP/SUP: Peptic ulcer prophylaxis/stress ulcer prophylaxis; SOD: Selective oropharyngeal decontamination; SSD: Subglottic secretion drai-ge; –: Not available.

* Only subjects treated in specific ICUs were included (≥2 days group *n*=29,768; <2 days group *n*=2956.).

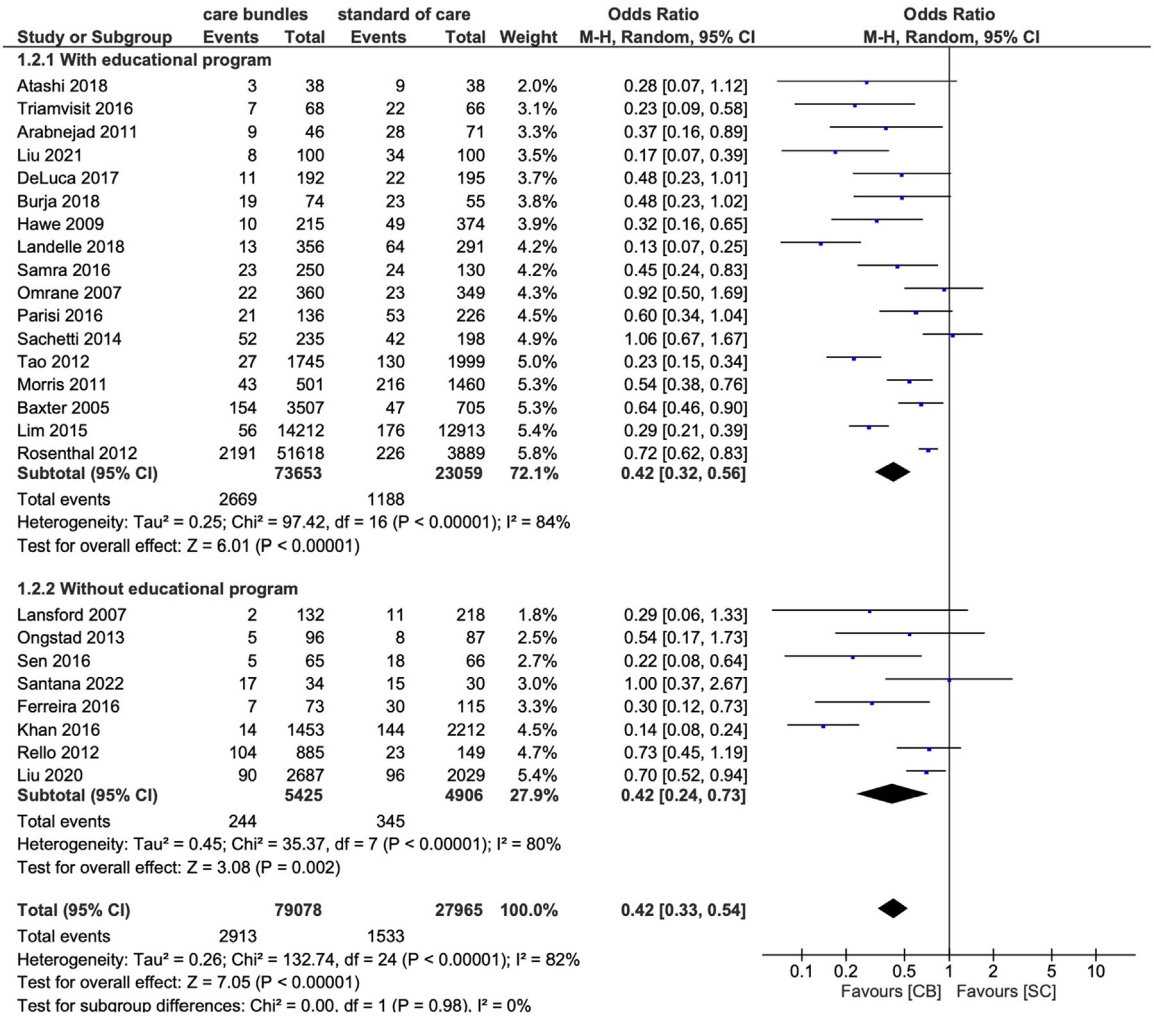

Figure 2. Forest plot based on VAP incidence from health centers that carried out educational interventions for implementing care bundles and health centers that did not conduct any educational intervention. VAP: Ventilator-associated pneumonia; CI: Confidence interval.

considerable heterogeneity (I^2=81%).In subgroup analyses, hospital length of stay was significantly reduced in studies that had educational activities as part of the bundle (MD=−1.24, 95% CI: −2.30, −0.18; Figure 5), and for the RCT subgroup (MD=−11, 95% CI: −18.08, −3.92; Supplementary Figure S3). Furthermore, one highlight of our findings is that VAP diagnosis by clinical and microbiological criteria and Clinical Pulmonary Infection Score (CPIS) criteria significantly reduced the length of hospital stays (Supplementary Figure S3). No significant differences were reported in other subgroup analyses (Supplementary Figure S3). No differences in ICU length of stay were observed (see Supplementary Figure S4).

Hospital mortality

Hospital mortality was reported in 14 studies.[23,26–28,30,31,33,34,39,42,43,48,49,54] Pooled results did not show differences in hospital mortality (OR=1.08, 95% CI: 0.51, 2.30; I^2=98%) between patients treated with ventilator care bundles and standard of care. In the subgroup analysis, when baseline measures were used as the standard of care, hospital mortality was lower in the group where a ventilator bundle was applied (OR=0.75, 95% CI: 0.60, 0.94; Figure 6). No significant differences were reported in other subgroup analyses (Supplementary Figure S5).

With the exclusion of the study by Khan et al.[33] hospital mortality tends to reduce (OR=0.83, 95% CI: 0.63, 1.08) with a lower but still considerable heterogeneity value (I^2=79%). The result was similar when the study by Khan et al.[33] was excluded from the subgroup analysis of studies with compliance of >70%. Hospital mortality tends to reduce (OR=0.78, 95% CI: 0.59, 1.04) with a lower heterogeneity value (ranging from 99% to 30%).

ICU mortality

ICU mortality was reported in five studies.[23,26,33,34,54] No differences between both groups were found (OR=1.08, 95% CI: 0.83, 1.40, I^2=73%). Details are available in Supplementary Figure S6.

Discussion

Our systematic review and meta-analysis study summarized information from 36 studies examining the effect of ventilator care bundles on the incidence of VAP, duration of MV, hospital length of stay, and mortality. Although the bundled care seemed to improve clinical outcomes, the quality of evidence was low, being an area requiring further research.

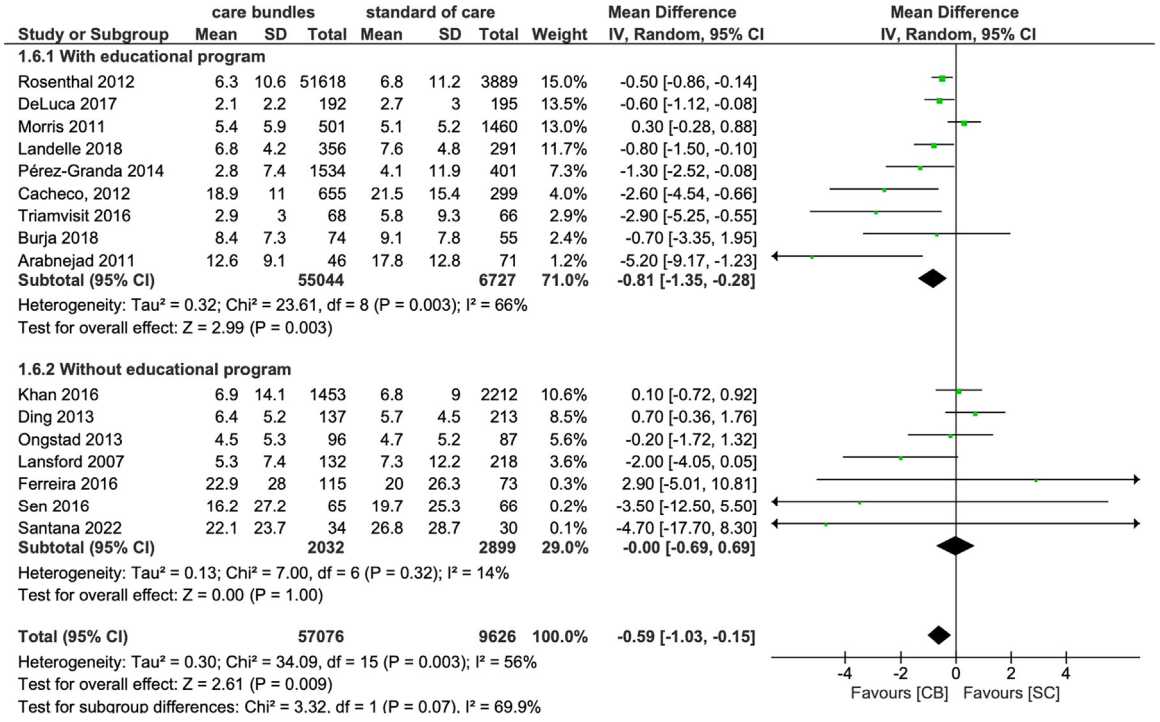

Figure 3. Forest plot based on the duration of MV (days) in health centers that carried out educational interventions for implementing care bundles and health centers that did not conduct any educational intervention. MV: Mechanical ventilation; CI: Confidence interval.

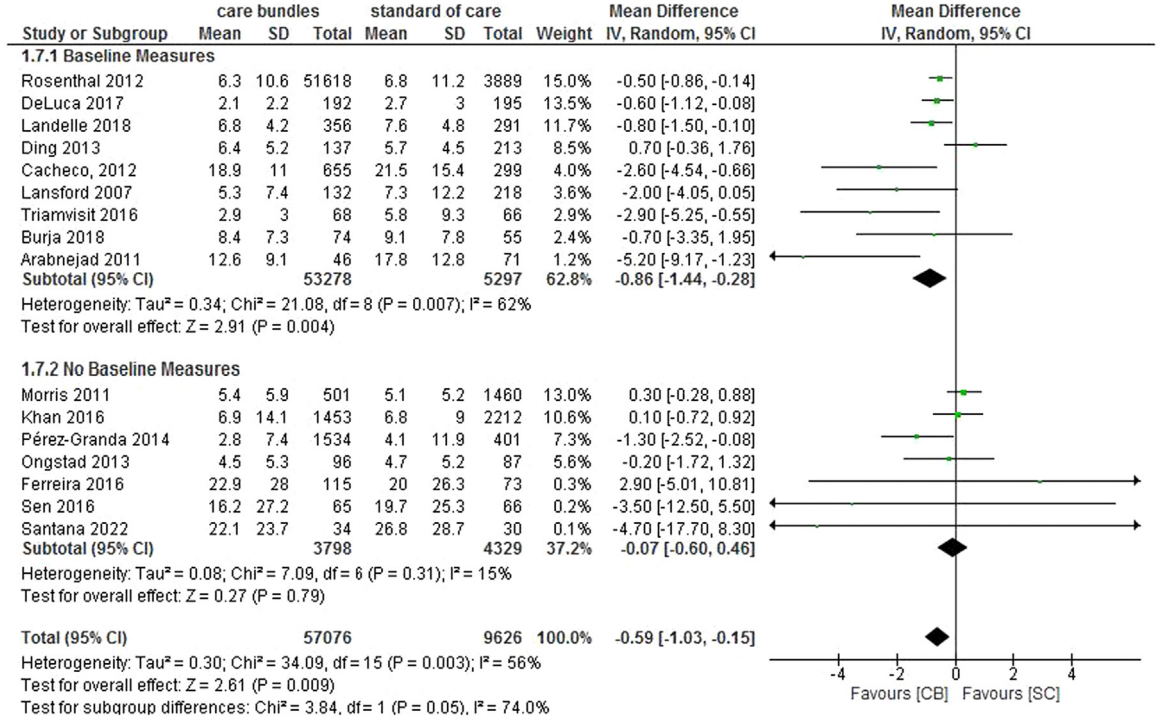

Figure 4. Forest plot based on the duration of MV (days) in studies where baseline measures were conducted in the non-care bundle group and studies that did not. MV: Mechanical ventilation; CI: Confidence interval.

The meta-analysis revealed a significant reduction in both VAP incidence and MV duration with the implementation of a care bundle. Included studies with a need for MV >15 days [21,54] showed a more representative reduction in ventilator-free days. No significant differences in the length of stay and hospital mortality were found. This finding could be due to the high number of other factors affecting these outcomes, some of which might not be modifiable.

The most commonly reported component of the ventilator care bundle was the head-of-bed elevation, followed by oral care and daily assessment of readiness to extubate. However, this study could not determine the effect of each individual com-

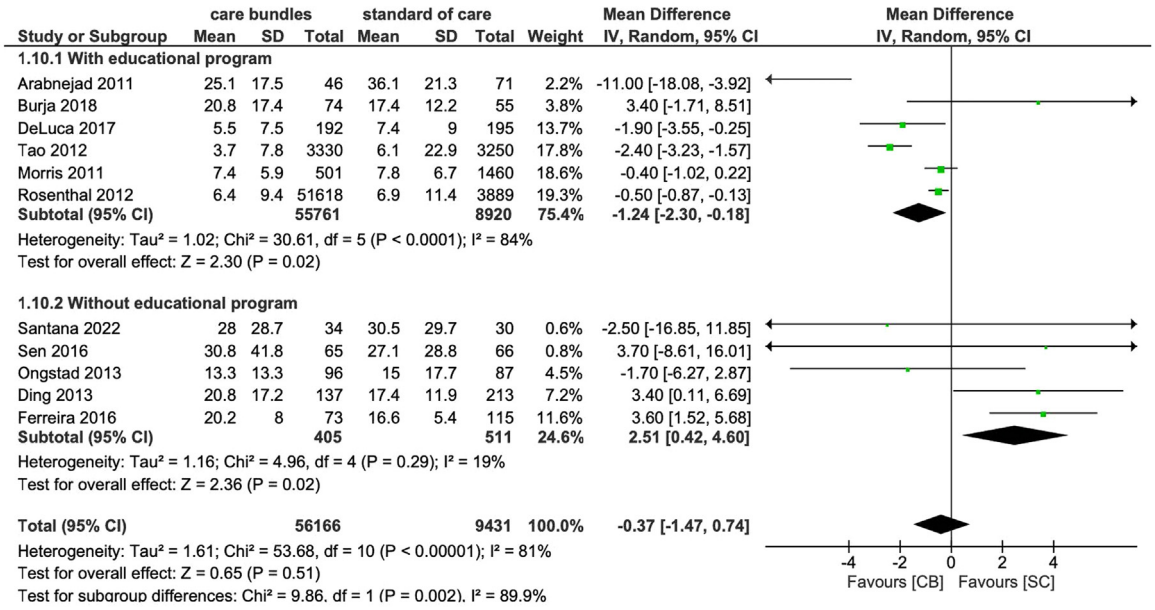

Figure 5. Forest plot based on hospital length of stay in health centers that carried out educational interventions for implementing care bundles and health centers that did not conduct any educational intervention. CI: Confidence interval.

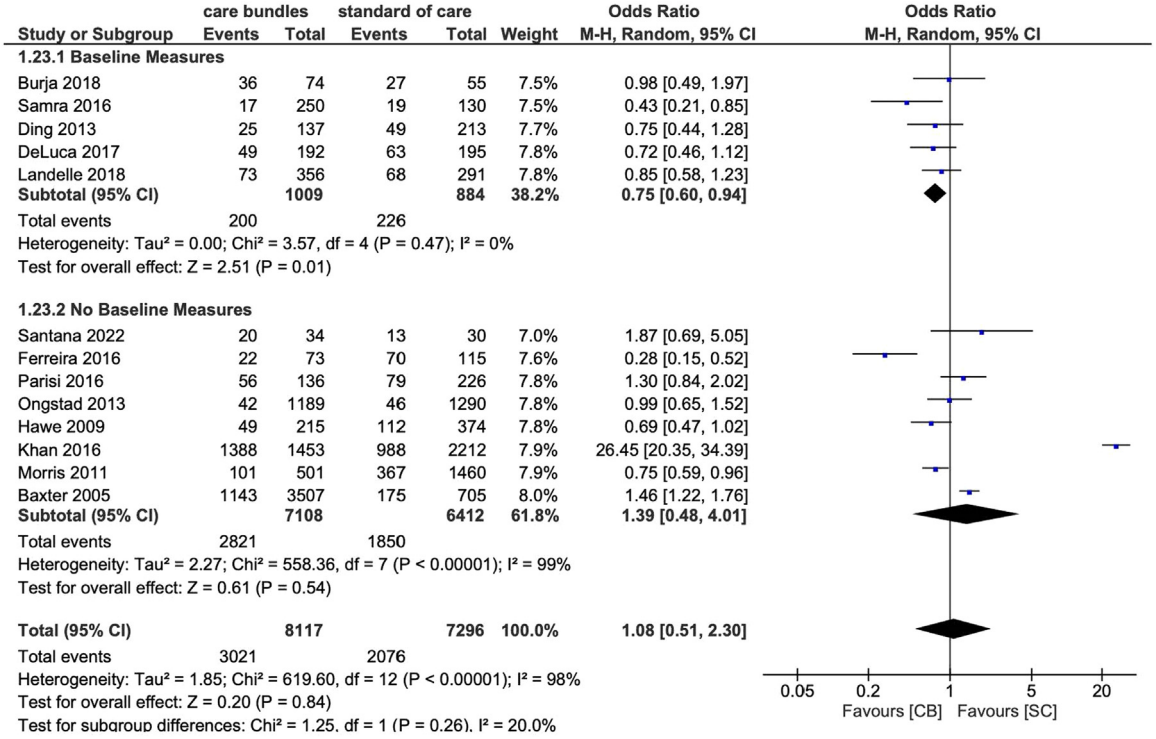

Figure 6. Forest plot based on hospital mortality in studies where baseline measures were conducted in the non-care bundle group and studies that did not. CI: Confidence interval.

ponent. Additionally, among VAP clinical practice guidelines [4,7,8], position strategies, such as semi-recumbent position and Head-of-bed elevation had been a consensus (Supplementary Table S4).

Improving outcomes and reducing the exposition to MV should be a priority and the objective of implementing bundles of prevention. Sedation strategy should be a core element of ventilatory care bundles. Targeting light sedation levels and using a sedation strategy including short-acting sedative-analgesic agents are preferred, thus helping to achieve early ventilator weaning and lowering pneumonia and mortality rates in ventilated patients in the ICU.[55–59]

Bundles including educational activities demonstrated a reduction in the duration of MV and hospital stay, whereas bundles without educational components did not alter these outcomes. Previous studies have found critical care nurses'

knowledge of and adherence to care bundles to be low [60,61] whereas active implementation strategies (including repeated educational sessions with and without hands-on demonstrations, guidelines, reminders, direct feedback, visual aids, fact sheets, and posters) have improved the level of knowledge, adherence, and clinical outcomes.[62]

High compliance level is an important factor in ensuring the clinical effectiveness of bundled care. However, compliance with bundled care varied widely (20%–100%), which may be due to the lack of knowledge, role ambiguities, and inadequate resources.[60,61] In the future, real-time monitoring should be performed in conjunction with VAP surveillance to provide direct feedback to healthcare providers.[5] Additionally, the effect of bundle compliance on VAP risk should be considered.[63]

Our findings are consistent with those of a previous systematic review and meta-analysis study by Pileggi et al.[1], which evaluated the effect of care bundles on mortality. However, the search was limited to articles published before June 2017. This allowed us to add new evidence from the last 5 years.[20,26,34,37,38] Moreover, Pileggi et al.[1] excluded articles that did not report mortality data. In our case, articles documenting any of the predesigned outcomes were included, allowing us to include a larger number of articles. Pileggi et al.[1] included 13 articles (11,664 participants) in their systematic review and meta-analysis. About 7 of the 13 articles were evaluated in our study; the remaining 6 articles were excluded due to population characteristics or the presence of care bundles in the control group. The differences between the articles in the previous systematic reviews and our study and the reasons for exclusion are detailed in Supplementary Table S6. Our study included 29 articles in the quantitative analysis (n=116,873), adding 16 articles, thus providing a broader perspective on the topic. Care bundle components are subjected to progressing scientific insights. For what concerns oral care, care bundles usually recommend the use of chlorhexidine-based mouthwashes. However, this practice has become a subject of controversy. In a single-center cohort study (n=5537) aimed to evaluate the value of individual care bundle components on the incidence of ventilator-associated events, Klompas et al.[64] found chlorhexidine oral care to be significantly associated with mortality in patients ventilated for at least 3 days (hazard ratio [HR]=1.63, 95% CI: 1.15, 2.31), despite a non-significant trend toward less VAP (HR=0.27, 1.14). These data were added to a systematic review and meta-analysis of RCTs indicating an increased risk of death associated with chlorhexidine oral care (OR=1.25, 95% CI: 1.05, 1.50).[65] Additionally, large-scale epidemiological cohort studies demonstrated chlorhexidine oral care to be associated with an increased risk of mortality in ICU populations (OR=1.25, 95% CI: 1.16, 1.34) [65] as in general hospitalized populations (OR=2.61, 95% CI: 2.32, 2.92).[66] The assumed pathogenic mechanism is a disturbance in nitric oxide homeostasis provoked by eradicating essential oral bacteria by antiseptic mouthwashes.[67] This results in a condition of deficient nitric oxide bio-availability, which puts patients at a risk for ischemic heart events and sepsis. While this hypothesis is yet to be demonstrated, the controversy led to chlorhexidine de-adoption strategies, such as reported by Dale et al.[68] These investigators conducted a multicenter, stepped wedge, cluster-RCT in six ICUs to assess the effect of de-adopting chlorhexidine mouthwashes from their oral care routine. Instead, emphasis was placed on toothbrushing and non-antiseptic oral care cleansing. De-adopting chlorhexidine oral care did not alter infection-related ventilator-associated complications or mortality. More importantly, de-adopting chlorhexidine oral care was associated with improved oral health scores. The presumed risk of mortality associated with chlorhexidine oral care and the safe adoption of this practice has led to a call to abandon antiseptic mouthwashes and to restrict this practice to selected cases.[69]

Limitations

This systematic review and meta-analysis had certain limitations that should be considered when interpreting the results. First, high heterogeneity was observed among studies, which could be due to high variation in study design, applied care bundles, standard care, and patient population. In future studies, consideration of interventions that have proven to be effective for VAP prevention for inclusion in the ventilator bundle may be important. Second, the sample size was relatively small, and the study was underpowered to perform several subgroup analyses (by type of ICU, nurse-patient ratio, isolated quality improvement interventions, and others). However, other biases, such as selection biases and poor methodological quality, can also explain this limitation. Third, although a large amount of information was recorded, data on many endpoints were incomplete, because they were reported in a format that could not be extracted and assessed. Methodological quality was generally good, although only 2 out of 35 included studies were RCTs. Fourth, we did not consider the effect of the reason leading to MV on the efficacy of VAP prevention bundles. The analysis of the effect of coronavirus disease 2019 (COVID-19) was beyond the scope of this study. This was a strength because data presented in these cohorts were not influenced by the different COVID-19 surges.

Conclusions

Our study suggests that the application of a ventilator care bundle reduced VAP incidence and duration of MV. However, the quality of the evidence was low. The inclusion of educational activities in the bundle seemed to improve clinical outcomes.

Author Contributors

Raquel Martinez-Reviejo: Methodology, Software, Formal analysis, Writing-original draft. Sofia Tejada: Methodology, Formal analysis, Writing-original draft, Writing - Review & Editing. Miia Jansson: Writing - Review & Editing. Bert Maertens: Writing- Review & Editing. Alfonsina Ruiz-Spinelli: Writing - Review & Editing. Sergio Ramirez-Estrada: Methodology, Validation. Duygu Ege: Methodology. Tarsila Viceli: Validation. Stijn Blot: Conceptualization, Writing - Review & Editing. Jordi Rello: Conceptualization, Writing - Review & Editing, Supervision. All authors read and approved the final manuscript.

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Ethics Statement

Ethics committee approval was not required since the article was based on previously conducted studies and did not contain any new studies with human participants or animals.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.04.004.

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