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State of the Science Review

A systematic scoping review of the cost-impact of ventilator-associated pneumonia (VAP) intervention bundles in intensive care

Elyse Ladbrook BN, MNursPract [a], Damien Khaw BA(Hons), PhD [b,*], Stéphane Bouchoucha BSc(Hons), MSc(PH), PhD [c], Anastasia Hutchinson BN, GD-Clinical Epidemiology, GC-All, PhD [c]

[a] *The University of Canberra, Canberra, Australia*
[b] *Deakin University, Centre for Quality and Patient Safety Research, Epworth-Deakin Partnership and School of Nursing & Midwifery, Burwood, Victoria, Australia*
[c] *Deakin University, Centre for Quality and Patient Safety Research, School of Nursing & Midwifery, Burwood, Victoria, Australia*

Key Words:
Patient care bundles
Cost-benefit
Cost-modeling
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Background: Evidence-based economic decision making is key in health care. Presently, however, studies reporting financial outcomes of ventilator-associated pneumonia (VAP) care bundles have not been systematically evaluated.
Method: This scoping review investigated the characteristics and findings of studies of the economic impact of VAP bundle implementation. A systematic search of electronic databases (MEDLINE, CINAHL) for relevant English language studies was undertaken (January 2000-February 2020). Methodological quality was evaluated using a Joanna Briggs Institute quality appraisal checklist. Article screening and quality appraisals were performed by 2 reviewers. Reference lists of included studies were hand-searched for additional articles. Reporting followed PRISMA Extension for Scoping Reviews (PRISMA-ScR) standards.
Results: From 181 citations, 10 articles met inclusion criteria. Eight studies evaluated cost impacts on acute care and there were 2 cost-modeling studies. Results consistently indicated that effective VAP bundle implementation decreased healthcare costs. However, studies were heterogeneous with respect to research methods and objectives and were judged to have a moderate-to-high risk of bias.
Discussion: Effective implementation of VAP care bundles was associated with superior clinical and economic outcomes. However, despite finding a moderate volume of research, study heterogeneity inhibited strong conclusions being drawn regarding the degree of associated cost savings.
Conclusion: Additional research involving multisite/multijurisdiction studies using experimental designs are needed to progress the field and overcome gaps in the existing literature.

BACKGROUND

Initiatives to reduce rates of hospital-acquired infection (HAI) include care bundles focused on mitigating risk of ventilator-associated pneumonia (VAP).[1] Ventilator-associated pneumonia is a preventable HAI estimated to affect 8%-28% of intubated patients who require mechanical ventilation.[2,3] It is associated with substantial morbidity and mortality, involving crude death rates of between 5% and 65%[4] and considerable social, economic and psychological costs to patients and families.[5,6] VAP results in increased duration of invasive mechanical ventilation, intensive care unit (ICU), and hospital length of stay (LOS), and demand on health care resources.[4,7]

* Address correspondence to Damien Khaw, BA(Hons), PhD, Deakin University, Centre for Quality and Patient Safety Research, Epworth-Deakin Partnership and School of Nursing & Midwifery, 221 Burwood Highway, Burwood, VIC 3125, Australia.
E-mail address: Damien.Khaw@deakin.edu.au (D. Khaw).
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Although the Centers for Disease Control and Prevention (CDC) recommendations from 2013 have shifted the focus away from monitoring VAP to monitoring ventilator-associated events,[8,9] these updated surveillance targets have not been universally adopted internationally,[10] and published costing studies have continued to use VAP criteria.[11-13] VAP places significant demand on acute beds and is a key contributor to rising acute health care costs. On the basis of available financial data, VAP-related hospital costs are estimated to be between £6000 and £22000 per patient in the United Kingdom[14] and $25,000 to $28,000 USD per patient in the United States (US).[15] Estimates from the United States have identified that this adds an extra USD$1.45 billion annually to the overall cost of health care provision.[15]

In the context of the high levels of existing fiscal pressure on health care systems worldwide,[16] there is a global need to reduce the level of expenditure related to VAP. In the United States, ICU and hospital performance is monitored, and benchmarked against peer providers using Institute for Healthcare Improvement standardized criteria for HAIs – the number of VAP cases per 1,000 ventilator days.[17] Although there is some controversy over the effectiveness of financial incentives; in some jurisdictions, such as the United States, financial penalties have been introduced with health care funders not fully covering the additional cost of care associated with managing VAP.[18] In Australian health care facilities, a set of Healthcare-Associated Complications have been formulated that represent a focus for quality improvement activities and Key Performance Indicators for provider benchmarking. In some Australian states, financial disincentives for the occurrence of Healthcare-Associated Complications, for example the additional cost of care associated with respiratory complications,[19] will be introduced as a means to drive improvement in the quality and safety of healthcare delivery by health care providers.[19,20]

Cost-effective strategies to alleviate the risk of VAP should be incorporated into routine clinical practice to mitigate VAP-related costs and their associated financial burden,[16] and ensure patients receive the highest possible standard of care.[6,16] VAP care bundles, also known as ventilator bundles (VBs), which combine the use of several core evidence-based elements,[21] represent one evidenced-based approach to VAP prevention. There is significant heterogeneity in elements used within VBs, with the majority of ICUs tailoring the care bundle to meet their localized healthcare needs (as suggested by the Institute for Healthcare Improvement).[17] Core recommended elements include: elevation of the head of bed between 30° and 45°; daily sedation breaks and assessment of readiness to extubate; peptic ulcer disease prophylaxis; deep venous thrombosis prophylaxis and regular oral care.[17] Despite some studies reporting negative or inconclusive findings with respect to the clinical effectiveness of VBs, the balance of evidence strongly suggests that when adhered to, VB protocols have the potential to significantly reduce the rate of VAP infections.[22] When all of the elements are applied together consistently, the care bundle approach has demonstrated improved patient health outcomes,[4] with compliance over 90% of VB elements associated with a substantial reduction in VAP rates and when sustained supported the achievement of a VAP rates nearing zero.[22] In a before-after study in which overall compliance with VB elements was 70%,[23] the authors found a significant reduction in the number of patients with ICU LOS exceeding 48 hours, 6 days, and 14 days (all *P*-values < .001).

There is an abundance of evidence supporting the use of VBs to mitigate the risk for ventilator-associated pneumonia. However, to-date, the body of literature reporting economic outcomes of implementing VBs in ICU has not been reviewed systematically. Consequently, the overall pattern of economic findings and the volume and quality of the research that supports it is unclear. In this paper, we report the findings of a systematic scoping review of literature reporting economic outcomes associated with the implementation of VBs in intensive care. The aims of this review were to (1) describe the number, design, and outcome measures of studies that have reported the cost-impact of VB implementation on acute care costs; (2) explore patterns of study characteristics and findings; and (3) help inform future research in this area, by identifying the strength of existing research and gaps in the extant literature.

MATERIALS AND METHODS

Design

We undertook a scoping review of the literature, involving a systematic search of relevant electronic bibliographic databases and hand searching of reference lists.[24] Study reporting followed the standards indicated by the Preferred Reporting Items for Systematic Reviews and Meta−Analyses Extension for Scoping Reviews checklist (PRISMA-ScR).[25]

Search strategy

We performed electronic searches of MEDLINE Complete and CINAHL Complete via the EBSCOhost platform. Search terms were combined according to a PICO search strategy (Patient, Intervention, Comparison, Outcome)[26] and included *"ventilator-acquired pneumonia', "intensive care," "bundle," "cost*,"* and their variants (see Supplementary File 1). Relevant Medical Subject Headings (MeSH)[27] were also included in the search algorithm: *'Pneumonia, Ventilator-Associated;"| "critical care;" "critical care nursing;" "intensive care units;" "patient care bundles;" "costs and cost analysis."* Reference lists of included studies were examined for additional relevant articles.

To ensure that potentially relevant studies using updated CDC terminology related to VAE were not missed, the search was repeated using the keywords *"ventilator-associated events," "ventilator-associated conditions," "ventilator-associated complications," "VAE," "VAC,"* and *"IVAC."* No additional studies that analyzed cost outcomes were found.

Inclusion/exclusion criteria

Inclusion criteria were (1) primary research studies using experimental, quasiexperimental or observational designs; (2) conducted in an intensive care/critical care setting; (3) reporting cost outcomes associated with the implementation or use of VBs; (4) published in English; and (5) studies published between January 2000 and February 2020. Studies published more than 20 years ago were excluded as changes to economic conditions and funding models, outlined in older studies do not provided relevant estimations to the current cost impact of VB implementation. Studies that only evaluated the costs of antimicrobial therapy were excluded. Studies not meeting the above criteria were excluded from the review.

Study screening, quality appraisal, and data analysis

Management of the systematic review was undertaken in Covidence.[28] Two researchers (EL and DK) independently screened citations by title and abstract to exclude irrelevant articles, and identify studies that appeared to fit the inclusion criteria or required full-text review to clarify inclusion/exclusion status. The same researchers reviewed the full text of articles retained following initial screening. Final decisions to include or exclude studies from the review were made independently, with discrepancies resolved by a third reviewer (AH). Data from included studies was extracted into a spreadsheet: author; publication year; bundle components; study setting; study design; sample characteristics; cost outcome measures; source of cost outcomes; and study findings. One author (DK) separately checked the data extraction of study findings.

Articles included in the review were appraised for methodological quality using the Joanna Briggs Institute Appraisal Checklist for Economic Evaluation.[29] As the purpose of this review was to scope extant peer-reviewed publications, studies were not excluded from analyses on the basis of poor quality. Two broad types of studies that estimated the impact of VBs on acute care costs were included. First, studies that reported actual or estimated net benefits in acute health care cost reduction with respect to the implementation or use of VBs (“*cost-benefit studies*”). Second, studies involving the use of decision trees or Markov modeling to estimate health and cost outcomes following the hypothetical implementation of VB components (“*health economic modeling studies*”).

RESULTS

Number of studies included in scoping review

Results of the systematic literature search and study screening are described in Figure 1. A total of 190 records (181 nonduplicate citations) were identified via searching electronic databases and the reference lists of included articles. We screened the titles and abstracts of all nonduplicate citations against inclusion criteria. Thirty-one articles were selected for full-text screening. Of these, 10 articles met all inclusion criteria and were included in this review.

Eight articles included in this review reported cost-benefit studies involving direct measurement of actual hospital costs (n = 4)[11, 12,30,31] or estimates of probable costs derived from past research (n = 4).[13,32-34] The remaining 2 included studies employed health economic modeling derived from hospital data and previously published research.[35,36]

Quality appraisal of included studies

Quality appraisal items (see Table 1) were rated in accordance with the guidance provided on the appraisal checklist.[29] The research objectives of all included studies were clearly stated, and studies were judged to have well-defined research questions (item 1) with sufficiently detailed descriptions of intervention and comparison groups (item 2). The 2 health economic modeling studies accounted

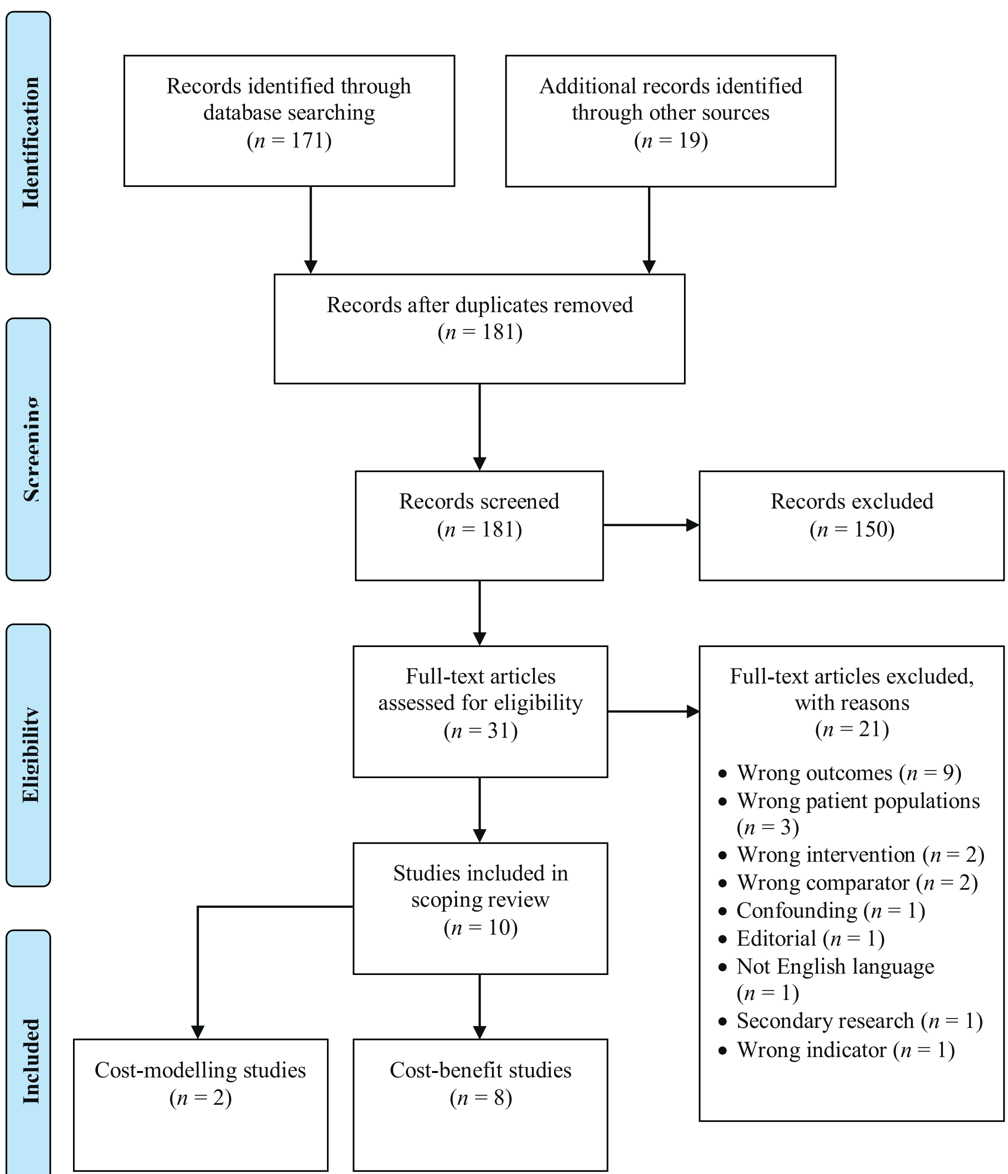

Fig 1. PRISMA flow diagram of literature search outcomes for studies reporting economic outcomes associated with the implementation of ventilator-associated pneumonia (VAP) care bundles *(1.5 column fitting image).*

Table 1
Risk of bias in included studies[29]

	1. Is there a well-defined question?	2. Is there a comprehensive description of alternatives?	3. Are all important and relevant costs and outcomes for each alternative identified?	4. Has clinical effectiveness been established?	5. Are costs and outcomes measured accurately?	6. Are costs and outcomes valued credibly?	7. Are costs and outcomes adjusted for differential timing?	8. Is there an incremental analysis of costs and consequences?	9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	10. Do study results include all issues of concern to users?	11. Are the results generalizable to the setting of interest in the review?
Cost-benefit studies (measured costs)											
Cocanour (2006) [27]	+	+	-	?	-	+	+	-	-	-	?
DuBose (2010) [28]	+	+	-	+	-	+	+	-	-	-	?
Ferreira (2016) [29]	+	+	-	+	-	+	+	+	-	-	-
Robinson (2018) [30]	-	+	-	+	-	+	+	-	-	-	?
Cost-benefit studies (estimated costs)											
Al-Tawfiq (2010) [31]	+	+	-	+	-	-	-	+	-	-	?
Bird (2010) [32]	+	+	-	?	-	-	-	-	-	-	?
Bukhari (2012) [33]	+	+	-	+	-	-	-	-	-	-	?
Sedwick (2012) [34]	+	+	-	+	-	-	-	-	-	-	?
Health economic modelling studies											
Branch-Elliman (2015) [35]	+	+	+	+	+	+	+	+	+	+	+
Møller (2012) [36]	+	+	+	+	+	+	-	+	+	-	?

Note. +Yes; -No; ?unclear

for range of relevant costs, such as costs incurred by VB implementation, use of probiotics and antibiotics, patient mortality, and costs due to oral care, nursing time and other treatments.[35,36] However, included cost-benefit studies did not explicitly identify all relevant costs (item 3), but only analyzed cost data with respect to total or daily treatment costs[12,13,29,30,33] and costs attributed to ICU bed days.[31,32,34] As not all relevant costs were identified, the financial data and reported estimated impact on acute care costs were potentially vulnerable to bias (item 5). Furthermore, all cost-estimates were derived from historical averages from the US health care system and were not adjusted to the local patient mix, or for inflation, or differences between jurisdictions and countries.[32−34, 13] Consequently, these studies were rated as having potential threats to the credibility of cost measurement (item 6) and to not have adjusted for differential timing in costs (item 7).

Four of the 10 studies included in this review accounted for both costs added and costs avoided by the use of VBs and were therefore judged to have reported incremental analyses of cost outcomes (item 8).[12,32,35,36] The remaining 6 studies only assessed the consequences of VB implementation with respect to the costs avoided by the prevention of VAP cases.[11,30,31,33] Sensitivity analyses were only reported by the authors of the 2 cost-modeling studies (item 9).[35,36] Only one study, the health economic cost-modeling study undertaken by Branch-Elliman et al[35] addressed all issues of concern to users with the remainder demonstrating clinical relevance with minimal information relating to specific costs (item 10). Due to the high overall quality of the modeling approach in the study reported by Branch-Eliman et al,[35] findings were likely generalizable to similar US settings (item 11). However, the generalizability of study findings was unclear in 8 studies due to the focus of analyzing local institutional financial data,[11,30,31] reliance on financial data possibly subject to bias,[32-34, 13] and due to the dearth of other research on VB implementation in the Danish health care sector.[36]

Cost-benefit studies that measured the impact on acute care costs

Table 2 describes the characteristics of the four studies that collected financial data from hospital sites: before-after studies (n = 2)[11, 12]; and time-series (n = 2).[30,31] These studies varied by VAP care bundle components, study country, and the types of costs reported. The VBs implemented included the use of head-of-bed elevation and prophylactic treatment for peptic ulcer disease and deep venous thrombosis,[11, 12, 30, 31] oral care [30,31] in addition to a hand washing protocol and subglottic suctioning,[30] readiness-to-extubate assessments and oral care,[31] and daily sedation breaks.[12,31] Three studies reported economic outcomes with respect to total costs[30,12] and hospital charges[11] per VAP case. The time-series study reported by Robinson et al[31] derived estimates of costs avoided by preventing VAP episodes from previously published national data, but used institutional administrative data to estimate the staff costs associated with using RN champions to facilitate implementation.

Although the findings of all included studies suggested superior financial outcomes following VB implementation, there was considerable variation in the types of analyses reported and the strength accompanying findings. Cocanour et al[30] reported 9 months of time-series data, prior to and following, the implementation of a VB in the ICU of a Level 1 trauma center. Economic outcomes were reported graphically and demonstrated a sustained reduction in both costs, and variation in costs, for mechanically ventilated patients postintervention. However, the absence of both cost reporting using exact numerical amounts and the use of significance testing limited interpretation. DuBose et al[11] implemented the Quality Rounding Checklist in a trauma ICU and reported that full bundle compliance was associated with lower: VAP rates (P= .04), ventilator days (P < 001), ICU and hospital LOS (P < .001), and hospital costs per patient (mean difference = −$168,376, P < .001), (see Table 1). Ferreira et al[12] investigated the cost impact of a VB using a before-after study involving 12 months or pre- and 15 months of postintervention data. The authors reported a small, but statistically significant reduction in mean daily costs following VB implementation (mean difference = −R $360.86, P< .05). Finally, a multisite time-series study conducted by Robinson et al[31] in 7 US ICUs found a that effective bundle implementation (>95% compliance) was associated with sustained decreases in VAP rates over a 5-year follow-up period (decreased 11.6 per 1,000 ventilator bed days to 2.5 per 1,000 ventilator bed days). The impact of VB implementation on acute care costs was estimated to be US $179,572, per VAP case avoided.

Table 3 describes the characteristics of the 4 studies that estimated the net impact on acute care costs of implementing VBs on the basis of previously published research data.[31-34] Studies varied by

Table 2
Summary of cost-benefit studies that measured costs associated with ventilator-associated pneumonia (VAP) care bundle implementation

First author, year	Intervention	Study setting	Study design	Sample	Economic outcome measures	Clinical outcomes(VAP rate/1,000 ventilator days)		Average change in length of Stay	Impact on acute care costs
						Pre	Post	Change	Cost per VAP case
Cocanour (2006)[30]	a, d, g, f, h, i	20-bed Shock trauma ICU (US)	Time series	Not reported	Average cost per VAP patient	Range 22.3-32.7	Range 0 and 12.8	Not reported	US$49413.94 [year: 2002-2003]
Robinson (2018)[31]	a, b, c, d, e, f	7 ICUs (US)	Time-series	Not reported	Total cost / VAP case/ ICU length of stay	11.6	2.5	−9.1 (over a 5-year follow-up)	Estimated Cost of ICU bed-day, US $8592 Additional cost = US $179572 per case [year: 2013]
DuBose (2010)[11]	a, b, d, e	Trauma ICU (US)	Before-after	*Pre-* (n = 577) *Post-* (n = 570)	Total acute care cost per patient Difference in costs between Full and Partial Bundle compliance.	12.41 **Full Compliance** VAP Rate 5.29 Duration of MV 6.2 (±4.5) ICU LOS 9.4 (±7.7)	8.74 **Partial Compliance** VAP rate 9.23 Duration of MV 14.8 (±13.5) ICU LOS 18 (±12.5)	3.67 **Full vs Partial** VAP rate 3.94 Duration of MV 8.6 Days ICU LOS 8.6 days	Not reported **Full vs Partial** US$168376 [year: not reported]
Ferreira (2016)[12]	a, b, d, e, i	8-bed ICU in private hospital (Brazil)	Before-after	Pre- (n = 115) Post- (n = 73)	Cost/day	**Bundle** % VAP, 30 (26%) R$ 6339.3 ± 24529.4 [year: 2011-2013]	**No bundle** % VAP, 7 (9.6%) R$ 6700.2 ± 26154.3 [year: 2011-2013]	**VAP cases** 23 cases 3 bed days / case	**Cost saving per bed day** R$360.86 ($P$< .05) [year: 2011-2013]
						No VAP R$ 2248.11 ± 607.20 [year: 2011-2013]	**VAP** R$ 9550.8 ± 6172.2 [year: 2011-2013]	**Cost saving per VAP Case avoided** R$ 7302.7 [year: 2011-2013]	**Total Cost saving** R$ 167962.1 [year: 2011-2013]

LOS, length of stay; *MV,* mechanical ventilation; *VAP,* ventilator-associated pneumonia.
Interventions: (a) Head-of-bed elevation; (b) daily sedation vacation; (c) readiness-to-extubate assessment; (d) peptic ulcer disease prophylaxis, (e) deep vein thrombosis prophylaxis; (f) oral care; (g) hand-washing protocol; (h) subglottic suctioning; (i) other; ICU – intensive care unit; Cost-benefit studies that estimated cost outcomes.

Table 3
Summary of cost-benefit studies that estimated costs associated with ventilator-associated pneumonia (VAP) care bundle implementation

First author, year	Intervention	Study setting	Study design	Sample	Clinical outcomes(VAP rate/1,000 ventilator days)			Economic outcome measures	Estimates derived from		Impact on ICU LOS	Economic outcomes reported		
					Pre	Post	Change			Cost	Days	Pre	Post	Change
Al-Tawfiq (2010)[32]	a, b, c, d, e	18-bed ICU (Saudi Arabia)	Time-series	Not reported	9.3	Yr 1-3 Yr 2-2.1	-7.2	Cost to treat VAP case/hospital stay	Retrospective matched cohort study (n = 9,080) US[3]	US $40,000 [year: 1998-1999]	+10 days	Bed-days 290	Bed-days 95	Total attributed VAP US$38,0 000 [year: 1998-1999] Potential costs avoided US$78,0 000 [year: 1998-1999]
Bird (2010)[33]	a, b, c, d, e	Two surgical ICUs (12- and 16-bed) US	Time-series	Not reported	10.2	3.4	−6.8	Total cost to treat VAP case	Average costs from various studies [3,37,38]	US$30,000 ±$20,000 [year: 1998-2003]		Derived from estimated 36 VAP cases avoided		US$1.08 m (US$36,0 000-$1.8 m) [year: 1998-2003]
Bukhari (2012) [34]	a, b, c, d, e	18-bed medical-surgical ICU (Saudi Arabia)	Case-series	2,747 patients on mechanical ventilation	3.39	1.98	−1.41	Cost to treat VAP case/hospital length of stay	Before-after study (n = 1147) US [11]	US$40,000 [year: not reported]	+10 days	Cost saving of US$56 400 per 1000 vent days [year: not reported]		Annual saving US$154,930 (reduction of 2,447 ventilator days) [year: not reported]
Sedwick (2012)[13]	a, b, c, d, e, f, g, h	ICUs of one hospital (US)	Case-series	Not reported	9.47	1.9	7.57	Total cost to treat VAP case	IHI 5 Million Lives Campaign[#]	US$40,000-US$5,7000/case [year: not reported]	47 cases reduced to 9 cases at average cost / case US$40,000 [year: not reported]			Est savings - $1.5 million [year: not reported]

LOS, length of stay; *VAP*, ventilator-associated pneumonia.
Interventions: (a) Head-of-bed elevation; (b) daily sedation vacation; (c) readiness-to-extubate assessment; (d) peptic ulcer disease prophylaxis, (e) deep vein thrombosis prophylaxis; (f) oral care; (g) hand-washing protocol; (h) subglottic suctioning; ICU – intensive care unit; Health economic modelling studies.

design: time-series (n = 2)[32,33]; and case series (n = 2)[34,13]; and were conducted in the United States[33, 13] and Saudi Arabia.[32, 34] All US studies estimated the total costs avoided due to decreases in the number of VAP cases following VB implementation.[33,13] The 2 Saudi Arabian studies only reported estimated costs to treat VAP cases due to increased hospital stay.[32,34] Cost estimates in three studies, 1 US and 2 Saudi Arabian,[32–34] were derived from previously published research in US ICU settings. The remaining US study estimated costs on the basis of uncited literature derived from the IHI 5 Million Lives campaign.[13] Overall, in this group of studies, acute care cost savings per VAP case were estimated to range between $10,000 and $57,000 USD (mean = $39,625 USD, *SD* = $7, 565 USD).

Table 4 describes the characteristics of the 2 included health economic modeling studies.[35,36] These studies differed according to: the components that comprised the VB intervention; the study country; modeling approach; and range of costs reported.

Branch-Elliman et al[35] used Markov modeling to investigate the projected impacts of 120 VAP prevention strategies on VAP avoidance during ICU admissions of 1 month's duration within a US ICU. The authors found that VAP prevention strategies with the optimal cost-benefit ratio and the optimal health outcomes, assuming cost thresholds between $50,000 and 100,000 USD per VAP case avoided, both involved the use of the IHI VB. Branch-Elliman et al[35] demonstrated that there were minimal differences between the preferred strategies of both societal and hospital perspectives, noting key differences such as in the inclusion of oral decontamination and oral care from a societal perspective. In both instances selective gut decontamination was not identified as a preferred VAP prevention strategy. The authors noted that the cost effectiveness of the IHI VB due is sensitive to nursing time and the cost of nursing wages and drew the conclusion that cost-effectiveness would depend on the local setting.

Møller et al[36] explored the use of a Danish VB that included oral care, but not peptic ulcer prophylaxis. Health economic outcomes were modeled using an unspecified cohort model, with cost inputs derived from a combination of cost data from a Danish hospital and previously published research. Møller et al[36] show that despite increased costs associated with implementation of VB, in most cases VB implementation was generally cost effective and often cost saving in relation to VAP prevented and deaths avoided.

DISCUSSION

This systematic scoping review yielded a moderate volume of studies that examined the cost impact of VB implementation into ICU settings (n = 10 studies). Most studies were time series (n = 4), followed by before-after studies (n = 2), case series (n = 2), and health economic modeling studies (n = 2). Findings were highly consistent, such that all included studies indicated or suggested, superior economic outcomes following the implementation of VBs, with no published studies indicating that VBs did not have a positive impact on acute care costs. However, despite this, the overall level of evidence in this body of literature was low. Aside from the 2 health economic modeling studies, the literature comprised only quasiexperimental and observational studies, and no studies with experimental designs, such as pre-/postcluster randomized trials were found. Furthermore, the limited use of interrupted time series analysis, the vulnerabilities to bias identified in many studies, and the high degree of heterogeneity between studies in research objectives, settings, methods and analyses, was such that strong conclusions about the degree of cost-effectiveness from VB implementation could not be drawn.

Eight of the 10 studies included in this scoping review examined the clinical and financial impact of implementing VBs into routine care.[11-13,30, 31-34] With the exception of two studies, one which reported the prevalence of VAP[12] and one that reported VAP rate per 1,000 patient days,[31] included studies reported VAP outcomes using

Table 4
Summary of health economic modeling studies of ventilator-associated pneumonia (VAP) care bundles

First author, year	Study setting	Modelling approach	Sample	Economic outcome measures	Estimated from	Cost outcomes	
Branch-Elliman (2015)[35]	US	Cost-benefit decision model using Markov Modeling Techniques Primary outcome: Preferred combination of VAP prevention strategies Robustness of model – one-way sensitivity analyses and threshold analyses were performed.	Simulation model of 28 days in ICU with a theoretical cohort of 10,000,000 patients. Model based on the following outcomes: −83.8% of patients survived, 20% developed VAP, and 15.4% died.	Evaluated the cost-effectiveness of 120 unique VAP prevention combinations – based on previous estimates of risk reduction for each intervention.	No bundle condition – estimated from Esteban et al 2002 ICU Costs estimated on a daily recurrent basis. Wages costs were estimated from US department of labour statistics. Nursing time costs for each strategy – based on previous models	Cost-benefit ratio – hospital perspective 1 Subglottal suction endotracheal tube, 2 IHI bundle without oral care 3 Probiotics	Preferred strategy – societal perspective 1. Sub-glottal suction endotracheal tube, 2.IHI bundle including oral care, 3.Use of probiotics, 4. Use of selective oral decontamination.
Møller (2012)[36]	Denmark	Decision analytic model Outcome: Cost effectiveness analysis of implementing Ventilator Bundle (VB) in comparison to standard procedure. One-way sensitivity analysis Probabilistic sensitivity analysis	Simulated model of ICU patients ventilated for >46 hours – Denmark	Cohort simulation of 140 patients 1,000 Hypothetical evaluated deaths prevented and cost effectiveness VB had better effect than standard.	Cost of ventilator bundle estimated from study site ICU and pharmacy departments. Length of stay estimated based on Rello et al. [3]	Cost per VAP prevented = €4451 [year: 2010] Cost/death prevented = €31792 [year: 2010]	Incremental cost-effectiveness VB 99.9% more effective in VAP prevention, 42.6% lower cost. Demonstrated cost effectiveness for more than 80% of VAP cases prevented and 50% of deaths prevented.

ICU, intensive care unit; *IHI*, Institute for Healthcare Improvement; *VAP*, ventilator-associated pneumonia; *VB*, ventilator bundle.

IHI criteria (the number of VAP cases per 1,000 ventilator days),[11,13,30,32-34] or modeled data on previously reported VAP incidence rates.[35,36] The clinical effectiveness of implementing VBs was sufficiently demonstrated in 8 included studies via sustained decreases in VAP rates per 1,000 ventilator days,[11-13,30, 31-34] significantly lower prevalence of postintervention VAP cases,[12] relative risk reduction,[35] and positive associations between VAP compliance and VAP rates.[11,34] However, the clinical effectiveness of VBs was indeterminate in 2 studies. First, Cocanour et al[30] reported a considerable reduction in the VAP rate per 1,000 ventilator days following care bundle implementation, however, postintervention rates did not exceed the 95% confidence interval of preintervention rates in 4 of the 9 months observed following the intervention. Second, Bukhari et al[34] only reported a modest reduction in VAP rates (−1.41/1,000 ventilator bed days) that may be within the range for natural variation in VAP rates over time.

A previous review by Klompas (2009)[39] suggested that because VAP criteria are overly-inclusive of patients with less severe conditions, VAP prevention measures may help reduce VAP rates, but fail to significantly improve other patient outcomes such as LOS and mortality. Findings from the cost-benefit studies included in the present review, however, suggested real improvements to the efficiency and effectiveness of care following VB implementation due to reduced ICU and acute care LOS[11,31,32,34] and associated cost savings.[12,32-34] The disparity between these results and those reported by Klompas[39] may therefore reflect differences in individual patient factors not quantified by measurement of the accepted benchmarking measure of "VAP rates per 1,000 ventilator bed days," such as severity of illness, risk of VAP due to the duration of ventilation, and comorbidity burden.

Although included cost-benefit studies provided a broad indication of reduced acute care costs following VB implementation, financial impacts were not the primary outcomes of this group of studies, and the strength of findings was limited by a moderate-to-high degree of methodological bias. Of key concern, these studies primarily focused on cost-avoidance, with only 2 such studies explicitly accounting for costs *added* by the use of VBs.[12,32] Overall, clinical studies that used local institutional administrative data to measure the financial impact of VBs[11, 12, 30, 31] provided minimal information about how ICU costs were derived, and no details were reported regarding the elements included when calculating the cost of an "ICU bed-day," limiting generalizability. In addition, studies that used previously published cost estimates, applied historical pricing from the US health care system (obtained 7-17 years previously) to local settings using a process of simple adaptation. The authors provided no indication that these estimates were adjusted for inflation, differences due to local jurisdictions or exchange rates, or changes in economic conditions, consequently, current estimates were judged as potentially inaccurate.[40]

The two cost-modeling studies identified in this review established that VBs are likely to be a key component of VAP prevention, and associated cost-reduction in ICUs. Modeled projections by Branch-Elliman et al[35] found that the IHI VB was part of preventative strategies with both the optimal cost-benefit ratio (*"hospital-preferred strategy"*) and the optimal health outcomes assuming cost thresholds between $50,000 and $100,000 USD per VAP case avoided (*"society-preferred strategy"*). Evaluation of incremental cost effectiveness by Møller et al[36] found that the use of a Danish VB was likely to yield a combination of both lower costs and more effective prevention VAP episodes and VAP associated ICU deaths. However, threats to the validity of the reviewed cost-modeling studies included: the age of inputs for the clinical outcomes of VAP (17 years), possible overgeneralization of findings due to cross-validation of the model against the study from which initial input data were derived[35]; and the use of international financial data without adjusting for regional differences or exchange rates.[36]

This scoping review identified several key gaps within the existing body of literature. First, because most studies were designed to evaluate the outcomes of local interventions, and due to the low overall volume of existing evidence from specific localities, the generalizability of findings to other settings were low. Future studies should be conducted to optimize benchmarking between sites. To achieve this, there is a specific need for additional multisite and multijurisdiction comparative cost-impact and cost-modeling research. A related research gap was the small number of studies that reported costing data produced outside of the US health care system with only 2 such studies were found in this review.[12,36] While the consistency of existing research findings suggested that implementation of VBs will be cost-effective internationally, more rigorously designed experimental research conducted outside of the United States is needed. On the basis of this review, we recommend that to maximize the accuracy and credibility of pricing, at present, researchers outside the United States should use local institutional financial data. If estimates from previously published US data are used, attempts should be made to account for variation related to the degree of transferability of data inputs.[40]

Finally, it is necessary for future research in this field to identify all key costs. For patients requiring ICU admission, both overall ICU LOS and the number of days requiring mechanical ventilation are key drivers in acute care costs.[41] In addition to direct patient costs there are additional costs that must be considered when evaluating the cost effectiveness of a VB, such as cost of consumables and delivery of care. Calculating the cost of resources used in the providing direct patient care to patients requiring ventilation varies depending on location.[35] Consideration must be given to the setting of this model as there are significant differences in patient care and nurse patient ratios depending on the location of the health care facility.[35] For instance, in some locations the provision of respiratory care is performed by respiratory technicians with registered nurses managing other aspects of patient care while in Australia, the registered nurses working within the ICU manage all aspects of respiratory care including mechanical ventilation.[42] Staffing costs associated with effective VB implementation may therefore differ according to clinicians' scope of practice and whether or not additional staff is needed.[43]

Limitations

This systematic scoping review had several limitations. Due to resource restrictions in accessing translation services, only English language studies were included. Consequently, it is possible that relevant research reported in languages other than English was missed. However, meta-analytic studies have suggested no substantial biasing effect from excluding non-English language reports from systematic reviews of medical literature.[44,45] In addition, as the present review sought to evaluate the body of published research literature, only peer-reviewed articles were reviewed, and the possibility of publication bias within this literature was not examined. Future reviews in this area could compare published findings with those in unpublished reports and reports from the grey literature.

CONCLUSIONS

There is limited literature reporting economic outcomes of implementing VAP bundles in ICU. This review has identified and described studies that have reported the impact of VB implementation on acute care costs and helped inform future research in this area, by identifying the strength of existing research and gaps in the extant literature.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2020.11.027.

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