Supplemental Material

Table S1. Prisma checklist

Section and Topic	Item #	Checklist item	Page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			

Section and Topic	Item #	Checklist item	Page where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Table S2. List of Terms of the Search Strategy

#1	"Pneumonia, ventilator associated" [MeSH]
#2	Ventilator associated pneumonia [tiab]
#3	Ventilator acquired pneumonia [tiab]
#4	Ventilator pneumonia [tiab]
#5	VAP [tiab]
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	“Patient care bundles” [MeSH]
#8	Care bundle [tiab]
#9	Ventilator bundle [tiab]
#10	VAP bundle [tiab]
#11	VAP prevention bundle* [tiab]
#12	Prevention [tiab]
#13	#7 OR #8 OR #9 OR #10 OR 311 OR #12
#14	#6 AND #13

Table S3. VAP diagnostic criteria followed in each study.

Author, year [ref]	VAP diagnostic criteria
Al-Tawfiq, 2010 [19]	VAP was diagnosed according to the CDC criteria.
Álvarez-Lerma, 2018 [20]	VAP was diagnosed according to the CDC and the Annual meeting of the National Nosocomial Infection Surveillance Study Registry in ICU (ENVIN-HELICS registry) criteria.
Arabnejad, 2011 [21]	VAP was diagnosed according to the CPIS. Early VAP is defined as development of VAP within 48 to 72 hours after intubation, in which microorganisms such as *Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pneumonia* have the highest prevalence. On the contrary, late-onset VAP occurs usually 96 hours after ventilation, in which methicillin resistant *staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and Enterobacter are generally involved. The results of some studies have also pointed to VAP development by multiple organisms in most patients.
Atashi, 2017 [22]	VAP was diagnosed according to the CPIS system. It consists of six components of temperature, volume of respiratory secretions, changes in white blood cell count, presence of infiltration in chest radiograph, hypoxemia, and secretion culture results. The overall score of this scale ranges between 0 and 10. Scores of 6 and higher indicate the presence of VAP.
Baxter, 2005 [23]	VAP was diagnosed according to the CDC criteria by a staff intensivist. They used standard clinical diagnostic criteria: New and persistent (>48 hours) pulmonary infiltrates on x-ray; fever >38.5ºC or <35ºC without other apparent source; leucocytosis >109·L–1 or <3 × 109·L–1; impaired gas exchange; change in sputum quality ± positive sputum culture; BAL cultures in some patients.
Birds, 2010 [24]	VAP was diagnosed according to the CDC criteria and radiological evidence.
Bukhari, 2012 [25]	VAP was diagnosed as clinical factors (fever, cough with purulent sputum), in combination with radiological evidence of pulmonary infilitrate, leukocytosis, a suggestive gram stain and growth of bacteria in cultures of sputum, tracheal aspirate, pleural fluid or blood.
Burja, 2018 [26]	VAP was diagnosed as inflammatory changes on a chest radiograph >48 hours after intubation, aspiration of purulent fluid >48 hours after the intubation, or VAP as a discharge diagnosis. Early VAP (≤ 7 days after intubation) and late VAP (>8 days after intubation).
Cacheco, 2012 [54]	The CMS definition of VAP was used, which includes (1) new or evolving infiltrate or consolidation on two or more serial chest radiograms, (2) temperature 938-C with no other cause, leukopenia (WBC G4,000/mm3), or leukocytosis (WBC Q12,000/mm3), and (3) new-onset purulent sputum or change of character of the sputum or worsening hypoxia.
DeLuca, 2017 [27]	Patients were diagnosed with VAP if they had a new, persistent infiltrate on chest x-ray after ≥48 hours of continuous MV, temperature >38°C or <36°C, and leukocytes >12,000 or <4,000, or microbiologic evidence of VAP (eg, growth of a predominant organism on BAL). Discharge summaries, microbiologic data, and antibiotic therapy were reviewed to confirm the diagnosis.
Ding, 2013 [28]	VAP was diagnosed clinically according to six different previous clinical definitions and the newly recommended VAE algorithm: loose definition, rigorous definition, the CPIS and the Canadian Critical Care Trials Group classification (possible type), the International Sepsis Forum Consensus definition (probable type), the CDC criteria, and the new VAE algorithm.

Eom, 2013 [29]	VAP was diagnosed according to the CDC criteria by training infection control professionals. It was defined by infiltrates on chest-X-ray in patients receiving MV for >48 hours in the ICU. Along with at leash two of the following: temperature >38º or <35º, leukocytosis or leukopenia, purulent ETT secretions, potentially pathogenic bateria isolated from the ETT aspirate, and increasing oxygen requirement.
Ferreira, 2016 [30]	VAP was diagnosed as MV patients whose condition has evolved to the point where a new or progressive pulmonary infiltrate in a chest X-ray. The definition also requires at least two clinical signs and/or laboratory abnormalities that suggest an infectious process such as: fever (>38ºC); leukocytosis or leukopenia; presence of purulent tracheal secretion after 48 hours of ventilation.
Hawe, 2009 [31]	-
Kao, 2019 [32]	VAP was diagnosed only if it occurred 48 hours after the ETT was inserted with a MV and was based on radiological evidence (new or progressive infiltration on chest radiography or computed tomography images), clinical condition (body temperature >38ºC or <36ºC, tachypnea, hypoxia/desaturation, respiratory distress, and purulent sputum), and laboratory data (abnormal white blood cell count, C-reactive protein, and gas exchange).
Khan, 2016 [33]	VAP was diagnosed according to CDC criteria. It was defined as pneumonia that developed >48 hours after endotracheal intubation. It was diagnosed clinically as two or more serial chest radiographs with at least 1 of the following: new, progressive, or persistent infiltrates; consolidation; or cavitation; with 2 of the following: core temperature >38.5º or <36ºC, leukocytosis (>12,000/ mm3), leukopenia (white blood cell count <1500/mm3); or new-onset purulent bronchial secretions,without another cause and a significant positive culture from blood, BAL fluid, or endotracheal aspirate or culture from another relevant site of infection. Tracheal aspirates were considered purulent at a neutrophil count with Gram stain of >25 per high-power field on lightmicroscopy.
Landelle, 2018 [34]	VAP was diagnosed according to the criteria established by Hospitals in Europe Linked for Infection Control through Surveillance, and a CPIS >6. Provable VAP required the presence of Rx changes with systemic inflammation (temperature ≥38 °C, or leukocyte count >12,000 or <4000 cells/mL) with clinical pulmonary signs (i.e. purulent tracheal secretions). Definite VAP was defined by the addition of positive quantitative cultures of distal pulmonary sampling obtained by BAL (significant threshold ≥10^4 colony-forming units/mL) or mini-BAL (significant threshold ≥ 10^3 colony-forming units/mL).
Lansford, 2007 [35]	VAP was diagnosed according to the CDC criteria. Established by the National Nosocomial Infections Surveillance System criteria, including radiographic evidence of at least one of the following: new or progressive infiltrate, consolidation, or pneumatoceles. Also required is fever or leukopenia. Finally, at least two of the following conditions must be present: New onset of purulent sputum, worsening cough, rales, or worsening gas exchange.
Lim, 2015 [36]	VAP was diagnosed as a respiratory tract infection developed after 48 hours of intubation with MV or within 48 hours after disconnecting the ventilator. The respiratory tract infection follows the definition in the Nosocomial Infection Surveillance guideline from the Taiwan Centers for Disease Control, and it is determined by the clinicians according to the clinical presentations after ruling out all other cause-induced systemic inflammatory response syndrome. The ventilators were limited to the invasive types by either tracheostomy or ETT only, and other noninvasive ventilation devices were excluded.
Liu, 2020 [38]	VAP was diagnosed based on the “VAP prevention, diagnosis and treatment guideline” published by the Intensive Care Branch of the Chinese Medical Association in 2013. This guideline was revised and actualised in 2019.
Liu, 2021 [37]	-

Morris, 2011 [39]	Diagnosis of VAP was made independently by the treating clinical team. Chest radiograph interpretation was undertaken “off-line” and by clinicians who were independent of the treating team. For VAP diagnosis, Hospitals in Europe Linked for Infection Control through Surveillance has a two-stage definition: first, clinically suspected VAP based on clinical criteria; and second, microbiologically confirmed VAP based on further investigations. From 2005 to 2008, we were unable to decrease the incidence of clinically diagnosed VAP but we had shown that increasing the use of quantitative analysis of BAL fluid for microbiological diagnosis resulted in a decrease in the reported incidence of microbiologically confirmed VAP, which was explained by superior test specificity compared with analysis of tracheal aspirates.
Okgün, 2016 [40]	VAP was diagnosed according to the CDC criteria. It was defined during daily surveillance rounds by trained infection control commitee members. The infection preventionists verified all suspected cases with radiographs and microbiologic analyses.
Omrane, 2007 [41]	VAP was diagnosed as the occurrence of a first episode for each patient. It was defined as either the presence of a new and persistent (>72 hours) radiographic infiltrate with one of the following findings: positive pleural or blood cultures for the same organism as that recovered in the tracheal aspirate or sputum; radiographic cavitation; histopathologic evidence of pneumonia; or 2 of the following: (fever (>38.3°C), leukocytosis (white blood cells [WBC] >10 x10^3/µL) or leukopenia (WBC <4 x10^3/µL), purulent tracheal aspirate or sputum (>25 leukocytes/hpf determined by Gram stain). Furthermore, the patient had to have been ventilated >48 hours to be diagnosed with VAP.
Ongstad, 2013 [42]	VAP was diagnosed according to the NHSN criteria and it was identified by an experienced infection control nurse.
Parisi, 2016 [43]	VAP was diagnosed according to the guidelines by the supervising physician. Specifically, the presence of a new infiltrate on the chest radiograph and 2 of 3 clinical criteria (leukocytosis, purulent secretions, fever), together with tracheobronchial secretions, confirmed the occurrence of VAP for the physician. Also, the CPIS was calculated, and a score greater than 6 was used to verify the diagnosis.
Pérez-Granda, 2014 [44]	VAP was diagnosed according to the CDC criteria. Patients ventilated for >48 hours were diagnosed with VAP based on the presence of new and/or progressive pulmonary infiltrates on the chest radiograph plus two or more of the following criteria: fever >38.5°C or hypo 109/ thermia <36°C, leukocytosis =12 × L, purulent tra cheobronchial secretions, and a =15% reduction in PaO2/FiO2. Patients with a CPIS higher than 6 were also considered to have pneumonia. The isolation of one or more pathogenic microorganisms in significant bacterial counts was required to confirm the diagnosis of VAP.
Rello, 2012 [45]	VAP was diagnosed according to the CDC criteria by the attending physician team. An independent investigator (intensivist), who was not part of the team caring for the patient made the final diagnosis of pneumonia, using quantitative respiratory cultures, using standardized thresholds.
Rosenthal, 2012 [46]	VAP was diagnosed according to the CDC/NHSN criteria. It was diagnosed in a MV patient with a chest radiograph that shows new or progressive infiltrates, consolidation, cavitation, or pleural effusion. The patient also must meet at least one of the following criteria: new onset of purulent sputum or change in character of sputum, organism cultured from blood, or isolation of an etiologic agent from a specimen obtained by tracheal aspirate, bronchial brushing or BAL, or biopsy.
Sachetti, 2014 [47]	VAP were defined as including all of the cases for which the area intensivist physician had registered that diagnosis.

Samra, 2016 [48]	VAP was diagnosed according to the CDC criteria. It was diagnosed as a pneumonia that occurs in a patient who was intubated and ventilated ≥48 hours. The patient has to present new or progressive infiltrates, consolidation or cavitations on chest X-ray with one of the following: new onset purulent bronchial secretions, leucopenia (white blood cell<1500/mm3) or leukocytosis (>12,000/mm3), c- Core temperature >38 ºC or <36 ºC without other cause, positive culture from blood, BAL or endotracheal aspirate.
Santana, 2022 [49]	VAP was diagnosed according to the Brazilian National Regulatory Health Agency. Itis characterized by a pulmonary infection occurring after 48 hours of endotracheal MV, associated with one or more chest radiographs with the presence of a new, persistent or progressive infiltrate, fever (>38°C) or leukocytosis or leukopenia, worsening pulmonary secretions or worsening pulmonary function.
Sen, 2016 [50]	VAP was diagnosed according to the CDC/NHSN criteria by infection control staff. It was diagnosed as including clinical, microbiologic, and radiographic data. The clinical criteria used included the following: fever, presence of infiltrate on chest radiography, quantitative bacterial culture identified through mini-BAL or bronchoscopy. Organisms that are reported are based either on mini-BAL or bronchoscopy.
Talbot, 2015 [51]	VAP was defined according to the CDC criteria. It was defined by trained infection preventionists who were masked to patient-specific bundle adherence data. Every weekday the infection practitioners reviewed every respiratory culture. Patients with an identified culture specimen then underwent medical chart review with examination of chest radiographs and clinical signs and symptoms.
Tao, 2012 [52]	VAP was defined according to the CDC/NHSN criteria. It was indicated in a MV patient with a chest radiograph that shows new or progressive infiltrates, consolidation, cavitation, or pleural effusion. The patient must also meet at least 1 of the following criteria: new onset of purulent sputum or change in character of sputum, organism cultured from blood, or isolation of an etiologic agent from a specimen obtained by tracheal aspirate, bronchial brushing, or BAL, or biopsy.
Triamvisit, 2016 [53]	VAP was defined according to the CDC criteria by 10-year-experienced staff. VAP diagnosis is HAP that occurs after using a MV >48 hours. It was diagnosed including a new persistent or progression of either opacity or cavitation on serial chest films together with high fever (>38.0°C), leukopenia (<4,000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3), altered mental status with no other causes in older than 70-years-old patients, and purulent sputum or change in sputum character or increased respiratory secretions, or increased required suction.

BAL: Bronchoalveolar Lavage; CDC: Centers for Disease Control and Prevention; CPIS: Clinical Pulmonary Infection Score; ETT: Endotracheal Tube; MV: Mechanical Ventilation; NHSN: National Health Safety Network; VAE: Ventilator Associated Event; VAP: Ventilator-Associated Pneumonia.

Table S4. Care bundles recommendations by each clinical practice guideline

	Dodek, 2004 [8]	IHI's care bundles, 2012 [4]	Torres, 2017 [2]	Alvarez-Lerma, 2019 [7]
Physical strategies				
Oral endotracheal intubation	R	–	–	–
Daily assessment of readiness to extubate	–	R	–	–
Deep venous thrombosis prophylaxis	–	R	–	–
Hand hygiene	–	–	–	R
Cuff pressure control	–	–	–	R
Heat and moisture exchanger	R	–	–	–
Closed suction system	R	–	–	–
Drainage of subglottic secretions	C	–	–	R
Search for maxillary sinusitis	NR	–	–	–
Scheduled change of ventilator circuit and humidifiers	NR	–	–	NR
Chest physiotherapy	NR	–	–	–
Early tracheostomy	NR	–	–	–

Position strategies				
Semi-recumbent positioning/ Head of bed	R	R	–	R
Kinetic beds	C	–	–	–
Prone positioning	NR	–	–	–
Pharmacologic strategies				
Selective oral decontamination	NR	–	R	R
"Sedation vacation"	–	R	–	–
Peptic ulcer prophylaxis	–	R	–	–
Oral Care	–	R	–	–
Stress ulcer prophylaxis	R	–	–	–
Narrow-spectrum antibiotics in early VAP and low risk of resistance	–	–	R	–
Broad-spectrum therapy targeting Pseudomonas and B-lactamase producing bacteria in patients with risk of antibiotic resistance	–	–	R	–
Selective digestive decontamination	NR	–	NR	R
Prophylactic antibiotics	NR	–	–	–
Other strategies				

Lower respiratory tract samples before starting antibiotic therapy	–	–	R	–
Training in appropriate airway management	–	–	–	–

Table S5. The quality assessment for 35 included studies by The Downs and Blacks

Author, year [ref]	REPORTING										EXTERNAL VALIDITY			INTERNAL VALIDITY - BIAS-							INTERNAL VALIDITY - CONFOUNDING (SELECTION BIAS)-						POWER	SCORE
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Liu, 2021 [37]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	26
Atashi, 2017 [22]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	26
Rello, 2012 [45]	1	1	1	1	2	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	24
DeLuca, 2017 [27]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23
Khan, 2016 [33]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23
Parisi, 2016 [43]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23
Triamvisit, 2016 [53]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23
Lim, 2015 [36]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23
Ding, 2013 [28]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23
Omrane, 2007 [41]	1	1	1	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	23

Liu, 2020 [38]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	**22**
Okgün, 2016 [40]	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	**22**
Álvarez-Lerma, 2018 [20]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**21**
Ferreira, 2016 [30]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**21**
Samra, 2016 [48]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**21**
Sen, 2016 [50]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**21**
Ongstad, 2013 [42]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**21**
Hawe, 2009 [31]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**21**
Santana, 2022 [49]	1	1	1	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	0	**20**
Burja, 2018 [26]	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Landelle, 2018 [34]	1	1	0	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Pérez-Granda, 2014 [44]	1	1	0	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Bukhari, 2012 [25]	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Tao, 2012 [52]	1	1	0	1	2	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**

Arabnejad, 2011 [21]	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Al-Tawfiq, 2010 [19]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Lansford, 2007 [35]	1	1	1	1	2	1	1	0	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Baxter, 2005 [23]	1	1	1	1	1	1	1	1	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**20**
Talbot, 2015 [51]	1	1	0	1	0	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	1	1	**19**
Rosenthal, 2012 [46]	1	1	0	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**19**
Morris, 2011 [39]	1	1	0	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**19**
Cacheco, 2012 [54]	1	1	0	1	1	1	1	1	0	0	1	1	1	0	0	1	1	1	1	1	1	0	0	0	1	0	1	**18**
Sachetti, 2014 [47]	1	1	1	1	0	1	1	0	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**18**
Kao, 2019 [32]	1	1	0	1	0	1	1	0	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**17**
Eom, 2013 [29]	1	1	0	1	0	1	1	0	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**17**
Bird, 2010 [24]	1	1	0	1	0	1	1	0	0	1	1	0	1	1	0	1	1	1	1	1	1	0	0	0	1	0	1	**17**
Total	**36**	**36**	**25**	**36**	**52**	**36**	**36**	**5**	**14**	**35**	**36**	**27**	**36**	**36**	**0**	**36**	**36**	**36**	**36**	**36**	**36**	**1**	**1**	**1**	**36**	**13**	**35**	

(<14 points) - Poor quality evidence; (14-18 points) - Fair quality evidence; (19-23) - Good quality evidence; (24-28) – Excellent quality of evidence.

The 27 questions have to be graded as “Yes”, “No” and “Unable to determine” as per the available information. There are 5 sections which include: study quality (10 items), external validity (3 items), study bias (7 items), confounding and selection bias (6 items), and power (1 item). Each question if answered “yes” gets a score of 1,

except for the 5th question which can get a score of 2 if answered “yes”. Thus the total score is out of 28. The modified version makes a simplification of the power question, awarding only 1 point if a study had adequate power to recognize a clinically significant effect. If a study did not mention statistical power, it was deemed either “no” or “unable to determine” and given a score of 0.

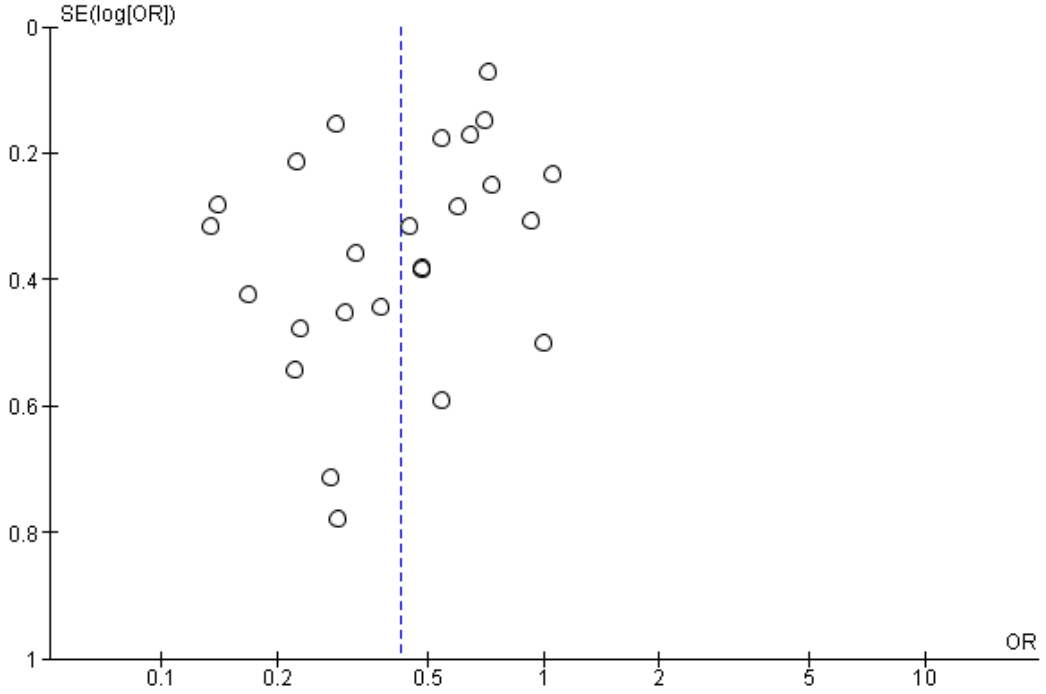
REPORTING: 1. Is the hypothesis/aim/objective of the study clearly described?; 2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?; 3. Are the characteristics of the patients included in the study clearly described?; 4. Are the interventions of interest clearly described?; 5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?; 6. Are the main findings of the study clearly described?; 7. Does the study provide estimates of the random variability in the data for the main outcomes?; 8. Have all important adverse events that may be a consequence of the intervention been reported?; 9. Have the characteristics of patients lost to follow-up been described?; 10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?. **EXTERNAL VALIDITY:** 11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; 12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; 13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?. **INTERNAL VALIDITY (BIAS):** 14. Was an attempt made to blind study subjects to the intervention they have received?; 15. Was an attempt made to blind those measuring the main outcomes of the intervention?; 16. If any of the results of the study were based on “data dredging”, was this made clear?; 17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?; 18. Were the statistical tests used to assess the main outcomes appropriate?; 19. Was compliance with the intervention/s reliable?; 20. Were the main outcome measures used accurate (valid and reliable)?. **INTERNAL VALIDITY (CONFOUNDING SELECTION BIAS):** 21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?; 22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?; 23. Were study subjects randomized to intervention groups?; 24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?; 25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; 26. Were losses of patients to follow-up taken into account?. **POWER:** 27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

Table S6. Comparison between previous systematic reviews and the current study

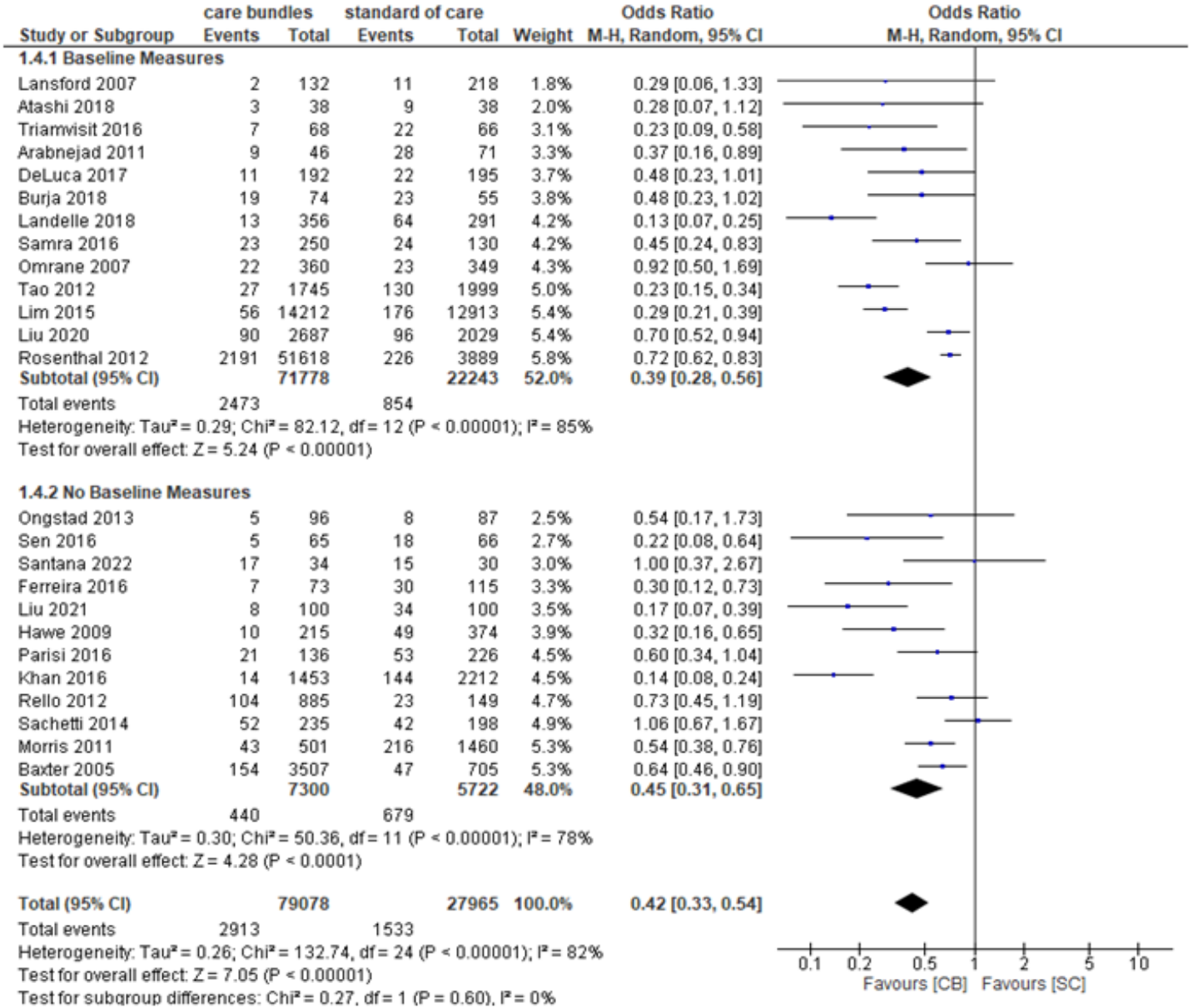
	Current study	Pileggi *et al.* 2018 [1]
Study Design	Systematic Review & Meta-analysis	Systematic Review & Meta-analysis
Period of publication	January 1985 to July 2022	Until June 2017
Databases	Pubmed, Cochrane Library, Web of Science	Pubmed, Scopus, Cochrane Library, Web of Science
Eligible study design	RCTs and Observational studies	RCTs and Observational studies
PROSPERO register	CRD42022341780	CRD42017054268
Inclusion criteria	-Adult (≥18 years) ICU patients under mechanical ventilation -Application of care bundles only in the intervention group, control group did not receive care bundles.	-Adult (≥18 years) ICU patients under mechanical ventilation -Make reference to a ventilator bundle -Assess mortality (report enough data to estimate RR or OR)
Exclusion criteria	-Patients admitted with pneumonia and patients with nosocomial pneumonia other than VAP.	-Care bundles for prevention of other hospital acquired infections.
Outcomes	**-Main:** VAP occurrence **-Other:** Duration of MV, ICU and hospital length of stay, ICU and hospital mortality, VAP-related mortality and length of stay, compliance	**-Main:** Mortality (overall, hospital, ICU and VAP-related mortality) -**Other:** VAP occurrence, ICU and hospital length of stay, duration of mechanical ventilation, days of antibiotic therapy, compliance
Age, years	≥18 years	≥18 years
N studies included	29	13
N Subjects	116,873	11,664

Figure S1. Funnel plot (A) and Forest plots (B-G) on **VAP episodes** reported in the care bundles and standard care.

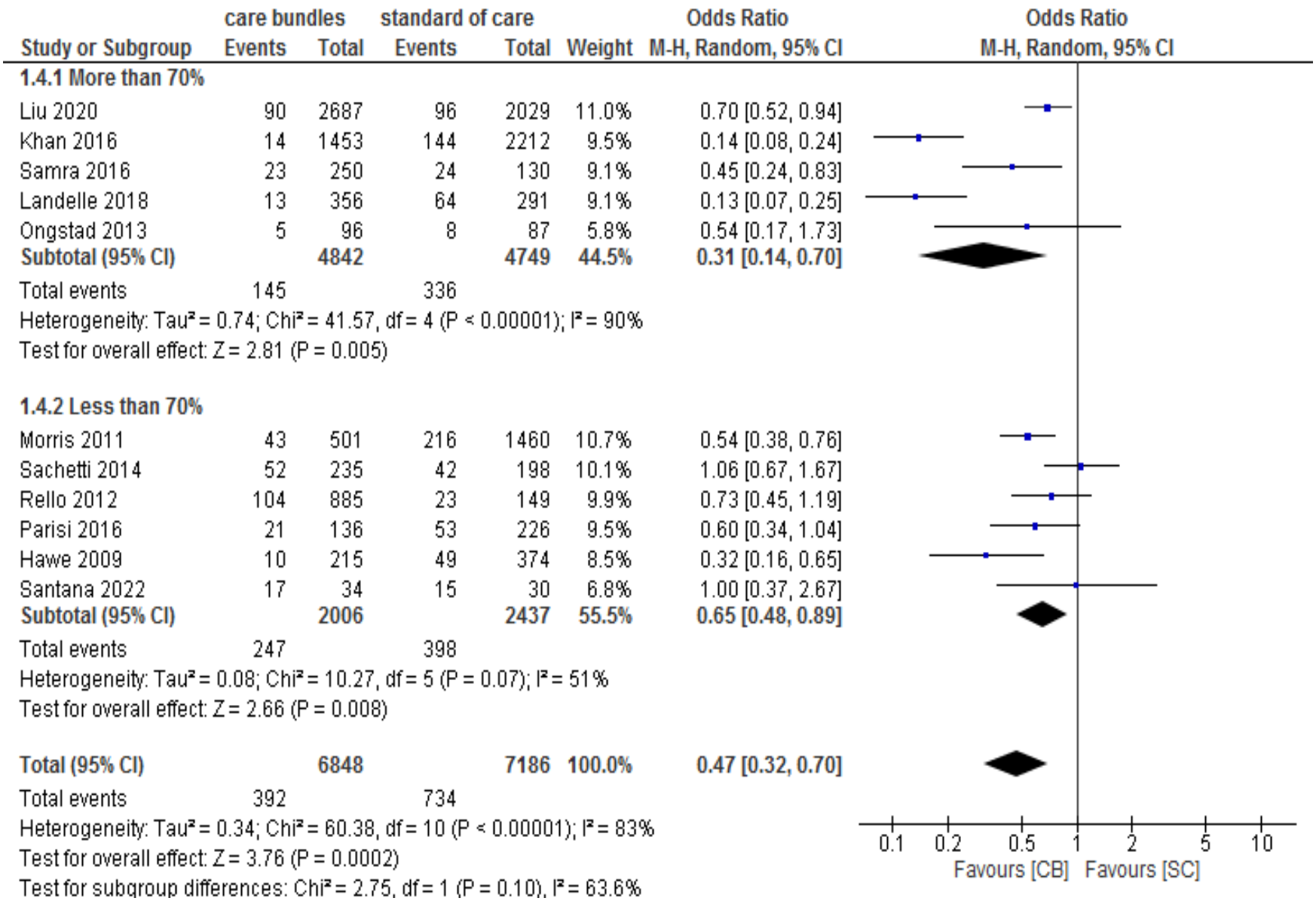
A) Funnel plot of studies reporting data about VAP episodes in the care bundles and standard care groups.



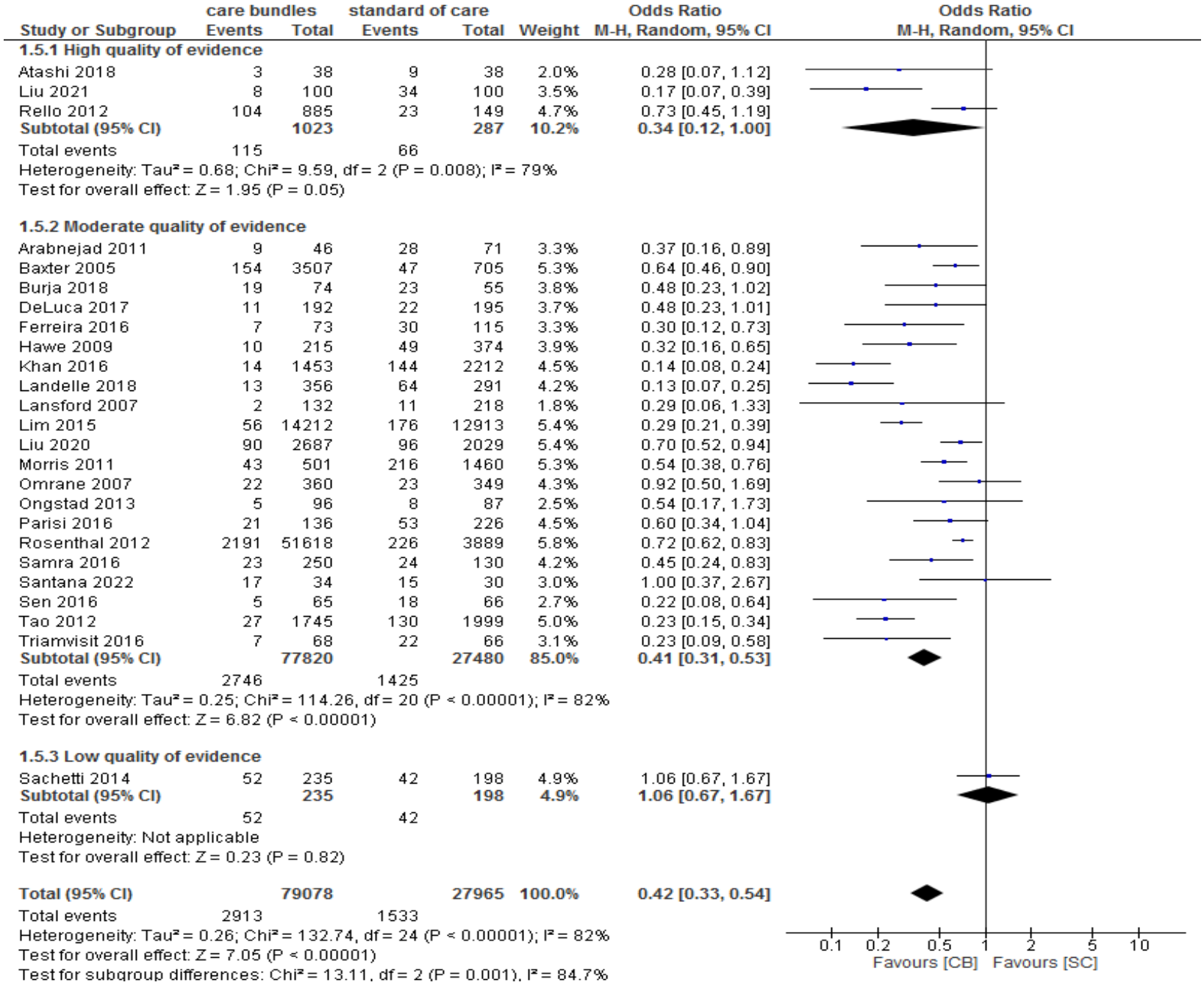
B) Forest plot of VAP episodes by baseline measures subgroups.



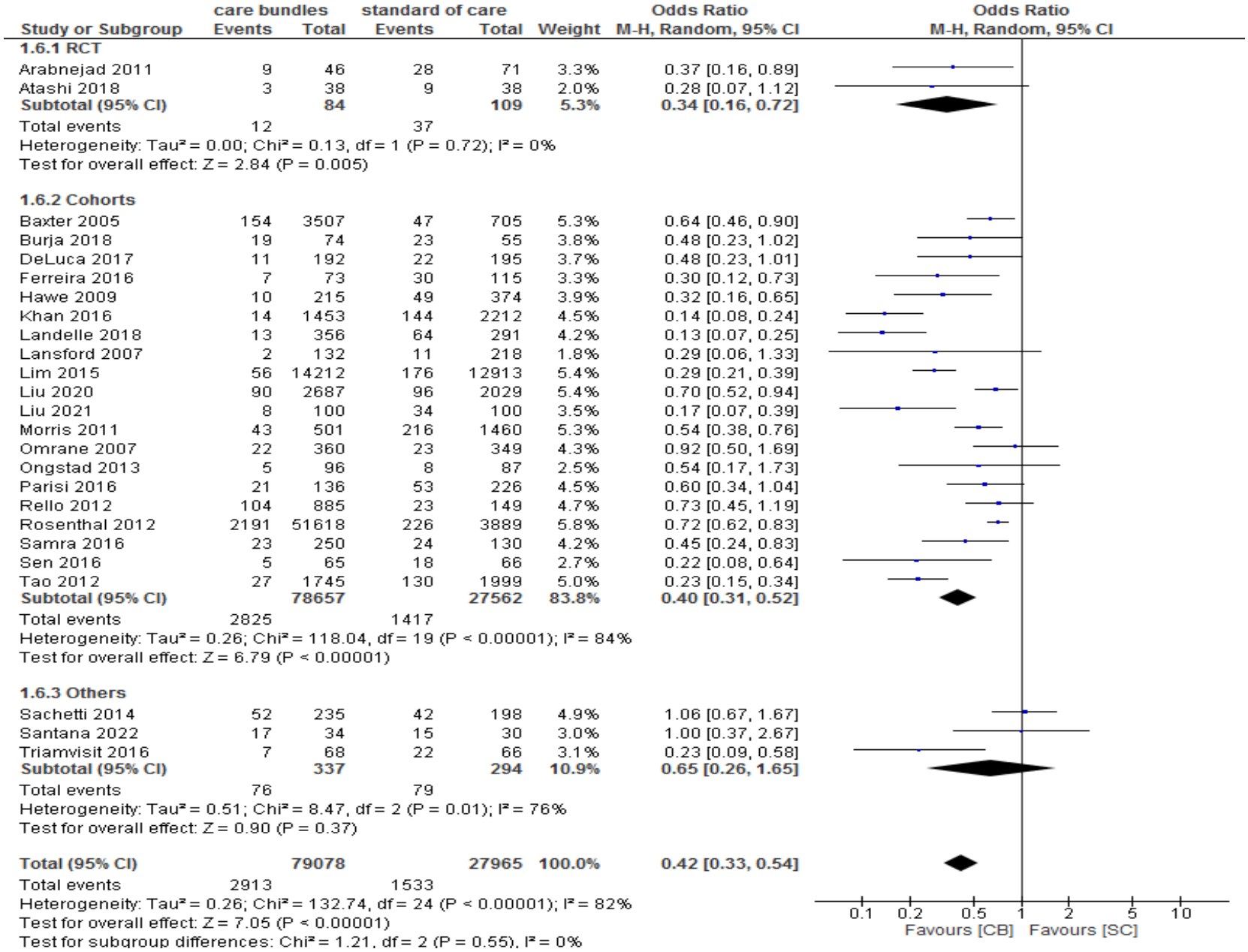
C) Forest plot of VAP episodes by compliance subgroups.



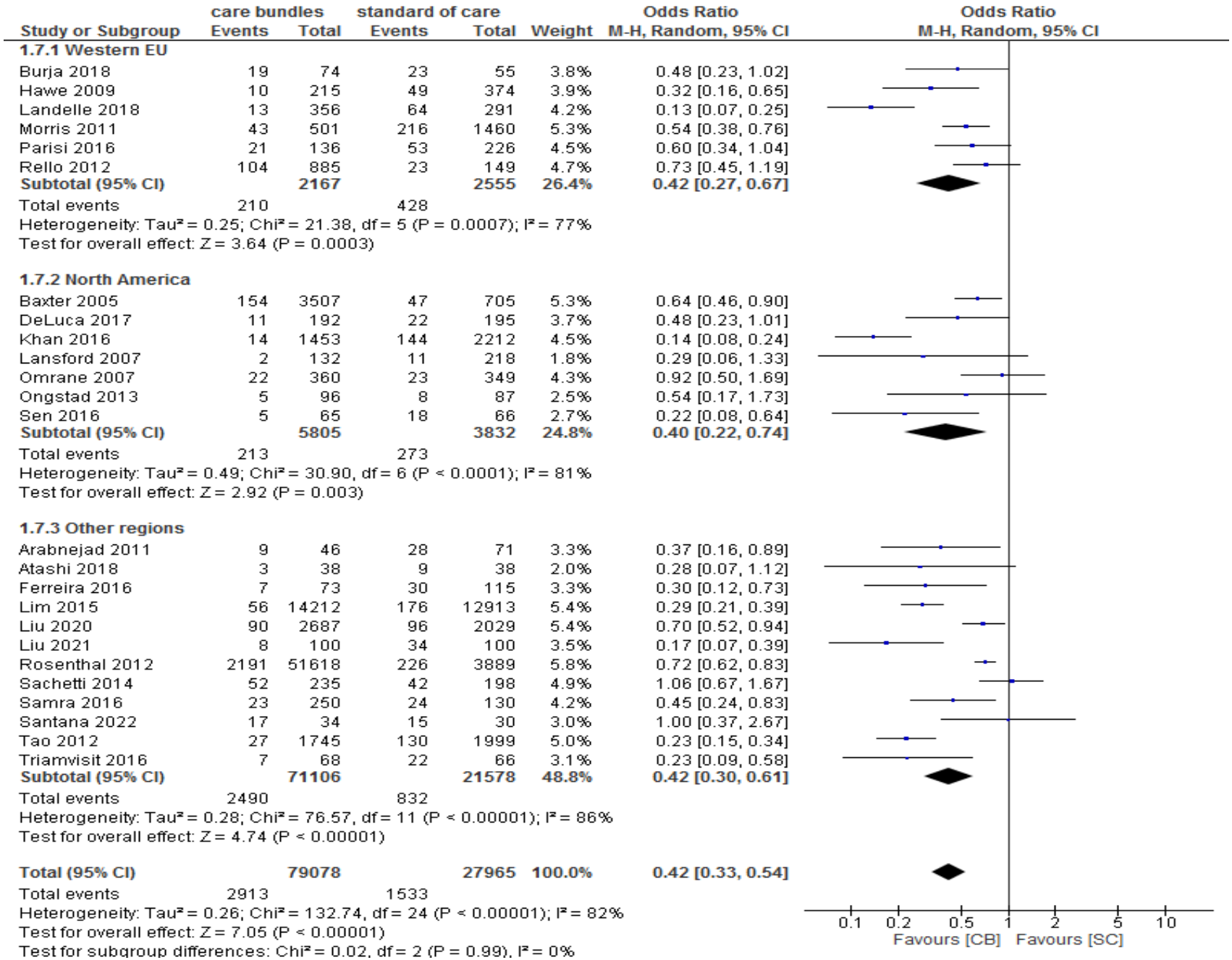
D) Forest plot of VAP episodes by quality of evidence (risk of bias) subgroups.



E) Forest plot of VAP episodes by study design subgroups.



F) Forest plot of VAP episodes by country subgroups.



G) Forest plot of VAP episodes by VAP diagnostic criteria subgroups.

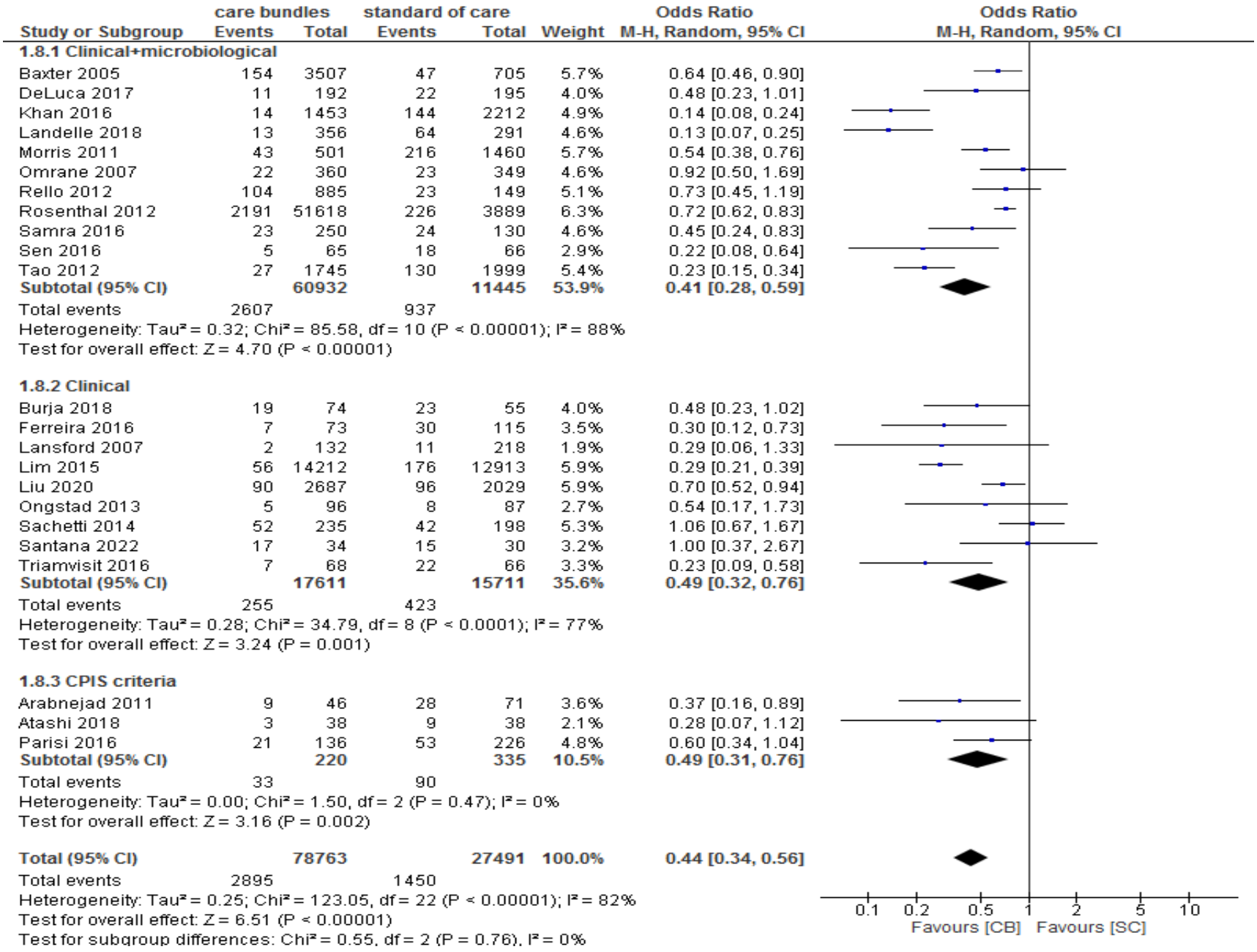
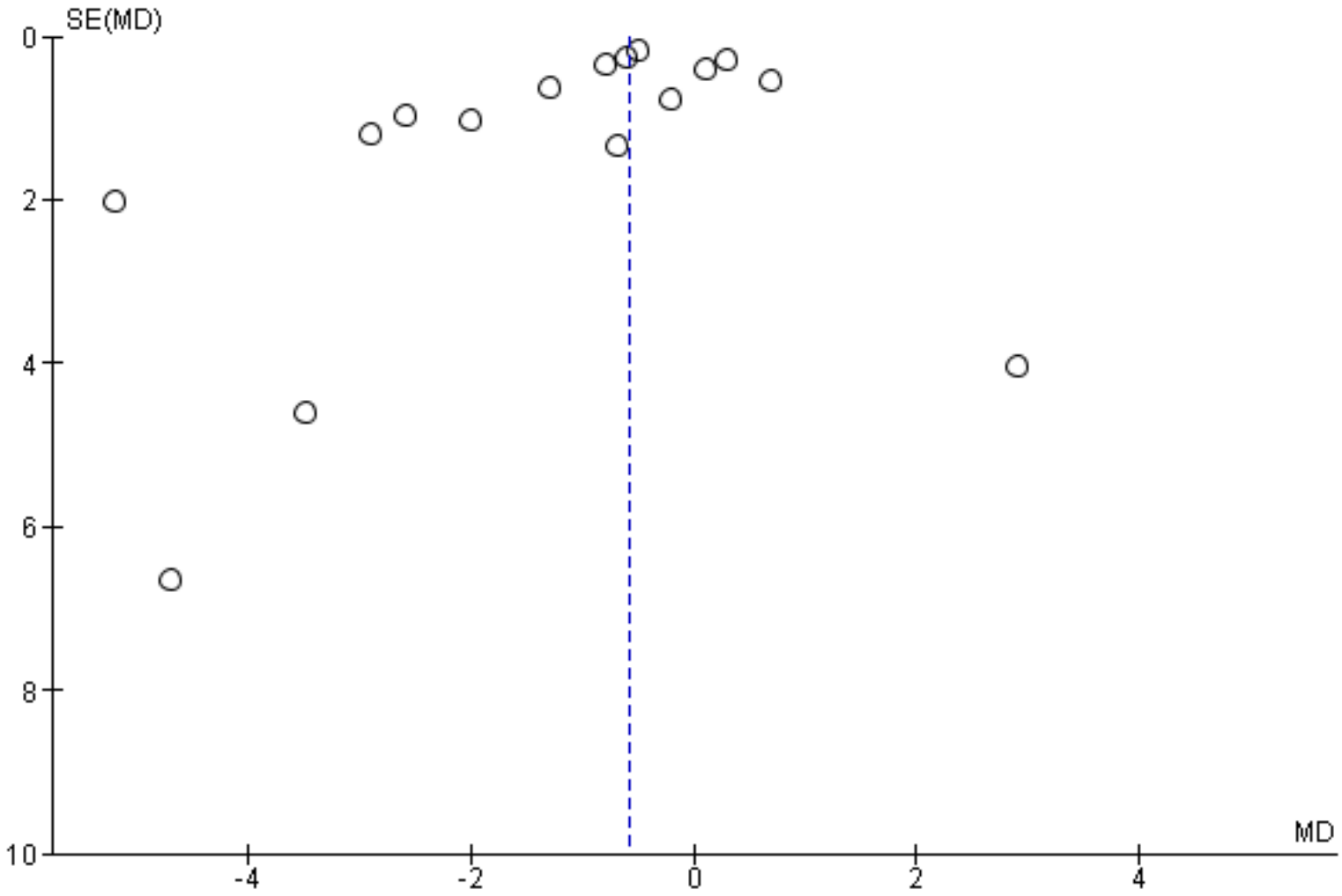
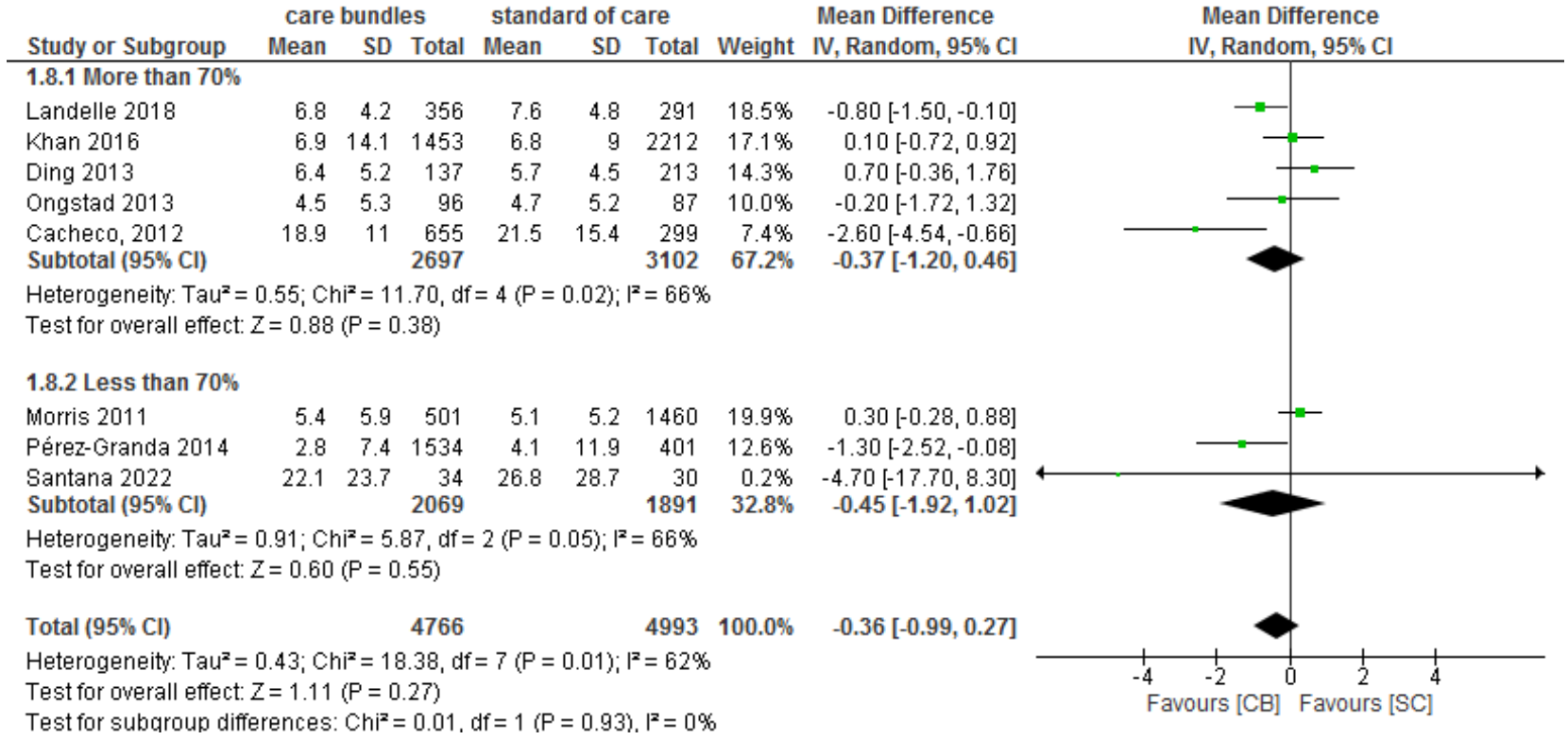


Figure S2. Funnel plot (A) and Forest plots (B-F) on **days on mechanical ventilation** in subjects treated with care bundles or standard care.

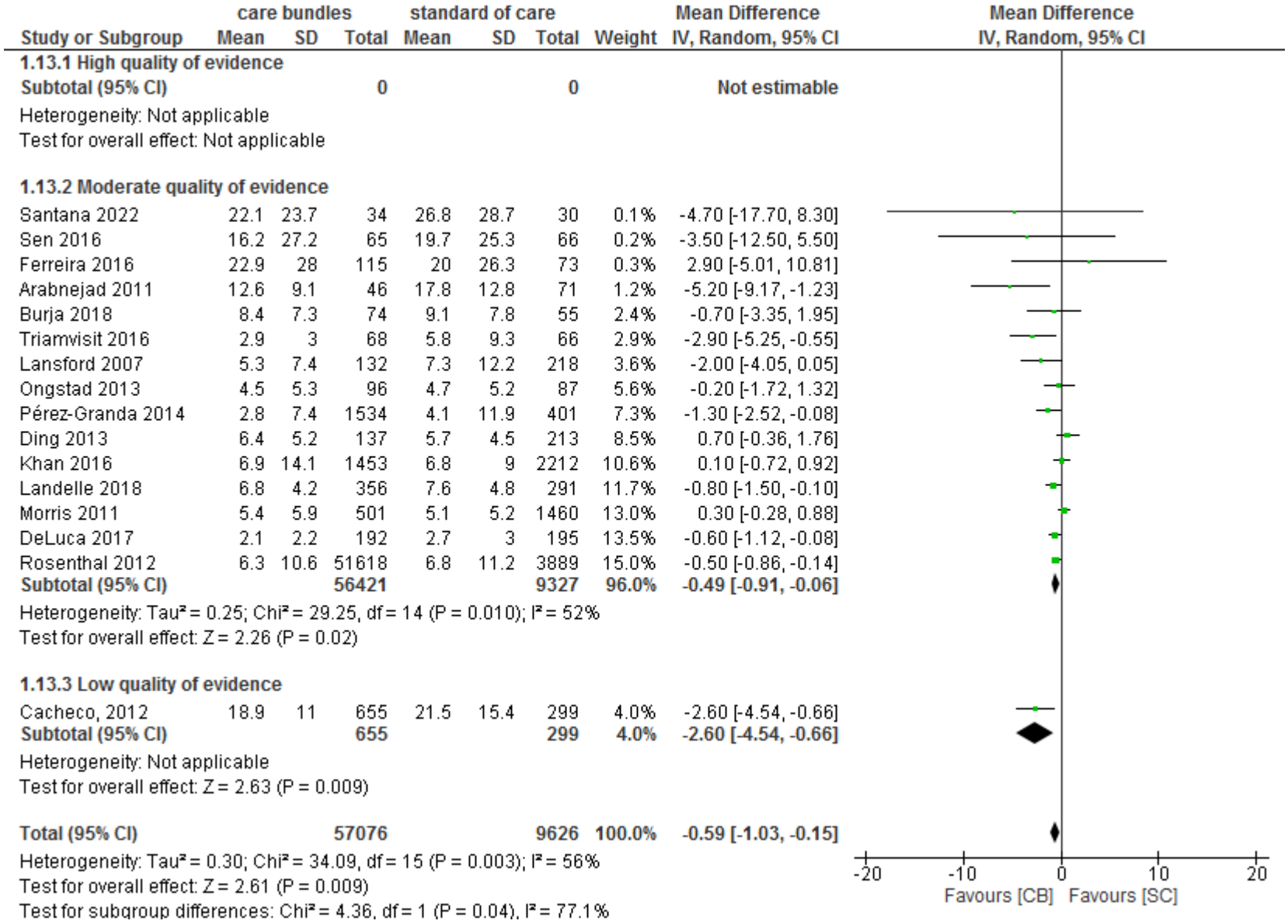
A) Funnel plot on days of mechanical ventilation in subjects treated with care bundles or standard care.



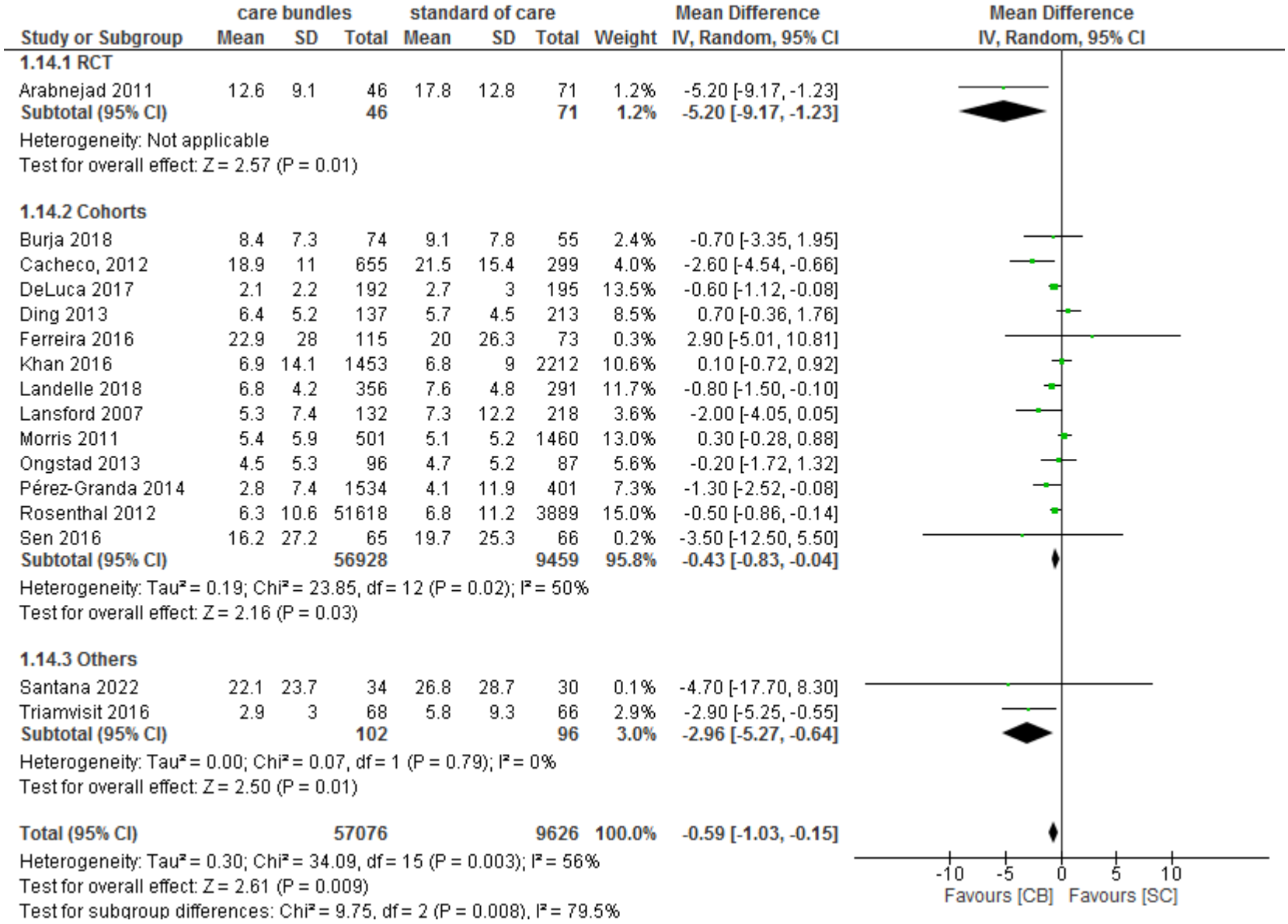
B) Forest plot on days of mechanical ventilation by compliance subgroups.



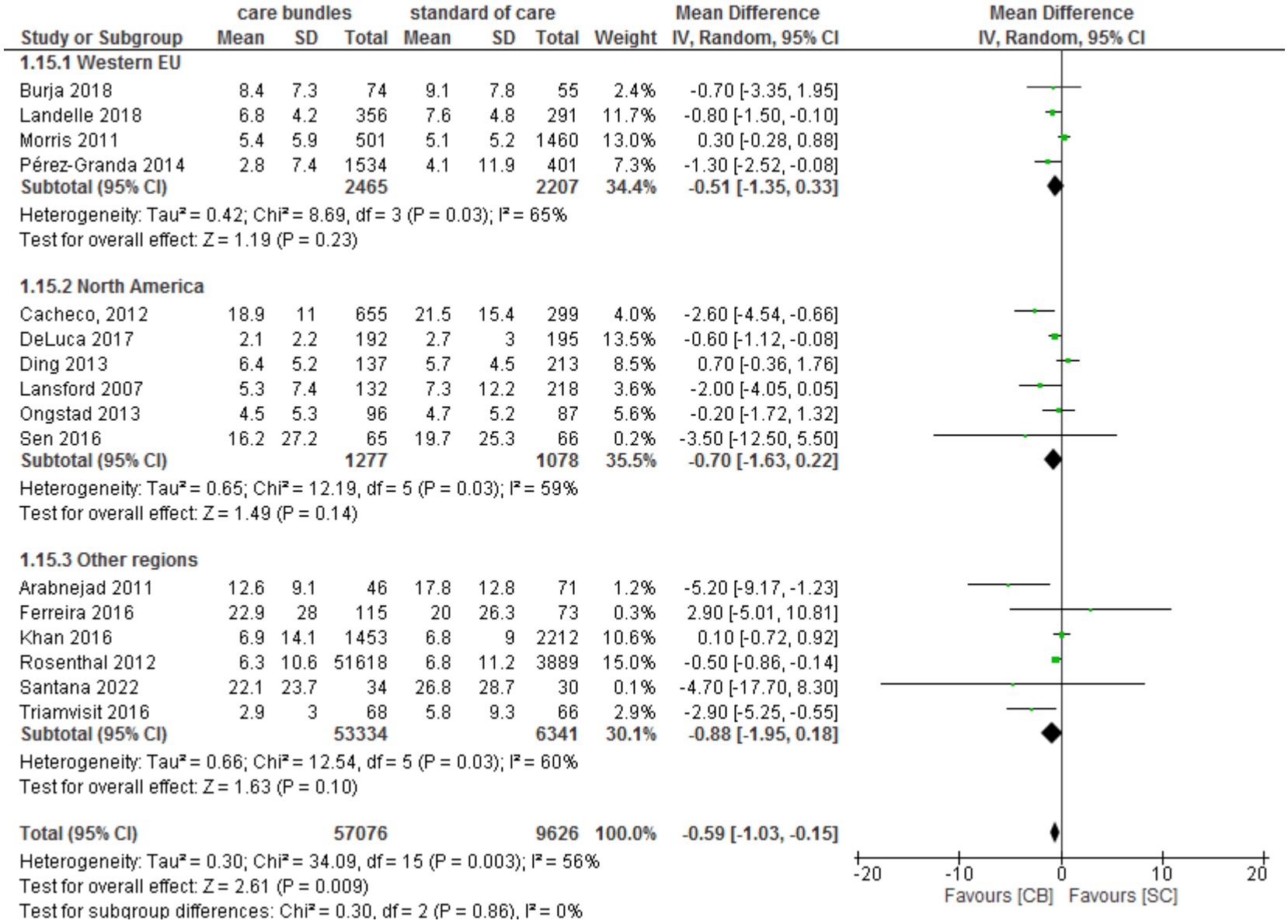
C) Forest plot on days of mechanical ventilation by quality of evidence (risk of bias) subgroups.



D) Forest plot on days of mechanical ventilation by study design subgroups.



E) Forest plot on days of mechanical ventilation by country subgroups.



F) Forest plot on days of mechanical ventilation by VAP diagnostic criteria subgroups.

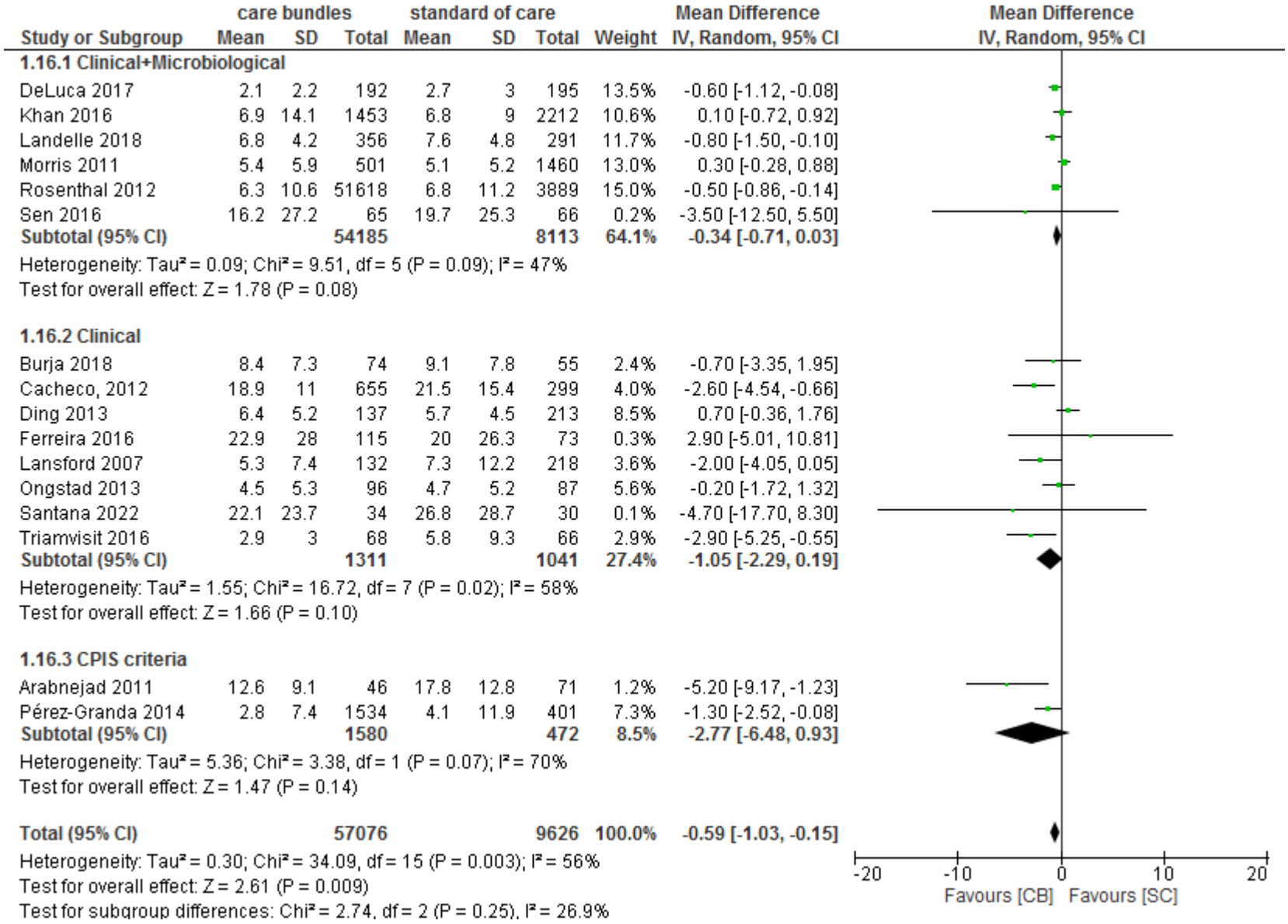
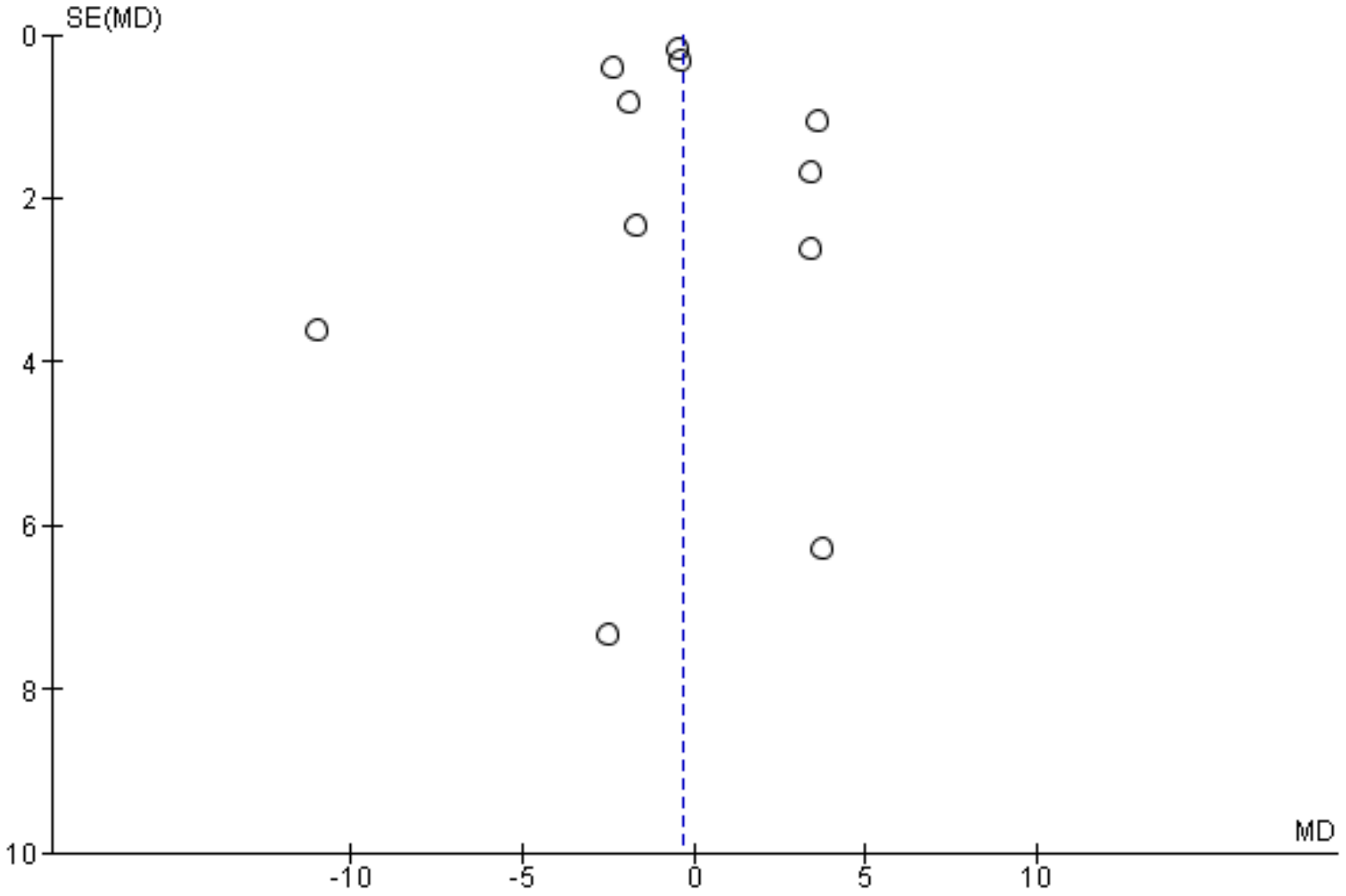
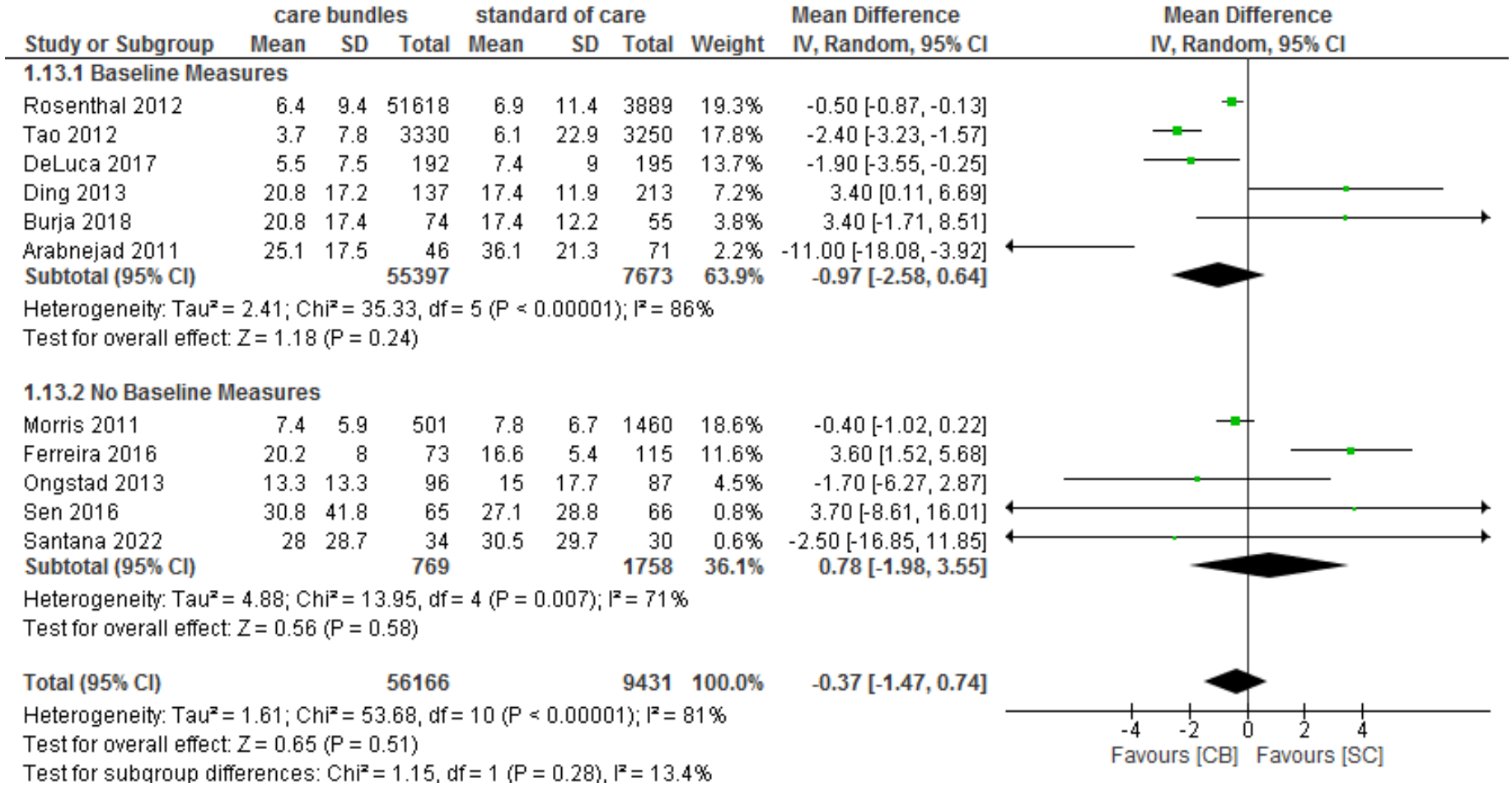


Figure S3. Funnel plot (A) and Forest (B-F) plots on **hospital length of stay** in subjects treated with care bundles or standard care.

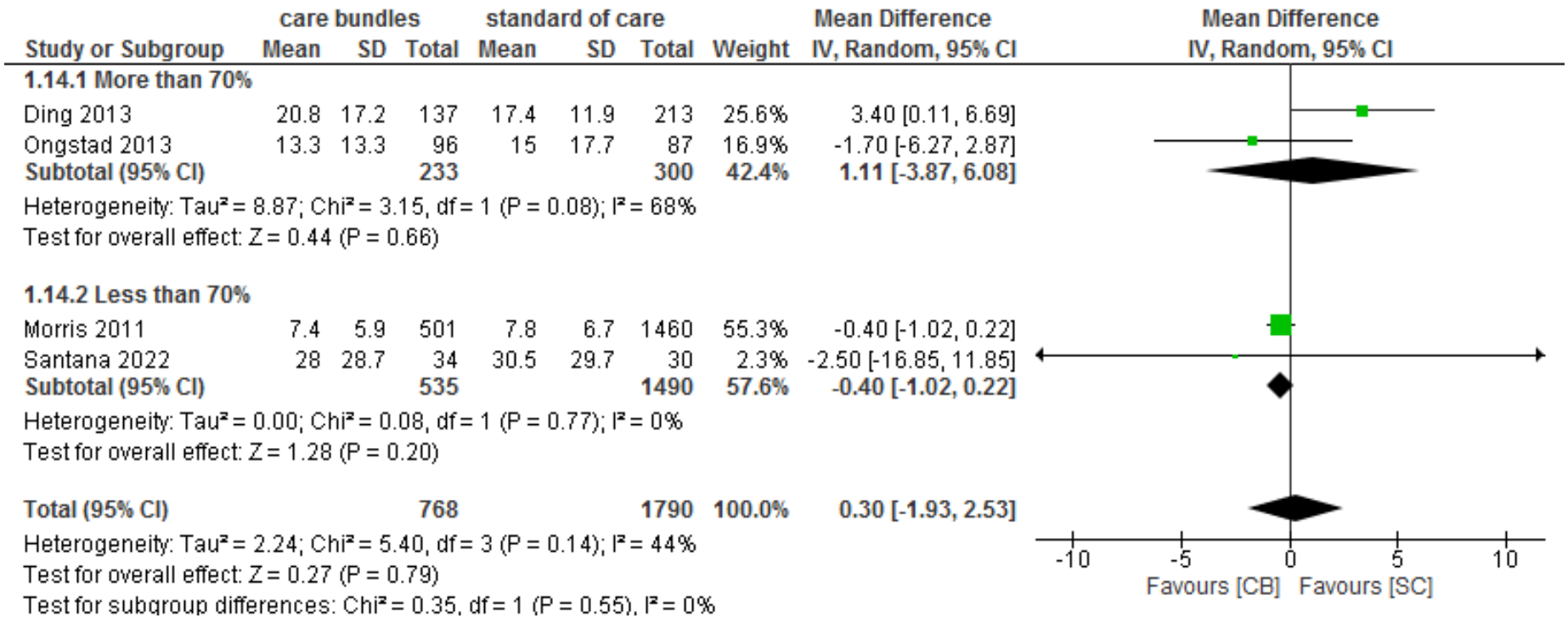
A) Funnel plot on length of hospital stay in subjects treated with care bundles or standard care.



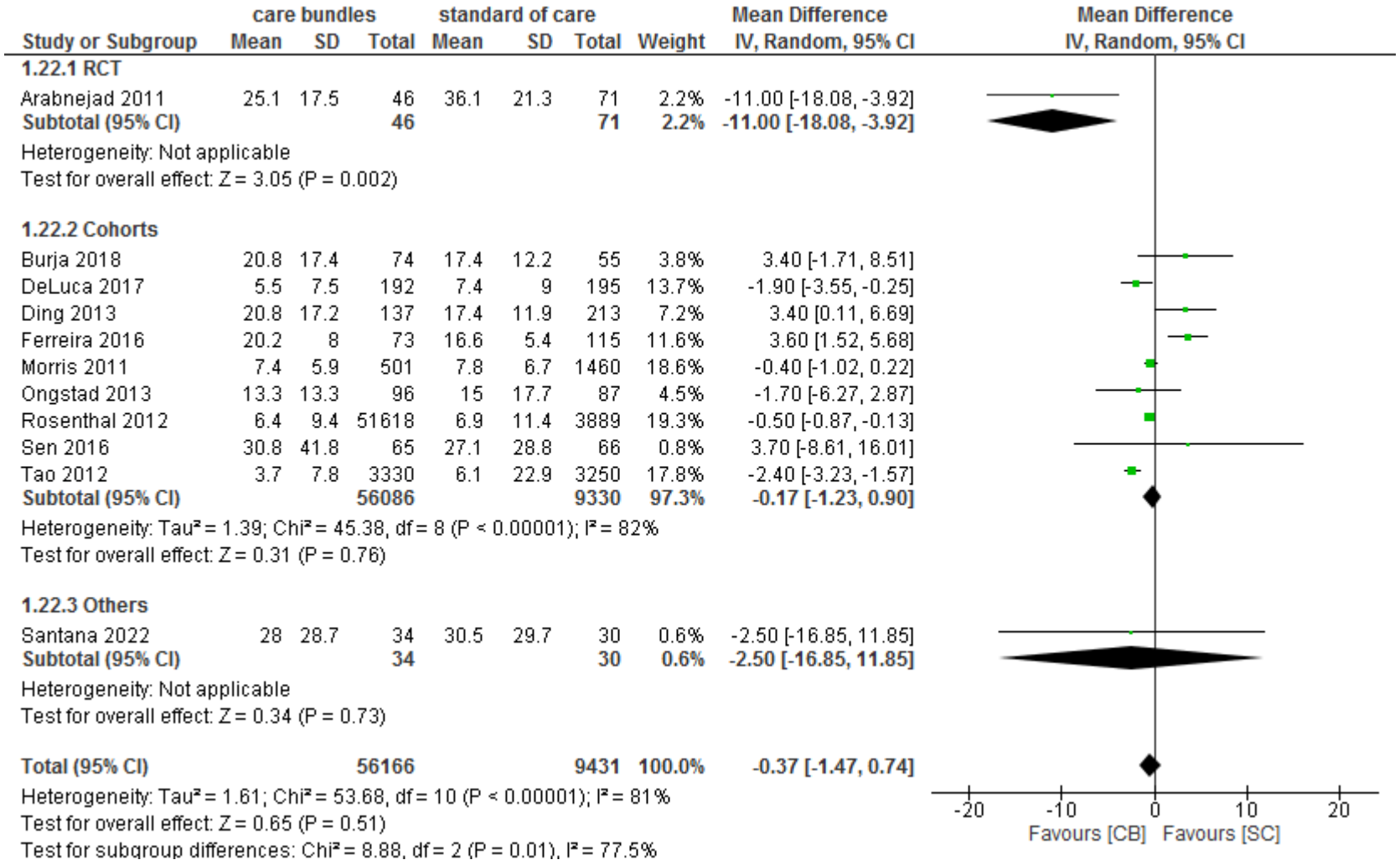
B) Forest plot on length of hospital stay by baseline measures subgroups.



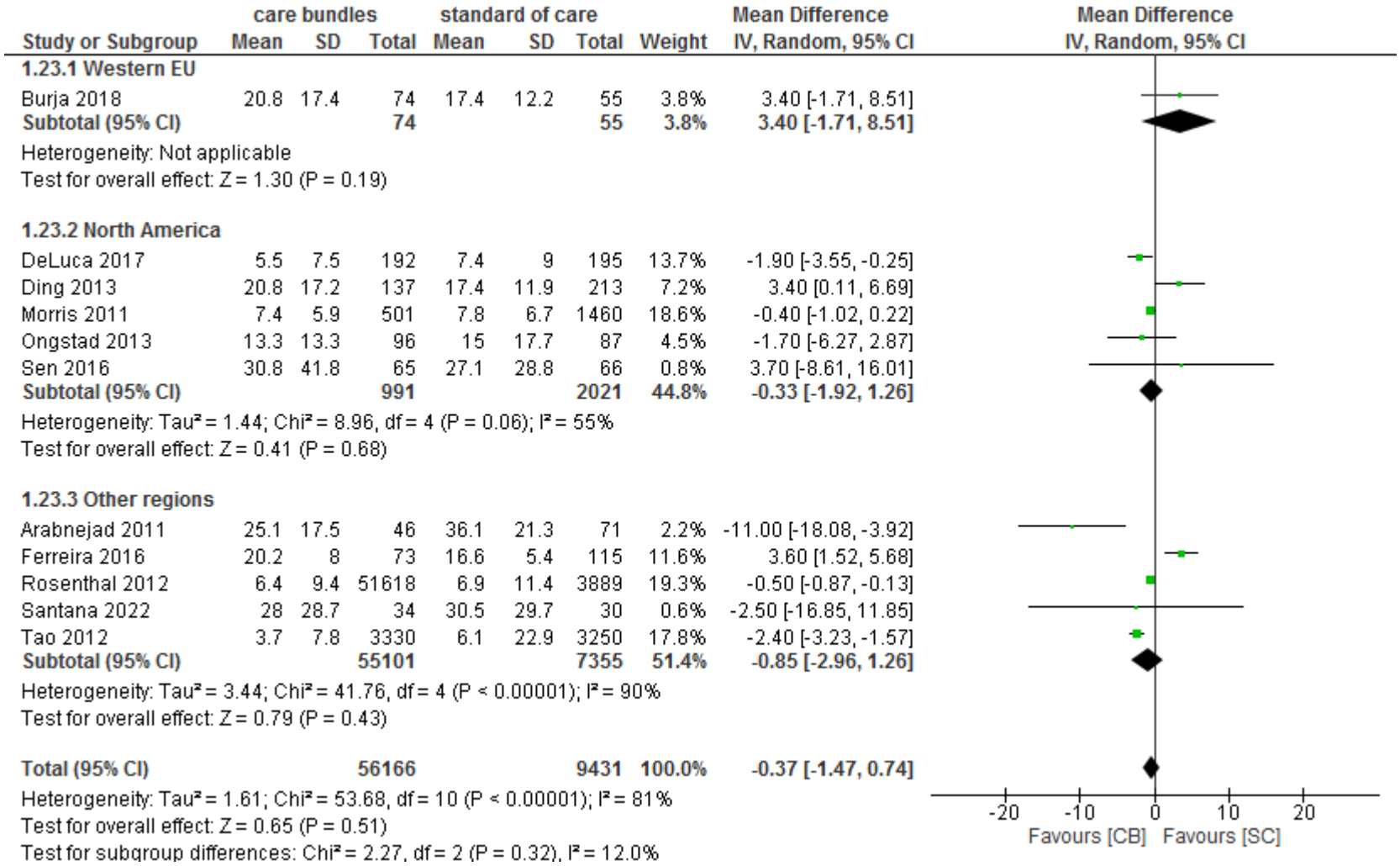
C) Forest plot on length of hospital stay by compliance subgroups.



D) Forest plot on length of hospital stay by study design subgroups.



E) Forest plot on length of hospital stay by country subgroups.



F) Forest plot on length of hospital stay by VAP diagnostic criteria subgroups.

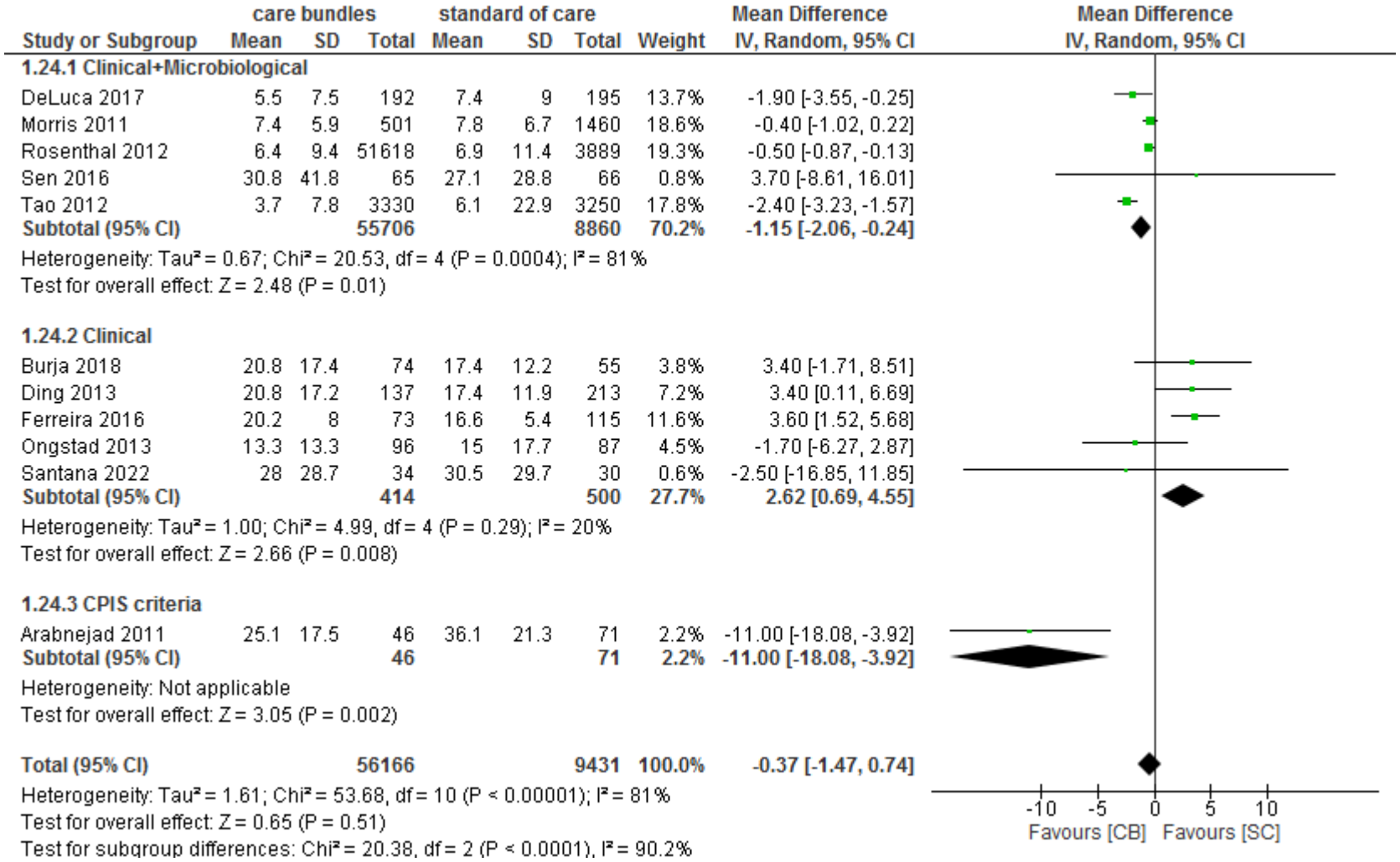
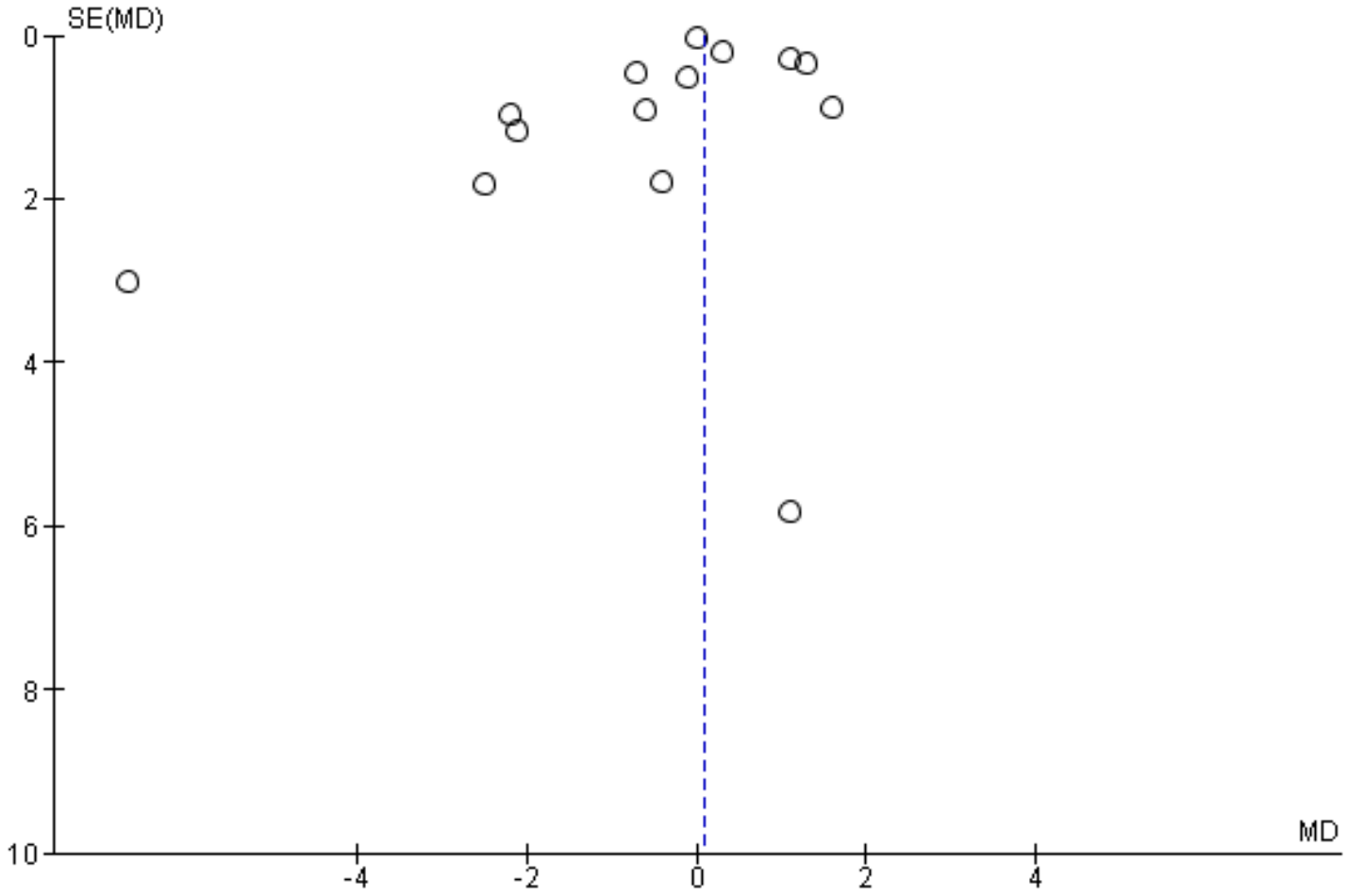
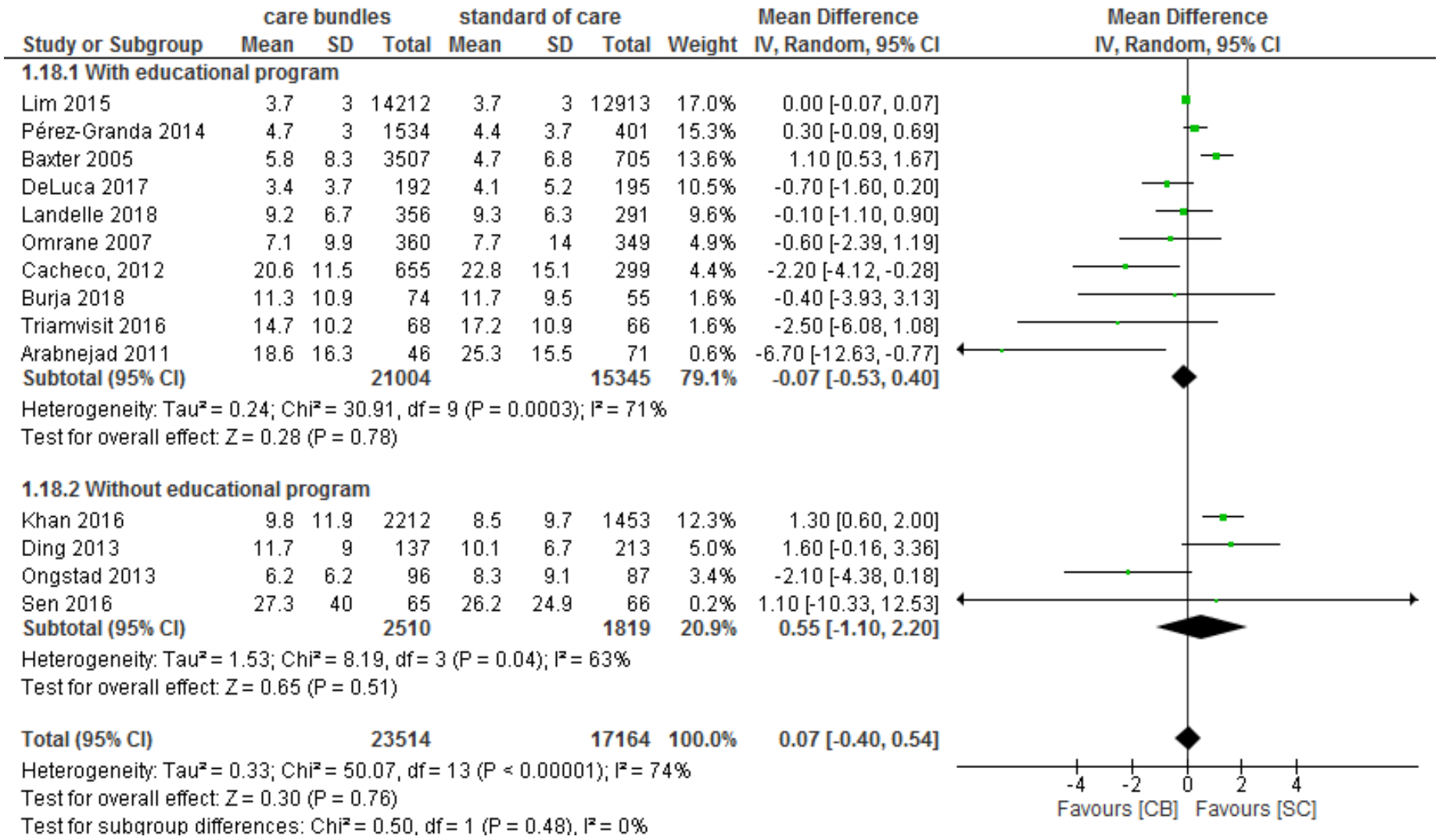


Figure S4. Funnel plot (A) and Forest plots (B-F) on **ICU length of stay** in subjects treated with care bundles or standard care.

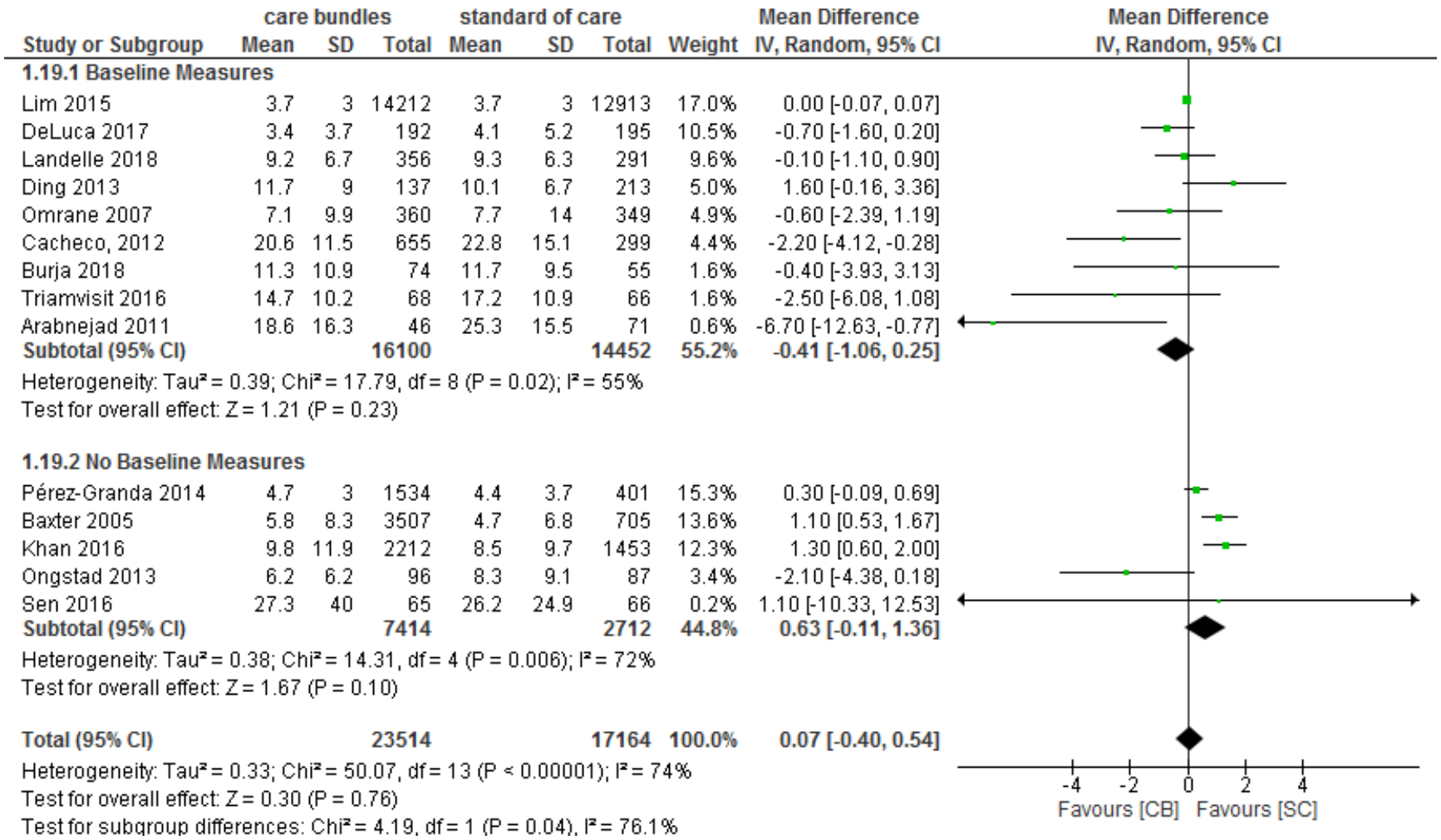
A) Funnel plot on ICU length of stay in subjects treated with care bundles or standard care.



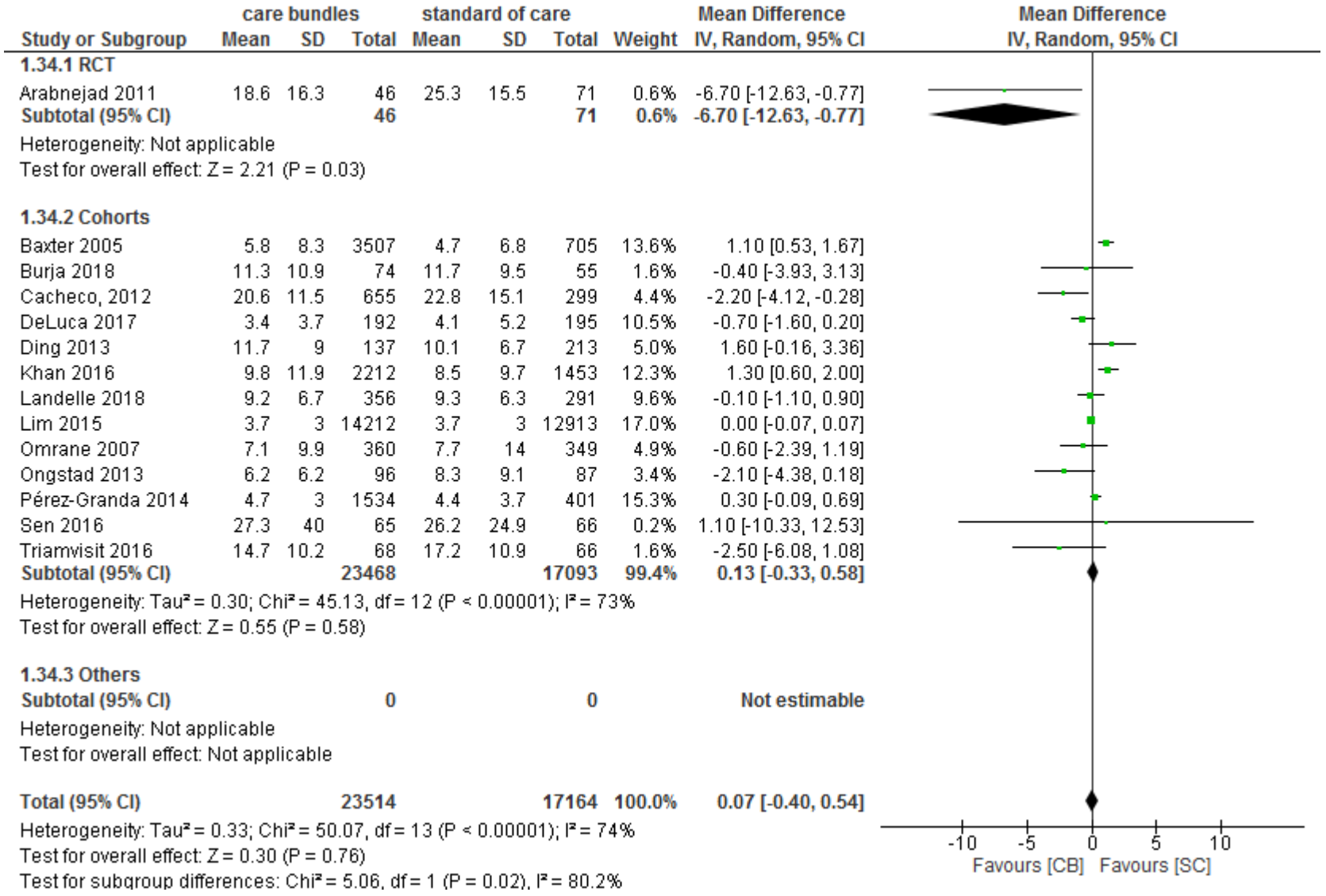
B) Forest plot on ICU length of stay by educational interventions subgroups.



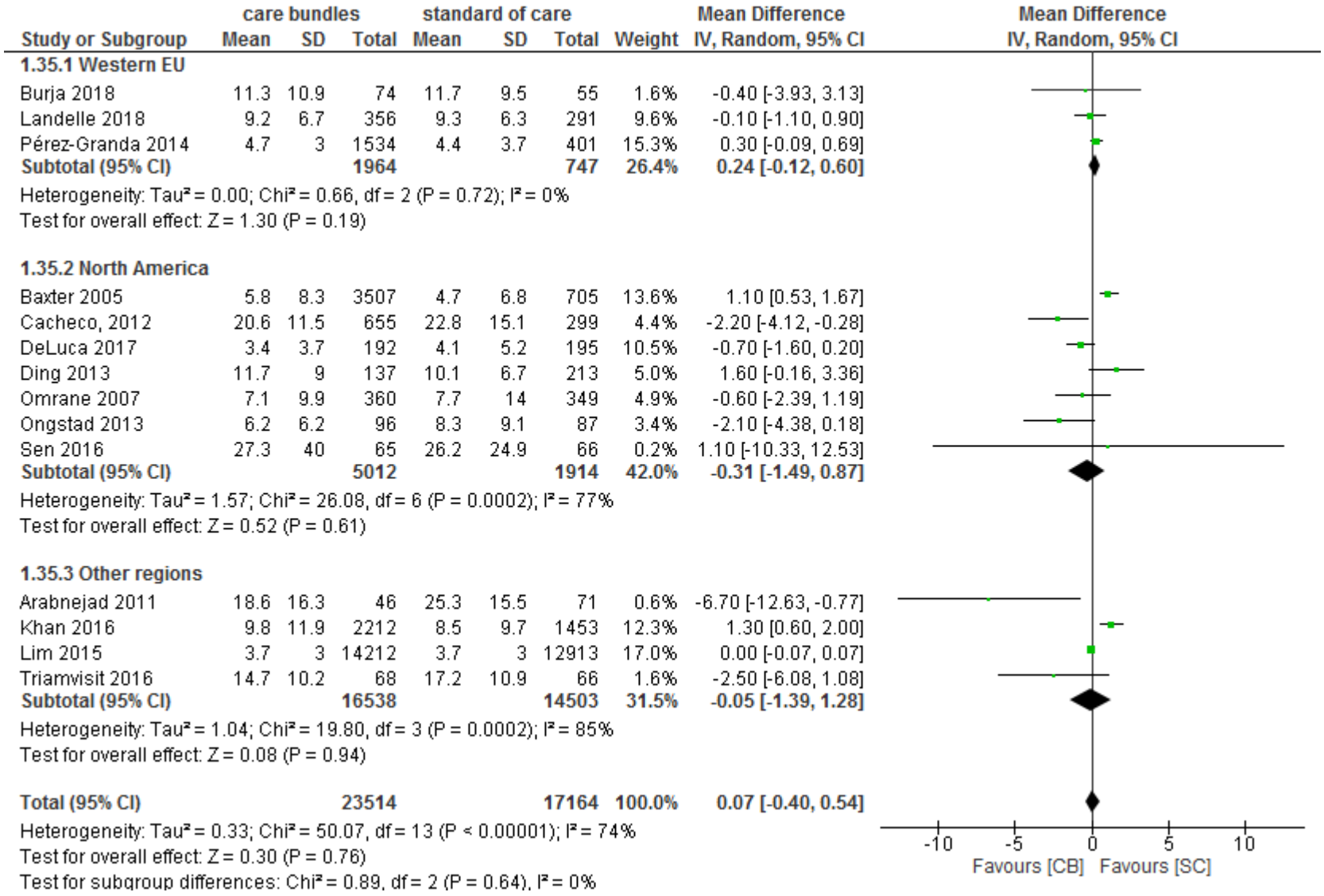
C) Forest plot on ICU length of stay by baseline measures subgroups.



D) Forest plot on ICU length of stay by study design subgroups.



E) Forest plot on ICU length of stay by country subgroups.



F) Forest plot on ICU length of stay by VAP diagnostic criteria subgroups.

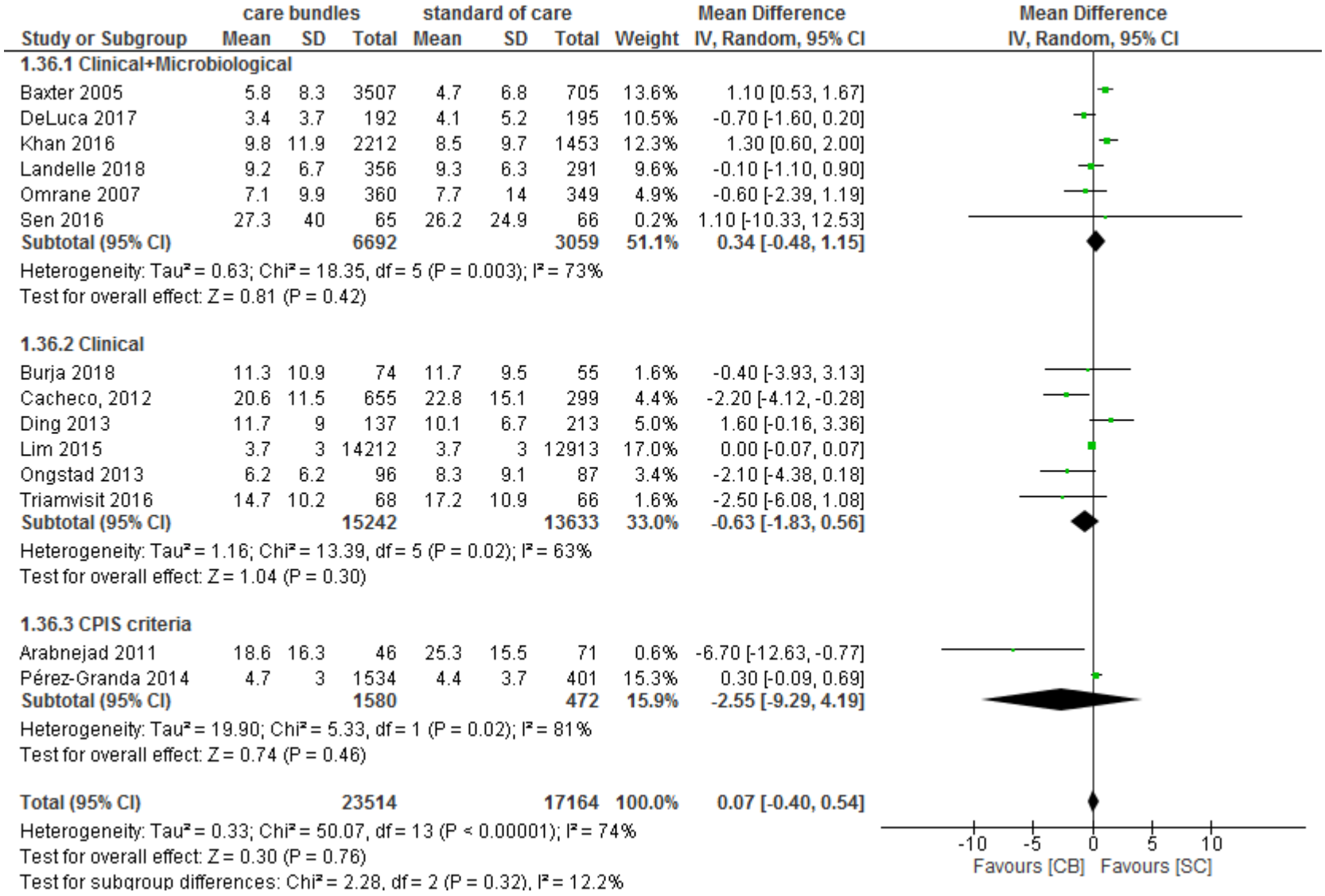
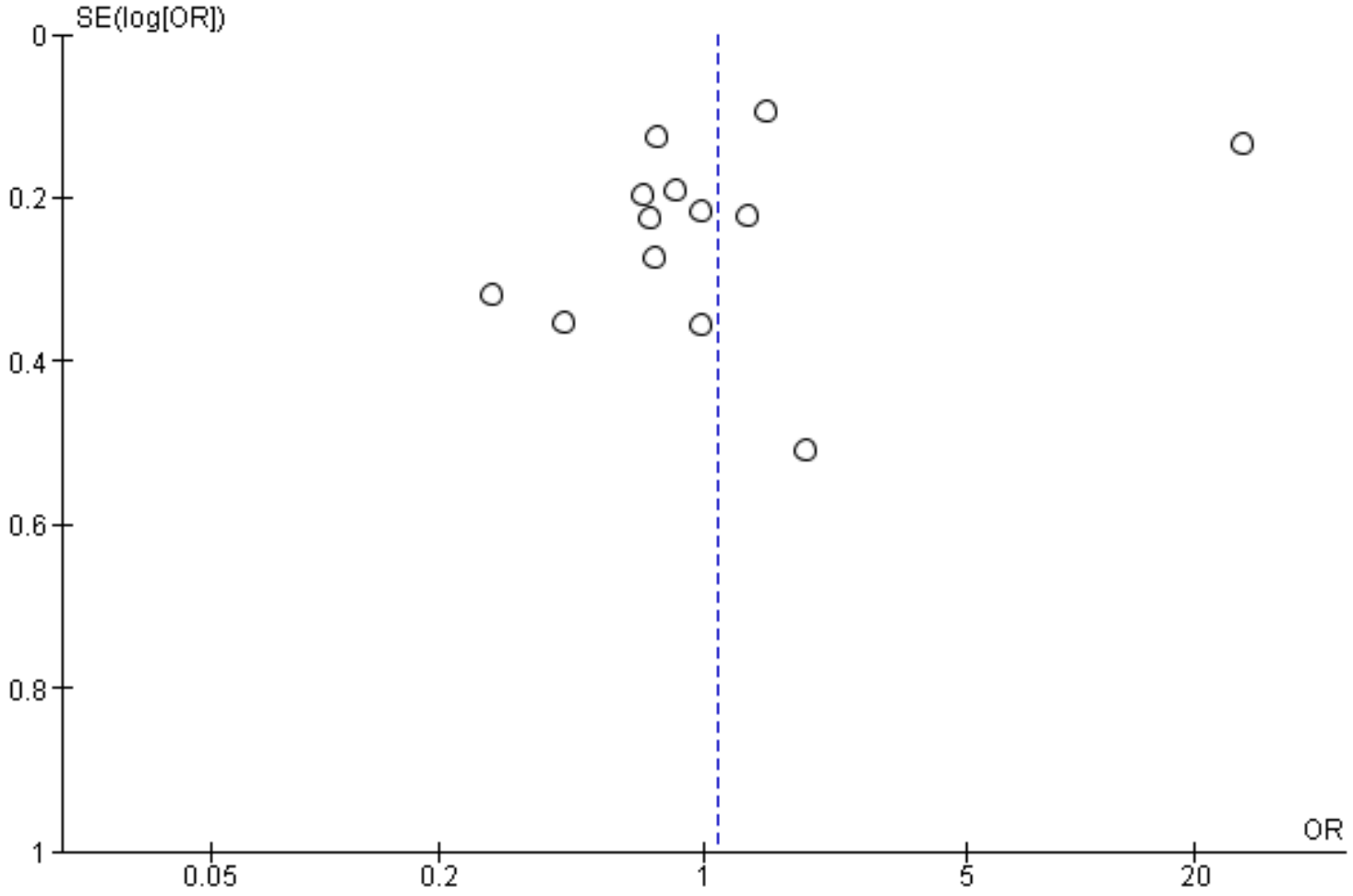
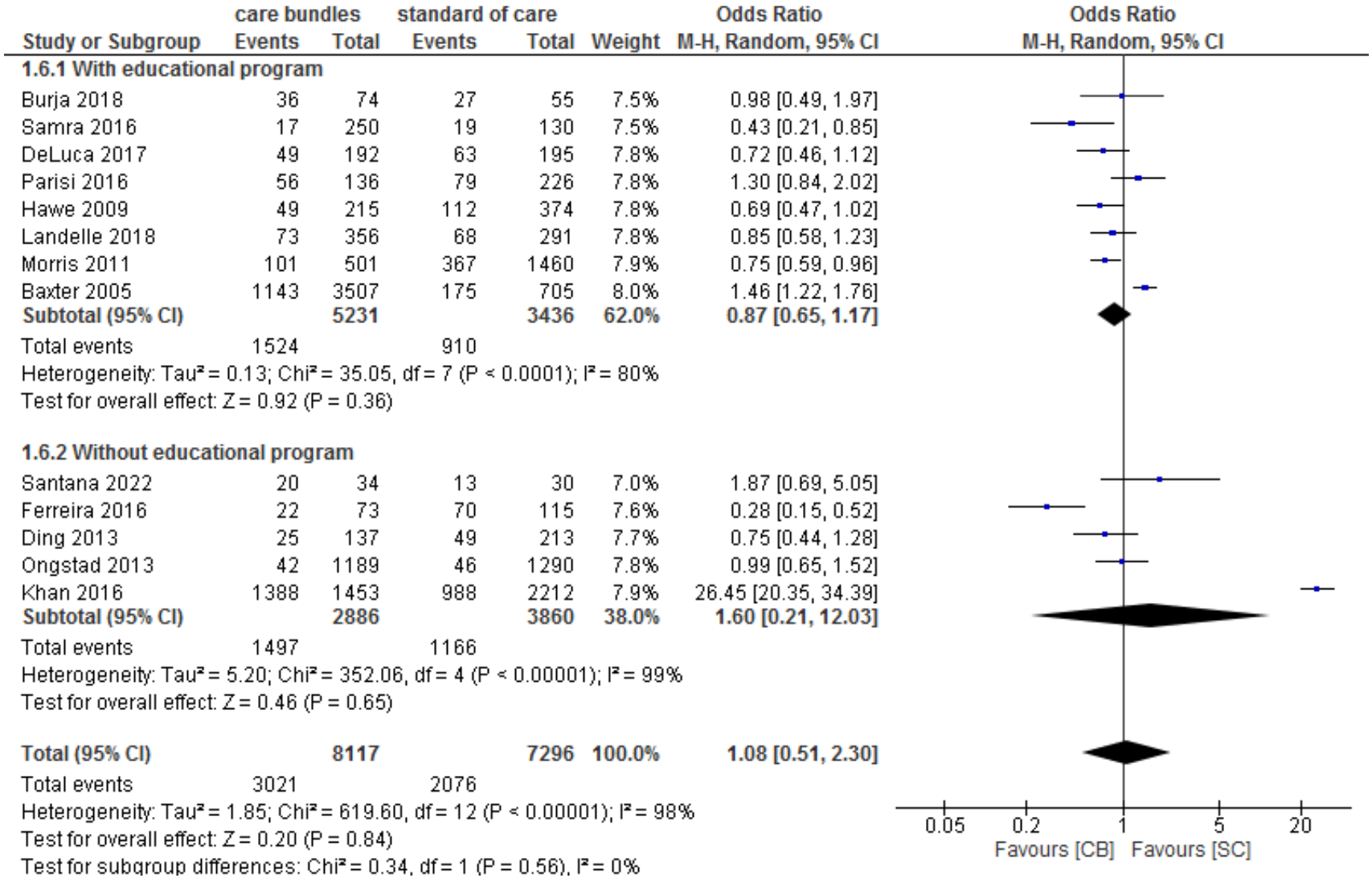


Figure S5. Funnel plot (A) and Forest plots (B-E) on **hospital mortality** in subjects treated with care bundles or standard care.

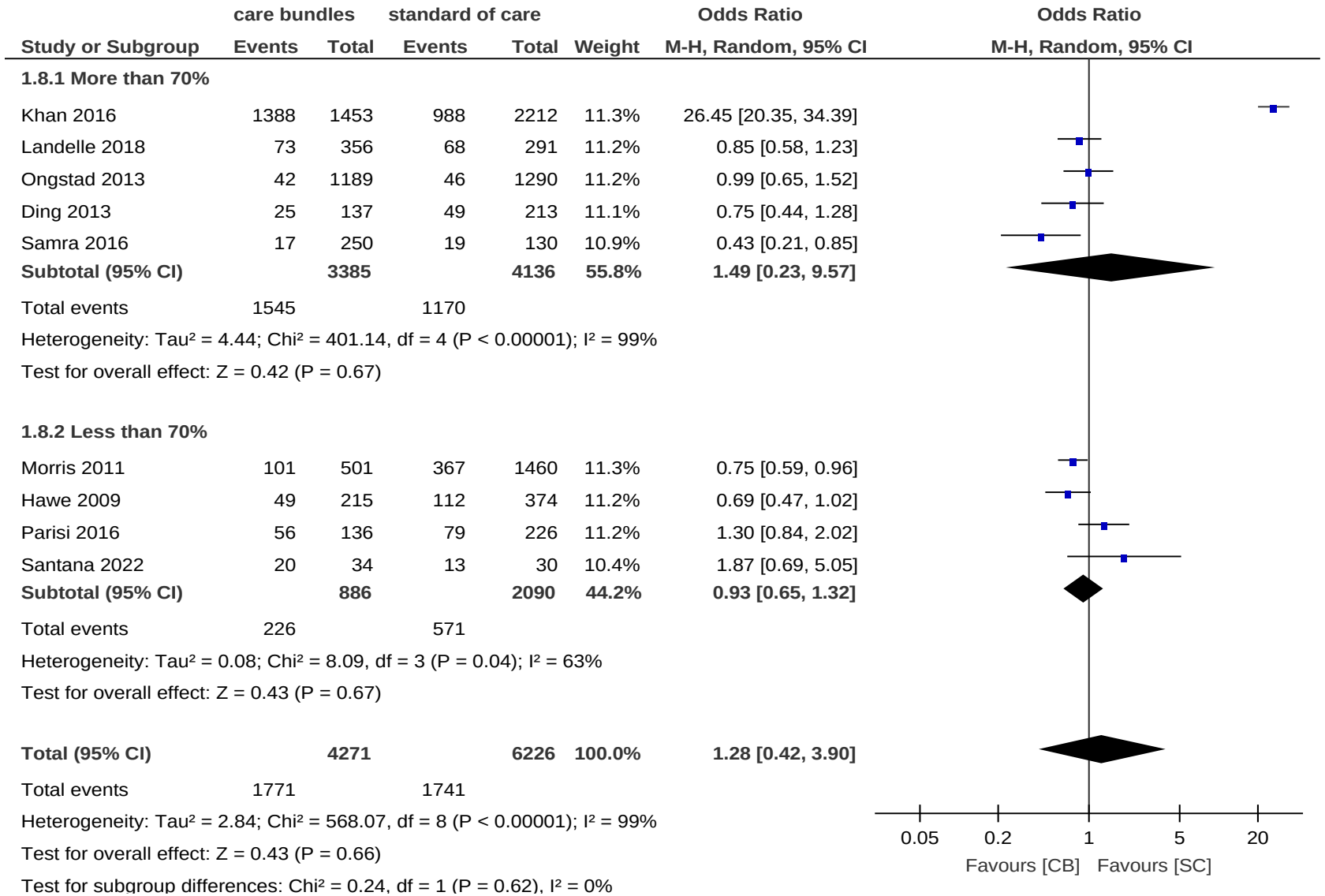
A) Funnel plot on hospital mortality in subjects treated with care bundles or standard care.



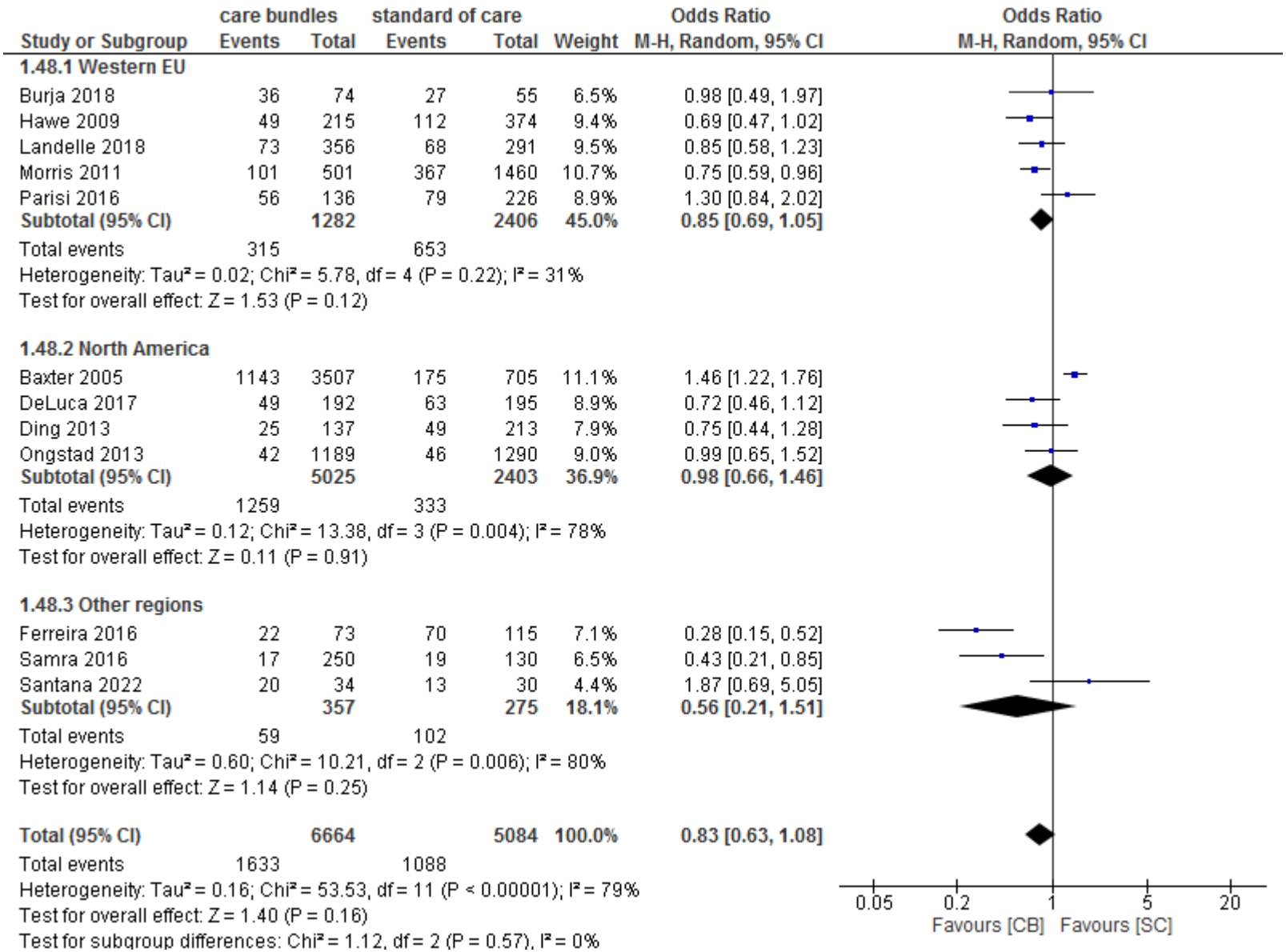
B) Forest plot on hospital mortality by educational interventions subgroups.



C) Forest plot on hospital mortality by compliance subgroups.



D) Forest plot on hospital mortality by country subgroups.



E) Forest plot on hospital mortality by VAP diagnostic criteria subgroups.

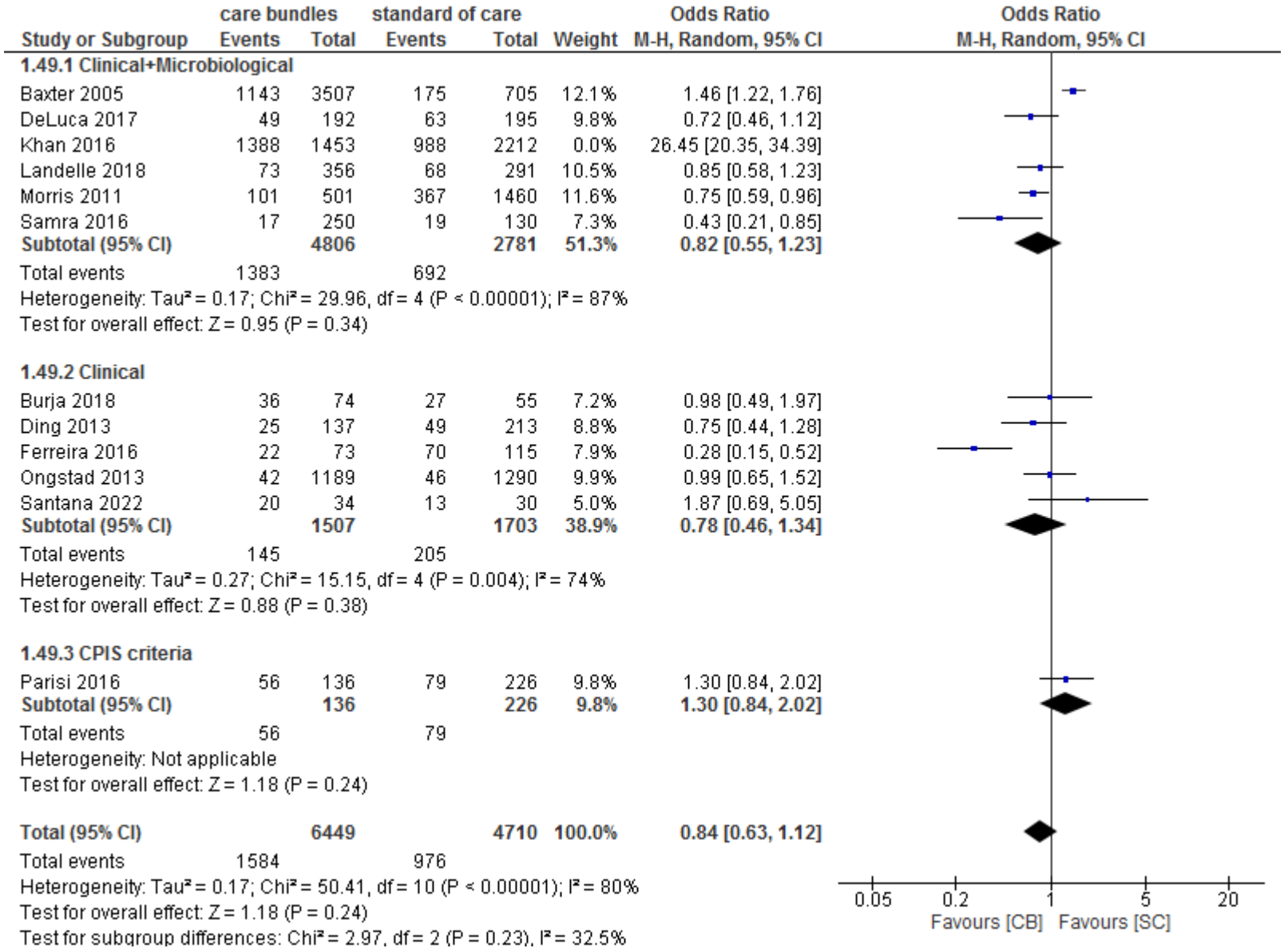


Figure S6. Forest plot on **ICU mortality** in subjects treated with care bundles or standard care.

A) Forest plot on ICU mortality by baseline measures subgroups.