Preventing Ventilator-Associated Pneumonia: Review of the Evidence

Hong Kong Symposium on Prevention of Healthcare-associated Infections in Hospitals and Community Institutions

January 19, 2019

Michael Klompas MD, MPH, FIDSA, FSHEA

Harvard Medical School, Harvard Pilgrim Health Care Institute, and Brigham and Women's Hospital, Boston, MA

Disclosures

- **Grant funding**
  - Centers for Disease Control and Prevention
  - Massachusetts Department of Public Health
- **Royalties**
  - UpToDate

Ventilator-associated pneumonia

- Affects ~5-10% of ventilated patients
- Increases ICU length of stay by ~4-7 days
- Increases hospital length of stay by ~14 days
- Crude mortality rate 30-50%
- Attributable mortality 8-12%
- Adds ~$10,000 to $40,000 to cost of hospital stay

Safdar et al, *Crit Care Med* 2005; 33:2184
Tejerina et al, *J Crit Care* 2006; 21:56
Muscedere et al, *J Crit Care* 2008;23:5-10
Eber et al, *Arch Intern Med* 2010;170:347-353
Nguile-Makao et al, *Intensive Care Med* 2010;36:781-9
Melsen et al, *Lancet Infect Dis* 2013;13:665-671
Kollef et al., *Infection Control Hosp Epidemiol* 2012;33:250-256
Ohannessian et al. *Crit Care Med* 2018;46:1093-1098

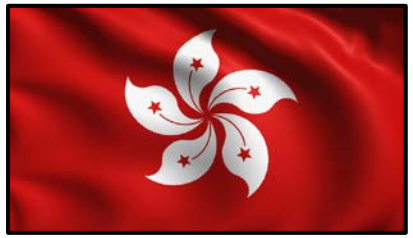

VAP?
NOT ON MY WATCH.
from doctorrw.blogspot.com

Guidelines for Preventing Health-Care–Associated Pneumonia, 2003

Defining, treating and preventing hospital acquired pneumonia: European perspective

Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Prevention☆

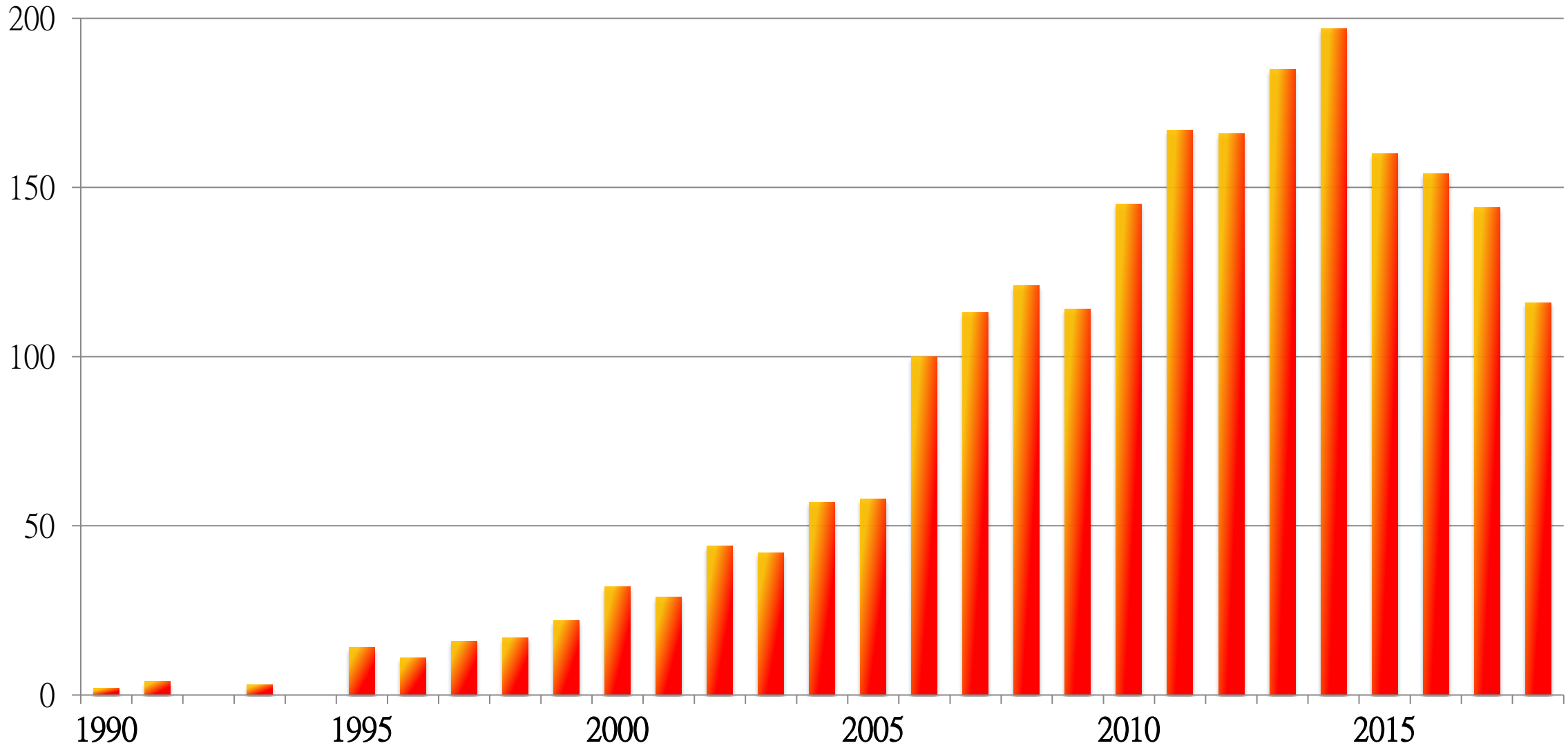
Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals



Recommendations on Prevention of Ventilator-Associated Pneumonia

Count of VAP Prevention Publications by Year

PubMed, 1990-2018



Potential Strategies to Prevent VAP

1. Avoid intubation
2. Minimize sedation
3. Daily interruption of sedation
4. Spontaneous breathing trials
5. Early mobility
6. Head of bed elevation
7. Trendelenburg position
8. Subglottic secretion drainage
9. Maintain ETT cuff pressure
10. Tapered endotracheal cuffs
11. Ultrathin polyurethane cuffs
12. Avoid inhalers
13. Closed suctioning systems
14. Avoid patient transport
15. Tight glycemic control
16. Improve hand hygiene
17. Regular oral care
18. Toothbrushing / scaling
19. Oral care with chlorhexidine
20. Oral decontamination
21. Digestive decontamination
22. Use probiotics
23. Early enteral feeding
24. Acidify gastric contents
25. Avoid gastric distention
26. Silver-coated ETT tubes
27. Mucous shaver
28. Early tracheostomy
29. Change vent circuits only when soiled
30. Saline instillation prior to suctioning
31. Non-invasive positive pressure ventilation
32. High flow O2 by nasal cannula
33. Prophylactic antibiotics
34. Even to negative fluid balance
35. Minimize blood tranfusions
36. Avoid paralytics
37. Conduct VAP surveillance
38. Educate staff
39. Provide feedback to staff on rates and processes
40. Bundle interventions

Strategic Framework to Prevent VAP

Avoid intubation if possible

- High flow O2 by nasal cannula
- Non-invasive positive pressure ventilation

Minimize duration of intubation

- Minimize sedation
- Spontaneous awakening trials
- Spontaneous breathing trials
- Early mobility

Reduce colonization of the aerodigestive tract

- Regular oral care
- Oral antiseptics
- Probiotics
- Oral / digestive decontamination

Minimize aspiration of secretions around endotracheal tube cuff

- Head of bed elevation
- Subglottic secretion drainage
- Maintain cuff pressure
- Novel cuff materials & shapes

Minimize contamination of equipment

- Silver-coated endotracheal tubes
- Mucous shaver
- Change vent circuits only when soiled

How do we choose from this list?

What works?

What should we prioritize?

The VAP Prevention Paradox

	VAP Rates	Vent Days	ICU Days	Hospital Days	Death
Oral care with chlorhexidine	↓	—	—	—	—
Silver-coated endotracheal tubes	↓	—	—	—	—
Subglottic secretion drainage	↓	—	—	—	—
Head-of-bed elevation	↓	—	—	—	—

Critical Care 2009;13:315

Many strategies lower VAP rates but have no impact on other outcomes!

Why the mismatch?

Reasons for the Prevention Paradox

VAP diagnosis is subjective

The case of oral care with chlorhexidine

VAP diagnosis is non-specific

The case of silver-coated ETTs & subglottic secretion drainage

Many VAP studies are under-powered

The case of head of bed elevation

Reasons for the Prevention Paradox

VAP diagnosis is subjective

The case of oral care with chlorhexidine

VAP diagnosis is non-specific

The case of silver-coated ETTs & subglottic secretion drainage

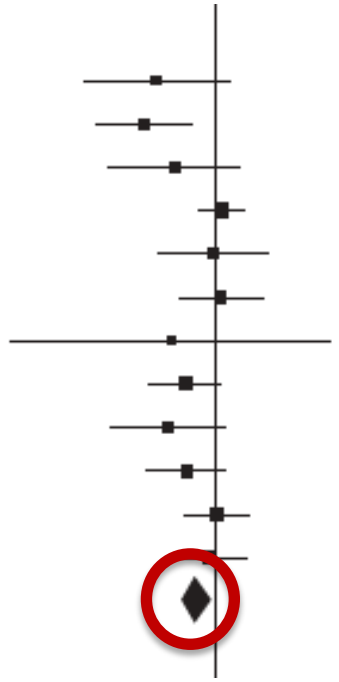
Many VAP studies are under-powered

The case of head of bed elevation

Oral Care with Chlorhexidine

Meta-analysis of Randomized Studies: *lower* VAP rates

Chlorhexidine					
De Riso et al (1996)[18]	3	173	9	180	3·8%
Fourrier et al (2000)[13]	5	30	18	30	7·0%
Houston et al (2002)[20]	4	270	9	291	4·4%
MacNaughton et al (2004)[22]	32	91	28	88	14·1%
Grap et al (2004)[14]	4	7	3	5	5·9%
Fourrier et al (2005)[19]	13	114	12	114	8·3%
Bopp et al (2006)[17]	0	2	1	3	0·9%
Koeman et al (2006)[21]	13	127	23	130	9·9%
Tantipong et al (2008)[23]	5	102	12	105	5·5%
Scannapieco et al (2009)[26]	14	116	12	59	8·8%
Bellisimo-Rodriguez et al (2009)[24]	16	64	17	69	10·6%
Panchabhai et al (2009)[25]	14	88	15	83	9·4%
Subtotal (95% CI)		**1184**		**1157**	**88·5%**
Total events	123		159		
Heterogeneity: τ^2=0·06, χ^2=15·54, df=11 (p=0·16); I^2=29%					
Test for overall effect: Z=2·40 (p=0·02)					



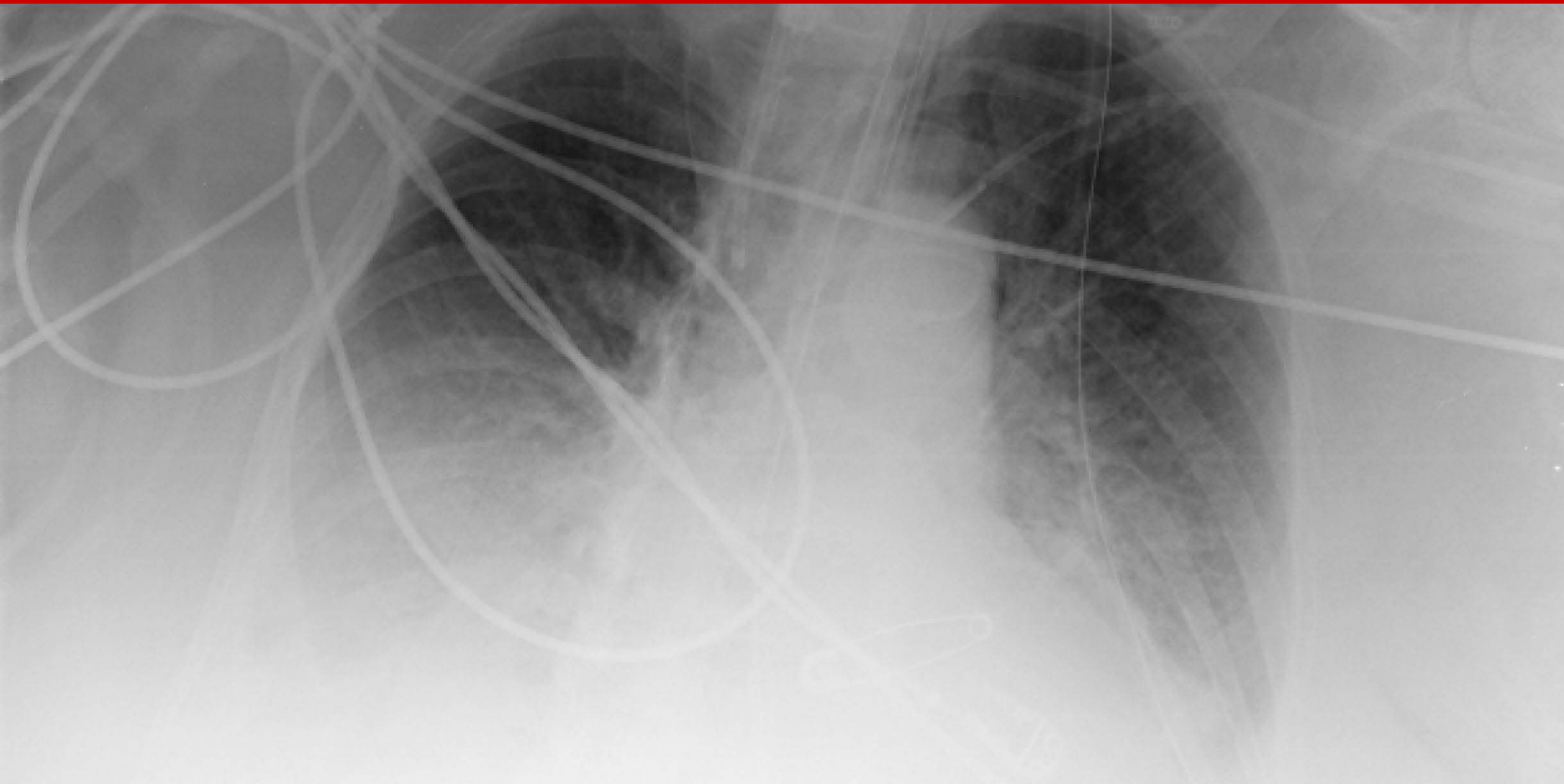
	0·35 (0·10–1·26)
	0·28 (0·12–0·65)
	0·48 (0·15–1·54)
	1·11 (0·73–1·67)
	0·95 (0·36–2·49)
	1·08 (0·52–2·27)
	0·44 (0·03–7·52)
	0·58 (0·31–1·09)
	0·43 (0·16–1·17)
	0·59 (0·29–1·20)
	1·01 (0·56–1·83)
	0·88 (0·45–1·71)
	0·72 (0·55–0·94)

Lower VAP Rates

Risk Ratio 0.72 (0.55-0.94)

Lancet Infectious Dis 2011;11:845

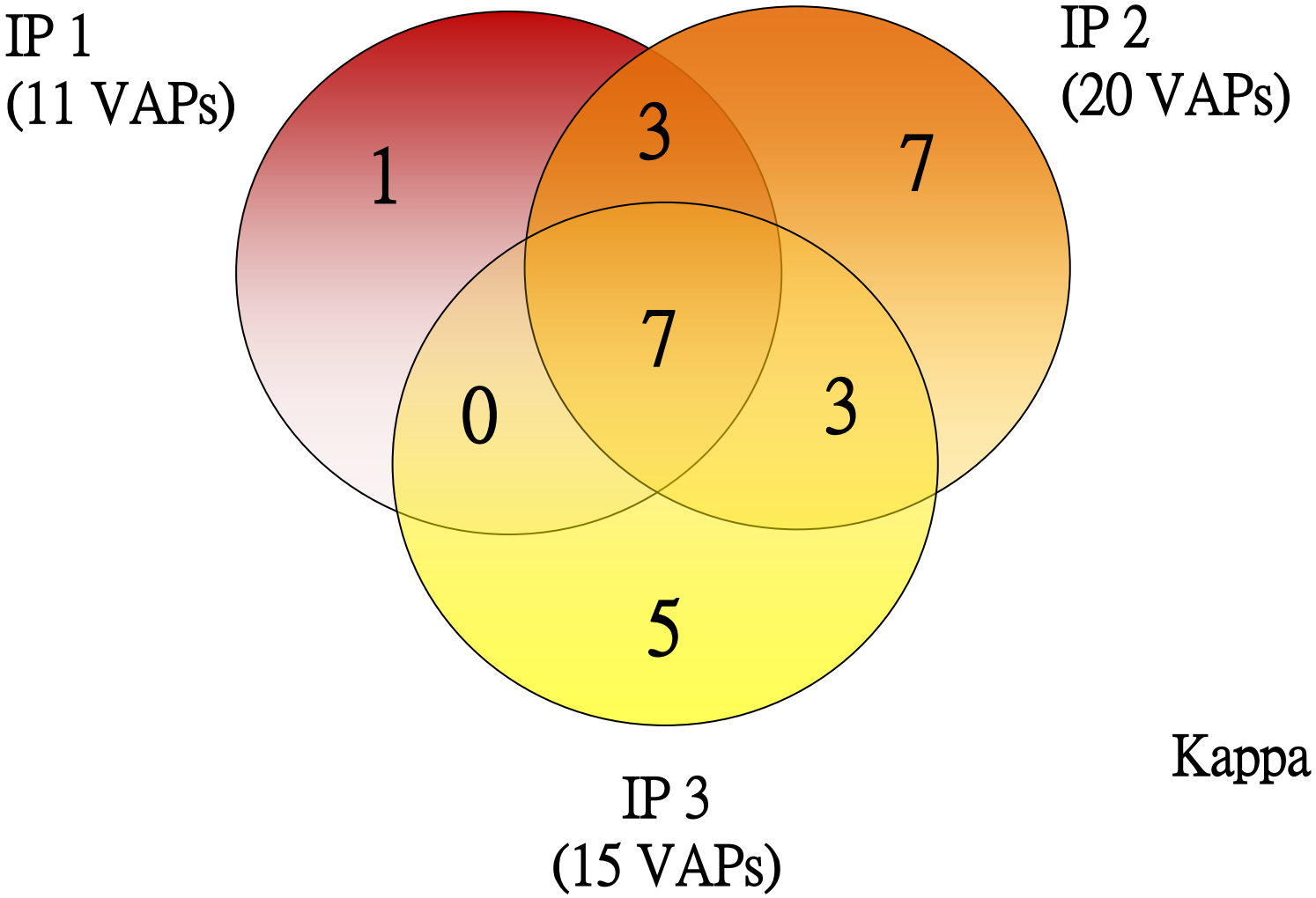
Does this patient have VAP?



Are there more secretions today?

Interobserver Agreement in VAP Diagnosis

50 ventilated patients with respiratory deterioration



Kappa = 0.40

Am J Infection Control 2010:38:237

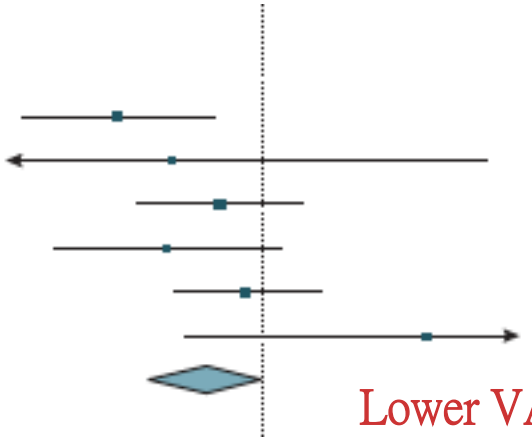
VAP Prevention Studies are at High Risk for Bias

Especially Open Label studies

Open Label vs Double Blind Studies

Open Label Randomized Controlled Trials:

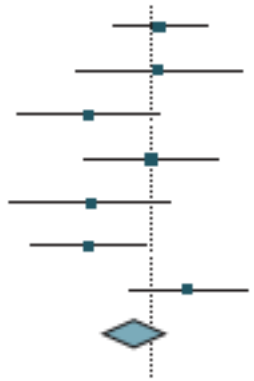
Open-label Studies					
Fourrier et al,[20] 2000	5	30	18	30	0.28 (0.12-0.65)
Bopp et al,[22] 2006	0	2	1	3	0.44 (0.03-7.52)
Jafari et al,[19] 2007	9	40	13	40	0.69 (0.33-1.43)
Tantipong et al,[24] 2008	5	102	12	105	0.43 (0.16-1.17)
Panchabhai et al,[26] 2009	14	88	15	83	0.88 (0.45-1.71)
Berry et al,[28] 2011	4	71	1	78	4.39 (0.50-38.39)
Subtotal	37	333	60	339	0.61 (0.35-1.04)



Lower VAP Rates!
RR 0.61 (0.35-1.04)

Double-Blind Randomized Controlled Trials:

Macnaughton et al,[18] 2004	32	91	28	88	1.11 (0.73-1.67)
Fourrier et al,[21] 2005	13	114	12	114	1.08 (0.52-2.27)
Koeman et al,[23] 2006	13	127	23	130	0.58 (0.31-1.09)
Bellissimo-Rodrigues et al,[25] 2009	16	64	17	69	1.01 (0.56-1.83)
Scannapieco et al,[27] 2009	14	116	12	59	0.59 (0.29-1.20)
Ozcaka et al,[30] 2012	12	32	22	34	0.58 (0.35-0.97)
Meinberg et al,[23] 2012	18	28	11	24	1.40 (0.84-2.35)
Subtotal	118	572	125	518	0.88 (0.66-1.16)



No Difference!
RR 0.88 (0.66-1.16)

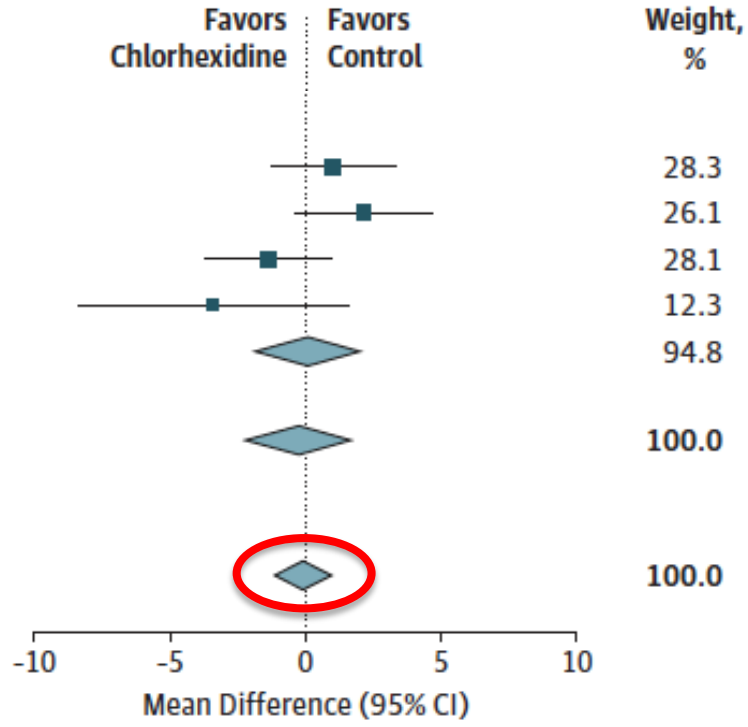
JAMA Internal Med 2014;174:751

Need to look at objective outcomes

Duration of Mechanical Ventilation

Randomized trials of oral care with chlorhexidine vs control solution

Study or Subgroup	Chlorhexidine Mean (SD)	Chlorhexidine Total	Control Mean (SD)	Control Total	Mean Difference (95% CI)	Weight, %
Double-blind Studies						
Fourrier et al,[21] 2005	11.7 (8.7)	114	10.6 (8.7)	114	1.10 (-1.16 to 3.36)	28.3
Koeman et al,[23] 2006	9.2 (12)	127	7 (8.1)	130	2.20 (-0.31 to 4.71)	26.1
Scannapieco et al,[27] 2009	8.4 (5.2)	50	9.7 (6.3)	49	-1.30 (-3.58 to 0.98)	28.1
Ozcaka et al,[30] 2012	9 (8.3)	32	12.3 (11.9)	34	-3.30 (-8.23 to 1.63)	12.3
Subtotal		323		327	0.13 (-1.90 to 2.17)	94.8
Total		**353**		**357**	**-0.15 (-2.18 to 1.89)**	**100.0**
All Studies						
Total		**838**		**826**	**0.01 (-1.12 to 1.14)**	**100.0**



No Difference!

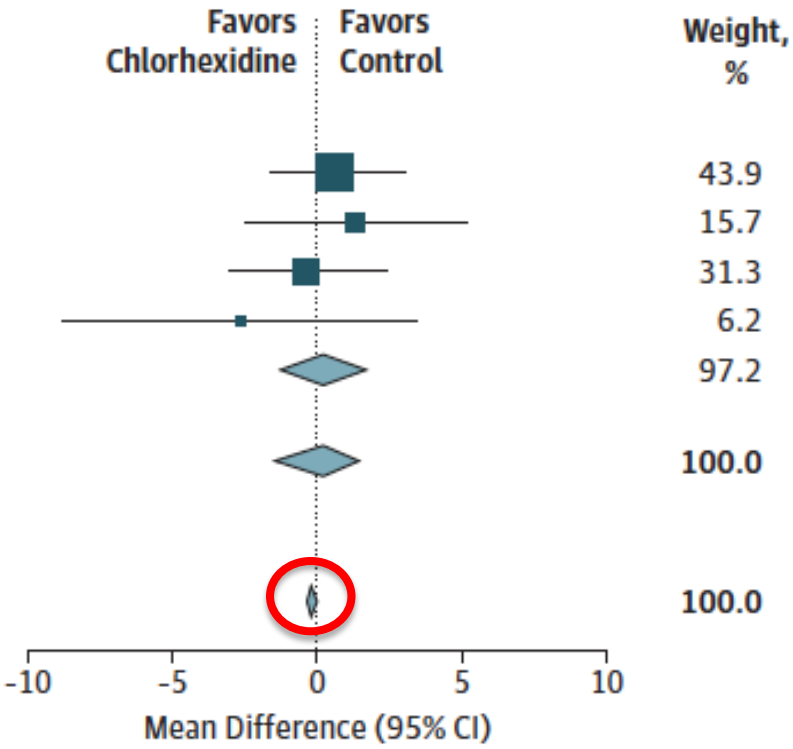
Mean Difference 0.01 days (-1.12 to 1.14)

JAMA Internal Med 2014;174:751-761

ICU Length of Stay

Randomized trials of oral care with chlorhexidine vs control solution

Study or Subgroup	Chlorhexidine Mean (SD)	Chlorhexidine Total	Control Mean (SD)	Control Total	Mean Difference (95% CI)	Weight, %
Double-blind Studies						
Fourrier et al,[21] 2005	14 (8.5)	114	13.3 (8.8)	114	0.70 (-1.55 to 2.95)	43.9
Koeman et al,[23] 2006	13.8 (17.4)	127	12.5 (12.9)	130	1.30 (-2.45 to 5.05)	15.7
Scannapieco et al,[27] 2009	11 (6.8)	50	11.3 (6.7)	49	-0.30 (-2.96 to 2.36)	31.3
Ozcaka et al,[30] 2012	12.7 (11.3)	32	15.4 (13.5)	34	-2.70 (-8.69 to 3.29)	6.2
Subtotal		323		327	0.26 (-1.25 to 1.77)	97.2
Total		**353**		**357**	**0.08 (-1.41 to 1.57)**	**100.0**
All Studies						
Total		**838**		**826**	**-0.10 (-0.25 to 0.05)**	**100.0**



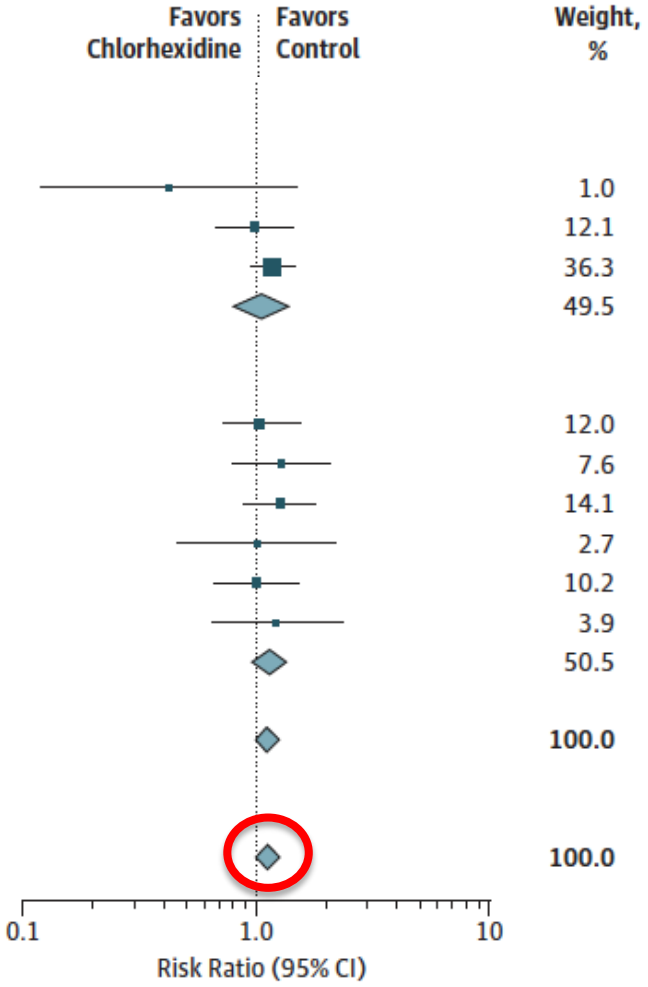
No Difference!

Mean Difference -0.10 days (-0.25 to 0.05)

JAMA Internal Med 2014;174:751-761

Mortality

Study or Subgroup	Chlorhexidine Events	Chlorhexidine Patients	Control Events	Control Patients	Risk Ratio (95% CI)	Weight, %
Non-Cardiac Surgery Studies						
Open-label Studies						
Fourrier et al,[20] 2000	3	30	7	30	0.43 (0.12-1.50)	1.0
Tantipong et al,[24] 2008	36	102	37	105	1.00 (0.69-1.45)	12.1
Panchabhai et al,[26] 2009	64	88	51	83	1.18 (0.96-1.46)	36.3
Subtotal	103	220	95	218	1.06 (0.80-1.41)	49.5
Double-blind Studies						
Macnaughton et al,[18] 2004	36	91	33	88	1.05 (0.73-1.53)	12.0
Fourrier et al,[21] 2005	31	114	24	114	1.29 (0.81-2.06)	7.6
Koeman et al,[23] 2006	49	127	39	130	1.29 (0.91-1.81)	14.1
Scannapieco et al,[27] 2009	16	97	8	49	1.01 (0.46-2.20)	2.7
Ozcaka et al,[30] 2012	19	32	20	34	1.01 (0.68-1.51)	10.2
Meinberg et al,[29] 2012	13	28	9	24	1.24 (0.65-2.38)	3.9
Subtotal	164	489	133	439	1.15 (0.96-1.38)	50.5
Total	**267**	**709**	**228**	**657**	**1.13 (0.99-1.29)**	**100.0**
All Studies						
Total	**283**	**1637**	**247**	**1597**	**1.13 (0.99-1.28)**	**100.0**



Trend to Higher Mortality!

RR 1.13 (0.99 to 1.28)

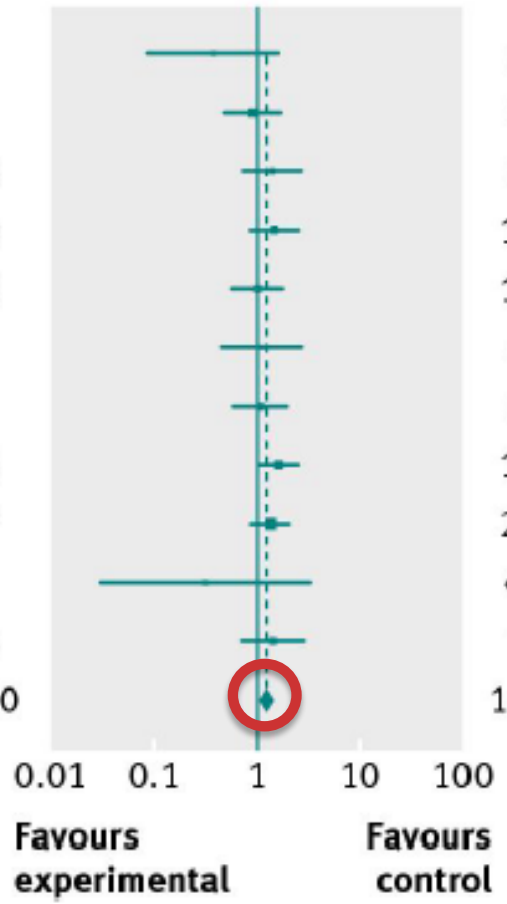
JAMA Internal Med 2014;174:751-761

Second Meta-Analysis of RCTs: *Significantly Higher* Mortality

Study	No of events/total Treatment	Control	Mortality Odds ratio, M-H random (95% CI)	Weight (%)	Mortality Odds ratio, M-H random (95% CI)
Fourier 2000	3/30	7/30		2	0.37 (0.08 to 1.58)
MacNaughton 2004	29/101	29/93		8	0.89 (0.48 to 1.64)
Fourrier 2005	31/114	24/114		9	1.40 (0.76 to 2.58)
Koeman 2006	49/127	39/130		12	1.47 (0.87 to 2.46)
Tantipong 2008	36/102	37/105		10	1.00 (0.57 to 1.77)
Scannapieco 2009	19/116	9/59		4	1.09 (0.46 to 2.58)
Bellissimo-Rodrigues 2009	35/98	33/96		9	1.06 (0.59 to 1.91)
Munro 2009	69/275	47/272		18	1.60 (1.06 to 2.43)
Panchabhai 2009	78/224	70/247		21	1.35 (0.91 to 2.00)
Cabov 2010	1/30	3/30		<1	0.31 (0.03 to 3.17)
Berry 2011	17/71	28/154		7	1.42 (0.72 to 2.80)
Total (95% CI)	367/1288	326/1330		100	1.25 (1.05 to 1.50)

Test for heterogeneity: $\tau^2=0.00$, $\chi^2=8.41$, df=10, P=0.59, $I^2=0\%$

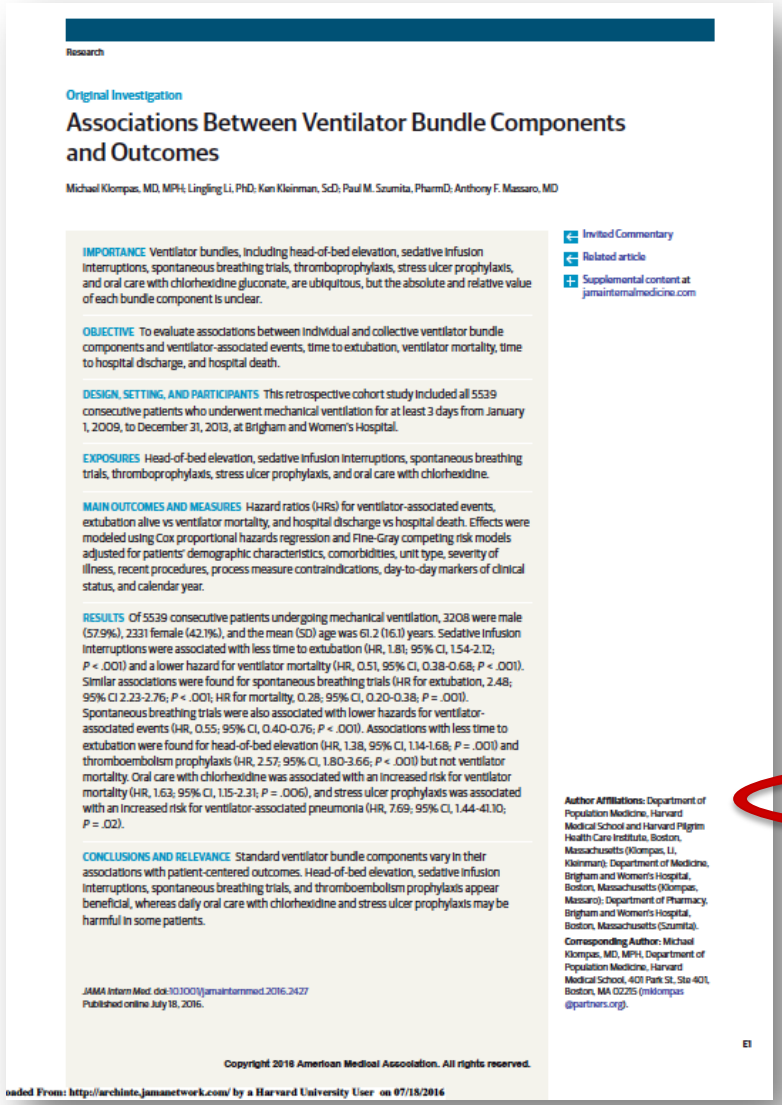
Test for overall effect: z=2.47, P=0.01



Odds Ratio
1.25 (1.05-1.50)

BMJ 2014;348:g2197

Independent Signal



Research

Original Investigation

Associations Between Ventilator Bundle Components and Outcomes

Michael Klompas, MD, MPH; Lingling Li, PhD; Ken Kleinman, ScD; Paul M. Szumita, PharmD; Anthony F. Massaro, MD

IMPORTANCE Ventilator bundles, including head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with chlorhexidine gluconate, are ubiquitous, but the absolute and relative value of each bundle component is unclear.

OBJECTIVE To evaluate associations between individual and collective ventilator bundle components and ventilator-associated events, time to extubation, ventilator mortality, time to hospital discharge, and hospital death.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included all 5539 consecutive patients who underwent mechanical ventilation for at least 3 days from January 1, 2009, to December 31, 2013, at Brigham and Women's Hospital.

EXPOSURES Head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with chlorhexidine.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for ventilator-associated events, extubation alive vs ventilator mortality, and hospital discharge vs hospital death. Effects were modeled using Cox proportional hazards regression and Fine-Gray competing risk models adjusted for patients' demographic characteristics, comorbidities, unit type, severity of illness, recent procedures, process measure contraindications, day-to-day markers of clinical status, and calendar year.

RESULTS Of 5539 consecutive patients undergoing mechanical ventilation, 3208 were male (57.9%), 2331 female (42.1%), and the mean (SD) age was 61.2 (16.1) years. Sedative infusion interruptions were associated with less time to extubation (HR, 1.81; 95% CI, 1.54-2.12; $P < .001$) and a lower hazard for ventilator mortality (HR, 0.51; 95% CI, 0.38-0.68; $P < .001$). Similar associations were found for spontaneous breathing trials (HR for extubation, 2.48; 95% CI 2.23-2.76; $P < .001$; HR for mortality, 0.28; 95% CI, 0.20-0.38; $P = .001$). Spontaneous breathing trials were also associated with lower hazards for ventilator-associated events (HR, 0.55; 95% CI, 0.40-0.76; $P < .001$). Associations with less time to extubation were found for head-of-bed elevation (HR, 1.38, 95% CI, 1.14-1.68; $P = .001$) and thromboembolism prophylaxis (HR, 2.57; 95% CI, 1.80-3.66; $P < .001$) but not ventilator mortality. Oral care with chlorhexidine was associated with an increased risk for ventilator mortality (HR, 1.63; 95% CI, 1.15-2.31; $P = .006$), and stress ulcer prophylaxis was associated with an increased risk for ventilator-associated pneumonia (HR, 7.69; 95% CI, 1.44-41.10; $P = .02$).

CONCLUSIONS AND RELEVANCE Standard ventilator bundle components vary in their associations with patient-centered outcomes. Head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, and thromboembolism prophylaxis appear beneficial, whereas daily oral care with chlorhexidine and stress ulcer prophylaxis may be harmful in some patients.

JAMA Intern Med. doi:10.1001/jamainternmed.2016.2427
Published online July 18, 2016.

Invited Commentary
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Author Affiliations: Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Klompas, Li, Kleinman); Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Klompas, Massaro); Department of Pharmacy, Brigham and Women's Hospital, Boston, Massachusetts (Szumita).
Corresponding Author: Michael Klompas, MD, MPH, Department of Population Medicine, Harvard Medical School, 401 Park St, Ste 401, Boston, MA 02215 (mklompas@partners.org).

Retrospective cohort analysis
5,539 patients on mechanical ventilation
adjusted for comorbidities, severity of illness, contraindications, etc.

Spontaneous breathing trials

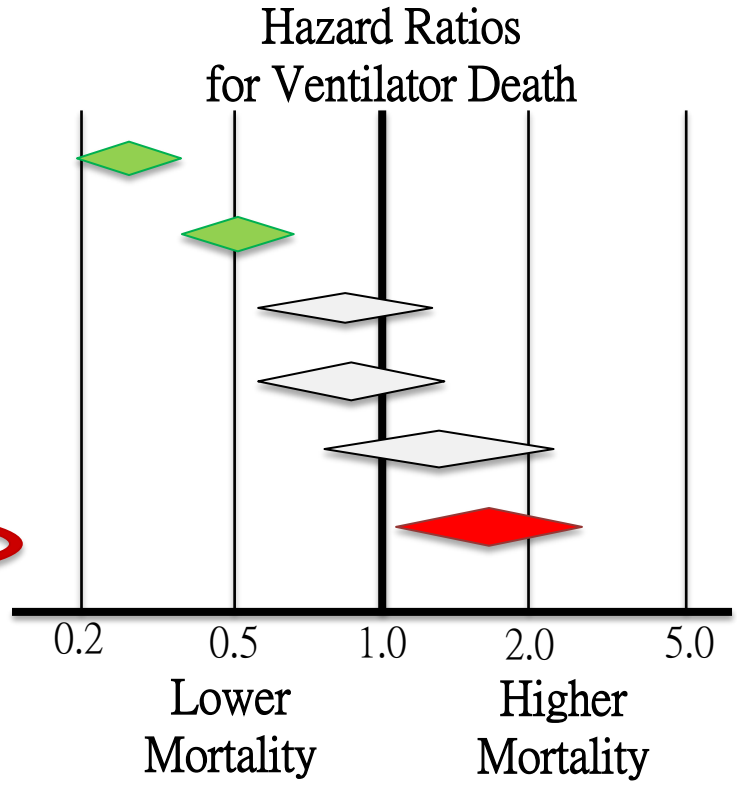
Spontaneous awakening trials

Head of bed elevation

Stress ulcer prophylaxis

Thromboprophylaxis

Oral care with chlorhexidine



JAMA Internal Med 2016;176:1277-1283

But what’ s the mechanism?

Oral Ulcers Associated with 2% Chlorhexidine

Bleeding Ulcer

White Plaques

Intensive Care Med 2016;42:620-621

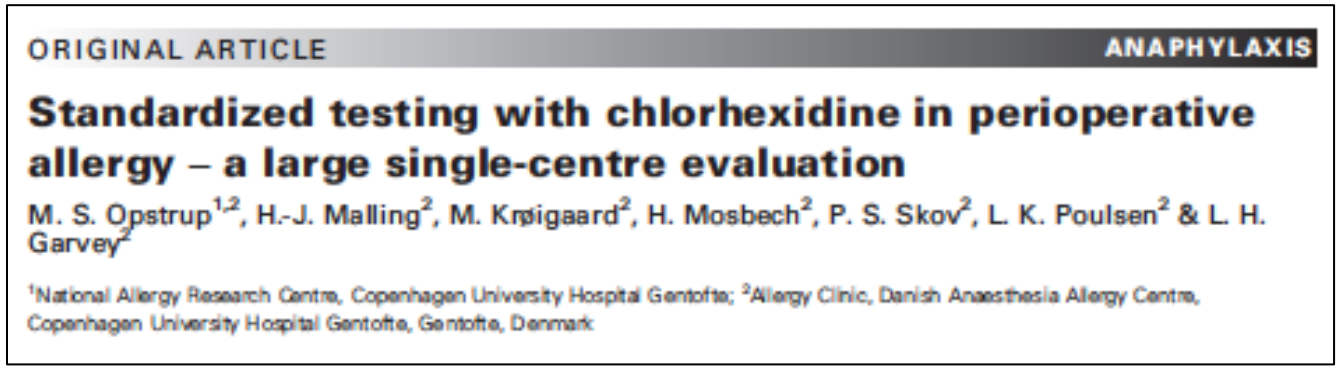
Oral Ulcers Associated with 2% Chlorhexidine

Bleeding Mouth

Dry Tongue, Apthous Lesions

Intensive Care Med 2016;42:620-621

Case Reports of Allergies and Anaphylaxis



ORIGINAL ARTICLE ANAPHYLAXIS

Standardized testing with chlorhexidine in perioperative allergy – a large single-centre evaluation

M. S. Opstrup[1,2], H.-J. Malling[2], M. Krøigaard[2], H. Mosbech[2], P. S. Skov[2], L. K. Poulsen[2] & L. H. Garvey[2]

[1]National Allergy Research Centre, Copenhagen University Hospital Gentofte; [2]Allergy Clinic, Danish Anaesthesia Allergy Centre, Copenhagen University Hospital Gentofte, Gentofte, Denmark

9% of perioperative allergic reactions attributed to chlorhexidine

Acta Anaesthesiol Scand 2001; 45: 1290–1294

ACTA ANAESTHESIOLOGICA SCANDINAVICA
ISSN 0001-5172

Case Report

Anaphylactic reactions in anaesthetised patients – four cases of chlorhexidine allergy

L. H. GARVEY[1], J. ROED-PETERSEN[2] and B. HUSUM[1]
Departments of [1]Anaesthesiology and [2]Dermatology, Gentofte University Hospital, Copenhagen, Denmark

Case reports of anaphylaxis

Allergy 2014;69(10):1390-1396
Acta Anaesthesiol Scand 2001;45:1290-1294

Case Reports of ARDS following Aspiration

Chlorhexidine Gluconate Ingestion Resulting in Fatal Respiratory Distress Syndrome

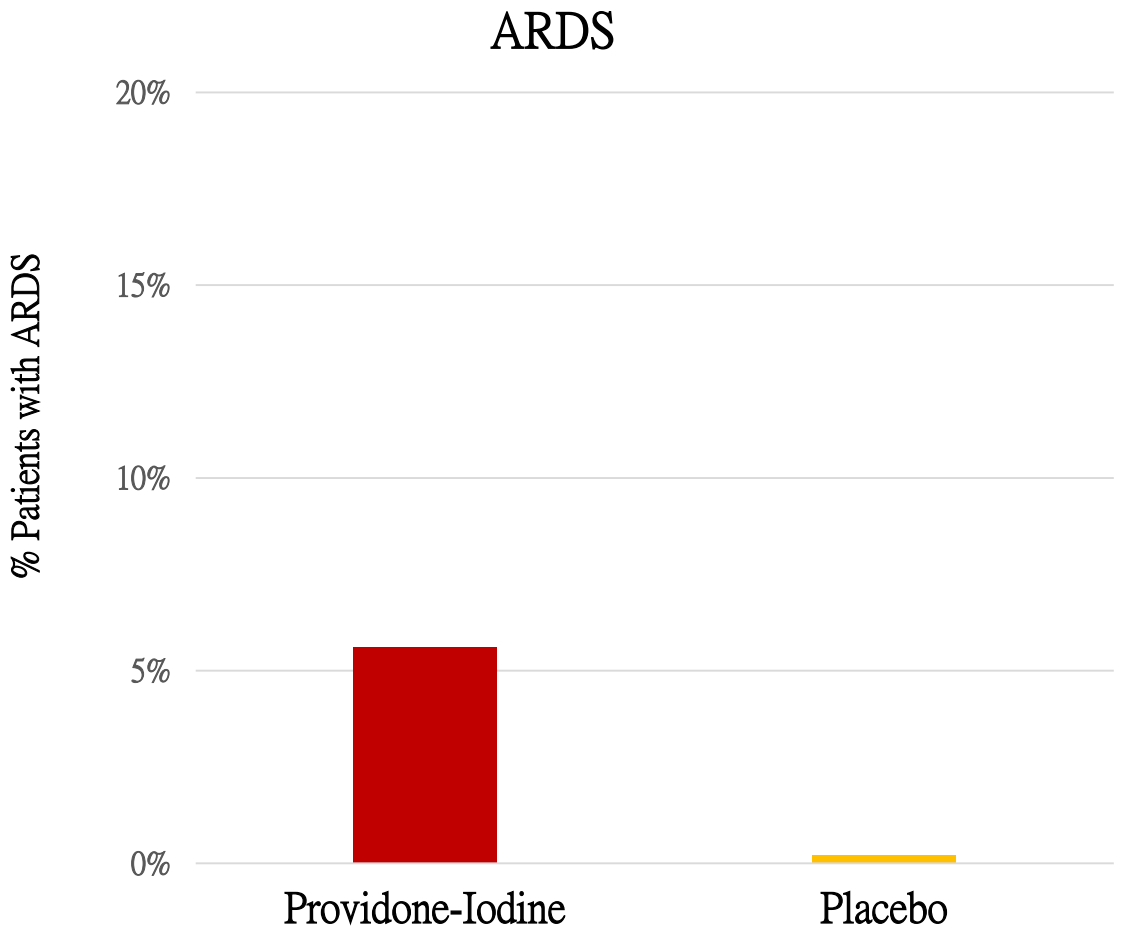
Kiyotaka Hirata PhD
Department of Pharmacy, Nippon Medical School Hospital, 1-1-5 Sendagi Bunkyo-ku, Tokyo, 113-8603, Japan

Akira Kurokawa MD
Department of Emergency and Critical Care Medicine, Nippon Medical School, Tama Nagayama Hospital, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan

Vet Hum Toxicol 2002;44:89-91

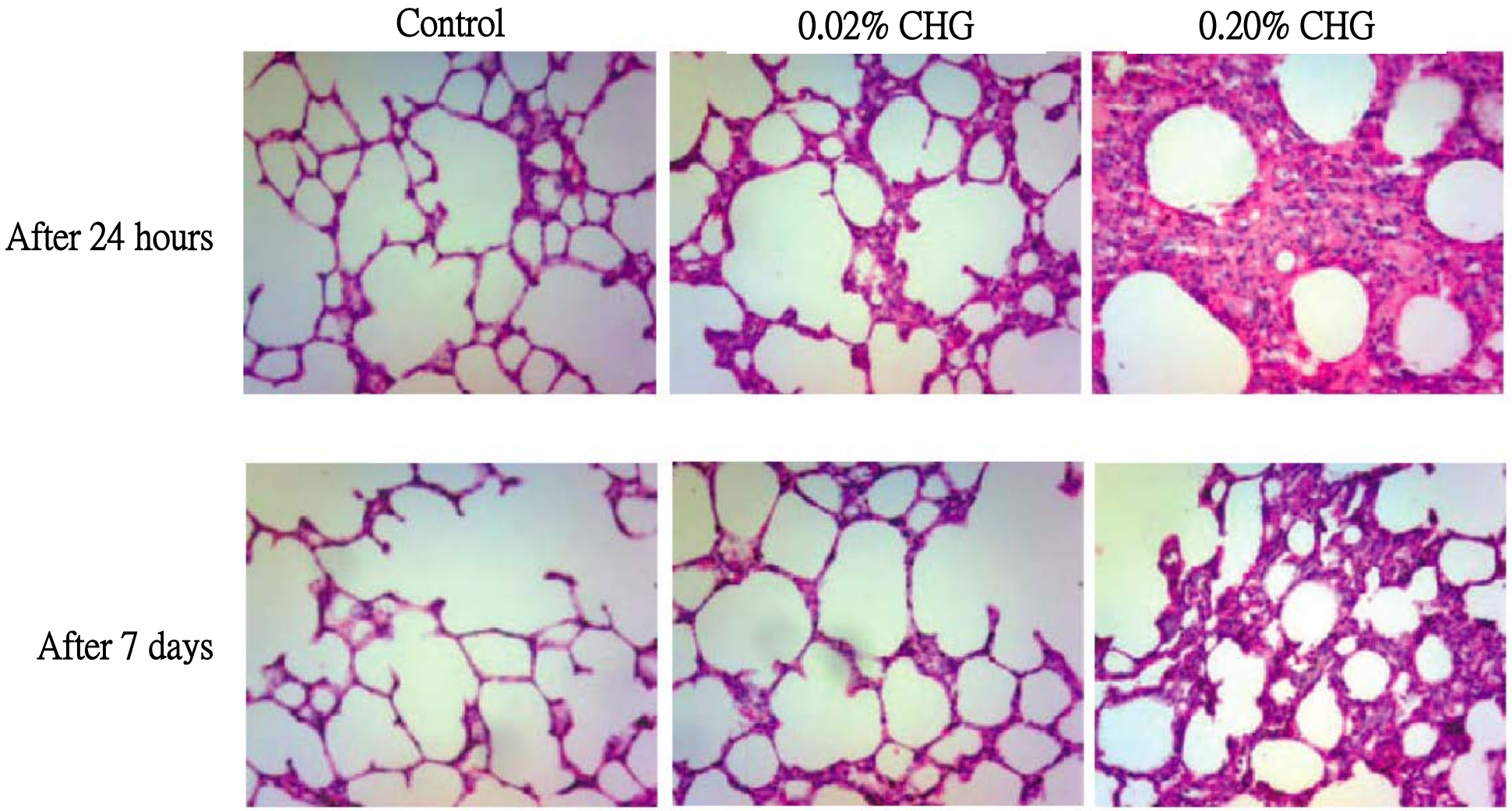
Aspiration of Oral Antiseptics and ARDS

Randomized controlled trial of providone-iodine vs placebo to prevent VAP



Crit Care Med 2014;42:1-8

Chlorhexidine Instillation into Rat Lungs



Human and Experimental Toxicology 2011;30:1795-1803

Reasons for the Prevention Paradox

VAP diagnosis is subjective

The case of oral care with chlorhexidine

VAP diagnosis is non-specific

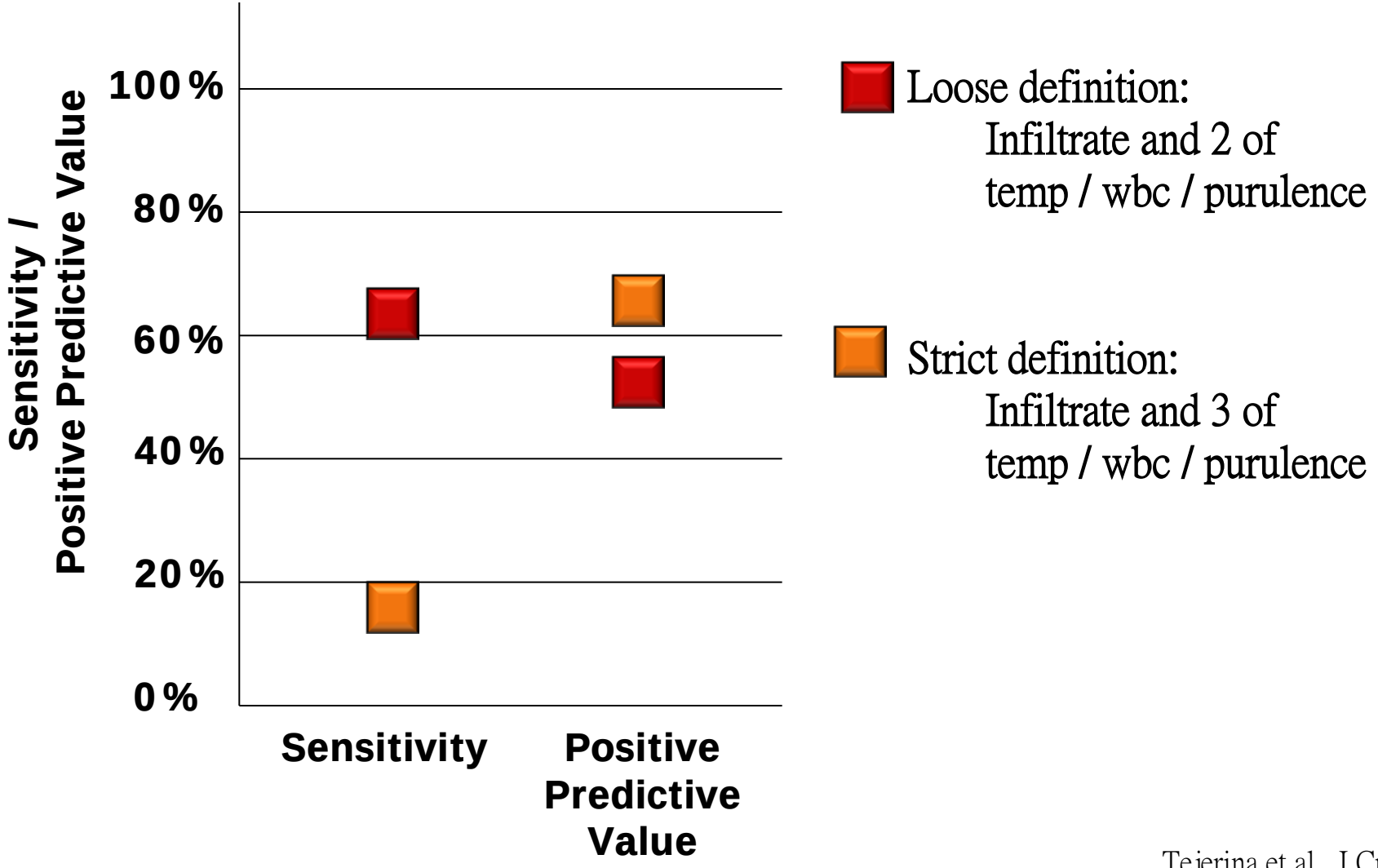
The case of silver-coated ETTs & subglottic secretion drainage

Many VAP studies are under-powered

The case of head of bed elevation

Accuracy of clinical diagnosis of VAP

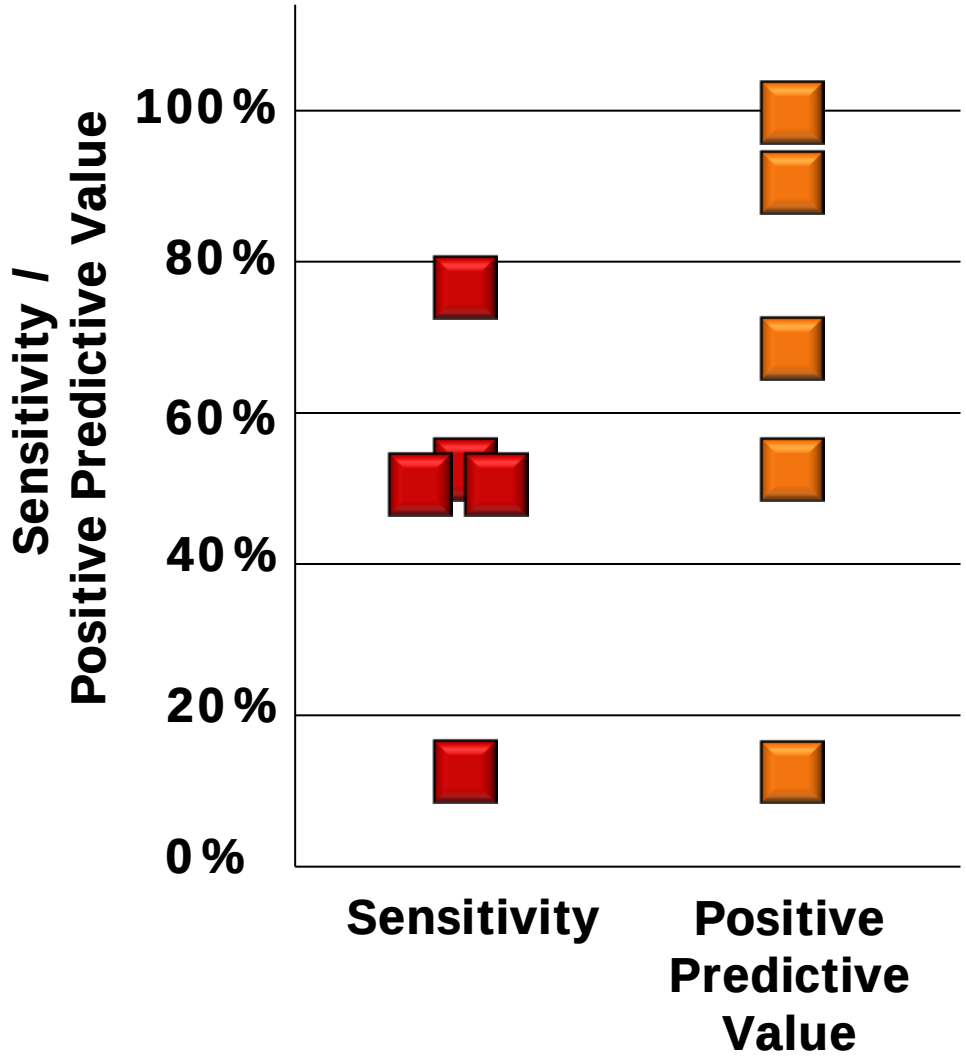
Relative to 253 autopsies



Tejerina et al., J Critical Care 2010;25:62

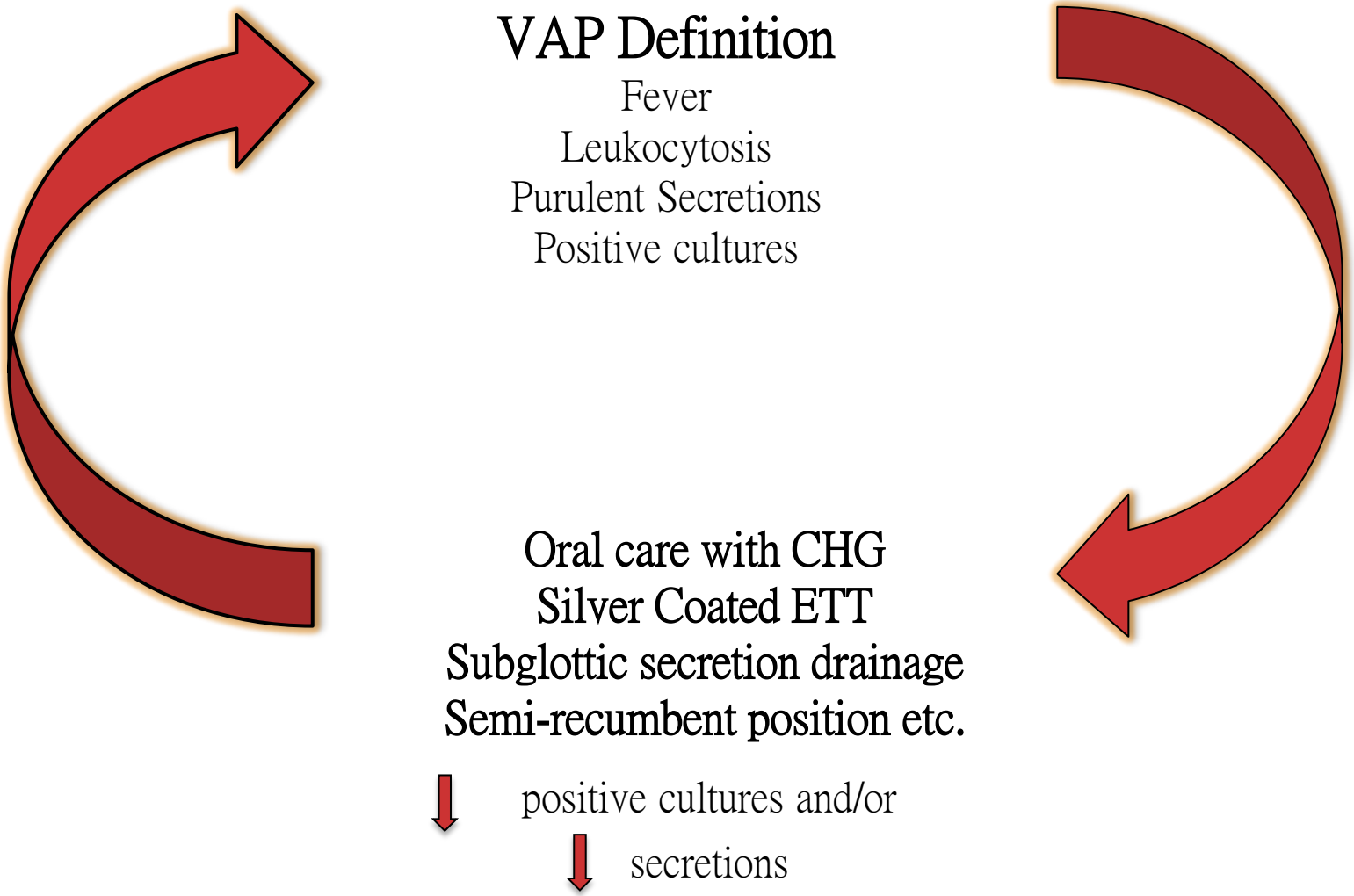
Accuracy of BAL cultures

Relative to histology



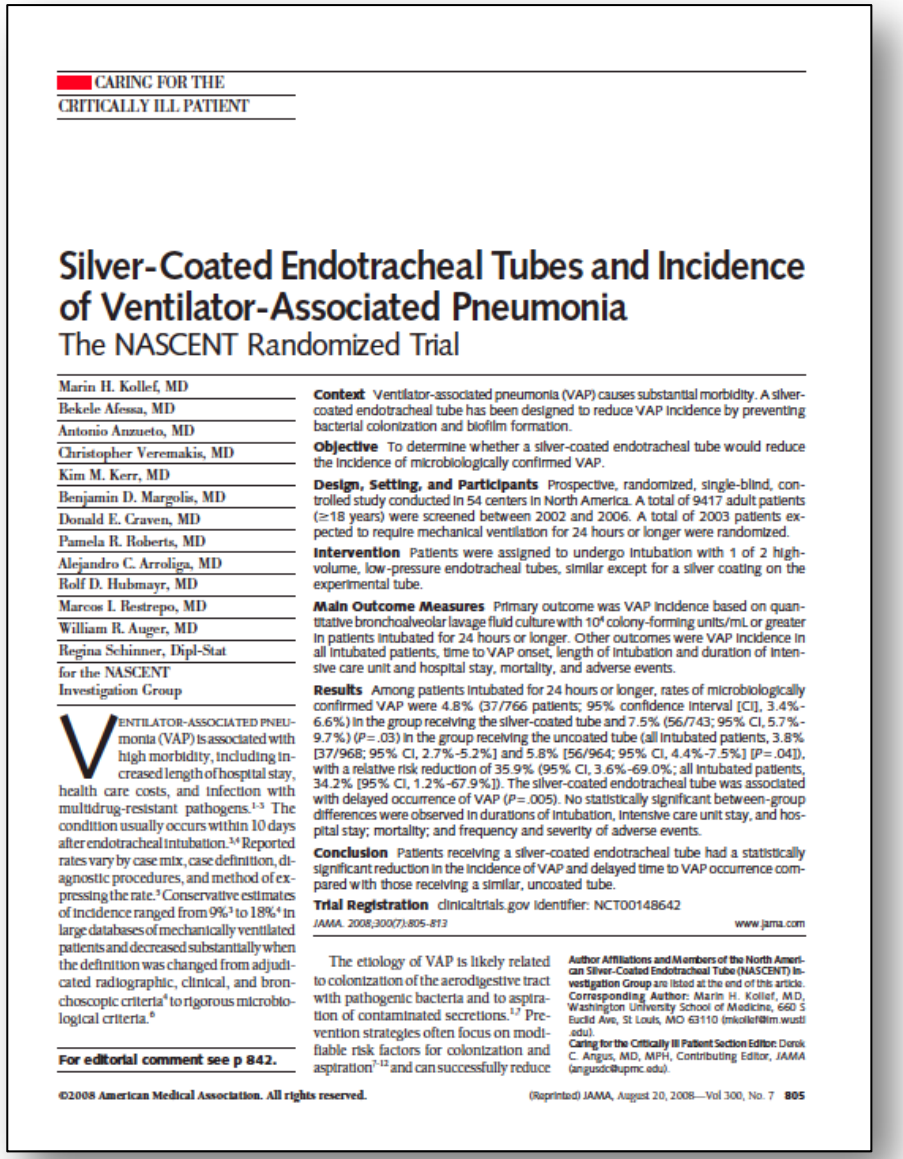
Kirtland, *Chest* 1997;112:445
Fabregas, *Thorax* 1999;54:867
Chastre, *Am Rev Respir Dis* 1984;130:924
Torres, *Am J Resp Crit Care Med* 1994;149:324
Marquette, *Am J Resp Crit Care Med* 1995;151:1878
Papazian, *Am J Resp Crit Care Med* 1995;152:1982

Circularity Between VAP Preventive Practices and the VAP Definition



This means that even studies with
Double Blinding &
Objective Diagnostic Criteria
are still at risk of bias

Silver-Coated Endotracheal Tubes



CARING FOR THE CRITICALLY ILL PATIENT

Silver-Coated Endotracheal Tubes and Incidence of Ventilator-Associated Pneumonia

The NASCENT Randomized Trial

Marin H. Kollef, MD
Bekele Afessa, MD
Antonio Anzueto, MD
Christopher Veremakis, MD
Kim M. Kerr, MD
Benjamin D. Margolis, MD
Donald E. Craven, MD
Pamela R. Roberts, MD
Alejandro C. Arroliga, MD
Rolf D. Hubmayr, MD
Marcos I. Restrepo, MD
William R. Auger, MD
Regina Schinner, Dipl-Stat
for the NASCENT Investigation Group

Context Ventilator-associated pneumonia (VAP) causes substantial morbidity. A silver-coated endotracheal tube has been designed to reduce VAP incidence by preventing bacterial colonization and biofilm formation.

Objective To determine whether a silver-coated endotracheal tube would reduce the incidence of microbiologically confirmed VAP.

Design, Setting, and Participants Prospective, randomized, single-blind, controlled study conducted in 54 centers in North America. A total of 9417 adult patients (≥18 years) were screened between 2002 and 2006. A total of 2003 patients expected to require mechanical ventilation for 24 hours or longer were randomized.

Intervention Patients were assigned to undergo intubation with 1 of 2 high-volume, low-pressure endotracheal tubes, similar except for a silver coating on the experimental tube.

Main Outcome Measures Primary outcome was VAP incidence based on quantitative bronchoalveolar lavage fluid culture with 10^4 colony-forming units/mL or greater in patients intubated for 24 hours or longer. Other outcomes were VAP incidence in all intubated patients, time to VAP onset, length of intubation and duration of intensive care unit and hospital stay, mortality, and adverse events.

Results Among patients intubated for 24 hours or longer, rates of microbiologically confirmed VAP were 4.8% (37/766 patients; 95% confidence interval [CI], 3.4%-6.6%) in the group receiving the silver-coated tube and 7.5% (56/743; 95% CI, 5.7%-9.7%) ($P=.03$) in the group receiving the uncoated tube (all intubated patients, 3.8% [37/968; 95% CI, 2.7%-5.2%] and 5.8% [56/964; 95% CI, 4.4%-7.5%] [$P=.04$]), with a relative risk reduction of 35.9% (95% CI, 3.6%-69.0%; all intubated patients, 34.2% [95% CI, 1.2%-67.9%]). The silver-coated endotracheal tube was associated with delayed occurrence of VAP ($P=.005$). No statistically significant between-group differences were observed in durations of intubation, intensive care unit stay, and hospital stay; mortality; and frequency and severity of adverse events.

Conclusion Patients receiving a silver-coated endotracheal tube had a statistically significant reduction in the incidence of VAP and delayed time to VAP occurrence compared with those receiving a similar, uncoated tube.

Trial Registration clinicaltrials.gov identifier: NCT00148642

JAMA. 2008;300(7):805-813 www.jama.com

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) is associated with high morbidity, including increased length of hospital stay, health care costs, and infection with multidrug-resistant pathogens.[1-3] The condition usually occurs within 10 days after endotracheal intubation.[3,4] Reported rates vary by case mix, case definition, diagnostic procedures, and method of expressing the rate.[3] Conservative estimates of incidence ranged from 9%[3] to 18%[4] in large databases of mechanically ventilated patients and decreased substantially when the definition was changed from adjudicated radiographic, clinical, and bronchoscopic criteria[4] to rigorous microbiological criteria.[6]

For editorial comment see p 842.

The etiology of VAP is likely related to colonization of the aerodigestive tract with pathogenic bacteria and to aspiration of contaminated secretions.[1,7] Prevention strategies often focus on modifiable risk factors for colonization and aspiration[7-12] and can successfully reduce

Author Affiliations and Members of the North American Silver-Coated Endotracheal Tube (NASCENT) Investigation Group are listed at the end of this article.
Corresponding Author: Marin H. Kollef, MD, Washington University School of Medicine, 660 S Euclid Ave, St Louis, MO 63110 (mkollef@im.wustl.edu).
Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA* (angusdc@upmc.edu).

- Randomized controlled trial of 2,003 patients to silver coated vs conventional endotracheal tubes
- VAP defined as present if quantitative BAL fluid culture with $>10^4$ colony forming units/mL

36%

fewer VAPs in patients randomized to silver-coated endotracheal tubes

JAMA 2008;300:805-813

Silver-Coated Endotracheal Tubes

Table 2. Incidence of Microbiologically Confirmed Ventilator-Associated Pneumonia (VAP)[a]

	Evaluable Patients With VAP, No./Total (%) [95% CI]	
	Silver-Coated Tube	Uncoated Tube
Microbiology[b]		
Staphylococcus aureus	9	16
Methicillin-resistant *S aureus*	3	7
Pseudomonas aeruginosa	8	11
Enterobacteriaceae	10	5
Yeast	5	7
Streptococcus species	4	7
Haemophilus influenzae	3	3
Acinetobacter baumannii	1	5
Other[c]	5	17

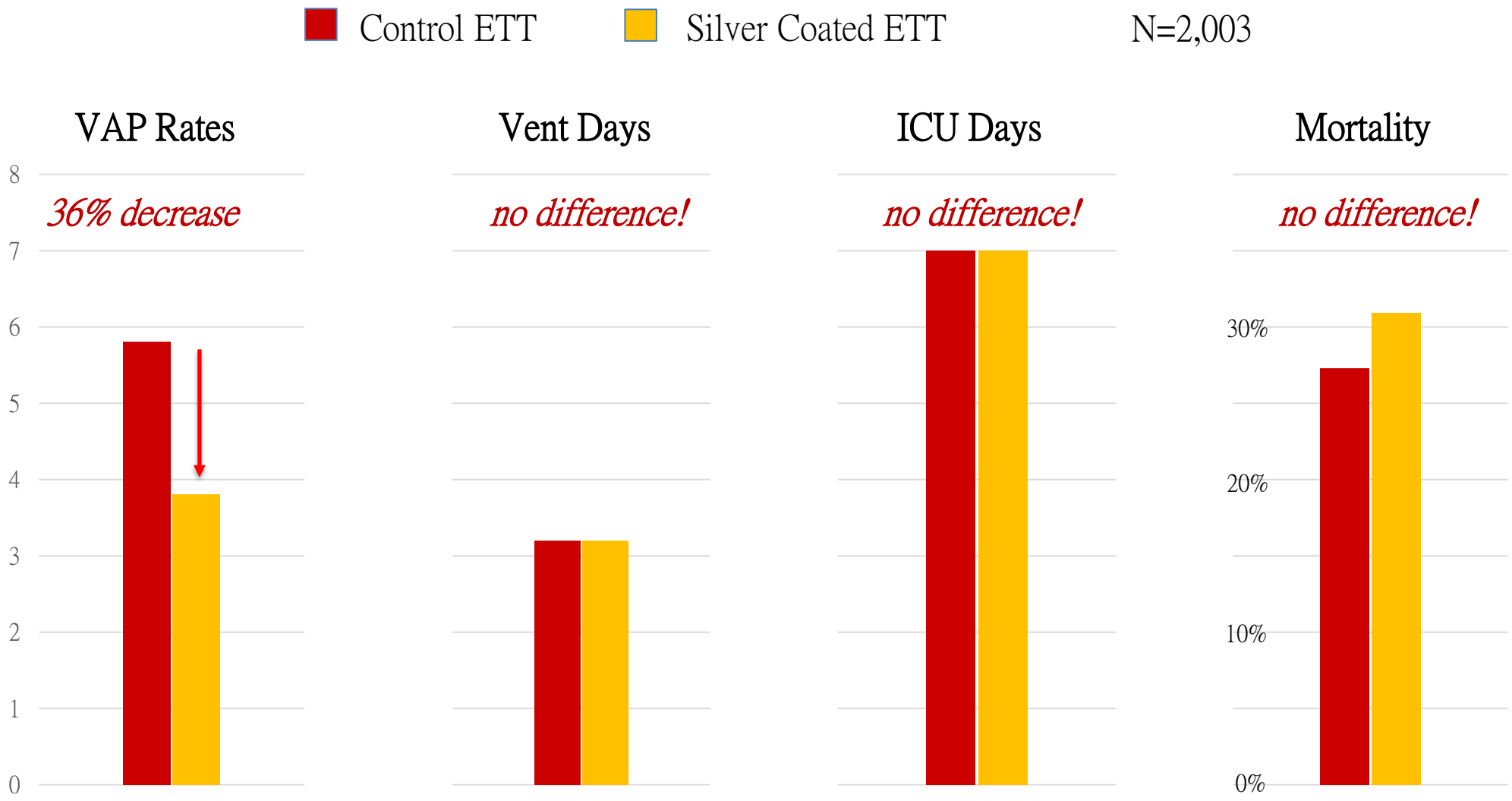
Abbreviations: CI, confidence interval; RR, relative risk.
[a] Patients with at least 10^4 colony-forming units/mL in bronchoalveolar lavage fluid.
[b] Twenty patients had polymicrobial infections. In the group receiving the silver-coated endotracheal tube, 6 patients had 2 microorganisms and 1 patient had 3. In the group receiving the uncoated tube, 11 patients had 2 microorganisms and 2 patients had 3.
[c] Other microorganisms in the group receiving the silver-coated endotracheal tube were normal flora (n = 4) and *Stenotrophomonas maltophilia* (n = 1). Other microorganisms in the group receiving the uncoated tube were normal flora (n = 8), *S maltophilia* (n = 2), *Neisseria* (n = 2), coagulase-negative staphylococci (n = 3), vancomycin-resistant enterococcus (n = 1), and *Burkholderia cepacia* (n = 1).

VAP Counts Included:

Normal flora
Candida species
Enterococcus, &
Coagulase-Negative Staphylococci

JAMA 2008;300:805-813

Silver Coated Endotracheal Tubes



JAMA 2008;300:805-813

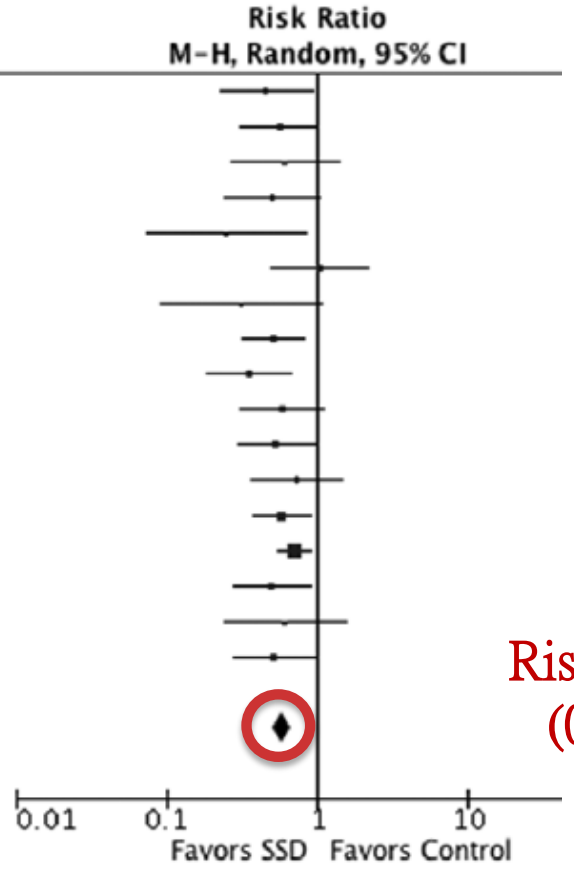
Subglottic Secretion Drainage

Meta-Analysis of randomized trials: ***Significantly Lower VAP Rates***

Study or Subgroup	SSD Events	SSD Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Mahul 1992	9	70	21	75	3.8%	0.46 [0.23, 0.93]	1992
Valles 1995	14	95	25	95	5.5%	0.56 [0.31, 1.01]	1995
Kollef 1999	8	160	15	183	2.8%	0.61 [0.27, 1.40]	1999
Bo 2000	8	35	15	33	3.7%	0.50 [0.25, 1.03]	2000
Smulders 2002	3	75	12	75	1.3%	0.25 [0.07, 0.85]	2002
Girou 2004	5	8	6	10	3.5%	1.04 [0.50, 2.18]	2004
Liu S 2006	3	48	10	50	1.3%	0.31 [0.09, 1.07]	2006
Liu Q 2006	14	41	30	45	8.5%	0.51 [0.32, 0.82]	2006
Lorente 2007	11	140	31	140	4.6%	0.35 [0.19, 0.68]	2007
Zheng 2008	9	30	16	31	4.6%	0.58 [0.31, 1.11]	2008
Yang 2008	12	48	20	43	5.6%	0.54 [0.30, 0.97]	2008
Bouza 2008	13	345	19	369	4.0%	0.73 [0.37, 1.46]	2008
Lacherade 2010	25	169	42	164	9.6%	0.58 [0.37, 0.90]	2010
Tao 2014	52	102	34	47	28.3%	0.70 [0.54, 0.91]	2014
Damas 2014	15	170	32	182	5.7%	0.50 [0.28, 0.89]	2014
Koker 2014	5	23	10	28	2.3%	0.61 [0.24, 1.53]	2014
Gopal 2015	13	120	25	120	5.0%	0.52 [0.28, 0.97]	2015
Total (95% CI)		**1679**		**1690**	**100.0%**	**0.58 [0.51, 0.67]**	
Total events	219		363				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.12$, df = 16 (P = 0.74); $I^2 = 0\%$

Test for overall effect: Z = 7.71 (P < 0.00001)



Risk Ratio 0.58
(0.51- 0.67)

Crit Care Med 2016;44:830-840

Subglottic Secretion Drainage

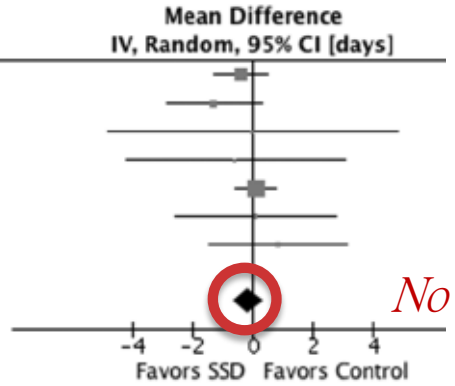
Meta-Analysis of randomized trials: *No Impact on Ventilator Days or ICU Days*

Ventilator Days

	SSD			Control				Mean Difference	
Study or Subgroup	Mean [days]	SD [days]	Total	Mean [days]	SD [days]	Total	Weight	IV, Random, 95% CI [days]	Year
Kollef 1999	1.5	3.3	160	1.9	5.1	183	29.1%	-0.40 [-1.30, 0.50]	1999
Smulders 2002	5.8	4.4	75	7.1	5.4	75	9.5%	-1.30 [-2.88, 0.28]	2002
Liu S 2006	15	14	48	15	10	50	1.0%	0.00 [-4.83, 4.83]	2006
Lorente 2007	10.5	15.91	140	11.1	15.19	140	1.8%	-0.60 [-4.24, 3.04]	2007
Bouza 2008	2	5.3	345	1.9	3.8	369	50.8%	0.10 [-0.58, 0.78]	2008
Lacherade 2010	10.9	10.6	169	10.8	14	164	3.3%	0.10 [-2.57, 2.77]	2010
Damas 2014	11.71	11.87	170	10.87	9.79	182	4.5%	0.84 [-1.44, 3.12]	2014
Total (95% CI)			**1107**			**1163**	**100.0%**	**-0.16 [-0.64, 0.33]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.68$, df = 6 (P = 0.72); $I^2 = 0\%$

Test for overall effect: Z = 0.64 (P = 0.52)



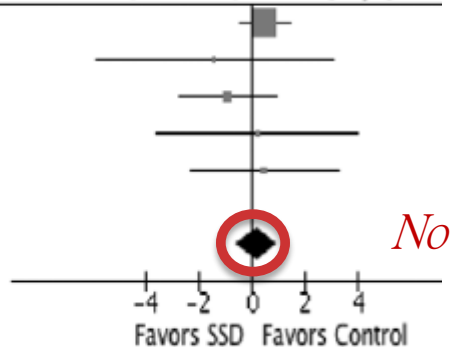
No difference!

ICU Days

	SSD			Control				Mean Difference	
Study or Subgroup	Mean [days]	SD [days]	Total	Mean [days]	SD [days]	Total	Weight	IV, Random, 95% CI [days]	Year
Kollef 1999	3.7	4.6	160	3.2	4.5	183	66.3%	0.50 [-0.47, 1.47]	1999
Lorente 2007	14.1	17.91	140	15.5	19.93	140	3.1%	-1.40 [-5.84, 3.04]	2007
Bouza 2008	5.6	10.7	345	6.5	14.2	369	18.3%	-0.90 [-2.74, 0.94]	2008
Lacherade 2010	15.9	14.4	169	15.7	20.4	164	4.3%	0.20 [-3.60, 4.00]	2010
Damas 2014	16.2	13.52	170	15.76	13.15	182	8.0%	0.44 [-2.35, 3.23]	2014
Total (95% CI)			**984**			**1038**	**100.0%**	**0.17 [-0.62, 0.95]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.27$, df = 4 (P = 0.69); $I^2 = 0\%$

Test for overall effect: Z = 0.41 (P = 0.68)



No difference!

Crit Care Med 2016;44:830-840

Reasons for the Prevention Paradox

VAP diagnosis is subjective

The case of oral care with chlorhexidine

VAP diagnosis is non-specific

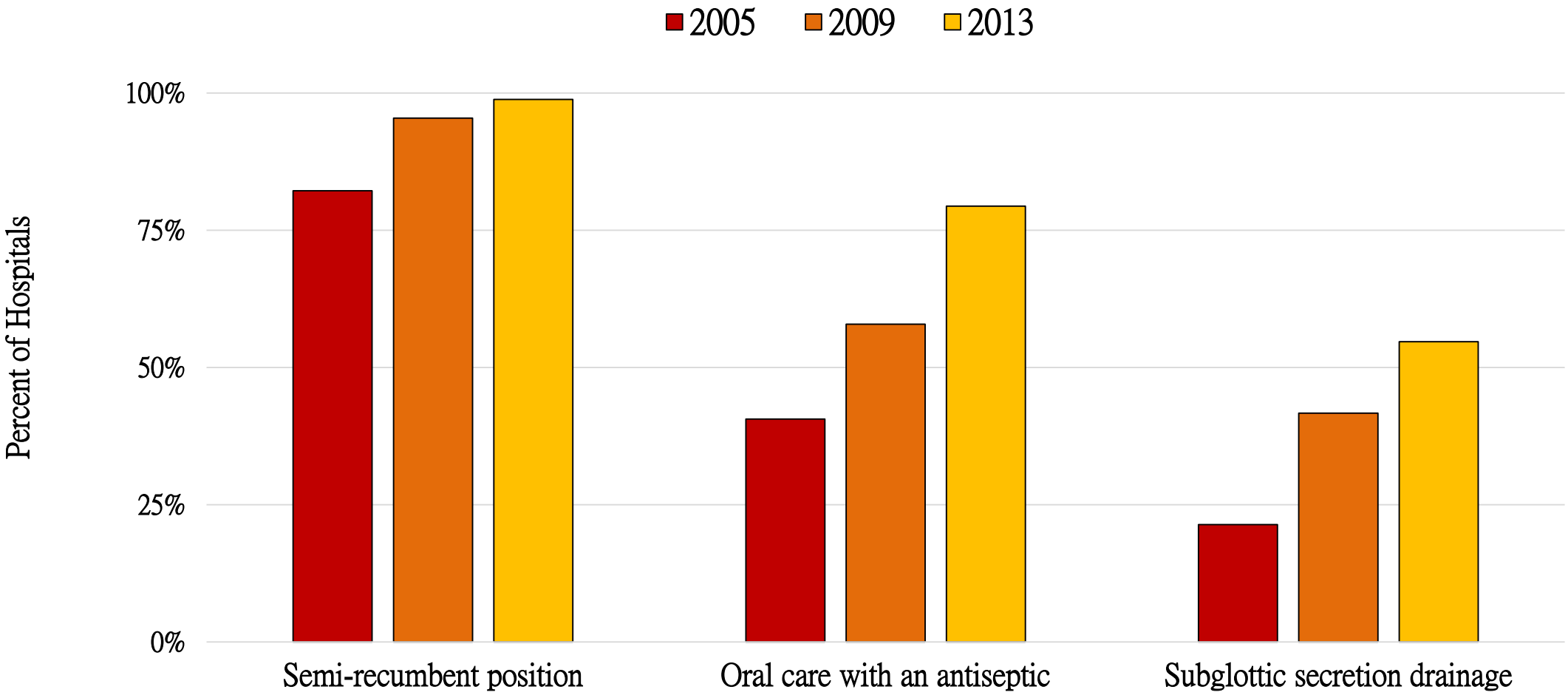
The case of silver-coated ETTs & subglottic secretion drainage

Many VAP studies are under-powered

The case of head of bed elevation

Preventive Practices in U.S. Hospitals

Random samples of ~600 U.S. acute care hospitals, 2005-2013



BMJ Quality Safety 2015;24:385-392

Head of Bed Elevation Studies

Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial

Lancet 1999; **354:** 1851–58

N=86

Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study*

Crit Care Med 2006; 34:396–402

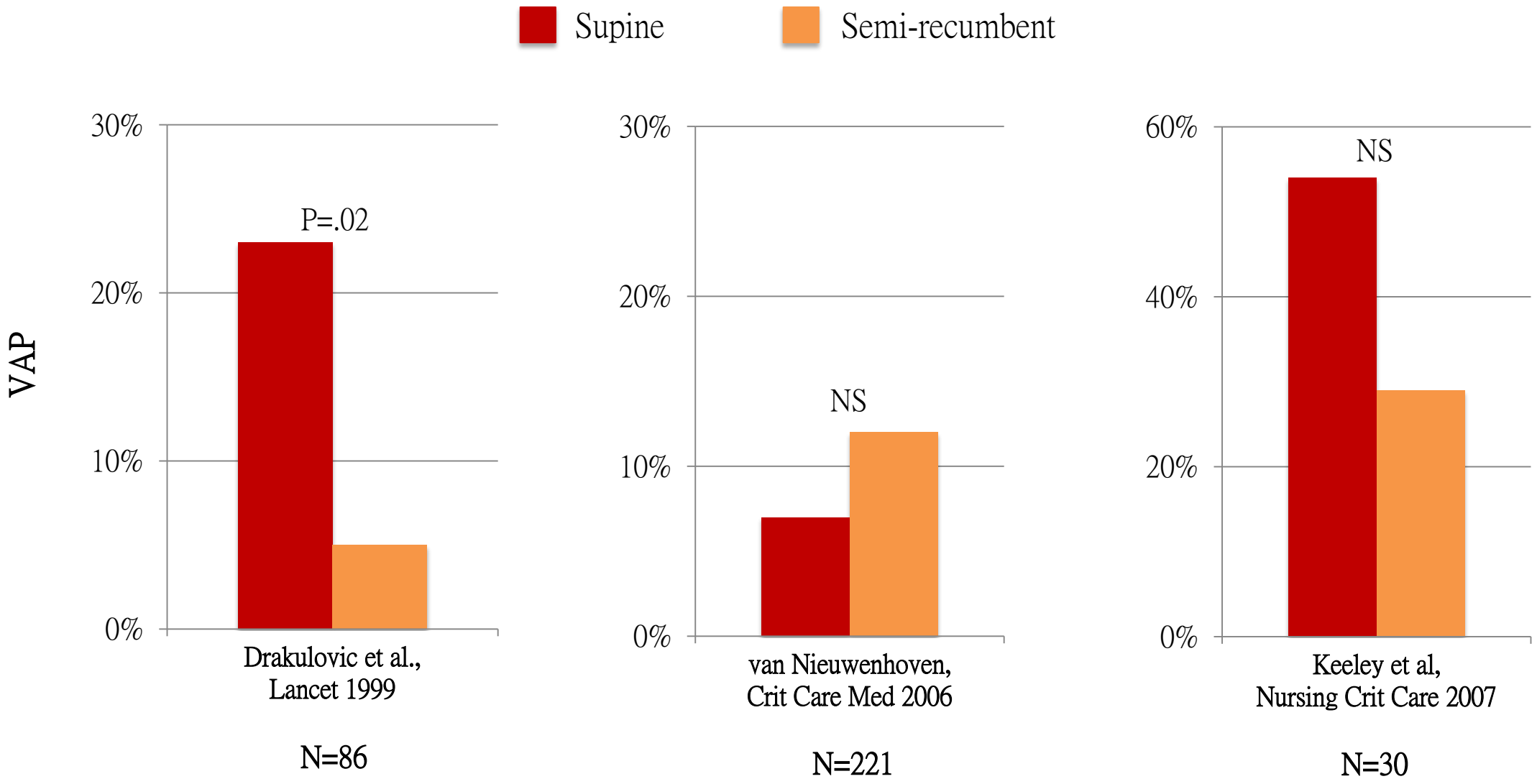
N=221

Reducing the risk of ventilator-acquired pneumonia through head of bed elevation

Nursing Crit Care 2007;12:287

N=30

Head-of-Bed Elevation and VAP Rates



Semi-recumbent vs Supine Position

Lower VAP Rates

Study or subgroup	semirecumbent position n/N	supine position n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cai 2006	4/27	13/27		9.6 %	0.31 [0.11, 0.82]
Drakulovic 1999	3/39	16/47		7.4 %	0.23 [0.07, 0.72]
Hang 2012	3/20	9/19		7.5 %	0.32 [0.10, 1.00]
Hu 2012	8/43	21/43		15.8 %	0.38 [0.19, 0.76]
van Nieuwenhoven 2006	16/112	20/109		18.9 %	0.78 [0.43, 1.42]
Wu 2009	11/56	48/56		21.3 %	0.23 [0.13, 0.39]
Xue 2012	4/48	12/48		8.5 %	0.33 [0.12, 0.96]
Yu 2012	5/33	14/32		11.0 %	0.35 [0.14, 0.85]
Total (95% CI)	**378**	**381**		**100.0 %**	**0.36 [0.25, 0.50]**
Total events: 54 (semirecumbent position), 153 (supine position)					

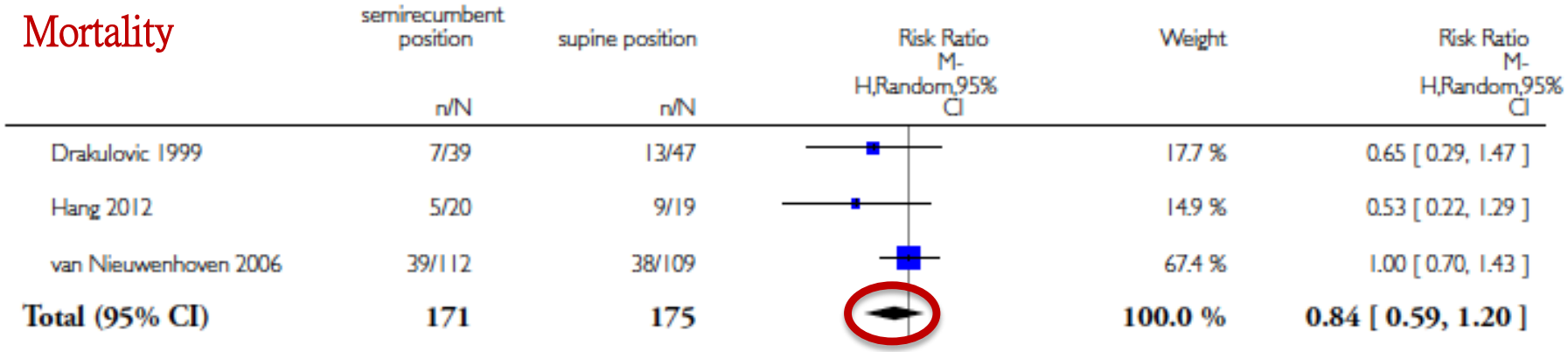
64% decrease in VAP risk ratio

Cochrane Review 2016;1:CD009946

Semi-recumbent vs Supine Position

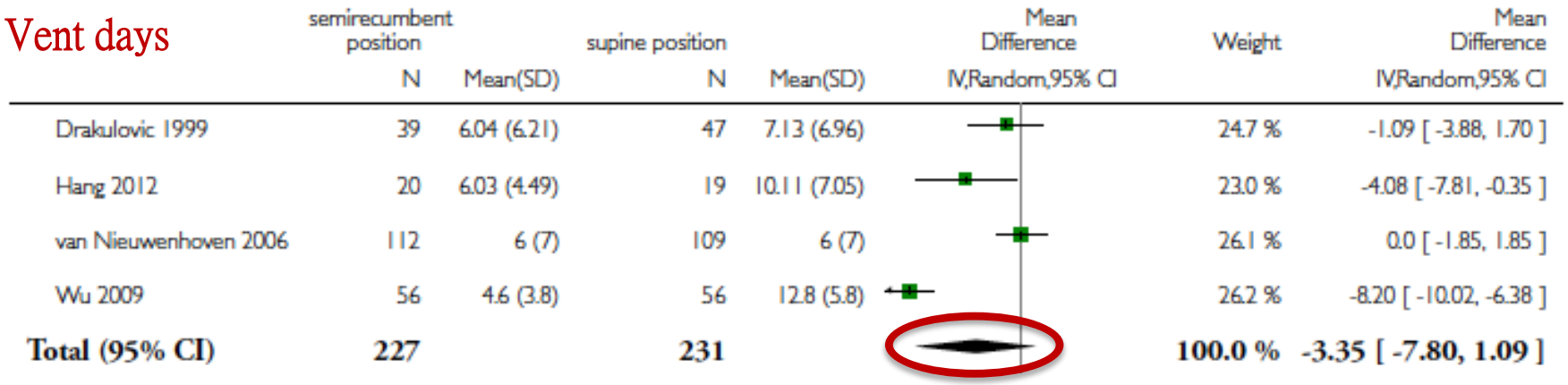
…no difference in mortality or duration of mechanical ventilation

Mortality



	semirecumbent position n/N	supine position n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Drakulovic 1999	7/39	13/47		17.7 %	0.65 [0.29, 1.47]
Hang 2012	5/20	9/19		14.9 %	0.53 [0.22, 1.29]
van Nieuwenhoven 2006	39/112	38/109		67.4 %	1.00 [0.70, 1.43]
Total (95% CI)	**171**	**175**		**100.0 %**	**0.84 [0.59, 1.20]**

Vent days

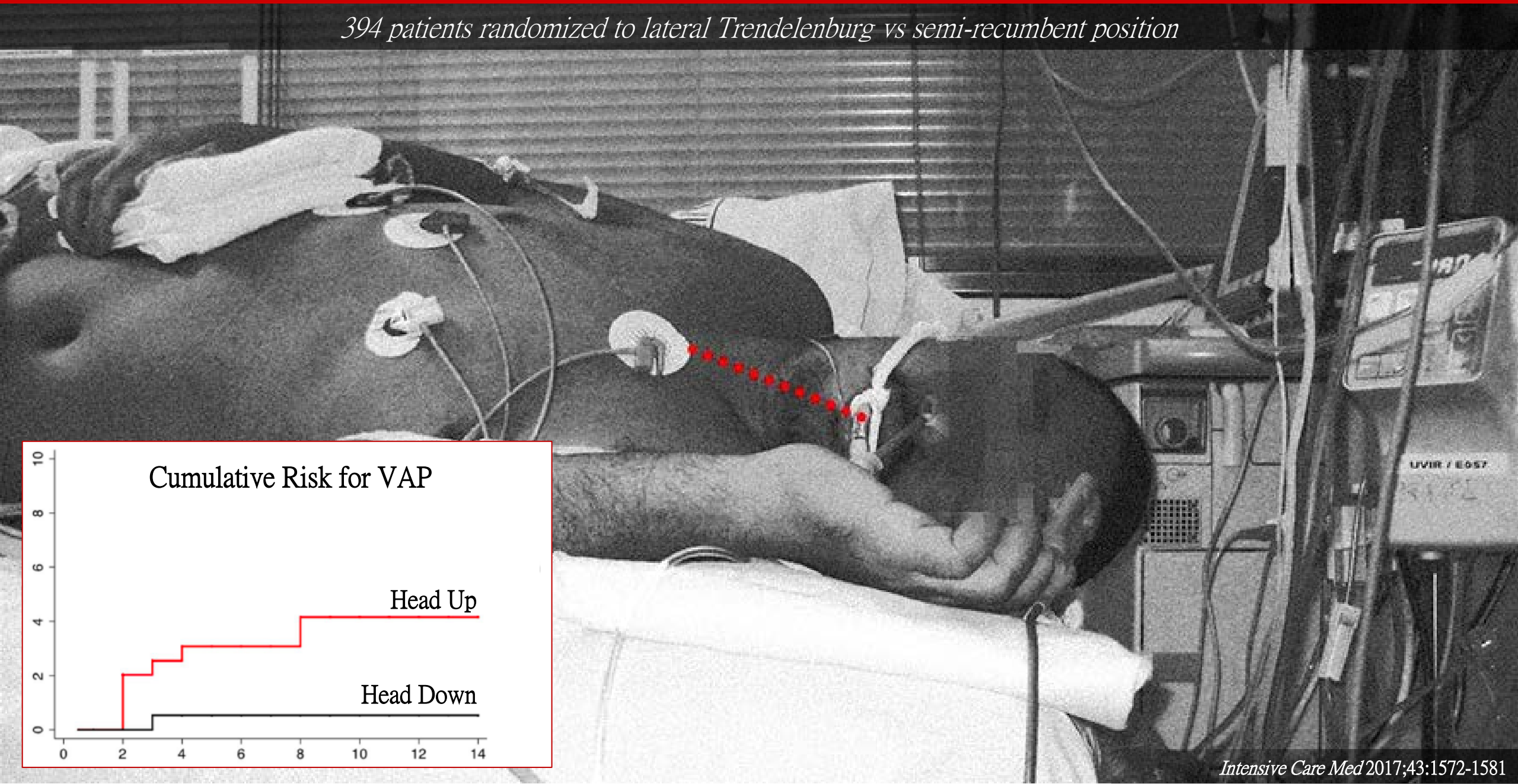


	semirecumbent position N	Mean(SD)	supine position N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Drakulovic 1999	39	6.04 (6.21)	47	7.13 (6.96)		24.7 %	-1.09 [-3.88, 1.70]
Hang 2012	20	6.03 (4.49)	19	10.11 (7.05)		23.0 %	-4.08 [-7.81, -0.35]
van Nieuwenhoven 2006	112	6 (7)	109	6 (7)		26.1 %	0.0 [-1.85, 1.85]
Wu 2009	56	4.6 (3.8)	56	12.8 (5.8)		26.2 %	-8.20 [-10.02, -6.38]
Total (95% CI)	**227**		**231**			**100.0 %**	**-3.35 [-7.80, 1.09]**

Cochrane Review 2016;1:CD009946

Maybe Head Down is Better than Head Up?

394 patients randomized to lateral Trendelenburg vs semi-recumbent position



Intensive Care Med 2017;43:1572-1581

Maybe Head Down is Better than Head Up?

394 patients randomized to lateral Trendelenburg vs semi-recumbent position

- VAP
  - 0.5% vs 4.0% (P=.04)
- Antibiotic Utilization
  - No difference
- 28-day mortality
  - No difference
- Adverse Events
  - 6 in lateral Trendelenburg group vs 0 in semi-recumbent
    - Oxygen desaturation, hemodynamic instability, intracranial hemorrhage, brachial plexus injury
- Trial stopped early

Intensive Care Med 2017;43:1572-1581

Joint Commission Journal on Quality and Patient Safety

100K Lives Campaign

Using a Bundle Approach to Improve Ventilator Care Processes and Reduce Ventilator-Associated Pneumonia

Roger Resar, M.D.
Peter Pronovost, M.D., Ph.D.
Carol Haraden, Ph.D.
Terri Simmonds, R.N.
Thomas Rainey, M.D.
Thomas Nolan, Ph.D.

Joint Commission Journal on Quality and Patient Safety 2005;31:243-248

The Classic Ventilator Bundle

Elevate the head of the bed

Daily sedative interruptions

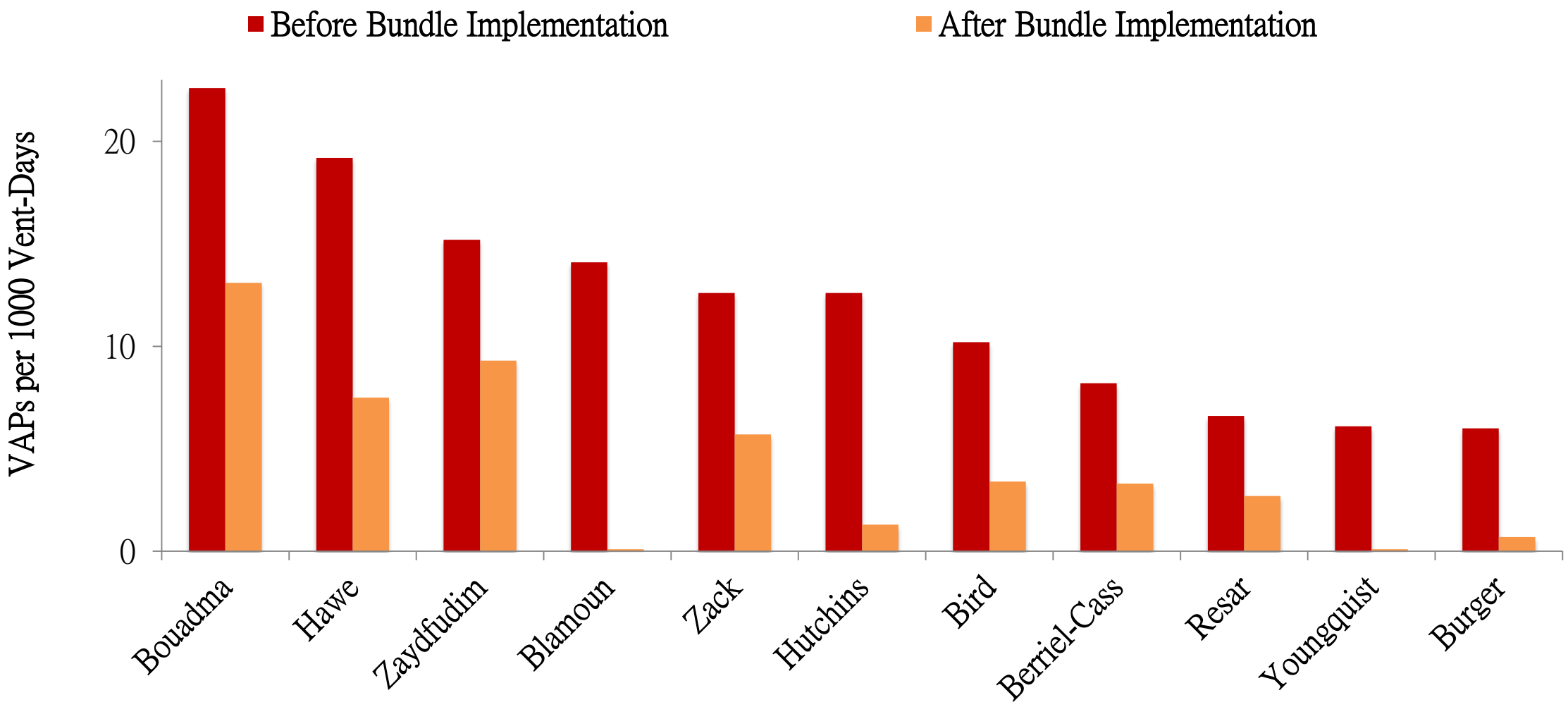
Spontaneous breathing trials

Stress ulcer prophylaxis

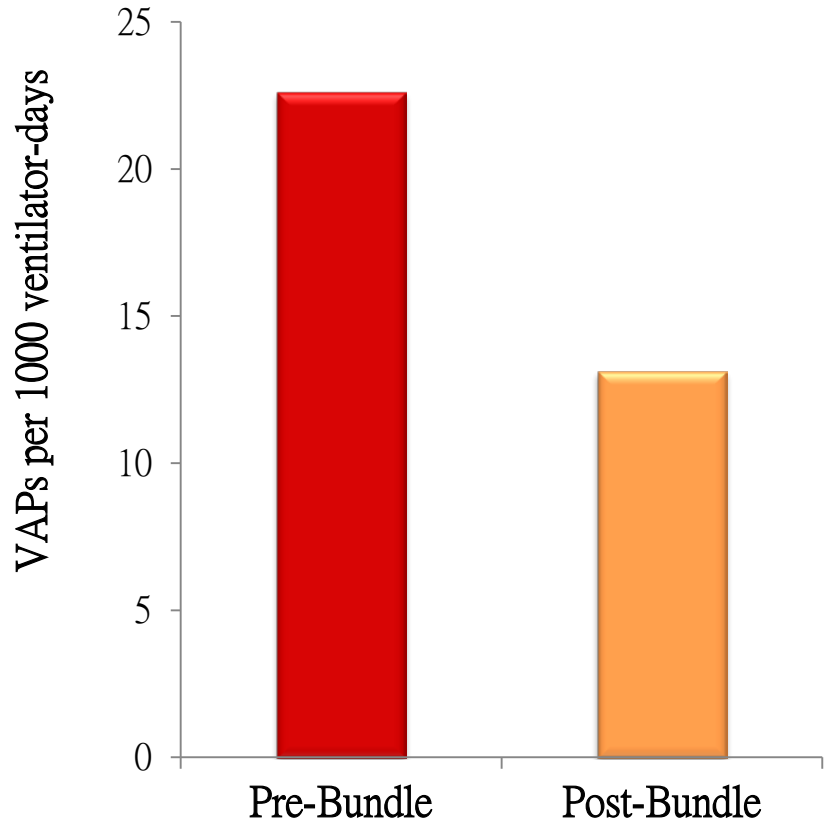
DVT prophylaxis

Oral care with chlorhexidine

Bundles Associated with Lower VAP Rates



How do we interpret a drop in VAP rates?



Better Care?

Stricter Surveillance?

Less colonization vs less VAP?

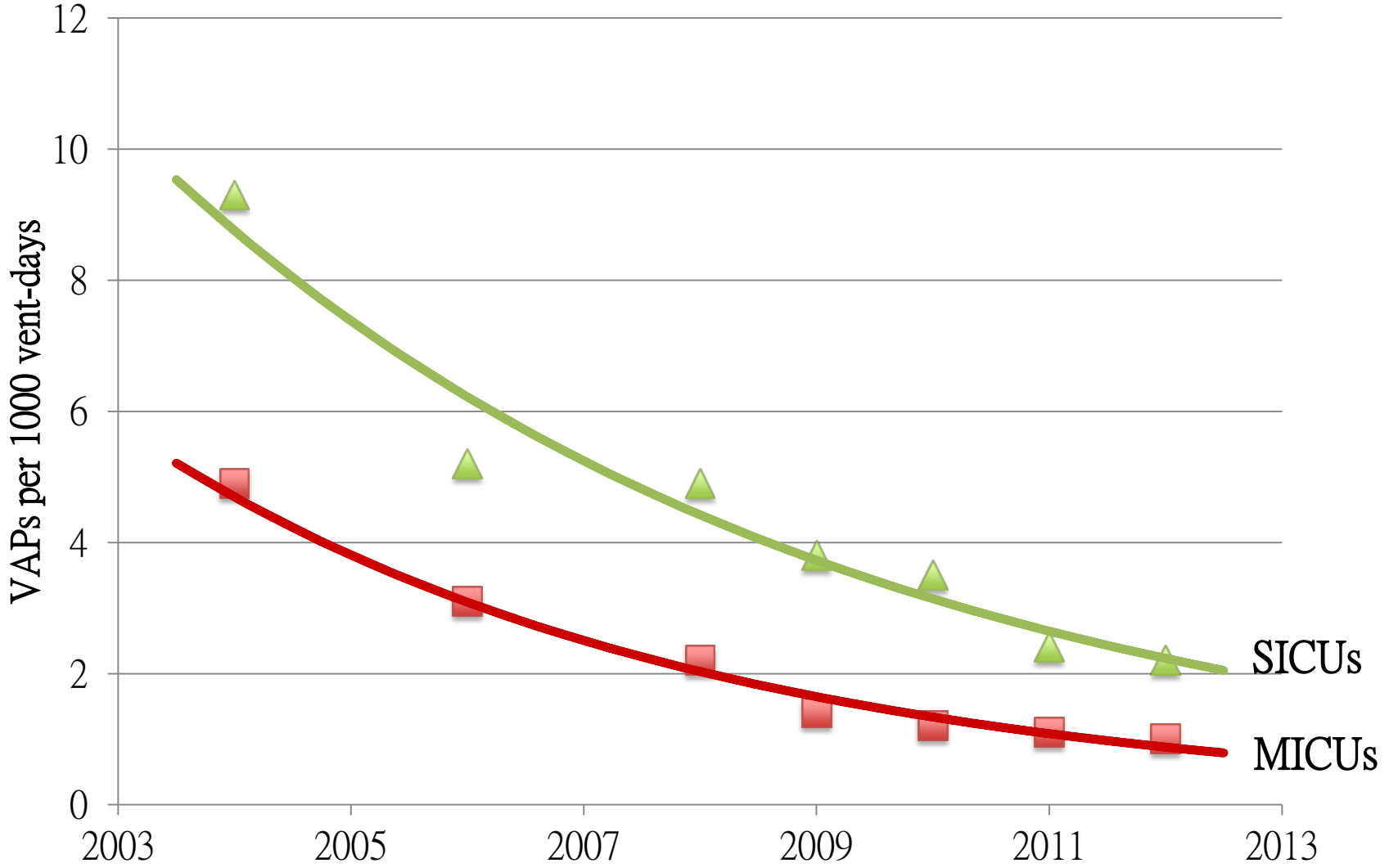
Change in case mix?

Some combination of the above?

Am J Infect Control 2012;40:408-410

U.S. National VAP Rates

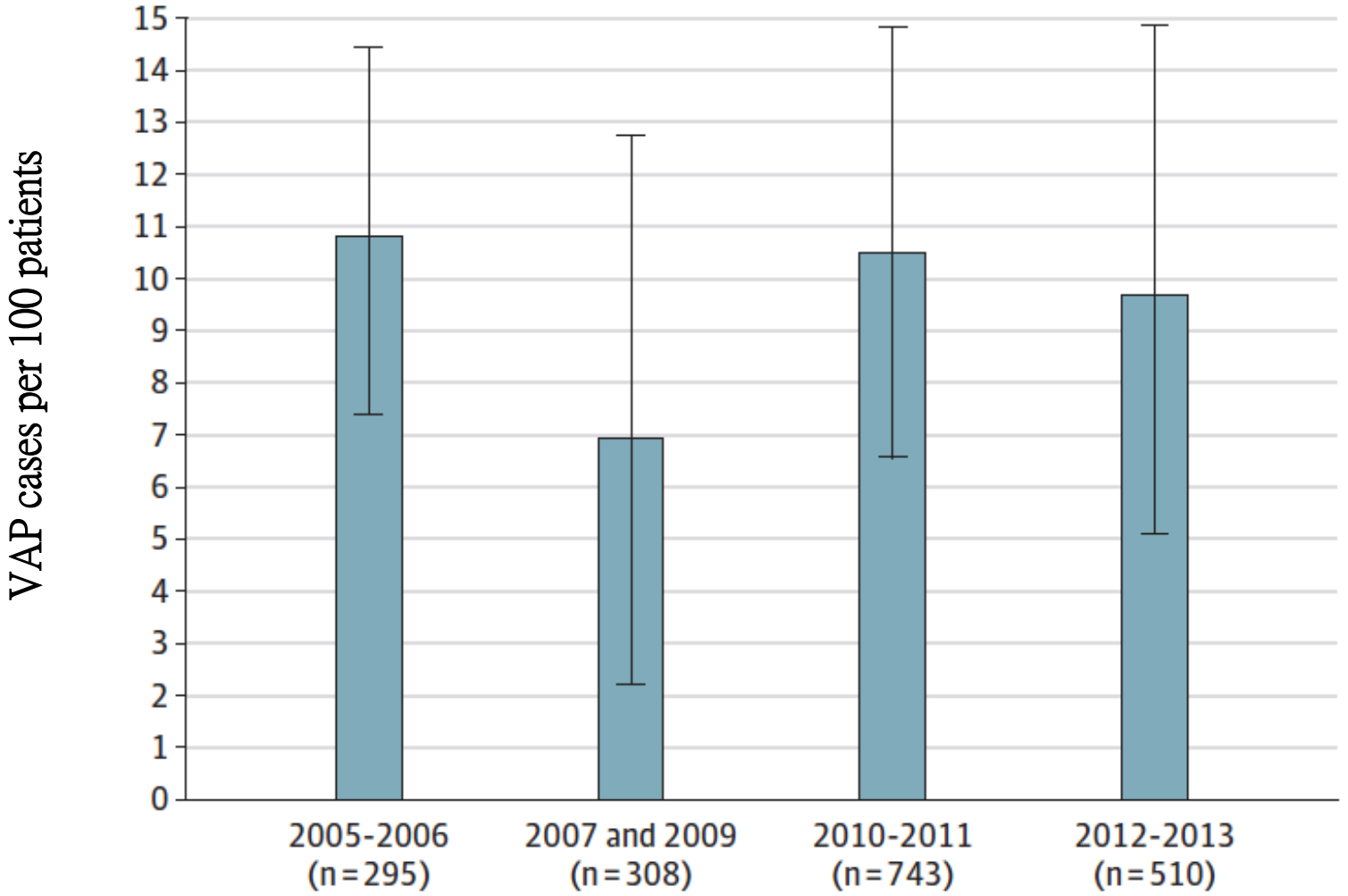
Cases Reported to CDC by Hospitals, 2004-2012



Source: CDC NNIS and NHSN

U.S. National VAP Rates, 2005-2013

Centers for Medicare and Medicaid Services Audits



JAMA 2016;316:2427-2429

Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals: 2014 Update

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2014, VOL. 35, NO. 8

"Given the uncertainty surrounding the accuracy and reproducibility of VAP diagnoses ⋯ we prioritize VAP interventions that have been shown to **improve objective outcomes, such as duration of mechanical ventilation, intensive care or hospital length of stay, mortality, and/or costs** in randomized controlled trials."

Infection Control Hospital Epidemiol 2014;8:915

Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals: 2014 Update

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2014, VOL. 35, NO. 8

Basic Practices

Interventions that improve objective outcomes and confer little risk of harm

Interventions that are outcome neutral but cost saving

Special Practices

Interventions that improve objective outcomes but confer some risk of harm

Interventions that decrease VAP rates but insufficient data available on their impact on objective outcomes

Infection Control Hospital Epidemiol 2014;8:915

Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals: 2014 Update

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2014, VOL. 35, NO. 8

Basic Practices

Interventions that improve objective outcomes and confer little risk of harm

Interventions that are outcome neutral but cost saving

Special Practices

Interventions that improve objective outcomes but confer some risk of harm

Interventions that decrease VAP rates but insufficient data available on their impact on objective outcomes

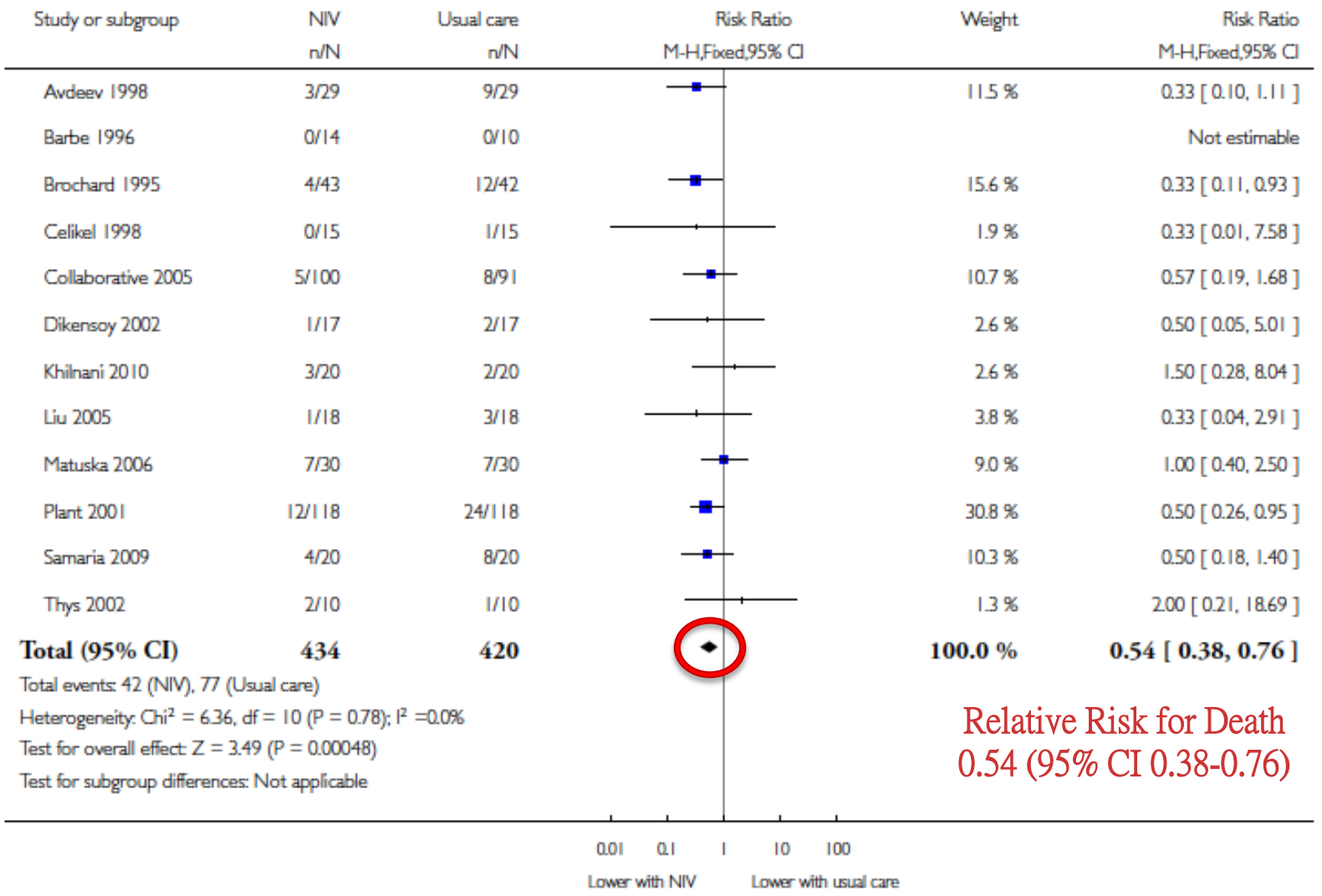
Infection Control Hospital Epidemiol 2014;8:915

Basic Practices: Improve Objective Outcomes, Little Risk of Harm

- Use non-invasive positive pressure ventilation in selected populations
- Manage patients without sedation whenever possible
- Interrupt sedation daily
- Assess readiness to extubate daily
- Perform spontaneous breathing trials with sedatives turned off
- Facilitate early mobility

Non-Invasive Positive Pressure Ventilation

Randomized trials of non-invasive ventilation for acute hypercapnic respiratory failure due to COPD exacerbations



Relative Risk for Death
0.54 (95% CI 0.38-0.76)

Cochrane Review 2017;7:CD004104

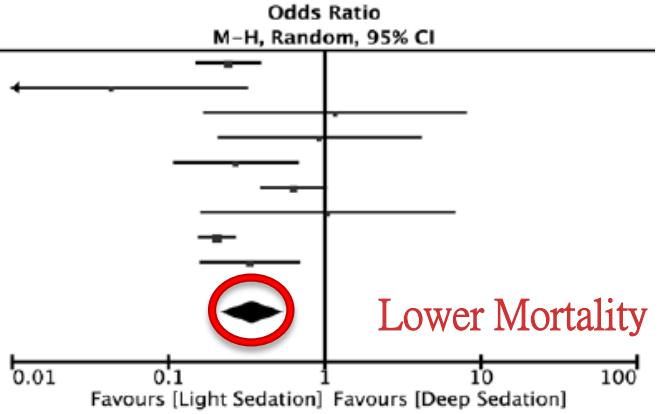
Lighter Sedation: Lower Mortality, Fewer Vent Days

Mortality

Study or Subgroup	Light Sedation Events	Light Sedation Total	Deep Sedation Events	Deep Sedation Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
van den Boogaard 2012	41	1017	37	249	17.2%	0.24 [0.15, 0.38]	2012
Shehabi 2012	1	80	39	171	4.3%	0.04 [0.01, 0.32]	2012
Shehabi 2013 Australia Pilot	3	21	2	16	4.6%	1.17 [0.17, 7.96]	2013
Shehabi 2013 Malaysia	4	31	4	29	6.7%	0.93 [0.21, 4.10]	2013
Shehabi 2013	6	45	76	209	11.7%	0.27 [0.11, 0.67]	2013
Tanaka 2014	73	209	52	113	17.2%	0.63 [0.39, 1.00]	2014
Samarin 2014	3	39	2	27	4.8%	1.04 [0.16, 6.69]	2014
Balzer 2015	131	1371	175	513	19.6%	0.20 [0.16, 0.26]	2015
Stephens 2017	10	137	47	244	13.9%	0.33 [0.16, 0.68]	2017
Total (95% CI)		**2950**		**1571**	**100.0%**	**0.34 [0.21, 0.54]**	
Total events	272		434				

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 27.87$, df = 8 (P = 0.0005); $I^2 = 71\%$

Test for overall effect: Z = 4.52 (P < 0.00001)

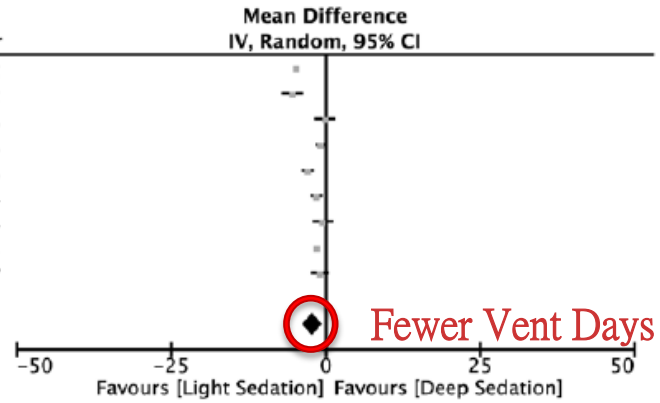


Ventilator Days

Study or Subgroup	Light Sedation Mean	Light Sedation SD	Light Sedation Total	Deep Sedation Mean	Deep Sedation SD	Deep Sedation Total	Weight	Mean Difference IV, Random, 95% CI	Year
Shehabi 2012	2.7	0.39	80	7.5	0.58	171	11.7%	-4.80 [-4.92, -4.68]	2012
van den Boogaard 2012	1.9	5.9	1017	7.3	11.7	249	10.5%	-5.40 [-6.90, -3.90]	2012
Shehabi 2013 Australia Pilot	3.3	2.2	21	3.4	2.3	16	10.5%	-0.10 [-1.57, 1.37]	2013
Shehabi 2013 Malaysia	2.5	0.39	31	3.4	1.3	29	11.5%	-0.90 [-1.39, -0.41]	2013
Shehabi 2013	4.4	1.5	45	7.3	5.1	209	11.3%	-2.90 [-3.72, -2.08]	2013
Tanaka 2014	5.5	3.1	209	7	3	113	11.4%	-1.50 [-2.19, -0.81]	2014
Samarin 2014	1.6	2.1	39	2.1	3.4	27	10.6%	-0.50 [-1.94, 0.94]	2014
Balzer 2015	0.88	0.09	1371	2.3	2.2	513	11.6%	-1.42 [-1.61, -1.23]	2015
Stephens 2017	4.6	5.3	137	5.6	6.1	244	10.9%	-1.00 [-2.17, 0.17]	2017
Total (95% CI)			**2950**			**1571**	**100.0%**	**-2.07 [-3.60, -0.53]**	

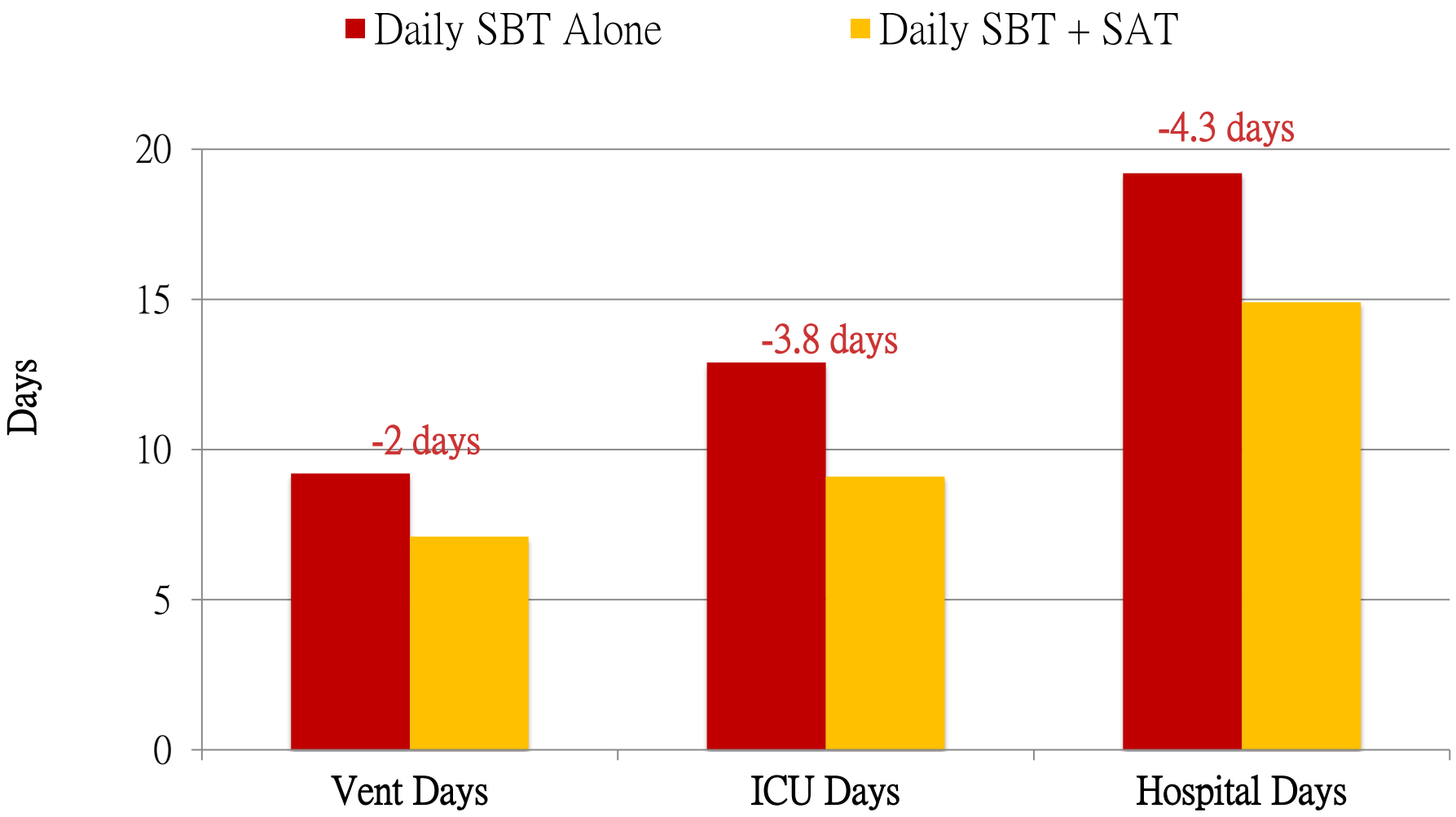
Heterogeneity: $Tau^2 = 5.24$; $Chi^2 = 1092.97$, df = 8 (P < 0.00001); $I^2 = 99\%$

Test for overall effect: Z = 2.64 (P = 0.008)



Crit Care Med 2018;46:471-479

Paired Sedative Interruptions & Breathing Trials



Lancet 2008;371:126-34

Early mobility

http://69.36.35.38/images/CHESTPhysician/CritCareCom0610Fig2.jpg

- May encourage & facilitate less sedation
- May help prevent delirium
  - These benefits may by synergistic with other ventilator bundle components such as spontaneous awakening and breathing trials.
- Data on outcomes are mixed. Some studies show less time to extubation while others do not.

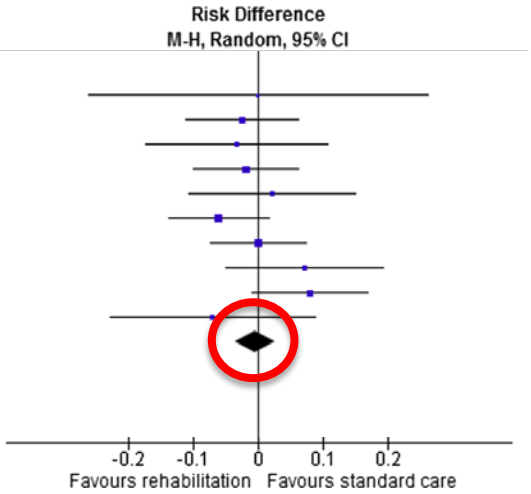
Thorax 2018;73:213-221
JAMA 2016;315:2694-2702
Lancet 2016;388:1377 – 88
Crit Care Med 2013;41:717
Lancet 2009;373:1874
Arch Phys Med Rehabil 2010;91:536

Early Mobility

Hospital Death

Study or Subgroup	Rehabilitation Events	Total	Standard Care Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.1.2 Mortality at hospital discharge						
Brummel 2014	6	22	6	22	1.4%	0.00 [-0.26, 0.26]
Denehy 2013	5	74	7	76	13.4%	-0.02 [-0.11, 0.06]
Dong 2014	2	30	3	30	5.1%	-0.03 [-0.17, 0.11]
Dong 2016	2	53	3	53	15.4%	-0.02 [-0.10, 0.06]
Hodgson 2016	2	29	1	21	6.0%	0.02 [-0.11, 0.15]
Morris 2008	20	165	30	165	16.9%	-0.06 [-0.14, 0.02]
Morris 2016	18	150	18	150	18.5%	0.00 [-0.07, 0.07]
Moss 2016	10	59	6	61	6.8%	0.07 [-0.05, 0.19]
Schaller 2016	17	104	8	96	12.4%	0.08 [-0.01, 0.17]
Schweickert 2009	9	49	14	55	4.0%	-0.07 [-0.23, 0.09]
Subtotal (95% CI)		**735**		**729**	**100.0%**	**-0.00 [-0.04, 0.03]**
Total events	91		96			

Heterogeneity: Tau² = 0.00; Chi² = 8.26, df = 9 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)



No impact on hospital death rates…

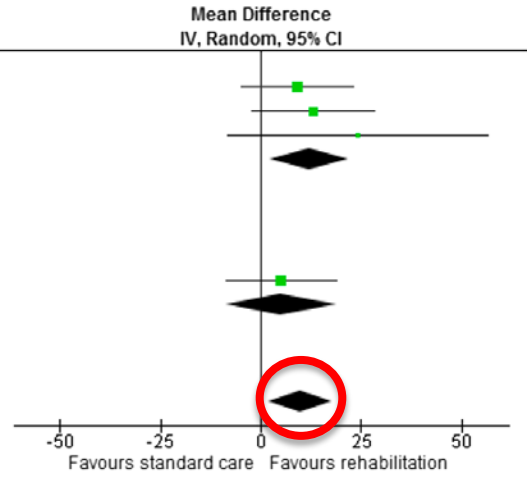
Days Alive and Out of Hospital to 180 days

Study or Subgroup	Rehabilitation Mean	SD	Total	Standard Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.26.1 Early and low dose rehabilitation								
Hanekom 2012	160	43	96	151	55	97	32.8%	9.00 [-4.92, 22.92]
Hodgson 2016	156	27	29	143	27	21	27.6%	13.00 [-2.16, 28.16]
Wolfe 2013	115	78	48	91	83	48	6.1%	24.00 [-8.22, 56.22]
Subtotal (95% CI)			**173**			**166**	**66.6%**	**12.04 [2.27, 21.81]**
1.26.2 Late and high dose rehabilitation								
Moss 2016	151	31	59	146	45	61	33.4%	5.00 [-8.79, 18.79]
Subtotal (95% CI)			**59**			**61**	**33.4%**	**5.00 [-8.79, 18.79]**
Total (95% CI)			**232**			**227**	**100.0%**	**9.69 [1.71, 17.66]**

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.38 (P = 0.02)
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%



…but more days alive and out of hospital

Intensive Care Med 2017;43:171-183

Ventilator Bundle Compliance and Death

Retrospective analysis of 5,539 patients on mechanical ventilation

adjusted for comorbidities, severity of illness, contraindications, etc.

Spontaneous breathing trials

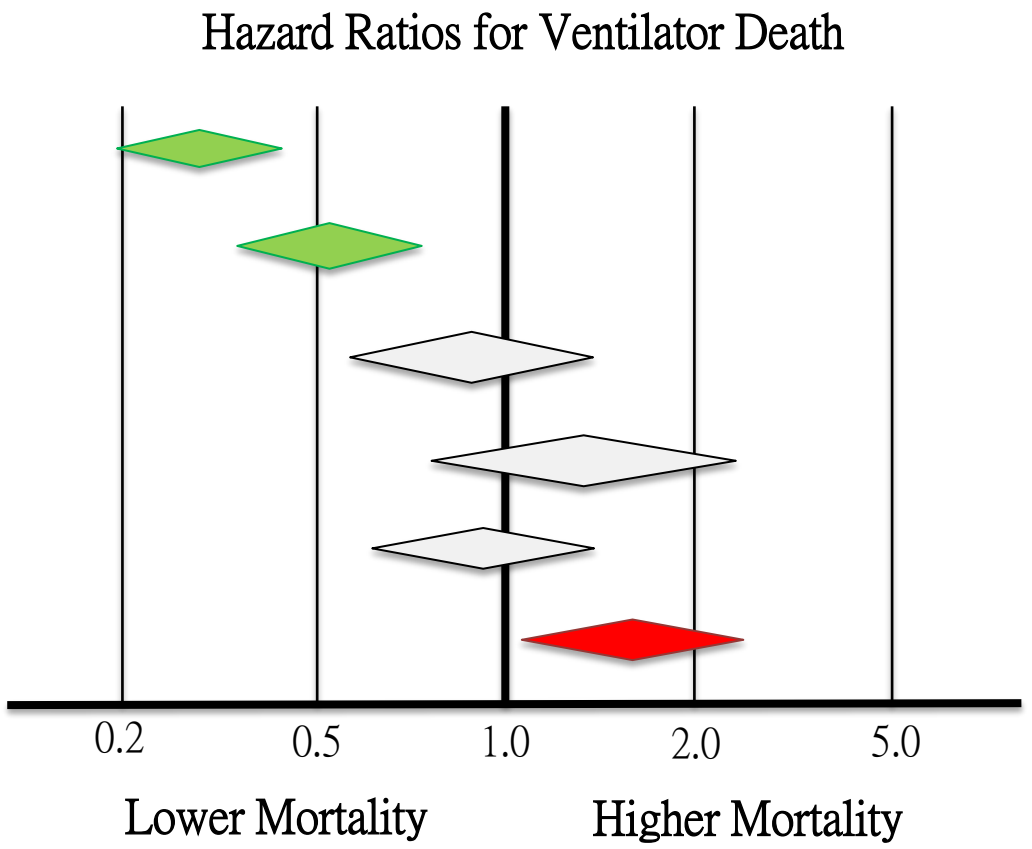
Spontaneous awakening trials

Head of bed elevation

Thromboprophylaxis

Stress ulcer prophylaxis

Oral care with chlorhexidine



JAMA Internal Med 2016;176:1277-1283

Ventilator Bundle Compliance and Time to Extubation Alive

Retrospective analysis of 5,539 patients on mechanical ventilation

adjusted for comorbidities, severity of illness, contraindications, etc.

Thromboprophylaxis

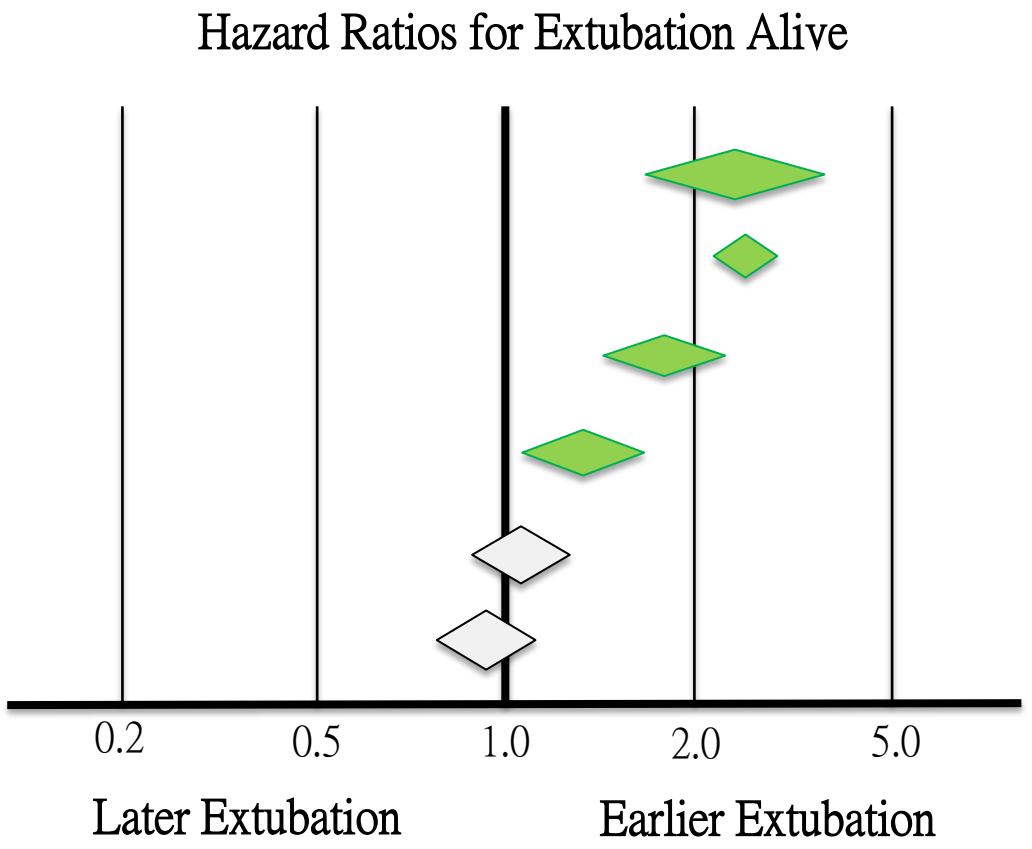
Spontaneous breathing trials

Spontaneous awakening trials

Head of bed elevation

Stress ulcer prophylaxis

Oral care with chlorhexidine



JAMA Internal Med 2016;176:1277-1283

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Basic Practices

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Infection Control Hospital Epidemiol 2014;8:915

Basic Practices: Outcome Neutral but Cost Saving

Change ventilator circuits only when visibly soiled or malfunctioning

Multiple RCTs

No impact on VAP rates

No impact on duration of mechanical ventilation, ICU length of stay, or mortality

BUT … cost saving!

Am Rev Respir Dis 1991;143:738
Ann Intern Med 1995;123:168
Infect Control Hosp Epidemiol 1996;17:14
Infect Control Hosp Epidemiol 2004;25:1077

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Infection Control Hospital Epidemiol 2014;8:915

Special Practice: Better Outcomes but Possible Risks

Selective oral & digestive decontamination

www.ukenglish.org.uk/idiom-of-the-week-elephant-in-the-room

Selective Oral & Digestive Decontamination

Selective Oral Decontamination

Oropharyngeal antibiotic paste applied 4x/day

- Tobramycin
- Colistin
- Amphotericin B

Designed to target *Staph aureus,* aerobic gram negatives, and yeast

Selective Digestive Decontamination

Oropharyngeal paste applied 4x/day

- Same antibiotics as SOD

Plus…

Antibiotic suspension via NG tube

- Same antibiotics as SOD

Plus…

4-day course of intravenous cefotaxime

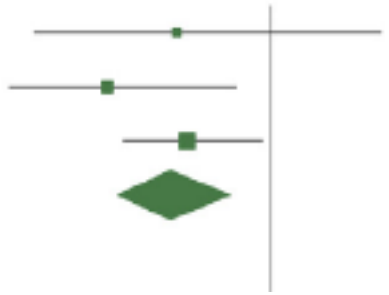
Clin Microbiol Infect 2018;24:505-513

Selective Oral & Digestive Decontamination

Individual patient level meta-analysis of randomized trials, N=16,528 patients

Digestive Decontamination vs Control

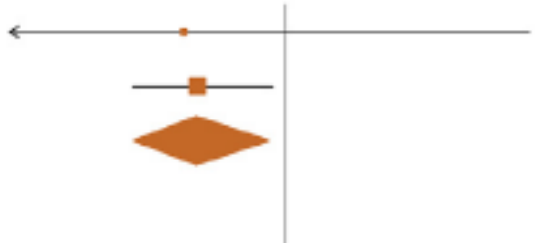
	aOR (95%-CI)
Krueger et al. 2002	0.83 (0.57 - 1.20)
de Jonge et al. 2003	0.70 (0.53 - 0.94)
de Smet et al. 2009	0.85 (0.73 - 0.98)
pooled OR (fixed)	**0.82 (0.72 - 0.93)**
I-statistic (p-value Cochran Q-test)	1.0% (0.52)



Mortality Odds Ratio
0.82 (95% CI 0.72-0.93)
N=5,304

Oral Decontamination vs Control

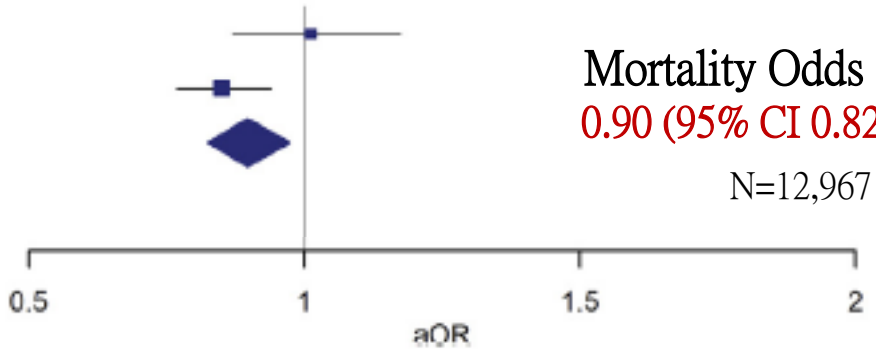
	aOR (95%-CI)
Bergmans et al. 2001	0.82 (0.46 - 1.44)
de Smet et al. 2009	0.84 (0.72 - 0.98)
pooled OR (fixed)	**0.84 (0.73 - 0.97)**
I-statistic (p-value Cochran Q-test)	1.0% (0.92)



Mortality Odds Ratio
0.84 (95% CI 0.73-0.97)
N=3,921

Digestive vs Oral Decontamination

	aOR (95%-CI)
de Smet et al. 2009	1.01 (0.87 - 1.17)
Oostdijk et al. 2014	0.85 (0.77 - 0.94)
pooled OR (fixed)	**0.90 (0.82 - 0.97)**
I-statistic (p-value Cochran Q-test)	72.4% (0.06)



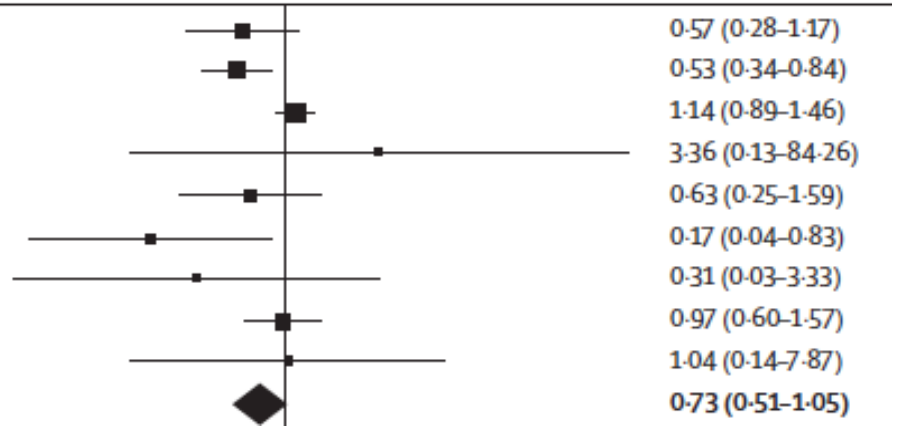
Mortality Odds Ratio
0.90 (95% CI 0.82-0.97)
N=12,967

Clin Microbiol Infect 2018;24:505-513

Impact on Antibiotic Resistance

Meta-analysis of 9 trials of digestive decontamination that included data on resistance rates

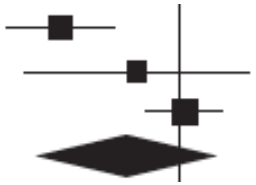
Aminoglycoside resistance: OR 0.73 (0.51-1.05)



Camus et al[73] (2005)	14	130	22	126	0·57 (0·28–1·17)
De Jonge et al[69] (2003)	33	378	60	395	0·53 (0·34–0·84)
De Smet et al[82] (2011)	227	1714	104	881	1·14 (0·89–1·46)
Flaherty et al[31] (1990)	1	51	0	56	3·36 (0·13–84·26)
Krueger et al[65] (2002)	8	175	12	171	0·63 (0·25–1·59)
Rocha et al[42] (1992)	2	47	11	54	0·17 (0·04–0·83)
Unertl et al[26] (1987)	1	19	3	20	0·31 (0·03–3·33)
Verwaest et al[57] (1997)	60	393	29	185	0·97 (0·60–1·57)
Wiener et al[53] (1995)	2	30	2	31	1·04 (0·14–7·87)
Total (95% CI)	**348**	**2937**	**243**	**1919**	**0·73 (0·51–1·05)**

Odds Ratio
0.73 (0.51-1.05)

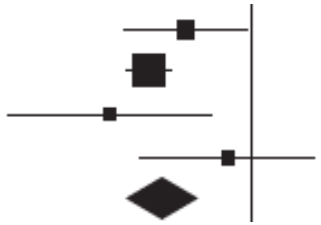
Fluoroquinolone resistance: OR 0.52 (0.16-1.68)



De Jonge et al[69] (2003)	10	378	44	395	0·22 (0·11–0·44)
Krueger et al[65] (2002)	3	175	5	171	0·58 (0·14–2·46)
Verwaest et al[57] (1997)	63	393	28	185	1·07 (0·66–1·74)
Total (95% CI)	**76**	**946**	**77**	**751**	**0·52 (0·16–1·68)**

Odds Ratio
0.52 (0.16-1.68)

Cephalosporin resistance: OR 0.33 (0.20-0.52)



De Jonge et al[69] (2003)	9	378	21	395	0·43 (0·20–0·96)
De Smet et al[82] (2011)	76	1714	130	881	0·27 (0·20–0·36)
Rocha et al[42] (1992)	3	47	16	54	0·16 (0·04–0·60)
Verwaest et al[57] (1997)	8	393	5	185	0·75 (0·24–2·32)
Total (95% CI)	**96**	**2532**	**172**	**1515**	**0·33 (0·20–0·52)**

Odds Ratio
0.33 (0.20-0.52)

Lancet Infect Dis 2013;13:328

How can it be that giving antibiotics to everyone leads to less resistance???

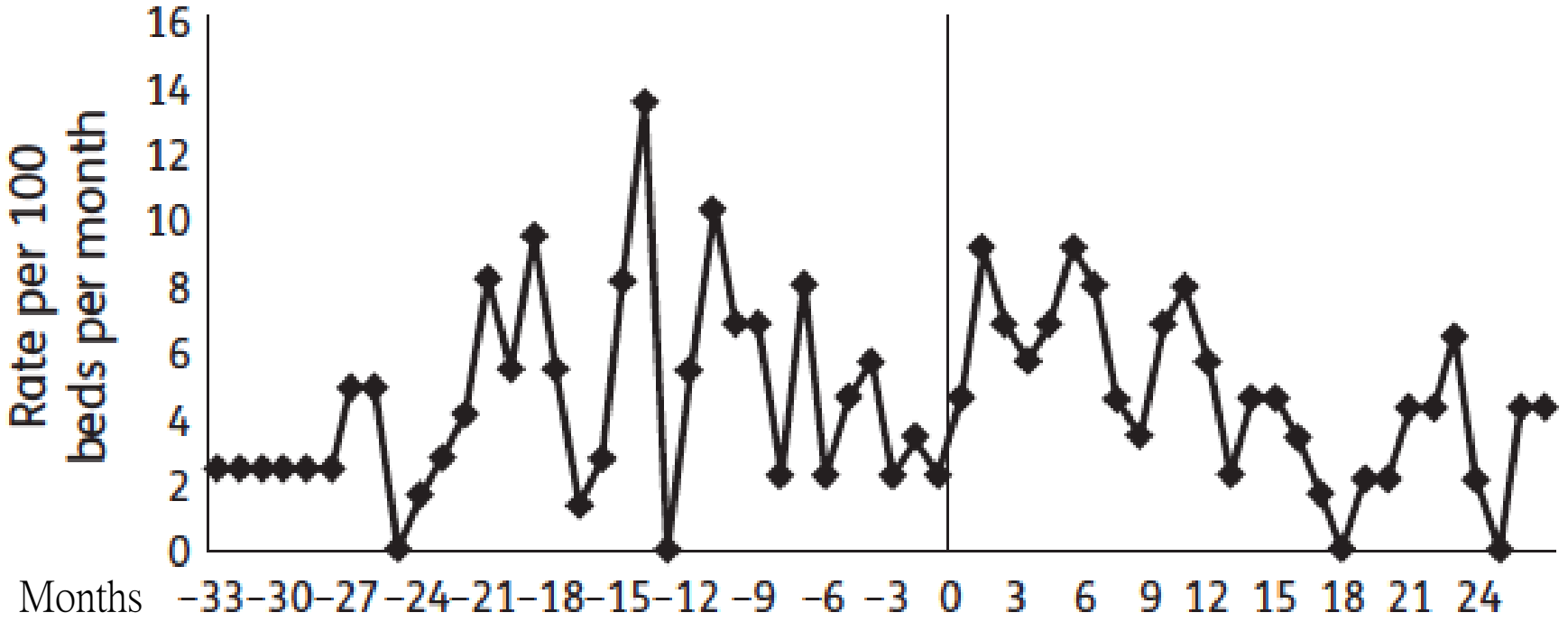
Fewer infections overall in the digestive decontamination group

Fewer infections = fewer resistant infections

Fewer infections leads to less overall antibiotic usage

Is the effect sustained?

Cefotaxime resistance rates in respiratory isolates amongst 8 Dutch ICUs for 24 months following introduction of selective digestive decontamination versus the preceding 33 months

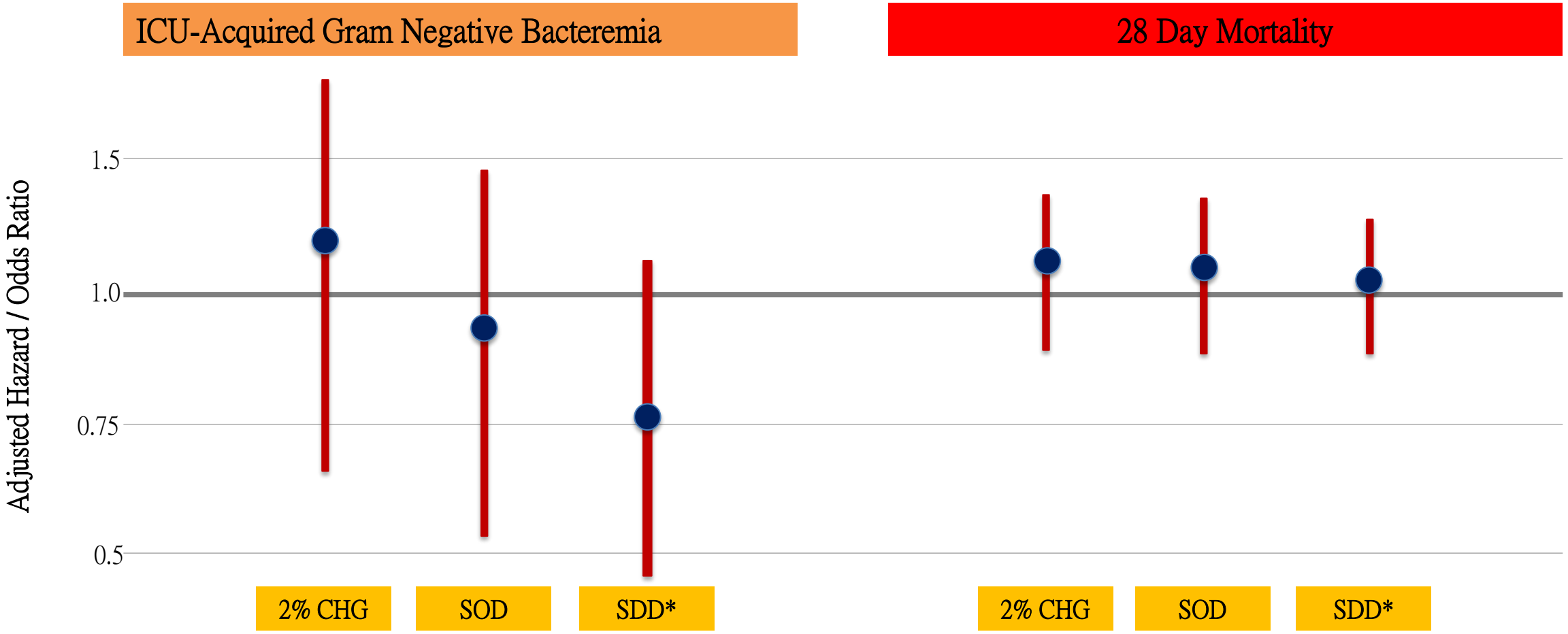


No apparent sustained change in resistance rates over time

J Antimicrob Chemother 2014;69:797

Does SDD generalize to high resistance settings?

Cluster randomized trial of usual care vs 2% CHG oral care vs selective oral decontamination vs selective digestive decontamination in 13 ICUs with high baseline rates of antibiotic utilization and resistant organisms*



*SDD included oral antibiotic paste and gastric suspension but no intravenous antibiotics

JAMA 2018;320:2087-2098

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Infection Control Hospital Epidemiol 2014;8:915

Special Practices: Lower VAP Rates, Insufficient Data on Other Outcomes

- Probiotics
- Automated control of endotracheal tube cuff pressures
- Saline instillation before tracheal suctioning
- Mechanical toothbrushing

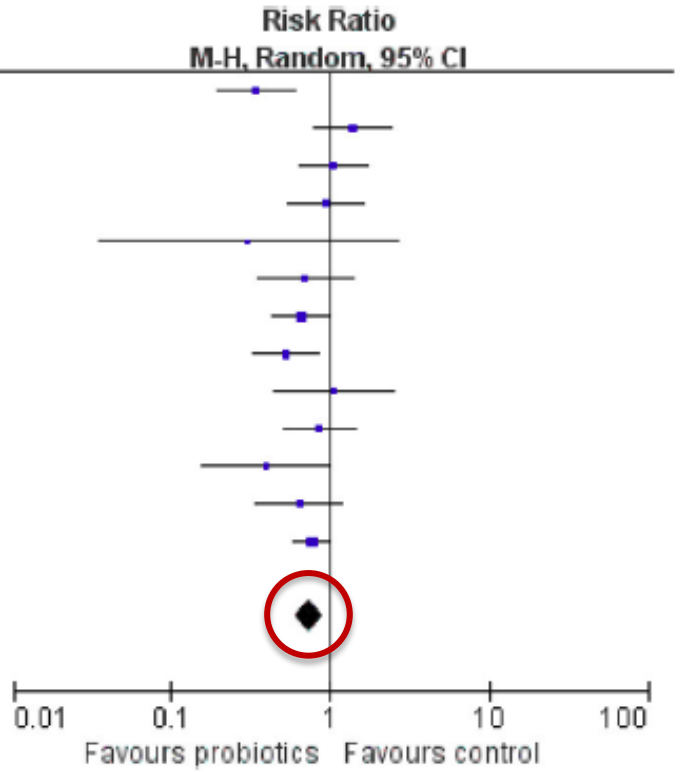
Probiotics

Ventilator-associated pneumonia

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Banupriya 2015	12	75	35	75	7.8%	0.34 [0.19, 0.61]
Barraud 2010	23	78	15	71	8.0%	1.40 [0.79, 2.46]
Forestier 2008	24	102	24	106	9.3%	1.04 [0.63, 1.71]
Giamarellos-Bourboulis 2009	15	36	16	36	8.6%	0.94 [0.55, 1.60]
Klarin 2008	1	23	3	21	0.8%	0.30 [0.03, 2.70]
Knight 2009	12	130	17	129	6.0%	0.70 [0.35, 1.41]
Li 2012	24	82	37	83	11.2%	0.66 [0.43, 0.99]
Morrow 2010	17	68	33	70	9.6%	0.53 [0.33, 0.86]
Oudhuis 2011	10	130	9	124	4.3%	1.06 [0.45, 2.52]
Rongrungruang 2015	18	72	22	75	8.6%	0.85 [0.50, 1.45]
Spindler-Vesel 2007	4	26	34	87	3.8%	0.39 [0.15, 1.01]
Tan 2011	7	16	13	19	6.9%	0.64 [0.34, 1.21]
Zeng 2016	48	118	62	117	15.1%	0.77 [0.58, 1.01]
Total (95% CI)		**956**		**1013**	**100.0%**	**0.73 [0.60, 0.89]**
Total events	215		320			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 20.16$, $df = 12$ ($P = 0.06$); $I^2 = 40\%$

Test for overall effect: $Z = 3.06$ ($P = 0.002$)



Risk Ratio for VAP
0.73 (95% 0.60-0.89)

Frontiers in Pharmacology 2017;8:717

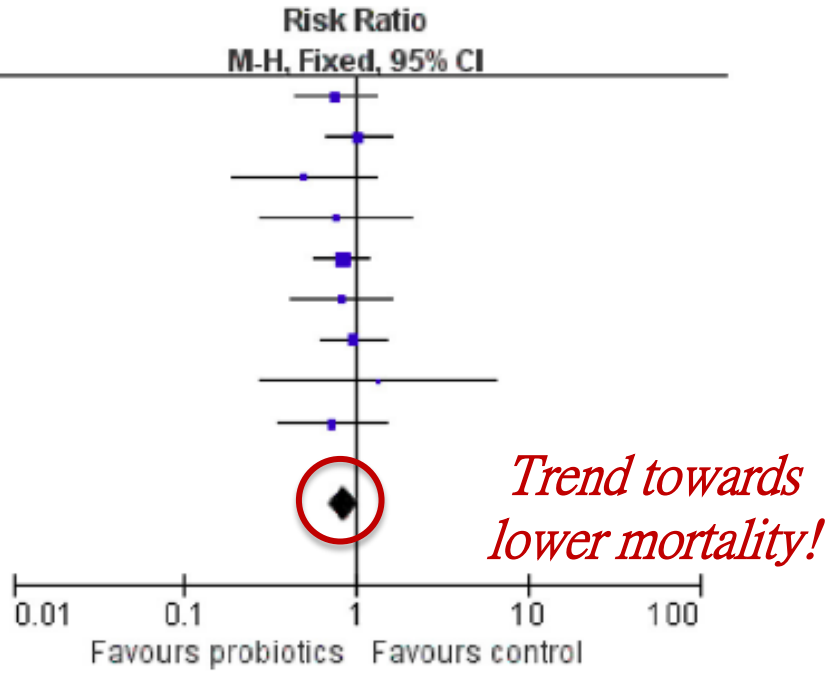
Probiotics

Overall Mortality

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Banupriya 2015	17	70	23	72	13.8%	0.76 [0.45, 1.30]
Barraud 2010	27	87	24	80	15.2%	1.03 [0.65, 1.64]
Giamarellos-Bourboulis 2009	5	36	10	36	6.1%	0.50 [0.19, 1.32]
Klarin 2008	5	23	6	21	3.8%	0.76 [0.27, 2.13]
Knight 2009	35	130	42	129	25.6%	0.83 [0.57, 1.21]
Morrow 2010	12	68	15	70	9.0%	0.82 [0.42, 1.63]
Rongrungruang 2015	25	75	26	75	15.8%	0.96 [0.62, 1.50]
Spindler-Vesel 2007	2	26	5	87	1.4%	1.34 [0.28, 6.50]
Zeng 2016	11	103	16	108	9.5%	0.72 [0.35, 1.48]
Total (95% CI)		**618**		**678**	**100.0%**	**0.84 [0.70, 1.02]**
Total events	139		167			

Heterogeneity: Chi² = 2.92, df = 8 (P = 0.94); I² = 0%

Test for overall effect: Z = 1.71 (P = 0.09)



Trend towards lower mortality!

Parallel <u>non-significant</u> trends towards fewer ventilator days and shorter ICU length-of-stay

Frontiers in Pharmacology 2017;8:717

Generally Not Recommended

No impact on VAP and/or objective outcomes

- Oral chlorhexidine
- Stress ulcer prophylaxis
- Tapered endotracheal tubes
- Subglottic secretion drainage
- Silver-coated endotracheal tubes
- Monitoring residual gastric volumes
- Early parenteral nutrition
- Kinetic beds
- Prone positioning

Stress Ulcer Prophylaxis

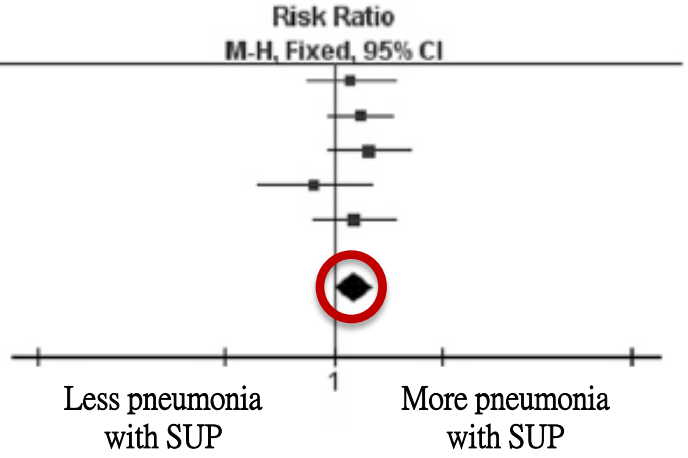
Randomized controlled trials of ulcer prophylaxis vs placebo in patients getting enteral nutrition

Ventilator-associated pneumonia

	Antacid		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Alhazzani 2017	10	49	6	42	18.5%	1.43 [0.57, 3.60]
Apte 1992	11	16	7	18	18.8%	1.77 [0.91, 3.44]
Ben-menachem 1994	25	200	6	100	22.9%	2.08 [0.88, 4.91]
Lin 2016	4	60	6	60	17.2%	0.67 [0.20, 2.24]
Selvanderan 2016	12	106	8	108	22.7%	1.53 [0.65, 3.59]
Total (95% CI)		**431**		**328**	**100.0%**	**1.53 [1.04, 2.27]**
Total events	62		33			

Heterogeneity: Chi² = 2.50, df = 4 (P = 0.65); I² = 0%

Test for overall effect: Z = 2.14 (P = 0.03)



OR 1.53 (95% CI 1.04-2.27)

Higher risk for VAP!

Critical Care 2018;22:20

Stress Ulcer Prophylaxis

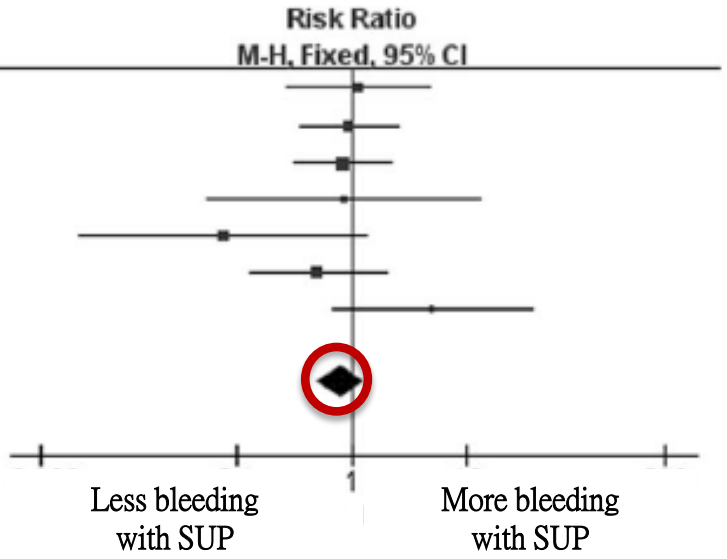
Randomized trials of stress ulcer prophylaxis vs placebo in patients getting enteral nutrition

Gastrointestinal Bleeding

	Antacid		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Alhazzani 2017	4	49	3	42	10.3%	1.14 [0.27, 4.82]
Apte 1992	5	16	6	18	18.0%	0.94 [0.35, 2.49]
Ben-menachem 1994	10	200	6	100	25.5%	0.83 [0.31, 2.23]
El-Kersh 2017	1	55	1	47	3.4%	0.85 [0.05, 13.29]
Lin 2016	0	60	6	60	20.7%	0.08 [0.00, 1.34]
Selvanderan 2016	3	106	6	108	18.9%	0.51 [0.13, 1.98]
Van den Berg 1985	5	14	1	14	3.2%	5.00 [0.67, 37.51]
Total (95% CI)		**500**		**389**	**100.0%**	**0.80 [0.49, 1.31]**
Total events	28		29			

Heterogeneity: $Chi^2 = 6.53$, $df = 6$ ($P = 0.37$); $I^2 = 8\%$

Test for overall effect: $Z = 0.89$ ($P = 0.37$)

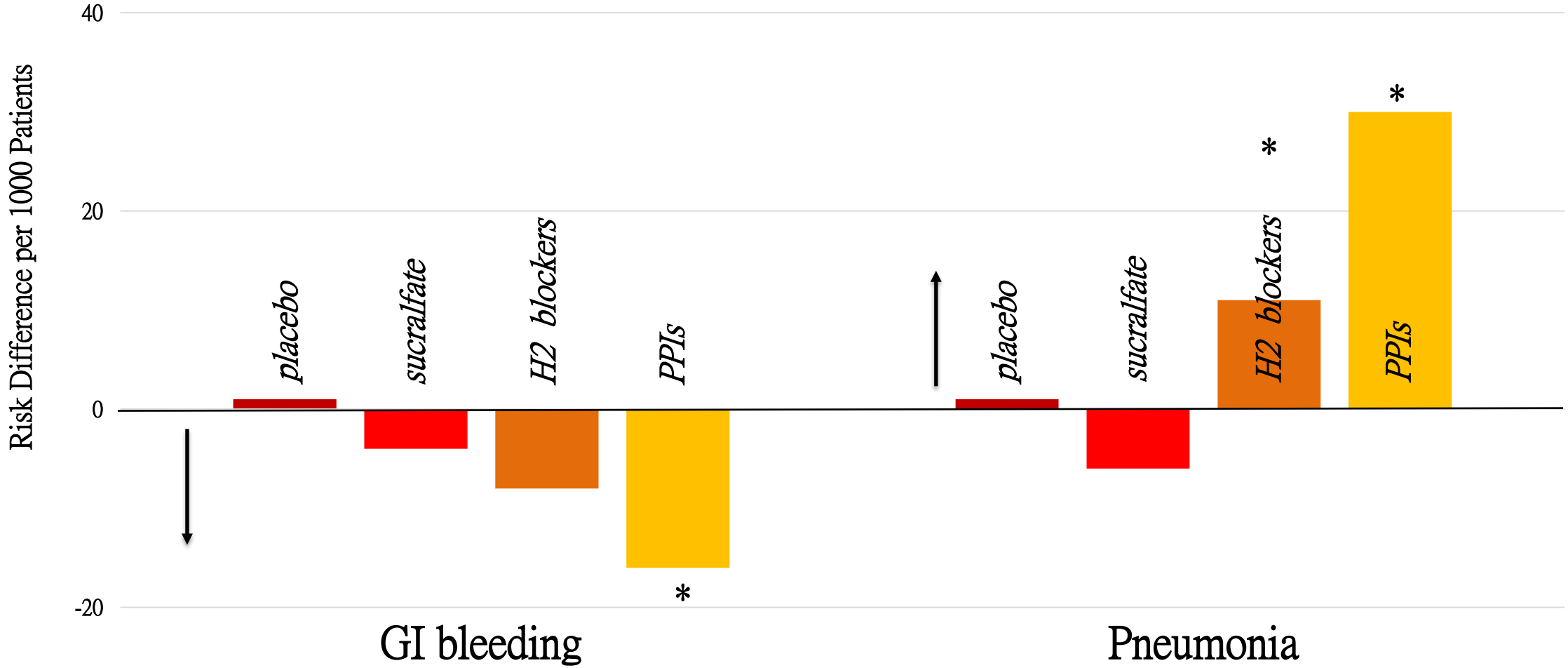


No clear decrease in bleeding!

Critical Care 2018;22:20

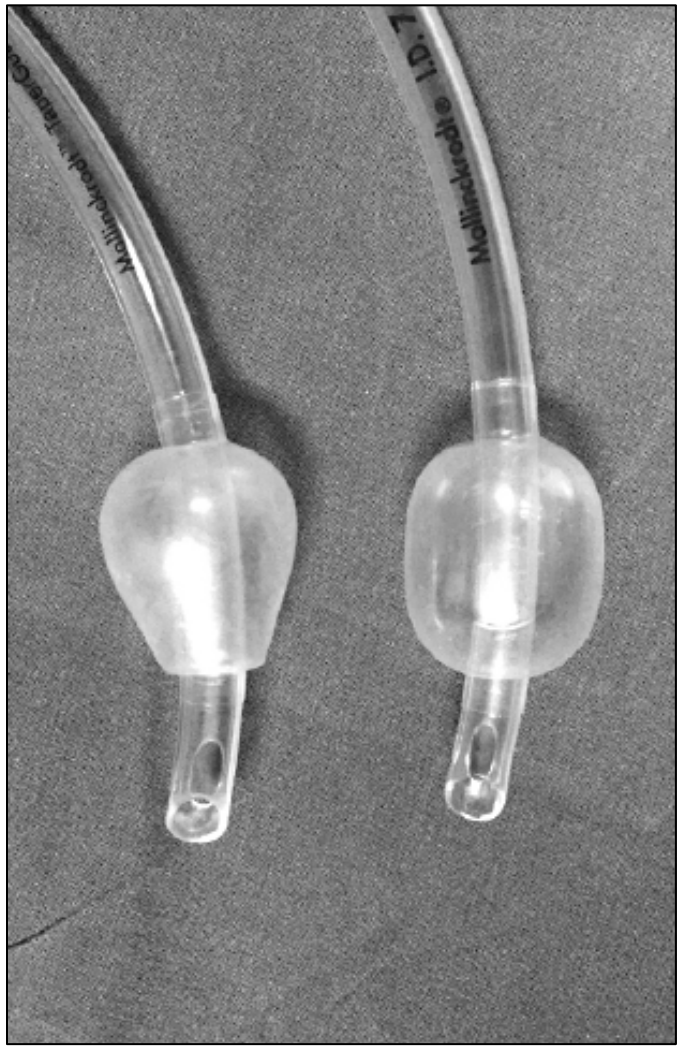
Stress Ulcer Prophylaxis

Network meta-analysis of 57 randomized controlled trials, N=7,293



Intensive Care Med 2018;44:1-11

Tapered vs Conical Endotracheal Tube Cuffs



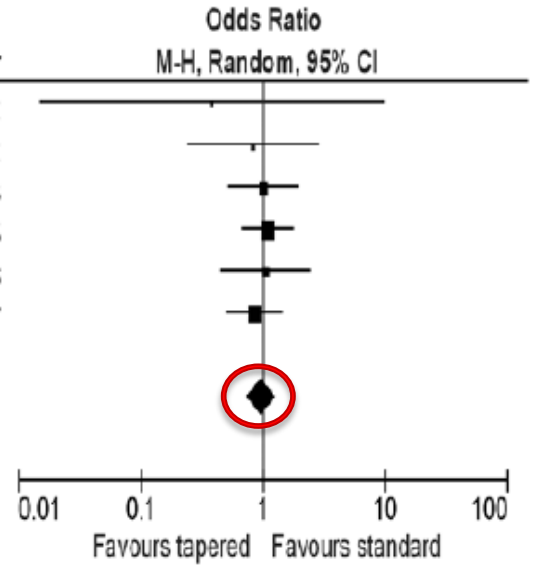
Anesth Pain Med 2017;12:275-280

Animal studies suggest that a tapered cuff may better protect against seepage of secretions around the endotracheal tube cuff

Study or Subgroup	Tapered cuffs Events	Total	Standard cuffs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Bent et al.	0	37	1	43	0.8%	0.38 [0.01, 9.56]	2012
Mahmoodpoor et al.	6	32	7	32	5.4%	0.82 [0.24, 2.79]	2012
Saito et al.	23	106	23	106	18.9%	1.00 [0.52, 1.92]	2013
Philippart et al.	42	282	35	252	34.3%	1.08 [0.67, 1.76]	2015
Monsel et al.	15	52	16	57	11.6%	1.04 [0.45, 2.39]	2016
Jaillette et al.	33	162	38	163	29.0%	0.84 [0.50, 1.43]	2017
Total (95% CI)		**671**		**653**	**100.0%**	**0.97 [0.73, 1.28]**	
Total events	119		120				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.91$, df = 5 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 0.25 (P = 0.81)



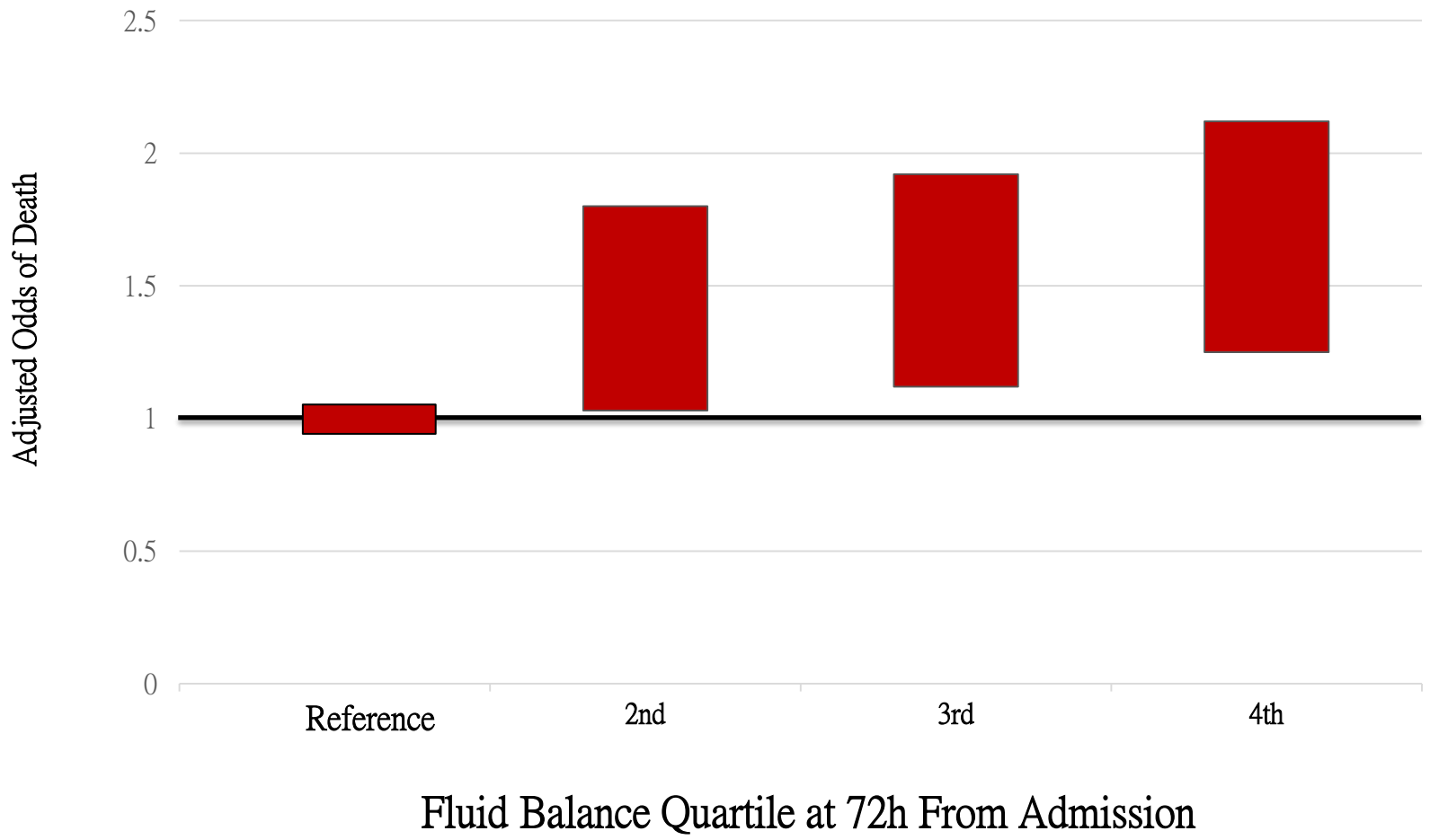
No Impact on VAP Rates !

Crit Care Med 2018;46:316 – 323
Intensive Care Med 2017;43:1562-1571

What’ s missing?

Cumulative Fluid Balance and Risk of Death

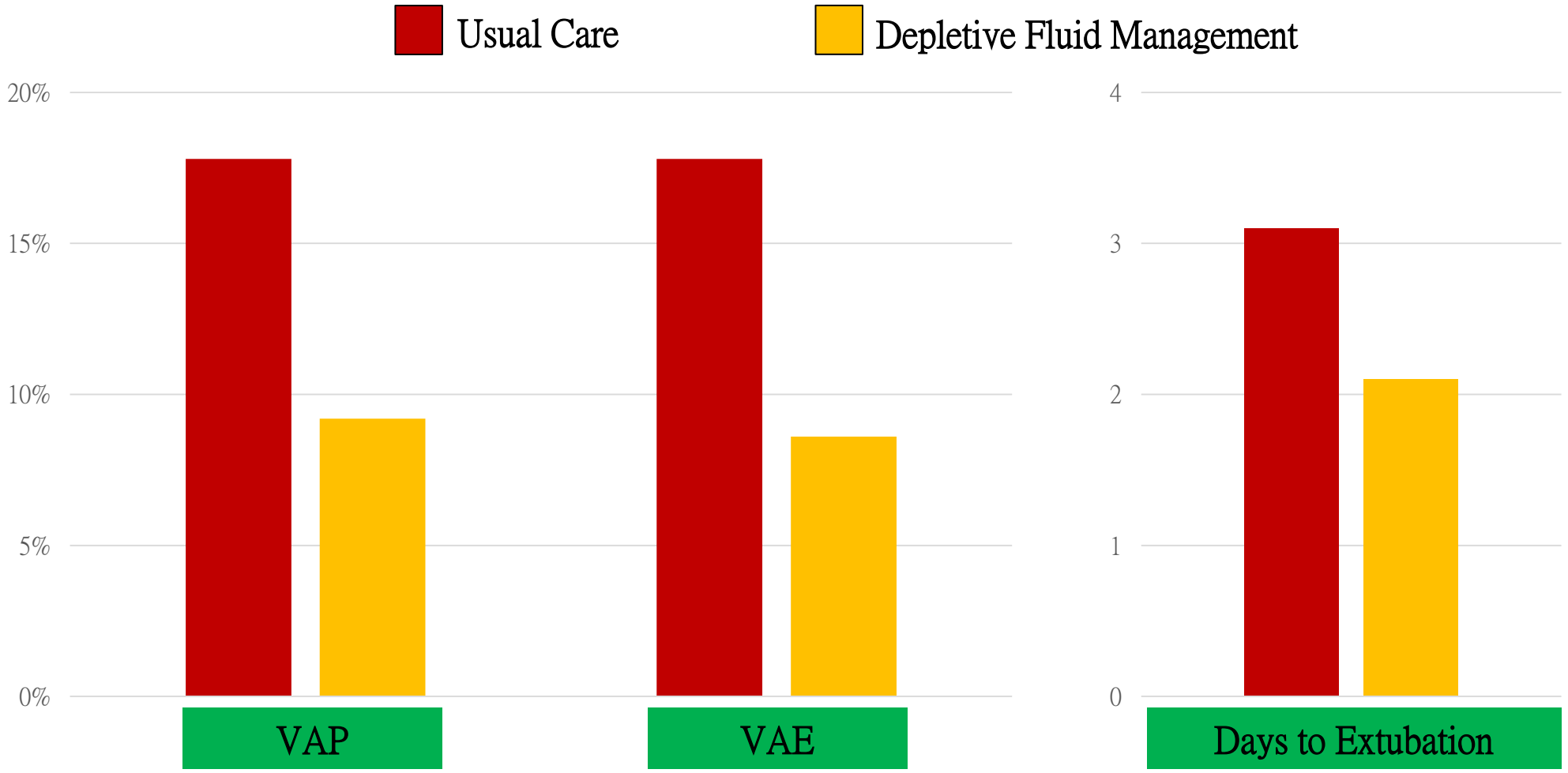
International survey of 1,808 patients with sepsis admitted to an intensive care unit



Crit Care Med 2017:45:386-394

Depletive Fluid Management and VAP

Randomized controlled trial of depletive fluid management during ventilator weaning (smaller volume infusions, more diuresis), N=304



Chest 2014;146:58-65

Summary

- Many interventions proposed to prevent VAP
- Many reported to lower VAP rates but few have been associated with improvements in objective outcomes.
- Possible reasons for the VAP Prevention Paradox
  - VAP diagnosis is subjective (observer bias may favor lower VAP rates)
  - VAP signs are non-specific (interventions may decrease colonization more than infection)
  - Lack of power
- Implication: need to look at objective outcomes for corollary evidence of benefit when evaluating prevention studies

My Recommendations

- Avoid intubation if possible (use non-invasive strategies)
- Elevate the head of the bed
- Provide oral care *without* chlorhexidine
- Minimize sedation
- Paired daily spontaneous awakening and breathing trials
- Early mobility
- Thromboprophylaxis
- Conservative fluid management
- +/- Selective digestive decontamination

Thank You!

mklompas@bwh.harvard.edu