11.2 Supplemental Antioxidant Nutrients: Parenteral Selenium

Question: Does parenteral selenium supplementation (alone or in combination with other antioxidants) result in improved outcomes in the critically ill patient?

Summary of evidence: Of the 22 included studies there were 6 level 1 studies and 16 level 2 studies reviewed. Twelve compared selenium supplementation to none (Kuklinski 1991, Zimmerman 1997, Berger 2001, Lindner 2004, Angstwurm 2007, Forceville 2007, El-Attar 2009, Manzanares 2011, Woth 2014, Chelkelba 2015, Bloos 2016 and Freitas 2017), five that compared higher amounts of selenium to low dose selenium (Angstwurm 1999, Mishra 2007, González 2009, Valenta 2009 & Andrews 2011) and five (Berger 1998, Porter, Berger 2007, Berger 2008, Heyland 2013) that studied selenium supplementation in addition to other antioxidants (copper, zinc, vit E, C, N-acetylcysteine). One study was published in 2 parts (Berger et al Intensive Care Medicine 2001;27:91-100 and Berger et al Nutrition Research (21):41-54). This study had two intervention arms (selenium alone and selenium combined with zinc and α tocopherol compared to placebo) and the data from the two groups have been combined in the meta-analysis. One study (Woth 2014) did not describe the control group.

Mortality: When the attributable data from 21 studies were aggregated, selenium supplementation had no effect on mortality (RR 0.98, 95 % CI 0.90, 1.08, p = 0.69, heterogeneity I^2=0%) (figure 1). When a meta-analysis was done without the Kuklinski study (poor methodological score), there remained no effect on mortality (RR 0.98, 95% % CI 0.90, 1.08, p = 0.74, heterogeneity I^2=0%) (figure 2).

Subgroup analyses: Several subgroup analyses were done to elucidate the effects of selenium on mortality. The details are as follows:

PN selenium monotherapy vs combined: Subgroup analyses showed that PN selenium monotherapy supplementation was associated with a trend in the reduction in mortality (RR= 0.92, 95% CI 0.81, 1.04, P= 0.19; figure 3). PN antioxidants cocktails with selenium had no effect on mortality (RR= 1.08, 95% CI 0.92, 1.25, P= 0.35; figure 3). There was a trend towards a difference in subgroups (P= 0.12; figure 3). Note that in this subgroup analysis, only the monotherapy selenium group from Berger 2001 was included, not the combined selenium group.

PN selenium loading dose vs no loading dose: Subgroup analyses showed that a PN loading dose had no effect on mortality (RR= 0.90, 95% CI 0.75, 1.08, P= 0.27; test for heterogeneity I^2 =18%; figure 4). The same was seen when the studies that did not have a loading dose were aggregated (RR= 1.01, 95% CI 0.89, 1.08, P= 0.88; figure 4). The test for subgroup differences was not statistically significant (P=0.31; figure 4).

PN selenium high dose vs low dose: Subgroup analyses showed that high daily dose of PN Selenium >500µg (RR= 0.97, 95% CI 0.86, 1.11, P= 0.69; figure 5), doses =500µg (RR= 0.87, 95% CI 0.57, 1.32, P= 0.50; figure 5) and low doses <500µg (RR 0.93, 95% CI 0.66, 1.30, P= 0.67; figure 5) had no effects on mortality. The test for subgroup differences was not significant (P= 0.31; figure 5).

Infections: A total of 15 studies reported on infections. Berger 1998, Berger 2007, Mishra 2007 and Woth 2014 did not report on the number of patients with infections, while Forceville 2007 reported on a subgroup of infections. Hence, only the data from 9 studies were included in the meta-analysis, and when aggregated, selenium supplementation was associated with a trend towards a reduction in infectious complications (RR 0.95, 95 % CI 0.88, 1.02, p = 0.16, test for heterogeneity I^2=0%, figure 6).

Subgroup analyses: Several subgroup analyses were done to elucidate the effects of selenium on infections. The details are as follows:

PN selenium monotherapy vs combined: Subgroup analyses showed that selenium monotherapy was not associated with a reduction in infectious complications (RR= 0.96, 95% CI 0.82, 1.09, P= 0.46; figure 7), but selenium in combined therapy was associated with a trend towards reduction in infectious complications (RR 0.90, 95% CI 0.77, 1.05, P= 0.16; figure 7); test for subgroup differences was not significant (P=0.59; figure 7). Note that in this subgroup analysis, only the monotherapy selenium group from Berger 2001 was included, not the combined selenium group.

PN selenium loading dose vs no loading dose: Subgroup analyses showed that a PN loading dose showed no effect in infectious complications (RR= 0.99, 95% CI 0.90, 1.09, P=0.84; figure 8). Meanwhile, PN selenium without a loading dose showed a significant reduction on infections (RR 0.87, 95% CI 0.77, 0.99, P=0.04; figure 8); there was a trend towards subgroup differences (P=0.12; figure 8).

PN selenium high dose vs low dose: Subgroup analyses showed that PN doses >500µg/d had no effect on infections (RR= 0.97, 95% CI 0.89, 1.05, P= 0.46; figure 9). Doses =500µg/d also showed no effect on infections (RR= 0.91, 95% CI 0.67, 1.22, P=0.51; figure 9). Whereas, doses <500µg/d showed a trend towards a reduction in infections (RR= 0.86, 95% CI 0.71, 1.04, P= 0.13; figure 9). The test for subgroup differences was not significant (P= 0.53; figure 9).

Ventilator Associated Pneumonia (VAP): When the 4 studies were aggregated, selenium supplementation (alone or in combination), was associated with a significant reduction in the occurrence of VAP (RR 0.69, 95% CI 0.55, 0.86, p=0.0008; figure 10).

LOS and Ventilator days: Eleven studies reported ICU LOS as a mean ± standard deviation but there were no significant differences between the groups when the data were aggregated (WMD 0.27. 95% CI -1.01, 1.55, p = 0.68, heterogeneity I^2=10%) (see figure 11). When the 7 studies that reported hospital LOS as a mean ± standard deviation were aggregated, there were no significant differences between the groups (WMD -0.80, 95

% CI -3.66, 2.05, p = 0.58, heterogeneity I^2=0%) (figure 12). The Bloos study did not report on LOS in mean and standard deviation but found a trend towards a reduction in ICU LOS (p=0.08) and a significant reduction in hospital LOS (p=0.015) in the group supplemented with selenium. When the 7 studies that reported ventilator days as mean ± standard deviation were aggregated, there was a trend in the reduction of ventilator days in the selenium group (WMD -2.14, 95% CI -4.94, 0.66, p=0.13, heterogeneity I^2=76%; figure 13).

Quality of Life (QOL) Outcomes: Berger 2008 and Andrews 2011 reported on QOL outcomes. Berger 2008 conducted the SF-36 questionnaire at 3 months and found a trend towards improved physical activity score in the selenium group. There was no difference between the groups for physical limitation, physical pain and perceived health scores (Table 2). Andrews 2011 completed the SF-12 physical and mental composite scale score and the EQ-5D instrument at 3 and 6 months with survivors and found no significant difference between groups (Table 2).

Conclusions:

1) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) has no effect on mortality in critically ill patients
2) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) may be associated with a reduction in infectious complications in the critically ill but if real, the treatment effect is likely small.
3) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) has no effect on ICU length of stay or hospital length of stay
4) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) may be associated with a reduction in ventilator days.
5) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) has no effect on the QOL of critically ill patients.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized Studies Evaluating Selenium Supplementation In Critically Ill Patients

Study	Population	Methods score	Intervention
1) Kuklinski 1991	Patients with acute pancreatic necrosis N=17	C. Random: not sure ITT: no Blinding: no (4)	PN + selenium supplementation (500 μg /d) vs. PN without selenium supplementation
2) Zimmerman 1997	Patients with SIRS and sepsis, APACHE > 15 and multiorgan failure score >6 N=40	C. Random: no ITT: yes Blinding: no (6)	IV Selenium as sodium selenite 1000 μg as a bolus and then 1000μg sodium selenite 24 hrs as a continuous infusion over 28 days vs. standard
3) Berger 1998	Burns > 30 % TBSA N=20	C. Random: yes ITT: yes Blinding: double blind (12)	IV Copper (40.4 μmol), selenium (159 μg), zinc (406 μmol) + standard trace elements vs. standard trace elements (Copper 20 μmol, selenium 32 μg, zinc 100 μmol) from day 0- 8, all received early EN
4) Angstwurm 1999	Patients with systematic inflammatory response syndrome and sepsis from 11 ICUs N=42	C. Random: not sure ITT: yes Blinding: no (10)	PN with high dose selenium (535 μg x 3 days, 285 μg x 3 days and 155 μg x 3 days and 35 μg thereafter) vs. low dose selenium (35 μg/day for duration of study)
5) Porter 1999	Surgical ICU Penetrating trauma patients with injury severity score ≥ 25 N=18	C. Random: yes ITT: yes Blinding: no (9)	50 μg selenium IV q 6 hrs + 400 IU Vit E, 100 mg Vit. C q 8 hrs and 8 g of N-acetylcysteine (NAC) q 6 hrs via nasogastric or oral route, from Day 0-7 vs. none
6) Berger 2001	Trauma patients, surgical ICU N=32	C. Random: yes ITT: no Blinding: double (9)	IV Selenium supplementation (500 μg/day) vs. placebo (Selenium group randomized further to two groups: 500 μg Selenium alone vs. 500 μg Selenium + 150 mg α tocopherol + 13 mg zinc) given slowly for 1st 5 days after injury (All groups received EN)
7) Lindner 2004	Patients with acute pancreatitis admitted to the ICU N=70	C. Random: not sure ITT: no Blinding: single (9)	IV sodium selenite dose of 2000 μg on day 1, 1000 μg on days 2-5, and 300 μg from day 6 until discharge vs placebo (isotonic 0.9% IV NaCl solution).

8) Angstwurm 2007	Septic patients, multicentre mixed ICUs N=249	C.Random: not sure ITT: no Blinding: double (8)	1000μg Selenium IV within 1 hr followed by 1000μg Selenium for 14 days vs. NaCl (0.9%) (all patients received EN or PN)
9) Berger 2007	Burns > 20 % TBSA N=21	C.Random: not sure ITT: yes Blinding: no (8)	IV 100 ml of Copper (59 μmol) + Selenium (375 μgm + zinc (574 μmol) vs. NaCl (0.9%) from admission for 5-15 days. Both groups were on EN.
10) Forceville 2007	Septic shock patients from 7 ICUs N=60	C.Random: not sure ITT: no Blinding: double (8)	4000μg Selenium IV on day 1 followed by 1000μg Selenium for 9 days vs. NaCl (0.9%) (all patients received EN or PN)
11) Mishra 2007	Septic ICU patients N=40	C.Random: not sure ITT: yes Blinding: double (9)	474 μg Selenium IV x 3 days followed by 316 μg x 3 days, 158 μg x 3 days and 31.6 μg thereafter vs. 31.6 μg Selenium (all patients received EN or PN).
12) Berger 2008	Mixed ICU N=200	C.Random: not sure ITT: yes Blinding: no (10)	IV Selenium supplementation loading dose 540 μg/day + zinc (60 mg) + Vit C 2700 mg + Vit B 305 mg + Vit E enteral 600 mg + Vit E 12.8 mg IV for 2 days followed by half the dose of all vs. standard vitamins. (All groups received EN or PN)
13) El-Attar 2009	COPD patients N=80	C.Random: yes ITT: yes Blinding: yes (12)	IV selenium as sodium selenite 100 μg/day, zinc 2 mg/day and manganese 0.4 mg/day vs. none. TE were administered during the period on mechanical ventilation
14) González 2009	Medical/surgical ICU pts N=68	C.Random: yes ITT: yes Blinding: double (7)	day 1 IV sodium selenite 1000μg , day 2 sodium selenite 500 μg and thereafter 200 μg during seven additional days vs selenite 100 μg/d
15) Andrews 2011	Mixed ICU, multicentre N=502	C. Random: yes ITT: yes Blinding: double blind (13)	500μg selenium supplemented PN (12.5g nitrogen, 2000kcal) vs. standard PN (12.5g nitrogen, 2000kcal) initiated after ICU admission (actual median 2.6 days) for 7 days (actual duration, mean 4.1 days).

16) Manzanares 2011	Septic or trauma patients N=31	C. Random: not sure ITT: no (except mortality) Blinding: single blind (9)	IV Selenium supplementation loading dose 2000 μg (2 hours) on day 1 followed by 1600μg/day for 10 days vs. NaCl as placebo
17) Valenta et al, 2011	Patients with sepsis or SIRS N=150	C. Random: not sure ITT: yes Blinding: no (8)	IV Selenium supplementation loading dose 1000 μg on day 1 followed by 500μg/day for 5-14 days + <75μg/day of Na-selenite added to PN. vs. NaCl + <75μg/day of Na-selenite added to PN.
18) Heyland 2013	Multicenter mixed ICUs N=1218	C. Random: yes ITT: yes Blinding: double (12)	500 μg selenium via PN + 300 μg selenium, 20 mg zinc, 10 mg beta carotene, 500 mg vitamin E, 1500 mg vitamin C via EN vs. placebo via PN and EN
19) Woth 2014	Mixed ICU, severe septic pts w multi-organ failure N=40	C. Random: not sure ITT: yes Blinding: no (6)	1000-μg/30 minutes loading dose of Na selenite and 1000-μg/die treatment for a maximum of 14 days vs control group (not described).
20) Chelkeba 2015	Single centre ICU pts with sepsis or septic shock enrolled 6 hours after diagnosis. N=54	C. Random: yes ITT: yes Blinding: no (11)	IV loading dose of 2000 μg of sodium selenite in 100 mL of normal saline given over 1 hour within the first 6 hrs of diagnosis of sepsis followed by 1500 μg of sodium selenite in 250 mL given for 12 hrs continuously for 14 days vs standard nutrition therapy (included EN or PN as per hospital best practice)
21) Bloos 2016	Multicentre Mixed ICU pts with severe sepsis or septic shock in last 24 hrs. N=1180	C. Random: yes ITT: yes Blinding: double (12)	IV loading dose of 1000 μg sodium selenite followed by continuous IV of 1000 μg sodium selenite daily until ICU discharge or for 21 days, whichever comes first.vs. placebo (NaCl)
22) Freitas 2017	Single centre ICU patients with high CRP receiving PN as main nutrition source. N=20	C. Random: no ITT: no Blinding: double (5)	Standard PN supplemented with an additional 60 micrograms (0.75 micromol) of selenious acid vs standard PN.

D5W: dextrose 5% in water
ICU: intensive care unit
SIRS: systemic inflammatory response syndrome
COPD: chronic obstructive pulmonary disease
ITT: intention to treat; IV: intravenous
C.Random: concealed randomization
N: number of patients
TBSA: total body surface area.
EN: enteral nutrition
PN: parenteral nutrition

Table 1. Randomized Studies Evaluating Selenium Supplementation In Critically Ill Patients (continued)

Study	Mortality (%) Experimental	Mortality (%) Control	Infections (%) Experimental	Infections (%) Control	LOS days Experimental	LOS days Control	Renal Parameters
1) Kuklinski 1991	ICU 0/8 (0)	ICU 8/9 (89)	NR	NR	NR	NR	NR
2) Zimmerman 1997	3/20 (15)	8/20 (40)	NR	NR	NR	NR	NR
3) Berger 1998	1/10 (10)	0/10 (0)	1.9 ± 0.9 (1-4) per patient	3.1 ± 1.1 (2-5) per patient	ICU 30 ± 12 (10) Hospital 54 ± 27 (10)	ICU 39 ± 13 (10) Hospital 66 ± 31 (10)	Exp Control CRRT required 0 1 (13d duration)
4) Angstwurm 1999	Hospital 7/21 (33)	Hospital 11/21 (52)	NR	NR	NR	NR	*Excluded pts with chronic renal failure Exp Control CVVHD, p=0.04 3/21 9/21 Median serum creatinine Day 0 were identical, afterwards lower in experimental group Day 3, p=0.034 Day 7, p=0.03 Day 14, p=0.057
5) Porter 1999	0/9 (0)	0/9 (0)	5/9 (56)	8/9 (89)	ICU 22 ± 25.2 Hospital 31.3 ± 23.4	ICU 35.8 ± 21.9 Hospital 49 ± 30	Exp Control Renal organ dysfunction (s. creatinine >2 mg/dL or need for dialysis) 0/9 2/9
6) Berger 2001	Selenium alone 2/9 (22) Selenium + zinc + α tocopherol 0/11 (0)	1/11 (9)	Selenium alone 5/9 (56) Selenium + zinc + α tocopherol 3/11 (27)	3/11 (27)	Selenium alone ICU 8.0 ± 4.0 (9) Hospital 82 ± 78 (9) Selenium + zinc + α tocopherol ICU 5.8 ± 4.4 (11) Hospital 60 ± 48 (11)	ICU 8.6 ± 8.1 (11) Hospital 64 ± 39 (11)	*Excluded pts with pre-existing renal failure Selenium Control Complications: renal failure 0/9 0/11 Ventilator Days 5.1 ± 3.7 (20) 4.2 ± 5.2 (11)

					Selenium groups combined ICU 6.1 ± 3.9 (20) Hospital 68 ± 60 (20)		
7) Linder 2004	Not specified 5/32 (15.6)	Not specified 3/35 (8.6)	NA	NA	Hospital 24 (9-44)	Hospital 26 (11-46)	Exp Control Renal Insufficiency (s. creatinine > 150 µmol) 6/32 2/35
8) Angstwurm 2007	28 day 46/116 (40)	28 day 61/122 (50)	New infections (HAP) 10/116 (9)	New infections (HAP) 10/122 (8)	ICU 15.1 ± 10 (116)	ICU 12.7± 9 (122)	Rate of renal failure was not different between groups and not related to high selenium levels. The need for dialysis was not different between groups
9) Berger 2007	1/11 (9)	1/10 (10)	2.1 ± 1.0 per patient	3.6 ± per patient	ICU 35 ± 27 (11)	ICU 47 ± 37 (10)	*excluded severe renal failure (creatinine clearance <60 mL/min on admission)
10) Forceville 2007	28 day 14/31 (45) 6 Month 18/31 (59) 1 year 66%	28 day 13/29 (45) 6 Month 20/29 (68) 1 year 71%	Superinfection**** 1/31 (3)	Superinfection**** 2/29(7)	ICU 21 (7-40) Hospital 25 (7-68)	ICU 18 (10-31) Hospital 33 (11-51)	*excluded end phase chronic disease – unclear if this includes CKD Exp Control SAE – renal failure, p=0.483 0/31 1/29 (3%) Dialysis free days, p=0.303 37±55 26±49
11) Mishra 2007	ICU 8/18 (44) Hospital 11/18 (61) 28 day 8/18 (44)	ICU 11/22 (61) Hospital 15/22 (68) 28 day 11/22 (50)	1.5 ± 1.9 per patient	1.8 ± 1.6 per patient	ICU 21.3 ± 16.2 (18)	ICU 20.8 ± 21.8 (18)	*excluded chronic renal failure pts* Exp Control CRRT, p=0.99 5/18 7/22 RRT free days, p=0.2 83.8% 88.1% No significant change in eGFR by day 14 in either group or any significant difference in eGFR between the two groups (table 3). No significant difference in plasma creatinine (table 3) Dialysis, day 0 11% 22% Dialysis, day 3 25% 28% Dialysis, day 7 0% 19% Dialysis, day 14 9% 26%

12) Berger 2008	ICU 8/102 (8) Hospital 14/102 (14) 3 month 14/102 (14)	ICU 5/98 (5) Hospital 9/98 (11) 3 month 11/98 (11)	36/102 (35)	34/98 (35)	ICU 5.8 ± 5.4 (102) Hospital 23 ± 20 (102)	ICU 5.4 ± 5.7 (98) Hospital 26 ± 20 (98)	Exp Control AKI, any grade, p=0.11 29/102 (30%) 36/98 (37%) ARF increase 50 micromol/L, p=not significant 15/102 (15%) 17/98 (17%) ARF increase of 90 micromol/L, p=not significant 7/102 (7%) 9/98 (9%) CVVH (6/7 had pre-existing renal failure), p=0.05 6/102 1/98 Persistent renal failure, p=not significant 4/102 (4%) 7/98 (7%)
13) El-Attar 2009	ICU 2/40 (5.6)	ICU 1/40 (2.9)	VAP 5/36 (14)	VAP 7/34 (21)	NR	NR	**to eliminate confounding variables, patients with concomitant renal disease were excluded*
14) González 2009	Hospital 6/34 (18)	Hospital 8/34 (24)	NR	NR	Hospital 12(12-14)	Hospital 17(14-20)	NR
15) Andrews 2011	ICU 84/251 (33) 6-month 107/251 (43)	ICU 84/251 (33) 6-month 114/251 (45)	Confirmed 104/251 (41)	Confirmed 121/251 (48)	ICU 13.2 (IQR 7.8- 23.7) Hospital 29.8 (IQR 14.7-52.4)	ICU 15.1 (IQR 8.3-28.4) Hospital 31.2 (IQR 15.1-57.8)	**excluded pts with estimated glomerular filtration rate <10 ml/min and not receiving renal replacement therapy*
16) Manzanares 2011	ICU 3/15 (20) Hospital 5/15 (33)	ICU 5/16 (31) Hospital 7/16 (44)	VAP 3/15 (20)	VAP 7/16 (44)	ICU 14 ± 11 (15)	ICU 13 ± 6 (16)	**excluded chronic renal failure pts* Use of RRT 0 0 AKI, p=0.82 7/15 (44%) 8/16 (50%)
17) Valenta 2011	28-day 19/75 (25)	28-day 24/75 (32)	NR	NR	NR	NR	NR
18) Heyland 2013	Hospital 216/617 (35) 14-day 154/617 (25) 28-day 190/617 (31) 3-month 239 6-month 250	Hospital 199/601 (33) 14-day 132/601 (22) 28-day 173/601 (29) 3-month 222 6-month 235	All 168/617 (27) VAP 71/617 (12)	All 181/601 (30) VAP 95/601 (16)	ICU 14.2 ± 22.7 (617) Hospital 31.2 ± 50.2 (617)	ICU 13.8 ± 23.1 (601) Hospital 29.5 ± 44.8 (601)	NR

19) Woth 2014	In 14 day study period 9/21 (43)	In 14 day study period 11/19 (58)	Gram negative 8/21 (38) Gram positive 3/21 (14) Fungal 1/21 (5)	Gram negative 3/19 (16) Gram positive 2/19 (11) Fungal 0/19 (0)	NR	NR	NR
20) Chelkeba 2015	28 day 9/29 (31)	28 day 10/25 (40)	VAP 16/29(55.2) Early VAP 15/29 (51.7) Late VAP 5/29 (17.2)	VAP 21/25 (84%) Early VAP 15/25 (60%) Late VAP 11/25 (44%)	ICU 19.7 ± 11 (29) Hospital 25.2 ± 10 (29)	ICU 23.8 ± 13 (25) Hospital 24.5 ± 9 (25)	NR
21) Bloos 2016	28 day 152/543 (28) 90 day 198/543 (38)	28 day 137/546 (25) 90 day 201/546 (38)	Secondary infections, Day 14 243/543 (44.7%) Secondary infections, Day 21 319/543 (58.8%)	Secondary infections, Day 14 269/546 (49.3%) Secondary infections, Day 21 323/546 (59.2%)	ICU 11 (5-22) Hospital 26 (16-42)	ICU 12 (6-24) Hospital 29 (17-50)	No renal dysfunction (n=497) OR 1.3 (0.8; 2.1), p=0.337 Subgroup: AND no post-baseline dialysis (n=427) OR 1.3 (0.7; 2.1), p=0.463 Subgroup: AND post-baseline dialysis (n=67) OR 1.3 (0.4; 3.9), p=0.652 Renal dysfunction (n=458) OR 1.0 (0.7; 1.5), p=0.925 Subgroup: AND no post-baseline dialysis (n=212) OR 1.2 (0.6; 2.3), p=0.584 Subgroup: AND post-baseline dialysis (n=235) OR 0.9 (0.5; 1.5), p=0.562 RRT Free days Exp/PCT 8(3-17) Exp/NoPCT 8(3-17) ctrl/PCT 7(3-18) ctrl/NoPCT 7(3-16)
22) Freitas 2017	14 day 1/8	14 day 3/12	NR	NR	NR	NR	NR

COPD: chronic obstructive pulmonary disease
HAP: hospital acquired pneumonia
NR: non reported
SIRS: systemic inflammatory response syndrome
C.Random: concealed randomization
ICU: intensive care unit
PN: parenteral nutrition
TBSA: total body surface area
EN: enteral nutrition
ITT: intent to treat
Hosp: hospital
VAP: ventilator associated pneumonia
NA: non attribuible
IV: intravenous

Table 2. Quality of Life (QOL) Outcomes

Study	QOL Outcomes
12) Berger 2008	AOX: Short Form (SF) 36-item health survey Physical Activity Score: 24.2 ± 4.9 Physical Limitation: 5.8 ± 1.4 Physical Pain: 8.9 ± 2.4 Perceived Health: 18.9 ± 4.5 Control: Short Form (SF) 36-item health survey Physical Activity Score: 22.8 ± 5.7, p=0.14 Physical Limitation: 5.5 ± 1.5, p=NS Physical Pain: 9.0 _ 2.7, p=NS Perceived Health: 19.2 ± 4.1, p=NS
15) Andrews 2011	Gln / Gln+Se / Se / Neither SF-12 PCS at 3 months: 35.2 ± 9.8 (49) / 33.3 ± 11.1 (50) / 33.9 ± 9.8 (52) / 36.6 ± 11.6 (59) SF-12 PCS at 6 months: 35.9 ± 9.3 (45) / 35.9 ± 10.9 (43) / 36.3 ± 10.0 (46) / 39.9 ± 10.5 (53) SF-12 MCS at 3 months: 420 ± 11.8 (49) / 40.3 ± 12.0 (50) / 41.9 ± 11.9 (52) / 42.2 ± 12.2 (59) SF-12 MCS at 6 months: 43.4 ± 11.9 (45) / 44.8 ± 11.9 (43) / 44.1 ± 11.6 (46) / 43.3 ± 12.1 (53) EQ-5D at 3 months: 0.47 ± 0.41 (52) / 0.51 ± 0.35 (52) / 0.49 ± 0.35 (55) / 0.56 ± 0.34 (61 EQ-5D at 6 months: 0.53 ± 0.35 (49) / 0.60 ± 0.30 (51) / 0.53 ± 0.33 (47) / 0.63 ± 0.28 (55)

NS: not significant

Figure 1. Mortality (including Kuklinski)

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kuklinski	0	8	8	9	0.1%	0.07 [0.00, 0.98]	1991
Zimmerman	3	20	8	20	0.6%	0.38 [0.12, 1.21]	1997
Berger 1998	1	10	0	10	0.1%	3.00 [0.14, 65.90]	1998
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Porter	0	9	0	9		Not estimable	1999
Berger 2001	2	20	1	11	0.2%	1.10 [0.11, 10.81]	2001
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
Mishra	11	18	15	22	3.9%	0.90 [0.56, 1.43]	2007
Berger 2007	1	11	1	10	0.1%	0.91 [0.07, 12.69]	2007
Angstwurm 2007	46	116	61	122	10.3%	0.79 [0.60, 1.06]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
Montoya	6	34	8	34	0.9%	0.75 [0.29, 1.93]	2009
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Manzanares	3	15	5	16	0.5%	0.64 [0.18, 2.22]	2011
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Andrews	84	251	84	251	13.9%	1.00 [0.78, 1.28]	2011
Heyland	216	617	199	601	34.6%	1.06 [0.90, 1.24]	2013
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Chelkeba	9	29	10	25	1.6%	0.78 [0.38, 1.60]	2015
Bloos	152	543	137	546	21.6%	1.12 [0.92, 1.36]	2016
Freitas	1	8	3	12	0.2%	0.50 [0.06, 4.00]	2017
Total (95% CI)		**1999**		**1980**	**100.0%**	**0.98 [0.90, 1.08]**	
Total events	600		609				

Heterogeneity: Tau² = 0.00; Chi² = 17.56, df = 19 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

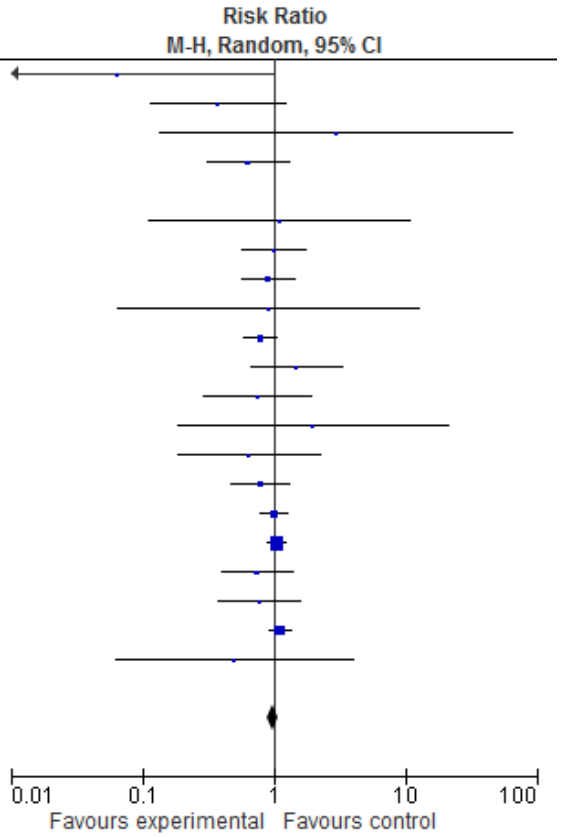

Figure 2. Mortality (excluding Kuklinski)

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Zimmerman	3	20	8	20	0.6%	0.38 [0.12, 1.21]	1997
Berger 1998	1	10	0	10	0.1%	3.00 [0.14, 65.90]	1998
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Porter	0	9	0	9		Not estimable	1999
Berger 2001	2	20	1	11	0.2%	1.10 [0.11, 10.81]	2001
Mishra	11	18	15	22	3.9%	0.90 [0.56, 1.43]	2007
Angstwurm 2007	46	116	61	122	10.4%	0.79 [0.60, 1.06]	2007
Berger 2007	1	11	1	10	0.1%	0.91 [0.07, 12.69]	2007
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Montoya	6	34	8	34	0.9%	0.75 [0.29, 1.93]	2009
Andrews	84	251	84	251	13.9%	1.00 [0.78, 1.28]	2011
Manzanares	3	15	5	16	0.5%	0.64 [0.18, 2.22]	2011
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Heyland	216	617	199	601	34.6%	1.06 [0.90, 1.24]	2013
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Chelkeba	9	29	10	25	1.6%	0.78 [0.38, 1.60]	2015
Bloos	152	543	137	546	21.6%	1.12 [0.92, 1.36]	2016
Freitas	1	8	3	12	0.2%	0.50 [0.06, 4.00]	2017
Total (95% CI)		**1991**		**1971**	**100.0%**	**0.98 [0.90, 1.08]**	
Total events	600		601				

Heterogeneity: Tau² = 0.00; Chi² = 13.74, df = 18 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

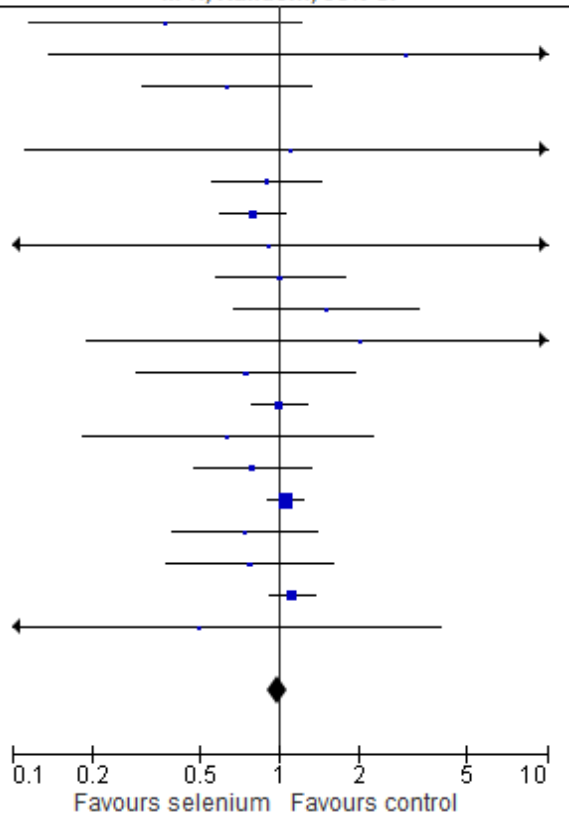

Figure 3 SUBGROUP ANALYSES: MORTALITY: PN selenium monotherapy vs combined

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
4.3.1 PN Selenium Monotherapy							
Kuklinski	0	8	8	9	0.1%	0.07 [0.00, 0.98]	1991
Zimmerman	3	20	8	20	0.6%	0.38 [0.12, 1.21]	1997
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Berger 2001	2	9	1	11	0.2%	2.44 [0.26, 22.80]	2001
Mishra	11	18	15	22	3.9%	0.90 [0.56, 1.43]	2007
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
Angstwurm 2007	46	116	61	122	10.3%	0.79 [0.60, 1.06]	2007
Montoya	6	34	8	34	0.9%	0.75 [0.29, 1.93]	2009
Manzanares	3	15	5	16	0.5%	0.64 [0.18, 2.22]	2011
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Andrews	84	251	84	251	13.9%	1.00 [0.78, 1.28]	2011
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Chelkeba	9	29	10	25	1.6%	0.78 [0.38, 1.60]	2015
Bloos	152	543	137	546	21.6%	1.12 [0.92, 1.36]	2016
Freitas	1	8	3	12	0.2%	0.50 [0.06, 4.00]	2017
Subtotal (95% CI)		**1199**		**1212**	**63.7%**	**0.92 [0.81, 1.04]**	
Total events	366		399				
Heterogeneity: Tau² = 0.00; Chi² = 14.65, df = 14 (P = 0.40); I² = 4%							
Test for overall effect: Z = 1.30 (P = 0.19)							
4.3.2 PN Selenium Combined							
Berger 1998	1	10	0	10	0.1%	3.00 [0.14, 65.90]	1998
Porter	0	9	0	9		Not estimable	1999
Berger 2007	1	11	1	10	0.1%	0.91 [0.07, 12.69]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Heyland	216	617	199	601	34.6%	1.06 [0.90, 1.24]	2013
Subtotal (95% CI)		**789**		**768**	**36.3%**	**1.08 [0.92, 1.25]**	
Total events	234		210				
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 4 (P = 0.84); I² = 0%							
Test for overall effect: Z = 0.94 (P = 0.35)							
Total (95% CI)		**1988**		**1980**	**100.0%**	**0.98 [0.90, 1.08]**	
Total events	600		609				
Heterogeneity: Tau² = 0.00; Chi² = 18.19, df = 19 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.37 (P = 0.71)							
Test for subgroup differences: Chi² = 2.40, df = 1 (P = 0.12), I² = 58.4%							

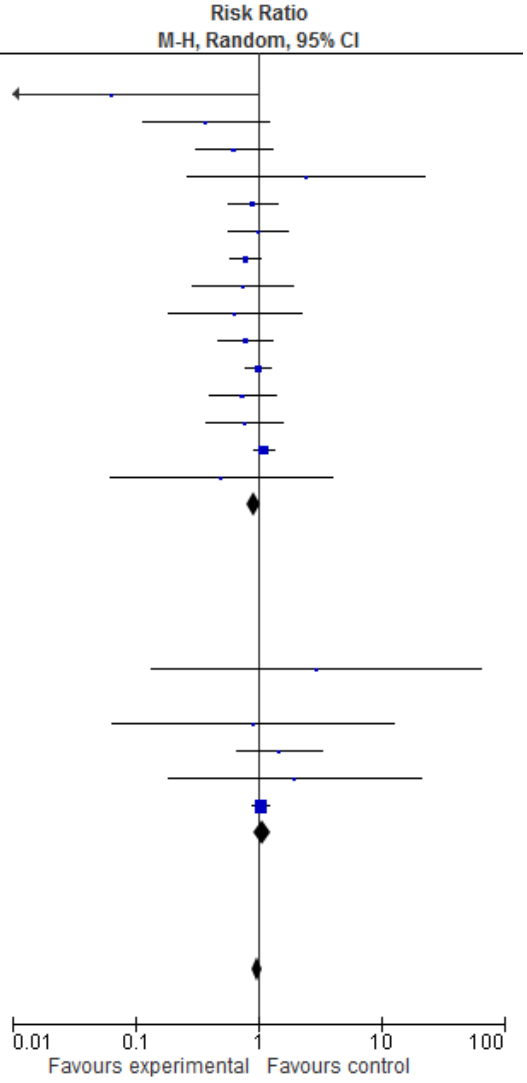

Figure 4 SUBGROUP ANALYSES: MORTALITY: PN Selenium loading dose vs no loading dose:

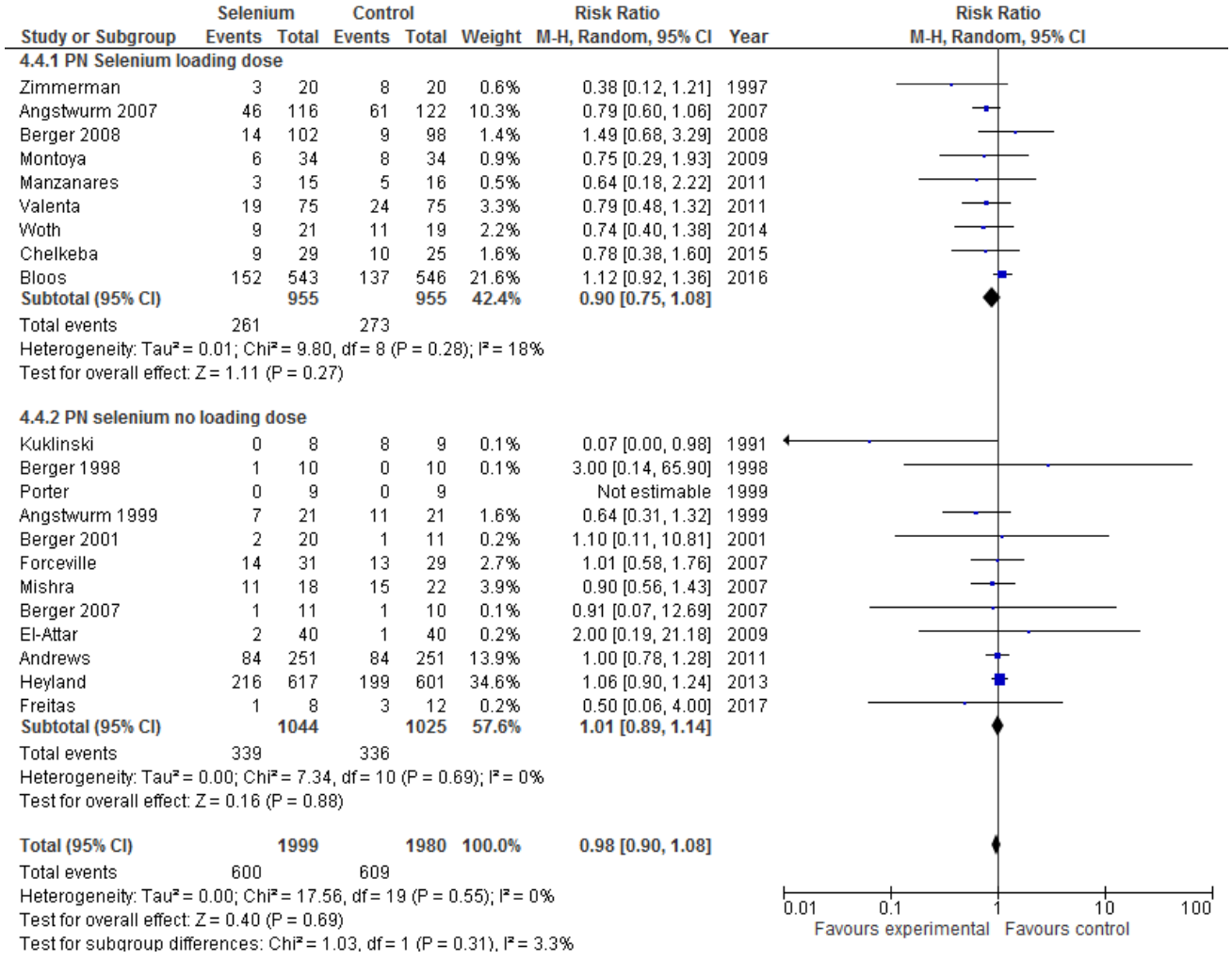

Figure 5. SUBGROUP ANALYSES: MORTALITY: PN Selenium high dose vs low dose

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
4.4.1 PN Selenium loading dose							
Zimmerman	3	20	8	20	0.6%	0.38 [0.12, 1.21]	1997
Angstwurm 2007	46	116	61	122	10.3%	0.79 [0.60, 1.06]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
Montoya	6	34	8	34	0.9%	0.75 [0.29, 1.93]	2009
Manzanares	3	15	5	16	0.5%	0.64 [0.18, 2.22]	2011
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Chelkeba	9	29	10	25	1.6%	0.78 [0.38, 1.60]	2015
Bloos	152	543	137	546	21.6%	1.12 [0.92, 1.36]	2016
Subtotal (95% CI)		**955**		**955**	**42.4%**	**0.90 [0.75, 1.08]**	
Total events	261		273				
Heterogeneity: Tau² = 0.01; Chi² = 9.80, df = 8 (P = 0.28); I² = 18%							
Test for overall effect: Z = 1.11 (P = 0.27)							
4.4.2 PN selenium no loading dose							
Kuklinski	0	8	8	9	0.1%	0.07 [0.00, 0.98]	1991
Berger 1998	1	10	0	10	0.1%	3.00 [0.14, 65.90]	1998
Porter	0	9	0	9		Not estimable	1999
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Berger 2001	2	20	1	11	0.2%	1.10 [0.11, 10.81]	2001
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
Mishra	11	18	15	22	3.9%	0.90 [0.56, 1.43]	2007
Berger 2007	1	11	1	10	0.1%	0.91 [0.07, 12.69]	2007
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Andrews	84	251	84	251	13.9%	1.00 [0.78, 1.28]	2011
Heyland	216	617	199	601	34.6%	1.06 [0.90, 1.24]	2013
Freitas	1	8	3	12	0.2%	0.50 [0.06, 4.00]	2017
Subtotal (95% CI)		**1044**		**1025**	**57.6%**	**1.01 [0.89, 1.14]**	
Total events	339		336				
Heterogeneity: Tau² = 0.00; Chi² = 7.34, df = 10 (P = 0.69); I² = 0%							
Test for overall effect: Z = 0.16 (P = 0.88)							
Total (95% CI)		**1999**		**1980**	**100.0%**	**0.98 [0.90, 1.08]**	
Total events	600		609				
Heterogeneity: Tau² = 0.00; Chi² = 17.56, df = 19 (P = 0.55); I² = 0%							
Test for overall effect: Z = 0.40 (P = 0.69)							
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 3.3%							

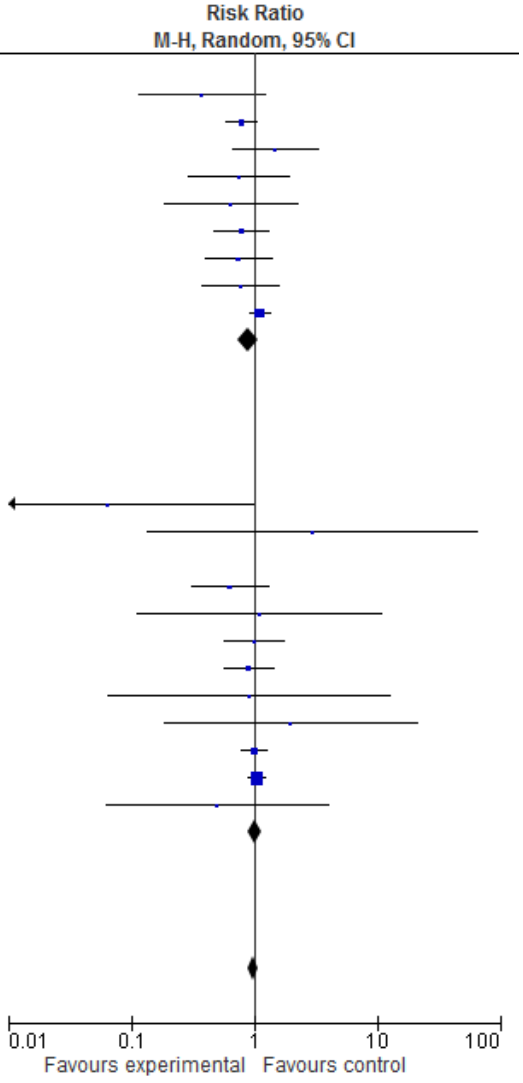

Figure 6. Infections

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Porter	5	9	8	9	1.5%	0.63 [0.33, 1.17]	1999
Berger 2001	8	20	3	11	0.5%	1.47 [0.49, 4.42]	2001
Angstwurm 2007	10	116	10	122	0.8%	1.05 [0.45, 2.43]	2007
Berger 2008	36	102	34	98	4.0%	1.02 [0.70, 1.48]	2008
El-Attar	5	36	7	34	0.5%	0.67 [0.24, 1.92]	2009
Andrews	104	251	121	251	15.2%	0.86 [0.71, 1.04]	2011
Manzanares	3	15	7	16	0.4%	0.46 [0.14, 1.45]	2011
Heyland	168	617	181	601	18.3%	0.90 [0.76, 1.08]	2013
Bloos	319	543	323	546	58.7%	0.99 [0.90, 1.10]	2016
Total (95% CI)		**1709**		**1688**	**100.0%**	**0.95 [0.88, 1.02]**	
Total events	658		694				

Heterogeneity: Tau² = 0.00; Chi² = 6.55, df = 8 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

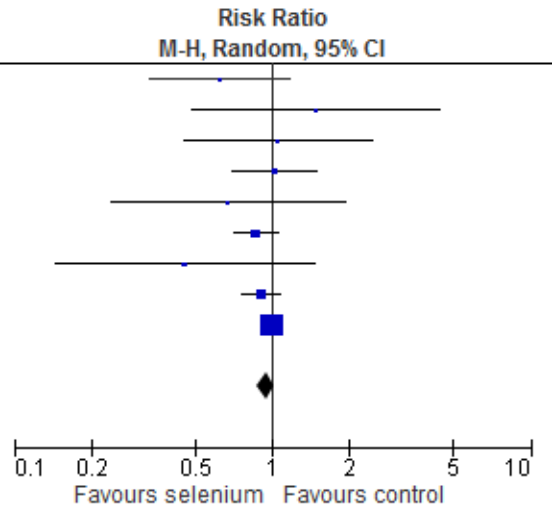

Figure 7 **SUBGROUP ANALYSES: INFECTIONS**: PN selenium monotherapy vs combined

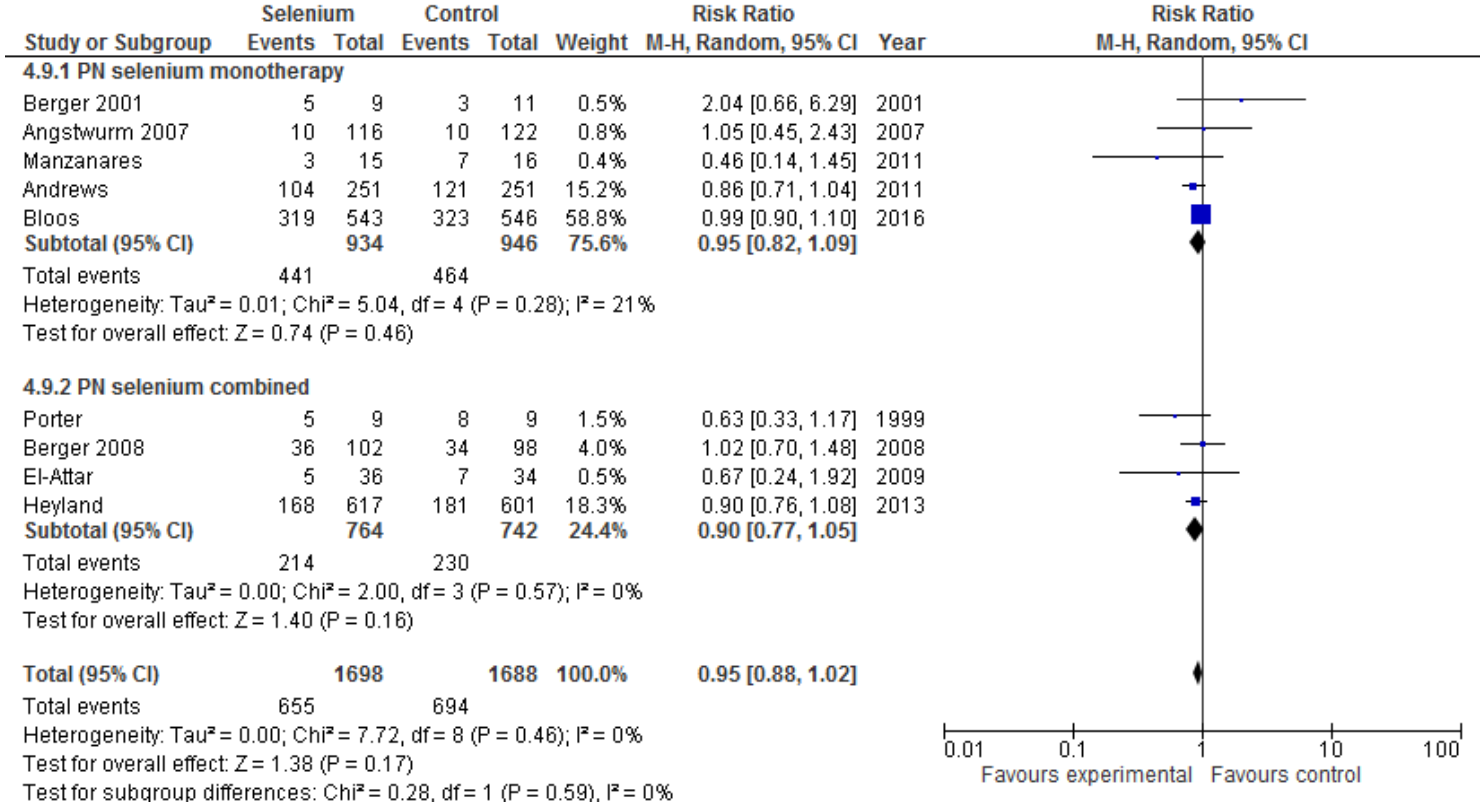

Figure 8 **SUBGROUP ANALYSES: INFECTIONS** PN Selenium loading dose vs no loading dose

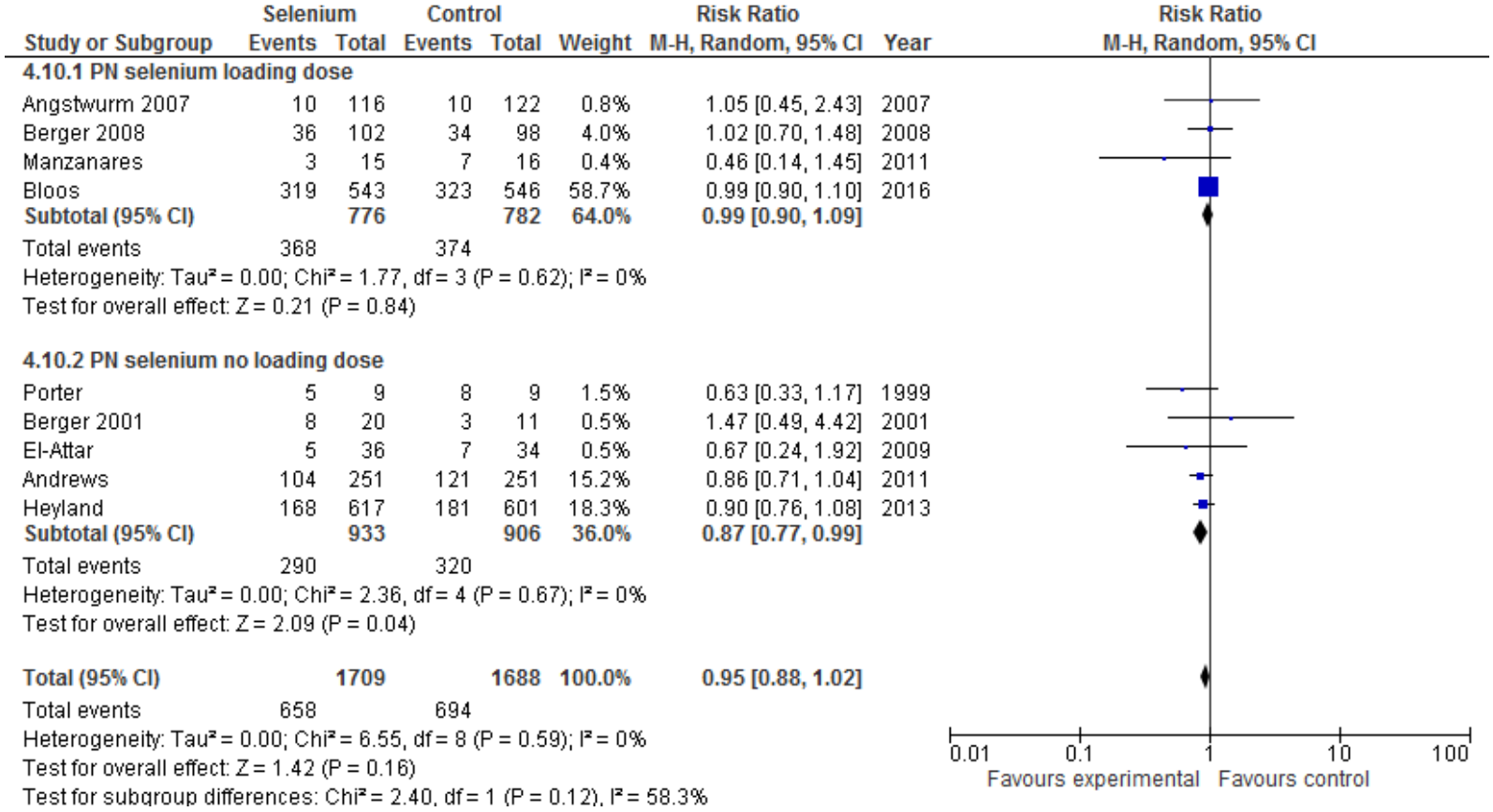

Figure 9 **SUBGROUP ANALYSES: INFECTIONS** PN Selenium high dose vs low dose

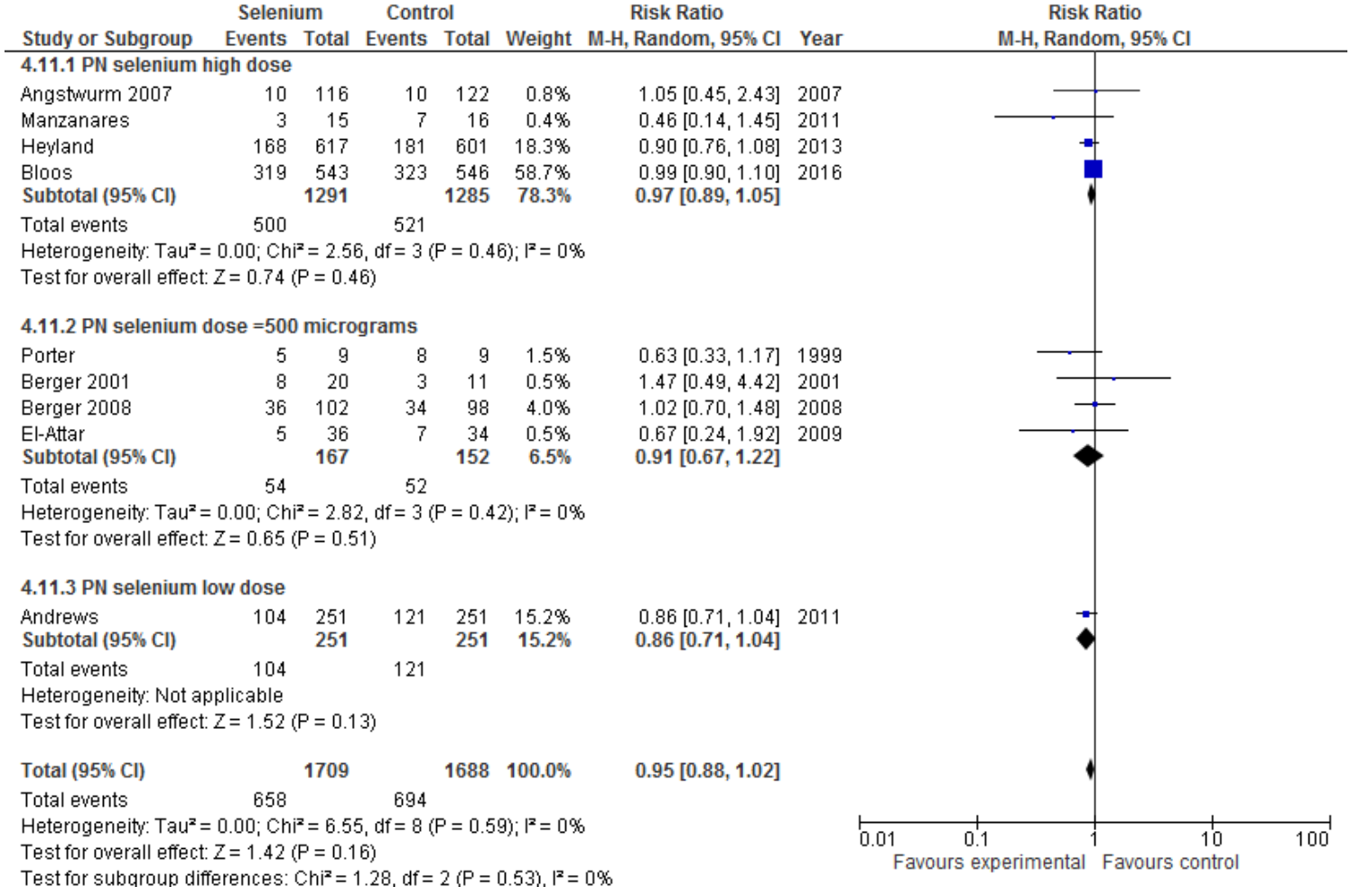

Figure 10. Ventilator Associated Pneumonia

Study or Subgroup	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
El-Attar	5	36	7	34	4.3%	0.67 [0.24, 1.92]	2009
Manzanares	3	15	7	16	3.5%	0.46 [0.14, 1.45]	2011
Heyland	71	617	95	601	57.7%	0.73 [0.55, 0.97]	2013
Chelkeba	16	29	21	25	34.5%	0.66 [0.45, 0.95]	2015
Total (95% CI)		**697**		**676**	**100.0%**	**0.69 [0.55, 0.86]**	
Total events	95		130				

Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.36 (P = 0.0008)

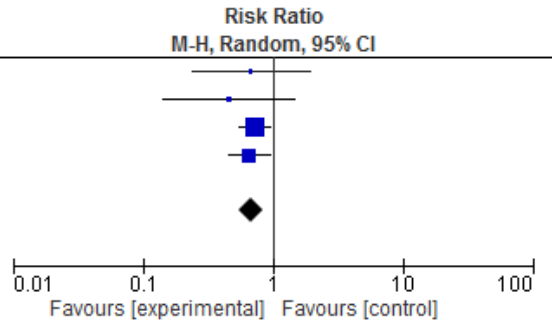

Figure 11. ICU LOS

Study or Subgroup	Selenium Mean	Selenium SD	Selenium Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Berger 1998	30	12	10	39	13	10	1.3%	-9.00 [-19.97, 1.97]	1998
Porter	22	25.2	9	35.8	21.9	9	0.3%	-13.80 [-35.61, 8.01]	1999
Berger 2001	6.1	3.9	20	8.6	8.1	11	5.9%	-2.50 [-7.58, 2.58]	2001
Angstwurm 2007	15.1	10	116	12.7	9	122	21.4%	2.40 [-0.02, 4.82]	2007
Mishra	21.3	16.2	18	20.8	21.8	22	1.2%	0.50 [-11.29, 12.29]	2007
Berger 2007	35	27	11	47	37	10	0.2%	-12.00 [-39.94, 15.94]	2007
Berger 2008	5.8	5.4	102	5.4	5.7	98	39.3%	0.40 [-1.14, 1.94]	2008
Manzanares	14	11	15	13	6	16	4.0%	1.00 [-5.30, 7.30]	2011
Heyland	14.2	22.7	617	13.8	23.1	601	19.5%	0.40 [-2.17, 2.97]	2013
Woth	11.9	12.83047	20	12.77778	9.77124	18	3.1%	-0.88 [-8.09, 6.33]	2014
Chelkeba	19.7	11	29	23.8	13	25	3.8%	-4.10 [-10.58, 2.38]	2015
Total (95% CI)			**967**			**942**	**100.0%**	**0.27 [-1.01, 1.55]**	

Heterogeneity: Tau² = 0.47; Chi² = 11.09, df = 10 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.42 (P = 0.68)

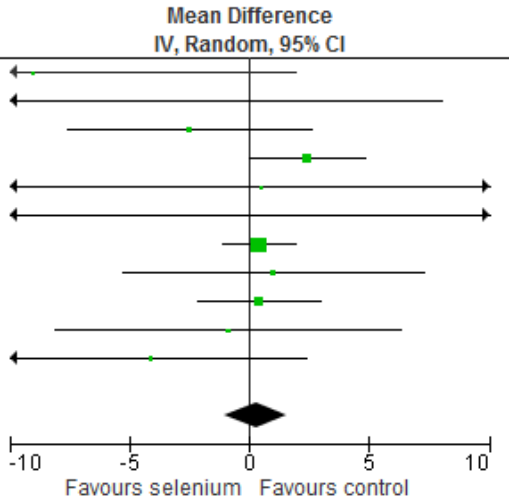

Figure 12. Hospital LOS

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Berger 1998	54	27	10	66	31	10	1.3%	-12.00 [-37.48, 13.48]	1998
Porter	31.3	23.4	9	49	30	9	1.3%	-17.70 [-42.56, 7.16]	1999
Berger 2001	68	60	20	64	39	11	0.7%	4.00 [-30.97, 38.97]	2001
Berger 2008	23	20	102	26	20	98	26.5%	-3.00 [-8.54, 2.54]	2008
Heyland	31.2	50.2	617	29.5	44.8	601	28.6%	1.70 [-3.64, 7.04]	2013
Woth	22.75	15.03986	20	26.33333	13.30192	18	10.0%	-3.58 [-12.59, 5.43]	2014
Chelkeba	25.2	10	29	24.5	9	25	31.7%	0.70 [-4.37, 5.77]	2015
Total (95% CI)			**807**			**772**	**100.0%**	**-0.80 [-3.66, 2.05]**	

Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)

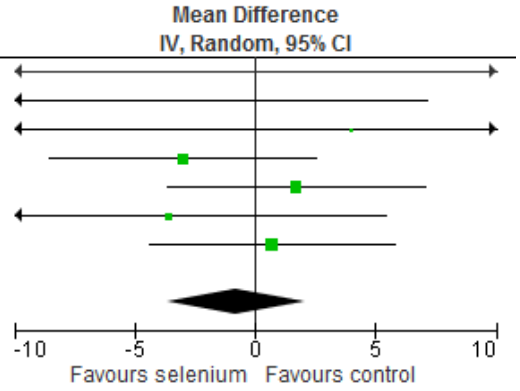

Figure 13. Ventilator Days

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Berger '98	9	10	10	12	9	10	7.3%	-3.00 [-11.34, 5.34]	1998
Berger 2001	5.1	3.7	20	4.2	5.2	11	15.6%	0.90 [-2.57, 4.37]	2001
Berger 2007	7.6	6	11	12.6	6	10	12.1%	-5.00 [-10.14, 0.14]	2007
El-Attar	9.4	7.3	40	17.8	7.6	40	16.1%	-8.40 [-11.67, -5.13]	2009
Manzanares	10	8	15	9	4	16	13.4%	1.00 [-3.50, 5.50]	2011
Heyland	10.9	21.4	617	10.5	19.7	601	18.0%	0.40 [-1.91, 2.71]	2013
Chelkeba	8.9	5	26	10.7	4.5	25	17.4%	-1.80 [-4.41, 0.81]	2015
Total (95% CI)			**739**			**713**	**100.0%**	**-2.14 [-4.94, 0.66]**	

Heterogeneity: Tau² = 9.90; Chi² = 24.55, df = 6 (P = 0.0004); I² = 76%
Test for overall effect: Z = 1.50 (P = 0.13)

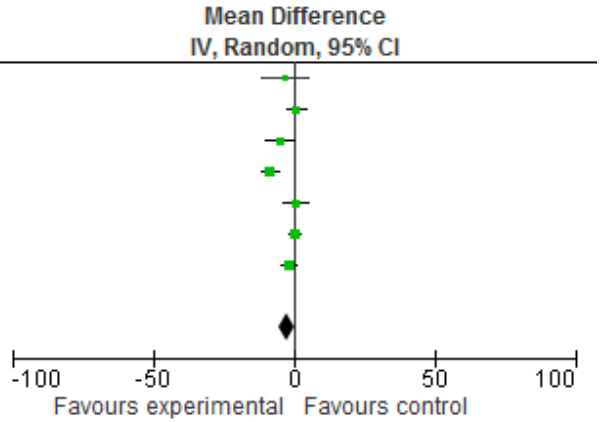

Table 3. Excluded Articles

#	Reason excluded	Citation
1	Abstract only	Sawyer MA, Mike JJ, Chavin K, Marino PL (1989) Antioxidant therapy and survival in ARDS. Crit Care Med 17: S153 (abstract)
2	Not ICU patients	Uden S, Bilton D, Nathan L, Hunt LP, Mains C, Braganza JM (1990) Antioxidant therapy for recurrent pancreatitis: placebo-controlled trial. Aliment Pharmacol Therap 4: 357-371
3	Obs Study of Kuklinski 1991	Kuklinski B, Buchner M, Muller T, Schweder R (1992) [Anti-oxidative therapy of pancreatitis--an 18-month interim evaluation] Z Gesamte Inn Med 47:239-245
4	Not ICU patients	Uden S, Schofield D, Miller PF, Day JP, Bottiglier T, Braganza JM. Antioxidant therapy for recurrent pancreatitis: biochemical profiles in a placebo-controlled trial. Aliment Pharmacol Ther. 1992 Apr;6(2):229-40.
5	No clinical outcomes	Lehmann C, Egerer K, Weber M, Krausch D, Wauer H, Newie T, Kox WJ (1997) Effect of selenium administration on various laboratory parameters of patients at risk for sepsis syndrome. Med Klin 15 (Suppl 3):14-16
6	Not ICU patients	Saito I, Asano T, Sano K, Takakura K, Abe H, Yoshimoto T, Kikuchi H, Ohta T, Ishibashi S (1998) Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. Neurosurgery 42:269-277
7	Not ICU patients	Yamaguchi T, Sano K, Takakura K, Saito I, Shinohara Y, Asano T, Yasuhara H (1998) Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. Ebselen Study Group. Stroke 29:12-17
8	Not ICU patients	Heaney AP, Sharer N, Rameh B, Braganza JM, Durrington PN. Prevention of recurrent pancreatitis in familial lipoprotein lipase deficiency with high-dose antioxidant therapy. J Clin Endocrinol Metab. 1999 Apr;84(4):1203-5.
9	Not ICU patients	Ogawa A, Yoshimoto T, Kikuchi H, Sano K, Saito I, Yamaguchi T, Yasuhara H. Ebselen in acute middle cerebral artery occlusion: a placebo-controlled, double-blind clinical trial. Cerebrovasc Dis. 1999 Mar-Apr;9(2):112-8.
10	Duplicate study of Angstwurm 1999	Angstwurm MW, Schopohl J, Gaertner R. Selenium substitution has no direct effect on thyroid hormone metabolism in critically ill patients. Eur J Endocrinol. 2004 Jul;151(1):47-54.
11	Systematic review	Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med. 2005 Mar;31(3):327-37.
12	Same as Berger AJCN 2007	Berger MM, Binnert C, Chiolero RL, Taylor W, Raffoul W, Cayeux MC, Benathan M, Shenkin A, Tappy L. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. Am J Clin Nutr. 2007 May;85(5):1301-6.
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