11.2 Supplemental Antioxidant Nutrients: Parenteral Selenium revised July 2016

2015 Recommendation: *Based on 6 level 1 and 14 level 2 studies, we do not recommend the use of IV/PN selenium supplementation, alone or in combination with other antioxidants, in critically ill patients.*

2015 Discussion: The committee noted that with the evidence from two new trials (Bloos in submission, Woth 2014), one of which was a large multicentre study involving 33 centres (Bloos in submission), parenteral selenium supplementation had no effect on mortality, length of stay in ICU, hospital or mechanical ventilation. With the addition of the Bloos infection data, the effect on infections was reduced to a trend. Subgroup analyses failed to show a difference in infections between the studies of monotherapy vs combined, loading dose vs no loading dose or high vs lower dose of parenteral selenium supplementation. The committee expressed concern regarding the heterogeneity in the trial designs, patient populations, and dosing ranges in the critically ill population. Given this, the committee felt that the recommendation should be downgraded for the use of IV/PN selenium supplementation.

2013 Recommendation: *The use IV/PN selenium supplementation, alone or in combination with other antioxidants, should be considered in critically ill patients.*

2013 Discussion: The committee noted that with the evidence from 7 new trials (Lindner 2004, El Attar 2009, González 2009, Andrews 2011, Manzanares 2011, Valenta 2011 and Heyland 2013), there was a significant treatment effect of selenium supplementation with respect to reduced infections. The small effect on mortality (was a trend) disappeared and this remain unchanged after the exclusion of one small study that had poor methodological quality (Kuklinski 1991). The committee expressed concern regarding the heterogeneity in the trial designs, patient populations, and dosing ranges in the critically ill population. Subgroup analyses suggested that high dose selenium monotherapy with a bolus administration may have the greatest treatment effect but clinical recommendations on these subgroup results are not warranted at this point. Given the signal of reduced infections, the committee felt that there was sufficient evidence to put forward a weak recommendation for the use of IV/PN selenium supplementation.

Semi Quantitative Scoring

Value	Definition	2009 Score (0,1,2,3)	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	2	0 (mortality) 1 (infection)	0 (mortality) 1 (infection)
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	2 mortality 2 infections	1 (mortality) 1 (infection)	1 (mortality) 1 (infection)
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	2	2.5
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2	3 (overall)	3 (overall)
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	2	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.	2	3	3
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	3	3	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3	3	3
Safe	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2	3	3

* refers to parenteral/IV selenium supplementation either alone or combined with other antioxidant nutrients.

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 20 included studies, there were 6 level 1 studies and14 level 2 studies reviewed. Ten compared selenium supplementation to none (Kuklinski 1991, Zimmerman 1997, Berger 2001, Lindner 2004, Angstwurm 2007, Forceville 2007, El-Attar 2009, Manzanares 2011, Woth 2014 and Bloos in submission), 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 i.e. selenium alone and selenium combined with zinc and α tocopherol compared to placebo and the data are presented in the meta-analysis are from the combined selenium group (combined data). One study (Woth 2014) did not describe the control group.

Mortality: When the attributable data from 20 studies were aggregated, selenium supplementation had no effect on mortality (RR 0.99, 95 % CI 0.90, 1.08, p = 0.79, 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 0.99 % CI 0.80, 1.09, p = 0.84, 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= 0.90, 95% CI 0.78, 1.04, P= 0.17; figure 3). PN antioxidants cocktails with selenium had no effect on mortality (RR= 1.08, 95% CI 0.93, 1.25, P= 0.33; figure 3). There was a trend towards a difference in subgroups P= 0.10; figure 3).

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 0.73, 1.10, P= 0.31; test for heterogeneity P=0.22, I^2 =26%; figure 4). The same was seen when the studies that not have a loading dose were aggregated (RR= 1.01, 95% CI 0.90, 1.14, P= 0.83; figure 4). The test for subgroup differences was not statistically significant (P=0.32; 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 0.85, 1.12, P= 0.70; figure 5), doses =500µg (RR= 0.88, 95% CI 0.57, 1.34, P= 0.54; figure 5) and low doses <500µg (RR 0.94, 95% CI 0.67, 1.33, P= 0.75; figure 5) had no effects on mortality. The test for subgroup differences was not significant (P= 0.90; 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 10 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 = 0.15, 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= 0.95, 95% CI 0.85, 1.06, P= 0.36; figure 7.1), but selenium in combined therapy was associated with a trend towards reduction in infectious complications (RR 0.90, 95% CI 0.78, 1.05, P= 0.18; figure 7.2); test for subgroup differences was not significant (P=0.59; figure 7).

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 8.1). Meanwhile, PN selenium without a loading dose showed a significant reduction on infections (RR 0.87, 95% CI 0.77, 0.99, P=0.03; figure 8.2); there was trend towards subgroup differences (P=0.11; 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 9.1) . Doses =500µg/d also showed no effect on infections (RR= 0.87, 95% CI 0.64, 1.19, P=0.39; figure 9.2). Whereas, doses <500µg/d showed a trend towards a reduction in infections (RR= 0.87, 95% CI 0.72, 1.05, P= 0.15; figure 9.3). The test for subgroup differences was not significant (P= 0.52; figure 9).

LOS and Ventilator days: Ten studies reported ICU LOS as a mean ± standard deviation but there were no significant differences between the groups when the data were aggregated (WMD 0.47. 95% CI -0.90, 1.87, p = 0.49, heterogeneity I I^2=0%, ^{2}= 6%) (see figure 10). When the 6 studies that reported hospital LOS as a mean ± standard deviation were aggregated, there were no significant differences between the groups (WMD -1.15, 95 % CI -4.88, 2.58, p = 0.55, heterogeneity I^2=0%) (figure 11). 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 a mean ± standard deviation were aggregated, there was no effect on ventilator days between the groups (WMD -1.76, 95% CI -4.90, 1.38, p=0.27, heterogeneity I^2=77%, p=0.0002; figure 12).

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) is associated with a trend towards a reduction in infectious complications in the critically ill.
3) IV/parenteral selenium supplementation (alone or in combination with other antioxidants) has no effect on ICU length of stay, hospital length of stay or ventilator days.

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, 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 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	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) 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)

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

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

Study	Mortality (%) Experimental	Control	Infections (%) Experimental	Control	LOS days Experimental	Control
1) Kuklinski 1991	ICU 0/8 (0)	ICU 8/9 (89)	NR	NR	NR	NR
2) Zimmerman 1997	3/20 (15)	8/20 (40)	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)
4) Angstwurm 1999	Hospital 7/21 (33)	Hospital 11/21 (52)	NR	NR	NR	NR
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
6) Berger 2001	(a) Selenium alone 2/9 (22) (b) Selenium + zinc + α tocopherol 0/11 (0)	1/12 (9)	(a) Selenium alone 5/9 (56) (b) Selenium + zinc + α tocopherol 3/11 (27)	5/12 (42)	(a) ICU 8.0 ± 4.0 (9) Hospital 82 ± 78 (9) (b) ICU 5.8 ± 4.4 (11) Hospital 60 ± 48 (11)	ICU 8.6 ± 8.1 (12) Hospital 64 ± 39 (12)
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)
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)
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)

<

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)
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)
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)
13) El-Attar 2009	ICU 2/40 (5.6)	ICU 1/40 (2.9)	VAP 5/36 (14)	VAP 7/34 (21)	NR	NR
14) González 2009	Hospital 6/34 (18)	Hospital 8/34 (24)	NR	NR	Hospital 12(12-14)	Hospital 17(14-20)
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)
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)
17) Valenta 2011	28-day 19/75 (25)	28-day 24/75 (32)	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)
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
20) 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)

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

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
Porter	0	9	0	9		Not estimable	1999
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Berger 2001b	0	11	1	12	0.1%	0.36 [0.02, 8.04]	2001
Berger 2001a	2	9	1	12	0.2%	2.67 [0.28, 25.04]	2001
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
Mishra	11	18	15	22	4.0%	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	10.5%	0.79 [0.60, 1.06]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
González	6	34	8	34	1.0%	0.75 [0.29, 1.93]	2009
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Andrews	84	251	84	251	14.2%	1.00 [0.78, 1.28]	2011
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Manzanares 2011	3	15	5	16	0.6%	0.64 [0.18, 2.22]	2011
Heyland	216	617	199	601	35.2%	1.06 [0.90, 1.24]	2013
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Bloos	152	543	137	546	22.0%	1.12 [0.92, 1.36]	2015
Total (95% CI)		**1962**		**1956**	**100.0%**	**0.99 [0.90, 1.08]**	
Total events	590		597				

Heterogeneity: Tau² = 0.00; Chi² = 17.89, df = 18 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

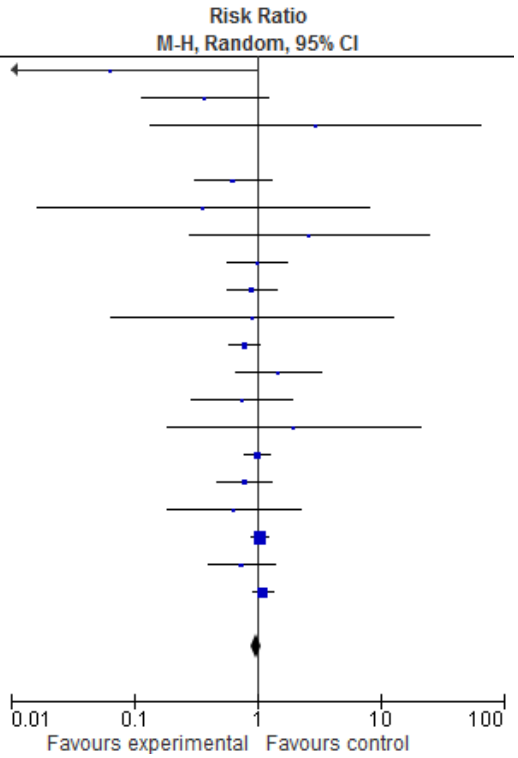

Figure 2. Mortality (excluding Kuklinski)

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
Porter	0	9	0	9		Not estimable	1999
Angstwurm 1999	7	21	11	21	1.6%	0.64 [0.31, 1.32]	1999
Berger 2001a	2	9	1	12	0.2%	2.67 [0.28, 25.04]	2001
Berger 2001b	0	11	1	12	0.1%	0.36 [0.02, 8.04]	2001
Berger 2007	1	11	1	10	0.1%	0.91 [0.07, 12.69]	2007
Angstwurm 2007	46	116	61	122	10.5%	0.79 [0.60, 1.06]	2007
Mishra	11	18	15	22	4.0%	0.90 [0.56, 1.43]	2007
Forceville	14	31	13	29	2.8%	1.01 [0.58, 1.76]	2007
Berger 2008	14	102	9	98	1.4%	1.49 [0.68, 3.29]	2008
González	6	34	8	34	1.0%	0.75 [0.29, 1.93]	2009
El-Attar	2	40	1	40	0.2%	2.00 [0.19, 21.18]	2009
Valenta	19	75	24	75	3.3%	0.79 [0.48, 1.32]	2011
Manzanares 2011	3	15	5	16	0.6%	0.64 [0.18, 2.22]	2011
Andrews	84	251	84	251	14.2%	1.00 [0.78, 1.28]	2011
Heyland	216	617	199	601	35.3%	1.06 [0.90, 1.24]	2013
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Bloos	152	543	137	546	22.0%	1.12 [0.92, 1.36]	2015
Total (95% CI)		**1954**		**1947**	**100.0%**	**0.99 [0.90, 1.09]**	
Total events	590		589				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.06$, df = 17 (P = 0.66); $I^2 = 0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

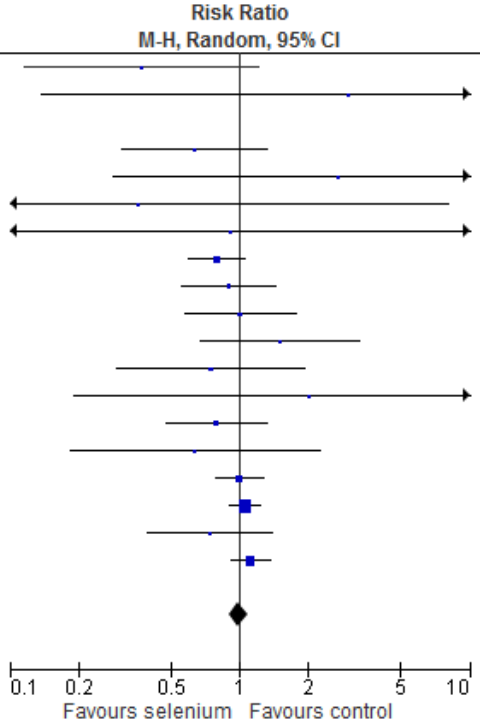

Figure 3 SUBGROUP ANALYSES: MORTALITY: PN selenium monotherapy vs combined

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
Mishra	11	18	15	22	4.0%	0.90 [0.56, 1.43]	2007
Angstwurm 2007	46	116	61	122	10.5%	0.79 [0.60, 1.06]	2007
Forceville	14	31	13	29	2.7%	1.01 [0.58, 1.76]	2007
González	6	34	8	34	1.0%	0.75 [0.29, 1.93]	2009
Manzanares 2011	3	15	5	16	0.6%	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	14.2%	1.00 [0.78, 1.28]	2011
Woth	9	21	11	19	2.2%	0.74 [0.40, 1.38]	2014
Bloos	152	543	137	546	22.0%	1.12 [0.92, 1.36]	2015
Subtotal (95% CI)		**1153**		**1164**	**62.8%**	**0.90 [0.78, 1.04]**	
Total events	354		385				
Heterogeneity: Tau² = 0.01; Chi² = 13.34, df = 11 (P = 0.27); I² = 18%							
Test for overall effect: Z = 1.38 (P = 0.17)							
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 2001a	2	9	1	12	0.2%	2.67 [0.28, 25.04]	2001
Berger 2001b	0	11	1	12	0.1%	0.36 [0.02, 8.04]	2001
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	35.2%	1.06 [0.90, 1.24]	2013
Subtotal (95% CI)		**809**		**792**	**37.2%**	**1.08 [0.93, 1.25]**	
Total events	236		212				
Heterogeneity: Tau² = 0.00; Chi² = 2.53, df = 6 (P = 0.86); I² = 0%							
Test for overall effect: Z = 0.96 (P = 0.33)							
Total (95% CI)		**1962**		**1956**	**100.0%**	**0.99 [0.90, 1.08]**	
Total events	590		597				
Heterogeneity: Tau² = 0.00; Chi² = 17.89, df = 18 (P = 0.46); I² = 0%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Chi² = 2.73, df = 1 (P = 0.10), I² = 63.4%							

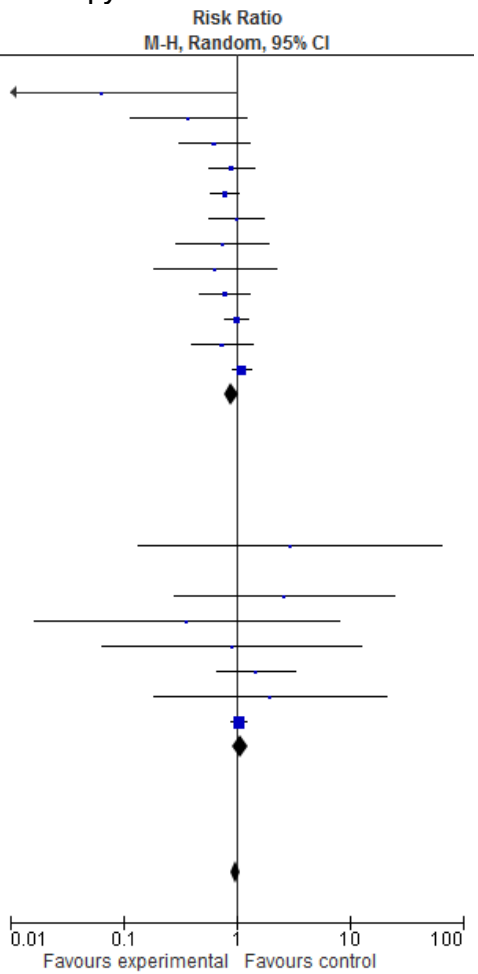

Figure 4 SUBGROUP ANALYSES: MORTALITY: PN Selenium loading dose vs no loading dose:

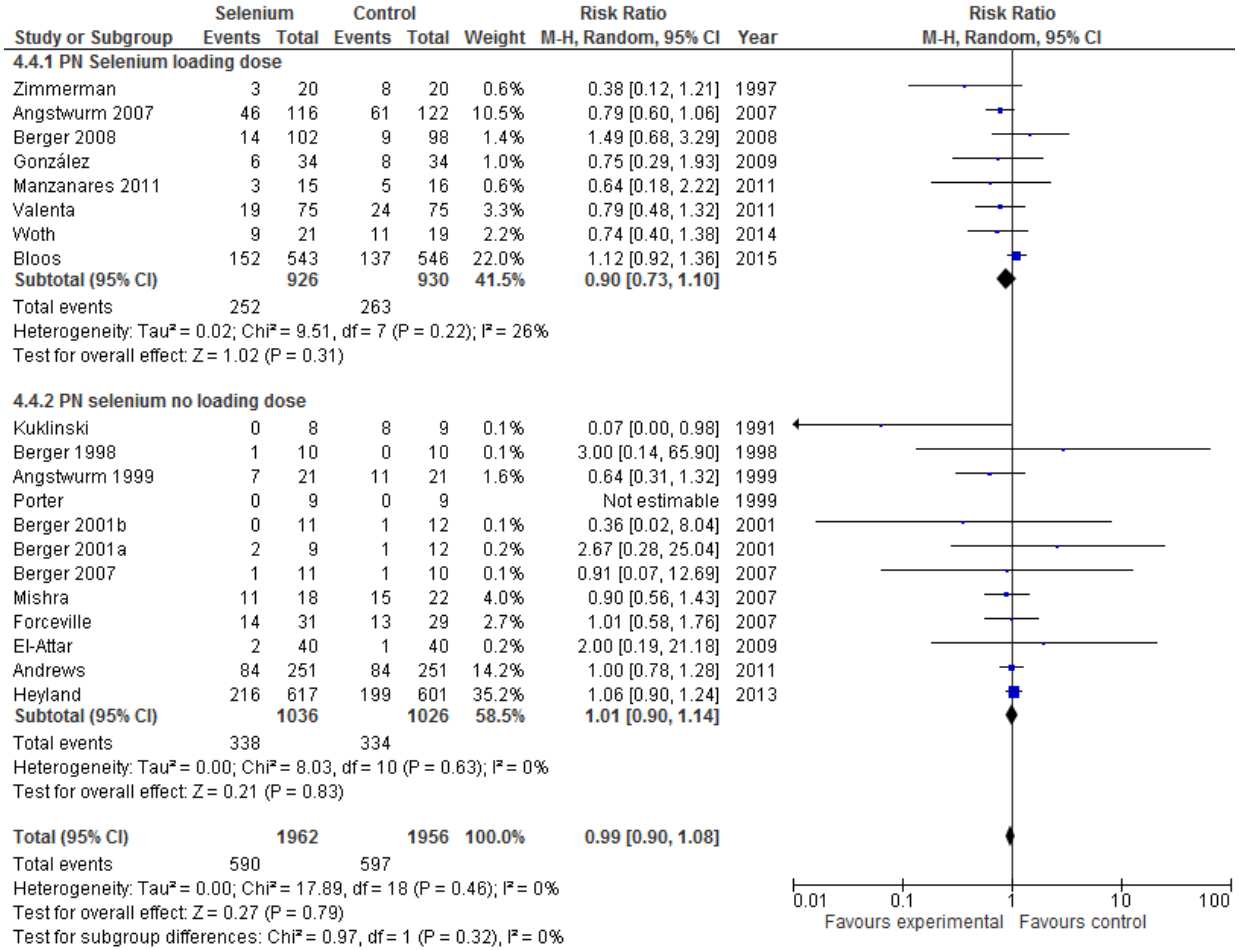

Figure 5. SUBGROUP ANALYSES: MORTALITY: PN Selenium high dose vs low dose

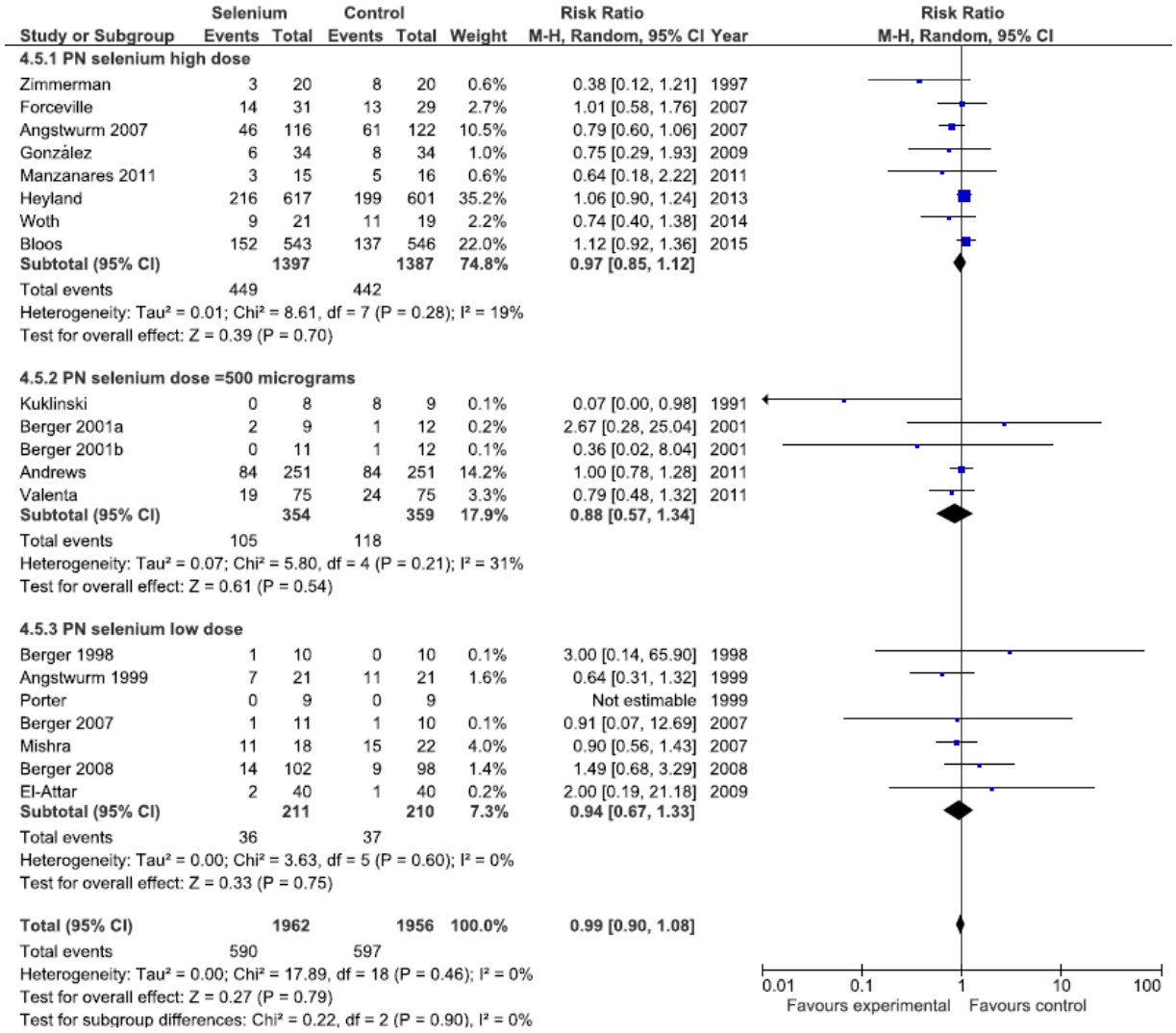

Figure 6. Infections

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 2001b	3	11	5	12	0.4%	0.65 [0.20, 2.12]	2001
Berger 2001a	5	9	5	12	0.7%	1.33 [0.55, 3.24]	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	15.1%	0.86 [0.71, 1.04]	2011
Manzanares 2011	3	15	7	16	0.4%	0.46 [0.14, 1.45]	2011
Heyland	168	617	181	601	18.2%	0.90 [0.76, 1.08]	2013
Bloos	319	543	323	546	58.4%	0.99 [0.90, 1.10]	2015
Total (95% CI)		**1709**		**1701**	**100.0%**	**0.95 [0.88, 1.02]**	
Total events	658		701				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.92$, df = 9 (P = 0.65); $I^2 = 0\%$

Test for overall effect: Z = 1.45 (P = 0.15)

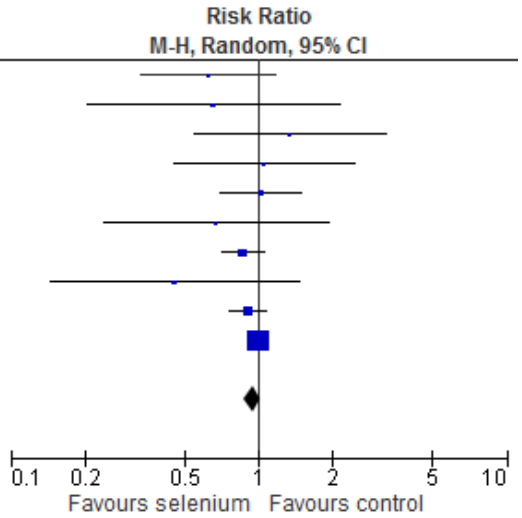

Figure 7 **SUBGROUP ANALYSES: INFECTIONS**: PN selenium monotherapy vs combined

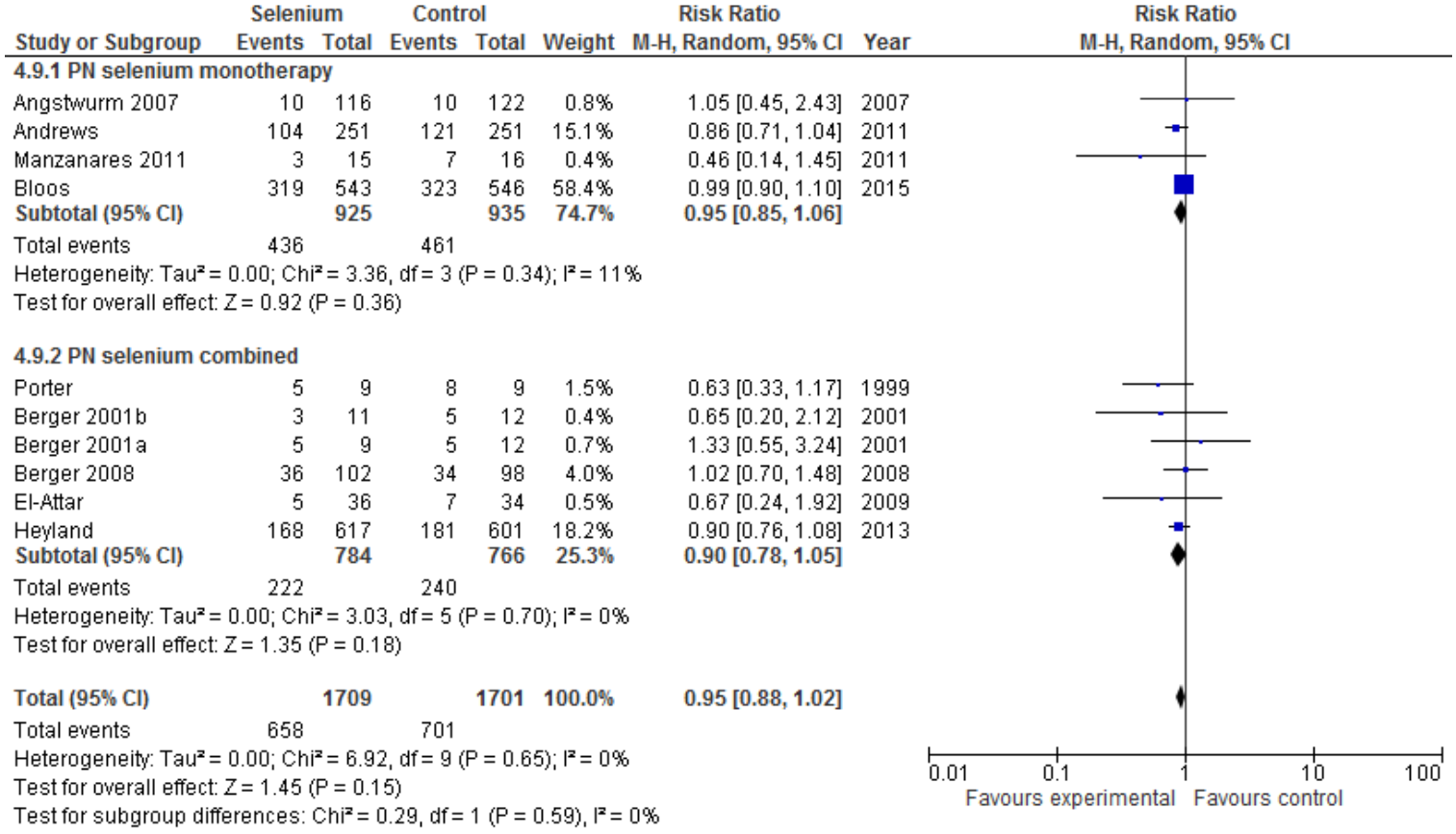

Figure 8 **SUBGROUP ANALYSES: INFECTIONS** PN Selenium loading dose vs no loading dose

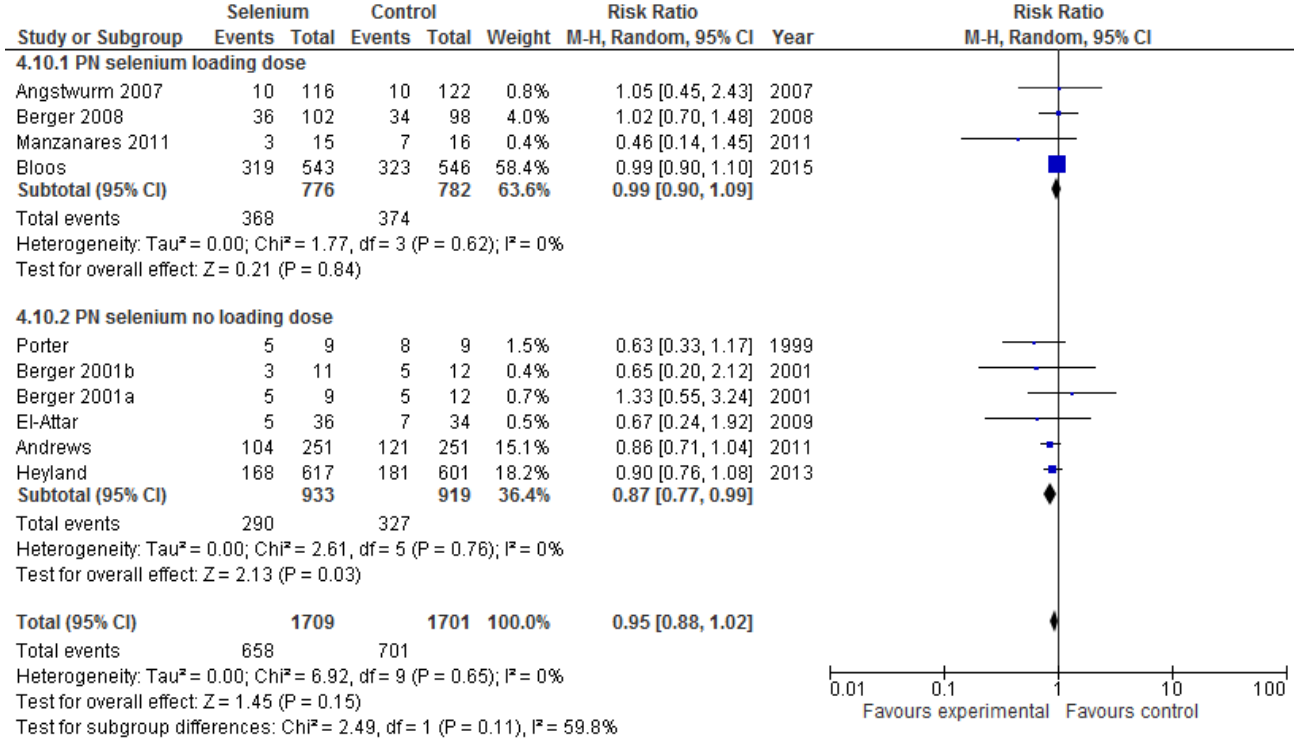

Figure 9 **SUBGROUP ANALYSES: INFECTIONS** PN Selenium high dose vs low dose

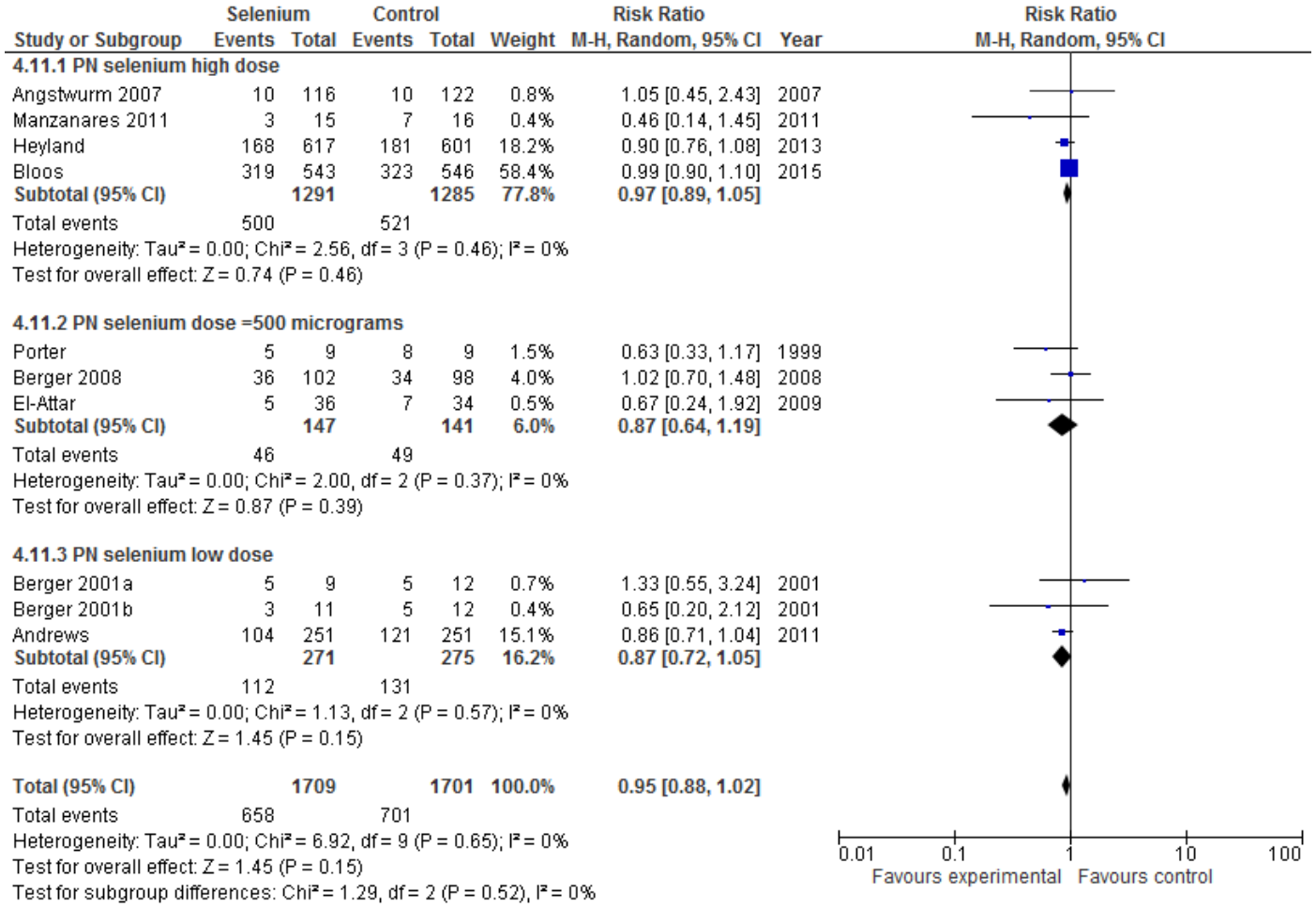

Figure 10. ICU LOS

Study or Subgroup	Selenium Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Berger 1998	30	12	10	39	13	10	1.1%	-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 2001b	5.8	4.4	11	8.6	8.1	12	4.8%	-2.80 [-8.07, 2.47]	2001
Berger 2001a	8	4	9	8.6	8.1	12	4.8%	-0.60 [-5.88, 4.68]	2001
Mishra	21.3	16.2	18	20.8	21.8	22	1.0%	0.50 [-11.29, 12.29]	2007
Berger 2007	35	27	11	47	37	10	0.2%	-12.00 [-39.94, 15.94]	2007
Angstwurm 2007	15.1	10	116	12.7	9	122	20.9%	2.40 [-0.02, 4.82]	2007
Berger 2008	5.8	5.4	102	5.4	5.7	98	44.9%	0.40 [-1.14, 1.94]	2008
Manzanares 2011	14	11	15	13	6	16	3.4%	1.00 [-5.30, 7.30]	2011
Heyland	14.2	22.7	617	13.8	23.1	601	18.7%	0.40 [-2.17, 2.97]	2013
Total (95% CI)			**918**			**912**	**100.0%**	**0.47 [-0.70, 1.64]**	

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 9.39$, df = 9 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 0.79 (P = 0.43)

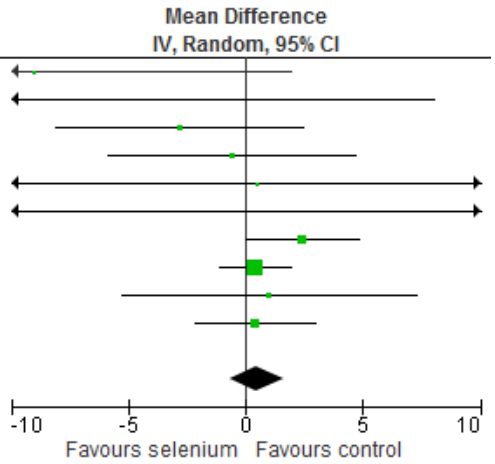

Figure 11. Hospital LOS

	Selenium			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Berger 1998	54	27	10	66	31	10	2.1%	-12.00 [-37.48, 13.48]	
Porter	31.3	23.4	9	49	30	9	2.3%	-17.70 [-42.56, 7.16]	
Berger 2001a	82	78	9	64	39	12	0.5%	18.00 [-37.53, 73.53]	
Berger 2001b	60	48	11	64	39	12	1.1%	-4.00 [-39.94, 31.94]	
Berger 2008	23	20	102	26	20	98	45.3%	-3.00 [-8.54, 2.54]	
Heyland	31.2	50.2	617	29.5	44.8	601	48.8%	1.70 [-3.64, 7.04]	
Total (95% CI)			**758**			**742**	**100.0%**	**-1.15 [-4.88, 2.58]**	

Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

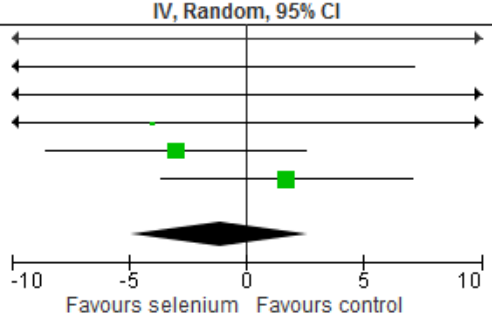

Figure 12. Ventilator Days

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	8.3%	-3.00 [-11.34, 5.34]	1998
Berger '01a	6.2	3.5	9	4.2	5.2	11	15.3%	2.00 [-1.83, 5.83]	2001a
Berger '01b	4.1	3.6	11	4.2	5.2	11	15.4%	-0.10 [-3.84, 3.64]	2001b
Berger 2007	7.6	6	11	12.6	6	10	12.9%	-5.00 [-10.14, 0.14]	2007
El-Attar	9.4	7.3	40	17.8	7.6	40	16.3%	-8.40 [-11.67, -5.13]	2009
Manzanares 2011	10	8	15	9	4	16	14.0%	1.00 [-3.50, 5.50]	2011
Heyland	10.9	21.4	617	10.5	19.7	601	17.8%	0.40 [-1.91, 2.71]	2013
Total (95% CI)			**713**			**699**	**100.0%**	**-1.76 [-4.90, 1.38]**	

Heterogeneity: $Tau^2 = 13.00$; $Chi^2 = 26.59$, df = 6 (P = 0.0002); $I^2 = 77\%$
Test for overall effect: Z = 1.10 (P = 0.27)