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[Intervention Review]

Selenium supplementation for critically ill adults

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ABSTRACT

Background

Selenium is a trace mineral essential to health and has an important role in immunity, defence against tissue damage and thyroid function. Improving selenium status could help protect against overwhelming tissue damage and infection in critically ill adults. This Cochrane review was originally published in 2004 updated in 2007 and again 2015.

Objectives

The primary objective was to examine the effect of nutrition supplemented with selenium or ebselen on mortality in critically ill patients.

The secondary objective was to examine the relationship between selenium or ebselen supplementation and number of infections, duration of mechanical ventilation, length of intensive care unit stay and length of hospital stay.

Search methods

In this update, we searched the current issue of the Cochrane Central Register of Controlled Trials, the Cochrane Library (2014, Issue 5); MEDLINE (Ovid SP, to May 20, 2014), EMBASE (Ovid SP, to May 20, 2014), CAB, BIOSIS and CINAHL. We handsearched the reference lists of the newest reviews and cross-checked with our search in MEDLINE. We contacted the main authors of included studies to request any missed, unreported or ongoing studies. The latest search was performed up to 21 May 2014. The search is now from inception until 21 May 2014.

Selection criteria

We included randomized controlled trials (RCTs) irrespective of publication status, date of publication, blinding status, outcomes published or language. We contacted the trial investigators and authors in order to retrieve relevant and missing data.

Data collection and analysis

Two review authors independently extracted data and we resolved any disagreements by discussion. Our primary outcome measure was all-cause mortality. We performed several subgroup and sensitivity analyses to assess the effects of selenium in critically ill patients. We presented pooled estimates of the effects of intervention as risk ratios (RRs) with 95% confidence intervals (CIs). We assessed the risk of bias through assessment of trial methodological components and the risk of random error through trial sequential analysis.

Main results

We included six new RCTs in this review update. In total we included 16 RCTs (2084 participants) in this review. Most trials were at high risk of bias. The availability of outcome data was limited and trials involving selenium supplementation were, with the exception of one trial, small regarding sample size. Thus the results must be interpreted with caution.

Thirteen trials of intravenous sodium selenite showed a statistically significant reduction in overall mortality (RR 0.82, 95% CI 0.72 to 0.93, 1391 participants, *very low quality of evidence*). However, the overall point estimate on mortality is primarily influenced by trials of high risk of bias. Meta-analysis of three trials of ebselen had a RR of 0.83 (95% CI 0.52 to 1.34, 693 participants, *very low quality of evidence*).

Nine trials of intravenous sodium selenite were analysed for 28 days mortality with no statistically significant difference (RR 0.84, 95% CI 0.69 to 1.02, 1180 participants, *very low quality of evidence*) while three trials were analysed for 90 days mortality with similar findings (RR 0.96, 95% CI 0.78 to 1.18, 614 participants, *very low quality of evidence*).

Two trials of ebselen were analysed for 90 days mortality and were not found to yield any benefit (RR 0.72, 95% CI 0.42 to 1.22, 588 participants, *very low quality of evidence*).

For mortality among intensive care patients selenium supplementation failed to indicate any statistically significant advantage (RR 0.88, 95% CI 0.77 to 1.01, nine trials, 1168 participants, *very low quality of evidence*).

Six trials of intravenous sodium selenite found no statistically significant difference for participants developing infection (RR 0.96, 95% CI 0.75 to 1.23, 934 patients, *very low quality of evidence*). Similarly, three trials of ebselen provided data for participants developing infections (pyrexia, respiratory infections or meningitis) with no obvious benefit (RR 0.60, 95% CI 0.36 to 1.02, 685 participants, *very low quality of evidence*).

Our analyses showed no effect of selenium or ebselen on adverse events (Selenium: RR 1.03, 95% CI 0.85 to 1.24; six trials, 925 participants; Ebselen: RR 1.16, 95% CI 0.40 to 3.36; two trials, 588 participants, *very low quality of evidence*).

No clear evidence emerged in favour of selenium supplementation for outcomes such as number of days on a ventilator (mean difference (MD) -0.86, 95% CI -4.39 to 2.67, four trials, 191 participants, *very low quality of evidence*), length of intensive care unit stay (MD 0.54, 95% CI -2.27 to 3.34, seven trials, 934 participants, *very low quality of evidence*) or length of hospital stay (MD -3.33, 95% CI -5.22 to -1.44, five trials, 693 participants, *very low quality of evidence*).

The quality of trial methodology was low. Due to high risk of bias in the included trials, results must be interpreted with caution.

Authors' conclusions

Despite publication of a number of trials, the current evidence to recommend supplementation of critically ill patients with selenium or ebselen remains disputed. Trials are required which overcome the methodological inadequacies of the reviewed studies, particularly in relation to sample size, design and outcomes.

PLAIN LANGUAGE SUMMARY

Selenium supplements for adults who are critically ill

Selenium is a mineral that is essential to health. It has an important role in defence against tissue damage and disease. Improving selenium status could help protect adults with serious illness.

In this updated review, Cochrane researchers assessed the effects of additional selenium supplementation for adults recovering from critical illness. We investigated whether the number of people who died changed by giving a selenium supplement during their treatment. Also we checked the impact of such a strategy on the rate of infections and other diseases for these patients while in hospital. We also examined whether selenium affected the duration of respiratory assistance for patients on ventilators and the length of their stay in the intensive care unit and the hospital.

We included 16 trials with 2084 participants. Thirteen trials carried out tests with selenium while three trials examined selenium-containing compound ebselen. Overall quality of the included trials was poor, with little information on quality indicators. The results were limited and these trials involving selenium supplementation were mostly small. In most trials, there was a high risk of poor or even incorrect information. Thus the results must be interpreted with caution. The evidence is current to 21 May 2014.

Thirteen trials of intravenous sodium selenite showed a statistically significant effect on death. Three trials of the selenium-containing compound ebselen showed no effect on death. No effects on infections or secondary diseases were observed.

No clear evidence emerged for the benefits of selenium or ebselen supplementation for days on a respirator, length of intensive care unit stay, length of hospital stay or quality of life. Due to the quality of included trials, one must be cautious when interpreting the strength of the evidence in favour of selenium supplementation despite a statistically significant finding.

Overall, there was low quality evidence from the studies for the all results. Trials are required which overcome the statistical uncertainty of the reviewed studies, particularly in relation to sample size, design and outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table 1

Selenium supplementation compared with control for critically ill adults

Patient or population: Patients with critical illnesses

Settings: ICU setting

Intervention: Selenium or ebselen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Selenium			
Overall mortality (regardless of the follow-up period)	All patients are high risk population		RR 0.82 , 95% CI 0.72 to 0.93)	1391 (13)	⊕⊕⊕⊕ very low ^{1,2}
ICU length of stay (selenium)	The mean length of stay in an ICU ranged across control groups from 9 days to 26.5 days	The mean length of stay in an ICU ranged across intervention groups from 7.5 days to 22.8 days	MD 0.54, 95% CI -2.27 to 3.34	934 (7)	⊕⊕⊕⊕ very low ^{1,3}
Days on ventilator (selenium)	The mean days on ventilator ranged across control groups from 6 days to 16 days	The mean days on ventilator ranged across intervention groups from 6 days to 19.8 days	MD -0.86, 95% CI -4.39 to 2.67	191 (4)	⊕⊕⊕⊕ very low ^{1,4}
Length of hospital stay (selenium)	The mean length of hospital stay ranged across control groups from 17 days to 62.8 days	The mean length of hospital stay ranged across intervention groups from 12.5 days to 83 days	MD -3.33. 95% CI -5.22 to -1.44	693 (5)	⊕⊕⊕⊕ very low ^{1,5}

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Abbreviations: CI: confidence interval; RR: risk ratio; MD: mean difference; ICU: intensive care unit.

¹With the exception of [SIGNET 2011](#), all included trials were at high risk of bias. Most studies were small and poorly described.

²The entry refers to: [Angstwurm 1999](#); [Angstwurm 2007](#); [Berger 2001](#); [Forceville 2007](#); [Janka 2013](#); [Kuklinski 1991](#); [Lindner 2004](#); [Manzanares 2011](#); [Mishra 2007](#); [Montoya 2009](#); [SIGNET 2011](#); [Valenta 2011](#); and [Zimmermann 1997](#).

³The entry refers to: [Angstwurm 1999](#); [Angstwurm 2007](#); [Berger 2001](#); [Forceville 2007](#); [Manzanares 2011](#); [Mishra 2007](#); and [SIGNET 2011](#).

⁴The entry refers to: [Angstwurm 1999](#); [Berger 2001](#); [Forceville 2007](#); and [Montoya 2009](#).

⁵The entry refers to: [Angstwurm 1999](#); [Berger 2001](#); [Forceville 2007](#); [Montoya 2009](#); and [SIGNET 2011](#).

BACKGROUND

Description of the condition

Critical illness is characterized by hyperinflammation, cellular immune dysfunction, oxidative stress and mitochondrial dysfunction. Oxidative stress reflects an imbalance between highly reactive oxygen molecules, known as free radicals, and the ability of the body to counteract their harmful effects through neutralization by antioxidants. Selenium is a trace mineral that is essential to this neutralization. Selenium-containing proteins include glutathione peroxidases and thioredoxin reductases (Angstwurm 2006), which are antioxidant enzymes essential for the removal of damaging reactive oxygen species (ROS). ROS damage proteins, polysaccharides, nucleic acids and polyunsaturated fatty acids, which may lead to cell death (Geoghegan 2006). Selenium deficiency impairs the immune response; and supplementation in replete people appears to enhance the immune response (Rayman 2012). The iodothyronine deiodinase enzymes, which control the production of the hormone triiodothyronine from thyroxine, also require selenium.

Description of the intervention

Selenium intake from plants (and thus animals) generally reflects the levels present in soils. There is particular concern that intake in people living in most parts of Europe is insufficient (Rayman 2012); intakes are generally higher in people living in North America. Selenium status is further impaired in people with poor quality diets, such as alcoholics, and when dietary intake is reduced, for example during a chronic illness and gastrointestinal malfunction.

Ebselen (2-phenyl-1,2-benziselenazol-3(2H)-one) is an organic selenium-containing compound which appears to act as a mimic of glutathione peroxidase; it may thus also have anti-oxidant properties (Parnham 2000).

How the intervention might work

Evidence suggests that excessive oxidative stress plays an important role in the development of complications of critical illness, such as the systemic inflammatory response which leads to acute respiratory distress syndrome (ARDS) and multiple organ failure (Bulger 2001). Selenium appears to be pivotal in this role (Manzanares 2009). Berger 2007 reported fewer infections after major burns compared with placebo when providing an antioxidant trace element supplement containing selenium, zinc and copper. Giladi 2011 similarly reported that antioxidant supplementation with vitamin C, vitamin E and selenium in people with severe trauma was associated with fewer infections and less organ dysfunction compared to placebo.

Why it is important to do this review

In the last two decades, several clinical trials have evaluated the role of antioxidant micronutrients either as a monotherapy or in combined therapy, as part of an antioxidant strategy for critically ill patients.

Several systematic reviews have reported reduced risk of mortality as a result of selenium supplementation (Heyland 2005; Huang 2013; Landucci 2014; Manzanares 2012).

The organic selenium-containing compound ebselen has also been investigated for its antioxidant properties in critical illness (Parnham 2000).

We aimed to systematically review randomized controlled trials (RCTs) of either selenium or ebselen supplementation in adults with critical illness. More compelling evidence is needed on this subject and on its potential benefits.

OBJECTIVES

The primary objective was to examine the effect of nutrition supplemented with selenium or ebselen on mortality in critically ill patients.

The secondary objective was to examine the relationship between selenium or ebselen supplementation and number of infections, duration of mechanical ventilation, length of intensive care unit stay and length of hospital stay.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of publication status, date of publication, blinding status, outcomes published or language. We contacted the trial investigators and authors for relevant data. We included unpublished trials only if trial data and methodological descriptions were provided either in written form or could be retrieved from the trial authors. We excluded cross-over trials. No cluster-RCTs were identified but we plan to include these, if found, in future updates.

Types of participants

We included studies on adults with critical illness (including patients with burns, head injury, brain haemorrhage, cerebrovascular accident) and those undergoing elective major surgery.

Studies reporting mixed groups of participants (for example, combined data of critically ill and medical patients) were included only if data could be provided separately for patients with critical illness.

We excluded trials including neonates and participants aged under 18 years.

Types of interventions

We included trials on nutritional interventions by the enteral or parenteral route, or both routes, supplemented with additional selenium versus nutritional care by the same route without additional selenium. We examined all types of selenium compounds including ebselen.

We undertook separate subgroup analyses of trials in which we calculated risk ratio (RR) for selenium/ebselen versus no selenium. If selenium was one of several components in an antioxidant supplement protocol, the trial was excluded based on our inability to assess the direct and isolated benefit of selenium.

Types of outcome measures

Primary outcomes

1. Overall mortality (longest follow-up, regardless of the period of follow-up).
2. Mortality by duration (studies reporting mortality for 28 and 90 days).

Secondary outcomes

1. Number of infectious complications (as defined in each of the included studies).
2. Adverse events.
3. Length of stay in an intensive care unit (ICU).
4. Number of days on a ventilator.
5. Length of hospital stay.
6. Quality of life after discharge (as defined in the included studies).
7. Economic outcomes.

Search methods for identification of studies

Electronic searches

In this review update, we performed a search update up to 20 May 2014. Thus, we searched the Cochrane Central Register of Controlled Trials (the Cochrane Library 2014, Issue 5; see [Appendix 1](#)). We updated our search of MEDLINE (Ovid SP, to May 20, 2014, see [Appendix 2](#)) and EMBASE (Ovid SP, to May 20, 2014, see [Appendix 3](#)). The search is now from inception until 21 May 2014

Searching other resources

We handsearched the reference lists of reviews ([Huang 2013](#); [Landucci 2014](#); [Manzanares 2012](#)), randomized and non-randomized studies, and editorials for additional studies. We searched the [ASPEN](#) and [ESPEN](#) databases without finding references to selenium or ebselen. References were crosschecked with our search in MEDLINE. We contacted the main authors of included studies to ask for any missed, unreported or ongoing studies.

We searched for ongoing clinical trials and unpublished studies on the following Internet sites:

1. <http://www.controlled-trials.com>
2. <http://clinicaltrials.gov>
3. <http://www.centerwatch.com>

No language restriction was applied to eligible reports. The latest search was performed 22 October 2014.

Data collection and analysis

Two review authors (MA, AA) independently screened and classified all citations as potential primary studies, review articles or other. Also, the two review authors independently examined all potential primary studies and decided on their inclusion in the review. Data on methodology and outcomes from each trial were independently extracted and evaluated in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreements by consensus among the review authors.

Selection of studies

We assessed the articles identified from the described searches and excluded obviously irrelevant reports. Two review authors (MA, AA) independently examined articles for eligibility and screened the titles and abstracts in order to identify studies for eligibility (see: [Characteristics of included studies](#); [Characteristics of excluded studies](#)). This process was performed without blinding of authors, institution, journal of publication or results. We resolved any disagreements by consensus among the review authors. We provide a detailed description of the search and assessment.

Data extraction and management

We independently extracted and collected the data without being blinded to the author, source institution or the publication source of trials. We resolved disagreements by discussion and approached all first authors of the included trials for additional information on risks of bias. For more detailed information please see the '[Contributions of authors](#)' section.

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each trial. Trials were evaluated for major potential sources of bias (random sequence generation, allocation concealment, blinding, intention-to-treat (ITT) analysis and completeness of follow-up). We assessed each trial quality factor separately and defined the trials as having low risk of bias only if they adequately fulfilled all of the below described criteria.

1. Random sequence generation

Assessment of randomization: sufficiency of the method in producing two comparable groups before intervention.

Grade: 'low risk': a truly random process (e.g. random computer number generator, coin tossing, throwing dice); 'high risk': any non-random process (e.g. date of birth, date of admission by hospital or clinic record number or by availability of the intervention); or 'unclear risk': insufficient information.

2. Allocation concealment

Allocation method prevented investigators or participants from foreseeing assignment.

Grade: 'low risk': central allocation or sealed opaque envelopes; 'high risk': using open allocation schedule or other unconcealed procedure; or 'unclear risk': insufficient information.

3. Blinding

Assessment of appropriate blinding of the team of investigators and participants: person responsible for participant care, participants and outcome assessors.

Grade: 'low risk': blinding considered adequate if participants and personnel were kept unaware of intervention allocations after inclusion of participants into the study, and if the method of blinding involved a placebo indistinguishable from the intervention, as mortality is an objective outcome; 'high risk': not double-blinded, categorized as an open label study, or without use of a placebo indistinguishable from the intervention; 'unclear risk': blinding not described.

4. Incomplete outcome data

Completeness of outcome data, including attritions and exclusions.

Grade: 'low risk': numbers and reasons for drop-outs and withdrawals in the intervention groups described, or no drop-outs or withdrawals was specified; 'high risk': no description of drop-outs and withdrawals provided; 'unclear risk': report gave the impression of no drop-outs or withdrawals, but this was not specifically stated.

5. Selective reporting

The possibility of selective outcome reporting.

Grade: 'low risk': reported outcomes prespecified in an available study protocol, or, if this is not available, published report includes all expected outcomes; 'high risk': not all prespecified outcomes reported, reported using non-prespecified subscales, reported incompletely or report fails to include a key outcome that would have been expected for such a study; 'unclear risk': insufficient information.

6. Funding bias

Assessment of any possible funding bias:

Grade: 'low risk': reported no funding, funding from universities or public institutions; 'high risk': funding from private investors, pharmaceutical companies or trial investigator employed by the pharmaceutical company; 'unclear risk': insufficient information.

7. Other bias

Assessment of any possible sources of bias not addressed in domains 1 to 6.

Grade: 'low risk': report appears to be free of such biases; 'high risk': at least one important bias is present that is related to study design, early stopping because of some data-dependent process, extreme baseline imbalance, academic bias, claimed fraudulence or other problems; or 'unclear risk': insufficient information, or evidence that an identified problem will introduce bias.

Measures of treatment effect

Dichotomous data

We calculated RRs with 95% confidence intervals (CIs) for dichotomous data (binary outcomes). These included:

Primary outcomes:

1. Mortality by duration and overall mortality.

Secondary outcomes:

1. Number of infectious complications.
2. Adverse events.

Continuous data

We used the mean difference (MD) or RR if data were continuous and measured in the same way between trials. These included:

1. Length of stay in an ICU.
2. Number of days on a ventilator.

3. Length of hospital stay.

Unit of analysis issues

Cross-over trials

We excluded cross-over trials from our meta-analyses because of the potential risk of "carry-over" of treatment effect.

Studies with multiple intervention groups

In studies designed with multiple intervention groups we combined groups to create a single pair wise comparison in accordance with Higgins 2011. In trials with two or more groups receiving different doses, we combined data for the primary and secondary outcomes.

Dealing with missing data

We contacted the authors of trials with missing data in order to retrieve the relevant information. For all included studies we noted levels of attrition and any exclusion of participants. In case of missing data, we chose 'complete-case analysis' for our primary outcomes, which excludes from the analysis all participants with the outcome missing. Selective outcome reporting occurs when non-significant results are selectively withheld from publication (Chan 2004), and is defined as the selection, on the basis of the results, of a subset of the original variables recorded for inclusion in publication of trials (Hutton 2000). The most important types of selective outcome reporting are: selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of different analyses using the same data; selective reporting of subsets of the data; and selective under-reporting of data (Higgins 2011).

Assessment of heterogeneity

We explored heterogeneity using the I^2 statistic and χ^2 test. An I^2 statistic above 50% represents substantial heterogeneity (Higgins 2003). In case of an I^2 statistic value > 0 (mortality outcome), we tried to determine the cause of heterogeneity by performing relevant subgroup analyses. We used the χ^2 test to provide an indication of heterogeneity between studies, with $P \leq 0.1$ considered significant.

Assessment of reporting biases

Funding bias is related to the possible publication delay or discouragement of undesired results in trials sponsored by the industry (Higgins 2011). To explore the role of funding, we planned to conduct a sensitivity analysis based on our primary endpoint.

Data synthesis

Using RevMan 5.3, we calculated RR with 95% CIs for dichotomous variables and MD with 95% CIs for continuous outcomes. We used the χ^2 test to provide an indication of heterogeneity between studies, with $P < 0.1$ considered significant. The degree of heterogeneity observed in the results was quantified using the I^2 statistic, which can be interpreted as the proportion of the total variation observed between the studies that is attributable to differences between studies rather than sampling error (Higgins 2002). An I^2 statistic value $> 75\%$ is considered very heterogeneous. We used both a random-effects model and a fixed-effect model. If the I^2 statistic value was 0 we only reported the results from the fixed-effect model; and in the case of the I^2 statistic value being > 0 we reported only the results from the random-effects model.

Trial sequential analysis

Trial sequential analysis (TSA) is a methodology that combines an information size calculation for meta-analysis with a threshold of statistical significance. TSA is a tool for quantifying the statistical reliability of data in a cumulative meta-analysis, adjusting significance levels for sparse data and repetitive testing on accumulating data. We conducted TSA ([Brok 2009](#); [Pogue 1997](#); [Thorlund 2009](#); [Wetterslev 2008](#)) at least on the primary outcomes and on the secondary outcomes if the accrued information size was an acceptable fraction of the estimated required information size to allow meaningful analyses (> 20). If the actual accrued information size was too low, we provided the required information size given the actual diversity in case of low risk of bias ([Wetterslev 2009](#)) or adjusted with a possible diversity of 25% in case of high risk of bias and absence of actual diversity.

Meta-analysis may result in type I errors due to random errors arising from sparse data or repeated significance testing when updating the meta-analysis with new trials ([Brok 2009](#); [Wetterslev 2008](#)). Bias (systematic error) from trials with low methodological quality, outcome measure bias, publication bias, early stopping for benefit and small trial bias may also result in spurious P values ([Brok 2009](#); [Higgins 2011](#); [Wetterslev 2008](#)).

In a single trial, interim analysis increases the risk of type I errors. To avoid these, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P value, i.e. the cumulative Z-curve crosses the monitoring boundaries ([Lan 1983](#)). Sequential monitoring boundaries can also be applied to meta-analysis, and are called trial sequential monitoring boundaries. In TSA, the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed.

The idea in TSA is that if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials may be needed (firm evidence). If the Z-curve does not cross the boundary, then there is insufficient evidence to reach a conclusion. To construct the trial sequential monitoring boundaries the required information size is needed and is calculated as the least number of participants needed in a well-powered single trial ([Brok 2009](#); [Pogue 1997](#); [Thorlund 2011](#); [Trial Sequential Analysis \(TSA\)](#); [Wetterslev 2008](#)). We aimed to apply TSA as it prevents an increase in the risk of type I error with sparse data or multiple updating in a cumulative meta-analysis. Hence, TSA provides us with important information in order to estimate the level of evidence of the experimental intervention, the need for additional trials and their sample size.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses:

1. Mortality by duration. We planned to use 28, 90 days and the longest follow-up period. If data were provided in 30 days we included them in the same analysis as 28 days.

2. Mortality among patients admitted in a general ICU.
3. Mortality among patients admitted under the diagnosis of acute pancreatitis.
4. Number of infected participants.
5. Number of participants with adverse event.
6. Length of stay in the ICU.
7. Number of days on a ventilator.
8. Length of hospital stay.

We considered P values < 0.05 as indicating significant interaction between the subgroup category.

Sensitivity analysis

We decided to carry out a sensitivity analysis on the results by applying fixed-effect and random-effects models to assess the impact of heterogeneity on our results.

Summary of findings

We used the principles of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to provide an overall assessment of the evidence relating to the following outcomes: Overall mortality (regardless of the follow-up period), ICU length of stay (selenium), Days on ventilator (selenium), Length of hospital stay (selenium) ([Summary of findings for the main comparison](#)).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#) sections.

Results of the search

In this updated review, 11 trials were identified via the search strategy, 6 were included, 5 were excluded, two were classified as ongoing and two are awaiting assessment. We have listed the reasons for excluding the 5 studies in the '[Characteristics of excluded studies](#)' table. Three included studies and three excluded studies were published in German only, and one included trial was in Spanish. Translations to English were performed for these studies. Some trials had multiple full text publications ([Angstwurm 1999](#); [Berger 2001](#); [Saito 1998](#); [SIGNET 2011](#); [Zimmermann 1997](#)). A total of 2084 patients were included in this review update.

Of the six new included studies, we found one by handsearching ([Montoya 2009](#)) and five using our search string ([Forceville 2007](#); [Janka 2013](#); [Manzanares 2011](#); [SIGNET 2011](#); [Valenta 2011](#)). We sought further details and obtained them for four studies ([Angstwurm 2007](#); [Angstwurm 1999](#); [Manzanares 2011](#); [Valenta 2011](#)). The flow chart for this updated review is given in [Figure 1](#).

Figure 1. Study flow diagram for the updated review. (In the original article, [Avenell 2004](#), 10 studies were included and 11 studies were excluded with reasons. Three were awaiting classification, of which one has now been excluded ([Kiessling 2006](#)). Two studies are still ongoing).

Included studies

The included trials were all published between 1997 and 2013 except for one trial which was published in 1991 ([Kuklinski 1991](#)). Three trials of ebselen were Japanese multicentre trials ([Ogawa 1999](#); [Saito 1998](#); [Yamaguchi 1998](#)). One trial of selenium was a multicentre trial in Germany ([Angstwurm 2007](#)), one was a multicentre trial in the UK ([SIGNET 2011](#)) and one was a multicentre trial in France ([Forceville 2007](#)). The remaining Selenium trials were single centre trials in the Czech Republic, Germany, Switzerland, the UK and Uruguay ([Angstwurm 1999](#); [Berger 2001](#); [Janka 2013](#); [Kuklinski 1991](#); [Lindner 2004](#); [Manzanares 2011](#); [Mishra 2007](#); [Valenta 2011](#); [Zimmermann 1997](#)). One trial did not state the location ([Montoya 2009](#)).

The 16 included studies involved a total of 2084 participants. We have provided the details of the included studies in the 'Characteristics of included studies' section. Eleven trials recruited more male than female participants ([Angstwurm 1999](#); [Angstwurm](#)

[2007](#); [Berger 2001](#); [Forceville 2007](#); [Janka 2013](#); [Lindner 2004](#); [Montoya 2009](#); [Ogawa 1999](#); [SIGNET 2011](#); [Valenta 2011](#); [Yamaguchi 1998](#)). One trial recruited only men ([Kuklinski 1991](#)), one did not report the sex of the participants ([Zimmermann 1997](#)) and three studies had more women than men ([Manzanares 2011](#); [Mishra 2007](#); [Saito 1998](#)). Where reported, the mean age of participants was greater than 50 years. Two trials excluded participants older than 75 and 71 years, respectively ([Berger 2001](#); [Saito 1998](#)).

Trials of selenium recruited participants with the following conditions: sepsis or systemic inflammatory response syndrome ([Angstwurm 2007](#); [Angstwurm 1999](#); [Forceville 2007](#); [Janka 2013](#); [Manzanares 2011](#); [Mishra 2007](#); [Montoya 2009](#); [Valenta 2011](#); [Zimmermann 1997](#)), severe multiple injury ([Berger 2001](#)), more serious cases of acute pancreatitis ([Kuklinski 1991](#); [Lindner 2004](#)) and gastrointestinal failure requiring parenteral nutrition (56% with sepsis; [SIGNET 2011](#)). The three trials of ebselen were conducted in participants with acute neurological conditions: acute middle

cerebral artery occlusion (Ogawa 1999), aneurysmal subarachnoid haemorrhage (Saito 1998) and acute ischaemic stroke (Yamaguchi 1998).

It is unclear whether ebselen and selenium have similar mechanisms of action and thus, we chose not to consider them as identical interventions. For the ebselen trials, no details were provided concerning the need for ventilation or the level of critical illness care required.

The three neurological trials of ebselen (Ogawa 1999; Saito 1998; Yamaguchi 1998) all used an enteral dose of 300 mg daily for 14 days that was compared to a matching placebo. The trials of selenium used intravenous selenium, usually given as a sodium selenite, as a continuous infusion over 24 hours, with doses of selenium ranging from 155 mcg to 4000 mcg (often decreasing the dose as time went on). Four studies gave loading bolus doses on the first day (Angstwurm 2007; Manzanares 2011; Montoya 2009; Zimmermann 1997) and a fifth (Valenta 2011) gave daily boluses. Only Zimmermann 1997 had no comparison infusion. No trial examined the impact of selenium or ebselen supplementation for more than 28 days.

Berger 2001 included three trial groups: selenium only, selenium combined with alpha-tocopherol and zinc, and placebo control. We have presented only the comparison between selenium and placebo. The SIGNET 2011 trial included four study groups: glutamine only, selenium only, selenium combined with glutamine,

and a placebo group. We pooled data for selenium only and selenium combined with glutamine as the treatment group, and glutamine only and placebo as the control group.

Excluded studies

We excluded 16 studies (Berger 1998; Berger 2004a; Berger 2004b; Berger 2005a; Berger 2005b; Berger 2008; Börner 1997; Collier 2008; Kiessling 2006; Porter 1999; REDOX 2011; Stoppe 2010; Thiele 1997; Uden 1990; Watters 2002; Wollschläger 1997) for the reasons detailed in the 'Characteristics of excluded studies' section.

Ongoing studies

Two studies are ongoing (Geoghegan 2009; Yamaguchi 2003; see the 'Characteristics of ongoing studies' section).

Awaiting classification

Two studies are awaiting classification (SREAL 2012; SISPECT; see the 'Characteristics of studies awaiting classification' section).

Risk of bias in included studies

The risk of bias of the included studies was high. The trials often failed to report trial methodology in sufficient detail. One trial had improved methodology after further details were obtained from one trial author (Angstwurm 1999). See Description of studies, Figure 2 and Figure 3

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Funding bias	Other bias
Angstwurm 1999	+	?	+	?	?	+	?	?
Angstwurm 2007	+	?	+	?	+	+	+	+
Berger 2001	+	+	+	?	+	+	?	?
Forceville 2007	+	?	+	?	+	+	+	+
Janka 2013	+	?	?	?	+	+	+	?
Kuklinski 1991	+	?	+	?	+	+	?	+
Lindner 2004	+	?	+	?	+	+	?	?
Manzanares 2011	+	?	+	?	+	+	+	?
Mishra 2007	+	?	+	?	+	+	+	+
Montoya 2009	+	+	+	?	+	+	?	+
Ogawa 1999	+	?	+	?	+	+	+	?
Saito 1998	+	?	+	+	+	+	+	?
SIGNET 2011	+	+	+	?	+	+	+	?
Valenta 2011	+	+	+	+	+	+	?	?
Yamaguchi 1998	+	?	+	?	+	+	?	?
Zimmermann 1997	+	+	+	?	+	+	?	?

All but one of the included studies were RCTs; [Valenta 2011](#) was a quasi-RCT.

In eight trials groups were clearly comparable at baseline ([Angstwurm 1999](#); [Kuklinski 1991](#); [Lindner 2004](#); [Janka 2013](#); [Montoya 2009](#); [Ogawa 1999](#); [SIGNET 2011](#); [Yamaguchi 1998](#)). Four trials did not clearly report following up all participants to the end of the trial ([Lindner 2004](#); [Mishra 2007](#); [Montoya 2009](#); [Zimmermann 1997](#)). All trials clearly reported the treatments given for the trial but no trial clearly described the co-interventions as being equally provided to all groups. Six trials gave objectively described definitions of trial outcomes ([Angstwurm 1999](#); [Berger 2001](#); [Manzanares 2011](#); [Ogawa 1999](#); [SIGNET 2011](#); [Yamaguchi 1998](#)).

Allocation

Concealment of allocation was confirmed in only three trials ([Berger 2001](#); [Montoya 2009](#); [SIGNET 2011](#)). The other trials did not clearly report the method of concealment of allocation. Although not always explicitly stated, ITT analysis was undertaken in seven of the 16 trials ([Angstwurm 1999](#); [Forceville 2007](#); [Kuklinski 1991](#); [Ogawa 1999](#); [Saito 1998](#); [SIGNET 2011](#); [Zimmermann 1997](#)). The risk of selection bias is high.

Blinding

Ten trials were reported to be blinded or double blinded ([Angstwurm 2007](#); [Berger 2001](#); [Lindner 2004](#); [Manzanares 2011](#); [Mishra 2007](#); [Montoya 2009](#); [Ogawa 1999](#); [Saito 1998](#); [SIGNET 2011](#); [Yamaguchi 1998](#)). For the outcomes assessed in this review, it was often unclear to whom the blinding referred. Only [Angstwurm 2007](#) and [Angstwurm 1999](#) recruited consecutive eligible patients. Due to the poorly described level of blinding in most trials, the risk of bias remains unclear.

Incomplete outcome data

One trial, [Montoya 2009](#), had a follow-up period of 10 days. The average (median) length of mechanical ventilation in the control group was 13 days compared to nine days in the intervention group. The median length of stay in hospital was 17 days for the control group and 12 days for the intervention group. It remains unclear how long the patients indeed were followed-up. Most trials poorly described or failed to describe the follow-up period ([Angstwurm 1999](#); [Lindner 2004](#); [Mishra 2007](#); [Montoya 2009](#); [SIGNET 2011](#); [Valenta 2011](#); [Zimmermann 1997](#)). The risk of attrition bias is thus high.

Selective reporting

Only two trials had published a protocol or registered the trial in an available database ([Forceville 2007](#); [SIGNET 2011](#)). Thus, for most trials we are unable to assess the degree of reporting bias. The overall risk of bias is high for selective reporting.

Other potential sources of bias

Funding bias

Four studies provided a conflict of interest statement ([Forceville 2007](#); [Manzanares 2011](#); [SIGNET 2011](#); [Valenta 2011](#)). Five trials reported receiving pharmaceutical company funding ([Angstwurm 2007](#); [Ogawa 1999](#); [Saito 1998](#); [SIGNET 2011](#); [Yamaguchi 1998](#)), and in one trial a study was acknowledged for providing the study drug ([Forceville 2007](#)).

Effects of interventions

See: [Summary of findings for the main comparison](#) Summary of findings table 1

The outcomes reported in the included studies are listed in the 'Characteristics of included studies' table. Where available, we have presented mortality results using denominators based on the numbers of participants at randomization. Generally, we have presented the results for other outcomes using denominators based on the numbers of participants available at follow-up.

Primary outcomes

Mortality

All 16 included studies provided mortality data, 13 trials used selenium as intravenous sodium selenite ([Angstwurm 1999](#); [Angstwurm 2007](#); [Berger 2001](#); [Forceville 2007](#); [Kuklinski 1991](#); [Janka 2013](#); [Lindner 2004](#); [Manzanares 2011](#); [Mishra 2007](#); [Montoya 2009](#); [SIGNET 2011](#); [Valenta 2011](#); [Zimmermann 1997](#)) and three trials used ebselen ([Ogawa 1999](#); [Saito 1998](#); [Yamaguchi 1998](#)).

In trials of selenium, overall mortality was reduced in the intervention group (RR 0.82, 95% CI 0.72 to 0.93, I^2 statistic = 0%, fixed-effect model) while for ebselen the RR in favour of intervention among trials was 0.83 (95% CI 0.52 to 1.34, I^2 statistic = 0%, fixed-effect model). Combined data for mortality showed a RR of 0.82 (95% CI 0.72 to 0.93; I^2 statistic = 0%, test for subgroup differences: I^2 statistic = 0%; [Analysis 1.1](#); [Figure 4](#)).

Figure 4. Funnel plot of comparison: 1.2 Overall mortality (regardless of the follow-up period).

Twenty-eight days mortality among selenium studies yielded a RR of 0.84 (95% CI 0.69 to 1.02, I^2 statistic = 21%, random-effects model) while at 90 days RR was 0.96 (95% CI 0.78 to 1.18, I^2 statistic = 0% random-effects model) (Analysis 2.1).

Inclusion of the data from the three trials of ebselen showed no statistically significant difference in mortality (RR 0.83, 95% CI 0.52 to 1.34; I^2 statistic = 0%). Only Ogawa 1999 reported mortality at 30 days (RR 1.78, 95% CI 0.53 to 5.95) while Saito 1998 and Yamaguchi 1998 reported mortality data at three months follow-up (RR 0.72, 95% CI 0.42 to 1.22) (Analysis 2.2).

Mortality in trials of selenium in intensive care patients (Angstwurm 1999; Angstwurm 2007; Berger 2001; Forceville 2007; Janka 2013; Manzanares 2011; Mishra 2007; SIGNET 2011; Valenta 2011; Zimmermann 1997) compared with trials in patients with acute pancreatitis (Kuklinski 1991; Lindner 2004) yielded a RR of 0.88 (95% CI 0.77 to 1.01, I^2 statistic = 0%, random-effects model). In patients with acute pancreatitis the RR was 0.40 (95% CI 0.01 to 12.30, I^2 statistic = 81% random-effects model) (Analysis 2.3).

Secondary outcomes

Number of infectious complications

Six trials of intravenous sodium selenite provided data on this outcome (Angstwurm 2007; Berger 2001; Forceville 2007; Lindner 2004; Manzanares 2011; SIGNET 2011).

Berger 2001 provided data for participants developing infections based on the number of participants requiring antibiotics. Angstwurm 2007 reported no significant difference in the incidence of new infections (for example the development of hospital acquired pneumonia, as well as the incidence of acute respiratory distress syndrome). Forceville 2007 reported participants with at least one episode of nosocomial pneumonia and one participant on selenium developing a superinfection. Similarly, Manzanares 2011 reported participants with ventilator-associated pneumonia. Lindner 2004 provided data on patients developing sepsis or peritonitis. SIGNET 2011 reported new infections at 14 days post-randomization (both clinically suspected infections (used in our meta-analysis)) and infections confirmed and based on Centers for Disease Control and Prevention criteria (reported odds ratio 0.75, 95% CI 0.52 to 1.08, P = 0.12). Based on data from these six trials, there was no statistically significant difference (RR 0.96, 95% CI 0.75 to 1.23, I^2 statistic = 16%, random-effects model; Analysis 3.1). Mishra 2007 reported an infection rate instead of number of infections; consequently the data could not be included but no significant difference between groups was found.

All three trials of ebselen (Ogawa 1999; Saito 1998; Yamaguchi 1998) provided data for participants developing infections (pyrexia, respiratory infections or meningitis) with no statistically significant difference (RR 0.60, 95% CI 0.36 to 1.02, I^2 statistic = 33%, random-effects model; Analysis 3.1).

Adverse events

Trial investigators reported a wide variety of individual adverse events, including: organ failure, shock, requirement for inotropic support, requirement for fluids or transfusion, gastrointestinal bleeding, cerebral infarction and haemorrhage, nausea and vomiting, acute myocardial infarction, pulmonary embolism, enterocolitis, pancreatitis and skin rash. [Angstwurm 1999](#) reported that renal failure requiring continuous veno-venous haemodialysis was required for three of the 21 participants receiving intravenous sodium selenite and nine of the 21 participants in the control group. [Angstwurm 2007](#) reported that the need for haemodialysis or vasopressor therapy was identical in the two groups and that adverse events occurred in 110/122 of the intravenous sodium selenite group and 119/124 of the placebo group. Three trials reported numbers of participants developing any serious adverse event ([Forceville 2007](#); [Manzanares 2011](#); [SIGNET 2011](#)). [Mishra 2007](#) reported that five of the 18 selenium supplemented participants required renal replacement compared with seven of the 22 controls. The RR for an adverse event from these six trials was 1.03 (95% CI 0.85 to 1.24, I^2 statistic = 41%; [Analysis 4.1](#)).

In the three trials of ebselen, the overall incidence of adverse events in the ebselen and placebo groups were reported as 7.3% and 3.3%, respectively ([Yamaguchi 1998](#)); 10% and 14%, respectively ([Saito 1998](#)); and as not significantly different ([Ogawa 1999](#)). Combining the results for [Saito 1998](#) and [Yamaguchi 1998](#) (no available data for [Ogawa 1999](#)) yielded a RR of 1.16 (95% CI 0.40 to 3.36, I^2 statistic = 68%; [Analysis 4.1](#)).

Length of stay in ICU

Seven trials of intravenous sodium selenite provided data on the length of stay in intensive care ([Angstwurm 1999](#); [Angstwurm 2007](#); [Berger 2001](#); [Forceville 2007](#); [Manzanares 2011](#); [Mishra 2007](#); [SIGNET 2011](#); [Table 1](#)). Three trials provided data directly suitable for meta-analysis ([Angstwurm 2007](#); [Manzanares 2011](#); [Mishra 2007](#)). Four trials ([Angstwurm 1999](#); [Berger 2001](#); [Forceville 2007](#); [SIGNET 2011](#)) provided data which had to be processed. The overall MD was 0.54 (95% CI -2.27 to 3.34, I^2 statistic = 72%, random-effects model; [Analysis 4.2](#)).

Number of days on a ventilator

Five trials of intravenous sodium selenite provided data for the number of days on a ventilator ([Table 2](#)). Four trials provided data suitable for meta-analysis ([Angstwurm 1999](#); [Berger 2001](#); [Forceville 2007](#); [Montoya 2009](#); [Table 2](#)). One trial, [Angstwurm 2007](#), reported the incidence and hours of mechanical ventilation as not significantly different between groups (mean of 13 days with selenium for 84 participants and 11 days with placebo for 95 participants), but stated no range of days. The overall MD was -0.86 (95% CI -4.39 to 2.67, I^2 statistic = 89%, random-effects model; [Analysis 4.3](#)).

Length of hospital stay

Five trials, all of intravenous sodium selenite, provided data on the length of hospital stay ([Angstwurm 1999](#); [Berger 2001](#); [Forceville](#)

[2007](#); [Montoya 2009](#); [SIGNET 2011](#); [Table 3](#)). The overall MD was -3.33 (95% CI -5.22 to -1.44, I^2 statistic = 42%, random-effects model; [Analysis 4.4](#)).

Quality of life after discharge

Trials of ebselen ([Ogawa 1999](#); [Saito 1998](#); [Yamaguchi 1998](#)) reported no statistically significant difference in Glasgow Outcome Scales ([Jennett 1975](#)) at final follow-up. However, [Yamaguchi 1998](#) reported that the Modified Barthel Index Score ([Shah 1989](#)), an assessment of functional status, was significantly improved by ebselen at a final follow-up time of three months.

Only one trial, [Ogawa 1999](#), stated the results in values. The other two trials, [Saito 1998](#) and [Yamaguchi 1998](#), showed only a graphical representation. Consequently, we were unable to make an analysis for this subgroup.

No trials of selenium have provided quality of life data.

Economic outcomes

No trials provided details of costs or economic outcomes.

Other findings

Six trials found significantly increased activity of the antioxidant selenoenzyme glutathione peroxidase, demonstrating the potential for intravenous selenium to improve antioxidant capacity in participants ([Angstwurm 2007](#); [Angstwurm 1999](#); [Berger 2001](#); [Manzanares 2011](#); [Mishra 2007](#); [Valenta 2011](#)). The measurement of selenium levels in the blood may be an unreliable marker of selenium status because levels fall with an acute phase response provoked by injury or infection ([Sattar 1997](#)).

Trials sequential analysis (TSA):

Since TSA was not part of the previous version of this review, [Avenell 2004](#), we used the calculated relative risk and event rates of [Analysis 1.1](#) to calculate the required information size. In our TSA of the impact of selenium supplementation on mortality among critically ill patients using a control event proportion of 32% found in the included trials, with a type 1 error of 5% and a 18% relative risk reduction (80% power), the trial sequential monitoring boundary for benefit is not crossed by the z-curve ([Figure 5](#)). However, these lines are very close to crossing each other. This may suggest a probability of lack of random error for the conclusion of an effect of 18% relative risk reduction even though the required information size (N = 2605) has not yet been reached. Nevertheless, one must exert caution when interpreting the results of our TSA on mortality since all included studies are at high risk of bias and the intervention effect is likely to have been overestimated in the traditional meta-analysis. This will inevitably influence the TSA result. As a general rule TSA is unable to adjust for risk of bias and is ideally designed for studies with low risk of bias. Thus, we anticipate a higher degree of heterogeneity and diversity, and consequently a different TSA output once the results of the ongoing large RCTs are published.

Figure 5. Trial sequential analysis (TSA) of all trials examining the effect of Selenium supplementation on mortality among critically ill. Using a control event proportion of 32% found in the included trials, with a type 1 error of 5% and a 18% relative risk reduction (80% power), the trial sequential monitoring boundary for benefit is not crossed by the z-curve. However, these lines are very close to crossing each other which may indicate a probability of lack of random error for the conclusion of an effect of 18% relative risk reduction even though the required information size (N = 2605) has not yet been reached. However, caution must be exerted when interpreting the results of this TSA since all included studies are at high risk of bias and the intervention effect is likely to have been overestimated in the traditional meta-analysis.

DISCUSSION

Summary of main results

In this review update we found no clear evidence that selenium supplementation reduces mortality in critically ill adults despite a statistically significant finding. This is mainly due to the high risk of bias, most likely overestimating the overall intervention effect. Even though we are unable to rule out a beneficial effect, the evidence remains dubious as a result of the poor methodological quality of the trials. For instance, only three trials clearly reported concealment of allocation (Berger 2001; Montoya 2009; SIGNET 2011). Few trials reported on outcomes other than mortality or clearly defined the reported outcomes. Periods of follow-up were often short and did not allow for the prolonged recovery from critical illness. There was insufficient data to examine the effect of methodological superiority or dose of selenium on the outcomes.

Selenium supplementation in the general ICU population with severe sepsis or septic shock has been investigated by [SISPCT](#), which with a sample size of 1180 and rigorous methodology may help clarifying a potential benefit or harm of selenium. The lead author of [SISPCT](#) expects to publish the results within the next year. Additionally, based on data from current published trials it remains at best uncertain as to whether loading bolus or continuous doses are preferred (Manzanares 2011).

There was no clear evidence of benefit from the use of ebselen in patients with stroke or subarachnoid haemorrhage. The results of one large trial, [Yamaguchi 2003](#), are still awaited.

Furthermore, we found no evidence to suggest that these interventions are harmful.

Overall completeness and applicability of evidence

We are confident that we identified all available studies from our search strategy. Several authors have been contacted but have not identified any additional trials for inclusion.

In contrast to [Avenell 2004](#), in this update we revised the primary endpoints, adding overall mortality regardless of the period of follow-up, and carried out TSA in order to reduce the risk of random error. Yet, the review conclusions remain the same.

The applicability of our results only refers to critically ill adult patients and as such there is insufficient evidence to support the routine use of this intervention.

Quality of the evidence

The RCT is considered the most rigorous method for determining whether a cause-effect relationship exists between an intervention and outcome. The strength of the RCT lies in the process of randomization.

No trials were reported as at overall low-risk of bias ([Figure 2](#); [Figure 3](#)). Fifteen of the 16 included trials were at high risk of bias regarding random sequence generation (selection bias). Only one trial has published the protocol ([SIGNET 2011](#)) and only two trials had been registered in a database ([Forceville 2007](#); [SIGNET 2011](#)), which is why we deemed 14 of the 16 included trials at high risk of reporting bias. All trials of ebselen were at high risk of funding bias. Thus, due to the overall high risk of bias in these included trials, the results should be interpreted with caution.

Application of the GRADE approach enables us to incorporate risk of bias, directness of evidence, heterogeneity, precision of effect estimate, and risk of publication bias. Based on the above mentioned criteria, the quality of evidence in this review was very low and there was a high risk of bias.

Potential biases in the review process

In this update we remained loyal to the original protocol, [Avenell 2002](#), with only minor changes in order to avoid bias. Two review authors (MA, AA) independently performed data extraction and 'Risk of bias' assessment. We consulted the Managing Editor and Trials Search Coordinator of the Cochrane Anaesthesia, Critical and Emergency Care Group throughout the entire process of the review update.

Despite our prior knowledge to the conclusions of other recently published systematic reviews ([Huang 2013](#); [Landucci 2014](#); [Manzanares 2012](#)), we have adhered to Cochrane methodology and applied additional statistical methods, such as TSA, to strengthen our conclusions and reduce the risk of random error.

Agreements and disagreements with other studies or reviews

The overall conclusions of this Cochrane review do not agree with the statements and findings of the most recently published systematic reviews and meta-analysis ([Huang 2013](#); [Landucci 2014](#);

[Manzanares 2012](#)). All three meta-analyses reported a significantly decreased mortality in the selenium group. However, two papers did not address the quality of studies included ([Huang 2013](#); [Manzanares 2012](#)). [Landucci 2014](#) reported the quality of evidence of the meta-analysis as low due to unclear quality of randomization in many studies. These papers did not adhere to PRISMA guidelines.

AUTHORS' CONCLUSIONS

Implications for practice

Despite a statistically significant finding on longest follow-up mortality (RR 0.82, 95% CI 0.72 to 0.93), one must be cautious when interpreting the strength of the evidence for the routine use of selenium or ebselen supplementation in critically ill patients. Serious methodological shortcomings of the included studies are likely to have influenced the overall intervention effect ([Summary of findings for the main comparison](#)). Additionally, we failed to show a reduced time on mechanical ventilation, length of stay in ICU or length of stay in hospital. Our review did not indicate any harmful effect of the intervention among critically ill patients.

The GRADE approach only reaffirmed our interpretation of the level of evidence and we are confident that at this stage the quality of evidence is very low and risk of bias very high.

Implications for research

We await the publication of the large multicentre RCT, [SISPCT](#), as it will provide important information essential to calculate the required information size in order to reject or accept a beneficial effect of selenium supplementation. Based on our current TSA, the required information size of 2605 patients is not far from the 2084 patients included in this paper. However, large, well-designed, adequately powered trials of selenium supplementation, at low risk of bias and conforming to the CONSORT statement ([Moher 2010](#)), will most likely increase the required information size. Future research should examine functional status, patient-perceived quality of life and include economic evaluation. Independent observers should assess outcomes and the period of follow-up should be extended and preferably exceed current arbitrary defined short limits (i.e. 28 days up to six months).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Angstwurm 1999

Methods	Method of randomization: states stratified randomization only Assessor blinding: states open label Intention to treat (ITT): carried out Lost to follow-up: none
Participants	Location: ICU, Klinikum Innenstadt, University of Munich, Germany Period of trial: recruitment March 1995 to August 1996 42 patients Inclusion criteria: APACHE score ≥ 15 , and clinical and laboratory signs of new systemic inflammatory response syndrome (SIRS) according to sepsis criteria (American College of Chest Physicians/Society of Critical Care Medicine), first 24 hours after admission

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Angstwurm 1999 (Continued)

Exclusion criteria: age < 18 years, pregnancy, after cardiopulmonary resuscitation, severe gastrointestinal bleeding, trauma, surgery, chronic renal failure, refusal to participate
Sex: 29 males, 13 females
Age: mean age 56 years (range 18 to 83 years)

Interventions	<p>Timing of intervention: from day of admission to intensive care for additional supplementation for nine days</p> <ol style="list-style-type: none"> 1. Continuous intravenous sodium selenite (535 mcg selenium for 3 days, 285 mcg selenium for 3 days, 155 mcg selenium for 3 days, 35 mcg selenium for remainder of total treatment time; and standard parenteral nutrition including glutamine 20 g/L 2. Continuous placebo of saline and intravenous 35 mcg selenium as sodium selenite, and standard parenteral nutrition including glutamine 20 g/L <p>Allocated: 21/21 Assessed: 21/21</p>
Outcomes	<p>Length of follow-up: until discharge</p> <p>Main outcomes:</p> <ul style="list-style-type: none"> • Mortality <p>Other outcomes:</p> <ul style="list-style-type: none"> • Number of days on a ventilator • Length of hospital stay
Notes	Request for further details of interventions sent 24 October 2003, reply received 17 November 2003.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were stratified randomly into two groups. No further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None stated
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	None stated

Angstwurm 1999 (Continued)

Other bias	Unclear risk	None
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Angstwurm 2007

Methods	Method of randomization: states randomized but no further details Assessor blinding: performed ITT: not performed Lost to follow-up: reported
Participants	Location: 11 independent German ICUs Period of trial: enrolment December 1999 to October 2004 249 patients Inclusion criteria: men and women > 18 years with APACHE III score (22) > 70 and at least two of the following criteria: rectal body temperature > 38°C or hypothermia < 36°C, heart rate > 90 per minute, respiratory frequency > 20 per minute and PaCO ₂ < 32 mmHg (< 4.3 kPa), leucocytes > 12 000/μL or < 4 000/μL or > 10% immature leucocytes, decrease of platelet count > 50 % within the first 24 hrs or platelets < 150,000/μL at admission; admission into the trial after diagnosis within 24 hours; beginning of treatment within 1 hour after inclusion. Exclusion criteria: pregnancy; missing informed consent of patient or relative/intimate friend; withdrawal of informed consent after inclusion into trial; participation in any clinical trial within last 30 days; prior participation in this clinical trial; cerebral injury due to hypoxia after cardiopulmonary resuscitation; primary concomitant disease with expected high mortality within 2 months; not for resuscitation; malignant primary disease as cause of systemic inflammatory response syndrome or sepsis, e.g. agranulocytosis as result of chemotherapy or idiopathic bone marrow aplasia; haemorrhagic-necrotising pancreatitis without infectious complications. Sex: 162 males, 76 females Age: 64.6 years (SD 14.0)
Interventions	Timing of intervention: admission into trial after diagnosis within 24 hours, trial treatment beginning within 1 hour after inclusion 1. 48 mL vial as bolus intravenous injection over 30 minutes providing 1000 mcg sodium selenite, followed by continuous infusion of 2 mL/hour over 24 hours for 14 days, total dose 15,000 mcg selenium. Allowed selenium from other preparations of up to 100 mcg/day. 2. Matching placebo of 0.9% sodium chloride give as same regimen. Allowed selenium from other preparations of up to 100 mcg/day. Allocated: unclear Assessed: 116/122
Outcomes	Length of follow-up: 28 days Main outcomes: <ul style="list-style-type: none">• 28 day mortality• Participants with new infections Other outcomes: <ul style="list-style-type: none">• Number of days on a ventilator• Length of ICU stay• Participants with adverse events
Notes	Email From Professor Gärtner on 8 August 2006 provided further details on participants with infections, length of ventilation, numbers randomized to each group, and details of the randomization process.

Risk of bias

Selenium supplementation for critically ill adults (Review)

Angstwurm 2007 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	249 randomized patients, 238 underwent ITT analysis. 14 patients failed exclusion/inclusion criteria after ITT analysis, 30 drug administration failure. 189 underwent per protocol analysis.
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	High risk	Sponsored by biosyn Arzneimittel GmbH, Fellbach, Germany
Other bias	High risk	The trial had two exclusion criteria which could lead to bias: primary concomitant disease with an expected high mortality within 2 months and patients with a "do-not-resuscitate code"

Berger 2001

Methods	Method of randomization: concealed Assessor blinding: states double-blinded but no further details ITT: performed Lost to follow-up: none
Participants	Location: surgical ICU of the Central Hospitalier Universitaire Vaudois, Lausanne, Switzerland Period of trial: before 2000 21 patients Inclusion criteria: severe multiple injury (injury Severity Score, ISS, > 15) involving at least two body systems, pathophysiological changes requiring ICU support, age 18 to 75 years, admission within 24 hours of injury Exclusion criteria: pre-existing renal or hepatic failure, foreseeable imminent death, no informed consent, documented hypothyroidism prior to accident Sex: 15 males, 6 females Age: age range 18 to 74 years
Interventions	Timing of intervention: from day of admission for five days 1. Slow intravenous infusion over 24 hours of 500 mcg selenium as sodium selenite/day 2. Infusion vehicle over 24 hours 3. Slow intravenous infusion over 24 hours of 500 mcg selenium/day and 13 mg zinc/day, 150 mg alpha-tocopherol in 5 ml 10% lipid emulsion (Lipovenös, Fresenius, Stans, Switzerland) as slow injection once daily upon initiation of intravenous infusion (data for this group not used in this review)

Selenium supplementation for critically ill adults (Review)

Berger 2001 (Continued)

Allocated: 9/12/11

Assessed: 9/12/11

Outcomes	Length of follow-up: appears followed up until died or left hospital, maximum length of stay 249 days Main outcomes: <ul style="list-style-type: none"> • Mortality • Numbers of patients with infection (defined as requiring antibiotics) Other outcomes: <ul style="list-style-type: none"> • Number of days on a ventilator • Length of ICU stay • Length of hospital stay
Notes	ITT data taken from paper in Nutrition Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Low risk	Concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. The trace element solutions were transparent, colourless, and clinically undetectable, identified with a number code known to the pharmacist only
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	Not stated
Other bias	Unclear risk	None

Forceville 2007

Methods	Method of randomization: stratified in each centre by blocks of four, sequentially numbered identical boxes provided to the investigator by the pharmacist, following the order of the randomization list Assessor blinding: states double-blind ITT: performed
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Forceville 2007 (Continued)

Lost to follow-up: none

Participants	<p>Location: 7 ICUs in France</p> <p>Period of trial: randomization from 8 February 2002 to 12 March 2004</p> <p>Inclusion criteria: severe documented infection (one or more of positive culture or Gram stain of normally sterile fluid, clinical focus of infection, nosocomial infection; need for mechanical ventilation; severe septic shock (circulatory failure requiring at least 1 L in previous 24 hours and treated for at least one hour with >15 mcg/kg/min dopamine or > 0.2 mcg/kg/min epinephrine or norepinephrine corresponding to class 4 of cardiovascular failure of Sequential Organ Failure Assessment score; Simplified Acute Physiologic Score II of 25 or more; consent from patients or representatives</p> <p>Exclusion criteria: pregnancy, end-stage chronic disease, limitation of care in place, preliminary circulatory failure, shock due to urinary infection without bacteraemia, peritonitis due to peritoneal dialysis or trauma, participant in another trial</p> <p>Sex: 38 males, 22 females</p> <p>Age: selenium 66 years (SD 14), placebo 69 years (SD 12)</p>
Interventions	<p>Timing of intervention: unclear when started, given for 10 days</p> <ol style="list-style-type: none"> 4000 mcg selenium as intravenous sodium selenite (in 192 mL saline) over 24 hrs, then 1000 mcg selenium as sodium selenite (in 48 mL saline) over 24 hrs for 9 days Matching saline placebo for 10 days <p>Allocated: 31/29</p> <p>Assessed: 31/29</p>
Outcomes	<p>Length of follow-up: one year after randomization</p> <p>Main outcomes:</p> <ul style="list-style-type: none"> Mortality Participants with infection Length of stay in an ICU Length of stay in hospital Adverse events
Notes	<p>The trial is registered at ClinicalTrials.gov. There is complete agreement between the information registered in the database and the results in the article.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. All patients, pharmacists, medical- and nursing staff remained blinded throughout the trial period. In each centre, sequentially identical numbered boxes containing the whole treatment for each patient were delivered to the investigator by the pharmacist following the order of the randomizations list.

Forceville 2007 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized patients were analysed according to the treatment group in which they were assigned
Selective reporting (reporting bias)	Low risk	None. trial details available on ClinicalTrials.gov (Forceville 2007)
Funding bias All outcomes	Low risk	Funding by grant from the Ministry of Health, France
Other bias	High risk	The principal Investigator, Xavier Forceville, is shareholder in a company named SÉRÉNITÉ-Forceville

Janka 2013

Methods	Method of randomization: Odd or even date of admission to ICU Assessor blinding: no details, prospective observational trial ITT: no details. Lost to follow-up: none
Participants	Location: The 1st Clinic of Anaesthesiology and Intensive Care Medicine, University Hospital of Louis Pasteur in Košice, Slovak Republic. Period of trial: January 2008. No end date stated. 72 patients Inclusion criteria: patients who developed sepsis, severe sepsis or septic shock during hospitalisation, APACHE 19-40 after admission. Exclusion criteria: APACHE < 19 Sex: 49 males, 23 females Age: mean age 53 years, 23 to 79
Interventions	Timing of intervention: immediately after admission to ICU department, no details. Trial intervention was for a maximum of six days. Case: continuous infusion, sodium selenite pentahydrate at 750 mg/day for 6 days Control: continuous infusion, NaCl 50 mL/day for 6 days
Outcomes	Length of follow-up: 28 days Main outcomes: <ul style="list-style-type: none"> 28-day mortality Other outcomes: <ul style="list-style-type: none"> APACHE II score
Notes	

Janka 2013 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Odd or even date of admission to ICU
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	95 patients included. 15 lost to follow-up, 8 died within the first day after admission (lost to follow-up). 72 patients underwent per protocol analyse.
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Low risk	Financially supported by Slovak grant agency for Science
Other bias	Unclear risk	None

Kuklinski 1991

Methods	Method of randomization: states randomized but no further details Assessor blinding: not reported ITT: carried out Lost to follow-up: none
Participants	Location: hospital, Rostock, Germany Period of trial: before 1991 17 patients Inclusion criteria: contrast CT scan showed pancreatic necrosis, < 72 hours since onset of pancreatitis Exclusion criteria: mild pancreatitis Sex: all male Age: range 28 to 65 years
Interventions	Timing of intervention: 28 days 1. Intravenous 500 mcg sodium selenite daily duration unclear (Selenase pro injektion, GN PHARM, Arzneimittel GmbH, Stuttgart) 2. No treatment Allocated: 8/9 Assessed: 8/9
Outcomes	Length of follow-up:

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Kuklinski 1991 (Continued)

Main outcome:

- Mortality

Notes

Request for further details on dose of selenium given sent 20 October 2003. Letter returned as author no longer at address in publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	Not stated
Other bias	High risk	Only men were included in the trial

Lindner 2004

Methods	Method of randomization: states randomized but no further details Assessor blinding: not reported ITT: not reported Lost to follow-up: details provided
Participants	Location: medical centre, Chemnitz, Germany Period of trial: enrolment January 1997 to November 1998 70 patients Inclusion criteria: severe acute pancreatitis managed on medical wards, severe abdominal pain, 3-fold increase of amylase and lipase, onset within 72 hours Exclusion criteria: none given Sex: 39 males, 28 females (completers) Age: median 50 to 52 years
Interventions	Timing of intervention: start unclear, given until discharged 1. Day 1 2000 mcg selenium as sodium selenite, days 2 to 5 1000 mcg/d, day 6 until discharged 300 mcg/d

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Lindner 2004 (Continued)

2. 0.9% sodium chloride placebo

Allocated: 35/35

Assessed: 32/35

Outcomes	Length of follow-up: until discharge Main outcomes: <ul style="list-style-type: none">• Mortality• Number of patients with infectious complications (sepsis)
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	State blinded, no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No details on follow-up
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	Not stated
Other bias	Unclear risk	None

Manzanares 2011

Methods	Method of randomization: states randomized but no further details Assessor blinding: states participants blinded ITT: not carried out Lost to follow-up: not complete, four patients excluded
Participants	Location: single centre, university hospital ICU, Montevideo, Uruguay Period of trial: randomization Decmber 2006 to January 2008 35 patients Inclusion criteria: patients with systemic inflammatory response and APACHE II score ≥ 15 and predicted mechanical ventilation > 48 hours.

Manzanares 2011 (Continued)

Exclusion criteria: age < 18 years, pregnancy, brain injury after cardiopulmonary arrest, malignant disease, immune deficiency, chronic renal failure, participation in another trial, limitation of care, refused consent.

Sex: 15 males, 16 females

Age: mean age 58 (17 SD) years for 15 in selenite group, 54 (SD 17) for 16 in placebo group

Interventions	<p>Timing of intervention: randomized within first 24 hours of ICU admission</p> <ol style="list-style-type: none"> 1. Intravenous selenium 2000 mcg (as selenious acid) bolus loading dose over 2 hours within 2 hours of enrolment; thereafter 1600 mcg/d in 240 mL 0.9% NaCl for 10 days 2. Matching placebo 0.9% NaCl only for 10 days <p>Allocated: 16/19 Assessed: 15/16</p>
Outcomes	<p>Length of follow-up: duration of hospital stay</p> <p>Main outcomes:</p> <ul style="list-style-type: none"> • Mortality at in intensive care and hospital • Infections <p>Other outcomes:</p> <ul style="list-style-type: none"> • Days on ventilator • Length of ICU stay
Notes	<p>We emailed Dr Manzanares 27 April 2011 for details of adverse events and deaths, who provided information on 28 April 2011</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blinded. Only patients were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up for the entire trial
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Low risk	Supported in part by grant from the Comisión Sectorial para la Investigación Científica and the Fondo Clemente Estable 2004 and Ministerio de Educación y Cultura, Uruguay.

Manzanares 2011 (Continued)

Other bias	Unclear risk	None
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Mishra 2007

Methods	Method of randomization: states randomized but no further details Assessor blinding: states double-blind ITT: not reported Lost to follow-up: no details provided
Participants	Location: ICU, Liverpool, UK Period of trial: before 2002 to 2004 40 patients Inclusion criteria: APACHE II score > 15, clinical suspicion of infection and > 1 organ dysfunction Exclusion criteria: chronic renal failure, alcoholic liver disease, immunodeficiency Sex: 19 males, 21 females Age: mean age 66 years
Interventions	Timing of intervention: within 24 hours of admission to intensive care and within 72 hours since diagnosis of sepsis, given until discharged 1. Intravenous selenium 470 mcg/day for 3 days, then 320 mcg/day for 3 days, then 160 mcg/day for 3 days, and 30 mcg/day thereafter 2. 30 mcg/day Allocated: 18/22 Assessed: 18/22 for mortality
Outcomes	Length of follow-up: 28 days Main outcomes: <ul style="list-style-type: none">• Mortality at 28 days• Infections Other outcomes: <ul style="list-style-type: none">• Length of ICU stay• Renal replacement therapy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. The investigators were blinded to the study treatment

Mishra 2007 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No data on follow-up
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Low risk	Supported by National Health Service trust with a Research and Development grant
Other bias	High risk	Trial designed to recruit 80 patients to provide adequate power to analyse clinical endpoints, but ended the trial after recruiting only 40 patients due to an unexpectedly low consent rate

Montoya 2009

Methods	Method of randomization: states randomized in sealed envelopes Assessor blinding: states double-blind in but no further details ITT: no details Lost to follow-up: None
Participants	Location: a single ICU, no further details Period of trial: October 2007 to February 2008 68 patients Inclusion criteria: diagnosis of sepsis, age over 18 years Exclusion criteria: chronic pro-inflammatory state, pregnant patients and patients receiving total parenteral nutrition. Sex: 38 males, 30 females Age: mean age 66 years
Interventions	Timing of intervention: no details Trial intervention was for 10 days Case: 1000 µg selenium the first day, 500 µg the second day and 200 µg/day until the end of the trial. Control: 100 µg/day selenium up to the end of the trial
Outcomes	Length of follow-up: no details Main outcomes: <ul style="list-style-type: none"> • SOFA score Other outcomes: <ul style="list-style-type: none"> • APACHE score and mortality
Notes	

Montoya 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	States nothing on follow-up
Selective reporting (reporting bias)	High risk	Reports to have a follow-up period of 10 days. The average length of mechanical ventilation in the control group is set to 13 days (median) compared to 9 days (median) in the intervention group. The length of stay in hospital is stated as 17 days (median) for the control group and 12 days (median), longest range 20 days for the intervention group. It is unclear how long the patients have been followed-up
Funding bias All outcomes	Unclear risk	None stated
Other bias	High risk	Does not describe the time from randomization to treatment initiation. Does not describe how many patients randomized (error in flow-chart)

Ogawa 1999

Methods	Method of randomization: states randomized list but no further details Assessor blinding: states double-blind but no further details ITT: ITT for mortality only Lost to follow-up: none
Participants	Location: 28 Japanese neurosurgical and neurological units Period of trial: recruitment June 1994 to November 1996 105 patients Inclusion criteria: acute stroke with complete occlusion of the M1 (M2) portion of the middle cerebral artery (MCA) on cerebral angiography and no low-density area (LDA) in the MCA territory on computed tomography (CT), could start drug treatment within 12 hours of stroke Exclusion criteria: distinct fresh LDA in the MCA territory on CT scans; stenosis or occlusion of trunk arteries, other than MCA; haemorrhagic stroke including subarachnoid haemorrhage; pregnancy; severe hepatorenal or metabolic disease Sex: 67 males, 32 females Age: mean age 66 years

Ogawa 1999 (Continued)

Interventions	<p>Timing of intervention: started within 12 hours of middle cerebral artery occlusion, given for 14 days</p> <ol style="list-style-type: none"> 1. Oral ebselen 150 mg twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness 2. Oral placebo granules twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness <p>Allocated: 48/57 Assessed: 48/57 for mortality</p>
Outcomes	<p>Length of follow-up: 14 days</p> <p>Main outcomes:</p> <ul style="list-style-type: none"> • Mortality • Numbers of patients with infection <p>Other outcomes:</p> <ul style="list-style-type: none"> • Quality of life - Glasgow Outcome Scale
Notes	Request for further details of denominators and infections sent 22 October 2003, but no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were randomized with the use of separate randomization lists balanced for each participating centre. No further details
Allocation concealment (selection bias)	Unclear risk	State, before code opening patients were assessed whether they fulfilled ex/inclusion criteria
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	105 patients were enrolled. Six patients were excluded from ITT analysis. Another 16 patients were excluded before protocol analysis. 83 patients were subjected to analysis
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	High risk	Supported by Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan
Other bias	Unclear risk	None

Saito 1998

Methods	Method of randomization: states randomized lists but no further details
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Selenium supplementation for critically ill adults (Review)

Saito 1998 (Continued)

Assessor blinding: states double-blind and blinded outcome assessment
ITT: performed
Lost to follow-up: none

Participants	Location: 84 Japanese neurosurgical units Period of trial: enrolled November 1992 to April 1994 286 patients Inclusion criteria: subarachnoid haemorrhage (SAH) from aneurysmal rupture within previous 96 hours, and SAH Hunt and Kosnik grade II to IV or World Federation of Neurosurgical Surgeons grade I to IV at admission Exclusion criteria: pregnancy; age < 20 years or > 71 years; major cardiopulmonary, hepatorenal or metabolic disease; large intracerebral or intraventricular clots Sex: 112 males, 174 females Age: mean age 56 years
Interventions	Timing of intervention: started within 96 hours of subarachnoid haemorrhage, given for 14 days <ol style="list-style-type: none"> 1. Oral ebselen 150 mg twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness 2. Oral placebo granules twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness Allocated: 145/141 Assessed: 145/141
Outcomes	Length of follow-up: 3 months Main outcomes: <ul style="list-style-type: none"> • Mortality • Numbers of patients with meningitis, respiratory infection Other outcomes: <ul style="list-style-type: none"> • Quality of life - Glasgow Outcome Scale
Notes	Request for further details of unpublished trial mentioned in main trial report, and numbers of patients with infections sent 21 October 2003, but no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States, separate balanced randomized lists for each participating centre, but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment
Incomplete outcome data (attrition bias)	Low risk	286 patients enrolled, all subjected to ITT analysis. 42 patients were excluded. 244 were subjected to protocol-compatible analysis

Saito 1998 (Continued)

All outcomes

Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	High risk	Supported by Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan.
Other bias	Unclear risk	None

SIGNET 2011

Methods	<p>Method of randomization: remote telephone computer system generated random allocation</p> <p>Assessor blinding: states double-blinded</p> <p>ITT: performed</p> <p>Lost to follow-up: none for mortality and infections</p>
Participants	<p>Location: 10 ICUs in Scotland (and associated high dependency units if also under the care of the same intensivists)</p> <p>Period of trial: recruitment June 2004 to November 2008</p> <p>502 patients</p> <p>Inclusion criteria: expected to be on intensive care and high dependency units (levels 2 and 3 care) under the care of the ICU consultants for at least 48 hours, aged ≥ 16 years or over, require parenteral nutrition and expected to have at least half of daily nutritional requirements given by that route</p> <p>Exclusion criteria: pregnant women, people whose expected stay in the UK is < six months, severe renal failure (creatinine clearance < 10 mL/min and not on renal replacement therapy)</p> <p>Sex: 304 males, 198 females</p> <p>Age: mean age 63.8 (SD 14.9) years</p>
Interventions	<p>Timing of intervention: from as soon as practicable by pharmacy, when decision made to commence parenteral nutrition for a maximum of 7 days, or until parenteral nutrition ceased</p> <ol style="list-style-type: none"> 20.2 g glutamine in standard parenteral nutrition 500 mcg selenium as sodium selenite added to standard parenteral nutrition Glutamine and in standard parenteral nutrition with 500mcg selenium as sodium selenite Standard parenteral nutrition only <p>Volume of feed could be reduced for men < 60 kg and women < 70 kg</p> <p>Allocated: 126/127/124/125</p> <p>Assessed: 126/127/124/125</p>
Outcomes	<p>Length of follow-up: 6 months after randomization</p> <p>Main outcomes:</p> <ul style="list-style-type: none"> Mortality Number of participants with infection in first 14 days (all clinically suspected, and all Centers for Disease Control and Prevention criteria confirmed infections) <p>Other outcomes:</p> <ul style="list-style-type: none"> Length of stay in an ICU Length of hospital stay Quality of life after discharge Adverse events

SIGNET 2011 (Continued)

- Economic outcomes

Notes	Alison Avenell and David Noble were SIGNET trial investigators. Data was extracted by their trial co-investigators John Barr and Tom Engelhardt. Funding was provided by Fresenius-Kabi and Oxford Nutrition. The trial is registered at The ISRCTN registry and the protocol is published. Except for minor changes regard to the number of primary endpoints, there is full agreement between registrars, protocol and the results in the article.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A remote telephone computer system generated random allocation
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, clinicians and investigators were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	1134 patients were screened for participation. 506 did not meet inclusion criteria. For 53 patients, trial parenteral nutrition was not immediately available, leaving 575 patients from whom consent was sought. 502 patients were randomized. No data on follow-up.
Selective reporting (reporting bias)	Low risk	None. Full protocol and trial registration available (SIGNET 2011)
Funding bias All outcomes	High risk	Funding was provided by Fresenius-Kabi and Oxford Nutrition as unrestricted grants for the trial nutrition components
Other bias	Unclear risk	None

Valenta 2011

Methods	Method of randomization: randomized according to date of birth Assessor blinding: open label ITT: not carried out Lost to follow-up: none
Participants	Location: single centre, university hospital mixed ICU Period of trial: March 2004 to April 2009 Inclusion criteria: over 18 years, admitted with systemic inflammatory response syndrome, sepsis, septic shock, SOFS score over 5

Valenta 2011 (Continued)

Exclusion criteria: expected hospital stay < 5 days, persistent vegetative state after hypoxic brain injury or traumatic brain injury, pregnancy, participation in another clinical trial, failure to gain consent, patient with limited care (e.g. do not resuscitate advance directive on file)

Sex: 97 males, 53 females (of 150 assessed)

Age: mean 60 years (SD 16) selenium, 60 years (SD 15) control

Interventions	<p>Timing of intervention: day one for 5 to 14 days</p> <ol style="list-style-type: none"> 1. 1000 mcg selenium as sodium selenite in 100 mL 0.9% NaCl over 30 minutes through central venous catheter at 9am on first day, thereafter 500 mcg/day over 30 minutes 2. No placebo <p>Allocated: 93/89</p> <p>Assessed: 75/75</p>
Outcomes	<p>Length of follow-up: 28 days</p> <p>Main outcome:</p> <p>Mortality</p>
Notes	Dr Helena Brodská gave details of randomization and control group intervention on 27 April 2011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomized according to date of birth
Allocation concealment (selection bias)	High risk	Quasi-randomized by hospital number
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Data on inclusion and follow-up not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	None lost to follow-up
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	Not stated
Other bias	Unclear risk	None

Yamaguchi 1998

Methods	Method of randomization: states randomized lists but no further details Assessor blinding: states double-blinded but no further details ITT: not carried out Lost to follow-up: incomplete, two patients excluded
Participants	Location: 68 Japanese neurological and neurosurgical units Period of trial: recruitment June 1994 to December 1996 302 patients Inclusion criteria: acute ischemic stroke, including thrombosis and embolism, by symptoms and CT scan; could receive drug treatment within 48 hours of onset Exclusion criteria: transient ischaemic attacks; pregnancy; surgery interfering with the assessment of neurological function; previous stroke with residual neurological impairment; major cardiopulmonary, hepatic, renal or metabolic disease; haemorrhagic stroke Sex: 189 males, 111 females Age: mean age 65 years, range 22 to 85 years
Interventions	Timing of intervention: started within 48 hours of stroke, given for 14 days 1. Oral ebselen 150 mg twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness 2. Oral placebo granules twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness Allocated: 152/150 Assessed: 151/149
Outcomes	Length of follow-up: 3 months Main outcomes: <ul style="list-style-type: none">• Mortality• Numbers of patients with respiratory infection Other outcomes: <ul style="list-style-type: none">• Quality of life - Glasgow Outcome Scale, modified Barthel Index

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States separate randomization lists balanced for each participating centre, but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	302 patients were enrolled in the trial, 2 patients were excluded before ITT-analysis. 300 patients were subjected to ITT analysis, 58 more patients were

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Yamaguchi 1998 (Continued)

All outcomes		excluded from PC analysis. 242 patients were subjected to protocol-compatible analysis.
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	Not stated
Other bias	Unclear risk	None

Zimmermann 1997

Methods	Method of randomization: states randomized but no further details Assessor blinding: not reported ITT: not reported Lost to follow-up: not reported
Participants	Location: university hospital, Dresden, Germany Period of trial: before 1997 40 patients Inclusion criteria: systemic inflammatory response syndrome and organ failure Exclusion criteria: none given Sex: not given Age: not given
Interventions	Timing of intervention: start unclear, given for 28 days 1. 1000 mcg bolus of sodium selenite, thereafter 1000 mcg/24 hours as continuous intravenous infusion, for 28 days 2. No treatment Allocated: 20/20 Assessed: ?20/?20
Outcomes	Length of follow-up: 28 days Main outcome: Mortality
Notes	Request for details of denominators and infections sent 21 October 2003, but no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	States randomized but no further details
Allocation concealment (selection bias)	High risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated

Zimmermann 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	No data on follow-up.
Selective reporting (reporting bias)	High risk	Protocol or trial registration not available. Protocol not registered on www.clinicaltrials.gov
Funding bias All outcomes	Unclear risk	Not stated
Other bias	Unclear risk	None

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berger 1998	RCT in adults with burns; selenium part of trace element supplement evaluated, which also contained copper and zinc
Berger 2004a	RCT in adults with burns; selenium part of trace element supplement evaluated, which also contained copper and zinc
Berger 2004b	RCT in adults with cardiac surgery; selenium part of antioxidant supplement evaluated.
Berger 2005a	Combined results of Berger 2004a and Berger 1998
Berger 2005b	RCT in adults with cardiac surgery, myocardial infarction, trauma or subarachnoid haemorrhage; selenium part of antioxidant supplement evaluated.
Berger 2008	Selenium part of trace element supplement evaluated
Börner 1997	Not a RCT, not adults
Collier 2008	Selenium part of trace element supplement evaluated
Kiessling 2006	Trial terminated without publishing data
Porter 1999	RCT of antioxidant therapy (including selenium) versus placebo in trauma patients
REDOXS 2011	Factorial RCT of parenteral and enteral glutamine, and antioxidants (parenterally as selenium 500 µg, and enteral selenium 300 µg, beta carotene 10 mg, vitamin E 500 mg, and vitamin C 1500 mg)
Stoppe 2010	Not a RCT, no outcomes relevant
Thiele 1997	Not a RCT, not critical care
Uden 1990	Randomized, crossover trial of antioxidant therapy (including selenium) versus placebo in the prevention of recurrence of pancreatitis

Study	Reason for exclusion
Watters 2002	RCT of micronutrients (including selenium) versus placebo in patients undergoing elective aneurysmectomy
Wollschläger 1997	Not a RCT, selenium supplementation in acute pancreatitis

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Geoghegan 2009](#)

Methods	RCT
Participants	Patients with subarachnoid haemorrhage (grade 2 to 5)
Interventions	1000 mcg/d versus 500 mcg/d versus no sodium selenite intravenously, on ICU to maximum of 14 days
Outcomes	28 day mortality, APACHE II and SOFA scores
Notes	We emailed author (m.geoghegan@qmul.ac.uk and pgsmd@qmul.ac.uk) on 21 October 2014 but received no answer

[Yamaguchi 2003](#)

Methods	Randomized, placebo-controlled trial
Participants	394 patients with acute non-lacunar stroke (cardio-embolic or atherothrombotic infarction < 24 hours)
Interventions	Ebselen 150 mg twice daily or placebo started within 24 hours of onset for 14 days
Outcomes	Glasgow Outcome Scale three months post stroke, National Institute of Health Stroke Scale and Barthel Index scores at one and three months
Notes	We emailed the author (tyamaguchi-rtec@umin.ac.jp) on 21 October 2014 but did not receive an answer.

Characteristics of ongoing studies *[ordered by study ID]*

[SREAL 2012](#)

Trial name or title	Selenium Replacement and Serum Selenium Level in Severe Sepsis and Septic Shock Patients
Methods	RCT
Participants	Not yet recruiting
Interventions	Selenium: 500 mcg (10 mL) mixed to 230 mL of normal saline will be infused continuously per day (10 mL/hour). Study drugs will be infused for 7 days.

SERIAL 2012 (Continued)

Placebo: 10 mL mixed with 230 mL of normal saline will be infused continuously per day (10 mL/hour). Study drugs will be infused for 7 days.

Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • 28-day mortality <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • ICU length of stay • Mortality at hospital discharge, • Development of the new infection • Ventilator days • Renal replacement therapy days • Oxidative stress marker • Changes in severity scores • 3-month mortality • Vasopressor days
Starting date	September 2012
Contact information	Professor Gil Joon Suh, suhgil@snu.ac.kr
Notes	Status of the trial has not been verified in more than two years after the expected end date on clinicaltrials.gov . We emailed author (suhgil@snu.ac.kr) on 21 October 2014 but received no answer.

SISPCT

Trial name or title	SISPCT
Methods	RCT
Participants	1180 adult participants with severe sepsis or septic shock
Interventions	Factorial designed, randomized trial of placebo-controlled selenium (bolus 2000 mcg, then 1000 mcg daily as 24-hour infusion for up to 21 days) and procalcitonin guided antibiotic therapy
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • 28 days all-cause mortality <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Mean total SOFA (Sequential Organ Failure Assessment)-score, and SOFA subscores • 90 days all-cause mortality • Frequency and duration of mechanical ventilation until day 90 • Frequency and duration of renal replacement therapy until day 90 • Frequency and duration of vasopressor support until day 90 • Frequencies of adverse and severe adverse events • Clinical cure and microbiological cure on day 4, 7, 10, and 14 (*) • Duration of antibiotic therapy (*) • Costs of antibiotic therapy (*) • Duration until change of antibiotic therapy (*) • Antibiotic exposure days (*) • Days alive without antibiotics (*)

SISPCT (Continued)

- Frequency of antibiotic resistance (*)
- ICU length of stay until day 90
- Hospital length of stay until day 90
- Number of surgical procedures for source control (*)
- Number of diagnostic procedures for searching the focus of infection (*)

(*) Endpoints are for the procalcitonin intervention only

Starting date	2009
Contact information	We obtained information from Frank Bloos via Frank.Bloos@med.uni-jena.de on 21 October 2014, the same day we emailed him. The trial group is currently writing the manuscript for publication and does not want to reveal data at this time. Publication is estimated to in 2015.
Notes	

DATA AND ANALYSES
Comparison 1. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall mortality (regardless of the period of follow-up)	16	2084	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.72, 0.93]
1.1 Overall mortality (Selenium)	13	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.72, 0.93]
1.2 Overall mortality (Ebselen)	3	693	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.52, 1.34]

Analysis 1.1. Comparison 1 Selenium versus no selenium, Outcome 1 Overall mortality (regardless of the period of follow-up).

Comparison 2. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality by duration (Selenium)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Selenium 28 day	9	1180	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
1.2 Selenium 90 day	3	614	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.18]
2 Mortality by duration (Ebselen)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Ebselen 30 day	1	105	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.53, 5.95]
2.2 Ebselen 3 month	2	588	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.42, 1.22]
3 Mortality: ICU and pancreatitis (Selenium)	11	1255	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.02]
3.1 General intensive care patients	9	1168	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.01]
3.2 Acute pancreatitis	2	87	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.01, 12.30]

Analysis 2.1. Comparison 2 Selenium versus no selenium, Outcome 1 Mortality by duration (Selenium).

Analysis 2.2. Comparison 2 Selenium versus no selenium, Outcome 2 Mortality by duration (Ebselen).

Analysis 2.3. Comparison 2 Selenium versus no selenium, Outcome 3 Mortality: ICU and pancreatitis (Selenium).

Comparison 3. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of infected participants	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Selenium	6	934	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.23]
1.2 Ebselen	3	685	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 1.02]

Analysis 3.1. Comparison 3 Selenium versus no selenium, Outcome 1 Number of infected participants.

Comparison 4. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with adverse event	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Selenium	6	925	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.24]
1.2 Ebselen	2	588	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.40, 3.36]
2 Length of stay in ICU (Selenium)	7	934	Mean Difference (IV, Random, 95% CI)	0.54 [-2.27, 3.34]
3 Number of days on a ventilator (Selenium)	4	191	Mean Difference (IV, Random, 95% CI)	-0.86 [-4.39, 2.67]
4 Length of hospital stay (Selenium)	5	693	Mean Difference (IV, Random, 95% CI)	-3.33 [-5.22, -1.44]

Analysis 4.1. Comparison 4 Selenium versus no selenium, Outcome 1 Number of participants with adverse event.

Analysis 4.2. Comparison 4 Selenium versus no selenium, Outcome 2 Length of stay in ICU (Selenium).

Analysis 4.3. Comparison 4 Selenium versus no selenium, Outcome 3 Number of days on a ventilator (Selenium).

Analysis 4.4. Comparison 4 Selenium versus no selenium, Outcome 4 Length of hospital stay (Selenium).

ADDITIONAL TABLES

Table 1. Length of stay in ICU

Trial	Selenium	Control
Angstwurm 1999	22.8 days (20.8)	26.5 days (22)
Angstwurm 2007	15.1 days (10)	12.7 days (9)
Berger 2001	7,5 days (3.5)	9 days (7.1)
Forceville 2007	22.3 days (9.6)	17 days (8.7)
Manzanares 2011	14 days (11)	13days (6)
Mishra 2007	21.3 days (16.2)	20.8 days (21.8)
SIGNET 2011	14.5 days (4.6)	16.7 days (5.9)
MD 0.54 (95% CI -2.27 to 3.34, I^2 statistic = 72%, random-effects model)		

Analysis 4.2

All findings given as mean (SD). If the original figures were provided in median (range) or interquartile range, we converted them to mean (SD) (Hozo 2005).

Table 2. Number of days on a ventilator

Trial	Selenium	Control
Angstwurm 1999	11 days (5.9)	16 (12.6)
Berger 2001	6 days (2.9)	6 days (5.7)
Forceville 2007	19.8 days (7.8)	14.8 days (4.4)
Montoya 2009	9.3 days (1.5)	12 days (1.8)
MD -0.86 (95% CI -4.39 to 2.67, I^2 statistic = 89%, random-effects model)		

Analysis 4.3)

All findings given as mean (SD). If the original figures were provided in median (range), we converted them to mean (SD) (Hozo 2005).

Table 3. Length of hospital stay

Trial	Selenium	Control
Angstwurm 1999	38.5 days (24.4)	39.5 days (15.7)
Berger 2001	83 days (73.5)	62.8 days (30.2)
Forceville 2007	31.3 days (18)	32 days (11.6)
Montoya 2009	12.5 days (0.6)	17 days (1.7)
SIGNET 2011	31.7 days (10.9)	33.8 days (12.4)
MD -3.33 (95% CI -5.22 to -1.44, I^2 statistic = 42%, random-effects model)		

Analysis 4.4

All findings given as mean (SD). If the original figures were provided in median (range) or interquartile range, we converted them to mean (SD) (Hozo 2005).

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials search strategy

```
#1 MeSH descriptor: [Selenium] explode all trees
#2 MeSH descriptor: [Selenium Compounds] explode all trees
#3 selen*
#4 ebselen
#5 #1 or #2 or #3 or #4
#6 #5
```

Appendix 2. MEDLINE (Ovid SP) and Healthstar search strategy

```
1. exp Selenium Compounds/ or exp Selenium/ or (selen* or ebselen*).mp.2. (randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals.sh not (humans.sh and animals.sh))
3. 1 and 2
```


Appendix 3. EMBASE (Ovid SP) search strategy

1. exp selenium derivative/ or exp selenium/ or (selen* or ebselen*).ti,ab.
2. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh.
3. 1 and 2

Appendix 4. CAB abstracts search strategy

1. random\$.tw
2. trials\$.tw
3. placebo\$.tw
4. 1 or 2 or 3
5. selen\$.tw
6. ebselen.tw
7. 5 or 6
8. 4 and 7

Appendix 5. BIOSIS search strategy

- #1 TI=selen* or TI=ebselen*
 #2 TS=(random* or trial* or placebo*)
 #3 #1 and #2

Appendix 6. CINAHL (EBSCOhost) search strategy

- S1 ((MM "Selenium") OR (MM "Selenium Compounds")) or selen* or ebselen*
 S2 random* or ((clinical or controlled) N3 trials) or placebo* or multicenter or prospective or ((blind* or mask*) N3 (single or double or triple or treble))
 S3 S1 and S2

WHAT'S NEW

Date	Event	Description
13 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 3, 2002
 Review first published: Issue 4, 2004

Date	Event	Description
22 April 2016	Amended	Typo corrected. The word significant was missing from one sentence in the plain language summary. The sentence has been corrected to read: 'Thirteen trials of intravenous sodium selenite showed a statistically significant effect on death.'
25 June 2015	New search has been performed	We searched the databases up to 21 May 2014. We included six new trials of selenium (2084 participants) in this review update (Forceville 2007 ; Janka 2013 ; Manzanares 2011 ; Montoya 2009 ; SIGNET 2011 ; Valenta 2011). This review now includes 16 studies in total. We updated the Methods , included full 'Risk of bias' tables and 'Summary of findings' tables. We used trial sequential analysis.

Date	Event	Description
25 June 2015	New citation required but conclusions have not changed	The previous review authors (Avenell A, Noble DW, Barr J, Engelhardt T) decided not to update this Cochrane review. Two new review authors have updated this review (Allingstrup M, Afshari A). The conclusions have not changed in this updated Cochrane review.
17 August 2007	New search has been performed	Three new trials are included. Two of these were previously classified as ongoing trials (Mishra 2005, Angstwurm 2006). The conclusions of the review are unchanged.
16 August 2007	New search has been performed	Search strategies reran until 17th August 2007
16 August 2007	New search has been performed	Search reran

CONTRIBUTIONS OF AUTHORS

Updated review

Mikkel Allingstrup (MA), Arash Afshari (AA).

MA and AA searched the literature, performed quality assessment and extraction of data from trials, and wrote the review update.

Original published review and first update

All four authors (Alison Avenell, David W Noble, John Barr, Thomas Engelhardt) were involved in protocol development, searched the literature, performed quality assessment and data abstraction of trials, and wrote the review (Avenell 2004).

DECLARATIONS OF INTEREST

Mikkel Allingstrup declares no conflicts of interest.

Arash Afshari declares no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Herlev Hospital, University of Copenhagen, Denmark.
Department of Anaesthesia and Intensive Care
- Rigshospitalet, University of Copenhagen, Denmark.
Anaesthesia and Surgical Clinic Department 4013

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this review update we have revised the first primary endpoint to overall mortality, which is the longest time of follow-up. Mortality by duration (28 and 90 days) is preserved as our second primary endpoint. We performed a TSA and included it in this review update.

NOTES

2015 update: we updated the methods, included full 'Risk of bias' tables and 'Summary of findings' tables. We used TSA.

This review was also updated in 2007 (Avenell 2004). At that time Cochrane updates did not earn a new citation unless they had new authors or a change to conclusions. The 2007 version of this review included three new trials; two of these were previously classified as ongoing

trials ([Angstwurm 2006](#); [Lindner 2004](#); [Mishra 2007](#)). The conclusions of the 2007 review were unchanged. Therefore the 2007 update did not earn a new citation

We thank Mathew Zacharias, Nathan Pace, Naji Abumrad, Daren Heyland, Saúl Rugeles, Ann Moller, Iveta Simera, Kathie Godfrey and Amy Godfrey Arkle for their help and editorial advice during the preparation of the original review ([Avenell 2004](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Antioxidants [adverse effects] [*therapeutic use]; Azoles [adverse effects] [*therapeutic use]; Critical Illness [mortality] [*therapy]; Isoindoles; Organoselenium Compounds [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Sodium Selenite [*therapeutic use]

MeSH check words

Adult; Humans