A systematic review of multivitamin and multimineral supplementation for infection

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**CRD summary**
The authors concluded that there was little evidence that supplements reduce infection, but the analyses were based on small numbers of studies and further research is required. This was a well-conducted review and the authors’ conclusions appear appropriate in view of the limited evidence.

**Authors’ objectives**
To determine if multivitamin and multimineral supplementation reduce infection.

**Searching**
MEDLINE (1966 to October 2002), EMBASE (1988 to December 2002), CAB Abstracts (1973 to December 2002), BIOSIS Previews (1985 to February 2003) and the Cochrane Controlled Trials Register (Issue 4, 2002) were searched. Details of the search strategy were reported to be available from the authors. In addition, trial registers, nutrition journals and reference lists were screened to August 2005. No restrictions were placed on language or publication status.

**Study selection**
Randomised controlled trials (RCTs) and quasi-randomised trials that compared the effects of supplements containing at least two vitamins or two minerals (or combinations of vitamins and minerals) of any type with no supplement or an alternative supplement, in participants with a mean age of at least 16 years, were eligible for inclusion. Supplements could be administered by any route. Participants could be of any nutritional or income status, and with or without existing illness. The primary review outcomes were deaths from infection, number of episodes of infection, number of participants with at least one infection, and duration of infection and antibiotic use. The secondary outcomes were length of hospital stay, number of health service contacts, quality of life, adverse effects and compliance.

All of the included studies were RCTs. Most supplements were administered orally. The duration of the included interventions ranged from 8 days to 8 years. Where reported, studies were conducted in the community, hospitals, outpatients, and nursing or residential homes. Half of the included studies were in healthy participants and half were in unwell participants. Some studies were in participants with a mean age over 60 or 65 years of age.

One reviewer identified potentially relevant studies. Two reviewers then agreed on which studies to include.

**Assessment of study quality**
Two reviewers independently assessed studies for allocation concealment, blinding, and intention-to-treat analysis.

**Data extraction**
Two reviewers independently extracted the data onto a standardised form. Authors were contacted if required.

**Methods of synthesis**
Where studies were similar, pooled relative risks and weighted mean differences (WMDs) were calculated, along with 95% confidence intervals (CIs), using fixed-effect models; a random-effects model was used where heterogeneity was significant.

Statistical heterogeneity was assessed using the I² statistic, taking values greater than 50% as indicating high heterogeneity. Pre-specified subgroup analyses were used to examine the influence of age (<65 years and ≥65 years), nutritional status (>50% of sample nourished/undernourished), health status (>50% of sample healthy/unwell), vaccination status, allocation concealment (adequate or not) and duration of the intervention (≤6 months and >6 months). Sensitivity analysis was undertaken by excluding the Chandra group studies (the authors stated that these studies had been found to have inadequately explained ‘statistical impossibilities’).
Results of the review
Twenty RCTs (n=35,740) were included. The sample size ranged from 17 to 29,133.

Five studies reported adequate allocation concealment. Four studies reported blinding of the participants, providers and outcome assessors. Nine studies clearly reported intention-to-treat analysis.

The authors stated that only small numbers of patients were included in the meta-analyses.

All studies.

For older people, supplements were associated with a statistically significant reduction in the number of days of infection (WMD -16.38, 95% CI: -17.85, -14.90, p<0.00001; based on 3 studies) and days of antibiotic use (WMD -19.06, 95% CI: -20.67, -17.45, p<0.00001; based on 2 studies). There were no significant differences between treatments for the number of episodes of infection (4 studies). Significant heterogeneity was found for all these analyses ($I^2$ 95 to 99%). For other age groups, supplements were associated with a statistically significant reduction in the number of episodes of infection (WMD -5.72, 95% CI: -6.40, -5.04, p<0.00001; based on 2 studies showing significant heterogeneity, $I^2$ 99%), days of infection (WMD -12.60, 95% CI: -13.62, -11.58, p<0.00001; based on 1 study) and days of antibiotic use (WMD -7.00, 95% CI: -13.14, -0.86, p=0.03; based on 1 study). Some analyses were strongly influenced by the Chandra studies.

In sensitivity analyses excluding the Chandra studies, for people aged 65 years and older, there was no statistically significant difference between supplements and control in the number of episodes of infections (2 studies). For other age groups, supplements were associated with a statistically significant reduction in the number of episodes of infection; WMD -1.20 (95% CI: -2.08, -0.32; p=0.008 based on 1 study).

For people aged at least 65 years and for other age groups, there was no statistically significant difference between supplements and control in the number of people with at least one infection (each analysis based on 4 studies).

Subgroup analyses showed that for undernourished people aged 65 years or older, there was a significant reduction in the number of infections in patients receiving supplements for at least 6 months compared with control (WMD -0.67, 95% CI: -1.24, -0.10, p=0.02; based on 2 studies).

There were no significant differences between treatment arms for mortality, (based on 3 studies in people aged 65 years or older) or the number of patients requiring medication for infection (based on 1 study in people aged 65 years or older).

Other results were also reported.

Cost information
The authors stated that 3 studies reported inconclusive information about economic outcomes.

Authors’ conclusions
There was little evidence that supplements reduce infection, but analyses were based on small numbers of studies and further research is required.

CRD commentary
The review question was stated clearly. Several relevant sources were searched and attempts were made to minimise publication and language bias. Appropriate methods were used to minimise reviewer error and bias during much of the review process. All of the included studies were RCTs, validity was assessed using specified criteria, and results were reported. The data were pooled using meta-analysis, statistical heterogeneity was assessed, and some potential sources of heterogeneity were examined. The authors’ conclusions appear appropriate in view of the limited evidence.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated the need for more large studies evaluating the effects of supplements given for at least 6 months, especially in older undernourished people.

Funding
The Health Services Research Unit is core funded by the Chief Scientist Office of the Scottish Executive Health Department.

Bibliographic details

PubMedID
16756533

DOI
10.1111/j.1365-277X.2006.00694.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Age Factors; Aged; Aged, 80 and over; Confidence Intervals; Dietary Supplements; Disease Susceptibility; Female; Humans; Infection /epidemiology; Infection Control /methods; Male; Malnutrition /drug therapy /immunology; Middle Aged; Minerals /administration & dosage; Nutritional Status; Randomized Controlled Trials as Topic; Risk; Treatment Outcome; Vitamins /administration & dosage

AccessionNumber
12006007388

Date bibliographic record published
07/02/2008

Date abstract record published
30/09/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.