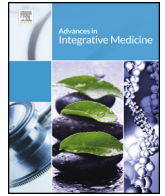




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Multivitamins for acute respiratory tract infections: a rapid review

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BRIEF OVERVIEW

Seven human clinical trials with some risk of bias suggest that multivitamins may be a safe and effective intervention to relieve some symptoms of respiratory tract infections, increase micronutrient status and immune function; however, further research is needed. There is currently insufficient evidence to recommend multivitamins as a therapy for the treatment or prevention of COVID-19.

Verdict

The overall quality of research examining the effect of prophylactic multivitamin supplementation on the effects of the acute respiratory tract infections (ARTI) is weak. Most of the available research included adults aged 50 years or over recruited through either the community or institutional settings (i.e. hospital facility, residential care facility). The multivitamin supplements used contained at least five vitamins and minerals and were administered between three months and two years (median: 15 months).

Based on the available evidence, multivitamin supplementation does not appear to reduce the incidence of ARTI or mortality (both ARTI-related and all-cause). The effect of multivitamins taken before infection on the duration of ARTI is unclear due to conflicting results across studies. Multivitamins may, however, reduce the symptoms associated with ARTI such as headache, conjunctivitis, and activity restriction but not the overall symptom scores. No differences in health service visits, inclusive of primary and tertiary care, has been identified for individuals taking a multivitamin prior to an ARTI.

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1. Background

Inadequate intake of vitamins is common [1] and has a detrimental effect on normal immune function [2]. Multivitamin supplementation at the recommended dietary allowance level thus can improved cellular immune parameters and reduce the risk of infections [3]. Multivitamins are frequently used by the general population [4], and are also frequently recommended by naturopaths [5]. The aim of this rapid review was to assess the effects of multivitamin supplementation on acute respiratory tract infections (ARTI) and associated complications.

2. Methods

The rapid review protocol was created a priori and not changed during the conduct of the review.

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2.1. Research Question

What are the effects of multivitamin supplementation on acute respiratory tract infections (ARTI) and associated complications?
Inclusion/exclusion criteria

- 1) **Participants:** Adult humans with an acute respiratory tract infection
- 2) **Intervention:**
 - a) Multivitamin supplementation or
 - b) Multivitamin supplementation in combination with conventional care
- 3) **Control:**
 - a) No treatment
 - b) Placebo
 - c) Conventional care alone
- 4) **Outcomes:**
 - a) Mortality
 - b) Duration of symptoms
 - c) Responder rates

- d) Number of days in hospital
 - e) Number of patients with adverse events
 - f) Any other reasonable clinical outcome
- 5) **Study type:**
- a) Randomized controlled trials or
 - b) randomized cross-over trials

2.2. Databases

Medline (Ovid), AMED (Ovid), CINAHL (EBSCO), EMBASE (Ovid) were searched from their inception through May 11, 2020.

2.3. Search terms (example)

The search strategy for Medline is shown in [Table 1](#).

2.4. Study selection and data extraction

Two review authors independently screened titles, abstracts and full-texts. Data were extracted from each paper by one review author, with two authors sharing data extraction across the included papers.

2.5. Risk of Bias Assessment

The risk of bias (RoB) of study findings in each included paper was assessed by one review author using the revised Cochrane RoB tool for randomised trials (RoB 2) (<https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?>

`authuser=0`). Two authors undertook this task for the included manuscripts.

3. Results

3.1. Description of included studies

The search identified 233 citations, including 36 duplicates. The remaining 198 citations were screened by title and abstract against the inclusion and exclusion criteria, and 180 citations were excluded. The full text of 18 citations were assessed for eligibility and 11 were excluded as they sampled the wrong population ($n=3$), were not reporting original research ($n=2$), reported a different outcome ($n=2$), were retracted ($n=2$), or used the wrong intervention or study design ($n=2$). The remaining seven studies were included in this rapid review.

All seven included studies were randomised controlled trials. Six studies were described as double-blind. [6, 11]. The level of blinding in the remaining study was not defined [12].

Most ($n=5$) studies were undertaken in the World Health Organisation (WHO) European region; this included two studies in France, [7, 8] one each in the Netherlands [9], UK [6], and Germany [11]. The remaining studies were conducted in the WHO South-East Asia Region (i.e. India) [12] and the WHO Region of the Americas (i.e. Canada) [10].

The seven included studies comprised a total pool of 3,644 participants. Sample sizes ranged between 36 and 910. All participants were adults aged ≥ 18 years; six of seven studies recruited adults aged ≥ 50 years. [6, 8, 11, 13] Participants were recruited from the community in four studies [6, 11, 13], and

Table 1
Complete search strategy for Medline.

1	Randomized Controlled Trials as Topic/
2	randomized controlled trial/
3	Random Allocation/
4	Double Blind Method/
5	Single Blind Method/
6	clinical trial/
7	clinical trial, phase i.pt.
8	clinical trial, phase ii.pt.
9	clinical trial, phase iii.pt.
10	clinical trial, phase iv.pt.
11	controlled clinical trial.pt.
12	randomized controlled trial.pt.
13	multicenter study.pt.
14	clinical trial.pt.
15	exp Clinical Trials as topic/
16	or/1-15
17	(clinical adj trial\$.tw.
18	((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
19	PLACEBOS/
20	placebo\$.tw.
21	randomly allocated.tw.
22	(allocated adj2 random\$.tw.
23	or/17-22
24	16 or 23
25	case report.tw.
26	letter/
27	historical article/
28	or/25-27
29	24 not 28
30	multivitamin\$.af.
31	Influenza, Human/ or Influenza A Virus, H1N1 Subtype/ or Influenza A Virus/ or Influenza A Virus, H3N2 Subtype/ or H1N1.mp.
32	MERS-COV.mp. or Middle East Respiratory Syndrome Coronavirus/
33	31 or 32
34	29 and 30 and 33
35	(breathing or lung or pulmonary or respir\$.af.
36	31 or 32 or 35
37	29 and 30 and 36

Table 2
Summary details of studies examining the effects of multivitamins on acute respiratory tract infections and associated complications

Author	Date	Country	Setting	Participants	Intervention	Comparison	Outcomes
Avenell et al	2005	United Kingdom	Communities associated with general practices	910 men and women aged 65 years or over who did not take vitamins or minerals	Daily over 12 months (oral): Vitamin A (acetate) [800 mcg], Vitamin C [60 mg], Vitamin D [5 mcg], Vitamin E [10 mg], thiamin [1.4 mg], riboflavin [1.6 mg], niacin [18 mg], pantothenic acid [6 mg], pyridoxine [2 mg], B12 [200 mcg], iron [14 mg], iodine [150 mcg], copper [0.75 mg], zinc [15 mg], manganese [1 mg]	Sorbitol placebo	<ul style="list-style-type: none"> - Number of contacts with primary care for infection (12 months) - Number of self-reported days of infection (12 months) - Quality of Life (12 months) - Number of antibiotic prescriptions in primary care (12 months) - Number of days that antibiotics were prescribed (12 months) - Number of hospital admissions (including those related to infection) (12 months) - Number of days in hospital with infection (12 months) - Number of infection-related and all outpatient visits (12 months) - Adverse events reported by participants (12 months)
Graat et al	2002	Netherlands	Community	652 men and women aged 60 years or over	Daily over 15 months (oral): Retinol (600 mcg), beta-carotene (1.2 mg), ascorbic acid (60 mg), vitamin E (10 mg), cholecalciferol (5 mcg), vitamin K (30 mcg), thiamin (1.4 mg), riboflavin (1.6 mg), niacin (18 mg), pantothenic acid (6 mg), pyridoxine (2.0 mg), biotin (150 mcg), folic acid (200 mcg), cyanocobalamin (1 mcg), zinc (10 mg), selenium (25 mcg), iron (4.0 mg), magnesium (30 mg), copper (1.0 mg), iodine (100 mcg), calcium (74 mg), phosphor (49 mg), manganese (1.0 mg), chromium (25 mcg), molybdenum (25 mcg), silicium (2 mcg). (2) VE: 200 mg/dL. (3) MV+VE. (4) Placebo	(1) Vitamin E; (2) MV+VE; (3) soybean oil	<ul style="list-style-type: none"> - Incidence of acute respiratory tract infections (15 months) - Severity of acute respiratory tract infections (15 months)
Jain	2002	India	Community	36 adults aged 51–78 years	Daily over 12 months (?) (oral): Vitamin A (400 RE), beta-carotene (16 mg), thiamin (2.2 mg), riboflavin (1.5 mg), niacin (16 mg), vitamin B6 (3.0 mg), folate (400 mcg), vitamin B12 (4.0 mcg), vitamin C (80 mg), vitamin D (4.0 mcg), vitamin E (44 mg), iron (16 mg), zinc (14 mg), copper (1.4 mg), selenium (20 mcg), iodine (200 mcg), calcium (200 mg), magnesium (100 mg)	Calcium (200 mg), magnesium (100 mg)	<ul style="list-style-type: none"> - Incidence of acute respiratory tract infections (12 months?) - Severity of acute respiratory tract infections (12 months?)
Girodon et al	1997	France	Geriatric centre	81 elderly subjects in a geriatric centre, 84.17 ± 8.1 years (range 65–102 years; 20 males, 61 females) with no acute illness or history of cancer, and not taking medication that might interfere with nutritional status or immunocompetence	Daily over 2 years (oral): Trace elements (zinc sulfate equiv 20 mg zinc, selenium 100 ug as sulfide) OR Vitamins (ascorbic acid 120 mg, beta carotene 6 mg = 1000 retinol equivalents, alpha-tocopherol 15 mg OR Trace elements + Vitamins	Visibly identical placebo (calcium phosphate and cellulose)	<ul style="list-style-type: none"> - Micronutrient status (6 months, 1 year, and 2 years) - Respiratory and symptomatic urogenital infections (6 months, 1 year, and 2 years) - Deaths total (2 years) - Deaths from infection (2 years)
Girodon et al	1999	France	25 geriatric centres	725 long-term institutionalised elderly patients aged 65 and over with no acute illness or history of cancer, and not taking medication that might interfere with nutritional status or immunocompetence.	Daily over 2 years (oral): Trace elements (zinc sulfate equiv 20 mg zinc, selenium 100 ug as sulfide) OR Vitamins (ascorbic acid 120 mg, beta carotene 6 mg = 1000 retinol equivalents, alpha-tocopherol 15 mg OR Trace elements + Vitamins	Placebo - calcium phosphate and microcrystalline cellulose. Identical to intervention.	<ul style="list-style-type: none"> - Delayed hypersensitivity skin response (6 months, 12 months) - Humoral response to influenza vaccine (injected 15 to 17 months after start of supplementation) (28, 90, 180, and 270 days) - Infectious morbidity and mortality (2 years)
Liu et al	2007	Canada	21 long-term care facilities (nursing homes)	763 participants; 70% female. Mean age at entry 85 (65–103).	Daily over 18 months plus 1 month run-in period (oral): Vitamin A 400 retinol equivalents, beta-carotene 16 mg, vitamin D 4 mg (160 IU), vitamin E 44 mg (74 IU), vitamin C 80 mg, thiamin 2.2 mg, riboflavin 1.5 mg, niacin 16 mg, vitamin B6 3 mg, vitamin B12 4 mcg, folate 400 mcg, calcium (elemental) 200 mg, magnesium 100 mg, iron (elemental) 16 mg, iodine 200 mcg, zinc 14 mg, copper 1.4 mg, and selenium 20 mcg.	Visibly identical placebo	<ul style="list-style-type: none"> - Infections Total (blood stream, skin and soft tissue, gastroenteritis, respiratory tract (upper/lower/total), urinary tract. See table 3 for breakdown) (18 months) - Antibiotic use (18 months) - Rate of hospitalization (Emergency department visits/Hospital admissions) (18 months)
Winkler et al	2005	Germany	Recruited by advertisements	477 healthy volunteers aged 18–70 (36 ± 13) years, without known congenital or acquired immune defects, allergies or other chronic diseases and acute diseases requiring treatment, alcohol or drug misuse or both, pregnancy or lactation, interfering dietary habits or vaccination against influenza within the last 12 months.	Daily over 3 to 5.5 months (oral): 5 × 10 ⁸ cfu (colony-forming units) of the spray-dried probiotic bacteria with vitamins and minerals.	Placebo - film-coated tablets with the same excipient ingredients, appearance, smell and taste. Details Table 1.	<ul style="list-style-type: none"> - Cellular immune response (14 days) - Single specific symptoms that appeared during the common cold episodes - Total symptom score expressing the overall severity of each episode (primary parameter) - Incidence and duration of common cold episodes

through institutional settings (i.e. hospital, residential care facility) in three [7,8,10].

Multivitamins were administered daily in oral form in all seven studies, either as tablets ($n=3$) [6,10,11] or capsules ($n=4$) [7,9,12]. All interventions contained a combination of at least five vitamins and minerals. Treatment duration ranged from three months to two years, with a median duration of 15 months. Control groups received either matching placebo ($n=4$) [7,8,10,11], other vitamin/mineral combination ($n=2$), [9,12] sorbitol ($n=1$) [6] or soybean oil ($n=1$). [9]

3.2. Risk of bias

In the first Domain (randomisation process), four studies were rated as having low risk of bias, [6,7,9,10] and three were assessed as having some risk of bias [8,11,12]. For Domain 2 (treatment assignment), most ($n=5$) studies were determined to have low risk of bias [6,7,9,11], with one rated as having some risk of bias [8], and one identified as having high risk of bias [12]. Under Domain 3 (missing outcome data), all studies were assessed as having low risk of bias, except Jain (2002), which was rated as having high risk of bias [12]. For Domain 4 (measure of outcomes), all studies were rated as having low risk of bias. In Domain 5 (selective reporting), all trials were identified as having some risk of bias. Overall, one study was rated as having high risk of bias [12], while the remaining six studies were judged as having some risk of bias [6,10,11]. These judgements should be taken into consideration when interpreting the findings of this review.

3.3. Summary of findings

The seven included studies reported on ten distinct outcomes, including incidence of ARTI, severity of ARTI, infectious morbidity and symptoms, mortality rate, health service contact rate, quality of life, antibiotic use, micronutrient status, cellular immune response and adverse events (see Table 2).

Four studies measured the incidence of ARTI [9,12]. In all four studies, the difference between groups in the incidence of ARTI was not found to be statistically significant.

Duration of ARTI was examined in four studies [6,9,11,12]. The study findings were inconsistent, with two studies reporting a statistically significant reduction in the duration of respiratory illness/ARTI symptoms [11,12], and two studies reporting no difference between groups in the duration of ARTI [6,13]. One study [13] did report a statistically significantly longer duration of ARTI symptoms among participants receiving multivitamin plus high-dose vitamin E when compared with placebo, but no difference was evident between multivitamin and placebo.

Two studies investigated infectious morbidity and symptoms; this included number of symptoms [9,11], presence/duration of fever [11,13], activity restriction [13], and total symptom score [11]. Studies reported a significant reduction in headache, conjunctivitis and activity restriction [9] in participants receiving multivitamins compared to placebo, but no difference between groups in total symptom score [11] or number of ARTI/influenza symptoms [11,13]. There were inconsistencies in the reported effect of multivitamins on the presence/duration of fever.

Mortality rate was measured in two studies, including all-cause mortality rate [7] and infection mortality rate [7,8]. Neither study found a significant difference between groups in participant mortality rates.

Two studies examined health service contact rate, including number of primary care contacts for infection [6], number of emergency department presentations [10], number of hospital admissions, number of days in hospital with infection [6] and number of outpatient visits for infection [6]. Neither study found a

difference in health service contact rate (for any service setting) between the intervention and control groups.

One study assessed quality of life, using both the EuroQoL and SF-12 [6]. The study found no significant difference between multivitamin and placebo groups in either quality of life measure.

Antibiotic use was examined in three studies; this included the number of antibiotic prescriptions [6,10] and number of antibiotic days [6,10,12]. Study findings were inconsistent, with two studies [6,10] reporting no difference in the number of antibiotic prescriptions or days of antibiotic use between intervention and control groups, and one study [12] reporting significantly fewer days of antibiotic use among participants receiving a multivitamin relative to a calcium-magnesium supplement.

Micronutrient status (i.e. serum micronutrient measurement) was assessed in one study [7]. A significant increase in vitamin and trace element serum levels was observed in all supplementation groups over the six months of study intervention.

One study examined changes in cellular immune response (i.e. white blood cell count and activity) [11]. The study reported a significantly greater increase in total leukocyte, lymphocyte, T-lymphocyte, CD4+ and CD8+ lymphocyte and monocyte count in the intervention group after 14 days of treatment when compared with placebo. No changes were observed in T-lymphocyte activation and phagocytic activity for either groups.

Adverse events were assessed in one study [6]. Fewer adverse events were reported in the intervention group when compared with placebo (28 [6.1%] vs. 37 [8.2%] cases). These events were classed as non-serious, and included symptoms such as headache, insomnia and gout.

4. Clinical significance

Based on the evidence identified in this rapid review, multivitamins may be a safe and effective intervention to relieve some symptoms of ARTI, increase micronutrient status and immune function. Effects on respiratory tract infection duration and antibiotics use are inconsistent; and multivitamins do not seem to reduce health services contact or mortality. At this time, there is insufficient evidence to recommend the use of multivitamins in the treatment or prevention of COVID-19.

5. Disclaimer

This article should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

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