INFECTIONS, PARTICULARLY RESPIRATORY TRACT INFECTIONS, ARE COMMON IN ELDERLY INDIVIDUALS, RESULTING IN INCREASED MORBIDITY, MORTALITY, AND USE OF HEALTH CARE SERVICES. VITAMIN E SUPPLEMENTATION HAS BEEN SHOWN TO IMPROVE IMMUNE RESPONSE IN ELDERLY PERSONS. HOWEVER, THE CLINICAL IMPORTANCE OF THESE FINDINGS HAS NOT BEEN DETERMINED.

OBJECTIVE To determine the effect of 1 year of vitamin E supplementation on respiratory tract infections in elderly nursing home residents.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled trial was conducted from April 1998 to August 2001 at 33 long-term care facilities in the Boston, Mass, area. A total of 617 persons aged at least 65 years and who met the study's eligibility criteria were enrolled; 451 (73%) completed the study.

INTERVENTION Vitamin E (200 IU) or placebo capsule administered daily; all participants received a capsule containing half the recommended daily allowance of essential vitamins and minerals.

MAIN OUTCOME MEASURES Incidence of respiratory tract infections, number of persons and number of days with respiratory tract infections (upper and lower), and number of new antibiotic prescriptions for respiratory tract infections among all participants randomized and those who completed the study.

RESULTS Vitamin E had no significant effect on incidence or number of days with infection for all, upper, or lower respiratory tract infections. However, fewer participants receiving vitamin E acquired 1 or more respiratory tract infections (60% vs 68%; risk ratio [RR], 0.88; 95% confidence interval [CI], 0.76-1.00; \( P = .048 \) for all participants; and 65% vs 74%; RR, 0.88; 95% CI, 0.75-0.99; \( P = .04 \) for completing participants), or upper respiratory tract infections (44% vs 52%; RR, 0.84; 95% CI, 0.69-1.00; \( P = .05 \) for all participants; and 50% vs 62%; RR, 0.81; 95% CI, 0.66-0.96; \( P = .01 \) for completing participants). When common colds were analyzed in a post hoc subgroup analysis, the vitamin E group had a lower incidence of common cold (0.67 vs 0.81 per person-year; RR, 0.83; 95% CI, 0.68-1.01; \( P = .06 \) for all participants; and 0.66 vs 0.83 per person-year; RR, 0.80; 95% CI, 0.64-0.98; \( P = .04 \) for completing participants) and fewer participants in the vitamin E group acquired 1 or more colds (40% vs 48%; RR, 0.83; 95% CI, 0.67-1.00; \( P = .05 \) for all participants; and 46% vs 57%; RR, 0.80; 95% CI, 0.64-0.96; \( P = .02 \) for completing participants). Vitamin E had no significant effect on antibiotic use.

CONCLUSIONS Supplementation with 200 IU per day of vitamin E did not have a statistically significant effect on lower respiratory tract infections in elderly nursing home residents. However, we observed a protective effect of vitamin E supplementation on upper respiratory tract infections, particularly the common cold, that merits further investigation.
cebo-controlled, double-blind trials in elderly persons, vitamin E supplementation improved immune response, including delayed-type hypersensitivity and response to vaccines. Furthermore, participants receiving vitamin E in the 6-month trial had a 30% lower incidence of infectious diseases (primarily respiratory tract infections) compared with those receiving placebo, but this result was not significant, perhaps because of insufficient power, and infections were self-reported. To overcome these limitations, the current study determined the effect of 1 year of supplementation with vitamin E on objectively recorded respiratory tract infections in elderly nursing home residents.

**METHODS**

**Study Design, Enrollment, and Randomization**

This randomized, double-blind, placebo-controlled trial to investigate the effect of 1 year of vitamin E supplementation on respiratory tract infections in a nursing home population was conducted from April 1998 to August 2001. The Tufts–New England Medical Center institutional review board approved the study protocol and informed consent form. Participants were recruited from 33 long-term care facilities in the Boston, Mass, area. A total of 2814 residents were initially identified as potential candidates (Figure). According to the nursing home staffs, 874 participants met the following eligibility criteria: aged 65 years or older; life expectancy greater than 6 months; no anticipated discharge within 3 months; not room-bound for the past 3 months; absence of active neoplastic disease; no tube feeding, no kidney dialysis; no intravenous or urethral catheters for the last 30 days; no tracheostomy or chronic ventilator; antibiotic-free for more than 2 weeks; no long-term steroid treatment greater than 10 mg/d, no use of immunosuppressive drugs, or greater than the recommended daily allowance (RDA) level of supplements of vitamins E, C, or B6, selenium, zinc, beta-carotene, or fish oil; body mass index of at least 18; serum albumin at least 3.0 g/dL; able to swallow pills; willing to receive influenza vaccine; and willing to provide informed consent (for patients with dementia, family members provided informed consent).

Subsequent rescreening by our study nurses led to exclusion of 173 participants who had given informed consent. An additional 84 candidates were not enrolled for various reasons detailed in the Figure. Participants were assigned to vitamin E or placebo with equal probability in blocks of 4 according to lists generated by the study's statistician, who used a computer program. Six randomization lists were constructed for each nursing home according to age (65-79, 80-89, and ≥90 years) and smoking or chronic obstructive pulmonary disease (COPD) status (yes or no). Identification codes of newly enrolled persons were entered in order by the study statistician into the next available slots in the appropriate list. Those enrolling the participants had no access to the randomization lists. Participants were unknown to the statistician. A total of 617 participants were randomized to the vitamin E (311 participants) or placebo (306 participants) groups.

**Interventions**

Nursing home residents have a heterogeneous intake of micronutrients, some of which are necessary for proper immune function. To reduce variability, all participants received a capsule containing 50% of the RDA for essential micronutrients. Fifty percent RDA was selected because few candidates meeting our eligibility criteria would have intakes less than 50% of the RDA for micronutrients.

The vitamin E group received a daily capsule containing 200 IU of vitamin E (dl-α-tocopherol), and the control group received a capsule containing 200 IU of a placebo multivitamin.

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**Figure. Study Profile**

- **2814 Individuals Identified as Potential Participants**
- **1940 Did Not Meet Inclusion Criteria**
- **874 Met Eligibility Requirements and Provided Informed Consent**
- **257 Not Enrolled**
  - 173 Ineligible Upon Rescreening
  - 53 Participant, Family, or Physician Withdraw Consent
  - 17 Died Before Study Initiation
  - 7 Transferred Out of Facility
  - 7 Medical or Surgical Contraindications to Participation
- **311 Assigned to Receive Vitamin E Plus Multivitamin**
- **306 Assigned to Receive Placebo Plus Multivitamin**
- **80 Did Not Complete Treatment**
  - 29 Died
  - 17 Discontinued by Physician
  - 17 Withdraw Consent
  - 6 Transferred Out of Facility
  - 1 Started Long-term Antibiotics
- **231 Completed Study**
  - 311 Included in Primary Analysis
  - 231 Included in Completers Analysis
- **220 Completed Study**
  - 306 Included in Primary Analysis
  - 220 Included in Completers Analysis

The multivitamin capsule contained 50% of the recommended daily allowance for essential micronutrients.

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group received a placebo capsule containing 4 IU of vitamin E, both in soybean oil. The vitamin E dose was based on earlier studies in elderly individuals in which 200 IU per day induced the most robust improvement in immune function.25 Capsules were manufactured by Tishcon Corporation (Westbury, NY) in 2 equal batches, with all ingredients from the same sources. The vitamin E and placebo capsules were soft gel and identical in color and taste. The manufacturer’s certified ingredient concentrations were confirmed by the investigators. The capsules were packed by Pharmasource Healthcare Inc (Marlboro, Mass) in 30-dose blister packs and administered by the clinical nursing home staff during routine medication rounds. Nurses and participants were blinded to treatment group. Adherence to study protocol was verified by nursing home medication records, returned pill count, and quarterly measurement of plasma vitamin E levels.

Outcomes
Primary outcomes of the study included incidence of, number of persons with, and number of days with respiratory tract infections (upper and lower), and number of new antibiotic prescriptions for respiratory tract infection. Because common colds constituted the majority of respiratory tract infection among all participants randomized and those who completed the study, a post hoc subgroup analysis was performed to determine the effect of vitamin E on common colds. Secondary outcomes included emergency department visits, hospitalization, and death.

Data Collection
Information about participant characteristics, baseline diseases and medications, and vaccination history was obtained from medical records. Fasting blood was collected at baseline and at study completion for clinical chemistries, complete blood cell count with differential, plasma vitamin E, and selected nutrient analyses, as previously described.30,31 In addition, blood was collected after 3, 6, and 9 months of supplementation to measure vitamin E levels.

The study nurses collected information weekly relating to infection, including respiratory and heart rates and temperature. Symptom and physical examination checklists, focused on the respiratory system, were used to record clinical findings. The nurses reviewed each participant’s medical record for documentation of laboratory analyses, radiography, medication, nutrient supplementation, weight, and nurse or physician descriptions of symptoms and signs relating to respiratory tract infection.

Study nurses were trained by a study physician to elicit relevant respiratory symptoms and to perform a focused physical examination of the respiratory system. Supervised practice evaluations were repeated throughout the study to reinforce the nurses’ clinical skills and ensure consistency of the respiratory tract infection data collection.

At the end of the study, data collected from the participants in each treatment group, by nursing home, were randomly assigned to 2 of the study physicians (B.C.F. and D.H.H.) for diagnosis of infections. Infection data from any one participant was evaluated by only 1 physician, except for 18 participants whose records were used to determine concurrence between physicians.

Diagnosis of Respiratory Tract Infection
The study physicians, who were blinded to the treatment group, evaluated data collected by the nurses from the participant examinations, interviews, and record reviews to determine incidence and duration of respiratory tract infection. Clinical definitions of respiratory tract infection were developed according to accepted definitions.13,32-37 To increase the specificity of the definitions, a diagnosis of respiratory tract infection had to include at least 1 physical sign and not be made on symptoms alone. An infection was considered resolved when all symptoms ceased. A new infection was defined as one occurring after at least 7 symptom-free days.

To assess the ability of the study physicians to apply the diagnostic criteria concordantly, the records of 18 participants were selected at random for each physician to evaluate independently. After each record was reviewed in its entirety, a total of 43 respiratory tract infections were identified. The probability that a physician would diagnose an infection if the other physician had diagnosed an infection was estimated to be 0.93.38,39

Clinical Diagnostic Criteria
Common Cold. At least 1 of the following signs or symptoms had to be present: rhinorrhea or stuffy nose (nasal obstruction) or sneezing plus 1 or more of the following: sore or scratchy throat, dry cough, hoarseness, or low-grade fever (temperature ≤1°C above normal range). Symptoms had to be new and not caused by allergies. Seasonal allergic rhinitis was defined as clear rhinorrhea or nasal congestion plus itchiness of the nose or eyes or watery eyes; fever, sore throat, and cough had to be absent; and symptoms had to manifest between April 1 and September 30 and include at least 1 objective sign of rhinitis.

Influenzalike Illness. Influenzalike illness was defined as temperature of at least 38°C plus new or increased dry cough and 1 or more signs or symptoms (chills, new headache or eye pain, myalgias, malaise or loss of appetite, or sore throat).

Pharyngitis. Pharyngitis was defined as symptoms of a sore or scratchy throat and at least 1 of the following abnormalities on pharyngeal examination: erythema, exudate, ulceration, vesicles, or edema.

Otitis Media. Otitis media was defined as ear pain plus either erythema or bulging of the tympanic membrane.

Sinusitis. Symptoms of sinusitis could include facial pain, purulent nasal discharge, and nasal congestion. If radiographs were available, the finding of mul-
comal thickening, opacities, or air fluid levels confirmed the diagnosis.

**Acute Bronchitis.** At least 2 of the following signs or symptoms had to be present to meet the criteria for acute bronchitis: increased frequency and severity of cough, new or increased sputum production, burning substernal chest discomfort with coughing or deep inspiration, and fever (temperature ≥38°C). Radiologic evidence of pneumonia excluded this diagnosis.

**Pneumonia.** Symptoms of pneumonia could include cough with or without sputum production, chest pain, dyspnea, and fever. Signs of infection included elevated temperature (≥38°C), tachycardia, tachypnea, abnormal breath sounds, and dullness to percussion of the chest. The diagnosis required radiologic findings of 1 or more new pulmonary infiltrates.

**Statistical Analysis**
Sample size was based on an estimated mean number of respiratory tract infections per person-year of 1.00 in the control group and 0.70 in the treatment group. The within-group SD was estimated at 1.27 according to data from a local nursing home. With an expected attrition rate of 25%, the sample size needed to give an 80% chance of detecting the difference in infection rates at the .05 level of significance was 320 per treatment group, for a total of 640 participants.

All randomized persons and all completers were compared at baseline, as were participants who had final measurements taken, by a t test for independent samples (continuous measures) and Pearson χ² test of homogeneity of proportions (categorical measures). Among completers, mean differences between the treatment groups with respect to changes in nutritional status were compared by using a t test for independent samples. Differences in changes in the fraction of completers who were judged nutritionally deficient were assessed by using a weighted least-squares linear model, with time, treatment, and their interaction as predictors. Data on race was collected from the nursing home medical record.

### Table 1. Baseline Characteristics of Elderly Persons by Completion Category and Treatment Groups

<table>
<thead>
<tr>
<th>Medical history, No. (%)</th>
<th>All Randomized</th>
<th>Completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD*</td>
<td>86 (28)</td>
<td>60 (26)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>116 (37)</td>
<td>80 (33)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>66 (21)</td>
<td>42 (18)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>151 (49)</td>
<td>122 (53)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>54 (17)†</td>
<td>39 (17)‡</td>
</tr>
<tr>
<td>Malignancy</td>
<td>26 (8)</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Dementia</td>
<td>164 (53)</td>
<td>127 (55)†</td>
</tr>
<tr>
<td>Alzheimer disease (%)</td>
<td>33 (20)</td>
<td>29 (23)</td>
</tr>
</tbody>
</table>

*Abbreviations: COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug.

<table>
<thead>
<tr>
<th>Participants taking NSAIDs, No. (%)</th>
<th>All Randomized</th>
<th>Completers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120 (39)</td>
<td>93 (40)</td>
</tr>
</tbody>
</table>

*COPD, chronic bronchitis, and asthma.

†P<.10 compared with placebo.

‡P=.04 compared with placebo.

### RESULTS

**Participant Characteristics**
The mean (SD) follow-up time was 317 (104) days for the vitamin E group and 321 (97) days for the placebo group. Of the 617 randomized persons, 231 (37%) and 220 (36%) in the vitamin E and placebo groups, respectively, completed the 1-year study period (Figure). The 2 groups did not differ statistically in the proportion or causes of discontinuation (Figure) or in mortality rates (12.5% [39/311] and 14.4% [44/306] for the vitamin E and placebo groups, respectively).

Table 1 shows participant characteristics for all who were enrolled in the study (all) and for those who completed 1 year (completers). The groups were well balanced with regard to baseline characteristics. One exception was a lower percentage of completers with diabetes mellitus in the vitamin E group compared with placebo (P=.04) (Table 1).

All participants received influenza vaccine, and the 2 groups did not differ statistically in the percentage of participants receiving pneumococcal vaccine (30/311 [9.6%] vitamin E vs 23/306 [7.5%] placebo, P=.53 for all; 29/231 [12.6%] vitamin E vs 19/220 [8.6%] placebo, P=.18 for completers). The mean number of days during which completers took immune-related medications during the study period did not differ significantly (nonsteroidal anti-inflammatory drugs [131 vs 110], antihistamines [4.5 vs 7.9], steroids [16.3 vs 9.2], or nutrient supplements [84 vs 92] for vitamin E and placebo groups, respectively).
Table 2. Nutritional Status of Elderly Persons Before and After Supplementation, by Treatment Group*

<table>
<thead>
<tr>
<th>Deficient Participants, %</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Measure of Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Albumin</td>
<td>19†</td>
<td>28†‡</td>
<td>27</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>32‡</td>
<td>31†</td>
<td>37</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>11</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>1</td>
<td>2‡</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Vitamin B1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>10</td>
<td>6‡</td>
<td>9</td>
</tr>
<tr>
<td>(pyridoxal phosphate),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12, µg/mL</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Folate, ng/mL</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zinc</td>
<td>48</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>Copper</td>
<td>6</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviation: AC, activity coefficient.

* n = 201 to 228 for albumin; hemoglobin; vitamins A, E, B6, and B12; folate; zinc; and copper; and n = 49 to 65 for carotenoids; vitamins D, B12, and B12 and ferritin.
† Significantly different (P<.05) from placebo group at the same time point.
‡ Significantly different (P<.05) from before for the same group.

Biochemical and hematological measurements before and after vitamin E supplementation indicated no difference between the 2 groups, except as otherwise specified (complete data available on request).

Adherence

Ninety-eight percent (442/451) of those completing the study consumed the capsules for at least 330 days (>90% of the 1-year supplementation period). The number of missed supplements did not differ statistically between the vitamin E and placebo groups (data available on request). Adherence was confirmed by plasma vitamin E measurement every 3 months.

Nutritional Status

Vitamin E and placebo groups did not differ statistically in body mass index or serum levels of vitamins and minerals before or after supplementation (data available on request). The vitamin E group had small but significantly higher hemoglobin levels than the placebo group before and after supplementation (mean [SD], 12.4 [1.4] vs 12.2 [1.3] g/dL before and 12.4 [1.3] vs 12.1 [1.5] g/dL after in the vitamin E and placebo groups, respectively; t = .02). Significantly fewer participants had low serum albumin levels in the vitamin E group compared with placebo at baseline and after supplementation (Table 2). The percentage of participants with low albumin levels increased significantly during the 1-year period for both groups, but the change over time in serum albumin between the 2 groups did not differ significantly.

Except for vitamin E, the level of micronutrients did not change significantly during the study period in either group. Plasma vitamin E levels increased significantly in the vitamin E group, which doubled after 3 months of supplementation with no further change (mean [SD], 1141 [391] vs 2119 [689] µg/dL before and after supplementation, respectively; t < .001). No significant change in serum vitamin E levels was observed in the placebo group (1148 [429] vs 1209 [408] µg/dL before and after supplementation, respectively). The fraction of participants with low serum vitamin A levels increased slightly but significantly, whereas the fraction of participants with low vitamin D and B6 levels decreased in both groups (Table 2), with no significant difference between treatments in change over time.

Significantly fewer participants had low hemoglobin levels in the vitamin E group before and after supplementation (Table 2). The fraction of participants with low hemoglobin levels in each group did not change significantly over time. Low serum zinc levels were equally prevalent in both groups (Table 2).

Respiratory Tract Infections

Results generally were similar whether the data from all participants (Table 3) or completing participants (Table 4) were compared. Adjustment for obstructive lung diseases, current smoking status, diabetes mellitus, dementia, year of enrollment, and baseline albumin and hemoglobin levels did not affect the outcomes, with a few exceptions, as noted in the text. Further adjustment for nursing home gave essentially the same results. Thus, only the unadjusted data are shown (Tables 3 and 4), except as noted in the text.

The highest incidence of respiratory tract infection occurred in the winter and the lowest in the summer (0.41 and 0.24 episodes per placebo participant, respectively). For all study participants, the rate of respiratory tract infection for vitamin E and placebo groups was 1.35 and 1.47 per person per year, respectively (Table 3), and for completers, 1.30 and 1.44 respiratory tract infections per person per year, respectively (Table 4). Rates of respiratory tract infections and number of days with respiratory tract infections per person-year (Tables 3 and 4), although lower in the vitamin E group, did not differ significantly in either group. However, significantly fewer persons in the vitamin E group contracted 1 or more respiratory tract infections (60% [186/311] vs 68% [207/306] for all participants, 65% [150/231] vs 74% [163/220] for completing participants in
the vitamin E and placebo groups, respectively.

The incidence, proportion, or number of sick days of lower respiratory tract infection (includes acute bronchitis and pneumonia) did not differ significantly between the 2 treatment groups (Tables 3 and 4).

The number of upper respiratory tract infections (URIs) per person-year and days with URI, although lower in the vitamin E group, were not significantly different between groups (Tables 3 and 4). However, significantly fewer participants in the vitamin E–treated group contracted 1 or more URIs compared with the placebo group (44% [137/311] vs 52% [159/306], respectively, for all participants [Table 3]; 50% [116/231] vs 62% [136/220], respectively, for completers [Table 4]). After adjusting for obstructive lung disease, current smoking status, diabetes mellitus, dementia, year of enrollment, and baseline albumin and hemoglobin levels, the RR for having at least 1 URI was 0.82 (95% CI, 0.66–0.98, P = .03) among all persons randomized to receive vitamin E.

Among the URIs, 84% [397/470] were common colds. Post hoc subgroup analysis indicated that vitamin E–supplemented participants who completed the study had a significantly lower incidence of common colds (Table 4). In addition, significantly in the vitamin E group acquired at least 1 cold (for all participants: 40% [125/311] vs 48% [147/306] in the placebo group [Table 3]; for completers: 46% [106/231] vs 57% [126/220] in the placebo group [Table 4]). After adjusting for obstructive lung disease, current smoking status, diabetes mellitus, dementia, year of enrollment, and baseline albumin and hemoglobin levels, the risk ratio for all persons randomized to vitamin E having at least 1 cold was 0.81 (95% CI, 0.64–0.98; P = .03). The vitamin E group had fewer days with common cold per person-year, but the result did not reach statistical significance (20% for all randomized in the vitamin E group [difference of 1.59 days with URI, although lower in the vitamin E group acquired 1 or more respiratory tract infections, as well as upper and lower (after adjustment for confounding factors). However, fewer persons in the vitamin E group acquired 1 or more respiratory tract infections or URIs. Common colds were the most frequent URIs, and in a post hoc subgroup analysis, participants in the vitamin E group who completed the study had significantly fewer common colds and a 20% lower risk of acquiring a cold than those in the placebo group. Further clinical trials of vitamin E supple-

### Table 3. Respiratory Tract Infection Among All Participants Enrolled in the Study†

<table>
<thead>
<tr>
<th>Incidence of infection</th>
<th>Vitamin E (n = 311)</th>
<th>Placebo (n = 306)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respiratory tract infections Infections, No.</td>
<td>365</td>
<td>394</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>1.35</td>
<td>1.47</td>
<td>0.92 (0.80 to 1.06)</td>
<td>.26</td>
</tr>
<tr>
<td>Lower respiratory tract infection Infections, No.</td>
<td>145</td>
<td>144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>0.54</td>
<td>0.54</td>
<td>1.00 (0.80 to 1.26)</td>
<td>.99</td>
</tr>
<tr>
<td>Upper respiratory tract infection Infections, No.</td>
<td>220</td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>0.82</td>
<td>0.93</td>
<td>0.88 (0.73 to 1.05)</td>
<td>.15</td>
</tr>
<tr>
<td>Colds Infections, No.</td>
<td>180</td>
<td>217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>0.67</td>
<td>0.81</td>
<td>0.83 (0.68 to 1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Antibiotic prescriptions for all respiratory tract infections Prescriptions, No.</td>
<td>185</td>
<td>168</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriptions per person per year</td>
<td>0.685</td>
<td>0.626</td>
<td>1.10 (0.89 to 1.35)</td>
<td>.39</td>
</tr>
</tbody>
</table>

### Table 4. Risk Ratio and Difference (Vitamin E–Placebo)‡

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>All respiratory tract infections</th>
<th>0.88 (0.76 to 1.00)</th>
<th>.048</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract infection</td>
<td>0.99 (0.78 to 1.23)</td>
<td>.63</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.84 (0.69 to 1.00)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Colds</td>
<td>0.83 (0.67 to 1.00)</td>
<td>.05</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference (Vitamin E–Placebo)</th>
<th>All respiratory tract infections</th>
<th>−1.64 (−4.56 to 1.29)</th>
<th>.27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract infection</td>
<td>−0.10 (−2.09 to 1.88)</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>−1.53 (−3.70 to 0.63)</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Colds</td>
<td>−1.59 (−3.56 to 0.38)</td>
<td>.11</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Total days in study: 98 594 vitamin E, 98 091 placebo.
†Bronchitis, pneumonia.
‡Common cold, influenzalike infection, pharyngitis, otitis media, sinusitis.

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(Reprinted) JAMA, August 18, 2004—Vol 292, No. 7 833
VITAMIN E AND RESPIRATORY TRACT INFECTIONS

mentation in elderly persons, with common cold as the primary outcome, are warranted.

Although our data suggest that vitamin E may protect against the common cold, the most frequently encountered form of URI in this study, vitamin E had no effect on the incidence or duration of other URIs or of lower respiratory tract infections, which may have been due to the small number of such episodes or differences in the types of pathogens responsible. Most URIs, especially the common cold, are caused by viruses. Animal studies suggest that vitamin E protects against viral but not bacterial infection in aged mice.42 We have found that although vitamin E supplementation did not protect old mice against primary pulmonary Staphylococcus aureus infection, it was protective against secondary S aureus infection after influenza infection.43

The respiratory tract infection definitions applied in our study were derived by using commonly accepted criteria from the medical literature.13,32-37 These criteria do not allow the differentiation of viral from bacterial etiology. Future studies should include detailed microbiologic methods to determine whether vitamin E has an effect on respiratory tract infections of viral vs bacterial etiology.

Vitamin E did not affect antibiotic use. If the effects of vitamin E were on URIs of viral etiology, this could explain the finding. In addition, overuse of antimicrobial agents in nursing homes44 may have impaired our ability to demonstrate an effect of vitamin E on antibiotic use.

Table 4. Respiratory Tract Infection Among Participants Completing the Study*

<table>
<thead>
<tr>
<th>Incidence of infection</th>
<th>Vitamin E (n = 231)</th>
<th>Placebo (n = 220)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respiratory tract infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections, No.</td>
<td>304</td>
<td>320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>1.30</td>
<td>1.44</td>
<td>0.91 (0.77 to 1.06)</td>
<td>.22</td>
</tr>
<tr>
<td>Lower respiratory tract infection†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections, No.</td>
<td>115</td>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>0.49</td>
<td>0.47</td>
<td>1.05 (0.80 to 1.36)</td>
<td>.74</td>
</tr>
<tr>
<td>Upper respiratory tract infection‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections, No.</td>
<td>189</td>
<td>215</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>0.81</td>
<td>0.96</td>
<td>0.84 (0.69 to 1.02)</td>
<td>.08</td>
</tr>
<tr>
<td>Colds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections, No.</td>
<td>155</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections per person per year</td>
<td>0.66</td>
<td>0.83</td>
<td>0.80 (0.64 to 0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>Antibiotic prescriptions for all respiratory tract infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriptions, No.</td>
<td>153</td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriptions per person per year</td>
<td>0.655</td>
<td>0.561</td>
<td>1.17 (0.92 to 1.47)</td>
<td>.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants with ≥1 infection, No.</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respiratory tract infections</td>
<td>150</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>76</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>116</td>
</tr>
<tr>
<td>Colds</td>
<td>106</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference (Vitamin E–Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of days with infection per person per year</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Colds</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Total days in study: 85 342 vitamin E, 81 436 placebo.
†Bronchitis, pneumonia.
‡Common cold, influenza-like infection, pharyngitis, otitis media, sinusitis.

Previous studies of vitamin E and infection in the elderly have demonstrated mixed results. A retrospective study showed that persons with plasma vitamin E levels above 1670 µg/dL had significantly fewer infections compared with those with plasma vitamin E levels below 1200 µg/dL (mean, 1.0 vs 2.3, respectively; 95% CI for difference, 0.12-2.48).45 A recent double-blind trial of Dutch elderly46 persons living in the community reported no difference for all respiratory tract infections among those receiving vs not receiving vitamin E (RR, 1.12; 95% CI, 0.88-1.25). Our population and diagnostic method differed from those of the Dutch study. In the Dutch study,46 participants self-reported their infections by telephone, and then the infections were confirmed by nurse visits. Lack of infection was not confirmed. In our study, the presence and type of respiratory tract infection, or absence, was documented by infectious disease specialists according to review of data gathered by trained research nurses during weekly participant interviews, review of medical records, and physical examination focused on respiratory tract infection according to standardized case definitions.13,32-35 Our results indicate that vitamin E may reduce URIs, particularly common colds, with no effect on lower respiratory tract infections or seasonal allergies. Graat et al46 did not differentiate between types of infections or between respiratory tract infections and allergies, and thus might have overlooked any effect of vitamin E on URI. Furthermore, in our study adherence was checked by nursing home medication records and by periodic plasma vitamin E measurements, whereas the study by Graat et al46 measured plasma vitamin E levels only at baseline.

Several potential limitations of our study merit comment. First, of the originally planned sample size of 640, 617 were enrolled. However, this limitation should not influence the reported results because the change in power to detect statistical significance was from 80% to 78.5%. Second, 27% (166/
617) of the enrolled persons did not complete the study because of withdrawal or death. This level of loss to follow-up was anticipated in our original study design. It demonstrates the challenges inherent in a 1-year study of a frail nursing home population. Because there were minimal differences in the characteristics of those who did and did not complete the study, this loss to follow-up did not have an impact on our overall results. Results among completers only were more likely to show an effect of vitamin E because attenuating plasma and tissue saturation levels of vitamin E requires several months. However, the analysis of all patients randomized is the most conservative analysis and showed fewer significant effects.

Third, the use of a half RDA multi-vitamin28 capsule for all participants might have lessened the impact of vitamin E on respiratory tract infection by improving the micronutrient status of the placebo group. However, we found no statistically significant differences between the vitamin E and placebo groups with change over time in the status of any nutrients other than vitamin E. Although our vitamin E group had a lower proportion of persons with low albumin and hemoglobin levels at baseline and follow-up, statistical adjustment for these potentially confounding factors did not change our conclusion. A high percentage of participants had low plasma zinc levels, but the 2 groups did not differ in the fraction of zinc-deficient participants before or after treatment and thus did not influence the reported results.

Fourth, the significant reduction in URIs with vitamin E supplementation was not consistent in all analyses, and the common cold analysis was post hoc. However, these results suggest that future randomized trials of vitamin E should concentrate on these end points. The common cold is generally less severe than influenza. However, its much higher incidence and its recognized morbidity in the elderly make it an important public health problem in this age group. This is particularly relevant because no clinically useful vaccine or antiviral therapy is available to combat colds.

In conclusion, we found no effect of vitamin E supplementation on the incidence or duration of respiratory tract infections. However, significantly fewer vitamin E participants acquired 1 or more respiratory tract infections, which was most evident in URIs. Post hoc subgroup analysis among individuals completing the study revealed a significantly lower incidence of common cold and fewer participants acquiring a cold. Common colds are frequent and associated with increased morbidity in this age group, and if confirmed, these findings suggest important implications for the well-being of the elderly. Future studies in elderly individuals should assess the effect of vitamin E supplementation on the common cold and incorporate microbiologic methods to allow for assessment of the impact of vitamin E on specific types of respiratory pathogens.

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Author Contributions: Dr Meydani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Meydani, Dallal, Keusch, Singer, Hamer. Acquisition of data: Meydani, Leka, Fine, Dallal, Hamer. Analysis and interpretation of data: Meydani, Leka, Fine, Dallal, Singh, Hamer. Drafting of the manuscript: Meydani, Leka, Dallal, Singh, Hamer. Critical revision of the manuscript for important intellectual content: Meydani, Leka, Fine, Dallal, Keusch, Singer, Hamer. Statistical analysis: Dallal. Obtained funding: Meydani, Keusch, Singer, Hamer. Administrative, technical, or material support: Meydani, Leka, Keusch, Singh, Hamer. Study supervision: Meydani, Leka, Singh, Hamer. Funding/Support: The research for this work was performed in the Nutritional Immunology Laboratory, Jean Mayer US Department of Agriculture/HNRCA at Tufts University, Boston, Mass. This work was supported by National Institute on Aging (NIA), National Institutes of Health grant 1R01 AG13975, and Department of Agriculture agreement 58-1950-9-001, and a grant for preparation of study capsules from Hoffmann-LaRoche Inc.

Role of the Sponsors: The funding organizations did not have input in the design or conduct of the study; the collection, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript. The NIA review panel provided input into data analysis of the study as part of the peer review process when the grant proposal was submitted for funding.

Acknowledgment: We are grateful for the contributions made by Paula Murphy-Gismondi, MSW, for help with recruitment, by the research nurses Susan Fritz, RN, Susan Horshford, RN, Christine Beck, RN, Karen Reed, RN, Karen Collins, RN, and Paula O’Connor, LPN, our phlebotomist Murielle Despeignes, the personnel in the JMUSDA-HNRCA Nutrition Evaluation Laboratory, the administration and staff at the participating nursing homes, and all the residents there who volunteered for this study.

REFERENCES

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Severe Acute Pancreatitis

To the Editor: Using Ranson’s criteria to forecast outcome in patients with pancreatitis would indicate that a 56-year-old individual with a glucose level of 201 mg/dL (11.2 mmol/L) and a white blood cell count of 16.1 × 10^9/µL has the same risk for adverse outcome as one who develops a Po2 of less than 60 mm Hg, has a decrease in hematocrit by 10%, and sequesters 6 L of abdominal fluid in 48 hours. I would call into question the validity of a scoring system that equally weights these disparate factors.

An important article by Ranson and Pasternack^2 used versions of stepwise regression analysis to search for the criteria most predictive of acute pancreatitis. In this article, the 11 variables of Ranson were not equivalent in predictive value. Elevated lactate dehydrogenase and aspartate aminotransferase in the several tested models had the greatest prognostic capability. I consider lactate dehydrogenase and aspartate aminotransferase to be covariates indicative of liver disease and think Ranson’s studies show that patients with unhealthy livers and pancreatitis are more likely to have poor outcomes. I believe the prognostic system proposed by Rabeneck et al^3 to be a better and simpler tool, relying on the presence or absence of illness in association with comorbidities to forecast outcome. I suggest that a continued endorsement of Ranson’s criteria seems out of place.

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To the Editor: Human immunodeficiency virus (HIV)-AIDS should be noted when considering recent trends in acute pancreatitis. In patients with AIDS, pancreatitis is 35 to 800 times more common than the annual incidence of 170 cases per million in the United States. Patients infected with HIV appear to be at extremely high risk for acute pancreatitis for several reasons. They are vulnerable to direct toxicity to pancreatic acinar cells from several medications that are frequently used in treatment. Didanosine, pentamidine, pentavalent antimony, sulfonamides, corticosteroids, and octreotide have definite association and zalcitabine has probable association with pancreatitis. Infections due to cytomegalovirus, Toxoplasma gondii, Mycobacterium avium intracellulare, Mycobacterium tuberculosis, and cryptosporidium are other causes for acute pancreatitis in this population.

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In Reply: Dr Piwinski has correctly stated the limitation of Ranson’s criteria in the assessment of severity of acute pancreatitis and believes that the prognostic system proposed by Rabeneck et al^3 is more useful. In our review, we cited the scoring systems of Ranson, Imrie, APACHE II, and Balthazar because these have been validated and extensively used in the literature. Space constraints for a short review did not permit us to discuss in detail the acknowledged imperfections and shortcomings of all of these systems, although we did note that Ranson’s criteria system has the disadvantage of a 48-hour delay for completion.

Although we agree with the general sentiments expressed by Dr Piwinski and believe that systems used to predict severity can and should be improved, it is our opinion that the system proposed by Rabeneck et al has not been validated in any prospective study and, therefore, is not a suitable replacement for those currently in use.

Space constraints also limited discussion of the various causes of acute pancreatitis, including those related to HIV-AIDS, as described by Dr Kashyap and colleagues.

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CORRECTION

Word Omitted: In the Original Contribution entitled “Vitamin E and Respiratory Tract Infections in Elderly Nursing Home Residents” published in the August 18, 2004, issue of The Journal (2004;292:828-836), an important word was omitted. On page 833, the third sentence of the third paragraph should have read “In addition, significantly fewer in the vitamin E group acquired at least 1 cold. . . .” The word “fewer” did not appear in the article.