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A Combination of High-dose Vitamin C Plus Zinc for the Common Cold

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Vitamin C and zinc play important roles in nutrition, immune defence and maintenance of health. Intake of both is often inadequate, even in affluent populations. The common cold continues to place a great burden on society in terms of suffering and economic loss. After an overview of the literature on the effects of the separate administration of either vitamin C or zinc against the common cold, this article presents data from two preliminary, double-blind, randomized, placebo-controlled trials, conducted with a combination of 1000 mg vitamin C plus 10 mg zinc in patients with the common cold. In both studies, a nonsignificant reduction of rhinorrhoea duration (range 9 – 27%) was seen. In pooled analyses of both studies (*n* = 94), vitamin C plus zinc was significantly more efficient than placebo at reducing rhinorrhoea over 5 days of treatment. Furthermore, symptom relief was quicker and the product was well tolerated. In view of the burden associated with the common cold, supplementation with vitamin C plus zinc may represent an efficacious measure, with a good safety profile, against this infectious viral disease.

KEY WORDS: Vitamin C; Zinc; Micronutrients; Common cold; Respiratory infections; Immune system

Vitamin C and zinc

Vitamin C (ascorbic acid) and zinc are two essential micronutrients that play important functional roles in nutrition, immune support and maintenance of health. Vitamin C is a cofactor for several enzymes involved in the biosynthesis of collagen, carnitine and neurotransmitters.[1,2] It is a highly effective antioxidant that protects proteins, lipids, carbohydrates and nucleic acids from damage by free radicals generated during normal metabolism, as well as through exposure to toxins and pollutants (e.g. smoking).[1 – 3] Marginal vitamin C deficiency results in fatigue, lack of well-being and poor concentration.[2] Severe vitamin C deficiency has been known for many centuries as the potentially fatal disease, scurvy. Scurvy causes weakening of collagenous structures, resulting in tooth loss, joint pain, bone and connective tissue disorders (e.g. impaired bone growth and disturbed ossification), poor wound healing and compromised immunity.[1 – 3] Zinc is a component of over 1000 transcription factors, including DNA-binding proteins with zinc fingers, and is required in over 300 metalloenzymes.[2,3] Zinc plays a central role in cellular differentiation and proliferation, and its deficiency causes growth retardation, skin changes, impaired immune response, increased susceptibility to infections, delayed wound healing,

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abnormal dark adaptation, delayed sexual maturation and impaired fertility.[2 – 5] Zinc deficiency is an important public health problem affecting 2 billion people worldwide,[2,5] including a considerable proportion of the Western population.[2,3]

Among the micronutrients required to ensure proper immune function, vitamin C and zinc hold central positions through their complementary roles in supporting components of both innate and adaptive immunity, such as epithelial barriers, cellular proliferation and antibody production.[2] Vitamin C is mainly necessary for cell-mediated immune responses including leucocyte and macrophage functions, neutrophil motility and phagocytosis, but also for antimicrobial activity, interferon synthesis and antihistamine properties.[2,3] It is further required for collagen synthesis and wound healing, with collagen being important to the physical infection barrier provided by the skin and the linings of all of the body openings.[2,3,6 – 11] Vitamin C generally has a limited effect on humoral immune responses such as antibody production.[2,3,12]

Zinc is necessary for optimal functioning of both innate and adaptive immunity; impaired immune function due to inadequate zinc status may be the most common cause of secondary immunodeficiency in humans.[13 – 15] Zinc status strongly affects T- and B-lymphocyte function and antibody formation, and is required by the thymus for the production of thymic hormone.[2,3,16,17] Finally, both vitamin C and zinc provide complementary antioxidant protection against exogenously derived and endogenously generated reactive oxygen species.[2,3] Immune cells are frequently exposed to alterations in the oxidant–antioxidant equilibrium, due to the high number of reactive oxygen species they produce in order to incapacitate pathogens as part of their normal function.[18] Immune cells need to protect themselves from reactive oxygen species in order to preserve their structure and function, and the oxidant–antioxidant balance is, therefore, an important determinant of immune function. Immune cells are particularly sensitive to changes in this balance because of the high levels of polyunsaturated fatty acids in their plasma membranes.[19]

Deficiencies of vitamin C[3,9,12,20,21] and zinc[13 – 15] both severely depress immune responses. Vitamin C deficiency results in decreased resistance to disease.[3,9,12,20 – 22] Zinc deficiency can have marked effects on virtually all components of the immune system, increasing susceptibility to a number of bacterial, viral and parasitic challenges.[13,23] Overall, there is a sound scientific rationale for taking a combination of vitamin C and zinc to support immune function, in order to realize better the body's potential for defence.[2,3]

The common cold

Viral respiratory tract infections, such as the common cold and influenza, are among the most common illnesses in humans. Despite great advances in medicine, the common cold continues to place a great burden on society in terms of suffering and economic loss.[24,25] The common cold is caused by a large variety of viruses that mutate frequently during reproduction, resulting in constantly changing viral strains.[25] Thus, successful immunization is highly improbable.

The occurrence of the common cold shows clear seasonality. In temperate regions of the northern hemisphere, the frequency of respiratory infections increases rapidly in the autumn, remains fairly high throughout the winter, and decreases again in spring.[25] In tropical areas, most colds arise during the

rainy season.[25] Adults have around two to four common-cold episodes annually, whereas children may have six to 10 colds per year (and up to 12 colds per year for school children).[25,26] Even if the common cold is mostly an uncomplicated disease, its social costs are important because of its frequency.

The best way to avoid a cold is to stay away from existing sufferers, to wash hands thoroughly and regularly, and to avoid touching the face. Antibacterial soap has no effect on the cold virus; it is the mechanical action of hand washing that removes virus particles from the skin.[25,27,28] Tobacco smoking has been shown to reduce antioxidant levels (vitamin C status, in particular)[3,29] and also weakens the immune system. Thus, smokers may experience colds more frequently than nonsmokers. Smokers are known to take more days off work with illness than nonsmokers.[30,31] As there is no clinically proven 'gold standard' medication directly targeting the causative pathogen for the common cold, there is no cure for this condition. Treatment is limited to symptomatic supportive options that maximize the comfort of the patient by reducing symptom severity and limiting the occurrence of complications.[25,27] The most frequent symptoms linked to the common cold are shown in Table 1.[27] Nasal symptoms including congestion, runny nose (rhinorrhoea) and sneezing are most common, occurring in 45 – 75% of patients.[27] The duration of these symptoms has been reported to vary between 4 days and up to 3 weeks.[27]

In addition to classical drugs (e.g. decongestants, analgesics), dietary supplements including echinacea,[32] propolis,[33] ginseng,[34,35] β-glucans,[36,37] vitamin E,[38] and especially vitamin C[2,3] and zinc,[26] have been studied for the prevention and treatment of the common cold and cold-related symptoms.

This article provides an overview of the available published data on the effects of the separate administration of either vitamin C or zinc against the common cold. In addition, it presents the results of two preliminary placebo-controlled studies carried out with a combination effervescent tablet containing high-dose (1000 mg) vitamin C plus 10 mg zinc (Redoxon® Double Action; Bayer Consumer Care Ltd, Basel, Switzerland) in patients with symptoms of a common cold.

Effects of vitamin C against the common cold

Based on its immunostimulatory properties, high doses of vitamin C have been postulated to be effective in ameliorating

TABLE 1:
Frequency of the usual symptoms of the common cold[27]

Location	Symptom	Incidence, %
Nasal	Rhinorrhoea	75
	Sneezing	60
	Nasal congestion/obstruction	45
Pharyngeal	Dry throat	50
	Throat irritation	30
Tracheal	Cough	40
General	Headache	40
	Fever	15
	Myalgia	15

and speeding the recovery from the common cold.[39] Endogenous vitamin C concentration falls rapidly with the onset of infection and tends to return to normal with the disappearance of symptoms, suggesting that its administration may be beneficial for the recovery process.[40,41]

The notion that vitamin C has no effect on the common cold seems to be based largely on a review article written in 1975 by Chalmers,[42] which was criticized as unreliable by Hemilä in the 1990s.[43,44] Chalmers' review showed several systematic flaws (such as not considering the amount of vitamin C used in the studies and including a trial administering only 25 – 50 mg/day ascorbic acid) and inconsistencies when compared with the original publications.[42] Since the publication of the Chalmers review, a large number of placebo-controlled, double-blind studies have been carried out. The results of these studies, summarized below, consistently support the conclusion that vitamin C supplementation has an effect in alleviating the symptoms of the common cold.

The results of 21 placebo-controlled studies performed between 1971 and 1988 were reviewed by Hemilä.[45] The main objective of these studies was to establish whether vitamin C given regularly at doses ≥ 1 g/day had any effect on the course of the common cold. Despite large variations in each of the 21 studies, regular vitamin C use consistently and significantly reduced both the duration of episodes and the severity of symptoms of the common cold by 23%.[45] Furthermore, regular vitamin C use also reduced the incidence of the common cold by 9% in the general population, although evidence for this reduction was not seen consistently in all 21 studies.[45] A further analysis of 23 studies, in which patients had been taking vitamin C ≥ 1 g/day regularly, was carried out to determine factors contributing to the variation in benefits observed in the above trials.[46] It appeared that the higher the dose per kg body weight, the greater the benefit; vitamin C produced a greater benefit in terms of cold duration for children than adults, and the magnitude of the benefit of vitamin C was greater with doses of ≥ 2 g/day than 1 g/day.[46] The trials analysed in this review used preventive vitamin C supplementation, but it is conceivable that therapeutic supplementation starting at the onset of a cold episode could produce comparable benefits.[46]

Over 60 studies (involving widely varying dosages) have examined the effects of vitamin C on the common cold. A 2007 Cochrane review evaluated whether oral doses of ≥ 200 mg/day of vitamin C reduced the incidence, duration or severity of the common cold when used either as continuous prophylaxis or after the onset of symptoms.[47] That review concluded there was a benefit of high-dose vitamin C (exceeding the recommended dietary allowance) in reducing the duration of cold symptoms.[47]

The meta-analysis of common-cold duration during prophylactic vitamin C intake included 30 studies involving 9676 respiratory episodes.[47] A consistent benefit was observed, representing a reduction in cold duration of 8% (95% confidence interval [CI] 3%, 13%) for adults and 13.6% (95% CI 5%, 22%) for children.[47] The reduction of cold duration in adults was lower than the 23% reduction reported by Hemilä,[45] but the Hemilä review included only studies using ≥ 1 g vitamin C; the higher vitamin C dose may explain the different findings.

The Cochrane review[47] revealed that vitamin C supplementation (≥ 200 mg/day) has not been shown to offer a preventive

effect regarding the incidence of the common cold in the general population. However, a subgroup of six trials – involving a total of 642 marathon runners, skiers and soldiers on subarctic exercises – showed that the pooled relative risk of developing a common cold was 0.50 (95% CI 0.38, 0.66) while taking prophylactic vitamin C.[47]

The meta-analysis of cold duration during therapy with vitamin C initiated after the onset of symptoms included seven trials involving 3294 respiratory episodes.[47] No significant differences from placebo were seen in these cases,[47] but the treatment period in some of the studies evaluated may have been too short (3 days) to detect a significant effect.[47] Again, the dose of vitamin C may also have contributed to the negative findings. Gorton and Jarvis[48] treated students (aged 18 – 32 years) reporting cold and flu symptoms with 1000 mg/h of vitamin C for 6 h, repeating the treatment for up to 3 days, followed by 1000 mg three times daily.[48] This treatment protocol resulted in an 85% reduction of reported flu and cold symptoms compared with the control group.[48] In another trial, either 4 g/day or 8 g/day of vitamin C was administered on the first day of illness.[49] The mean duration of cold episodes was 3.17 days in the 4 g/day group, 2.86 days in the 8 g/day group and 3.52 days in the placebo group.[49] The reduction seen with both vitamin C doses reached statistical significance.[49] The relationship between vitamin C dose and treatment benefits needs further exploration, and it is important to note that none of the studies analysed in the Cochrane or Hemilä reviews[44,45,47] took into account the patients' dietary intake of vitamin C or their vitamin C status.[50]

Overall, these data indicate that vitamin C supplementation plays a role in respiratory defence mechanisms. It appears that the elderly (who have been shown to have a lowered vitamin C status) may be more prone to infections than younger people,[3,12] and that patients exposed to continuous oxidative stress (such as chronic smokers[1 – 3] and persons exposed to heavy physical exercise and/or stress due to low temperatures[3]) may benefit from a moderate continuous vitamin C intake, in relation to respiratory infections such as the common cold.

Effects of zinc against the common cold

The immunostimulatory properties of zinc may also contribute to the management of the common cold. Zinc salts have been found to inhibit rhinovirus replication *in vitro*,[51] and it has been suggested that zinc salts may protect plasma membranes against lysis by cytotoxic agents (such as microbial toxins and components of activated complement).[52] Analyses of trials conducted between 1984 and 2000, investigating the role of zinc for alleviating symptoms of the common cold, yielded mixed results in terms of efficacy.[52,53] Inadequate treatment masking, reduced bioavailability of zinc from some formulations and overall dose have been cited as possible influencers of the results.[3,54]

A Cochrane review on zinc and the common cold was undertaken in 2011.[26] The review identified 15 randomized controlled trials enrolling 1360 participants of all age groups, comparing zinc (irrespective of the zinc salt or formulation used) versus placebo.[26] The Cochrane review in 2000 had assessed seven trials, involving 754 cases.[53] Zinc administered either as lozenges or syrup within 24 h of symptom onset was found to reduce the duration and severity of the common cold in otherwise healthy people.[26] In these therapeutic trials, 1.5 – 2-hourly

treatments with zinc (at doses of 10 – 23 mg) or placebo lozenges during waking hours were applied for > 6 h per day, for ≥ 5 consecutive days.[26] When supplemented for ≥ 5 months in the form of syrup (10 – 30 mg/day),[55,56] zinc further reduced the incidence of common colds, school absenteeism and the prescription of antibiotics in children.[26] In contrast, people taking zinc lozenges (not syrup or tablet form) were more likely to experience adverse events, including a bad taste and nausea.[26] Given the variability in the populations studied, dose, formulation and duration of administration in the included studies, more research is required to determine the optimal duration of treatment (as well as the dosage and formulations of zinc) that will produce clinical benefits without increasing adverse effects.

Hemilä[54] analysed a subset of studies from the Cochrane review, consisting of 13 placebo-controlled trials exclusively using zinc lozenges. This analysis considered both the type of zinc salts as well as the total amount of zinc used on the therapeutic effect of common-cold episodes of natural origin.[54] Five of the trials used a total daily zinc dose of < 75 mg and uniformly found no effect.[54] Three trials used zinc acetate in daily doses of > 75 mg, the pooled result indicating a 42% reduction in the duration of colds (95% CI 35%, 48%). Five trials used zinc salts other than acetate in daily doses of > 75 mg, the pooled result indicating a 20% reduction in the duration of colds (95% CI 12%, 28%).[54] Both the type of zinc salt used and the dose of zinc in the lozenges impacted on the benefits of supplementation in relation to the common cold.[54] These findings help to explain the mixed results observed in the reviews published in 2000.[52,53]

The postulated local mechanism of action of zinc lozenges (e.g. gluconate, acetate), differs in general from the well-documented, important actions of systemic zinc on immune defences.[57] This indicates a potential dual mode of action (i.e. local and systemic) for zinc, related to immune support. Due to the broad geographical distribution and high prevalence of zinc deficiency and the resulting impairment of immune function, individuals at risk of deficiency may benefit from a moderate continuous zinc intake to maintain respiratory health.[3]

Taken together, data from a number of clinical studies demonstrate that the separate administration of vitamin C or zinc results in a reduction of the duration and severity of common-cold symptoms in healthy individuals. To elicit these effects, vitamin C at doses > 200 mg is typically consumed as a prophylactic measure, whereas zinc is administered in the form of lozenges (10 – 23 mg of zinc at least six times daily) or syrup (10 – 30 mg/day) and taken within 24 h after symptom onset. There is also evidence showing that the prophylactic use of vitamin C or zinc may reduce the incidence of the common cold in some special populations.

Effect of combined vitamin C and zinc supplement against the common cold

RATIONALE

Redoxon® Double Action is a dietary supplement in the form of an effervescent tablet, typically consisting of 1000 mg vitamin C (ascorbic acid) and 10 mg zinc (as zinc citrate), sold as an over-the-counter drug in many countries of the world. It is indicated for the prevention and treatment of vitamin C and zinc deficiencies, during situations and conditions with increased requirements or increased risk of deficiencies. Symptoms of the common cold are closely related to the immune status of the host, and evidence supports the separate administration of

vitamin C and zinc. Therefore, an evaluation of the effect of 1000 mg vitamin C plus 10 mg zinc on the duration of the common cold and the intensity of cold-related symptoms appeared to be appropriate. Consequently, two preliminary, double-blind, randomized, parallel-group, placebo-controlled clinical studies were carried out to evaluate effervescent tablets containing a daily dose of 1000 mg vitamin C plus 10 mg zinc (as zinc citrate) in patients with the common cold.[b,c] Details of the two studies are summarized in Table 2. Both studies were conducted in accordance with the principles outlined in the Declaration of Helsinki, and with Good Clinical Practice.

STUDY 1

Aims

A double-blind, randomized, placebo-controlled pilot study was conducted in patients with common-cold symptoms, who received either 1000 mg vitamin C plus 10 mg zinc (one effervescent tablet daily, consumed in the morning) or a matching placebo.[b]

Patients and methods

Participants were enrolled consecutively by general practitioners, and treatment lasted for 5 days (Table 2). Standard demographic data were collected at baseline. Each day, between day 0 and day 5, participants were required to fill in a self-evaluation booklet.

Self-assessment

Patients were required to evaluate the intensity of the usual symptoms of the common cold (rhinorrhoea, sneezing, cough, laryngeal irritation, myalgia, headache, overall nasal obstruction/congestion and eye watering) every day in a self-evaluation booklet. Global assessment of the discomfort due to their symptoms was to be documented every day using a visual analogue scale (VAS) of 100 mm (0 mm, no discomfort; 100 mm, maximum possible discomfort). Discomfort caused especially by rhinorrhoea, sneezing, cough, laryngeal irritation, myalgia, headache, overall nasal obstruction/congestion, and watering of the eyes, was additionally assessed daily on a verbal rating scale (very severe; severe; moderate; mild and none).

Investigator assessment

Common-cold symptoms (rhinorrhoea, cough, laryngeal irritation, myalgia, headache, rectal temperature) were evaluated on day 0 and day 6 by the investigator (rectal temperature was measured; other symptoms evaluated with 'Yes' or 'No').

Tolerance of the investigational product was assessed by the incidence of adverse events; this was researched by asking open questions. If any adverse events were observed during the course of the study, the investigator had to note these in the case report form including the nature, onset, intensity, evolution, causality assessment and actions taken.

Results

The study included 30 patients: 13 males and 17 females. The 1000 mg vitamin C plus 10 mg zinc group included 14 patients (five males, nine females; mean ± SD age 37 ± 17 years; mean ± SD body mass index [BMI], 22.15 ± 2.90 kg/m^2). The placebo group included 16 patients (eight males, eight females; mean ± SD age, 43 ± 15 years; mean

[b]Data on file – Roche Consumer Health: Comparison of the efficacy and tolerance of REDOXON ZINC and placebo in the treatment of common cold. A double blind, parallel groups, pilot study on 30 patients for 5 days; 1997. Clinical Report No. 16 51 55.
[c]Data on file – Roche Consumer Health: Comparison of the efficacy and tolerance of REDOXON ZINC and placebo in the treatment of common cold. A double blind, parallel groups, placebo controlled study on 64 patients for 10 days; 1999. Clinical Report No. 16 52 12.

TABLE 2:
Summary of study protocol details from two preliminary studies with an effervescent tablet containing 1000 mg vitamin C plus 10 mg zinc

	Study 1	Study 2
Locations	Study conducted by general practitioners in Saint Martin d'Hères, Domène and Meylan (France)	Study conducted by general practitioners in Marseille and Angers (France)
Randomization method	• Treatment allocation according to randomization list provided by sponsor • Each treatment designated by its number	
Inclusion criteria	• Men or women > 18 years of age • Symptoms of a simple, uncomplicated, without superinfection, common cold with a bilateral and clear rhinorrhoea for < 3 days • Rectal temperature < 38 °C • Able to understand aims and constraints of study and complete self-evaluation booklet • Informed consent given	
Exclusion criteria	• Superinfected common cold (rectal temperature > 38 °C; and/or purulent rhinorrhoea; and/or purulent expectoration) • Pregnancy or breast-feeding, or delivery within 1 month before study commenced • Women of child-bearing potential who did not use any effective contraceptive method • Diagnosis of any disease that could decrease absorption or metabolism of trial drugs • Participation in another clinical study in previous 12 weeks • Diagnosis of a psychological disease or disorder that could interact with ability to understand aims and constraints of study, to give informed consent or to present good compliance • Currently taking any of the following drugs: aspirin, carbasalate calcium, nonsteroidal anti-inflammatory drugs, steroids including inhaled steroids, inhaled vasoconstrictors, antihistamines, anticongestants, parasympatholytics, modulators of immunity, treatments containing zinc or vitamin C	
Patient consent	• Written, informed consent obtained during enrolment, after a clear explanation of study aims and constraints, and before treatment allocation	
Ethics committee approval	• Reviewed and approved by Independent Ethics Committee of Nantes (France)	
Statistical analyses	• Nonparametric variables described by absolute and relative frequencies • Parametric variables described by means, standard deviation, minimum, maximum and median Intergroup comparisons tested by: • Wilcoxon's rank sum test for categorical variables • χ^2-test or Fisher's exact test for Boolean variables Evolution of symptoms and global discomfort tested by: • Analysis of variance on ranks for repeated measures with two factors (time and treatment) Details of statistical software were not available for either study	

TABLE 2 (continued):
Summary of study protocol details from two preliminary studies with an effervescent tablet containing 1000 mg vitamin C plus 10 mg zinc

Study 1	Study 2
Statistical analyses (continued)	Additional intergroup comparisons tested by: • Student's *t*-test or Wilcoxon's rank sum test in case of continuous variables depending on the distribution

± SD BMI 23.25 ± 3.32 kg/m^2). No demographic differences between the two groups were observed at baseline. An effervescent tablet containing 1000 mg vitamin C plus 10 mg zinc was found to reduce the mean duration of rhinorrhoea by 27% when compared with placebo (mean ± SD 4.14 ± 1.88 versus 5.25 ± 1.34 days, respectively). The difference did not reach statistical significance due to the small number of patients studied and the short treatment period. The course of other local symptoms was not different between the two groups. The tolerance was very good.

STUDY 2

Aims

A larger double-blind, randomized, placebo-controlled, pilot study was conducted in patients with common-cold symptoms who were given either 1000 mg vitamin C plus 10 mg zinc or placebo.[c]

Patients and methods

Participants were enrolled by general practitioners and treatment lasted for 10 days. Inclusion criteria and standard assessments were identical to those of Study 1 (Table 2). Participants were required to complete, daily, the same self-evaluation booklet as in Study 2, between day 0 and day 10.

Self-assessment

Patients carried out the same self-assessments as those in Study 1. In addition, in Study 2 the intensities of rhinorrhoea, sneezing and cough were assessed on a VAS of 100 mm (0 mm, no discomfort; 100 mm, maximum possible discomfort).

Investigator assessment

Common-cold symptoms (rhinorrhoea, cough, laryngeal irritation, myalgia, headache, rectal temperature) were evaluated on day 0 and day 11 by the investigator (rectal temperature was measured; other symptoms evaluated with 'Yes' or 'No'). Tolerance was assessed by the incidence of adverse events, recorded by asking open questions.

Results

The study enrolled 64 patients: 25 males and 39 females. The 1000 mg vitamin C plus 10 mg zinc group included 32 patients (15 males, 17 females; mean ± SD age 37 ± 12 years; mean ± SD BMI 24.16 ± 4.56 kg/m^2). The placebo group included 32 patients (10 males, 22 females; mean ± SD age 41 ± 15 years; mean ± SD BMI 23.39 ± 4.24 kg/m^2). No demographic differences were observed between the two groups at baseline. Although 1000 mg vitamin C plus 10 mg zinc reduced the mean duration of rhinorrhoea by 9% when compared with placebo (mean ± SD 5.63 ± 2.54 versus 6.13 ± 2.20 days, respectively), the difference did not reach statistical significance. With

regard to the relief of discomfort due to nasal obstruction, active treatment was more effective than placebo at day 3 (P = 0.05). The discomfort due to rhinorrhoea was also significantly lower in the active treatment than the placebo group at day 3 (P = 0.04).

POOLED ANALYSES

Since the protocols of the two pilot studies were similar,[b,c] individual data were pooled and overall analyses were performed retrospectively.[d] There were 46 patients in the active treatment (1000 mg vitamin C plus 10 mg zinc) group and 48 in the placebo group at day 0 in the pooled analyses. The groups were comparable at day 1 and each participant was diagnosed with an uncomplicated common cold with clear, bilateral, rhinorrhoea.

It was found that the rate of definite relief from rhinorrhoea was significantly higher in the active treatment group than in the placebo group over the 5-day assessment period (P = 0.03, Cox proportional hazards model). The percentages of asymptomatic patients with respect to rhinorrhoea (i.e. definite relief) are plotted in Fig. 1. Active treatment began to show a benefit relative to placebo at day 3, and the difference between groups continued to widen at days 4 and 5. The relief was quicker in the active treatment group, reaching statistical significance (P = 0.001, Cox proportional hazards model at day 4).

The course of the other local symptoms (i.e. relief from laryngeal irritation, cough, sneezing, headache and overall nasal) was not different between the two groups over the 5 days. Nevertheless, the active treatment group had significantly greater relief from

[d]Data on file – Roche Consumer Health: An overview of two randomised placebo controlled studies to determine the efficacy and tolerance of REDOXON ZINC in the treatment of common cold; 1999. Clinical Report No. 16 52 13.

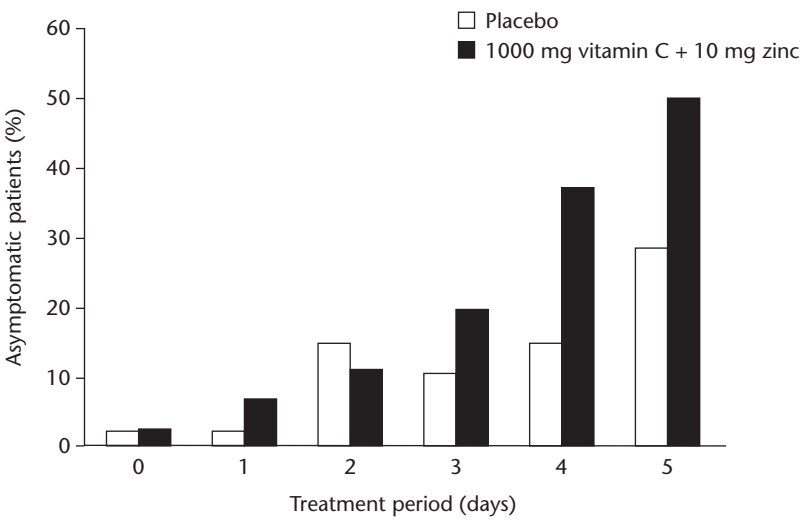

FIGURE 1: Pooled analysis showing the percentage of patients with a common cold who did not experience rhinorrhoea (i.e. asymptomatic) during once-daily treatment with either placebo effervescent tablets or effervescent tablets containing 1000 mg vitamin C plus 10 mg zinc. Rate of definite relief from rhinorrhoea was significantly higher in the active treatment group than in the placebo group over the 5-day assessment period (P = 0.03, Cox proportional hazard model)

some related symptoms, e.g. nasal obstruction at day 2, overall discomfort due to sneezing and overall evolution of eye watering (P = 0.02 for all three symptoms, analysis of variance; data not shown).

Table 3 shows the number of patients in each treatment group, the severity of rhinorrhoea symptoms (very severe, severe, moderate, mild and none) and the percentage of patients with no rhinorrhoea from day 0 to day 5.

In the pooled analyses,[d] active treatment was more effective than placebo in terms of the relief of rhinorrhoea during the first 5 days of treatment. Discomfort due to nasal obstruction, sneezing and eye watering was also less pronounced in the active treatment group. Although the pooled analyses were retrospective, their findings strongly suggest the benefits of combination treatment with 1000 mg vitamin C and 10 mg zinc on the most obvious symptom of upper respiratory infection, namely rhinorrhoea. In both pilot studies,[b,c] a reduction of rhinorrhoea duration was seen (between 9% and 27%), but this reduction did not reach statistical significance compared with placebo. These findings are in contrast to the 2011 Cochrane review, which reported that the therapeutic use of vitamin C after the onset of the common cold did not ameliorate its symptoms.[47] The difference may be due to the short duration of some of the studies in the Cochrane meta-analysis (3 days only),[47] the high dose of vitamin C (1000 mg) used in the two pilot studies and/or the presence of zinc in the active treatment used in these two studies. While supportive data for zinc lozenges and syrup on cold symptoms exist, no such data for zinc administered in the

TABLE 3:
Severity of rhinorrhoea in patients with a common cold receiving once-daily treatment with either placebo effervescent tablets or effervescent tablets containing 1000 mg vitamin C plus 10 mg zinc for 5 days (pooled analyses, two preliminary studies)

	1000 mg vitamin C plus 10 mg zinc, n = 46					
Severity of rhinorrhoea	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Very severe	16	9	4	2	1	1
Severe	14	11	6	4	2	1
Moderate	13	21	21	20	15	12
Mild	2	2	10	11	11	9
None	1	3	5	9	17	23
Asymptomatic patients, %	2.2	6.5	10.9	19.6	37.0	50.0
	Placebo, n = 48					
	Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Very severe	10	5	2	2	1	1
Severe	13	13	9	7	4	5
Moderate	24	27	25	21	20	11
Mild	0	2	5	13	16	18
None	1	1	7	5	7	13
Asymptomatic patients, %	2.1	2.1	14.6	10.4	14.6	27.1
Statistical significance[a]	NS	NS	NS	NS	P = 0.04	P = 0.05

Data presented as number of patients unless stated otherwise.
[a]1000 mg vitamin C plus 10 mg zinc versus placebo; analysis of variance.

form of an effervescent tablet have been reported to date. Thus, these findings for 1000 mg vitamin C plus 10 mg zinc merit further investigation.

The active treatment was very well tolerated in both pilot studies. This is in line with the results from the general literature[26,47,58] and was expected, since the levels of vitamin C and zinc in the product (i.e. 1000 mg vitamin C plus 10 mg zinc) are below the respective upper tolerable levels for chronic intake.[58 – 60]

Health issues in the 21st Century

Old, new or re-emerging infectious diseases continue to be major health issues, despite great advances in medicine (including the establishment of strong healthcare systems in various parts of the world, the development of vaccines and a number of other therapeutic options).[61] Infectious disease is the leading cause of death worldwide and is the third leading cause of death in the USA.[62] In recent decades, pathogenic infectious diseases have emerged including acquired immunodeficiency syndrome, multidrug-resistant tuberculosis, avian[63 – 67] and swine[68,69] flu and tick-borne diseases,[70 – 72] all of which represent substantial global threats to human health.

While multiple factors determine whether an individual will become unwell, the immune system remains the first line of defence against all external pathogens and noxious insults. Immune defences constantly protect the human body against fungi, bacteria, viruses and internal threats such as cancer cells. Over millions of years, the human-defence arsenal has coevolved to meet various attackers and now ranges from simple physical barriers (e.g. skin, mucosa) to sophisticated cells as well as biological and chemical defences (e.g. antibodies, cytokines and free radicals).[73 – 76]

Vitamin C and zinc hold central positions among the micronutrients required to ensure proper immune function.[2,3] Data from clinical studies demonstrate that the separate administration of either vitamin C[47] or zinc[26] results in a reduction in the duration and severity of common-cold symptoms in otherwise-healthy individuals. Vitamin C is typically consumed at doses > 200 mg as a prophylactic measure, and this regimen consistently leads to a reduction in cold duration.[47] There appears to be no preventive effect of vitamin C regarding the incidence of the common cold, with the exception of patients undergoing heavy physical stress (i.e. work, sport, those working in low temperatures).[3,47] Zinc is beneficial for alleviating symptoms of the common cold when administered in the form of lozenges (10 – 23 mg, 5 – 8 times daily) or syrup (10 – 30 mg/day) and taken within 24 h of the onset of symptoms.[26] However, some formulations – particularly lozenges – produce adverse events such as nausea.[26]

The functional interdependence of vitamin C and zinc – and their complementary roles in immune support, resistance to infectious diseases and health maintenance – indicate that there is a strong rationale for using them in combination. The effects of a combination product containing 1000 mg vitamin C and 10 mg zinc were investigated in two preliminary, double-blind, randomized, placebo-controlled clinical studies conducted in patients with symptoms of the common cold. There were a number of reasons for choosing the common cold as a model for infectious disease. First, it is the most common human disease. Secondly, it is self-limited, is in general uncomplicated and is effectively dealt with by the host's immune system. Thirdly, considerable support is available in the literature for the separate use

of vitamin C and zinc against the common cold. In the two preliminary studies reported here, compared with placebo, a non-significant reduction of rhinorrhoea duration in the range of 9 – 27% was observed in patients taking 1000 mg vitamin C plus 10 mg zinc. In the pooled analyses (n = 94), the combination of high-dose vitamin C plus zinc was found to be significantly more effective than placebo in terms of ameliorating rhinorrhoea (the most common symptom of a cold[27]) during the first 5 days of treatment. Results of the pooled analyses also showed that discomfort due to nasal obstruction, sneezing and eye watering also improved with active treatment. In addition, overall, 1000 mg vitamin C plus 10 mg zinc effervescent tablets were very well tolerated. Together, these findings indicate that high-dose vitamin C plus zinc could make a tangible contribution to improving quality of life and speeding up recovery in patients with symptoms of the common cold.

In conclusion, in view of the frequency of the common cold, coupled with the related social and economic costs and the limited treatment options, supplementation with vitamin C and zinc may represent an efficacious measure, with a good safety profile, to help ameliorate the symptoms of this infectious viral disease.

Conflicts of interest

S Maggini and S Beveridge are employed by Bayer Consumer Care Ltd, a manufacturer of multivitamins. M Suter is a retired employee of Roche Consumer Health, a company acquired by Bayer Consumer Care Ltd in 2005.

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