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Effects of Yeast (1,3)-(1,6)-Beta-Glucan on Severity of Upper Respiratory Tract Infections: A Double-Blind, Randomized, Placebo-Controlled Study in Healthy Subjects

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ABSTRACT

Objectives: Each year, adults suffer about two to four upper respiratory tract infections (URTIs), mostly in winter. The aim of the study was to evaluate the effects of brewers' yeast (1,3)-(1,6)-beta-glucan on incidence and severity of upper respiratory tract infections (URTIs).

Methods: Generally healthy men and women ($n = 299$) reporting at least three URTIs during the previous year were randomized to receive either a placebo or 900 mg of yeast beta-glucan daily for 16 weeks during winter. In cases of acute URTI, the severity of URTI symptoms was assessed via the WURSS-21 questionnaire and the Jackson scale, and a clinical confirmation was implemented by the investigator.

Results: Overall, 70 subjects under placebo and 71 subjects under yeast beta-glucan experienced at least one clinically confirmed URTI episode. The global severity using WURSS-21 had been quite similar between the study groups ($p = 0.5267$), whereas during the first days of URTIs the severity was less pronounced in the yeast beta-glucan group. On the episode level, the severity of physical symptoms was significantly lower for all investigated time intervals up to 7 days under yeast beta-glucan (WURSS (Q2-11) (days 1–2: $p = 0.0465$, days 1–3: $p = 0.0323$, days 1–4: $p = 0.0248$, days 1–7: $p = 0.0278$), also confirmed for the Jackson scale). The reduction of severity was accompanied by a significant increase in the joy subscore of the Perceived Stress Questionnaire (PSQ20) ($p = 0.0148$). In addition, there was a reduction of systolic ($p = 0.0458$) and diastolic ($p = 0.1439$) blood pressure.

Conclusion: Subjects supplementing with yeast beta-glucan benefit by a reduced severity of physical URTI symptoms during the first week of an episode, even though the incidence and global severity of common colds could not be altered in comparison to placebo. Furthermore, accompanying benefits in terms of blood pressure and mood were identified. Altogether, yeast beta-glucan supports the immune function.

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Dietary supplements; beta-glucan; upper respiratory tract infection; URTI; yeast

Introduction

Each year, adults suffer from upper respiratory tract infections (URTIs), mostly in the winter season (approximately 2–4 episodes), but few effective treatment options are available (1,2). URTIs may occur in any part of the respiratory mucosa, sometimes affecting all areas (simultaneously or at different times). Most often, URTI symptoms include sneezing, rhinorrhea (runny nose) or blocked nose, headache, and general malaise. Apart from nasal symptoms, half of the affected individuals suffer from a sore throat, and 40% of URTIs are accompanied by coughing (3). Common cold infections are mainly caused by viruses (typically rhinovirus, but also coronavirus and respiratory syncytial virus, or metapneumovirus, enterovirus, and others) (3,4). However, due to mucus layer disruption and dysbiosis within the respiratory tract following the virus infection, bacterial colonization may occur, which further leads to the enhancement of the inflammation process and prolonging of the recovery.

The effectiveness of the immune system is a key for rapid and successful eradication of the pathogen. The immune responses create a complex net of cellular and humoral components that exhibit the ability to detect non-self structures and confer protection against invading microbes, for example, bacteria, viruses, fungi, parasites, and control microbe-related inflammation (5). The cells of the innate immunity system, represented by monocytes, macrophages, natural killer (NK) cells, and granulocytes, monitor the organism, induce their effector function to stop further invasion (colonization of respiratory mucus layer) and alarm other immune cells by the release of chemokines. Classically, the innate immune cells were thought to act completely nonspecifically, without the ability to retain an immunological memory. Recently, this assumption has been challenged. According to the trained immunity concept, innate

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immunity cells, prior to sensitization with certain microbial components (including yeast-derived β-glucans), respond more efficiently, more quickly, and more strongly to viral and microbial infections. Thus, these cells challenged with the β-glucans exhibit a certain "memory" that strengthens their efficiency to fight infections (6,7).

Nutrition and its micronutrients play an important role in the immune system and functional responses (8,9). Besides vitamins and minerals like vitamin C and zinc, the class of beta-glucans is associated with immune-modulating properties (10). Beta-glucans are a heterogeneous group of natural polysaccharides consisting of D-glucose monomers linked by a beta-glycosidic bond. They are important structural elements of the cell wall and may serve as energy storage in bacteria, fungi including yeast, algae, and plants, while they are absent in vertebrate and invertebrate tissue (11,12). Depending on their origin, their linkage of glucose monomer differs. Especially beta-glucans derived from fungi and yeast and consisting of a (1,3)-beta-linked backbone with small numbers of (1,6)-beta-linked side chains are essentially known for their immune-modulating effects (13). It was shown that orally administered beta-glucans induce a cascade of innate and adaptive immune response (11,13,14). Within two independent randomized, double-blind, placebo-controlled clinical trials with brewers' yeast beta-glucan, a reduced incidence of common cold episodes during the cold season in otherwise healthy subjects was documented (15,16). Additionally, clinical studies with bakers' yeast beta-glucan demonstrated beneficial effects with respect to upper respiratory tract infections in different collectives (17,18). The immunomodulatory effects of brewers' yeast beta-glucans have been shown in regard to the stimulation of monocytes to release elevated levels of anti-inflammatory interleukin (IL)-10 (19).

Symptoms of URTIs usually last for a few days (reaching a peak in 1–3 days and clear by 1 week), with a few lingering symptoms such as coughing remaining for a longer period. Although they cause no mortality or serious morbidity, URTIs are responsible for considerable discomfort, sick certificates, and medical costs (1,3). In this context, besides the physical and cost-related impact, they affect the quality of life.

To assess symptoms and dimensions of a URTI, different scales are reported in literature. The Jackson scale, for example, was developed to define and evaluate an experimental common cold. Jackson's index includes eight symptoms, which are rated as absent, mild, moderate, or severe either by self-assessment or with clinician/researcher assistance (20). No items of the Jackson scale evaluate functional or quality-of-life domains. Validity, reliability, and responsiveness have not been thoroughly assessed (21).

Since 2002, a new instrument, the Wisconsin Upper Respiratory Symptom Survey (WURSS), has been developed by Barrett et al. with the aim to measure all significant health-related dimensions that are negatively affected by a common cold. Meanwhile, the questionnaire is a validated instrument available in different extents (WURSS-44, WURSS-21, WURSS-11) (22–24).

Scientific evidence of earlier studies with beta-glucan is questioned owing to the absence of validated instruments (12,16). To overcome these limitations and to get a comprehensive picture of URTI episodes, and taking into account the impact of quality of life, a clinical study was designed using the validated WURSS-21 questionnaire (23) as the primary endpoint. To get a comprehensive picture of all URTI episodes, global severity was calculated, considering incidence, severity, and duration of upper respiratory tract infections.

Materials and methods

Study population

Subjects were recruited via advertisement in local newspapers and public notice boards. Two hundred and ninety-one healthy subjects with reduced immunity defined as susceptibility to upper respiratory tract infections (URTIs) with at least three URTIs during the last year were randomized. Further inclusion criteria were written informed consent to participate, age 18–70 years, and body mass index (BMI) 18.5–32 kg/m^2. The main exclusion criteria were as follows: acute respiratory illness or body temperature $\geq$38 °C at study commencement, chronic respiratory illness including allergic rhinitis or asthma, presence of nasal ulcers/polyps, influenza vaccination within 3 weeks prior to or during study commencement, use of immune-modifying medications or dietary supplements affecting the immune system, pregnancy or nursing, vegan nutrition, or blood donation within 4 weeks prior to or during the beginning of the study.

Study design

This study was a prospective, monocentric, randomized, double-blind, placebo-controlled study with a parallel-group design, conducted in orientation to the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and in compliance with the declaration of Helsinki, and was reviewed by the ethics committee "Landesärztekammer Baden Württemberg" without concerns (F-2016-058, 2016-07-12). The study was registered in DRKS (DRKS00010954).

The nutrition study was performed from October 2016 to April 2017 at BioTeSys GmbH, Esslingen, Germany, an independent study site with focus on nutritional research. The study consisted of a screening visit and in total three routine visits, performed at baseline, after 8 weeks, and at the end of the study after 16 weeks of intervention. Additionally, subjects were advised to come to the study site on the third or fourth day of each URTI episode for clinical confirmation by the investigator.

After having given written informed consent and after completion of the screening procedures, subjects were invited for study visits. Subjects were randomly assigned to the two groups (ratio 1:1). For further details see the study flow in Figure 1.

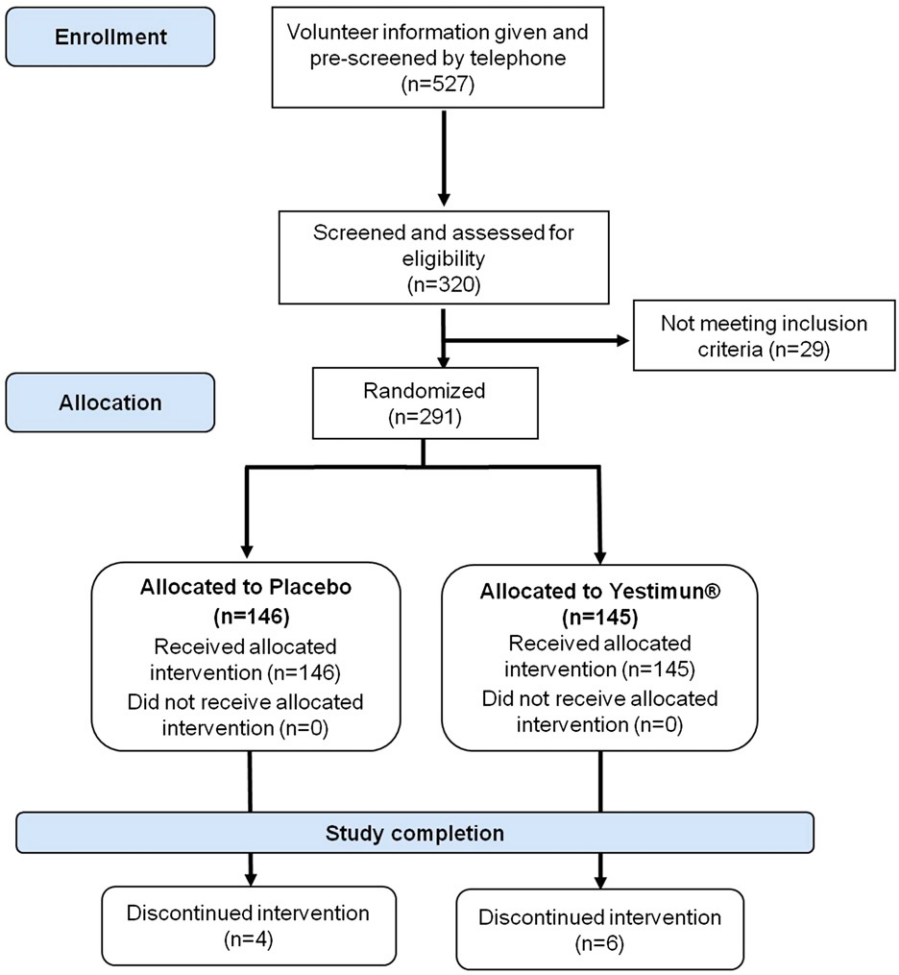

Figure 1. Subject participation and study progress.

During the conduct of the study, subjects were asked not to change their dietary or sports habits. They were not allowed to take any immune-modifying/prophylactic medications or dietary supplements. In case of an acute URTI, subjects were asked to reduce the intake of rescue medication (pain reliever etc.) to a minimum and only to use them in severe cases. Immune-stimulating products including vitamins and similar products were not allowed to alleviate symptoms.

Data collection

In order to assess the negative impact of an acute URTI, the WURSS-21 was used. This survey provides a comprehensive set of questions looking at 10 symptoms of URTI, 9 functional quality-of-life items, 1 global illness severity item (How sick do you feel today?), and 1 item assessing global change (Compared to yesterday, how do you feel?) (22,25). The survey allows subjects to score their symptoms using an 8-point Likert scale (0 = none, 1 = very mild, 3 = mild, 5 = moderate, 7 = severe). The WURSS-21 questionnaire is a validated instrument based on the long version covering 44 items. The construct validity is supported by measures of reliability and responsiveness of subjects (22,23).

As a second instrument for assessment of symptom severity, the Jackson Score questionnaire was used. The Jackson scale was designed to rate the presence of an experimental cold. Eight symptoms—sneezing, headache, malaise, chilliness, nasal discharge, nasal obstruction, sore throat, and cough—were selected for evaluation and graded as absent (0), mild (1), moderate (2), or severe (3) every day for 6 days after inoculation.

Subjects documented their product intake in a diary and stated daily whether they thought they were having a cold or were coming down with a cold. Each day subjects answered “yes,” WURSS-21 and Jackson questionnaires were retrospectively filled in every evening. URTIs were defined as ended when a subject was marked "0 = not sick" twice in a row on two subsequent days, but longest for a period of 14 days. The background of this limited observation was to avoid potential bias associated with very long illness or with people who were overly prone to rate themselves as sick.

Additionally, subjects were asked to come to the study site on the third or fourth day of an episode for clinical confirmation. The investigator judged for each episode whether it was valid or not, based on medical examination, documentation of symptoms via Jackson score, and differential diagnosis.

Adverse events and concomitant medication were recorded in volunteers' diaries throughout the study in accordance with ICH-GCP guidelines.

Definition of a valid trial episode to assess global severity (WURSS) was based on the recommendation of the WURSS description/developer (http://www.fammed.wisc.edu/wurss).

At visits 1 and 3, blood pressure was determined.

As stress might be a trigger or intensifier for susceptibility to URTI episodes, additionally, at visits 1 and 3 the Perceived Stress Questionnaire (PSQ20) was used to monitor stress level and control for possible confounding factors (26).

Further, the SF-12 questionnaire was used, which is a self-administered questionnaire containing 12 items assessing quality of life. For evaluation, two sum scores, a physical (PCS-12) sum score and a psychological (MCS-12) sum score, were analyzed.

Investigational product

Investigational products were 900 mg insoluble pure (1,3)-(1,6)-beta-glucan made from brewers' yeast (*Saccharomyces cerevisiae*) (Yestimun, Leiber GmbH, Germany) or placebo (900 mg maltodextrin) per day over a period of 16 weeks. During manufacturing of Yestimun, the yeast is multiply boiled and washed and therefore contains hardly any vitamins or minerals. In the morning and evening, one capsule containing 450 mg of study product was ingested together with a meal, respectively. Study products were delivered to the study center in prepacked boxes labeled with the respective subject number. Compliance was determined by counting residual returned capsules and considered sufficient if >80 and <120% of the correct quantity of the investigational product was consumed.

Subjects and researchers were blinded to the interventions until the final database lock.

Outcome measures

The primary objective of the present study, the global severity, was defined as the area under the time severity curve (AUC). AUC was calculated applying the trapezoidal rule, with the y-axis, defined by daily WURSS-21 scores, and the x-axis, defined as duration of illness, starting with the first symptoms and ending when the participant first indicated that he or she was no longer sick. There had to be at least two symptom-free days to define a new episode. Episodes occurring in the first week of supplementation were not considered. Furthermore, incidence and secondary severity scores were evaluated.

Statistics

The nutritional study was powered to detect 30% differences in global severity (AUC_{global}) between placebo and beta-glucan. Based on data provided by Barrett et al. (23) using global severity assessed as area under the curve with mean AUC for the WURSS-21 of 310.1 with a standard deviation of 251.0, a sample size of 115 per group provided approximately 80% power to detect a 30% difference between placebo and beta-glucan by using a significance level of 5%. Considering a dropout rate of 20%, 288 (1:1) subjects should have been included in the study.

The primary endpoint global severity score was evaluated by using zero-inflated regression models to control for potential confounders and adjust for those who do not report any cold. These models take into account both logistic (incidence) and linear (global severity) data. As covariates, age, sex, smoking status, and body mass index were used. As data were skewed, Box–Cox transformation was used in these models. The model was also applied for the secondary outcomes. Additionally, unadjusted between-group comparisons were performed by the Wilcoxon rank sum test, especially when evaluating only diseased subjects. Specified endpoints were additionally investigated for subgroup by gender. If appropriate, data sets were analyzed with respect to all subjects, analyzed with respect to only diseased subjects, and with respect to occurred episodes. Data are presented for the ITT population. All statistical tests were performed two-sided. A significance level of 0.05 was applied; p values of 0.05–0.1 are reported as a trend. The primary variable was used for confirmatory testing; all other variables were considered as secondary variables, which were evaluated as exploratory.

Results

Subject characteristics

In total, 320 subjects were screened for eligibility, of which 291 were enrolled in the study. Two hundred and eighty-one subjects finished the study successfully. Three dropouts occurred prior to "last subject in"; therefore, these subjects were replaced. Eight dropouts occurred prior to visit 2 and two prior to visit 3 (4 of placebo and 6 of Yestimun group [yeast beta-glucan]). Reasons for dropouts were adverse event (2), serious adverse event (3: Hanta virus infection, coronary, hospitalization with unknown indication), personal reasons (2), and lost-to-follow-up (3).

Baseline characteristics of subjects are summarized in Table 1. The baseline characteristics are comparable between groups with exception of the frequency of smokers. Overall, frequency of smokers was rather small (8.9% of total population) but there were by coincidence significantly more smokers in the placebo group than in the beta-glucan group ($p = 0.0016$, Fisher's exact test). As inclusion criterion the number of cigarettes was limited to a maximum of 15 cigarettes per day. On average, smokers of the placebo group indicated consuming 5.9 cigarettes/day and in the beta-glucan group 4.7 cigarettes/day.

Table 1. Baseline characteristics of subjects.

	Yeast beta-glucan (Yestimun)	Placebo
N	145	146
Sex (m/f)	47/98	47/99
Age (year)	37.6 ± 14.3	40.5 ± 16.4
BMI (kg/m^2)	23.8 ± 3.3	23.2 ± 3.0
URTIs (number/year)	4.3	4.3
Regular sports (*n*)	106	109
Smoker (*n*)	5	21

Note. URTI: upper respiratory tract infection.

Table 2. Distribution of incidences of clinically confirmed episodes (number and %).

	Placebo		Yeast beta-glucan	
URTI incidence of clinically confirmed episodes	Number (*n*)	(%)	Number (*n*)	(%)
No episodes	76	52.1	74	51.0
1 episode	45	30.8	53	36.6
2 episodes	21	14.4	11	7.6
3 episodes	3	2.1	5	3.4
4 episdoes	0	0.0	2	1.4
5 episodes	1	0.7	0	0.0
Total	146	100.0	145	100.0

Note. URTI: upper respiratory tract infection.

Incidence

Incidence of confirmed episodes was similar between study groups (101 episodes under placebo reported by 70 subjects and 98 episodes under yeast beta-glucan reported by 71 subjects); see Table 2.

The mean number of episodes per subject with at least one URTI was lower in the yeast beta-glucan group compared to the placebo group: 1.38 (95% CI: 1.2–1.56) vs. 1.44 (95% CI: 1.27–1.61), $p = 0.2918$, but did not reach statistical significance. Worth mentioning is that 53 subjects in the yeast beta-glucan group and 45 subjects in the placebo group had only one URTI episode, whereas the remaining concerned subjects experienced more than one URTI during the assessment period. Additionally to these clinically confirmed episodes, short-lasting episodes were recorded by volunteers that were not clinically confirmed at study site but confirmed by WURSS-21 criteria (additional 59 episodes); see Materials and methods section.

Considering all episodes confirmed by WURSS-21, a trend of lower mean number of colds can be seen with yeast beta-glucan in comparison to placebo (1.43 (95% CI 1.27–1.59) vs. 1.63 (95% CI: 1.43–1.82), $p = 0.0994$).

Investigation of URTI incidence by gender showed that 53.2% of men in the placebo group and only 38.3% of men receiving yeast beta-glucan experienced a clinically confirmed episode. In contrast, in women the overall URTI incidence was comparable. However, in women experienced at least one episode, the URTI incidence of episodes according to WURSS was by trend higher in the placebo group (1.71 ± 0.98) than in the yeast beta-glucan group (1.41 ± 0.69) ($p = 0.0845$).

Severity

The mean global severity score of confirmed episodes using the WURSS-21 questionnaire analyzing all randomized participants was comparable between the yeast beta-glucan group with 188.6 (95% CI: 133.4–243.7) and the placebo group with 182.2 (95% CI: 135.8–228.6) ($p = 0.5267$, zero-inflated multivariate regression model) and showed no statistical difference.

Further investigations evaluating severity on individual URTI episode level revealed that in the yeast beta-glucan receiving group, the symptom severity was less pronounced during the first days of episodes. For these evaluations, one extreme outlier was excluded from analysis. In Figure 2 the severity-time course of all episodes is depicted, exemplarily for the Jackson score. The observations were also confirmed for the physical symptoms WURSS (Q2-11) (data not shown).

Severity was evaluated for different time intervals up to 7 days of an episode (days 1–2, 1–3, 1–4, and 1–7). On an episode level, severity of physical symptoms was significantly lower for all investigated time intervals up to 7 days in the yeast beta-glucan group in comparison to the placebo group (WURSS [Q2–11]) (days 1–2: $p = 0.0465$, days 1–3: $p = 0.0323$, days 1–4: $p = 0.0248$, days 1–7: $p = 0.0278$), Figure 3). This finding is also confirmed for the Jackson score (days 1–2: $p = 0.0553$, days 1–3: $p = 0.0392$, days 1–4: $p = 0.0347$, days 1–7: $p = 0.0348$) (data not shown).

Also, episodes that lasted more than 7 days ($n = 40$ placebo group, $n = 43$ yeast beta-glucan group) showed in the episodes' first week a significantly lower severity during yeast beta-glucan intervention compared to placebo, as assessed by physical symptom dimension of WURSS (days 1–2: $p = 0.0128$; days 1–3: $p = 0.0036$; days 1–4: $p = 0.0040$; days 1–7: $p = 0.0259$) (Figure 4), and the same applies to Jackson score (days 1–2: $p = 0.0160$; days 1–3: $p = 0.0081$; days 1–4: $p = 0.0095$; days 1–7: $p = 0.0271$) (data not shown). Within this subgroup, also the total score WURSS-21 was significantly lower in episodes with the yeast beta-glucan in comparison to the placebo for the assessment periods days 1–2 ($p = 0.0421$), days 1–3 ($p = 0.0189$), and days 1–4 ($p = 0.0287$) (data not shown).

In case a subject experienced several episodes, severity scores were summed on subject level, and severity of URTI symptoms with focus on physical symptoms WURSS (Q2–11) over defined time intervals was calculated. Severity was significantly lower in the yeast beta-glucan group in comparison to the placebo group for the time intervals up to 4 days (days 1–2: $p = 0.0379$, days 1–3: $p = 0.0276$, days 1–4: $p = 0.0341$, days 1–7: $p = 0.1261$), which was confirmed by the results obtained in the Jackson questionnaire (days 1–2: $p = 0.0423$; days 1–3: $p = 0.0335$; days 1–4: $p = 0.0360$; days 1–7: $p = 0.1010$).

Considering the symptom burden of physical symptoms over the whole episode period in subjects experiencing clinically confirmed episodes, the findings just described are supported with a higher severity under placebo intervention in comparison to beta-glucan intervention, but without reaching statistical significance: placebo: 213.7 (95% CI: 173.1–254.2), yeast beta-glucan: 181.9 (95% CI: 146.8–217.0), $p = 0.2089$.

There was a high consistency between assessment instruments, indicating highly significant correlations (WURSS-21 score vs. Jackson score on all episode days of clinically

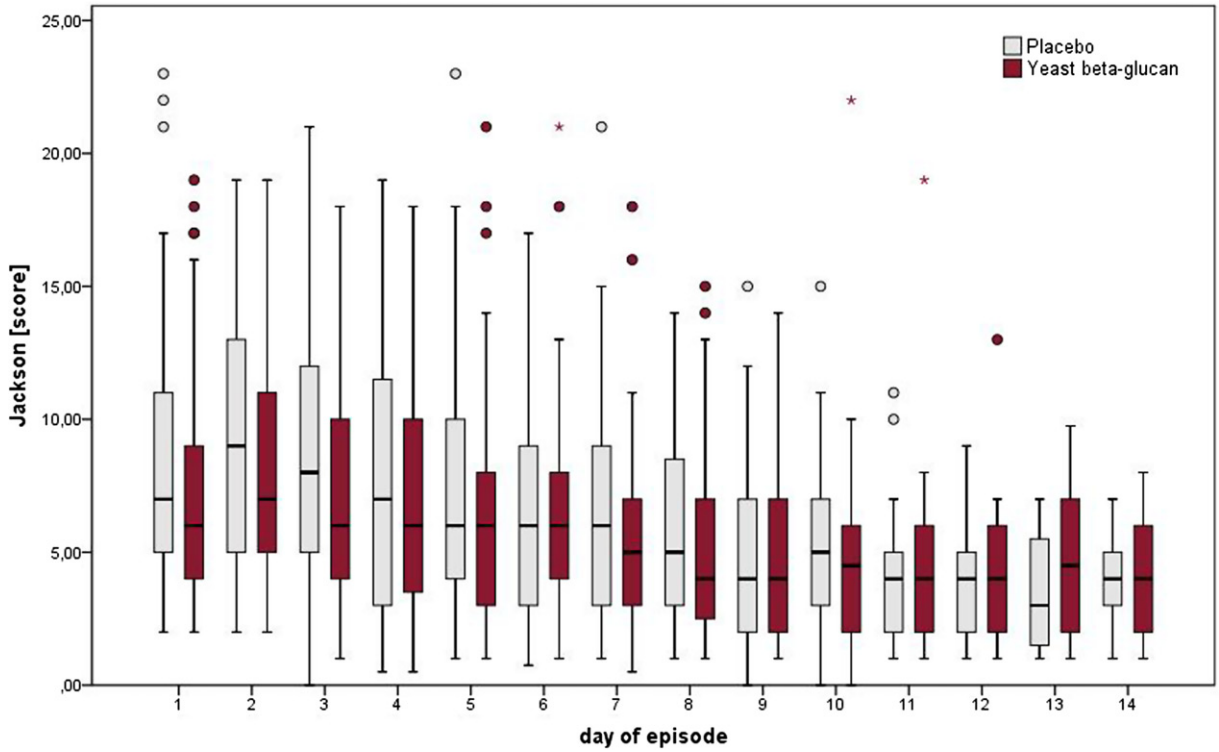

Figure 2. Distribution of daily Jackson scores of clinically confirmed episodes (box and whiskers) in placebo and yeast beta-glucan group on days with episodes.The x-axis: number of day of episode; y-axis: Jackson score; dots: outliers, more than 1.5 times the interquartile range; stars: extreme outliers: more than 3 times the interquartile range.

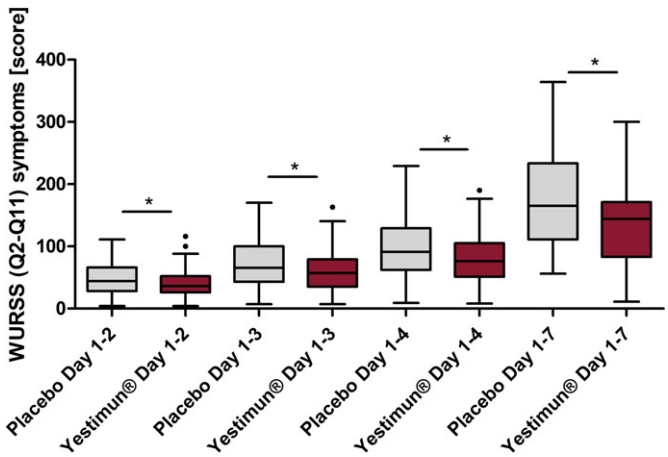

Figure 3. Sum of the WURSS physical symptoms (Q2–11) of clinically confirmed episodes on days 1–2, days 1–3, days 1–4, and days 1–7 are shown according to intervention assignment. Full clinically confirmed episodes corresponding to evaluation time were considered. The sum of symptom score over defined time period was calculated. Dots: outliers, more than 1.5 times the interquartile range; $^{*}p < 0.05$.

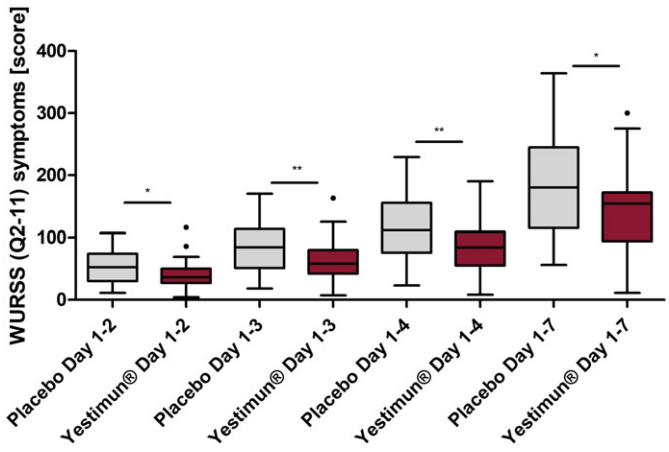

Figure 4. Sum of the WURSS (Q2–11) focusing on physical symptoms of clinically confirmed episodes in subgroup episodes >7 days on days 1–2, days 1–3, days 1–4, and days 1–7 are shown according to intervention assignment. Full clinically confirmed episodes corresponding to evaluation time were considered. The sum of symptom score over defined time period was calculated. Dots: outliers, more than 1.5 times interquartile range; $^{*}p < 0.05$, $^{**}p < 0.01$.

confirmed episodes, $r = 0.8787$, $p < 0.0001$, Spearman). The correlation is even higher with the physical symptom subscore of WURSS-21 (Q2–11) compared to the Jackson questionnaire ($r = 0.9038$, $p < 0.0001$, Spearman). Due to the different scales used in the questionnaire, the WURSS seems to be the more sensitive to depict differences over time.

Correlation of the two different domains of the WURSS questionnaire (physical symptom domain and quality of life domain) indicated a significant correlation ($p < 0.0001$); however, the Spearman correlation coefficient was minor, $r = 0.7876$. In consequence, symptom severity has an impact on quality of life, but also a low symptom scale can show a high burden of quality of life. This might explain why the subscore quality of life showed no differentiation for the various assessment periods between the intervention groups over the investigated time course.

Duration

The number of days spent being ill over the intervention period in subjects with at least one clinically confirmed

Table 3. Scores of PSQ20 subscore "joy" for baseline and end of intervention.

	PSQ20, Joy, placebo		PSQ20, Joy, yeast beta-glucan (Yestimun)	
	Baseline	End of intervention	Baseline	End of intervention
Mean	65.3 (95% CI 62.3–68.2)	62.9 (95% CI 59.6–66.2)	63.9 (95% CI 60.6–67.2)	65.7 (95% CI 62.2–69.3)

Note. PSQ: perceived stress questionnaire (26).

episode did not differ between yeast beta-glucan and placebo (10.8 and 10.7 days, respectively, $p = 0.6271$).

The amount of days staying at home (sick-leave days) showed no significant difference between the intervention groups (placebo: 139 days, yeast beta-glucan: 119 days, corresponding to an average of 1.99 sick-leave days per subject in the placebo group and 1.68 sick-leave days in the yeast beta-glucan group, $p = 0.4547$).

PSQ20

Overall perceived stress was comparable between study groups (V1: placebo: 30.7 ± 14.7, yeast beta-glucan: 30.0 ± 16.3), which also applies to the subscores. Over the study period, a slight but significant reduction of the joy score was reported in the placebo group ($p = 0.0473$). In contrast, there was a slight increase in the yeast beta-glucan group, thus resulting in significantly different changes between groups over the study period ($p = 0.0148$). For all other subscores and also the overall score there were no significant changes within and between study groups (Table 3).

SF-12

Baseline conditions in both aggregate summary measures were comparable between the placebo group and the yeast beta-glucan group (PCS12: $p = 0.4860$; MCS12: $p = 0.7135$).

Over the study period there was no change in the physical component score PCS12 within and between groups. However, in the placebo group the MCS12 score significantly declined between visit 1 and visit 3 (V1: 52.6 ± 6.6, V3: 51.4 ± 6.9, $p = 0.0011$). On average, also in the yeast beta-glucan group, there was a slight reduction in the MCS score (V1: 52.4 ± 6.0, V3: 52.1 ± 7.0); thus, possibly the winter season with shorter days might have influenced the mental health perception negatively. However, this was more pronounced in the placebo group, and comparing the delta changes between the placebo group and yeast beta-glucan group confirmed the significant differences between groups ($p = 0.0375$).

Blood pressure

Blood pressure was measured as a safety parameter. No safety concerns were identified. Subjects with elevated values were advised to clarify with their practitioner. Additionally, data were evaluated for effects of beta-glucan. As blood pressure values were measured only once at the study site, an outlier analysis was performed prior to evaluation of data. Data indicate a significant reduction of systolic blood pressure ($p = 0.0458$) in the yeast beta-glucan group in comparison to the placebo group (yeast beta-glucan mean values: baseline: 128/80, end of intervention: 122/74; placebo mean values: baseline: 128/80, end of intervention: 126/76; diastolic $p = 0.1439$). Evaluating data in subgroup of subjects with systole <130 and ≥ 130 mm Hg at baseline confirmed the findings especially in the subgroup with elevated blood pressure: (yeast beta-glucan mean values: baseline: 143/87, end of intervention: 133/81; placebo mean values: baseline: 143/86, end of intervention: 137/81 (systolic $p = 0.0394$; diastolic $p = 0.2791$). In the subgroup with normal blood pressure with systolic levels up to 130 mm Hg, the reduction of systolic and diastolic levels was more pronounced in the yeast beta-glucan group but not reaching significance (systolic $p = 0.3169$; diastolic $p = 0.3053$).

Safety evaluation

During intake of study preparations, in total 454 adverse events were reported by 116 volunteers in the placebo group and 502 adverse events by 118 volunteers in the yeast beta-glucan group. From these adverse events (AEs), 5 were classified as serious adverse events (SAE). Three of them led to drop-out of subjects.

From the reported AEs, most frequently URTIs were reported, confirming the susceptibility of the study collectively to common colds, followed by headache and gastrointestinal disorders.

Of the in total 956 reported adverse events during the intervention phase, only 5 subjects reported related adverse events (1 subject of the placebo group reporting 3 adverse events and 4 subjects of the yeast beta-glucan group reporting 11 adverse events). Related adverse events were predominantly gastrointestinal disorders like abdominal bloating (3×, placebo), diarrhea (3×, by 1 subject of yeast beta-glucan group), and nausea (7×, reported by 2 subjects in yeast beta-glucan group). Furthermore, one case of urticaria over the whole body was reported but classified as unlikely (1× yeast beta-glucan group), as the reason for this condition was—with high probability—a side reaction of amoxicillin intake. All other adverse events were not related.

Tolerability was quite "good," with only 7 volunteers of the placebo group and 6 volunteers of the yeast beta-glucan group rating the tolerability as "slightly unpleasant." Predominantly, the size of capsules and some minor gastrointestinal disorders were the reasons for these ratings.

The study results confirm the safety and good tolerability profile of yeast beta-glucan (Yestimun).

Discussion

Immunomodulatory effects of beta-glucan have been demonstrated in animal studies and *in vitro* models (27–29).

Binding of beta-glucans to dectin-1 or to toll-like receptors (TLR)-2/4 induces a cascade of innate (direct) and adaptive (indirect) immune responses (29,30). There is also promising evidence from *in vivo* studies with yeast beta-glucan on endpoints of immune function related to defense against pathogens in the upper respiratory tract (18,31). The current study, performed in the winter season, provides evidence for a significantly reduced symptom burden of an upper respiratory tract infection (URTI) during the first 7 days of an episode. During the 16 weeks of a placebo-controlled double-blind intervention study with Yestimun (yeast (1,3)-(1,6)-beta-glucan), incidence, severity, and duration of URTI episodes were assessed and global symptom burden was evaluated for each episode by the subject using the validated WURSS-21 instrument. A valid URTI episode was predefined according to Barrett et al. (21) and required a clinical confirmation by the investigator. The WURSS-21 instrument assesses URTI symptoms and the effects of symptoms on activities of daily life. According to our study, it seems that physical symptom severity has a great effect on the quality of life. However, a low symptom burden can already have a great impact on the quality of life. It could be rather the character of physical symptoms that affects the quality of life to a different extent, thus possibly covering intervention effects on physical symptoms in the current study. This might be one of the reasons why the primary endpoint "global severity" assessed by physical symptoms and their impact on the quality of life showed no statistical difference between the two investigated groups in the present study ($p = 0.5267$). This was in contrast to the significant reduction of physical symptoms in the first 7 days of an episode in the beta-glucan group in comparison to the placebo group as assessed by the WURSS subscore of physical symptoms and the Jackson score. The length of an episode might be influenced very subjectively and depend on the nature of infectious insult. Most clinically confirmed episodes resolved within a week (58.3%); however, in some of the volunteers an episode lasted much longer. Within the study, the observation period of an URTI was limited to 14 days. Longmier et al. found no significant association between participant and clinician prediction of severity or duration from an initial WURSS assessment at the beginning of an episode (32). The individual length of an episode might have confounded the evaluations of the primary endpoint in the present study.

The benefit of beta-glucan in symptom reduction stays in line with previous studies (16). In a study by Graubaum et al., beta-glucan significantly reduced the typical cold symptoms "sore throat," "hoarseness and/or cough," and "runny nose" at the beginning of an episode and total symptom scores were significantly lower during the first 5 days of an episode (12). In addition, in the study of Auinger et al., consumption of yeast beta-glucan caused a milder progression of the severe common cold episodes. Overall, the mean symptom score was 15% lower in the beta-glucan group in comparison to the placebo group ($p = 0.125$) (16). In contrast, Fuller et al., who investigated yeast derived beta-glucan in older subjects (age 50–70 years) using the WURSS-21 questionnaire, reported no effect of beta-glucan supplementation on symptom severity with the simultaneous decrease in URTI incidence (33). As there was no discriminated evaluation of data for the subscore of physical symptoms and impact on the quality of life, possible effects on the physical symptoms might have been covered. There was a trend to fewer illness days during beta-glucan intervention in comparison to placebo (33,34). Similarly, a positive impact of beta-glucan on incidence was reported by McFarlin et al. and Talbott et al. (17,35), who showed that the number of symptomatic days in marathon runners could be significantly reduced by the intake of beta-glucan after strenuous exercise. In contrast, in a study with healthy adults, a 12-week intervention phase did not show any significant differences in the incidence of symptomatic respiratory tract infections between the study groups (31). Also, the study from Nieman et al., who investigated oat beta-glucan in endurance athletes, showed no statistical difference in URTI incidence (36). In the study of Graubaum et al., the beta-glucan group had significantly more subjects without incidences of common cold than the placebo group (15.6% vs. 2%, respectively) (12). However, the incidence rate in diseased subjects was statistically not different. The study by Auinger et al. reported a 25% reduction of symptomatic common cold infections in the beta-glucan group in the per-protocol population (16). In summary, the effects of beta-glucan on incidence rate of URTI remain controversial.

In the current study, the number of valid episodes was comparable between the beta-glucan group and the placebo group, and there was no statistical difference in incidence rates. Therefore, the supplementation with yeast beta-glucan had only minor effects to completely prevent URTIs. However, worth mentioning is the finding that 53 subjects (74.6% of subjects with at least one URTI episode) in the yeast beta-glucan group and 45 subjects (64.3% of subjects with at least one URTI episode) in the placebo group had only one but no further URTI episode. This underlines the ability of beta-glucan to restore immune function in a diseased population.

Considering all episodes confirmed by WURSS-21, a trend to a lower mean number of colds could be seen on behalf of yeast beta-glucan (1.43 (95% CI 1.27–1.59) vs. 1.63 (95% CI: 1.43–1.82), $p = 0.0994$).

In the study, WURSS-21 and the Jackson questionnaire were used for the evaluation of URTI. The physical symptom part of the WURSS-21 questionnaire is comparable to the Jackson questionnaire. However, the rating scale to assess symptoms is different. Data indicate a high correlation between instruments and thus underline the consistency and validity of assessments by subjects. The high correlation of WURSS-21 versus Jackson was already confirmed during the validation studies for the WURSS-21 questionnaire (Pearson correlation $r = 0.849$). However, the WURSS-21 instrument is more sensitive instrument, as a 10-point change of the WURSS-21 score corresponds to a 1.8-point change on the Jackson score. Thus, lower sample sizes are needed to detect minimal important differences in a clinical study (25).

The incidence of URTI greatly depends on the virus and bacterial load to which subjects are exposed, next to the susceptibility of the immune system. The virus and bacterial load and the grade of aggressiveness depend on climatic conditions, including humidity and temperature, and can greatly differ from winter to winter. Based on the study of Auinger et al., slightly higher incidence rates were expected. In their ITT population, an incidence rate of 1.04 URTIs per subject in the beta-glucan group and 1.27 URTIs per subject in the placebo group was reported, whereas in our study the incidence of clinically confirmed episodes was 0.69 ± 0.88 in the placebo group and 0.68 ± 0.87 in the yeast beta-glucan group; 43.2% of subjects in the placebo group and 40.7% of subjects in the yeast beta-glucan group did not experience any cold episode which is in line with the findings of Denlinger et al., who reported that 49.8% of subjects did not experience at least one cold episode during a 12-week intervention period despite a very susceptible study collective with asthma patients (37).

Contrary to the assumption that women are more resistant to viral infection than men (38), in our study women of the placebo group experiencing at least one URTI episode had a higher severity and duration of episodes in comparison to men. However, the conclusion is slightly limited due to the small sample size of 45 women and 25 men fulfilling the criterion of at least one confirmed episode. From a scientific point of view, the gender difference is explained by estrogens and progesterone, which modulate immune function, and thus immunity is influenced by the menstrual cycle. The study of He et al. in a collective of male and female athletes also showed that women had more URTI days and their episodes lasted several days longer than those in men (39). Although there was no significant reduction of sick-leave days under beta-glucan intervention in comparison to placebo in the current study, other studies demonstrated substantial effects. None of the subjects during intervention with beta-glucan missed work or school due to colds, while subjects with colds in the placebo group missed on average 1.38 days, $p = 0.026$, as reported by Feldman et al. (31).

Overall, the reduction of severity under beta-glucan intervention was accompanied by a significant increase of the joy subscore of PSQ20 questionnaire ($p = 0.0148$) in comparison to placebo. Additionally, the MCS of the SF-12 questionnaire showed a significantly greater decrease in the placebo group compared to the yeast beta-glucan group ($p = 0.0375$), suggesting that subjects who had less episodes or fewer symptoms exhibit a higher joy rate or are less influenced by "winter mood." Similar findings of improved mood state also occurred in other studies investigating effects of beta-glucan on mood state in stressed women and marathon athletes (17,18).

As one mode of action of beta-glucan, selective IL-10 production from M2 polarized macrophages is being discussed (40,41). This was not only reported for *in vitro*, but also in dogs with inflammatory bowel disease (IBD) (42). Furthermore, increased IL-10 levels were measured after beta-glucan in overweight subjects (19,41). In the study of Mosikanon et al., the increase of IL-10 was also associated with a significant reduction of pro-inflammatory cytokines IL-6 and the tumor necrosis factor (TNF)-α. Bekkering et al. (6) showed that priming human monocytes with beta-glucan for 24 h, following a 5-day resting phase and restimulation with bacterial agents, leads to significantly higher levels of anti-inflammatory cytokines (IL-10, IL-1Ra) in comparison to the monocyte cultures only exposed to bacterial agents. This phenomenon may explain a positive effect of beta-glucan observed in the IBD animal model, as well as the results presented here. The pathoetiology of most of the URTIs involves the induction of inflammatory processes that occur within respiratory mucosa at the site of infection, but it also indirectly affects immune cells in the circulation. Following this concept, beta-glucan administration may train the monocytes to react more quickly and more efficiently by the robust production of anti-inflammatory cytokines that facilitate the blockage of the inflammatory process and the severity of the symptoms.

In very recent publications, an increase of IL-10 is linked to the prevention of depression. Studies with probiotics indicated the attenuation of stress-related activation of dendritic cells while increasing IL-10+ regulatory cells (43). Via the gut–brain axis, protection against stress-induced behavior is reported. In the light of this research, IL-10 might be one of the central links to support the effects of beta-glucan on mood and joy.

Next to the immunomodulating effects, significant systolic blood pressure lowering effects were seen for beta-glucan in comparison to placebo, which was especially pronounced in a subgroup of subjects with slightly elevated blood pressure at baseline (systolic $\geq$130 mm Hg). Similar observation was found in overweight subjects in Thailand (19) after a 6-week intervention of beta-glucan. Such blood pressure lowering effects were also reported for oat beta-glucan in obese subjects with elevated blood pressure. The results are discussed in the context of reduced insulinemia (44). Again, IL-10 is negatively associated with insulin resistance. Thus, IL-10 not only plays a crucial role in the innate immune system, but seems to play also a decisive role in metabolism explaining the different health benefits of beta-glucan.

Limitations

The common cold syndrome is characterized by high variability. Within the general healthy population there is a range of immune competency due to genetic differences, age, nutritional deficiencies, and lifestyle habits. The impact and interaction of all these factors is hardly understood. While there are indisputable links between infection, inflammation, symptoms, and quality-of-life impact, the degree of association between these domains is limited (21). A significant correlation with laboratory-assessed measures is described for WURSS and the Jackson questionnaires (21). Within the current study, the outcome measures were focused on the functional parameters, incidence, duration, and severity. No biomarkers were assessed during the study.

Therefore, no statements based on immune competence of the study collective at study commencement can be made. Furthermore, one limitation of the outpatient setting with healthy subjects is that the viral burden and the kind of viruses/bacteria causing the symptoms were not investigated. Upper respiratory infections can be caused by many different agents, including adenovirus, coronavirus, influenza virus, rhinovirus, and so on. According to Barrett et al., even the best laboratories still fail to identify etiological agents in anywhere from 25% to 75% of colds tested (25). Conversely, about 25% of those with documented infections fail to develop symptoms. The nature of the virus might have an impact on incidence, severity, and duration of URTI episodes, which was not standardized in the study and thus could affect study results but reflects the normal daily life situation. These environmental confounding factors might be one reason for the different outcomes of the clinical studies performed with beta-glucan. Nonetheless, they all in common report a positive impact on endpoints of immune function to defend against pathogens in the upper respiratory tract.

Another aspect for limitation is the difference in the number of smokers between the two groups. There were 21 subjects in the placebo and only 5 subjects in the beta-glucan group who stated they were regular smokers ($p = 0.0016$). All of these persons smoked at most 10 cigarettes per day. Due to these limited smoking habits of participants, a possible impact on URTI incidence is expected to be rather low. From the 21 smokers of the placebo group, only 10 experienced at least one URTI, which was comparable to the non-smoker placebo group with 60 out of 125.

Immunomodulatory effects of beta-glucan might differ depending on the linkage of glucose monomers. Especially beta-glucans derived from fungi and yeast and consisting of a (1,3)-beta-linked backbone with small numbers of (1,6)-beta-linked side chains are essentially known for their immune-modulating effects (13). Differences of extracts, however, might also contribute to the different outcome parameters and only allow comparison of comparable sources. In the literature, the research is focused on yeast beta-glucan. Research on oat beta-glucan with respect to URTI is rather limited and showed a negative outcome (36), whereas a study with beta-glucans from mushroom *Pleurotus ostreatus* showed significant reduction of the incidence of URTI symptoms (45).

To what extent placebo effects might have additionally confounded the study results is difficult to assess. However, in a study of Barrett et al. placebo effects in common cold treatment was investigated, identifying only modest placebo effects (46). Subjects who were randomly assigned to pills reported illness duration that was on average 0.16 to 0.69 days shorter and 8% to 17% less severe in comparison to those assigned to no pills. Effects were statistically not significant.

Conclusion

Subjects supplementing over a period of 16 weeks with beta-glucan benefit by a reduced severity of physical URTI symptoms during the first week in case of an episode, even though the incidence and global severity of common colds could not be altered in comparison to the placebo. Furthermore, accompanying benefits on blood pressure and mood were identified. In summary, especially during the most intense infection season, yeast beta-glucan supports the immune function to defend against pathogens in the upper respiratory tract.

Disclosure Statement

The authors declare no conflict of interest.

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