

Treatment of Recurrent Respiratory Tract Infections With a Polyvalent Bacterial Lysate: Results of an Open, Prospective, Multinational Study

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ABSTRACT

This multicenter, open study, carried out in 14 countries in Europe, Latin America, and Asia, recruited 4965 patients suffering from recurrent respiratory tract infections to investigate the safety and acceptability of the oral bacterial lysate immunomodulator LW 50020. Patients remained in the study for 4 months (two 4-week courses of LW 50020 separated by a 28-day treatment-free interval and follow-up). The incidence of all adverse events was 7.2%; that of adverse drug reactions was 0.6%. Adverse drug reactions were mild to moderate and not more frequent in the large subgroup of patients (77%) with a known history of allergies or underlying respiratory diseases; however, the incidence of adverse events in this subgroup was twofold higher than in the study population as a whole, probably indicating a generally increased vulnerability to disease. No clinically relevant changes in laboratory variables followed treatment. Comparison of the first study period (first course of LW 50020 and drug-free interval) with the second

study period (second course of LW 50020 and follow-up) showed an overall reduction of at least 50% in the number, severity, and duration of respiratory tract infections, the number of antibiotic and symptomatic treatments, and the number of days absent from school or work. Tolerability and acceptability were assessed as good or very good in 99% of patients who completed the study.

Keywords: recurrent respiratory tract infections; oral immunostimulation; bacterial lysate; safety study; large-scale study

INTRODUCTION

Respiratory tract infections (RTIs) are among the most frequently encountered diseases in children and adults worldwide. The accompanying morbidity continues to burden society, and the economic consequences of even relatively benign acute RTIs are substantial. In the United States, consumers spend about \$2 billion per year on over-the-counter medications, and the total annual cost of acute RTIs managed in outpatient settings is estimated to exceed \$10 billion.¹

Environmental and social factors, such as the standard of living and indoor and outdoor pollution, influence the frequency of RTIs,^{2,3} which is similar in developing and developed countries. The case-fatality rate, however, is much higher in developing countries, especially in children.^{1,4}

Both viruses and bacteria cause or aggravate respiratory diseases, inducing acute symptoms. Rhinoviruses, responsible for the common cold, occur most frequently in adults and are responsible for a substantial number of physician consultations.⁵ Influenza and parainfluenza viruses, also common in adults, can destroy the epithelium of both the upper and lower respiratory tracts, facilitating bacterial infections.⁶

In children, most RTIs are caused by viruses but are complicated by bacterial superinfections that take the form of acute otitis media, tonsillitis, and bronchitis. Over the years, susceptible children experience more infections that last longer.⁷ Bacteria determine the clinical picture and outcome in recurrent acute sinusitis in children and adults. In most cases, sinusitis is preceded by a recent upper RTI, usually of viral origin.⁶

Viral and bacterial infections aggravate asthma and chronic bronchitis. In children and adults with underlying asthma, RTIs commonly provoke an increase in symptoms.^{8,9} Bacterial RTIs may be involved in the development of bronchospasm and the progression of chronic obstructive pulmonary disease.¹⁰ In patients with chronic bronchitis who have frequent episodes of acute bronchitis, intercurrent viral infections are suspected to precipitate the acute symptoms by altering the host response to bacterial colonization.^{11,12}

Paoletti and his group investigated the consequences of RTIs in a general population.¹³ Individuals with recurrent infections during both childhood and adolescence-adulthood had the highest prevalence of respiratory symptoms and diseases and the lowest lung function values, regardless of smoking habits.

The majority of infections are acquired by way of the upper and lower respiratory tract mucosa.¹⁴ Patients with increased susceptibility to RTIs seem to have an impaired

mucosal immune response. A compromised host with even slight defects in the defense system may become sensitive to infections with microorganisms that are not normally pathogenic.⁶

Conventional symptomatic treatment and use of antibiotics do not prevent recurrent RTIs, therefore leaving these infections as a risk factor for respiratory diseases. Classic vaccines are not available for most pathogens that induce RTIs.

Investigations suggest that the oral immunomodulator LW 50020 (Luivac, Paspat[®] oral) exerts its pharmacodynamic effects by stimulating the mucosal immune system.

Antigenic priming of the gut-associated lymphoid tissue leads to an increase in nonspecific and specific immunity in all mucosal tissues, instigating proliferation and differentiation of immune cells.¹⁵⁻¹⁹ Enhanced inhibition of bacterial adherence and inactivation of pathogens in the respiratory mucosa are expected results of the primary stimulation of gut-associated lymphoid tissue with obligate or facultative bacteria in RTIs. Controlled clinical studies have confirmed that administration of LW 50020 reduces the number, duration, and severity of RTIs in children and adults.²⁰⁻²²

The SALUD study was carried out to investigate the safety and acceptance of LW 50020 in daily life in a large number of patients with a diagnosed increased susceptibility to RTIs.

PATIENTS AND METHODS

Study Population

The study was conducted in Europe (Portugal, Poland, Czech Republic), Central America (Dominican Republic, Ecuador, Mexico, Guatemala, Honduras), South America (Brazil, Chile, Colombia, Peru, Venezuela), and Asia (Thailand). Children and adults of both sexes and any ethnic group could take part if they were older than 3 years of age and had a history of recurrent RTIs (rhinitis, sinusitis, otitis, pharyngitis, laryngitis, bronchitis, or mixed forms) requiring medical treatment. The defined minimum number of infections in the preceding year was eight for 3- to 6-year-old children, six for 7- to 11-year-old children, and four for 12- to 18-year-old adolescents and adults. Alternatively, children or adults were recruited who had had at least three severe infections (lasting 2 weeks) in the previous year.

Patients with chronic infections, severe immunodeficiency, or other serious diseases were excluded because they were not expected to benefit from treatment with a bacterial lysate. Pregnant women also were excluded because of lack of experience, and the ethics committee requested that the lactation period be added as a routine criterion for exclusion.

Study Medication

The study medication was LW 50020 tablets containing 3 mg of a bacterial lysate mixture from seven different American Tissue Culture Collection (ATCC) strains (*Staphylococcus aureus*, *Streptococcus mitis*, *S. pyogenes*, *S. pneumoniae*, *Klebsiella pneu-*

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moniae, *Branhamella catarrhalis*, and *Haemophilus influenzae*; at least 10⁹ microorganisms of each strain). Excipients were mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and colloidal anhydrous silica.

Each patient was required to take one tablet daily for 28 days. A treatment-free period of 28 days was followed by another 28-day medication course, after which there was a 28-day follow-up period. The study lasted 4 months with five scheduled visits at beginning and end of the treatment courses (V1–V4) and at study end (V5). The first study period included V1–V3 (first treatment course and treatment-free interval); the second study period included V3–V5 (second treatment course and treatment-free follow-up).

Study Endpoints

The primary endpoint was safety, which encompassed the number of adverse events (AEs)/adverse drug reactions (ADRs), effect of LW 50020 on laboratory variables, and overall tolerability.

Secondary endpoints were acceptability and efficacy of therapy. The following variables were assessed for efficacy: number, duration, severity (three-point scale) and clinical score of RTIs (product of duration and severity); treatment of infections (with antibiotics or symptomatic agents); and number of days absent from school or incapable of working/running the household.

The clinical infection score was calculated by multiplying the duration by the severity to derive a total for all infections in the respective period.

Determination of Sample Size and Statistical Methods

A sample of 5000 patients was calculated to achieve a 99% probability that rare AEs (probability of occurrence .0009) would be captured. The actual study population was 4965 patients.

Estimates for the frequency of AEs and 95% confidence intervals (CIs) were based on the Poisson distribution. The overall evaluation of tolerability and the laboratory parameters were analyzed descriptively. All recruited patients were included in the safety evaluation.

Efficacy data were calculated for the per-protocol population as the relative percent change in values between periods V1–V3 and V3–V5. To account for differences in duration of the observation periods among individual patients, results of secondary endpoints were expressed as rates, ie, number of events in a 4-week period.

Data Collection

Demographic data, number of infections in the preceding year, and concomitant diseases and treatments were documented at the first visit (V1), as were risk factors for RTIs (allergies, susceptibility to eczema/neurodermatitis, hay fever/chronic rhinitis, conjunctivitis, susceptibility to bronchitis/recurrent cough, hyperactive bronchial system/bronchial asthma, positive allergy tests/increased IgE).

The following were determined in blood samples taken at V1 (baseline values) and V4 (end of treatment): hemoglobin, hematocrit, red and white blood cell counts, differential count (detection of pathologic forms), and serum immunoglobulins (IgA, IgE, IgG, IgM).

Patients who developed an acute RTI during the study were requested to contact their physician to document its severity, duration, and treatment. After the end of each infection, a final diagnosis was rendered as regards location (upper or lower respiratory tract or ear).

Any other diseases occurring during the study, complaints, or comments on the patients' general state of health and well-being were documented as AEs, including a diagnosis and details of severity, treatment, outcome, and possible causal relationship to the study medication.

In a final (manufacturer) assessment, each AE was evaluated according to the patient's history, especially risk factors documented at V1, concomitant diseases, temporal association with intake of study medication, and the patient's experience during the study.

An AE assessed as possibly or probably related to the study drug was classified as an ADR. An AE was classified as unrelated to study drug if: (1) there was no reasonable temporal association with drug use; (2) the AE was caused by an intercurrent or concomitant disease or by another medication; (3) it had been observed in the patient before the study (also true for severity); or (4) it did not reappear on challenge.

Compliance was checked by tablet counts at the end of the treatment cycles (V2, V4). Overall tolerability was assessed by the investigators at the final visit (V5).

RESULTS

Study Population

A total of 4965 patients were recruited at 133 centers in 14 countries between November 1995 and May 1997. These patients received at least one package of the study medication, and all entered the safety evaluation (intent-to-treat sample).

The percentages of patients recruited in each country were as follows: Brazil 30%, Venezuela 14%; Colombia 13%; Peru 10%; Chile 8%; Mexico 6%; Central America (Dominican Republic, El Salvador, Honduras, Guatemala) 10%; Portugal 4%; Poland and the Czech Republic 2% each; and Thailand 1%.

Data were available for 84% of patients ($n = 4153$) at V4, after the two treatment cycles, and for 80% ($n = 3963$) at visit V5, the final visit. In most cases, the reasons for premature discontinuation were nonmedical.

The study was carried out according to protocol in 70% of the sample. Reasons for exclusion from the per-protocol analysis were premature withdrawal from the study, missing documentation, violation of inclusion criteria, noncompliance, and nonadherence to the study schedule.

Demographic and safety data were evaluated for the safety population, efficacy data for the per-protocol population. Overall tolerability and acceptability of therapy were assessed for patients who attended V5.

The Table summarizes demographic and baseline characteristics.

Demographic and Baseline Characteristics

Characteristic

Sex, %	
M/F	48/52
Age, y	
Mean	19
Median	11
Range	3–86
Age group, %	
6 years (children)	35
7–11 years (children)	17
12–18 years (adolescents)	8
Adults*	39
School/work history, %	
Attending kindergarten/school	51
Attending school and working	6
Working	30
Smoking history	
Passive smokers	30
Active smokers	6

*Data missing for 1%.

Medical History

One or more risk factors for RTIs were present in 77% of patients (Fig 1). About half of the study population suffered from bronchitis and recurrent cough. Other risk factors in order of frequency were hay fever/chronic rhinitis/conjunctivitis, known allergies, and a hyperactive bronchial system or asthma.

During the previous year, patients experienced a mean of 7.8 infections of the upper and lower respiratory tract and ear (Fig 2) and 1.9 severe infections. The number of infections decreased with age.

Fig 1. Percentage of patients with allergies/risk factors for RTIs.

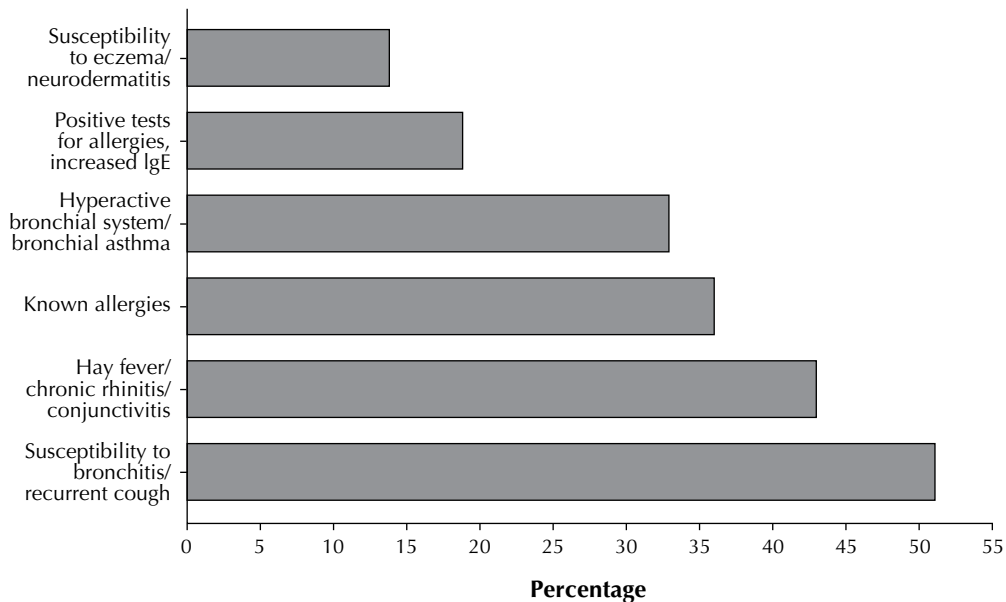
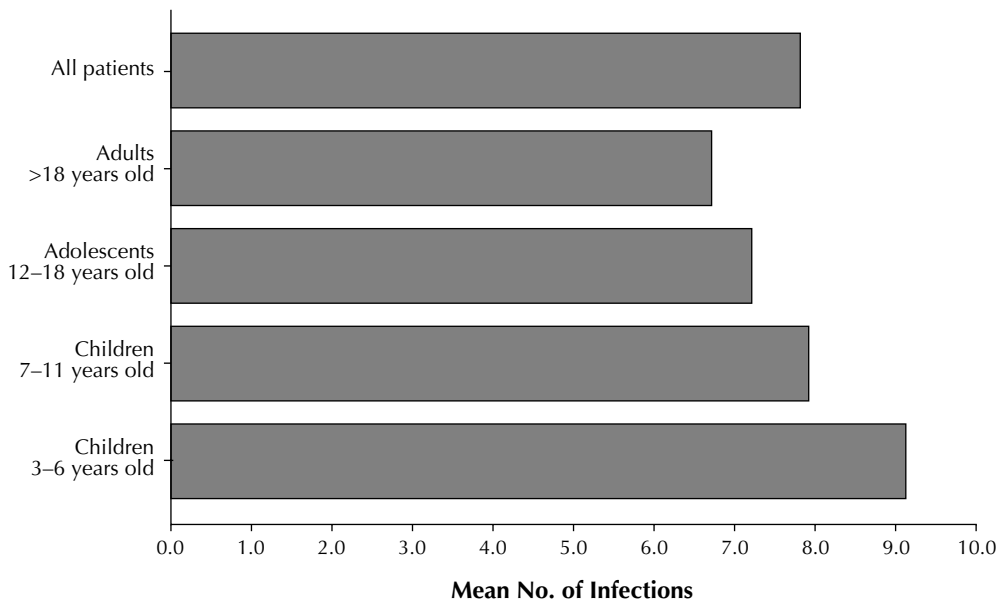


Fig 2. Mean number of infections in the previous year.



SAFETY

Adverse Events

A total of 358 AEs with or without a suspected causal relationship with LW 50020 were reported in 309 patients, corresponding to a frequency of 7.2% (95% CI 6.5, 8.0). The incidence of the most frequent AEs by body system was as follows: gastrointestinal tract 2.5%; skin 1.3%; infections, mostly childhood diseases, 1.0%; central nervous system, psychiatric, vision 0.8%; and respiratory tract (pneumonia and diseases other than infections) and urogenital tract 0.4% each.

No sex-, age-, or smoking-specific differences were seen in the number of patients with AEs, although patients with a known history of allergies and one or more risk factors for recurrent RTIs had twice as many AEs as those without these characteristics. Countries that predominantly recruited these types of patients reported increased rates of AEs. An AE incidence exceeding 10% occurred in Chile, Guatemala, Poland, and Thailand (15% of the study population); in all other countries the incidence was less than 10%.

A full 77% (n = 276) of AEs were mild; 19% (n = 67) were moderate, and 4% (n = 14) were severe. The severity of one AE (later classified as an ADR, see below) was not documented. None of the 18 serious adverse events (5%) was related to LW 50020.

Suspected Adverse Drug Reactions

Of the 358 AEs, 30 (in 27 patients) were judged to be possibly or probably related to the study medication and were therefore regarded as ADRs. The frequency of ADRs was 0.6% (95% CI 0.4, 0.9%), with a range between 0% and 3.6% across countries, and was similar in all subgroups previously defined.

None of the suspected ADRs was severe or serious; 21 (70%) were mild and 8 (27%) were moderate. The severity of 1 suspected ADR (3%) remained unknown (acute diarrhea that subsided after 3 days without medication).

Eighteen patients with suspected ADRs withdrew from the study prematurely, 16 of them because of the ADR.

The ADRs reported in this study had been described for LW 50020; 18 affected the gastrointestinal system, 11 were skin reactions, and 1 was a respiratory tract symptom (aggravation of rhinitis). According to an international classification, the frequency of gastrointestinal and skin reactions is defined as uncommon (between 1 per 100 and 1 per 1000) and that of respiratory tract symptoms as rare (less than 1 per 1000). New, as yet unknown, rare ADRs were not reported.

Laboratory Evaluations

No clinically relevant shifts were detected in any of the variables investigated. IgE values were reduced, though not significantly, in patients with and in those without risk factors for RTIs.

Overall Tolerability

Overall tolerability was assessed for patients who completed the study at the final visit (missing value for one patient). Tolerability was rated as very good or good in 99.5% and as moderate or poor in 0.5%. Some patients in the latter group had had AEs during the study, generally not drug related; in other patients no reasons for this rating were evident.

Overall Acceptability

Acceptability, which was evaluated in all patients who attended the final visit (missing value for one patient), was very good or good in 99.2% and moderate or poor in only 0.8% of the assessed population.

EFFICACY

Number, Duration, and Severity of Infections

The rate (number) of infections, number of days with infections, severity, and clinical score were lower during the third and fourth months than in the first and second months by between 52% and 62% (Fig 3). On the basis of results of a long-term double-blind study with LW 50020, it is presumed that reductions in the number and duration of infections remain stable over 1 year.²¹ A reduction of at least 1.7 infections and 14.3 days with infection per year per patient can be calculated from these data. The projection of the 1-year results was determined from baseline data evaluated under therapy comparing the second with the first treatment course; therefore, reductions in number, duration, and severity of infections after two treatment courses and the calculated reductions for 1 year may be even higher.

No significant differences in the rate of infections were found for sex, age, smoking habits, or history of allergy and risk factors. The reduction was similar for infections at different sites (upper or lower respiratory tract, ear), although upper RTIs were more frequent. A reduction in the frequency of infections occurred in all countries.

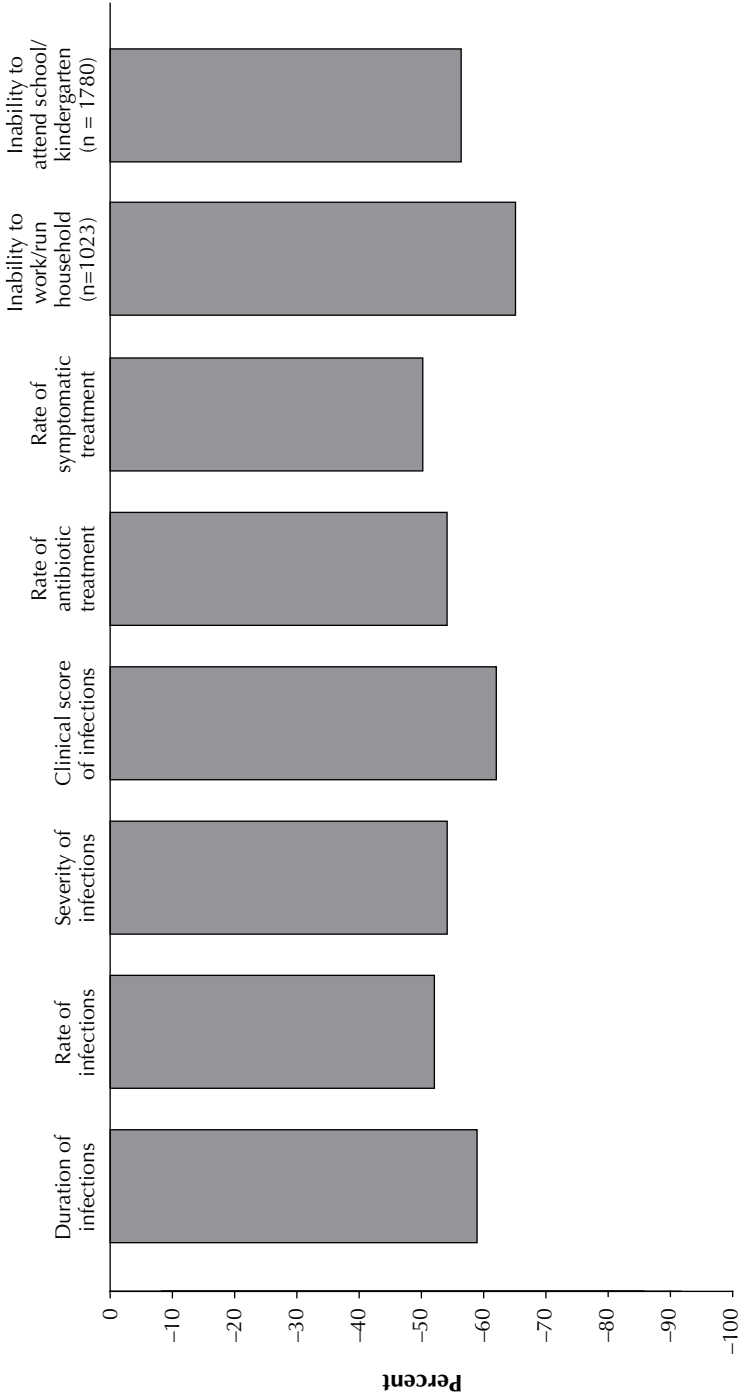
Number of Infections

The number of antibiotic and symptomatic treatments decreased by 54% (Fig 3) and 50%. The projection for 1-year results is a saving of 0.9 antibiotic and 1.1 symptomatic treatments.

Absence from School or Work

The number of days patients were absent from kindergarten/school ($n = 1780$) or were unable to work/run a household ($n = 1023$) decreased between 56% and 65%.

Fig 3. Relative reduction in efficacy endpoints.*



*Comparison of first (V1–V3) and second (V3–V5) study periods.

DISCUSSION

A common characteristic of the infection-prone SALUD study sample in different countries was the high percentage of patients (77%) with concomitant allergies and/or bronchial hyperreactivity and related diseases. Previous studies with LW 50020 also included large numbers of these patients.²³

Allergic diseases are a major risk factor for recurrent RTIs,^{24,25} an observation of apparent clinical importance as allergic conditions increase worldwide.²⁶ Epidemiologic studies confirm a link between allergic diseases and RTIs. A longitudinal, prospective study on the incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a large British cohort revealed that wheezing illness in early childhood was strongly and independently associated with pneumonia, hay fever, and eczema.²⁷ Weaker associations were found with abdominal pain and migraine. In Swedish schoolchildren, a high frequency of upper RTI was related to a high frequency of parental allergic disease. The covariation in parental background indicates a common genetic disposition.³ There also may be a general genetic vulnerability to disease in patients with recurrent RTIs. A study in schoolchildren⁷ showed that those who had recurrent RTIs belonged to families with health problems.

Other explanations for the frequent occurrence of allergic and infectious respiratory diseases have been proposed. Bacteria-induced local defects in the immune barrier of the upper respiratory tract may facilitate penetration of potential allergens and contribute to the development and perpetuation of atopic diseases.²⁸ Viruses upregulate an allergic inflammatory reaction, increase airway hyperresponsiveness in nonasthmatic patients, and provoke attacks of wheezing in patients with asthma.⁸ Thus it would seem important to prevent RTIs in both nonatopic and atopic patients.

The safety results of the present study demonstrate no need for restrictions on the use of the immunomodulator LW 50020 in the investigated risk groups of patients with known allergies, increased IgE levels, eczema, hay fever, rhinitis, conjunctivitis, bronchitis, hyperactive bronchial system, and bronchial asthma. All patients can expect to benefit.

The frequency of AEs with a suspected causal relationship to the study drug was generally low, and no increased frequency or severity could be detected in the risk groups investigated. No new, as yet undescribed, suspected ADRs were reported.

Nevertheless, reported AEs occurred up to twice as often in the risk groups described. This may be explained by the generally elevated vulnerability to disease in these patients already mentioned.⁷ Passive and active smoking is also a risk factor for recurrent RTIs.^{29,30} In our study, smoking habits did not influence the frequency of reported AEs or infection variables assessed, perhaps because of the relatively small proportion of passive (30%) and active (6%) smokers.

The mean incidence of RTIs in a normal population peaks at 4.9 in the first 2 years of life, decreasing to 2.8 between ages 5 and 19, to 2.2 in younger adults, and to 1.6 in adults over 40 years of age.⁵ The patients recruited for the SALUD study had substantially higher infection rates in their history: children up to 11 years old had experienced eight to nine infections during the past 12 months, and adults just under seven. The additional presence of allergies and underlying respiratory diseases in a high percentage of patients indicates that the study sample was very representative

of the general population known to be at high risk for RTIs. No differences were apparent between the decreases in rate, duration, and severity of infections in patients with and in those without historical risk factors.

Seasonal influences on the reduction in infection variables can largely be excluded. Fewer than 10% of the study population were recruited in Europe, where seasonal peaks are reported in the spring and autumn months.⁷ In most parts of Central and South America (except Chile), which contributed more than 80% of the patients, seasonal influences are of minor importance. Moreover, the study lasted about 2 years, making seasonal influences improbable.

The reduction in the infection rate observed was similar to results of controlled clinical trials in children and adults.²⁰⁻²² One of the placebo-controlled, double-blind studies had a total observation period of 1 year during which the reduction in frequency of infections remained stable.²¹ We therefore projected our findings over a 52-week period in terms of reduction of the infection rate, duration of infections, and savings in antibiotic and symptomatic treatments. The calculated reduction by 1.7 infections and 14 days of infection, with savings of one antibiotic or symptomatic treatment per year, has great clinical relevance that is underlined by the increasing prevalence of bacterial pathogens resistant to many antibiotics. Substantial savings in medical and other treatment costs can be expected, as demonstrated earlier in a German population.³¹ Reductions and savings may be even higher than projected because findings documented under treatment comprised the baseline for the projection.

CONCLUSIONS

In this large open study performed in patients from 14 countries, most participants with an increased susceptibility to RTIs also had a history of allergies and respiratory diseases. In all countries, the oral immunomodulator Luivac proved to be safe and effective in preventing RTIs in patients with and without such risk factors. These results confirm again that administration of Luivac is a safe and successful strategy for reducing the frequency, severity, and duration of ubiquitous RTIs as well as their socioeconomic costs.

ACKNOWLEDGMENTS

The authors thank the following physicians, along with other colleagues and local and international monitors, for their help in carrying out the SALUD study with such success: M. Ganança, M.D., Brazil; R. Sepúlveda, M.D., Chile; G. Jacques, M.D., Colombia; J. Janda, M.D., Czech Republic; A. Barrientos, M.D., Guatemala; W. Pozo Tovar, M.D., Peru; J. Haluszka M.D., Poland; S. Ruah, M.D., Portugal; C. Bunnag, M.D., Thailand. Also gratefully acknowledged are the biometrical evaluation of Mr. U. Elsasser and the quality assurance of M. Binder, Ph.D.

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