Effects of EPs 7630 on Illness Absence from Childcare or School due to Acute Bronchitis—A Meta-analysis

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Abstract

Objective In the pediatric population, acute bronchitis (AB) is a leading cause of illness absence from childcare, school, or apprenticeship. We report a meta-analysis of double-blind, randomized trials with children and adolescents with AB (aged 1–18 years), who were treated with *Pelargonium* extract EPs 7630 or placebo for 7 days.

Methods The average number of days absent from childcare, school, or apprenticeship due to illness and the proportion of patients still unable to return to their normal activities at treatment end were assessed.

Results Literature search identified two eligible trials with a total of 420 patients. Illness absence was reported for all but two patients under placebo at baseline and for 46.7% (EPs 7630) and 85.0% (placebo) of patients at day 7. Meta-analysis risk ratio for absence at day 7 was 0.55 (95% confidence interval: 0.47, 0.64) for all patients, 0.59 (0.46, 0.76) for children younger than 6 years, and 0.53 (0.44, 0.64) for participants aged 6 to 18 years, all favoring EPs 7630. Compared with placebo, average time until return to normal activities was reduced by EPs 7630 by 1.51 (1.16, 1.86) days for all subjects, by 1.50 (0.92, 20.7) days for those younger than 6 years, and by 1.54 (1.11, 1.97) days for those 6 to 18 years of age ($p < 0.001$ favoring EPs 7630 for all treatment group comparisons shown).

Conclusion For children and adolescents with AB, meta-analysis shows that EPs 7630 treatment for 7 days significantly reduces the average time of illness absence and significantly increases the proportion of patients able to return to normal activities within 1 week.

Keywords
- acute bronchitis
- adolescent
- child
- *Pelargonium*
- extracts

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Introduction

Acute respiratory tract infections (ARTIs) including acute bronchitis (AB) are the most common diseases worldwide, regardless of age and sex. Their incidence is particularly high in preschool and school-aged children and adolescents, and decreases with age.[1] According to data from the U.S. Household Influenza Vaccine Effectiveness study,[2] 40 to 59% of children younger than 5 years as well as 27 to 42% of children and adolescents aged 5 to 17 years suffered from between one and six episodes of ARTIs during each of three consecutive infection seasons between fall of 2010 and spring of 2013.[1] ARTIs are highly contagious and spread quickly in semiclosed settings such as childcare facilities or schools,[3] and it is therefore not surprising that an association between visit to a daycare center and the risk of respiratory infections has been observed in preschool children.[4] ARTIs vary in severity from mild to distressing or debilitating and cause profound distress in affected children. ARTIs have also been identified as major causes of parental stress, which can impair the psychological functioning of parents and even lead to symptoms such as anxiety or depression in the latter.[4] Infection during childhood is, however, not only a burden for children and to their families but a major cause of lost childcare and school days.[5–7] They are also a considerable financial burden to the society due to medical costs and loss of productivity and days off work of parents as well as daycare or school staff.[3,5,8–10] For school children, illness absence also causes loss of educational opportunities and may have a negative impact on the educational outcome.[11]

AB is an inflammation of the larger lower airways caused predominantly by viral infection.[12,13] The differential diagnosis is established solely based on clinical signs and symptoms.[12] The most common and persistent symptom, acute cough, has been reported to subside within 10 days in approximately 50% of affected children and adolescents and in approximately 90% by day 25.[14] Other common symptoms include fever, malaise, difficulty in breathing, and wheezing.[13,15] Although most AB episodes are uncomplicated, they can still have the detrimental effects on activities of daily life of children, adolescents, and parents, on the health care system, and on the economy in general, as described earlier.

Antibiotics are still widely prescribed in AB,[16] although they are generally not indicated in a disease whose etiology is viral in more than 90% of the cases[17,18] and even though they have no proven beneficial effect in children or adolescents with AB.[19,20] Results from a systematic review show that clinicians tend to prescribe antibiotics for acute childhood infections in primary care when they feel pressured to do so by parents or others (e.g., employers) or when they are concerned about clinical or social outcomes (i.e., prescribing "just in case"), while parents want antibiotics when they feel they would improve the current illness, and when they feel pressure from daycare providers or employers.[21] However, current disease management guidelines clearly advise against their use without evidence of bacterial infection.[19,22] Therefore, research is needed on effective and safe treatment options for AB in children and adolescents, which meet the expectations of patients, clinicians, and parents. Best practice and disease management guidelines for the management of AB in children and adolescents mainly advocate symptomatic treatment aiming at improving patients' well-being and restoring their ability to carry out daily activities.[23] In this respect, the restoration of the young patients' ability to attend childcare or school is of great importance.

Pelargonium sidoides root extract EPs 7630 (EPs® 7630 is a proprietary extract of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) has been approved as a medicinal product for the treatment of respiratory tract infections, including AB, in many countries in Asia, Europe, Australia, and Central and South America. In vitro studies with EPs 7630 and isolated constituents have demonstrated pharmacological activities including notable immune-modulatory capabilities and moderate direct antiviral and antibacterial actions. Immune-modulatory activities include activation of the mitogen-activated protein kinase pathway[24] and a subsequent regulation of various cytokines such as tumor necrosis factor α, interferon-β, or interleukin-22, depending on the experimental context.[25] Evaluation of pharmacodynamic activities of EPs 7630 in animal models further showed antitussive, secretolytic, and anti-inflammatory effects after oral administration at human equivalent doses.[26] Moreover, EPs 7630 was found to interfere with the replication of seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus, parainfluenza virus, and coxsackievirus,[27] some of which are among the species that predominantly cause AB, and to reduce rhinovirus infection of human bronchial epithelial cells.[28] In further in vitro experiments, EPs 7630 was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication and modulate innate immune responses in the human lung cell line Calu-3.[29,30]

With more than 30 clinical trials conducted over the past 25 years,[31] EPs 7630 is among the most rigorously studied medicinal products for herbal treatment of ARTIs. A total of 19 randomized, placebo-controlled clinical trials in adults and children have been conducted in indications including acute sinusitis, acute tonsillopharyngitis, acute rhinopharyngitis, and AB.[32] Together with active-controlled, open-label, and noninterventional studies, available evidence from systematic research is based on more than 10,000 patients in total (more than 8,000 exposed to EPs 7630), ~4,000 of whom were children and adolescents up to 18 years of age.[32] A wide range of systematic reviews and meta-analyses of randomized, controlled clinical trials investigating EPs 7630 were published, providing evidence for the efficacy and safety of the herbal medicinal product in the treatment of adults, adolescents, and children with AB, acute tonsillopharyngitis, acute rhinosinusitis, and the common cold.[32–46]

Controlled clinical trials with EPs 7630 in AB were conducted using a standardized clinical questionnaire to assess symptom severity: validated versions of the so-called bronchitis severity scale (BSS) are available for several age groups.[47–49] For adults with AB, a meta-analysis showed

that the proportion of patients being completely symptom free after a 7 days' treatment with EPs 7630 exceeded that in the placebo group by a factor of about six.[37] In addition, two placebo-controlled trials in AB assessing the association between EPs 7630 administration and illness absence from work found that adults treated with the herbal product were able to return to work sooner.[50,51] These results were recently confirmed in a meta-analysis with data from 1,001 adult patients from four placebo-controlled, randomized, multicenter trials.[46] Evidence from adult patients therefore suggests that EPs 7630 accelerates recovery from AB and thus also reduces the number of workdays lost. However, the research question whether EPs 7630 treatment also reduces the duration of disease-related absence from childcare or school has not been investigated by meta-analysis of placebo-controlled, randomized clinical trials so far. Since accelerated recovery of children suffering from AB would lead to a lower loss of educational opportunities, a less negative impact on the educational outcome, and to lower economic costs, the answer to this question would be an important insight.

Therefore, the objective of the present meta-analysis was to assess whether EPs 7630 treatment leads to an acceleration of recovery from AB in children and adolescents. Specifically, we investigated whether treatment with EPs 7630 reduced the number of days of disease-related absence from childcare or school.

Materials and Methods

We searched for double-blind, randomized, placebo-controlled clinical trials investigating the treatment of AB with EPs 7630 in children and adolescents. EPs 7630 is an herbal drug preparation from the roots of *P. sidoides*, drug extract ratio 1:8 - 10, extraction solvent: ethanol 11% (w/w), which is marketed as a solution, as tablets, and as a syrup for children.

Eligible trials had to cover the age range of 1 to 18 years and to report data on illness absence from childcare, school, or apprenticeship. Only studies that were reported as planned, conducted, and evaluated according to the principles of Good Clinical Practice and the Declaration of Helsinki were considered.

Clinical trials were identified by PubMed search using the search terms ('EPs 7630' or 'Pelargonium') AND 'clinical trial' AND 'acute bronchitis'. Publications identified by the search were then screened for compliance with our eligibility criteria, and full texts of articles still eligible after screening were assessed for final inclusion into the meta-analysis. Further data on the eligible trials were then obtained from the manufacturer of the herbal extract.

For meta-analysis, data were sought from the relevant assessment tools most used across the eligible trials. In the trials that met our eligibility criteria, assessments of whether a patient was able to attend childcare, school, or apprenticeship were obtained either during each scheduled visit or by means of a patient diary. From that we calculated the average number of sick days during the trial period as well as the number and proportion of subjects who were unable to attend daycare, school, or apprenticeship at baseline (immediately prior to the start of the investigational treatment) and at treatment day 7 (end of treatment).

The quality assessment of the trials selected for inclusion was evaluated using the Jadad score.[52] The Jadad score consisted of three items: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 points). The response to each item was either "yes" (1 point) or "no" (0 point). The final score ranged from 0 to 5 points, with higher scores indicating better reporting. Studies with a Jadad score of 2 or less were considered to have low quality and those with a Jadad score of 3 or more were considered to have high quality.

Analyses were performed in accordance with a prospectively defined analysis plan and based on the raw data of the included trials, which were obtained from the manufacturer of the herbal extract.

For each scheduled visit, the case report forms of the trials considered in the meta-analysis included an item for documenting whether the patient attended childcare, school, or apprenticeship. Calculation of the number of days missed due to AB was based on the number of days between baseline and the actual dates of the documented postbaseline visits. For patients who still stayed at home at the last visit, it was assumed that the child or adolescent had remained unable to attend childcare, school, or apprenticeship for another 3 days after the day of the last visit.

Procedures for handling of missing data were adapted from the corresponding procedures applied in the eligible trials. Missing data at treatment end were replaced by the last observed value (last observation carried forward). In case of missing data at baseline, patients were assumed to be unable to attend childcare/school/apprenticeship if there was at least one postbaseline assessment at which they had to stay at home.

All analyses were performed based on the full analysis set (FAS) of study participants in accordance with the definitions given in the original protocols of the trials analyzed. Sample characteristics were analyzed using applicable descriptive summary measures. For the number of days of illness absence, a meta-analysis was performed based on the difference between the within-study treatment group mean values and their 95% confidence intervals (CIs). A meta-analysis of the proportion of patients who were unable to attend childcare, school, or apprenticeship at treatment end was based on the risk ratio and its 95% CI. Heterogeneity between the primary trials was assessed using the I^2 statistic. According to the statistical analysis plan, random effect models were to be computed in case of $I^2 > 5\%$, and fixed effect models were used otherwise. However, since no heterogeneity requiring a random effect model was observed in this investigation, in fact, only fixed effect models were applied. Review Manager (RevMan) version 5.4 software was used for all meta-analyses.[53] All specified p-values are two sided. Treatment differences were considered descriptively significant if the 95% CI of the point estimate did not include the value of 0 for differences between means or the value of 1 for risk ratios, corresponding to a descriptive p-value of ≤ 0.05.

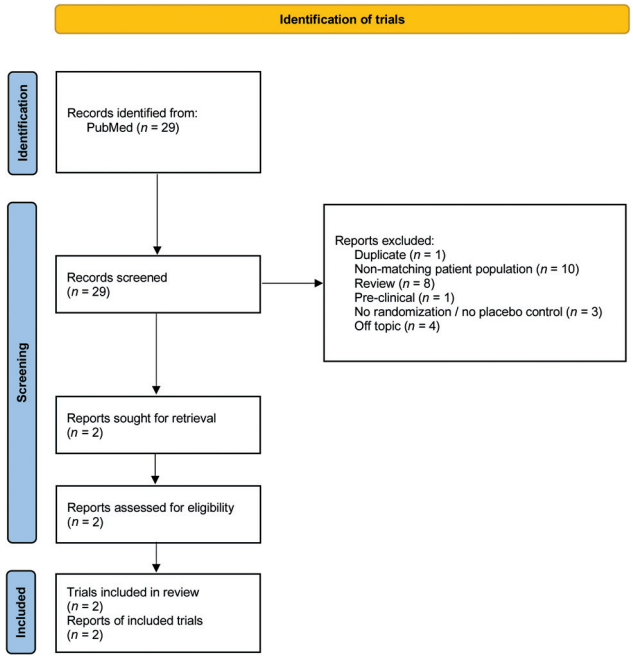

Fig. 1 Search results.

Results

We searched the literature from the earliest database record to the end of December 2021. Our searches identified a total of 29 potentially relevant publications that were then further screened for compliance with our selection criteria. ►**Fig. 1** shows that 27 articles were excluded already at the screening stage for the reasons indicated. The two publications that remained after screening reported on randomized, placebo-controlled clinical trials in which EPs 7630 was administered to children and adolescents aged 1 to 18 years suffering from AB and in which illness absence from childcare, school, or apprenticeship was solicited.[54,55] No further trial had to be removed during full-text check.

The two eligible studies were conducted as randomized, double-blind, placebo-controlled, multicenter trials and included male or female children and adolescents suffering from AB. Both studies were considered high quality (Jadad score of 5[54] and 4,[55] respectively). The trials were performed according to very similar protocols and included 200[54] and 220[55] children and adolescents, respectively. For enrollment into the trial, patients had to be between 1 and 18 years of age and had to be suffering from symptoms of AB for a period not exceeding 48 hours before inclusion. A total score $\geq$5 points on the validated BSS[48] (items: coughing, sputum production, pulmonary rales at auscultation, chest pain while coughing, and diarrhea; theoretical range: 0–20 points) was required at baseline. Vaccination status regarding seasonal influenza was not documented. Eligible patients were then randomly allocated to receive placebo or EPs 7630 liquid 3×10 drops/day for children 1 to 5 years of age, 3×20 drops/day for children 6 to 12 years of age, and 3×30 drops/day for children and adolescents older than 12 years, over a scheduled period of 7 days. Randomization was performed in a balanced way stratified to age groups according to a computer-generated randomization list prepared by using a validated random number generator, and study medication was assigned sequentially in the order the patients were included into the trial within each center and stratum. Assessments were scheduled at baseline, at 3 to 5 days after baseline, and at treatment end (day 7). In both trials, the predefined primary outcome measure for efficacy was the absolute change of the total score of the BSS[48] between baseline and treatment end. At each visit, guardians and/or participants were questioned whether the child or adolescent attended childcare, school, or apprenticeship.

The FAS of the eligible trials included a total of 420 patients, 124 of whom were between 1 and 5 years of age, while the remaining 296 were between 6 and 18 years of age. The treatment groups were well balanced for age and sex, and the distributions of these characteristics in the two trials were similar (descriptive summary statistics for age and sex are shown in ►**Table 1**).

All patients eligible for the FAS provided data about illness absences and could therefore be included into the meta-analysis. In each of the two trials, all subjects randomized to EPs 7630 and all subjects but one randomized to placebo were unable to attend childcare, school, or apprenticeship.

In each of the two trials eligible for meta-analysis, only one patient of the placebo group was able to attend daycare, school, or apprenticeship at baseline. The average number of days of illness absence calculated for the studies was 8.98 for EPs 7630 and 10.44 for placebo in Kamin et al (2010),[54] and 8.67 for EPs 7630 and 10.23 days for placebo in Kamin et al (2012),[55] respectively (►**Fig. 2**, Panel A). The meta-analysis shows a significant treatment group difference favoring EPs 7630 by an average of 1.51 days ($p < 0.001$), with a minimum average advantage of 1.16 days according to the lower bound of the associated 95% CI. The figure also shows that the observed between-study heterogeneity was minimal ($I^2 = 0$) and that the number of days of illness absence was significantly lower for EPs 7630 than for placebo in each study considered separately.

►**Fig. 2** also shows that the average numbers of days of illness absence were similar for children younger than 6 years (9.29 for EPs 7630 and 10.86 for placebo in Kamin et al, 2010[54] and 8.76 for EPs 7630 and 10.16 for placebo in Kamin et al, 2012,[55] respectively; Panel B) and for children and adolescents between 6 and 18 years of age (8.85 for EPs 7630 and 10.28 for placebo in Kamin et al, 2010[54] and 8.62 for EPs 7630 and 10.26 for placebo in Kamin et al, 2012,[55] respectively; Panel C). Moreover, with average advantages of 1.50 and 1.54 days of illness absence for EPs 7630 over placebo for younger children and for older children and adolescents, respectively, the magnitude of the treatment effect in both subsets was also comparable.

While approximately half of the children and adolescents treated with EPs 7630 had returned to childcare, school, or apprenticeship by the end of the 7-day treatment period, more than 80% of those in the placebo groups of the trials were still at home (►**Table 2**). The table also shows that the proportion of illness absence at the end of study was

Table 1 Characteristics of trials and patients included in the meta-analysis (full analysis set)

Age	Study	Treatment group	Age (y)		Sex, *n* (%)		*N*
			Mean (SD)	Median (minimum, maximum)	Male	Female	
Total	Kamin et al (2010)[54]	EPs 7630	9.44 (4.97)	9 (1, 17)	50 (48.5%)	53 (51.5%)	103
		Placebo	9.48 (5.12)	10 (1, 17)	45 (46.4%)	52 (53.6%)	97
	Kamin et al (2012)[55]	EPs 7630	8.73 (4.80)	8 (1, 17)	54 (48.6%)	57 (51.4%)	111
		Placebo	9.17 (5.19)	9 (1, 18)	55 (50.5%)	54 (49.5%)	109
	EPs 7630		9.07 (4.89)	8 (1, 17)	104 (48.6%)	110 (51.4%)	214
	Placebo		9.32 (5.15)	9 (1, 18)	100 (48.5%)	106 (51.5%)	206
1–5 y	Kamin et al (2010)[54]	EPs 7630	3.45 (1.23)	3 (1, 5)	13 (41.9%)	18 (58.1%)	31
		Placebo	3.21 (1.52)	3 (1, 5)	15 (53.6%)	13 (46.4%)	28
	Kamin et al (2012)[55]	EPs 7630	3.15 (1.28)	3 (1, 5)	15 (44.1%)	19 (55.9%)	34
		Placebo	2.97 (1.49)	3 (1, 5)	21 (67.7%)	10 (32.3%)	31
	EPs 7630		3.29 (1.26)	3 (1, 5)	28 (43.1%)	37 (56.9%)	65
	Placebo		3.08 (1.50)	3 (1, 5)	36 (61.0%)	23 (39.0%)	59
6–18 y	Kamin et al (2010)[54]	EPs 7630	12.01 (3.53)	12 (6, 17)	37 (51.4%)	35 (48.6%)	72
		Placebo	12.03 (3.64)	12 (6, 17)	30 (43.5%)	39 (56.5%)	69
	Kamin et al (2012)[55]	EPs 7630	11.19 (3.55)	12 (6, 17)	39 (50.6%)	38 (49.4%)	77
		Placebo	11.64 (3.90)	12 (6, 18)	34 (43.6%)	44 (56.4%)	78
	EPs 7630		11.59 (3.55)	12 (6, 17)	76 (51.0%)	73 (49.0%)	149
	Placebo		11.82 (3.78)	12 (6, 18)	64 (43.5%)	83 (56.5%)	147

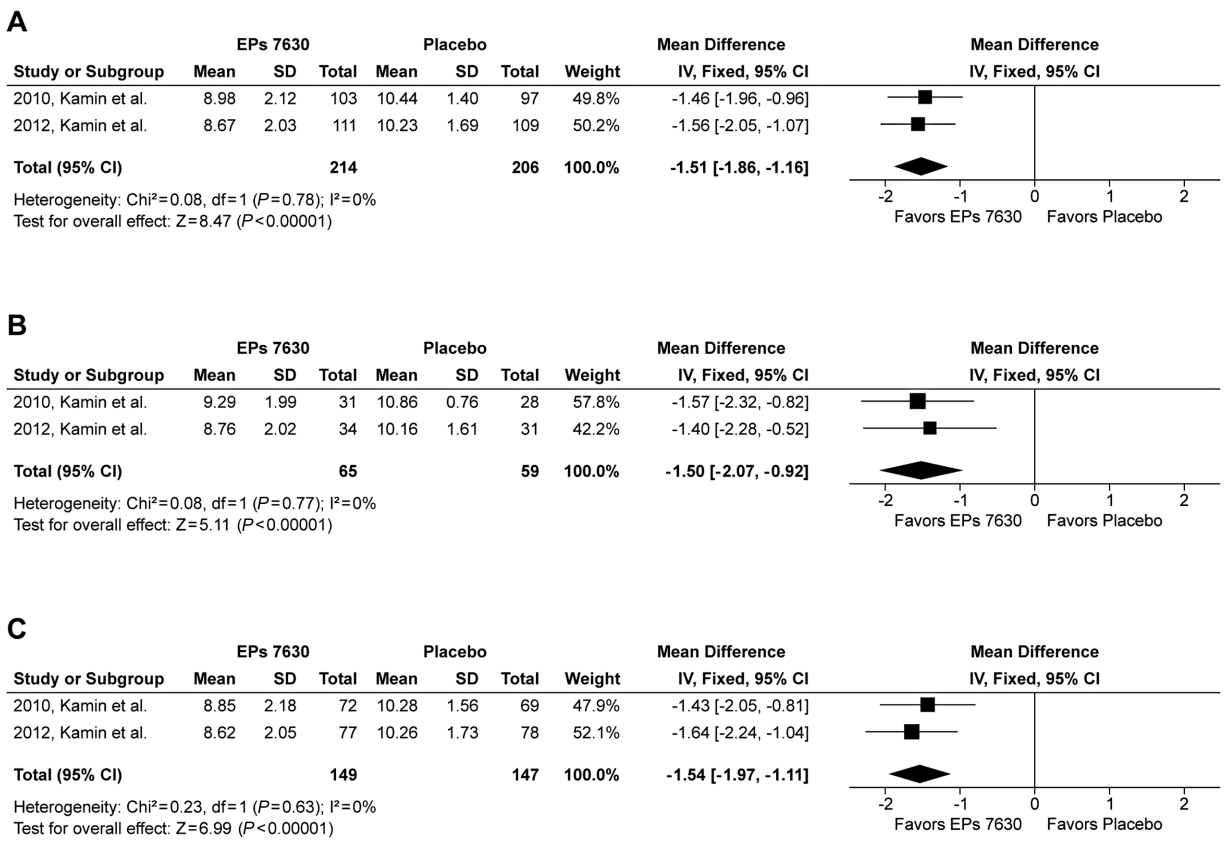

Fig. 2 Meta-analysis of number of days of illness absence (A—all subjects; B—age 1–5 years; and C—age 6–18 years).

Table 2 Subjects still not attending childcare, school, or apprenticeship at treatment end (full analysis set)

Age	Study	EPs 7630		Placebo	
		n (%)	*N*	*n* (%)	*N*
Total	Kamin et al (2010)[54]	53 (51.5)	103	85 (87.6)	97
	Kamin et al (2012)[55]	47 (42.3)	111	90 (82.6)	109
	Pooled	100 (46.7)	214	175 (85.0)	206
1–5 y	Kamin et al (2010)[54]	19 (61.3)	31	27 (96.4)	28
	Kamin et al (2012)[55]	15 (44.1)	34	25 (80.6)	31
	Pooled	34 (52.3)	65	52 (88.1)	59
6–18 y	Kamin et al (2010)[54]	34 (47.2)	72	58 (84.1)	69
	Kamin et al (2012)[55]	32 (41.6)	77	65 (83.3)	78
	Pooled	66 (44.3)	149	123 (83.7)	147

generally slightly higher in children younger than 6 years than in the older study participants.

For the proportion of subjects still absent at the end of treatment, ►**Fig. 3** shows that the results of the eligible trials were again homogeneous according to the I^2 statistic. With a meta-analysis risk ratio of 0.55 ($p < 0.001$) and the upper bound of the associated 95% CI at 0.64 (Panel A), the children and adolescents treated with EPs 7630 were at an about one-third lower risk of still having to stay at home after 1 week's treatment than those in the placebo group. The observed treatment effects in children younger than 6 years and in the older participants were again similar, with a slightly more pronounced risk reduction achieved in the EPs 7630 group in children and adolescents from the age of 6 years (Panels B

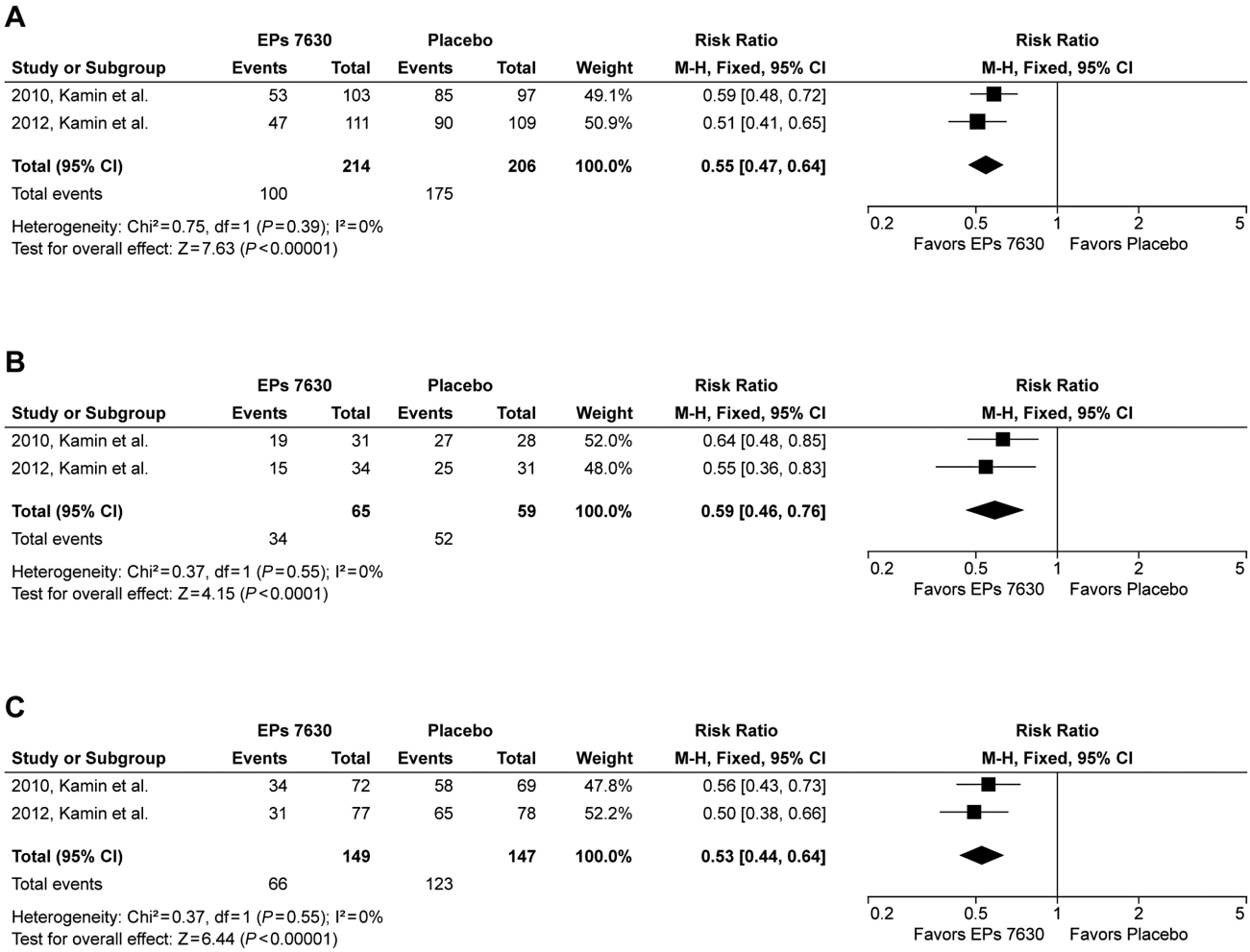

Fig. 3 Meta-analysis of number of subjects still absent at the end of study (A—all subjects; B—age 1–5 years; C—age 6–18 years).

and C). In the dataset analyzed as well as in both subsets defined by age, significant superiority of the herbal medicinal product over placebo was also observed for each of the two trials assessed individually, with risk ratios ranging between 0.64 and 0.50.

Discussion

This study is the first to investigate by meta-analysis whether EPs 7630 treatment reduces the number of days of disease-related absence from childcare, school, or apprenticeship. The key findings are that treatment with EPs 7630 in children and adolescents with AB not only accelerates symptom recovery as previously shown[33,37] but also enables pediatric patients to return to childcare, school, or apprenticeship sooner, with an estimated average benefit compared with placebo of approximately 1.5 days. In addition, a significant proportion of the children and adolescents treated with EPs 7630 was able to return to their normal daily activities within 1 week of treatment, in contrast to patients treated with placebo. Furthermore, these results apply not only for the total study population comprising children from 1 to 18 years but also for both subgroups according to age (<6 and 6–18 years).

The results of previous meta-analyses for the pediatric population have so far focused primarily on symptoms assessed by the BSS, which has been the primary outcome measure in most clinical trials investigating EPs 7630. The present study thus adds to the currently available evidence by presenting meta-analysis results for EPs 7630 treatment concerning the number of days of disease-related absence from childcare, school, or apprenticeship. Our newly derived results in this pediatric population are consistent with current evidence from a meta-analysis of four double-blind, randomized, controlled trials with a total of 1,011 adult patients with AB undergoing a 7-day treatment with EPs 7630, which demonstrated a reduction in sick leave of approximately 1.7 days compared with placebo.[46]

Although the vast majority of viral ARTIs such as AB have an uncomplicated course, they may nevertheless be associated with persistent and debilitating symptoms that cause profound discomfort and suffering, especially in children where such infections are more frequent than in the adult population.[1,12]

However, particularly in vulnerable populations such as children and adolescents, treatment of a condition such as AB that mainly has an uncomplicated natural course is only justifiable if it is associated with minimal risk, and the overall benefit–risk assessment is favorable. *Pelargonium sidoides* extract EPs 7630 has been demonstrated to significantly reduce AB-related symptoms including coughing and dyspnea, and to facilitate expectoration.[34,36,37,42,43] A recent meta-analysis also shows that children aged 6 to 10 years suffering from ARTIs and treated with EPs 7630 are administered paracetamol by their parents in a lower cumulative dose than those children receiving placebo, even though EPs 7630 has no known direct antipyretic effect.[40] The authors concluded that the reason for this was the acceleration of recovery induced by EPs 7630. The interpretation is consistent with the results of another meta-analysis demonstrating that the proportion of patients who were completely symptom free after 1 week of treatment was significantly higher with EPs 7630 compared with placebo.[37] At the same time, EPs 7630 was found to be safe to use in the pediatric population, with adverse event rates in controlled clinical trials at similar levels to placebo.[32,33] The results of our analysis showing the acceleration of recovery from AB symptoms observed under EPs 7630 treatment in placebo-controlled trials therefore show this extract to be a potential therapy option, which has practical implications, namely, that patients are enabled by EPs 7630 treatment to return to daycare, school, or apprenticeship significantly earlier.

Particularly in young children, the suffering of a child can also be a significant cause of parental stress and distress,[4] and if the child is unable to attend daycare or school, this often implies that one parent cannot go to work either.[3,8] It can therefore be assumed that, in addition to the advantages for the affected children and adolescents who miss fewer days of daycare, schooling, or apprenticeship, the earlier recovery may also have an impact on the parents who stay at home to care for their child, who can thus return to work earlier.

Moreover, viral respiratory infections are contagious and can therefore also attack daycare or school staff as well as the parents of the infected child, leading to further loss of productivity. Therefore, it is not surprising that "trivial" respiratory infections and their consequences have been recognized as a major economic burden.[56] A recent analysis conducted in Spain and investigating cost-effectiveness of hand hygiene programs for preventing respiratory infections revealed that one single day of lost productivity of a parent due to absence from paid work per day for caring for the sick child leads to costs of nearly 80 EUR.[10] Given the high prevalence of AB in the pediatric population,[1] a saving of disease-related inability to work in parents attending their ill children in the range of 1.5 days on average per episode may thus translate into a significant economic benefit.

However, this meta-analysis has some potential limitations that need to be considered. First, only two randomized, double-blind, placebo-controlled trials with a relatively small total number of 420 patients were eligible for analysis. Nevertheless, it should be taken into account that the sample size of each trial had been planned based on statistical considerations and had proved to be sufficient to demonstrate the superiority of EPs 7630 over placebo for the predefined primary outcome criterion. In addition, in a sensitive patient group such as children, the inclusion of more than the minimum number of patients required to achieve statistical significance, namely, the achievement of the primary endpoint, in a placebo-controlled clinical trial can hardly be justified from an ethical point of view.

Another methodological weakness could be that the exact number of days of illness absence could not be determined for a substantial proportion of participants. This was the case

because the clinical trials included in the meta-analysis were designed to demonstrate superiority of EPs 7630 over placebo with focus on the predefined primary outcome measure (BSS total score change between baseline and day 7). In the analyzed study population, the proportion of patients who had not returned to their usual daily activities at the end of treatment at day 7 ranged close to 50% in the EPs 7630 group and more than 80% in placebo-treated subjects. Moreover, instead of asking for the precise day of their return to daycare, school, or apprenticeship, subjects or their parents were asked whether the child/adolescent was still at home when they came to a scheduled visit. A focus on duration of absence due to illness would have required a more detailed assessment of the date of return to normal activities as well as a longer observation period. However, for patients who were able to leave their home already during the treatment period, failure to record the exact date may likely have resulted in an overestimation of the true period of illness absence since their return to their normal activities always occurred at or before the visit at which it was documented. Since this occurred more frequently in the EPs 7630 group than in the placebo group, it likely resulted in a conservative bias of the treatment group comparison.

Due to the 7-day treatment design of the underlying trials, it is self-evident that our analysis results cannot provide information on a longer treatment period or long-term effects in children or adolescents with AB. However, there are positive results from a noncomparative, prospective, observational study, in which 742 children aged up to 12 years, who suffered from AB (83.4%) or acute exacerbation of chronic bronchitis (14.3%), were treated with EPs 7630 for the somewhat longer duration of up to 14 days.[57] The authors did not report results on patients' duration of absence from daycare or school, but the BSS total score improved from 6.0 ± 3.0 points at baseline to 2.7 ± 2.5 points (day 7) and 1.4 ± 2.1 points (day 14), and 85.2% of patients were symptom free or reported a clear improvement or recovery at treatment end, while tolerability ratings were reported to be very good.

As our meta-analysis solely focused on the duration of the disease, our results cannot provide information on the safety of EPs 7630 treatment in children and adolescents suffering from AB. However, this question was already addressed in earlier research. A safety review, which covered 29 clinical trials and postmarketing surveillance studies in AB and other ARTIs, analyzed study data from more than 10,000 patients (including 3,939 infants, children, and adolescents up to the age of 18 years).[32] Results showed that EPs 7630 is well tolerated, also in the pediatric population. Further in-depth analysis of data from interventional and noninterventional studies in ARTIs such as AB, which focused on children younger than 6 years, could confirm the safety of EPs 7630 in this age group.[33] Further beneficial study results are available from a recently published open-label, randomized clinical trial comparing two dosage forms of EPs 7630 (syrup and solution) in the treatment of preschool children with AB.[58] It could be shown by this trial that both pharmaceutical forms are equally safe and well tolerated in this patient group. Therefore, one can assume that EPs 7630 achieves the beneficial effects shown by our meta-analysis with an excellent level of safety.

It is also understood that our results cannot provide any information on a comparison of EPs 7630 to other therapeutic options, since the reported work focused on the analysis of prospective, double-blind, randomized, placebo-controlled studies, which are considered to provide the highest quality of interventional evidence.

Finally, it should be considered that the present work is based on data which were gathered and published by authors of the same research group. The detected effect sizes might therefore exhibit potentially greater similarities than would be the case in studies from different research groups. This may result from the way how the distinct parameters were analyzed, how the patients were recruited and sampled, and how the data were assessed by the study interviewers.[59,60] However, the included trials were performed in accordance with Good Clinical Practice, and as such the data and the reported results should be considered robust and scientifically sound.

Conclusion

For children and adolescents between 1 and 18 years of age suffering from AB, the results of this meta-analysis demonstrate that a 7-day treatment with *P. sidoides* extract EPs 7630 significantly reduces the average number of days of illness absence from childcare, school, or apprenticeship and significantly increases the proportion of patients being able to return to their normal activities after a treatment period of 7 days. Since the risk of side effects of EPs 7630 is low,[32] the results encourage more frequent use of this therapeutic option in clinical practice, as EPs 7630 accelerates the return of pediatric patients to their normal activities and, as a consequence, might also enable parents who stay at home to care for their ill child to return to work earlier. This may additionally translate into a significant economic benefit.

Availability of Data and Material

Due to ethical reasons and in terms of data protection law, raw data cannot be shared. To the extent permitted by law, trial data required for validation purposes are already disclosed in results reports on corresponding databases. All relevant data are within the article. Reasonable requests to access the datasets should be directed to the corresponding author.

Ethical Approval and Consent to Participate

All clinical trials included in this meta-analysis were reported to adhere to the principles of Good Clinical practice and the Declaration of Helsinki. The trial protocols and other trial documents required were approved by the respective independent ethics committee and competent authorities. All participants of the single trials gave their informed consent or informed consent was provided by their legal representative, respectively.

Authors' Contribution

K.Z. and W.L. were involved in drafting the manuscript, made substantial contributions to the interpretation of data, revised the work critically for important intellectual content, and approved the version to be published. P.F. was involved in the conceptualization of the study design and medical writing, made substantial contributions to the interpretation of data, revised the work critically for important intellectual content, and approved the version to be published. A.Z. was involved in the conceptualization of the study design and the analysis of data, made substantial contributions to the interpretation of data, revised the work critically for important intellectual content, and approved the version to be published. W.K. was involved in drafting the manuscript, made substantial contributions to the interpretation of data, revised the work critically for important intellectual content, and approved the version to be published.

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Conflict of Interest

K.Z., M.L., and W.K. received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, for scientific services. P.F. and A.Z. are employees of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

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