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The Effectiveness and Safety of a Homeopathic Medicinal Product in Pediatric Upper Respiratory Tract Infections With Fever: A Randomized Controlled Trial

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Abstract

We investigated the clinical effectiveness of a homeopathic add-on therapy in a pediatric subpopulation with upper respiratory tract infections (URTI) in a randomized, controlled, multinational clinical trial. Patients received either on-demand symptomatic standard treatment (ST-group) or the same ST plus a homeopathic medication (Influcid; IFC-group) for 7 days. Outcome assessment was based on symptom and fever resolution and the Wisconsin Upper Respiratory Symptom Survey–21 (WURSS-21). A total of 261 pediatric (<12 years) patients (130 IFC-group; 131 ST-group) were recruited in Germany and the Ukraine. The IFC-group used less symptomatic medication, symptoms resolved significantly earlier ($P = .0001$), had higher proportions of fever-free children from day 3 onwards, and the WURSS-assessed global disease severity was significantly less ($P < .0001$) during the entire URTI episode. One adverse event (vomiting) was possibly related to IFC. IFC as add-on treatment in pediatric URTI reduced global disease severity, shortened symptom resolution, and was safe in use.

Keywords

upper respiratory tract infections, fever, pediatrics, randomized controlled clinical trial, homeopathy, Influcid®

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Introduction

Children are frequently affected by upper respiratory tract infections (URTI) or common colds, causing a lot of missed days from kindergarten or school,[1] as well as missed days off work for parents who have to take leave to take care of their child.[2,3] Each year young children may have as many as 6 to 8 or even more episodes.[4-6] The German Health Interview and Examination Survey for Children and Adolescents found that the 1-year average prevalence of URTI among children and adolescents amounts to 88.5%, with the highest prevalence of almost 94% among children aged 3 to 6 years.[7] Symptoms usually include sore throat, runny nose, general malaise, and low-grade fever at onset, followed by nasal congestion and cough, and peak at around day 3 or 4 after the onset of symptoms. Recovery is typically complete after about 7 to 10 days.[1,8] Viral pathogens like rhinoviruses,[6,9-11] and also influenza viruses,[12] are the major causes of URTI.

Since no universally accepted specific therapy for URTI exists, treatment is mainly symptomatic.[13] Antiviral drugs are only recommended in confirmed influenza

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cases in children under 2 years of age, immunocompromised and chronically ill children, and in cases with severe symptoms.[14] In all other cases antipyretics, anti-inflammatory drugs, expectorants, decongestants, and cough suppressants either alone or in combination can be used.[13] In Germany, medicines are used to treat the common cold and URTI in about 14% of children (7% prescribed and 7% over-the-counter), and about 12% of the prescribed medicines are antibiotics.[15] In general, antibiotics are widely prescribed.[16,17] Since URTI are mainly caused by viruses,[6] an antibiotic treatment is often inappropriate, and only indicated if there is a bacterial infection or to prevent superinfections.[13,18] Overuse further spreads the problem of antibiotics resistance, which is of significant concern from a public health point of view.[19,20]

Homeopathy is increasingly popular.[21] For instance in Germany, 60% of the population has used homeopathy. The great majority (87%) of these users report positive experiences, and the common cold and flu is the most frequently mentioned indication.[22] Homeopathy is the most commonly used complementary medicinal treatment in German children. It is estimated that around 16% of all homeopathic medicines used in children are for flu or rhinopharyngeal complaints.[23] One homeopathic preparation for the treatment of flu-like infections with fever and other acute viral URTI is Influcid® (IFC), which was marketed in its first form as a solution in Germany in 1928, and is currently available in 26 countries worldwide. Preliminary studies indicate that IFC is an effective and safe treatment of typical cold-related symptoms in both adults and children.[24,25]

Since there is no approved specific therapy for URTI and because conventional medicines sometimes lead to side-effects and inappropriate use of antibiotics, there is an interest in the identification and evaluation of alternative therapies with a beneficial risk-benefit profile. We therefore evaluated the effectiveness and safety of IFC as an add-on to symptomatic standard treatment in a randomized controlled trial in adult and pediatric URTI with fever. The primary outcome measure in this trial, "symptom and fever resolution" at day 4, was significantly superior in the IFC-group compared to the standard treatment group. For full results of this trial, see the publication by Thinesse-Mallwitz et al.[26] Given the wide use of homeopathy in children, we aimed to better distinguish and differentiate the effects in preadolescent children. This article reports the findings in this subpopulation.

Materials and Methods

We conducted a subgroup analysis of a randomized, symptomatic standard treatment controlled, parallel groups, open, multicenter, multinational clinical trial. This analysis of preadolescent children was planned in the protocol. The methods of the trial are summarized below and described in detail in the publication by Thinesse-Mallwitz et al.[26] Participants were recruited in the Ukraine and in Germany. Preadolescent children (1 to 11 years of age) with clinical signs and symptoms of an URTI with a duration of up to 24 hours, accompanied by fever ≥37.5°C (axillary body temperature), with at least 1 of 3 types of URTI symptoms (nasal, pharyngeal, cough) and at least 1 of 5 general symptoms (feeling tired, weakness, body aches, irritable/whiney, or less active), were eligible.

The children were randomized to receive either on-demand symptomatic standard treatment (paracetamol, ambroxol, and/or oxymetazoline; ST-group) or IFC tablets in addition to the same symptomatic standard treatment (IFC-group) as an add-on treatment.

IFC tablets, containing a fixed combination of 6 homeopathic single substances (Aconitum D3, Bryonia D2, Eupatorium perfoliatum D1, Gelsemium D3, Ipecacuanha D3, and Phosphorus D5), were administered to children in the IFC-group for a period of 7 days (8 tablets/day during the first 72 hours, 3 tablets/day during the following 96 hours). Paracetamol syrup, ambroxol syrup, and oxymetazoline nasal spray were offered as symptomatic standard medication to all children on an "as-needed" basis.

Parents completed a diary (child's axillary body temperature, symptoms, symptomatic standard medication intake), and the children were followed-up by the investigator for 14 days (baseline visit (day 1), follow-up visits on days 4 ± 1 and 8 ± 1, termination visit on day 15 ± 2, additional follow-up calls on days 2 and 3).

URTI symptoms were assessed using the Wisconsin Upper Respiratory Symptom Survey–21 (WURSS-21), which is a 21-item illness-specific symptom and health-related quality-of-life questionnaire containing 1 global severity item, 10 symptom-based items, 9 functional quality-of-life items, and 1 global change item, each of which are rated on a 0 to 7 Likert-type scale.[27] Six additional complaints questions were asked, whereof 2 questions (irritable/whiny; less active) were specifically applicable to children.

Symptom and fever resolution was defined as a combination of the following criteria: (*a*) WURSS-21 item 1 "How sick do you feel today?" being graded as 0 ("not sick") or 1 ("very mildly") in both the morning and evening and (*b*) mean daily axillary body temperature ≤37.2°C.

Further outcome measures were the time to the resolution of individual symptoms; the global severity and course of the infection; the absence of fever; the amount and duration of paracetamol, ambroxol, and oxymetazoline

consumption; treatment outcome as assessed by both the investigator and the children's parents, on the Integrative Medicine Outcome Scale (IMOS; complete recovery, major improvement, slight to moderate improvement, no change, deterioration); satisfaction with treatment on the Integrative Medicine Patient Satisfaction Scale (IMPSS; very satisfied, satisfied, neutral, dissatisfied, very dissatisfied) as assessed by the parents at the termination visit on day 15.

The safety assessment took place by analyzing the occurrence and nature of adverse events (AEs).

The statistical analysis was based on the intention-to-treat (ITT) principle. The analyzed population consisted of those children who started the treatment plan and had at least one postbaseline outcome assessment. Safety analysis included all randomized children who started the treatment plan. Since the analyses reported in this article are explorative, no type 1 error adjustment took place. The between-group difference in days until symptom resolution, as assessed with the WURSS-21 item 1, was quantified via the median of all pairwise differences, calculated from each groups' individuals' data values, that is, via the Hodges-Lehmann (HL) estimate of location shift[28] and its 95% confidence intervals (CIs); fever resolution was analyzed via calculation of the between-group difference in the proportion of children with absence of fever; global severity during the course of the URTI was analyzed by calculating the area under the curve (AUC) of the WURSS-21 total score (WURSS-21 items 2 to 20) as well as separately for the WURSS symptom subscores (WURSS-21 items 2 to 11) and quality-of-life subscores (WURSS-21 items 12 to 20), plus for the 2 additional children-specific questions. Missing fever and/or WURSS data were imputed based on the "last observation carried forward" method.

Results

Participants

A total of 264 children were randomized (101 in Germany, 163 in the Ukraine). The ITT population consisted of 130 children in the IFC-group and 131 in the ST-group. Figure 1 shows the flow and follow-up of patients in the trial.

Baseline demographic and clinical characteristics of children were similar in both treatment groups (Table 1), with the exception of the impaired ability to perform daily activities and cough, which were more prevalent in the ST-group. Testing for influenza viruses using the polymerase chain reaction (PCR) molecular assay indicated that 18% of the URTI cases were associated with an influenza virus infection.

Effectiveness Analysis

The occurrence of symptom resolution (WURSS-21 item 1) is depicted in Figure 2 as the time to symptom resolution for both groups. The between-group difference (HL: $\Delta_{IFC\text{-}ST}$) was −2 days (95% CI = −2 to −1 day), which indicates that symptom resolution occurred between 1 and 2 days earlier in the IFC-group (Mann-Whitney U test $P = .0001$). For example, symptom resolution in 50% of the children occurred 1.8 days earlier in the IFC-group compared to the ST-group, as shown in Figure 2 by the difference between the polynomial fit curves.

The between-group differences in the proportion of children with absence of fever during the course of the observation period are given in Figure 3. This figure reveals that the proportion of children without fever was statistically significantly higher in the IFC-group from study day 3 (ie, 2 days post baseline) to day 6 (ie, 5 days post baseline). From day 7 (ie, 6 days post baseline) there were no statistically significant differences between the groups, which is consistent with the self-limiting nature of URTI.

Figure 4 illustrates that the between-group difference in the proportion of children who fulfilled both criteria, symptom (WURSS-21 item 1) and fever resolution, became statistically significant at day 5 ($\Delta_{IFC\text{-}ST}$ = 14.9%, 95% CI = 4.4% to 25.5%) and continued until day 10 ($\Delta_{IFC\text{-}ST}$ = 18.8%, 95% CI = 7.3% to 30.3%).

The other WURSS-21 data are summarized in Table 2. The AUC sum score values of the global severity WURSS-21 score and the symptom and quality-of-life subscores indicated a significantly lower disease severity in the IFC-group during the course of the URTI. The between-group difference (HL: $\Delta_{IFC\text{-}ST}$) for the AUC of the global severity score was −235 points (95% CI = −349 to −125 points), demonstrating that the global severity in the IFC-group was less compared to the ST-group. Similarly, the HL shift for the symptom and quality of life subscores were −82 points (95% CI = −129 to −39 points) and −136 points (95% CI = −203 to −67 points), respectively, showing the same development in favor of the IFC-group. The absolute quality-of-life subscore was higher than the symptom subscore in both treatment groups. This points out that the quality-of-life dimension contributed the most to the global severity of URTI. This is even more explicit than what the absolute sum scores suggest, because the quality-of-life subscore is calculated based on 1 item less (9 items) than the symptom subscore (10 items).

The outcomes for the 2 additional complaints imply that children in the IFC-group were less whiny and more

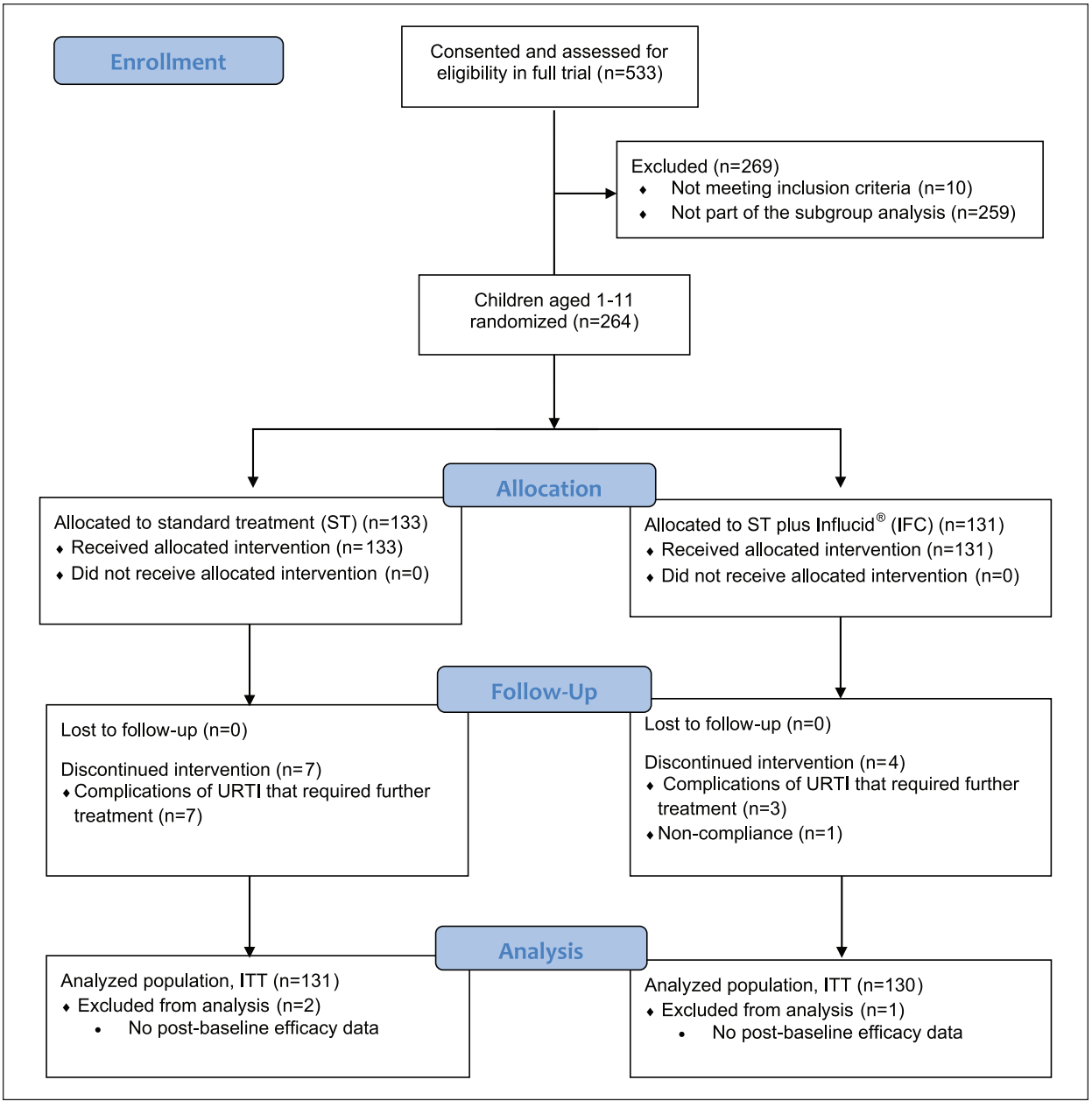

Figure 1. CONSORT trial flowchart.

active, which is consistent with the global severity score outcome data.

Analyses of the other outcome measures are given in Table 3. Fewer children consumed lower quantities of symptomatic drugs and stopped symptomatic drug intake earlier in the IFC-group. The dichotomized physician and parents rated IMOS data show that "complete recovery or major improvement" occurred more frequently in the IFC-group at the first and second follow-up visits on day 4 and day 8. There were no between-group differences at the termination visit on day 15. Analysis of the dichotomized parents' satisfaction data at the termination visit shows that the percentage of "highly satisfied" ratings was higher in the IFC-group and that a "neutral to dissatisfied" rating was more common in the ST-group.

Safety Assessment

Thirty-four children (13%) experienced at least 1 AE during the trial, 18 children (14%) in the IFC-group and

Table 1. Comparison of Demographic, Clinical, and Other Relevant Characteristics.

Characteristics	IFC-Group (n = 130)	ST-Group (n = 131)
Age, years (median [P25, P75])	4.0 [3.0, 7.0]	5.0 [3.0, 7.0]
Sex (male, n (%) / female, n (%))[a]	60 (46)/70 (54)	59 (45)/72 (55)
Height, cm (median [P25, P75])	110 [98, 126]	111 [94, 128]
Weight, kg (median [P25, P75])	19.3 [15.0, 25.0]	19.0 [14.8, 25.0]
Influenza test results (PCR analysis), n (%)[a]		
Influenza A and B negative	103[b] (79)	108 (82)
Influenza A positive	14 (11)	19 (15)
Influenza B positive	10 (8)	4 (3)
Body temperature at baseline, °C, mean (SD)	38.1 (0.5)	38.1 (0.5)
Main URTI symptoms at baseline, n (%)[a]		
Impaired ability to perform daily activities	105 (81)	117 (89)
Nasal symptoms	119 (92)	123 (94)
Pharyngeal symptoms	115 (89)	119 (91)
Cough	94 (72)	108 (82)
Feeling tired	127 (98)	127 (97)
Weakness	125 (96)	128 (98)
Body aches	85 (65)	91 (70)
Irritable/whiny	114 (88)	114 (87)
Less active	125 (96)	126 (96)

Abbreviations: IFC, Influcid; ST, standard treatment; PCR, polymerase chain reaction; SD, standard deviation; P25, 25th percentile; P75, 75th percentile.
[a]Percentages were rounded to the nearest integer.
[b]Test was not done or missing in 3 children.

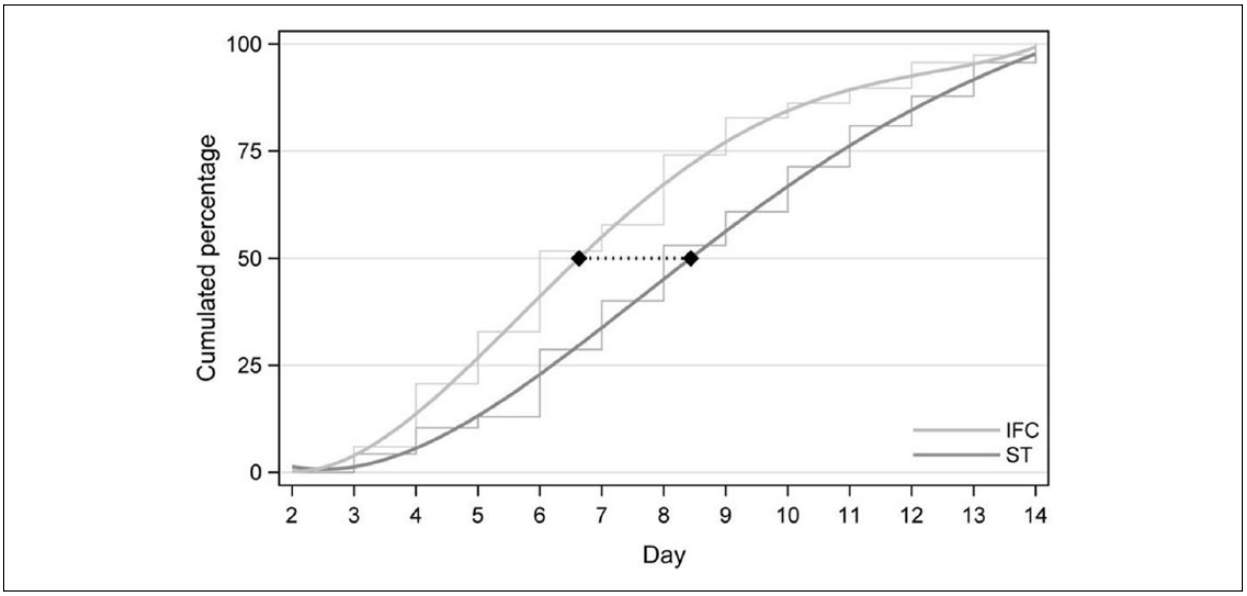

Figure 2. Days until symptom resolution (WURSS-21 item 1) in both treatment groups.
The light grey (IFC-group) and dark grey (ST-group) lines are polynomial fit curves. The dashed line estimates the between-group difference in the number of days after which 50% of patients had symptom resolution.

16 (12%) in the ST-group. A total of 50 single AEs were observed, none of which were assessed as serious. One AE (vomiting) was assessed as possibly related to IFC treatment, and 2 AEs (diarrhea, rash) in a single patient to the symptomatic standard treatment. Two AEs (both in the IFC-group) were of severe intensity, but judged to

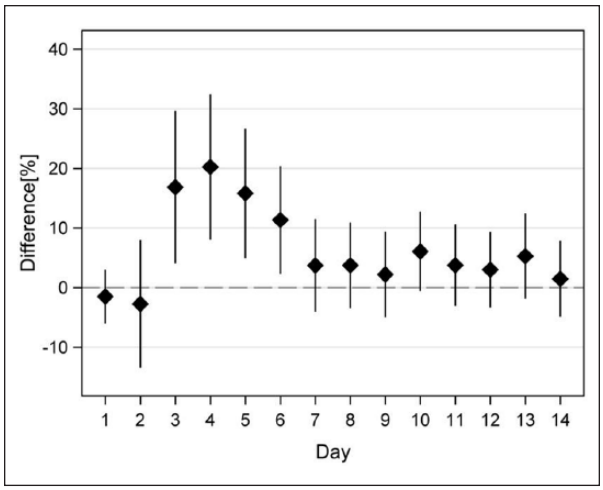

Figure 3. Between-group differences (IFC − ST) with 95% confidence intervals in the proportion of patients without fever during the observational period.
A difference (%) greater than zero indicates a higher proportion without fever in the IFC-group. Day 1 = Baseline.

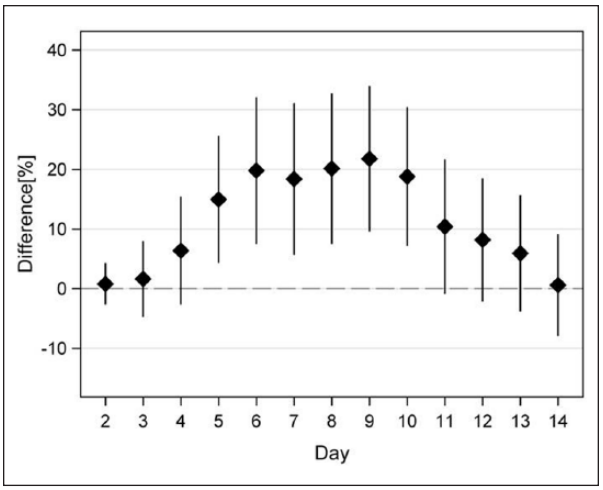

Figure 4. Between-group differences (IFC − ST) with 95% confidence intervals in the proportion of patients who showed symptom and fever resolution.
A difference (%) greater than zero indicates a higher proportion with symptom and fever resolution in the IFC-group.

be unrelated to the medication taken; the remaining AEs were mild to moderate. Three patients in the IFC-group and 7 patients in the ST-group were withdrawn from the study due to AEs classified as complications of URTI and treated as appropriate with antibiotics, glucocorticosteroids, immunomodulators, antihistamines, or antiviral drugs.

Discussion

IFC as an add-on treatment improved the resolution of fever and URTI-related symptoms in preadolescent children, led to earlier symptom alleviation, reduced the use of symptomatic medication, and was well tolerated. The significantly lower global disease severity during the course of the URTI in the IFC-group was highly clinically relevant. Typical symptoms such as whining and the child being less active were positively affected as well.

The main aspects of the study are briefly discussed below; for further details see the publication by Thinesse-Mallwitz et al.[26] The study was randomized, and care was taken to ensure allocation concealment. The population was well defined as URTI of viral origin, where the need for further treatment options is greatest. A further strength of this trial is the high external validity because its design is representative for routine clinical practice where the choice would be to offer IFC as an add-on treatment or not.

Due to the exploratory nature of this analysis, no type 1 error adjustment took place for testing multiple outcomes.

A limitation of this study was the absence of blinding to the treatment allocation, which could have led to a performance bias. In a study of Echinacea for URTI,[29] which included both a "blinded" and an "unblinded" echinacea treatment arm, it was found that the mean global severity in the blinded group (as assessed via the WURSS-21) was not different from the global severity in the unblinded group. This suggests that the possible influence of blinding on the outcome assessment of URTI symptoms using the WURSS-21 may be limited. Blinding could have been addressed in our study by giving an indistinguishable placebo to the control group, but we chose not to do so because we aimed to reflect usual practical care as closely as possible.

Overall, the results in the pediatric population were similar to the results in the full trial, which included adolescents and adults as well. This suggests that the effects of IFC in URTI are relatively stable across different age groups. The main difference from the full data set was a lower cumulative dose of symptomatic medication intake in children, as was to be expected in a pediatric population.

The 6 single homeopathic ingredients of IFC have a long tradition in the treatment of flu-like infections and URTI and the effectiveness and safety of IFC (German name: Nisylen®) in the treatment of URTI was investigated in one open observational study including 94 patients.[24] Another observational study, which included 600 patients (333 adults, 267 children) with URTI, reported an improvement in about 90% of patients after 3 days (M. Heger, 1997; Statistical Report, Deutsche

Table 2. WURSS-21 and Additional Complaints Cumulative Area Under the Curve Scores.

Outcome Measure	IFC-Group (n = 130)	ST-Group (n = 131)	MWU *P* Value
WURSS-21 AUC[a]			
WURSS-21 *global severity* score (items 2 to 20)	541.0 [402, 826]	836.0 [527, 1287]	<.0001
WURSS-21 *symptom* score (items 2 to 11)	245.0 [183, 402]	358.5 [244, 557]	.0003
WURSS-21 *quality-of-life* score (items 12 to 20)	303.0 [197, 470]	471.5 [283, 691]	<.0001
Additional complaints questionnaire AUC[a]			
Irritable, whiny	38.5 [22, 58]	53.0 [29, 80]	.0017
Less active	40.0 [26, 58]	55.0 [34, 78]	.0002

Abbreviations: WURSS-21, Wisconsin Upper Respiratory Symptom Survey–21; IFC, Influcid; ST, standard treatment; MWU, Mann-Whitney *U* test; P25, 25th percentile; P75, 75th percentile.
[a]AUC: Median area under the curve of the WURSS-21 and additional complaints scores during the course of the URTI [P25, P75].

Homöopathie-Union, Karlsruhe, Germany). A further study compared the effectiveness of IFC in children aged 3 to 6 years with URTI to a cohort of children treated with symptomatic medication.[25] In the IFC-group, clinical symptoms declined significantly earlier, as also shown in the present study. A limitation in the above-mentioned studies is the absence of an adequate randomized control group, which is why we conducted the current study.

The use of homeopathy in general and especially in children is common. A longitudinal study indicated that in Germany 28% of infants were treated with homeopathy during their second year of life,[30] and another German survey reported that common cold and flu is the most frequent indication where users (>16 years) report positive experiences with homeopathy.[22] Among adult homeopathy users in the United States, respiratory and ear, nose, and throat complaints are the most commonly treated conditions.[31] The current trial evidence in children on the homeopathic treatment of URTI concerns the prevention of URTI[32-35] and the treatment of chronic recurrent URTI.[36] Moreover, there exists evidence for the treatment of other conditions that can include URTI,[37-40] and some non–controlled studies are available that contain promising data on the treatment of chronic URTI,[41] cough,[42] and the safety of a complex homeopathic medicine in the treatment of acute respiratory tract infections.[43] A comparative cohort study conducted in France showed that homeopathically managed patients with URTI had significantly lower consumption of antibiotics compared to conventionally managed patients, while achieving comparable clinical outcomes,[44] pointing to potential benefits from a health economic perspective and to decrease the public health risk related to antibiotic resistance. While more evidence on the homeopathic treatment of pediatric URTI is needed, homeopathy merits consideration as a treatment option in the early symptom management of otherwise uncomplicated URTI.[45]

The need for safe and effective alternatives for the treatment of pediatric URTI is further increased by the overuse of antibiotics, particularly in preschool pediatric patients.[46] Data from 13 eastern European countries suggest that overuse of antibiotics is common practice.[16] Holstiege et al found that the use of antibiotics is higher in the winter months, which is a likely indicator of the inappropriate use of antibiotics in mostly viral infections.[17] Moreover, the available data suggest that in general the off-label use of antibiotics is particularly prevalent in pediatric patients.[47] This problem is compounded further by the widespread over-the-counter sales of antibiotics,[16] which is currently permitted in many countries.[48]

While controversial and subject to further confirmation, the mechanism of action of homeopathic medicines in infectious diseases is purported to take place via nanoparticles, supporting the natural immune functions of the body.[49,50] Such a mechanism is clearly different from that of antibiotics and in line with one of homeopathy's core principles: "Treat the patient, not the disease." In self-limiting diseases such as URTI, an improved immune function would express itself as a shorter and less severe symptomatic course of URTI, which is what we observed in our trial. It is known that single or intermittent repetitions of low-intensity levels of a foreign stressor or substance initiate a process of progressive endogenous response amplification over time.[50] Within the organism as a complex adaptive system or network, the intermittent administration of IFC might contribute to the body's intrinsic healing process in the sense of a stimulus or stressor.

Further controlled studies to investigate and confirm the role of homeopathic medicinal products including IFC in the treatment of URTI are warranted. Since there is a rising and increasingly intractable problem of antibiotics resistance,[51,52] homeopathy may also be able to contribute at a public health level to contain this problem due to an antibiotic sparing effect. The World Health Organization argues that there is an important role for the pharmacist, as an interface between the health care

Table 3. Other Outcome Measures.

Outcome Measure	IFC-Group (n = 130)	ST-Group (n = 131)	Statistical Test[a]	*P* Value
Symptomatic medication use[b]				
Patients with any symptomatic drug use, n (%)[c]	117 (91)	129 (99)	χ^2	.0055
Duration symptomatic drug use (median days [P25, P75])	6 [4, 9]	8 [7, 12]	MWU	<.001
Paracetamol (mg) total amount (median [P25, P75])	600.0 [0, 1600]	800.0 [200, 2200]	MWU	.0723
Ambroxol (mg) total amount (median [P25, P75])	75.0 [0, 225]	180.0 [83, 300]	MWU	<.001
Oxymetazoline (µg) total amount (median [P25, P75])	292.5 [0, 563]	495.0 [158, 855]	MWU	.0003
Overall outcome assessed by IMOS *physician* rating, n (%)[c]				
Complete recovery or major improvement at day 4 ± 1 visit	77 (59)	33 (25)	χ^2 (binary)	<.001
Complete recovery or major improvement at day 8 ± 1 visit	120 (92)	91 (71)	χ^2 (binary)	<.001
Complete recovery or major improvement at day 15 ± 2 visit	123 (96)	118 (94)	χ^2 (binary)	.526
Overall outcome assessed by IMOS *parents* rating, n (%)[c]				
Complete recovery or major improvement at day 4 ± 1 visit	71 (55)	32 (24)	χ^2 (binary)	<.001
Complete recovery or major improvement at day 8 ± 1 visit	123 (95)	91 (71)	χ^2 (binary)	<.001
Complete recovery or major improvement at day 15 ± 2 visit	123 (96)	118 (94)	χ^2 (binary)	.526
Satisfaction assessed by IMPSS parents rating day 15 ± 2, n (%)[c]				
Very satisfied	96 (75)	34 (27)	χ^2 (binary)[d]	<.0001
Satisfied	27 (21)	64 (51)		
Neutral	3 (2)	22 (18)		
Dissatisfied	2 (2)	3 (2)		
Very dissatisfied	0 (0)	1 (1)		

Abbreviations: IFC, Influcid; ST, standard treatment; MWU, Mann-Whitney *U* test; χ^2, chi-square test; IMOS, Integrative Medicine Outcome Scale; IMPSS, Integrative Medicine Patient Satisfaction Scale; P25, 25th percentile; P75, 75th percentile.
[a]MWU test or χ^2 test.
[b]Basis: Patients with existing diary data (IFC-group n = 129; ST-group n = 131).
[c]Percentages were rounded to the nearest integer.
[d]For the χ^2 test, the following binary categories were used ['Very satisfied' or 'Satisfied'] or ['Neutral' or 'Dissatisfied' or 'Very dissatisfied'].

system and the patient, to help dealing with the increasing problem of antibiotics resistance.[48] This fits well with the pharmacist also being an important interface with patients regarding the use of homeopathic medicines, particularly for self-limiting conditions such as URTI.

IFC as an add-on treatment for URTI in pediatric care reduced the global disease severity, resulted in significantly earlier symptom resolution, and was safe in use. While further confirmatory studies are needed, this study suggests that IFC could make a positive contribution to the management of URTI in pediatric patients.

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Authors' Note

This study was approved by the appropriate ethical committees (Ethics Committee of the Bavarian State Medical Association [Ethikkommision der Bayerischen Landesärztekammer], No. 10068; and Central Ethics Commission of Ministry of Healthcare of Ukraine, No 5.12-1109/KE) and has been conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. All subjects or their parents/legal guardians provided informed consent prior to inclusion in the study.

Author Contributions

RVH: Contributed to interpretation; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MTM: Contributed to conception and design; contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
VM: Contributed to conception and design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
SLB: Contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
SW: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KT: Contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
JB: Contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
PK: Contributed to conception and design; contributed to interpretation; critically revised manuscript, gave final approval, agrees to be accountable for all aspects of work ensuring integrity and accuracy

Declaration of Conflicting Interests

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