



Research Article

Homeopathic Treatments of Upper Respiratory and Otorhinolaryngologic Infections: A Review of Randomized and Observational Studies

Paolo Bellavite^{1*}, Marta Marzotto¹ and Beatrice Andreoli²

¹Department of Medicine, Section of General Pathology, University of Verona, Verona, Italy

²Homeopathic Medical School, Verona, Italy

Abstract

Introduction: Homeopathy is a therapeutic natural medical alternative that is widely and increasingly being used, even for pediatric patients. Given this trend, it is essential that clinicians have the resources to advise their patients as to the potential benefits and harms of this complementary therapy. The aim of this work is to describe the available literature cited in PubMed concerning the homeopathic treatments on human subjects (both children and adult) for common Upper Respiratory Tract Infections (URTI), otitis, rhinitis, sinusitis, rhinosinusitis, pharyngitis and tonsillitis.

Methods: The PubMed search made use of the keywords “homeopathy” or “homeopathic”, and the names of the indicated diseases. The report covers all forms of homeopathic therapy, namely: a) classical individualized homeopathy, b) ailment-specific medicines and complexes. In order to take into account the whole mass of literature, the evidence of the clinical effectiveness is summarized according to semi-quantitative criteria, based on the number of randomized and non-randomized papers published in each group of ailments. The medicines used in the various studies are classified and described.

Results: A total of 40 clinical studies, published until the ends of 2018, which assess the effectiveness of the homeopathic treatment in one of the abovementioned conditions are reported and classified. The studies are randomized or equivalence studies with control group (n=21), non randomized or observational (n=19) and concern different clinical approaches, namely individualized using high homeopathic dilutions or non-individualized using complex drug formu-

lations. Studies have revealed mixed results, suggesting that some homeopathic formulations may have significant effects in URTI and otorhinolaryngological infections. Several studies have demonstrated benefits to patients' quality of life and symptom scoring, or equivalence with the conventional medical approach. Scarcity of data and uncertainty still exists in literature on the effectiveness of individualized approach in URTIs. 21 different medicines were used in a minimum of two published reports.

Conclusion: Homeopathic formulations in upper respiratory tract and otorhinolaryngological infections are likely effective and the individualized approach in non severe otitis is possibly effective. Homeopathic treatments may help when use of antibiotics is not indicated. Due to the heterogeneity of approaches and of drugs used, additional studies will be required to evaluate the possible integration of homeopathy into the standard of care for the treatment of respiratory and otorhinolaryngologic ailments.

Keywords: Homeopathic complex formulations; Homeopathic medicines; Homeopathy; Otorhinolaryngologic infections; Upper respiratory tract infections

Introduction

Homeopathic medicines are often used in the hope of resolving ailments not successfully cured by conventional drugs, or as a complementary treatment to reduce the consumption of anti-inflammatory drugs or steroids that may have adverse effects, to relieve certain symptoms and improve the quality of life [1-8]. A worldwide median of 1.5% of patients are reported to use homeopathy, with great differences among nations (range 0.2-8.2%) [9]. Homeopathic medicines are also used in the treatment of common respiratory infections and ear-nose-throat ailments [10,11].

A systematic review revealed that antibiotics have no early effect on pain of acute Otitis Media (OAM) and only a modest effect on the number of children with tympanic perforations [12]. In this context, a Cochrane review reported that there is insufficient evidence as to the effectiveness of antibiotics in preventing recurrent sore throat [13]. There is growing knowledge of the problems of antibiotic side effects and resistance [14-17].

The homeopathic approach can be advantageous where effective and safe therapies are not available or not indicated. The majority of Upper Respiratory Tract Infections (URTI) is caused by rhinoviruses and antibiotics may provide only modest absolute benefits [18,19]. Bacterial infections are rare, supporting the concept that the common cold is almost exclusively a viral disease [20-22].

AOM is one of the most common diseases of childhood, mostly between ages 6 and 15 months, and is very often treated with antibiotics but at the earlier stages a mild AOM can be managed with a “wait and watch” approach [23-27]. Even the effect of systemic corticosteroids on important clinical outcomes in AOM remains uncertain [26]. Nowadays, different kinds of therapies for rhinitis are available and, in this context, one option for treating cold symptoms is with homeopathy as an adjunctive or first-line approach [28].

*Corresponding author: Paolo Bellavite, Department of Medicine, Section of General Pathology, University of Verona, Strada Le Grazie 8, 37134, Verona, Italy, Tel: +39 0458027120; Fax: +39 0458027127; E-mail: paolo.bellavite@univr.it

Citation: Bellavite P, Marzotto M, Andreoli B (2019) Homeopathic Treatments of Upper Respiratory and Otorhinolaryngologic Infections: A Review of Randomized and Observational Studies. J Altern Complement Integr Med 5: 068.

Received: May 28, 2019; **Accepted:** June 06, 2019; **Published:** June 13, 2019

Copyright: © 2019 Bellavite P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

A cross-sectional survey conducted in a pediatric otolaryngology clinic in Israel reported that 32% of parents considered complementary therapies in their previous or current use and 36% of them used homeopathy [29]. Evidence sustains its use, due to its greater safety, speed of improvement and cost savings [30]. An international survey of acute pediatric tonsillopharyngitis showed that 62% of participants used homeopathy and suggested that an integrative approach may reduce excessive antibiotic prescriptions [31]. Homeopathy is controversial, but demonstrably safe [32-35]. Consequently, it is important to provide clear information about the effectiveness of complementary and alternative treatments including homeopathy, through high-quality studies carried out with a rigorous methodology. Besides the classic placebo-controlled and randomized trials, for clinical trials of homeopathy to be accurate representations of practice, we need more modified approaches that take into account the complexity of homeopathic intervention [36-38].

Our previous systematic review on the effect of homeopathy in immunological disorders also included non-peer-reviewed papers published until 2010, but in this report we have restricted the report to clinical trials and observational studies cited by PubMed, which is considered the most important search system of bibliographic resources, also for homeopathy and other CAMs [38-40]. As it is known (see for example <https://www.nlm.nih.gov/lstrc/jsel.html>), the scientific merit of a journal's content is the primary consideration in selecting journals for indexing in PubMed, especially on the explicit process of external peer review and adherence to ethical guidelines. The publication of a paper in a journal cited by PubMed is not in itself a guarantee of quality, but it can be considered an important criterion of validity, since it is certain that the work was judged by experts in the field before is accepted. Therefore, it could be useful to explore information present in this bibliographic system on the safety and effectiveness of homeopathy in clinical fields in which it is most frequently used. While acknowledging that additional relevant studies might be contained in other databases that we have not searched, we present the overall body of evidence reported in PubMed, showing some technical details in tables, we discuss the most relevant published papers and finally we summarize the positive and negative findings, weighting them according to semi-quantitative criteria.

Since homeopathic medicines are often used in complex formulations, it is interesting to see which medicines occur more frequently in such formulations and to compare the traditional statements of *Materia Medica* with the more modern evidence derived from scientific literature.

Methods

Eligibility criteria included all the available literature on human subjects in the mentioned fields, from 1981 to 2018, published in Journals included in PubMed, in any language. In this review, all forms of homeopathic therapy have been included, namely: a) classical individualized homeopathy, b) ailment-specific medicines and complexes.

The initial strategy of the search included all the PubMed papers with keywords "homeopathy" or "homeopathic" AND suitable other keywords related to different ailments included in the categories of URTI and/or otorhinolaryngologic ailments (e.g., "homeopathy" or "homeopathic" AND "infections"). Then, an article had to satisfy the following criteria to be included in the analysis: (i) the study

subjects were humans, (ii) the study was original, involved at least one homeopathic medicine, (iii) sufficient information concerning study type, number of subjects, diagnosis, treatment (s) and outcomes was provided. The last search was done on May 21st, 2019. Retrieved papers were read by two investigators (P. B. and B. A.), who classified papers according to the type of study and type of homeopathic approach, then recorded the relevant data concerning number of patients included and main outcomes. As a part of this step, the study type was assessed using the following scale: 1a: Randomized Controlled Trial (RCT) carried out in double-blind conditions; 1b: randomized (open) controlled study or equivalence study; 2: non randomized controlled clinical trials, 3: prospective observational study, without control group; 4: retrospective study of case series. Reviews, single cases and expert opinions were excluded. Each study was critically evaluated based on methodology to determine if the approach fulfilled the inclusion criteria. All processes for obtaining and confirming data were discussed by the team.

Upper Respiratory Tract Infections (URTI) is defined as "An infectious process affecting the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea). Symptoms include congestion, sneezing, coughing, fever and sore throat." The 2019 ICD-10-CM Diagnosis Code J06 (Acute upper respiratory infections of multiple and unspecified sites) was applied to papers naming "URTI" without further precise diagnostic criteria? Other papers including the study of more precise ailments (e.g., tonsillitis, otitis media, etc.) have been included in the broad categories defined by the disease, without precise ICD codes, because the original papers did not report them.

The components of the homeopathic medicines have been identified from the methods of each paper or, if not reported, from the data sheets and consumer medicine information published by pharmaceutical companies. A summary of the traditional knowledge of the medicines used in a minimum of two scientific papers was extracted by the authors from the generalities of the *Boericke Materia Medica* [41].

To standardize the nomenclature of medicines, the centesimal (x 100 dilution at each step) and decimal (x 10 dilution at each step) homeopathic dilutions/dynamizations were here designed as "C" and "D" respectively, and the numerical grade of dilution. MT means mother tincture. Where indicated, "High" dilutions were designed as those that were above the Avogadro-Loschmidt limit, set by convention at C12 or D24.

Results

Using keywords "homeopathy" or "homeopathic", 6506 papers were retrieved. Most of these papers were excluded from analysis since they concerned basic research, reviews, discussions, or ailments not included in the topics of this study. In fact, adding further keywords to the search, the following number of papers was retrieved: Homeopathy OR homeopathic AND "infections" = 310; AND "rhinitis" = 96, AND "URTI" = 17, AND "otitis" = 43, AND "pharyngitis" = 13, AND "tonsillitis" = 12, AND "common cold" = 28, AND "sinusitis" = 29, AND "rhinosinusitis" = 9. After excluding duplicates in these different searches and reading the papers, according to the topics and criteria described in Methods, 40 different papers were retrieved and included in this review.

The papers included in the review, with methodologic details and main outcomes, are reported in table 1, in chronologic order.

1 st Author and year	Study type ^a	N. of subjects	Conditions (diagnosis)	Treatment (s)	Outcomes	Key results	Ref.
Gassinger 1981	1b	53	Acute rhinitis	Eupatorium perfoliatum vs. aspirin	Symptoms severity score	Equivalence between homeopathy and allopathy	[42]
Maiwald 1988	1b	170	Acute rhinitis	Homeopathic complex Gripheel vs. aspirin	Symptoms severity score	Equivalence between homeopathy and allopathy	[43]
de Lange de Klerk 1994	1a	170 children	URTI	Individualized vs. placebo	Frequency, duration and severity of rhinitis, pharyngitis episodes	Little, not significant, effect of homeopathy vs. placebo	[44]
Friese 1997	2	131 children	AOM	Individualized vs. allopathy	Duration of pain and therapy	Homeopathy slightly better than conventional therapy	[45]
Wiesenauer 1998	3	107	Acute tonsillitis	Low-dilution homeopathic complex of <i>Phytolacca americana</i> , <i>Guajacum officinale</i> , <i>Capsicum annuum</i>	Subjective and objective symptoms	Decrease of symptoms in most patients (uncontrolled)	[46]
Adler 1999	3	119	Acute sinusitis	Homeopathic complex <i>Sinusitis PMD</i>	Symptoms	Trend to positive (uncontrolled)	[47]
Rau 2000	3	48 both adults and children	Acute tonsillitis	Complex of <i>Phytolacca americana</i> , <i>Guajacum officinale</i> , <i>Capsicum annuum</i>	Symptoms	Decrease of symptoms in most patients (uncontrolled) with no adverse effects	[48]
Frei 2001	3	230 children	AOM	Individualized	Individualized	Improvement in 39% of patients after 6 h, another 33% after 12 h (uncontrolled)	[49]
Riley 2001	2	456	URTI	Individualized homeopathy vs. allopathy	Healing or a major improvement after 14 days of treatment, adverse effects	Improvement in 82.6% of homeopathic patients, 68% of allopathic	[50]
Jacobs 2001	1a	75 children	AOM	Individualized vs. placebo	Treatment failure and symptoms score	Less failure in verum group, not significant; little and significant decrease of symptoms in verum group	[51]
Rabe 2004	2	485	URTI	Homeopathic complex <i>rippheel</i> vs. anti-inflammatory agents	Symptoms	Equivalence between homeopathy and allopathy	[52]
Ammerschlager 2005	2	739	Rhinitis and sinusitis	Low-dilution homeopathic complex formulation <i>Euphorbium compositum</i> , nasal spray vs. xylometazoline	Symptoms and tolerability	Equivalent efficacy	[53]
Steinsbekk 2005 (a)	1a	251 children	URTI	Parents-selected homeopathic medicines vs. placebo	Prevention of new episodes, symptoms scores	No effectiveness of homeopathy over placebo	[54]
Steinsbekk 2005 (b)	1b	169 children	URTI	Individualized vs. conventional care	Symptoms score	Decrease of days with symptoms in homeopathic group	[55]
Trichard 2005	4	499 children	Acute rhinopharyngitis	Homeopathic strategy vs. allopathic strategy (e.g. antibiotics).	Number of episodes, quality of life, costs	Various indices significantly in favor of homeopathic strategy, lower medical costs (case series, uncontrolled)	[56]
Schmiedel 2006	3	397	Acute rhinitis	Homeopathic complex <i>Engystol</i> vs. conventional treatment	General and local symptoms	Homeopathic medicine equivalent to the conventional treatment	[57]
Steinsbekk 2007	1a	208 children	URTI	Individualized vs. parents-selected medicines	Prevention of new episodes, symptoms scores	No difference between the two methods of prescription	[58]
Haidvogel 2007	2	1557	URTI	Homeopathic strategy vs. allopathic (e.g. anti-inflammatory drugs, antibiotics)	Healing or major improvement after 14 days of treatment	Homeopathic treatment not inferior to the allopathic and best tolerated	[59]
Zabolotnyi 2007	1a	113	Maxillary sinusitis	Homeopathic complex Sinfrontal vs placebo	Symptoms	Significant improvement over placebo	[60]
Kneis 2009	1a	113	Maxillary sinusitis	Homeopathic complex Sinfrontal vs placebo and vs antibacterials	Cost savings	Significant cost savings comparing both with placebo and antibacterials	[61]
Witt 2009	3	134	Chronic sinusitis	Individualized	Symptoms, quality of life	Major improvement persisting at least 2 years (not controlled)	[62]
Ramchandani 2010	3	30 children	URTI	Individualized	Number of episodes during 6 months before and after treatment	Decrease of episodes after homeopathic treatment	[63]

Taylor 2011	1a	119 children	AOM	Standard therapy alone vs standard therapy plus homeopathic ear drops	Symptoms	Lower symptoms and faster improvement in children receiving ear drops	[64]
Bernstein 2011	1a	42	Nonallergic rhinitis	Homeopathic complex <i>Sinus Buster (Capsicum annuum and Eucalyptol)</i> vs placebo	Symptoms	Improvement of symptoms	[65]
Sinha 2012	1a	81	AOM	Individualized homeopathy vs conventional treatment	Symptoms and tympanic membrane examination over 21 days	No significant differences; quicker improvement and less use of antibiotics in homeopathy group	[66]
Nayak 2012	3	628 both children and adults	Chronic sinusitis	Individualized homeopathy	Symptoms and X-ray appearances	Highly significant improvement	[67]
Taylor 2014	1a	206 children	AOM	Antibiotic vs antibiotic plus homeopathic ear drops	Filling of antibiotic during the follow-up	Less antibiotic use in children treated with homeopathic ear drops	[68]
Zanasi 2014	1a	80	URTI	Homeopathic complex <i>Stodal (Anemone pulsatilla, Rumex crispus, Bryonia dioica, Ipecacuanha, Spongia tosta, Sticta pulmonaria, Antimonium tartaricum, Myocarde, Coccus cacti, Drosera)</i> vs placebo	Cough severity and sputum viscosity	Improvement of clinical parameters	[69]
Grimaldi Bensouda 2014	3	518 (on 8559)	URTIs	Homeopathic prescription vs conventional prescription	Clinical	Less use of antibiotics and antipyretic/anti-inflammatory drugs in people treated with homeopathy alone or homeopathy plus conventional therapy	[70]
Malapane 2014	1a	30 children	Acute viral tonsillitis	Homeopathic complex <i>Tonzolyt (Atropa belladonna, Calcarea phosphorica, Hepar sulphur, Kalium bichromium, Kalium muriaticum, Mercurius protoiodid, Mercurius biniodid)</i> vs placebo	Signs and symptoms and intensity of pain	Improvement of symptoms and pain	[71]
Michalsen 2015	3	1050 both adults and children	Viral rhinitis	Homeopathic complex <i>Contramutan N Saft</i>	Safety and effectiveness of the product	Safety and effectiveness both in adults and children	[72]
Zanasi 2015	3	85 children	URTI	Homeopathic syrup (<i>Stodal</i>) vs homeopathic syrup plus antibiotic	Symptoms and adverse side effects	Equal reduction of symptoms; more adverse side effects in the second group	[73]
Thinesse Mallwitz 2015	1b	523 both children and adults	URTI	Standard treatment alone vs standard treatment plus homeopathic complex <i>Influcid (Aconitum, Bryonia, Eupatorium perfoliatum, Gelsemium, Ipecacuanha, and Phosphorus)</i>	Clinical	Less use of symptomatic medications, earlier improvement of symptoms and better tolerability in the second group	[74]
Beghi 2016	4	459	Respiratory tract infections (not specified)	Oscillococinum vs no treatment	Clinical	Reduction of respiratory infection episodes during time	[75]
Jong 2016	1b	200 children	URTI	Homeopathic complex <i>CalSuli-4-02 (Calcium carbonicum, Calcium fluoratum, Calcium phosphoricum, Sulphur iodatum)</i> vs homeopathic complex (<i>Gentiana, Aconitum, Bryonia, Ferrum phosphoricum, Acidum sarcolacticum</i>)	Symptoms, treatment satisfaction, antibiotic use, safety, tolerability	Comparable reduction of symptoms and antibiotic use; better treatment satisfaction and tolerability with CalSuli-4-02	[76]
Pedrero Escalas 2016	1a	97	Otitis media with effusion	Aerosol standard therapy (mucolytic and steroids) plus placebo vs aerosol standard therapy plus homeopathic complex	PNO examination and tympanometry	No significant differences and similar adverse effects	[77]
Van Haselen 2016	1b	261 children	URTI	Standard treatment alone vs standard treatment plus homeopathic complex <i>Influcid</i>	Symptoms and fever resolution	Less use of symptomatic medications and earlier improvement of symptoms and fever in the second group	[78,78]

Jacobs 2016	1a	154 children	URTI	Homeopathic complex (<i>Allium Cepa, Hepar Sulph Calc, Natrum Muriaticum Phosphorous, Pulsatilla, Sulphur, Hydrastis</i>) vs placebo	Symptoms severity (Runny nose, Sneeze, Cough, Congestion)	No immediate relieving effect, improvement in composite symptoms score, especially in the first day of treatment	[79]
Palm 2017	1b	256	Moderate recurrent tonsillitis	Standard symptomatic treatment alone vs standard symptomatic treatment plus homeopathy complex <i>Sil-Atro-5-90</i>	Mean time period between consecutive ATI	Lower risk of ATI in patients treated also with homeopathy	[80]
Voss 2018	1b	89 children	URTI	Homeopathic complex (<i>Drosera, Coccus Cacti, Cuprum sulphuricum, Ipecachuana</i>) vs placebo	Clinical	Improvement of symptoms and equal tolerability	[81]
Allaert 2018	3	414 children	URTI	Management of cough with two homeopathic syrups or with allopathic drugs by pharmacists	Cough disappearance and patient satisfaction	Better improvement with homeopathic syrups and same satisfaction	[82]

Table 1: Homeopathic clinical studies in the fields of infections of upper airways and ear-nose-throat ailments.

***Clinical trial:** 1a: double-blind randomized controlled; 1b: non-blinded randomized (open) controlled or equivalence study; 2: non randomized controlled clinical trial; 3: prospective observational study, without control group; 4: retrospective study of case series.

Randomized Trials of Individualized Homeopathy

De Lange and coworkers carried out a double-blind, randomized study which they used to evaluate the frequency, duration and severity of rhinitis, pharyngitis and tonsillitis in a group of children [44]. The homeopathic prescription included “constitutional” medicines for preventive purposes and medicines for the treatment of acute phases. The year-long therapy was continuously adjusted on an individual basis, and the data was collected by means of diaries kept by the parents and attending physicians. The results showed that the homeopathic therapy was slightly but not significantly better than the placebo: the mean number of infective episodes was 7.9/year in the treated group and 8.4/year in the control group. The children in the active group experienced episodes that were generally shorter and less severe; the percentage of children not requiring antibiotics was 62% vs. 49% in homeopathy and conventional therapy respectively. The authors concluded that the differences between the two treatments were interesting but small (odds ratio favoring homeopathy versus placebo: 1.67, 95% CI: 0.96-28.9).

A randomized double-blind placebo controlled pilot study was carried out on children with otitis media [51]. Subjects presenting middle ear effusion and ear pain and/or fever for no more than 36 h were enrolled in the trial. They received either an individualized homeopathic medicine or a placebo; administered orally three times daily for 5 days or until symptoms subsided. The 4 most commonly medicines prescribed included *Pulsatilla*, *Chamomilla*, *Sulphur* and *Calcarea carbonica*. Outcome measures included the number of treatment failures after 5 days, 2 weeks and 6 weeks. Diary symptom scores during the first 3 days and middle ear effusion at 2 and 6 weeks after treatment were also evaluated. There were fewer treatment failures in the group receiving homeopathy after 5 days, 2 weeks and 6 weeks. However these differences were not statistically significant. Diary scores showed a significant decrease in symptoms at 24 and 64 h after treatment, in favor of homeopathy ($P < 0.05$).

In summary, randomized trials of individualized homeopathy are few and the results are conflicting, thus preventing any possible conclusion.

Randomized Trials of Ailment Specific Formulations

Although people are best treated with an individualized medicine chosen by a professional homeopath, the use of complex homeopathic medications is very popular essentially because it is easier to match the drug with the symptoms of the disease. A series of medicines for non allergic rhinitis, prepared from various combinations of *Luffa opercolata*, *Kalium bichromicum* and *Cinnabaris* (in low homeopathic dilutions) were compared with a placebo in a double-blind trial [83]. Criteria for the therapeutic result were headache, blocked nasal breathing, trigeminal tenderness, reddening and swelling of nasal mucosa and postnasal secretion. All combinations were ineffective in the treatment of those sinusitis symptoms. The author’s conclusion was that, unless other data emerge from a study of individualized homeopathic prescriptions (“repertorisation”), the drugs should not be considered active in acute or chronic sinusitis in the general population. They also point out that similar negative results have been obtained with antibiotics, nasal decongestants and drainage of the nasal cavities.

Sinfrontal is a complex homeopathic medication (containing *Cinnabaris* 4D, *Ferrum phosphoricum* 3D, *Mercurius solubilis* 6D) that is used for a variety of upper respiratory tract infections and has shown promise as a treatment for rhinosinusitis. A prospective, randomized, double-blind, placebo-controlled trial, carried out in Ukraine, investigated the efficacy of this complex homeopathic medication compared to a placebo, in patients with maxillary sinusitis [60]. Fifty-seven patients received *Sinfrontal* and 56 patients received placebo. Between day zero and day seven, *Sinfrontal* produced a significant reduction in the total symptom score compared to the placebo ($p < 0.0001$). After three weeks, 68.4% patients on active medication had a complete remission compared with 8.9% of placebo patients. Eight adverse events were reported, assessed as being of mild or moderate intensity. The authors suggest that this complex homeopathic medication is safe and appears to be an effective treatment for acute maxillary sinusitis.

A cost-utility analysis based on data from this trial calculated that *Sinfrontal* led to incremental savings of €275 per patient compared with the placebo over 22 days, essentially due to markedly reduced absenteeism from work [61].

A randomized, double-blind, parallel trial was carried out in 2011 to investigate the efficacy and safety of *ICX72*, or “*Sinus Buster*”, a proprietary homeopathic preparation of *Capsicum annum* 3D (chili pepper) and *Eucalyptol*, versus placebo administered continuously over 2 weeks in subjects with nonallergic rhinitis [65]. In this trial, two kinds of endpoints were established: the primary one was the change in Total Nasal Symptom Scores (TNSS) from baseline to end of study, then the secondary ones included changes in Individual Symptom Scores (ISS) over 2 weeks and average time to first relief. Authors recorded mean TNSS and ISS after single dosing at different intervals over 60 minutes and they analyzed rhinitis quality of life, rescue medication and safety endpoints. The study has shown significant differences in changes from baselines to the end of the study for both TNSS and ISS parameters. Patients treated with *ICX72* reported an improvement in nasal congestion, sinus pain, sinus pressure, and headache at 5, 10, 15 and 30 minutes, persisting at 60 minutes for nasal congestion and sinus pain ($P < .05$). In addition, there were no differences in adverse side 14 effects, rescue medication, rebound congestion or impaired olfaction at the end of the study when compared with placebo patients. They concluded that intranasal capsaicin, when used continuously over 2 weeks, rapidly and safely improve symptoms in non-allergic rhinitis subjects. Interestingly, in this therapeutic context *Capsicum annum* can be seen as working according the traditional “similia” rule, or “hormesis” concept in modern terms [84-86]. In fact its active principle is capsaicin, a strongly irritating compound whose initial receptor excitation is followed by a refractory period. The use of low doses exploits the rebound reaction utilizing the long-lasting refractory period to decrease mucosal irritation and related symptoms. Recently the use of capsaicin in non-allergic rhinitis has also been suggested in non-homeopathic literature and a Cochrane review has suggested that capsaicin may be an option for alleviating the symptoms of idiopathic non-allergic rhinitis [87,88].

A randomized trial was carried out to assess the effectiveness of a homeopathic ear drop for treatment of otalgia in children with acute otitis media [64]. Patients were 120 children aged from 6 months to 11 years old, diagnosed with AOM, tympanic membrane (s) distinctly abnormal and significant discomfort. Exclusion criteria were a chronic medical condition, a treatment with antibiotics within the previous 2 days or with homeopathic medicine during the previous 30 days, a diagnosis of AOM received during the preceding 30 days or a perforated tympanic membrane. Every patient, after the enrollment phase, received an immediate prescription for an oral antibiotic, or a delayed antibiotic prescription, as well as treatments for otalgia such as acetaminophen, ibuprofen, or topical benzocaine ear drops. In addition to these, the severity of the child’s AOM at presentation was assessed using (a) the “Otoscopy Scale” (OS-8), after which only children with an OS-8 score of ≥ 4 were eligible for the study and (b) parental rating of symptoms using the faces scale, after which only children whose parents indicated that the symptom severity was 4 or greater (corresponding to a ‘moderate problem’ or more) were eligible for the study. At enrollment, patients were randomized by a computer to standard therapy alone or standard therapy plus homeopathic ear drops named *Hy-lands Earache Drops*® (containing a combination of six medicines: *Pulsatilla*, *Chamomilla*, *Sul-phur*, *Calcarea carbonica*, *Belladonna* and *Lycopodium*, all in the 30C potency range). Ear drops were administered in the following way: 3-4 drops up to 3 times/day, as needed for relief of AOM symptoms for a maximum of 5 days. Compared to children receiving standard therapy alone, those who also

received ear drops had faster symptom relief, with significantly milder symptoms at the second and third assessments, which approximately correspond to the period of 24-36 h after the diagnosis of AOM, suggesting that homeopathic ear drops may be most effective in the early period after a diagnosis of AOM and could possibly reduce the use of delayed antibiotics. This trial concluded that homeopathic ear drops are moderately effective in treating otalgia in children with AOM and that they may be most effective in the early period after a diagnosis of AOM.

A further randomized trial was conducted on a pediatric population of 206 children aged from 6 months to 11 years, with diagnosis of AOM and managed with a delayed antibiotic approach [68]. They were randomized to receive homeopathic ear drops plus standard therapy or standard therapy alone. Only 26.9% of children of the “homeopathy group” received antibiotic therapy, versus 41.2% of children randomized in the other group ($P=0.032$). Based on this data, the authors suggested that homeopathic ailment specific therapies may be helpful in reducing the prescriptions of antibiotics in children with AOM.

A single-center, randomized, double-blind, placebo-controlled clinical trial was published in 2014 to test the efficacy of a homeopathic syrup in treating cough, due to non-complicated URTI in adults [69]. The administered homeopathic syrup was *Stodal*® composed by *Anemone pulsatilla* 6C, *Rumex crispus* 6C, *Bryonia dioica* 3C, *Ipecacuanha* 3C, *Spongia tosta* 3C, *Sticta pulmonaria* 3C, *Antimonium tartaricum* 6C, *Myocarde* 6C, *Coccus cacti* 3C, *Drosera* MT. Patients were treated with the homeopathic syrup or with a placebo (using a computer program to generate block randomization) for a week; they recorded cough severity in a diary for two weeks and their sputum viscosity was assessed with a viscosimeter before and after 4 days of treatment and by a subjective evaluation of it. Patients were instructed to take a dose of 15 ml, four times a day for 7 days, then cough severity was measured by a validated verbal category-descriptive score. Overall, 80 patients were enrolled, 40 were randomized to the homeopathic group and 40 were randomized to the placebo group. In the first four days of treatment the mean severity of cough decreased from score 4 (indicating serious coughing, very frequent and interfering with normal daily life or sleep) to 2 (indicating some short periods of cough, without much hardship) in the homeopathic group and remains greater than score 3 (indicating frequent coughing) in the other one. Viscosity was significantly lower in the homeopathic group ($p = 0.018$). The subjective evaluation was not significantly different between the two groups ($p = 0.059$). No adverse side effects were reported. Authors concluded that the homeopathic syrup administered in the study was able to effectively reduce cough severity and sputum viscosity.

A randomized, double-blind, placebo-controlled, 6-day pilot study was carried out to determine the efficacy of an homeopathic complex on the symptoms of acute viral tonsillitis in African children in South Africa [71]. Acute viral tonsillitis is a very common medical condition in school-aged children. This study enrolled 30 children aged from 6 to 12 years old, complaining of viral tonsillitis, from a primary school in Gauteng. They were treated with a homeopathic complex, two table spoonfuls four times daily, or with a placebo. The homeopathic complex (“*Tonzolyt*”) was composed as follows: *Atropa belladonna* 4D, *Calcarea phosphoricum* 4D, *Hepar sulphuris* 4D, *Kalium bichromat* 4D, *Kalium muriaticum* 4D, *Mercurius protoiodid*

10D, and *Mercurius biniodid* 10D. In 16 the study the intensity of pain was measured with a Pain Rating Scale and changes in tonsillitis signs and symptoms were assessed with a Symptom Grading Scale. Results shown that there were significant differences between the groups in pain associated with tonsillitis, pain in swallowing, erythema and inflammation of the pharynx and tonsil size. Authors concluded that the administered complex exhibited significant anti-inflammatory and pain-relieving qualities in children with acute viral tonsillitis and that a larger, more inclusive research study should be undertaken to verify the findings of this study.

A randomized, controlled, multinational clinical trial analyzed the effectiveness of homeopathic treatment in URTI [74]. A population of 523 patients aged 1 to 65 years old was treated with on-demand symptomatic standard treatment or homeopathic medication (*Influcid*) together with the same treatment. Influcid tablets, containing a fixed combination of 6 homeopathic single substances (*Aconitum* 3D, *Bryonia* 2D, *Eupatorium perfoliatum* 1D, *Gelsemium* 3D, *Ipecacuanha* 3D and *Phosphorus* 5D), were administered to children in the homeopathic 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. The most important outcome measure was the response at day 4 (absence of fever and absence or very mild symptoms). The conclusion was that homeopathic treatment shortened URTI duration, reduced the use of symptomatic medication and was well tolerated.

A randomized, controlled, multinational clinical trial analyzed the clinical effectiveness of a homeopathic medicine in 261 children affected by URTI [78]. Patients were divided in two groups: both received on-demand symptomatic standard treatment but only one received a homeopathic therapy with the above-mentioned formulation *Influcid*. This medicine, used as add-on treatment in pediatric URTI, reduced global disease severity, shortened symptom resolution, and was safe to use.

A study conducted in 2016 analyzed the treatment of cold symptoms (runny nose, cough, congestion and sneezing) in young children, using an homeopathic syrup or a placebo. Tested medicine was “Cold’n’ Cough for Kids”, composed by *Allium Cepa* 6D, *Hepar Sulphuris* 12D, *Natrum Muriaticum* 6D, *Phosphorus* 12D, *Pulsatilla* 6D, *Sulphur* 12D, *Hydrastis* 6D [79]. Enrolled patients were aged from 2 to 5 years old and they were randomized in two groups (treatment or placebo). Therapy was administered by parents, according to the assessment of the severity of each symptom. Results show there was no significant difference in improvement one hour after the dose for any symptom between the two groups (primary outcome), but in the course of the first day the severity of cold symptoms decreased faster among those receiving the cold syrup, when compared to placebo recipients.

A prospective randomized, double blinded interventional placebo control study was conducted to assess the effectiveness of homeopathy in the treatment of Otitis Media with Effusion (OME) in children [77]. Homeopathy was not used alone, but as an adjuvant treatment, with aerosol therapy (mucolytics and corticosteroids). Children treated with homeopathy received a homeopathic complex (*Agraphis nutans* 5C, *Thuya Occidentalis* 5C, *Kalium muriaticum* 9C and *Arsenicum iodatum* 9C), and this protocol did not result in being an effective adjuvant in children with OME who had already received aerosol therapy, including mucolytics and corticosteroids.

A controlled, pragmatic, randomized clinical trial evaluated the effectiveness and safety of a homeopathic complex called *SilAtro-5-90*, administered together with conventional symptomatic therapy, in the treatment of recurrent tonsillitis [80]. *SilAtro-5-90* is a complex homeopathic medicinal product containing *Atropinum sulfuricum* 5D, *Mercurius bijodatus* 8D, *Hepar sulfuris* 3D, *Ka-lium bichromicum* 4D, *Silicea* 2D. Authors enrolled 256 patients and randomized them into two groups: one was treated with standard therapy alone and the other with both allopathic and homeopathic medicines (standard therapy plus *SilAtro-5-90*). Second group showed a significantly lower risk of getting an ATI over time, with a reduction in tonsillitis symptoms and need for antibiotics.

Another randomized, placebo-controlled clinical trial studied the effect of an homeopathic complex (“*Monapax*”) composed of low dilutions of *Drosera* TM, *Coccus cacti* 1D, *Cuprum sulfuricum* 4D and *Ipecacuanha* 4D which are some medicines that include the cough in their clinical indications [81]. The trial was conducted in a pediatric population, composed of 89 children from 5 months to 12 years of age. The improvement in children receiving the verum and not the placebo resulted in being statistically significantly higher, with non-inferior tolerance.

In summary, randomized trials of ailment-specific formulations are 5 for URTI and 7 for otorhino-laryngological infections, constituting a body of predominantly positive results.

Equivalence Trials of Individualized Homeopathy

Friese and coworkers reported studies comparing the results obtained in otitis media in children, treated using two different medical approaches: a) classical homeopathic medicines (e.g., *Aconitum*, *Apis*, *Belladonna*, *Lachesis*, *Pulsatilla*, *Silicea*, *Lycopodium*, *Chamomilla* and *Capsicum*) prescribed after an individual homeopathic case analysis (repertorisation), b) conventional therapy based on antibiotics, mucolytics and antipyretics [45,89,90]. The mean duration of pain was two days in the homeopathic group and three days in the conventional therapy group (n.s.) and the duration of therapy was four and ten days respectively. The latter difference was statistically significant ($p < 0.01$). By following-up the children for six weeks, in the homeopathic group, 70.7% of the children who completed the study did not experience any recurrence; in the allopathic group, 64% of the children completing the study remained relapse free (n.s.). The average duration of pain in the two groups was respectively three days and four days (n.s.). Therefore, this study suggested a similar effectiveness of the homeopathic and conventional treatments.

An interesting multi-centre, prospective, observational study in a real-world medical setting compared the effectiveness of homeopathy with that of conventional medicine [50]. Thirty investigators with conventional medical licenses at six clinical sites in four countries enrolled a series of patients with at least one of the following three conditions: upper respiratory tract complaints, lower respiratory tract complaints, ear complaints. The response to treatment (healing or a major improvement after 14 days of treatment) was 82.6% among the patients receiving homeopathy and 68% among those receiving conventional medicine. The rate of adverse side effects in the conventional therapy group was 22.3%, versus 7.8% for the homeopathy group. Since the trial was not randomized, no statistical comparisons could be made between groups. In any case, the authors suggest that homeopathy appeared to be at least as effective as conventional medical

care in the treatment of patients with these three conditions. A replication of this study was carried out as an international, multicentre, comparative cohort study of non-randomized design [59]. Therapeutic outcomes were measured in terms of the response rate, defined as the proportion of patients experiencing 'complete recovery' or 'major improvement' in each treatment group. The full analysis evaluated data for 1577 patients, out of which 857 received homeopathic (H) and 720 conventional (C) treatments. The majority of patients in both groups reported their outcomes, after 14 days of treatment, as either complete recovery or major improvement ($p = 0.0003$ for non-inferiority testing). The response rates after 7 and 28 days also showed no significant differences between the two treatment groups. However, onset of improvement within the first 7 days after treatment was significantly faster for the homeopathic treatment in both children ($p = 0.0488$) and adults ($p = 0.0001$). Adverse drug reactions occurred more frequently among adults in the conventional group than in the homeopathic group (C: 7.6%; H: 3.1%, $p = 0.0032$), whereas in children the occurrence of adverse drug reactions was not significantly different.

A pragmatic, randomized, equivalence trial was performed by Steinsbekk and coworkers, investigating whether individualized treatment by a homeopath is effective in preventing childhood upper respiratory tract infections [55]. Children recruited via mailed letters, from a group previously diagnosed with upper respiratory tract infections, were randomly assigned to receive either homeopathic care or conventional health care for 12 weeks. There was a significant difference in the median total symptom score in favor of homeopathic care (24 points) compared to the control group (44 points) ($p = 0.026$). The number of days with symptoms was 8 and 13 for the homeopathic and reference groups respectively ($p = 0.006$). Negative results were obtained by the same group in a double-blind placebo controlled randomized trial investigating the effect of self treatment with one of three self selected homeopathic medicines for the prevention of childhood upper respiratory tract infections [54]. A large group of children, recruited by post from those previously diagnosed with upper respiratory tract infections, were randomly assigned to receive either placebo or highly diluted medicines, administered twice weekly for 12 weeks. Parents chose the medicine based on simplified constitutional indications. No difference was found between the frequency and scores of infection of the two groups. In a further study, the same group of researchers compared homeopathic care (individual homeopathic consultations with any medicine in any potency being prescribed) to self treatment with one of three self-prescribed medicines in 30c dilution, administered twice weekly, for 12 weeks [58]. The results indicated that there were no significant differences in clinical effects between the two types of homeopathic therapy for symptoms scores of upper respiratory tract infections.

Another study compared the effectiveness and costs of two treatment strategies ('homeopathic strategy' vs. 'antibiotic strategy') used in routine medical practice by allopathic and homeopathic GPs in the treatment of recurrent acute rhinopharyngitis in children [56]. Data from a large set of patients, clinically observed for 6 months, was analyzed and grouped according to the type of drug prescribed and the episodes of acute rhinopharyngitis, complications, and adverse side effects. The results showed that the 'homeopathic strategy' yielded significantly better results than the 'antibiotic strategy' in terms of the number of episodes of rhinopharyngitis (2.71 vs. 3.97, $p < 0.001$), number of complications (1.25 vs. 1.95, $p < 0.001$), and quality of life

(global score: 21.38 vs. 30.43, $p < 0.001$), with lower direct medical costs in favor of homeopathy (€88 vs. €99, $p < 0.05$). The authors suggest that homeopathy may be a cost-effective alternative to antibiotics in the treatment of recurrent infantile rhinopharyngitis.

A nationwide survey of primary care practice was conducted in a representative sample of General Practitioners (GPs) from across France and their patients between 2007 and 2008 [70]. Objectives were to describe and compare antibiotic and antipyretic/anti-inflammatory drugs use, URTI symptoms' resolution and occurrence of potentially-associated infections in patients seeking care from General Practitioners (GPs) who exclusively prescribe Conventional Medications (GP-CM), or who regularly prescribe homeopathy within a mixed practice (GP-Mx), or who are certified homeopathic GPs (GP-Ho). The study was organized with three follow-up interviews, at one, three and twelve months. Consumption of antibiotics and antipyretic/anti-inflammatory drugs for URTI was defined as the proportion of patients who used at least one drug from a definite list. Use of antibiotics and antipyretic/anti-inflammatory drugs was defined as at least one usage for URTI. Resolution of the URTI was defined by self-reporting of complete resolution or significant improvement of baseline symptoms. Infections potentially associated with URTI were defined by self-reporting of at least one declaration of a diagnosis of otitis media, otitis externa or sinusitis (with or without treatment). The survey enrolled 825 GPs and 8,559 patients: 518 of the patients agreed to participate and responded to all three follow-up interviews and therefore were included in the analysis. Most communal complaints were rhinopharyngitis (73.9%), bronchitis (28.0%), flu-like symptoms (12.7%), Strep-A negative viral angina (8.7%) and bronchiolitis (5.2%). Generally, patients suffering from URTI who choose a GP-Ho used half the amount of antibiotics and antipyretic/anti-inflammatory drugs, when compared to patients choosing a conventional medicine practitioner. No difference in the resolution of the URTI symptoms was observed between groups, but there was a lack of statistical validity for this outcome. No difference was seen in patients from the GP-Mx group, which was comparable to the GP-CM group in all outcomes [70].

A pilot study, randomized placebo-controlled parallel group, was conducted at Regional Research Institute of Homeopathy, Jaipur, (Rajasthan), India of CCRH from May 2009 to April 2010 [66]. It compared the effectiveness of Homeopathy and Conventional therapy in AOM. Patients were randomized by a computer and receive individualized homeopathic medicines or conventional treatment. Homeopathic medicines were administered in Fifty Millesimal (LM) potencies and Medicines were selected after repertorization with CARA Software. Medicines which were used were *Pulsatilla nigricans*, *Mercurius solubilis*, *Silicea*, *Chamomilla*, *Lycopodium clavatum* and *Sulphur*. Conventional treatments included analgesics, antipyretics and anti-inflammatory drugs. Patients who did not improve were treated with antibiotics on the third day and the secondary objective of the trial was to evaluate how many patients required antibiotic treatment in both groups. Outcomes were assessed over 21 days by a scale called AOM-Severity of Symptoms and by tympanic membrane examination. Patients were 81 children of both sexes, between 2 and 6 years of age, suffering from earache of not more than 36 hours' duration and with tympanic membrane bulging and loss of landmarks. 80 patients completed follow-up, 40 for conventional and 40 for homeopathic treatment. In the first group, 100% of patients were cured, in the second group, 95% were cured while 5% were lost to the last two

follow-up. By the third day of treatment, in the first group one patient was cured while in the second one, four patients were cured. In the first group, 97.5% of patient's required antibiotics but no antibiotics were required in the homeopathic group. The study results showed that conventional and homeopathy medicines are equally effective in the treatment of AOM [66]. Furthermore, homeopathic medicines did not have side effects. Results showed that in acute conditions homeopathy can act fast and that individualized homeopathy can reduce or avoid use of antibiotic in children with diagnosis of AOM.

A letter published in 2012 commented on Sinha's trial, which showed the effectiveness of homeopathy in treating AOM [66,91]. The author praised the individualized homeopathic treatment, the intention-to-treat analysis with last value carried forward in those lost to follow-up and the stringent definition of "cure". The finding of equivalent results in patients treated with homeopathy, compared to those treated with antibiotics is an important first step in order to assess the effectiveness of either clinical approach to this disease.

In summary, equivalence trials of individualized homeopathy are few, but together show that homeopathic treatments may have positive outcomes, similar or even better than conventional approach.

Equivalence Trials of Ailment Specific Formulations

One of the earliest of these was the study by Gassinger and co-workers in 1981 [42]. In a controlled clinical trial, patients suffering from the common cold were randomly assigned to treatment with acetylsalicylic acid or with the medicine *Eupatorium perfoliatum* in a low dilution. The efficacy of the drugs was assessed on days 1, 4 and 10 of the infection through symptom check lists and physical examinations. Neither the subjective symptoms, nor body temperature, nor the laboratory data differed significantly between the two groups, leading the authors to conclude that the homeopathic treatment was as effective as the allopathic treatment. Similar results to those of the above study were also obtained by Maiwald and coworkers in 1988 in a simple blind randomized trial on a group of soldiers in the German Army suffering from the common cold, and treated with acetylsalicylic acid or with a complex homeopathic preparation called *Grippheel* (made from low potencies of *Aconitum*, *Bryonia*, *Lachesis*, *Eupatorium perfoliatum* and *Phosphorus*). A comparison between changes in clinical status and subjective disorders on days 4 and 10, and between the length of time taken off work for the two groups, revealed no significant differences, leading the researchers to conclude that the two therapeutic approaches are equi-effective. The same homeopathic complex was evaluated in a prospective, observational cohort study on patients suffering from mild viral infections of the upper respiratory tract, with encouraging results, showing an equivalent effectiveness of homeopathy and conventional medications [52].

An open, multicentre, prospective, active-controlled cohort study was carried out on the homeopathic complex *Euphorbium compositum* (nasal spray), whose effectiveness and tolerability were compared with the reference allopathic drug xylometazoline [53]. The formulation contains *Euphorbium* 4D, *Pulsatilla* 2D, *Luffa operculata* 2D, *Mercurius bijodatus* 8D, *Mucosa nasalis suis* 8D, *Hepar sulfuris* 10D, *Argentum nitricum* 10D, *Sinusitis-Nosode* 13D. Clinically relevant reductions in the intensities of disease-specific symptoms were observed in both groups. Non-inferiority of the homeopathic complex medicine to xylometazoline could be shown for all the studied variables. Tolerability was good with both therapies.

A different complex that has been used in these kinds of respiratory complaints is *Engystol-N* (made of *Vincetoxicum* 6D, 10D and 30D, *Sulfur* 4D and 10D). In a non-randomized, observational study Schmiedel and Klein compared the effects of *Engystol* with those of conventional therapies with antihistamines, antitussives, and nonsteroidal antiinflammatory drugs on upper respiratory symptoms of the common cold, over a treatment period of two weeks [57]. The effects of treatment were evaluated in the variables of fatigue, sensation of illness, chill/tremor, aching joints, overall severity of illness, sum of all clinical variables, temperature and time to symptomatic improvement. Both treatment regimens provided significant symptomatic relief, and significantly more patients ($p < 0.05$) using *Engystol*-based therapy reported improvement within 3 days (77.1% vs 61.7% for the control group). Investigating the possible action mechanism, various authors reported *in vitro* studies of this homeopathic complex that showed antiviral and immunostimulating effects [93-96].

A prospective, multicenter, randomized, open, clinical trial carried out in Russia analyzed a single homeopathic complex, called *CalSuli-4-02*, on prevention of URTI in children [76]. *CalSuli-4-02* is a complex homeopathic medicinal product containing four active ingredients: *Calcium carbonicum Hahnemanni* 6D, *Calcium fluoratum* 6D, *Calcium phosphoricum* 6D and *Sulfur jodatum* 12D. The Russian regulatory authorities requested a comparison of the effectiveness and safety of *CalSuli-4-02* tablets with a comparable homeopathic product, already marketed in Russia, for the prevention of URTIs (*Gentiana* 1D, *Aconitum* 6D, *Bryonia* 6D, *Ferrum phosphoricum* 12D, and *Acidum sar-colacticum* 12D). It showed that both complexes determined a similar reduction of URTIs, with higher treatment satisfaction and tolerability in the group treated with *CalSuli-4-02*.

In 2018, a prospective observational study was conducted with the aim of understanding the choice of Pharmacists in prescribing cough syrups in 414 children [82]. Regarding the two homeopathic syrups, the results - were recorded by pharmacists were as follows: "*Drosetux*" (*Drosera* 3C, *Arni-ca montana* 3C, *Belladonna* 3C, *Cina* 3C, *Coccus cacti* 3C, *Corallium rubrum* 3C, *Cuprum metallicum* 3C, *Ferrum phosphoricum* 3C, *Ipeca* 3C, *Solidago virga aurea* 1C) or "*Stodal*" (*Antimonium tartaricum* 6C, *Bryonia* 3C, *Coccus cacti* 3C, *Drosera* MT, *Ipeca* 3C, *Myocardium* 6C, *Pulsatilla* 6C, *Rumex crispus* 6C, *Spongia tosta* 3C, *Sticta pulmonaria* 3C, *Tolu* syrup, *Polygala* syrup). Authors assessed the evolution of the cough, tolerance and satisfaction with the treatment, administering a questionnaire after 5 days of treatment. Two-third of parents showed satisfaction; both with homeopathic or allopathic medicines, and adverse effects were higher in children treated with allopathic drugs. Based on these observations, the authors suggested that homeopathy may have a positive role to play in the treatment of cough in children [82]. A quantitative comparison between the two different syrups used in the study was not reported.

In summary, equivalence trials of ailment-specific homeopathic formulations show encouraging results that together with randomized studies suggest the effectiveness of these medicines.

Observational Studies of Individualized Homeopathy

The purpose of the observational study of Frei and Thurneysen was to find out how many children with AOM are relieved of pain with individualized homeopathic treatment [49]. A group of children with this condition first received an individualized homeopathic

medicine in the pediatric office. If pain-reduction was not sufficient after 6 h, a second (different) homeopathic medicine was given. After a further 6 h, children who had not reached acceptable pain control levels were started on antibiotics. The six more frequently prescribed medicines were *Pulsatilla*, *Belladonna*, *Sulphur*, *Phosphorus*, *Calcium carbonicum*, *Lycopodium*. Acceptable pain control was achieved in 39% of the patients after 6 h and another 33% after 12 h. Compared with literature's data, the authors stated that the resolution rate is 2.4 times faster than in untreated cases.

A multi-centre, observational, prospective study evaluated the therapeutic usefulness of homeopathic medicine in the management of chronic sinusitis [67]. As a secondary objective, it also assessed the effect of the same medicines on change in the radiological appearance of inflammatory signs. It was conducted at Institutes and Units of the Central Council for Research in Homoeopathy, India and patients were recruited between October 2005 and March 2010. Included patients totaled 628, aged between 10 and 60 years, of both sexes, with positive findings of sinusitis in X-rays, who were able to stop all other treatments for at least 2 weeks before enrollment. Patients were selected from eight centers and resided within reasonable travelling distance from the study site. The homeopathic prescription was classically based on repertorization and Materia Medica and started with 30C potency, in a single dose (four globules daily) followed by placebo (four pills of unmediated globules, daily). Follow up was weekly for the first month, fortnightly for the next two months and monthly for the remaining period, until six months. 39 patients dropped out from the study after 3 months of treatment. The study revealed highly significant improvement in symptoms and X-ray appearances between baseline and end of treatment in patients with CS, for which homeopathy maybe effective. Among the first 17 medicines ranking first or second grade in the rubric "inflamma-24 tion, chronic, sinusitis", *Silicea*, *Calcarea carbonica*, *Lycopodium*, *Phosphorus*, *Kali iodatum* were found to be most useful, having marked improvement.

Witt and coworkers evaluated homeopathic treatment of sinusitis in a large prospective multi-centre observational study population. Most frequently prescribed medicines were *Sepia*, *Pulsatilla*, *Lycopodium*, *Phosphorus*, *Carcinosinum*, *Nux vomica*, *Sulphur*, *Natrium muriaticum*, *Staphisagria*, *Silicea* [62]. Successive patients presenting for homeopathic treatment were followed up for 2 years, and complaint severity, health-related quality of life, and medication use were regularly recorded. There were significant improvements in complaint severity and in quality of life scores at 3, 12, and 24 months, but the observed improvements were still present in the 8-year follow-up. Due to the observational nature of the study, the authors correctly conclude that the observed results may be due to treatment but the extent to which the clinical improvement may be due to the life-style regulation and placebo or context effects needs clarification in future explanatory studies.

An observational study of the individualized homeopathic treatment of recurrent upper respiratory tract infections in children below the age of 5 was carried out at a private Homoeopathic Medical College [63]. The number of attacks of URTI during the 6-month period preceding the date of starting homeopathic treatment (Control value), and during the 6-month period following the start of treatment (Treatment value) were compared. The results of the study indicate statistically significant differences ($p < 0.001$) between the two data sets in favor of the homeopathically treated cases.

In summary, the reported observational studies of individualized homeopathy are 3 and 5 for URTI and otorhinolaryngological infections respectively. Results are mainly positive but, due to the study design, no conclusions can be drawn about efficacy.

Observational Studies of Ailment-Specific Formulations

One of the major problems of URTI treatments, i.e., the decision of whether or not to use antibiotics, was the object of an observational study carried out in Italy [73]. The aim of this prospective, observational study was to investigate the effect of an homeopathic syrup, or of the homeopathic syrup plus antibiotic, in the treatment of acute cough caused by non-complicated upper respiratory tract infections in children. It was conducted on 85 children, treated for 7 days. The syrup used was "Stodal", composed of *Anemone pulsatilla* 6 C, *Rumex crispus* 6C, *Bryonia dioica* 3C, *Ipecacuanha* 3C, *Spongia tosta* 3C, *Sticta pulmonaria* 3C, *Antimonium tartaricum* 6C, *Myocardec 6 C*, *Coccus cacti* 3C, *Drosera* MT. Both groups showed a significant reduction in symptoms, but additional antibiotic prescription was related to more adverse side effects than the homeopathic syrup alone.

The effectiveness of homeopathy in acute tonsillitis was evaluated in an open trial [46]. A fixed combination of low dilutions of three plant substances (*Phytolacca americana*, *Guajacum officinale*, *Capsicum annum*) was used in patients with this condition and no antibiotics were administered. According to the Materia Medica, this homeopathic complex medicine should be characterized by immunomodulatory, analgesic, and anti-inflammatory properties. A decrease in the objective and subjective symptoms of acute tonsillitis symptoms was observed as early as 2.5 days after starting treatment; no serious adverse side effects were reported. Similar results were then reported by another observational study, that tested the same plant combinations in 48 patients with symptoms of acute tonsillitis, more than half of whom experienced alleviation of the principal symptom (moderate or severe difficulty in swallowing), within the first 5 days of treatment [48].

The efficacy and safety of a fixed-combination homeopathic medication (*Sinusitis PMD*) consisting of *Lobaria pulmonaria*, *Luffa operculata*, and *Potassium dichromate* were investigated in an open-label practice-based study of patients with acute sinusitis [47]. Most patients received only the test medication and no antibiotics. After a mean of 4 days of treatment, secretolysis had increased significantly and typical sinusitis symptoms, such as headache, pressure pain at nerve exit points, and irritating cough, were reduced. The average treatment duration was 2 weeks. At the end of the treatment, 81.5% of patients described themselves as symptom free or significantly improved. Ad-verse drug-related side effects were not reported.

A non-interventional study, conducted to study the safety and effectiveness of a homeopathic complex (*Contramutan N Safi*) was carried out on 1,050 patients of different ages, affected by the common cold and treated for 8 days [72]. The used preparation is composed of low doses (4.5 mg/100 ml) of mother tinctures of *Echinacea angustifolia* and *Eupatorium perfoliatum*, plus 9 mg of *Aconitum napellus* 4D and *Belladonna* 4D. It assessed the safety, compliance and possible influence on symptoms, in patients suffering from acute infections of the upper airways (flu-like infection and inflammatory disorders of the nose and throat). Visits were performed by 64 practices headed by general practitioners and pediatricians, with practical experience in treatments with complementary medicines and homeopathy.

The study was organized in two visits, one at the start and one the end of the study, and then additional phone contacts were possible. Enrolled patients were older than 1 year and suffering from symptoms of an acute catarrhal disease of the respiratory tract. They were divided into three groups by age. Results showed that - it was very well tolerated, with a high treatment satisfaction and effectiveness. The product resulted as safe and effective in adults, as in children, with very rare adverse reactions of mild to moderate intensity over a very short time. The frequency of homeopathic aggravations was very low, just like homeopathic “proving” symptoms [72].

A controlled, observational study is a retrospective analysis of the role of homeopathy in the prevention of respiratory tract infections (without specification if of upper or lower tract) [75]. It was conducted on 459 patients from a single setting, 248 treated with *Oscilloco-cinum* (a high dilution of duck It was conducted on 459 patients from a single setting, 248 treated with *Oscilloco-cinum* (a high dilution of duck liver and heart extract) and 211 not treated. The first group showed a greater reduction of RTIs episodes after the treatment, but did not specify which kind of RTIs were diagnosed in the observed

patients. The same drug had been previously tested with partially positive results in the treatment of influenza [38,97,98].

In summary, the reported observational studies of ailment-specific medicines are 5 and 4 for URTI and otorhinolaryngological infections respectively. Results are mainly positive and are in agreement with the results of randomized trials.

Components of the Medicines

Although several homeopathic medicines have been recently studied in experimental and clinical settings, most components of the mixed formulations have their justification only inside the traditional experiences made by accidental exposure or by pathogenetic trials. Table 2 reports a list of components frequently included in homeopathic medicines for cough and upper respiratory diseases and that have been used with positive results in the investigations reported in this review. The main active ingredients of the medicines are known and also their toxicological effects at high doses on the organism, while their healing effects were presumed on the basis of the “similia” principle [99]. And are reported in traditional Materia Medicas.

	Name	Taxonomic classification and active ingredients	Traditional Materia Medica (minimum extract from generalities) [41]	Contained in medicine
Plant origin	<i>Aconitum napellus</i>	Ranunculaceae. Contains aconitine, tyramine dopamine.	Fear, anxiety, restlessness, fright; complaints and tension caused by exposure to dry, cold weather; inflammatory fevers, serous membranes affected markedly.	Individualized in equivalence trials [45,45,89,90]. Component of homeopathic formulation <i>Grippheel</i> [92], <i>Contramutan N Saft</i> [72], and <i>Influcid</i> [74,78].
	<i>Belladonna (Atropa belladonna, deadly night shade)</i>	One of the most poisonous plants, contains tropane alkaloids including atropine, scopolamine, and hyoscyamine, which are used as anticholinergics. These alkaloids can be very toxic at high dose.	Acts upon nervous system, producing active congestion, excitement; marked action on the vascular system, skin and glands; associated with hot, red skin, flushed face, glaring eyes, throbbing carotids, excited mental state, hyperaesthesia of all senses, dryness of mouth and throat with aversion to water; traditionally indicated for scarlet fever [100]. Toxicological properties reviewed in Kwakye [101].	Individualized in equivalence trial [45]. Individualized in observational study [49]. Component of <i>Tonzolyt</i> [71], <i>Hyland's Ear drops</i> [64,68], <i>Contramutan N Saft</i> [72], and <i>Drosetux</i> [82]. Intoxication with homeopathic medicine described in a case [102].
	<i>Bryonia dioica (or alba)</i>	Cucurbitaceae. The major active components are cucurbitacin glucosides. The biological activities of these compounds are associated with biosynthesis of eicosanoids and corticosteroids, which are important mediators in the immune, endocrine and nervous systems. Potential adaptogen (stress protective) [103,104]. Dihydrocucurbitacin D inhibits macrophage nitric oxide generation [105]. Antioxidant activity [106].	Acts on serous membranes, aching in every muscle; pain worse by motion, irritable; dry cough, rheumatic pains and swellings; choriza, tough mucus in larynx and trachea.	Component of homeopathic formulation <i>Grippheel</i> [92], <i>Stodal</i> [69,73,82], and <i>Influcid</i> [74,78]. Phytotherapeutic use in chronic obstructive pulmonary disease [107]. Component of immunostimulant formulation [108].
	<i>Capsicum annuum</i>	A species of the plant genus <i>Capsicum</i> (peppers) native to southern. This species is the most common and extensively cultivated of the domesticated capsicums	Diminished vital heat, indolent person; affects the mucous membranes, producing a sensation of constriction; burning pains and general chilliness.	Individualized in equivalence trial [45]. Component of homeopathic formulation [46,48] and of <i>ICX72</i> [65].
	<i>Chamomilla</i>	<i>Matricaria chamomilla</i> is an annual plant of the composite family Asteraceae. Active ingredients include terpene bisabolol, farnesene, chamazulene and flavonoids	Sensitive, irritable; oversensitiveness, night-sweats; sensitive to cold air and cold things.	Individualized in randomized trial [51]. Component of homeopathic formula Component of homeopathic formulation <i>Hyland's Ear drops</i> [64,68]. Individualized in equivalence trial [66].
	<i>Drosera rotundifolia</i>	Droseraceae. Contains glucides, various acids, flavonoid pigments, proteases, naphthoquinones.	Affects markedly the respiratory organs; gastric irritation and profuse expectoration; spasmodic, dry irritative cough, like whooping-cough, the paroxysms following each other very rapidly.	Component of homeopathic formulation <i>Stodal</i> [69,73,82], <i>Monapax</i> [81], and <i>Drosetux</i> [82].

	<i>Eupatorium perfoliatum</i>	Known as common boneset or just boneset, is a North American perennial plant in the aster family. Sesquiterpene lactones are signature compounds of the large Eupatorium genus and of the Asteraceae family in general.	Relieves pain in bones, limbs and muscles that accompanies some forms of febrile disease; acts principally upon the gastro-hepatic organs and bronchial mucous membrane.	Tested in equivalence trial [42]. Component of homeopathic formulation <i>Grippheel</i> [92] <i>Contramutan N Saft</i> [72] <i>Influcid</i> [74,78].
	<i>Ipecacuanha</i>	Rubiaceae. Contains emetine, cephaline psycotrine (alkaloid), ipecacuanic acid (tannin), ipecacuanine (eteroside)	Action is on the ramifications of the pneumogastric nerve, producing spasmodic irritation in chest and stomach; persistent nausea and vomiting, which form the chief guiding symptoms; warm, moist weather.	Component of homeopathic formulation <i>Stodal</i> [69,73,82], <i>Influcid</i> [74,78], <i>Monapax</i> [81], and <i>Drosetux</i> [82].
	<i>Lycopodium clavatum</i>	The most widespread species in the genus Lycopodium in the clubmoss family. Bioactive secondary metabolites in clubmosses include triterpenoids with acetylcholinesterase inhibitor activity isolated from this species.	Ailments gradually developing, functional power weakening, with failures of the digestive powers, where the function of the liver is disturbed; temperaments of lymphatic constitution, with catarrhal tendencies; symptoms characteristically run from right to left, acts especially on right side of body, and are worse from about 4 to 8 p.m. Lacks vital heat; has poor circulation, cold extremities. Sensitive to noise and odors.	Individualized in equivalence trials [45,66]. Individualized in observational studies [49,62,67]. Component of homeopathic formulation Hyland's Ear drops [64,68].
	<i>Pulsatilla nigricans (pratensis)</i>	Ranunculaceae. Contains anemonine, roanemonine (alkaloids)	Especially for mild, gentle, yielding disposition; sad, crying readily; weeps when talking; changeable, contradictory; mucous membranes are all affected; great sensitiveness.	Individualized in randomized trial [51]. Individualized in equivalence trials [45,66]. Individualized in observational studies [49,62]. Component of homeopathic formulation Euphorbium compositum [53], Hyland's Ear drops [64,68], <i>Stodal</i> [69,73,73,82], and Cold'n' Cough for Kids [79].
Animal origin	<i>Calcarea carbonica</i>	Made from the middle layer of shells. In chemical terms, Calcarea carbonica is impure calcium carbonate, CaCO ₃ .	Chief action is centered in the vegetative sphere, impaired nutrition being the keynote of its action; increased perspiration, swelling of glands, scrofulous and rachitic conditions; tickling cough, fleeting chest pains, nausea; gets out of breath easily; great sensitiveness to cold.	Individualized in randomized trial [51]. Individualized in observational studies [49,67]. Component of homeopathic formulation Hyland's Ear drops, [64,68] and <i>CalSuli-4-02</i> [76].
	<i>Coccus cacti</i>	Cocciniglia, insect (Hemiptera) infesting cactus plants. The dried bodies of the female are used for making a tincture. Carminic Acid e myristicin	Spasmodic and whooping coughs, and catarrhal conditions of the bladder; spasmodic pains in kidneys, with visceral tenesmus; coryza, with inflamed fauces; accumulation of thick viscid mucus, which is expectorated with great difficulty; tickling in larynx.	Component of homeopathic formulation <i>Stodal</i> [69,73,82], <i>Monapax</i> [81], and <i>Drosetux</i> [82].
Mineral Origin	<i>Calcarea carbonica</i>	Made from the middle layer of shells. In chemical terms, Calcarea carbonica is impure calcium carbonate, CaCO ₃ .	Chief action is centered in the vegetative sphere, impaired nutrition being the keynote of its action; increased perspiration, swelling of glands, scrofulous and rachitic conditions; tickling cough, fleeting chest pains, nausea; gets out of breath easily; great sensitiveness to cold.	Individualized in randomized trial [51]. Individualized in observational studies [49,67]. Component of homeopathic formulation Hyland's Ear drops [64,68] and <i>CalSuli-4-02</i> [76].
	<i>Ferrum phosphoricum</i>	Phosphate of iron	In the early stages of febrile conditions; the typical subject is nervous, sensitive, anaemic; prostration marked; susceptibility to chest troubles; bronchitis of young children.	Component of homeopathic formulation <i>Sinfrontal</i> [60] and <i>Drosetux</i> [82].
	<i>Hepar sulphuris calcareum</i>	A burned combination the inner layer of oyster shells (Calcarea carbonica) with flowers of sulfur. It is also known as calcium sulfide. Hepar is the Latin word for liver, as certain compounds of sulfur had the color of liver.	Lymphatic constitutions; unhealthy skin; great sensitiveness to all impressions; special affinity to the respiratory mucous membrane, producing catarrhal inflammation, profuse secretion; marked tendency to suppuration; chilliness, hypersensitiveness, feeling as if wind were blowing on some part.	Component of <i>Tonzolyt</i> [71], <i>Euphorbium compositum</i> [53], Cold'n' Cough for Kids [79], <i>SiAltro-5-90</i> [80].
	<i>Kalium bichromicum</i>	Potassium dichromate	Affects mucous membrane of stomach, bowels, and airpassages; especially indicated for fleshy, fat, light complexioned persons subject to catarrhs; symptoms are worse in the morning; more adapted to subacute rather than the violent acute stage; mucous membranes everywhere are affected; catarrh of pharynx larynx, bronchi and nose.	Component of <i>Tonzolyt</i> [71], <i>Sinusitis PMD</i> [47], <i>SiAltro-5-90</i> [80]. In double-blind trial decreased tracheal secretions in patients with chronic obstructive pulmonary disease [109].
	<i>Mercurius (biiodatus or solubilis)</i>	A liquid metallic chemical element with the symbol 'Hg'	The lymphatic system is especially affected; traditionally indicated in the secondary stage of syphilis; symptoms are worse at night, from warmth of bed, from damp, cold, rainy weather; complaints increase with the sweat and rest; all associated with a great deal of weariness, prostration, and trembling; sensitive to heat and cold; breath, excretions and body smell foul.	Individualized in equivalence trial [66]. Component of <i>Tonzolyt</i> [71], <i>Euphorbium compositum</i> [53], <i>SiAltro-5-90</i> [80], <i>Sinfrontal</i> [60].

<i>Natrum muriaticum</i>	Sea salt containing NaCl, potassium chloride, magnesium chloride, calcium, aluminum and other minerals mucous membranes. mucous membranes.	Symptoms of salt retention, and oedemas; remedy for certain forms of intermittent fever, anaemia, leukocytosis, many disturbances of the alimentary tract and skin; great debility; most weakness felt in the morning in bed; great liability to take cold; dry	Individualized in observational study [62]. Component of homeopathic formulation Cold'n' Cough for Kids [79].
<i>Phosphorous</i>	Chemical element with symbol P and atomic number 15. Elemental phosphorus exists in two major forms, white phosphorus and red phosphorus. It is highly flammable and pyrophoric (self-igniting) upon contact with air.	Irritates, inflames and degenerates mucous membranes; causes yellow atrophy of the liver and sub-acute hepatitis; tall, slender persons, narrow chested, with thin, transparent skin; nervous debility, emaciation, amative tendencies; susceptibility to external impressions, to light, sound, odors, touch, electrical changes; inflammation of the respiratory tract.	Individualized in observational studies [49,62,67]. Component of Cold'n' Cough for Kids [79], <i>Grippheerl</i> [92], <i>Influcid</i> [74,78].
<i>Silicea</i>	Silica is a mineral and is prepared from silicon dioxide found in flint, quartz, sandstone, and many other common rocks	Increased susceptibility to nervous stimuli and exaggerated reflexes; diseases of bones, caries and necrosis; stimulates the organism to re-absorb fibrotic conditions and scar-tissue; rachitic children; suppurative processes; silica patient is cold, chilly, wants plenty warm clothing, worse in winter.	Individualized in equivalence trials [45,66]. Individualized in observational studies [62,67]. Component of SilAltro-5-90 [80].
<i>Sulphur (Sulfur)</i>	Mineral with atomic number 16. Sulfur is often referred to as brimstone or flowers of sulfur	Elective affinity for the skin, where it produces heat and burning, with itching; made worse by heat of bed; dislike of water, dry and hard hair and skin, red orifices; aversion to being washed; arouses the reactionary powers of the organism.	Elective affinity for the skin, where it produces heat and burning, with itching; made worse by heat of bed; dislike of water, dry and hard hair and skin, red orifices; aversion to being washed; arouses the Individualized in equivalence trial [66]. Component of homeopathic formulation Engystol-N [57], Hyland's Ear drops, [64,68] Influcid [74,78], Cold'n' Cough for Kids [79].

Table 2: Homeopathic medicines for the treatment of patients with symptoms of URTIs and otorhinolaryngologic infections. Only the medicines used in a minimum of two scientific papers described in the review are reported.

Discussion

We have taken 40 original clinical studies on URTI and otorhinologic complaints from PubMed. The overview of the literature in the considered field shows that there are several promising studies tending to support a clinically demonstrable activity of homeopathic medicines. However, the body of randomized studies within the various fields is small, and “hard” proofs of efficacy, particularly when considering single drugs or single clinical approaches, remains fragmentary. Though the number of papers published in peer-reviewed journals is increasing, many homeopathic clinical studies are still characterized by low standards of methodology a problem which is, however, equally common in the conventional medical literature [110].

The problems of measuring the quality, the model validity and the risk of bias of the literature on homeopathic treatments are considerable. A systematic review of the homeopathy RCT literature in 24 different medical conditions by Mathie et al found 32 eligible trials, 12 of which were classed ‘uncertain risk of bias’, while 20 trials were classed ‘high risk of bias’ [111]. Further reviews found significant inadequacies, with the majority of studies demonstrating uncertain or high risk of bias. Of the 26 RCTs of non-individualized homeopathy

that were judged ‘not at high risk of bias’, only nine have been rated ‘acceptable model validity’ [112-114]. Observational studies have even higher “intrinsic” risk of bias due to design, even if properly done and with high number of patients included. A consensus about the quality criteria of observational studies in homeopathy has still to be reached.

The papers reported in this review are highly heterogeneous, in terms of the investigated disease conditions, the tested drugs, and their experimental designs. A meta-analysis was beyond the scope and style of the current overview and we adopted a narrative approach, using a semi-quantitative evaluation, where multiple studies on the same homeopathic approach for the same group of conditions are available (Table 3). In summary, the reported literature shows a positive evidence of homeopathic treatments in URTI (with the exception of individualized prescription, where the evidence is more conflicting) and otorhinolaryngologic infections, especially with the use of ailment specific formulations. It is probable that the greatest number of studies done with homeopathic formulas with respect to individualized homeopathy reflects technical motivations (easier study of a precise drug compared to the individualized approach) and commercial ones.

Ailment	Treatment type	Results				Effectiveness Rating ^a
		Positive evidence (vs. no therapy or vs. placebo)	Positive evidence (equivalence with conventional care)	Uncertain or border line	Negative evidence	
Upper respiratory tract infections (ICD-10-CM diagnosis code J06)	Individualized prescription	Ramchandani 2010 [63]	Steinsbekk 2005 [55] Riley 2001 [50] Haidvogel 2007 [59]	de Lange de Klerk 1994 [44]	Steinsbekk 2005^b [54]	Uncertain ^c
	Ailment specific formulations	Zanasi 2014 [69] Thinesse-Mallwitz 2015 [74] Jong 2016 [76] Van Haselen 2016 [78] [4] Voss 2018 [81] Beghi 2016 [75] Allaert 2018 [82]	Rabe 2004 [52] Grimaldi-Bensouda 2014 [70] Zanasi 2015 [73]			Likely effective
Oto-rhino-laryngological infections	Individualized Prescription	Jacobs 2001 [51] Frei 2001 [49] Witt 2009 [62] Nayak 2012 [67]	Sinha 2012 [66] Fiese 1997 [45] Trichard 2005 [56]			Possibly effective
	Ailments specific formulations	Zabolotnyi 2007 [60] Taylor 2011 [64] Bernstein 2011 [65] Taylor 2014 [68] Malapane 2014 [71] Jacobs 2016 [79] Palm 2017 [80] [4] Michalsen 2015 [72] Wiesenaue 1998 [46] Rau 2000 [48]	Gassinger 1981 [42] Maiwald 1988 [92] Ammerschlag 2005 [53] Schmiedel 2006 [57]	Adler 1999 [47]	Pedrero-Escalas 2016 [77] ^d	Likely effective

Table 3: Summary of homeopathic treatments classified for specific indications and outcomes. Randomized studies are reported in bold characters.

^aTo summarize the effectiveness, we used the criteria of Natural Medicines (<https://naturalmedicines.therapeuticresearch.com/about-us/editorial-principles-and-process.aspx>) (see text). ^bIt employed a method of uncertain validity, where one of 3 pre-selected drugs was chosen by parents; ^cAccording to the criteria mentholated in Methods, the effectiveness of this approach is “possibly ineffective”, but it can be judged as “possibly effective” by excluding the paper of Steinsbekk 2005 for the reasons described in the text and in the previous note [b]; ^dAdjunctive homeopathic therapy to conventional therapy [54].

According to “Natural Medicines”, an authoritative resource for complementary alternative and integrative therapies, a treatment can be rated as “Likely effective” where the evidence is from multiple (2+) RCT, without valid evidence to the contrary, or as “Possibly effective” where the evidence is from one or more RCT or two or more population based or epidemiological studies and valid positive evidence outweighs contrary evidence. Following these criteria, the ailment-specific formulations in Table 3 are tentatively rated as “Likely effective”, while the individualized treatment of otorhinolaryngological infections is rated as “possibly effective”. Despite the uncertainties about the quality of the studies, the amount of research published may be sufficient to refute any judgment claiming that homeopathy is not effective in these diseases.

A recent review selected double-blind, Randomized Controlled Trials (RCTs) or double-blind cluster-RCTs comparing oral homeopathy medicinal products with identical placebo or self selected conventional treatments to prevent or treat ARTIs (acute respiratory tract infections) in children aged 0 to 16 years [115]. Authors included only 8 papers with very different methods and drugs and made their evaluation on “meta-analysis” of only two prevention and two treatment trials. Due to the heterogeneity of methods and outcomes, this review concluded that “pooling of two prevention and two treatment studies did not show any benefit of homeopathic medicinal products compared to placebo in acute respiratory tract infections recurrence or cure rates in children”. Therefore, the negative conclusion could be reached by excluding the vast majority of results reported in the literature and even in the 8 papers included in the review itself, by analyzing separately prevention and treatment outcomes and by “pooling” only two papers in each category. This procedure of “eliminating” papers that do not fit in the scheme of analysis recalls the meta-analysis of Shang where to conclude that homeopathy lacks clinical effect,

more than 90% of the available clinical trials had to be disregarded [116]. Another drawback of excluding a large number of studies is that the composition of the finally analyzed mix of conditions becomes very important to the conclusion. Here, one must remember that the overall conclusion made in meta-analyses relates to the overall efficacy of a heterogeneous group of treatments for a heterogeneous group of diseases. Also for this reason, we have given up trying to obtain “certain” conclusions as to the drug efficacy through a meta-analysis and, to provide a wider and more realistic perspective into the current state of play, we thus described all the PubMed-referenced literature, including also observational studies, studies made on adult patients. Compared with the cited review, we excluded the 2016 study of Siqueira, since it was a trial on influenza [115,117].

Besides conventional randomized placebo-controlled trials, observational studies allow the use of individualized patient treatment, generally without the use of placebo or control group. By this way, they can have less restricted inclusion criteria, to mimic the “real life” setting of homeopathic practice. A pragmatic framework evaluating long-term effects in different settings, in conjunction with other healthcare services was reported in a review on homeopathic treatment of otitis media [118]. More recently, a review considered the studies conducted after 1994 in URTIs and included 9 Randomized Controlled Trials (RCTs) and 8 observational/cohort studies [119]. Results for homeopathy treatment were positive overall, with faster resolution, reduced use of antibiotics and possible prophylactic and longer-term benefits. Authors concluded that at least an equivalence exists between homeopathic and allopathic treatments and suggested that homeopathy may represent a possible alternative in the treatment for uncomplicated URTIs, having regard to the growing problem of the antibiotic resistance.

Literature on homeopathy for otitis is relatively small; nevertheless this literature overview suggests that in many instances it is as effective as a standard treatment. The suggestion is that management of otitis media should begin with patient observation. At this time, homeopathic medicines may help decrease pain and lead to faster resolution. Key factors in implementing a “wait and watch” strategy were (a) a method to classify AOM severity; (b) parent education; (c) management of AOM symptoms; (d) access to follow-up care; and (e) use of an effective antibiotic regimen, when needed. When these caveats are observed, “wait and watch” may be an acceptable alternative to immediate antibiotics for some children with non-severe AOM [24]. More randomized controlled studies are expected to assess the efficacy and safety of specific formulations. The research needs to be reproduced and its conclusions need to be confirmed, before being used as indications in clinical practice for the general population. It is important to remember and underline once again that “absence of evidence” is not synonymous with “evidence of absence”.

There is sharp controversy concerning the “plausibility” of homeopathy [120-123]. Though we do not have space here to discuss the purported mechanisms of homeopathic effects, it is worth mentioning that even basic *in vitro* experimental studies provide evidence that the effects of homeopathic solutions differ from pure diluting solvent [86,124-129]. The results of basic research experiments may invigorate new clinical trials that investigate complementary treatments for infectious diseases [130]. Some homeopathic medicines showed direct effects on the immune system cells [131-136], or exerted antiviral action [93,136-138].

The limitation of this study is the lack of a detailed quality analysis of each included study, because our object was essentially descriptive and not to draw quantitative conclusions, or clinical recommendations. Although a publication bias cannot be excluded, we assumed that publications in peer-reviewed journal and reviewed by PubMed had sufficient quality for inclusion, since the papers have been examined by experts in their sector before being published. Neither have we attempted any meta-analysis of clinical trials, since there is a marked heterogeneity between studies, either in the different methods of homeopathic treatment (e.g., Individualized or complex, worth different drugs), or in the models of study, that in homeopathy are still under scrutiny [139]. Others have shown that pooling data from heterogeneous clinical trials in homeopathy and using funnel plot to analyze papers with largely different sample sizes, as done in a famous meta-analysis on homeopathy, may lead to flawed conclusions [110,116,140].

Another limitation of our present study concerns the tentative conclusions made about ailment specific products. While the evaluation of the literature provided a basic evidence of a likely therapeutic effect in URTI and otorhinolaryngologic ailments, the existence of many different homeopathic products with different composition precludes the identification of the substance that is actually responsible for the purported curative effect. What emerges from this overview is an efficacy/effectiveness paradox, similar to that found in several other areas of complementary medicine research, with weak evidence in favor of homeopathy when studies are done in randomized and double-blind conditions, yet documented effectiveness in equivalence studies comparing homeopathy and conventional medicine, and documented usefulness in general practice through observational studies: the therapy seems useful when applied in open practice and produces substantive effects, even in patients with chronic diseases [38]. Most of the studies reviewed here suggest that homeopathic medicines in

high dilutions, prescribed by trained professionals, are safe and unlikely to provoke severe adverse reactions. This leads us to conclude that, even though most decisions about treatments still rest in the hands of the individual judgments of clinicians and patients, additional clinical research, both experimental and observational, including studies using different approaches, is necessary for further developing the base of evidence for homeopathy. It would also be interesting to compare the effectiveness of different forms of homeopathy for the same condition. However the small sizes of the studied populations and the differences between them, have thus far not permitted any reliable quantitative evaluation.

Conclusion

In this work we have described and classified the most important homeopathic investigations in the fields considered and put forward a semi-quantitative evaluation criterion, which allows evaluating the whole set of results without discarding any work, as they did instead previous meta-analyses. In a relatively small field like homeopathy, where scientific research is still in its infancy and there is no consensus on the model validity of different approaches, we have the advantage of including the contribution, albeit partial, of each publication of sufficient validity and therefore of having an overall view of literature. In the light of the clinical findings, the use of individualized homeopathy or homeopathic medicines could be regarded as a possible option in the fields reviewed in this work particularly in the infections of upper airways, otitis and rhinopharyngitis provided that the homeopathic diagnosis and prescription is correct and is integrated with other possible effective treatments. However, much more work is needed both to produce new evidence with ever more precise and correct clinical research, and to refine the criteria for evaluating the homeopathic literature according to parameters shared by the homeopathic community.

Conflict of Interest

The authors declare there is no conflict of interest. The paper was written without funding. Sponsors of previous and current research carried out by the group at Verona University did not interfere with the design of the study, collection, analysis or interpretation of data.

References

1. Blanc PD, Trupin L, Earnest G, Katz PP, Yelin EH, et al. (2001) Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis: data from a population-based survey. *Chest* 120: 1461-1467.
2. Schäfer T, Riehle A, Wichmann HE, Ring J (2002) Alternative medicine in allergies - prevalence, patterns of use, and costs. *Allergy* 57: 694-700.
3. Chandrashekar S, Anilkumar T, Jamuna S (2002) Complementary and alternative drug therapy in arthritis. *J Assoc Physicians India* 50: 225-227.
4. Schafer T (2004) Epidemiology of complementary alternative medicine for asthma and allergy in Europe and Germany. *Ann Allergy Asthma Immunol* 93: 5-10.
5. Bielory L, Russin J, Zuckerman GB (2004) Clinical efficacy, mechanisms of action, and adverse effects of complementary and alternative medicine therapies for asthma. *Allergy Asthma Proc* 25: 283-291.
6. Becker-Witt C, Lütke R, Weissshuhn TE, Willich SN (2004) Diagnoses and treatment in homeopathic medical practice. *Forsch Komplementarmed Klass Naturheilkd* 11: 98-103.
7. Sevar R (2005) Audit of outcome in 455 consecutive patients treated with homeopathic medicines. *Homeopathy* 94: 215-221.

8. Breuer GS, Orbach H, Elkayam O, Berkun Y, Paran D, et al. (2006) Use of complementary and alternative medicine among patients attending rheumatology clinics in Israel. *Isr Med Assoc J* 8: 184-187.
9. Relton C1, Cooper K2, Viksveen P3, Fibert P4, Thomas K5 (2017) Prevalence of homeopathy use by the general population worldwide: a systematic review. *Homeopathy* 106: 69-78.
10. Italia S, Brand H, Heinrich J, Berdel D, von Berg A, et al. (2015) Utilization of Complementary and Alternative Medicine (CAM) among children from a German birth cohort (GINIplus): patterns, costs, and trends of use. *BMC Complement Altern Med* 15: 49.
11. Rossi E, Picchi M, Di Stefano M, Marongiu AM, Scarsini P (2015) The homeopathic choice for children: a qualitative research on the decision making process of the families. *Homeopathy* 104: 176-181.
12. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM (2013) Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 1: CD000219.
13. Ng GJY, Tan S, Vu AN, Del Mar CB, van Driel ML (2015) Antibiotics for preventing recurrent sore throat. *Cochrane Database Syst Rev* 7: CD008911.
14. MacKay D (2003) Can CAM therapies help reduce antibiotic resistance? *Altern Med Rev* 8: 28-42.
15. Keith T, Saxena S, Murray J, Sharland M (2010) Risk-benefit analysis of restricting antimicrobial prescribing in children: what do we really know? *Curr Opin Infect Dis* 23: 242-248.
16. ESCMID Sore Throat Guideline Group, Pelucchi C, Grigoryan L, Galeone C, Esposito S, et al. (2012) Guideline for the management of acute sore throat. *Clin Microbiol Infect* 1: 1-28.
17. Lunn AD (2018) Reducing inappropriate antibiotic prescribing in upper respiratory tract infection in a primary care setting in Kolkata, India. *BMJ Open* 7: 000217.
18. Gwaltney JM (2002) Clinical significance and pathogenesis of viral respiratory infections. *Am J Med* 6: 13-18.
19. Spinks A, Glasziou PP, Del Mar CB (2013) Antibiotics for sore throat. *Cochrane Database Syst Rev* CD000023.
20. Mäkelä MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, et al. (1998) Viruses and bacteria in the etiology of the common cold. *J Clin Microbiol* 36: 539-542.
21. Renner B, Mueller CA, Shephard A (2012) Environmental and non-infectious factors in the aetiology of pharyngitis (sore throat). *Inflamm Res* 61: 1041-1052.
22. Oliver J, Malliya Wadu E, Pierse N, Moreland NJ, Williamson DA, et al. (2018) Group A Streptococcus pharyngitis and pharyngeal carriage: A meta-analysis. *PLoS Negl Trop Dis* 12: 0006335.
23. Williams MR, Greene G, Naik G, Hughes K, Butler CC, et al. (2018) Antibiotic prescribing quality for children in primary care: an observational study. *Br J Gen Pract* 68: 90-96.
24. McCormick DP, Chonmaitree T, Pittman C, Saeed K, Friedman NR, et al. (2005) Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 115: 1455-1465.
25. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R (2017) Delayed antibiotic prescriptions for respiratory infections. *Cochrane Database Syst Rev* 9: CD004417.
26. Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, et al. (2018) Systemic corticosteroids for acute otitis media in children. *Cochrane Database Syst Rev* 3: CD012289.
27. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, et al. (2016) Clinical Practice Guideline: Otitis Media with Effusion (Update). *Otolaryngol Head Neck Surg* 154: 1-41.
28. Surda P, Fokkens WJ (2016) Novel, Alternative, and Controversial Therapies of Rhinitis. *Immunol Allergy Clin North Am* 36: 401-423.
29. Gruber M, Ben-Arye E, Kerem N, Cohen-Kerem R (2014) Use of complementary alternative medicine in pediatric otolaryngology patients: a survey. *Int J Pediatr Otorhinolaryngol* 78: 248-252.
30. Bell IR, Boyer NN (2013) Homeopathic medications as clinical alternatives for symptomatic care of acute otitis media and upper respiratory infections in children. *Glob Adv Health Med* 2: 32-43.
31. Salatino S, Gray A (2016) Integrative management of pediatric tonsillopharyngitis: An international survey. *Complement Ther Clin Pract* 29-32.
32. Marchisio P, Bianchini S, Galeone C, Baggi E, Rossi E, et al. (2011) Use of complementary and alternative medicine in children with recurrent acute otitis media in Italy. *Int J Immunopathol Pharmacol* 24: 441-449.
33. Mowry JB, Spyker DA, Cantilena LR Jr, McMillan N, Ford M (2014) 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. *Clin Toxicol (Phila)* 52: 1032-1283.
34. Stub T, Kristoffersen AE, Alræk T, Musial F, Steinsbekk A (2015) Risk in homeopathy: Classification of adverse events and homeopathic aggravations--A cross sectional study among Norwegian homeopath patients. *Complement Ther Med* 23: 535-543.
35. Dossett ML, Yeh GY (2018) Homeopathy Use in the United States and Implications for Public Health: A Review. *Homeopathy* 107: 3-9.
36. Weatherley-Jones E, Thompson EA, Thomas KJ (2004) The placebo-controlled trial as a test of complementary and alternative medicine: observations from research experience of individualised homeopathic treatment. *Homeopathy* 93: 186-189.
37. Walach H, Falkenberg T, Fønnebo V, Lewith G, Jonas WB (2006) Circular instead of hierarchical: methodological principles for the evaluation of complex interventions. *BMC Med Res Methodol* 6: 29.
38. Bellavite P, Marzotto M, Chirumbolo S, Conforti A (2011) Advances in homeopathy and immunology: a review of clinical research. *Front Biosci (Schol Ed)* 3: 1363-1389.
39. Corrao S, Natoli G (2017) The case of homeopathy, "how to search PubMed" may be a first step. *Eur J Intern Med* 41: 8-9.
40. Corrao S, Argano C, Colomba D, Ippolito C, Gargano V, et al. (2013) Information management and complementary alternative medicine: the anatomy of information about CAMs through PubMed. *Intern Emerg Med* 8: 627-634.
41. W Boericke (1978) Pocket manual of Materia Medica and Repertory. BJain, New Delhi India.
42. Gassinger CA, Wünstel G, Netter P (1981) A controlled clinical trial for testing the efficacy of the homeopathic drug eupatorium perfoliatum D2 in the treatment of common cold (author's transl). *Arzneimittelforschung* 31: 732-736.
43. L Maiwald, Omotossicologia (1988) una metodica scientificamente comprovata e di sperimentata efficacia. *Riv Ital Omotossicol* VII: 2-9.
44. de Lange de Klerk ES, Blommers J, Kuik DJ, Bezemer PD, Feenstra L (1994) Effect of homeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections. *BMJ* 309: 1329-1332.
45. Friese KH, Kruse S, Lüdtke R, Moeller H (1997) The homeopathic treatment of otitis media in children--comparisons with conventional therapy. *Int J Clin Pharmacol Ther* 35: 296-301.
46. M Wiesenuer (1998) Comparison of solid and liquid forms of homeopathic remedies for tonsillitis. *Adv Ther* 15: 362-371.
47. M Adler (1999) Efficacy and safety of a fixed-combination homeopathic therapy for sinusitis. *Adv Ther* 16: 103-111.

48. E Rau (2000) Treatment of acute tonsillitis with a fixed-combination herbal preparation. *Adv Ther* 17: 197-203.
49. H Frei, A Thurneysen (2001) Homeopathy in acute otitis media in children: Treatment effect or spontaneous resolution?. *Br Homeopath J* 90: 180-182.
50. Riley D, Fischer M, Singh B, Haidvogel M, Heger M (2001) Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. *J Altern Complement Med* 7: 149-159.
51. Jacobs J, Springer DA, Crothers D (2001) Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. *Pediatr Infect Dis J* 20: 177-183.
52. Rabe A, Weiser M, Klein P (2004) Effectiveness and tolerability of a homeopathic remedy compared with conventional therapy for mild viral infections. *Int J Clin Pract* 58: 827-832.
53. Ammerschläger H, Klein P, Weiser M, Oberbaum M (2005) [Treatment of inflammatory diseases of the upper respiratory tract -- comparison of a homeopathic complex remedy with xylometazoline]. *Forsch Komplementarmed Klass Naturheilkd* 12: 24-31.
54. Steinsbekk A, Bentzen N, Fønnebo V, Lewith G (2005) Self treatment with one of three self selected, ultramolecular homeopathic medicines for the prevention of upper respiratory tract infections in children. A double-blind randomized placebo controlled trial. *Br J Clin Pharmacol* 59: 447-455.
55. Steinsbekk A, Fønnebo V, Lewith G, Bentzen N (2005) Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomised, controlled trial comparing individualised homeopathic care and waiting-list controls. *Complement Ther Med* 13: 231-238.
56. Trichard M, Chaufferin G, Nicoloyannis N (2005) Pharmacoeconomic comparison between homeopathic and antibiotic treatment strategies in recurrent acute rhinopharyngitis in children. *Homeopathy* 94: 3-9.
57. Schmiedel V, Klein P (2006) A complex homeopathic preparation for the symptomatic treatment of upper respiratory infections associated with the common cold: An observational study. *Explore (NY)* 2: 109-114.
58. Steinsbekk A, Lewith G, Fønnebo V, Bentzen N (2007) An exploratory study of the contextual effect of homeopathic care. A randomised controlled trial of homeopathic care vs. self-prescribed homeopathic medicine in the prevention of upper respiratory tract infections in children. *Prev Med* 45: 274-279.
59. Haidvogel M, Riley DS, Heger M, Brien S, Jong M, et al. (2007) Homeopathic and conventional treatment for acute respiratory and ear complaints: a comparative study on outcome in the primary care setting. *BMC Complement Alter Med* 7: 7.
60. Zabolotnyi DI, Kneis KC, Richardson A, Rettenberger R, Heger M, et al. (2007) Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. *Explore (NY)* 3: 98-109.
61. Kneis KC, Gandjour A (2009) Economic evaluation of Sinfrontal in the treatment of acute maxillary sinusitis in adults. *Appl Health Econ Health Policy* 7: 181-191.
62. Witt CM, Lüdtke R, Willich SN (2009) Homeopathic treatment of patients with chronic sinusitis: A prospective observational study with 8 years follow-up. *BMC Ear Nose Throat Disord* 9: 7.
63. Ramchandani NM (2010) Homeopathic treatment of upper respiratory tract infections in children: Evaluation of thirty case series. *Complement Ther Clin Pract* 16: 101-108.
64. Taylor JA, Jacobs J (2011) Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media. *Homeopathy* 100: 109-115.
65. Bernstein JA, Davis BP, Picard JK, Cooper JP, Zheng S (2011) A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. *Ann Allergy Asthma Immunol* 107: 171-178.
66. Sinha MN, Siddiqui VA, Nayak C, Singh V, Dixit R, et al. (2012) Randomized controlled pilot study to compare Homeopathy and Conventional therapy in Acute Otitis Media. *Homeopathy* 101: 5-12.
67. Nayak C, Singh V, Singh VP, Oberai P, Roja V, et al. (2002) Homeopathy in chronic sinusitis: a prospective multi-centric observational study. *Homeopathy* 101: 84-91.
68. Taylor JA, Jacobs J (2014) Homeopathic Ear Drops as an Adjunct in Reducing Antibiotic Usage in Children With Acute Otitis Media. *Glob Pediatr Health* 1.
69. Zanasi A, Mazzolini M, Tursi F, Morselli-Labate AM, Paccapelo A, et al. (2014) Homeopathic medicine for acute cough in upper respiratory tract infections and acute bronchitis: a randomized, double-blind, placebo-controlled trial. *Pulm Pharmacol Ther* 27: 102-108.
70. Grimaldi-Bensouda L, Bégaud B, Rossignol M, Avouac B, Lert F, et al. (2017) Management of upper respiratory tract infections by different medical practices, including homeopathy, and consumption of antibiotics in primary care: the EPI3 cohort study in France 2007-2008. *PLoS One* 9: 89990.
71. Malapane E, Solomon EM, Pellow J (2014) Efficacy of a homeopathic complex on acute viral tonsillitis. *J Altern Complement Med* 20: 868-873.
72. Michalsen A, Uehleke B, Stange R (2015) Safety and compliance of a complex homeopathic drug (Contramutan N Saft) in the treatment of acute respiratory tract infections: A large observational (non-interventional) study in children and adults focussing on homeopathy specific adverse reactions versus adverse drug reactions. *Regul Toxicol Pharmacol* 72: 179-184.
73. Zanasi A, Cazzato S, Mazzolini M, Ierna CM, Mastroberto M, et al. (2015) Does additional antimicrobial treatment have a better effect on URTI cough resolution than homeopathic symptomatic therapy alone? A real-life preliminary observational study in a pediatric population. *Multidiscip Respir Med* 10: 25.
74. Thinesse-Mallwitz M, Maydannik V, Keller T, Klement P (2015) A Homeopathic Combination Preparation in the Treatment of Feverish Upper Respiratory Tract Infections: An International Randomized Controlled Trial. *Forsch Komplementmed* 22: 163-170.
75. Beghi GM, Morselli-Labate AM (2016) Does homeopathic medicine have a preventive effect on respiratory tract infections? A real life observational study. *Multidiscip Respir Med* 11: 12.
76. Jong MC, Buskin SL, Ilyenko L, Kholodova I, Burkart J, et al. (2016) Effectiveness, safety and tolerability of a complex homeopathic medicinal product in the prevention of recurrent acute upper respiratory tract infections in children: a multicenter, open, comparative, randomized, controlled clinical trial. *Multidiscip Respir Med* 11: 19.
77. Pedrero-Escalas MF, Jimenez-Antolin J, Lassaletta L, Diaz-Saez G, Gavilán J (2016) Hospital clinical trial: Homeopathy (Agraphis nutans 5CH, Thuya occidentalis 5CH, Kalium muriaticum 9CH and Arsenicum iodatum 9CH) as adjuvant, in children with otitis media with effusion. *Int J Pediatr Otorhinolaryngol* 8: 217-223.
78. van Haselen R, Thinesse-Mallwitz M, Maidannyk V, Buskin SL, Weber S, et al. (2016) The Effectiveness and Safety of a Homeopathic Medicinal Product in Pediatric Upper Respiratory Tract Infections With Fever: A Randomized Controlled Trial. *Glob Pediatr Health* 3.
79. Jacobs J, Taylor JA (2016) A randomized controlled trial of a homeopathic syrup in the treatment of cold symptoms in young children. *Complement Ther Med* 29: 229-234.

80. Palm J, Kishchuk VV, Ulied A, Fernández JP, De Jaegere S, et al. (2017) Effectiveness of an add-on treatment with the homeopathic medication SilAto-5-90 in recurrent tonsillitis: An international, pragmatic, randomized, controlled clinical trial. *Complement Ther Clin Pract* 28: 181-191.
81. Voß HW, Michalsen A, Brünjes R (2018) Efficacy and tolerability of a complex homeopathic drug in children suffering from dry cough-A double-blind, placebo-controlled, clinical trial. *Drug Res (Stuttg)* 68: 444-449.
82. Allaert FA, Villet S, Vincent S, Sauve L (2018) Observational study on the dispensing of cough syrups to children with acute cough by community pharmacists in France. *Minerva Pediatr* 70: 117-126.
83. Wiesenauer M, Gaus W, Bohnacker U, Häussler S (1989) Efficiency of homeopathic preparation combinations in sinusitis. Results of a randomized double blind study with general practitioners. *Arzneimittelforschung* 39: 620-625.
84. Bellavite P, Chirumbolo S, Marzotto M (2010) Hormesis and its relationship with homeopathy. *Hum Exp Toxicol* 16: 11-18.
85. Van Wijk R, Wiegant FA (2011) Postconditioning hormesis and the similia principle. *Front Biosci (Elite Ed)* 3: 1128-1138.
86. Bell IR, Schwartz GE (2013) Adaptive network nanomedicine: An integrated model for homeopathic medicine. *Front Biosci (Schol Ed)* 5: 685-708.
87. Fokkens W, Hellings P, Segboer C (2016) Capsaicin for Rhinitis. *Curr Allergy Asthma Rep* 16: 60.
88. Gevorgyan A, Segboer C, Gorissen R, van Drunen CM, Fokkens W, et al. (2015) Capsaicin for non-allergic rhinitis. *Cochrane Database Syst Rev* CD010591.
89. Friese KH, Kruse S, Moeller H (1996) Acute otitis media in children. Comparison between conventional and homeopathic therapy *HNO* 44: 462-466.
90. Kruse, S. Otitis media bei kindern. 1998. Stuttgart, Edition Forschung. Hippokrates Verlag. Ref Type: Pamphlet
91. Jacobs J (2012) Homeopathy for acute otitis media-time for a definitive trial. *Homeopathy* 101: 3.
92. Maiwald VL, Weinfurter T, Mau J, Connert WD (1988) Therapy of common cold with a homeopathic combination preparation in comparison with acetylsalicylic acid. A controlled, randomized double-blind study. *Arzneimittelforschung*, 38 (1988) 578-582.
93. Oberbaum M, Glatthaar-Saalmüller B, Stolt P, Weiser M (2005) Antiviral activity of Engystol: an in vitro analysis. *J. Altern. Complement Med* 11: 855-862.
94. Roeska K, Seilheimer B (2010) Antiviral activity of Engystol® and Gripp-Heel®: An in-vitro assessment. *J Immune Based Ther Vaccines* 8: 6.
95. Fimiani V, Cavallaro A, Ainis O, Bottari C (2000) Immunomodulatory effect of the homeopathic drug Engystol-N on some activities of isolated human leukocytes and in whole blood. *Immunopharmacol Immunotoxicol* 22: 103-115.
96. Enbergs H (2006) Effects of the homeopathic preparation Engystol on interferon-gamma production by human T-lymphocytes. *Immunol Invest* 35: 19-27.
97. Marrari LA1, Terzan L, Chaffuerin G (2012) Oscilloccinum for influenza treatment. *Ann Ist Super Sanita* 48: 105-109.
98. Mathie RT, Frye J, Fisher P (2015) Homeopathic Oscilloccinum(R) for preventing and treating influenza and influenza-like illness. *Cochrane Database Syst Rev* 1: CD001957.
99. Bellavite P, Conforti A, Piasere V, Ortolani R (2005) Immunology and homeopathy. 1. Historical background, *Ecamm* 2: 441-452.
100. Jacobs J (2018) Homeopathic Prevention and Management of Epidemic Diseases. *Homeopathy*, 107: 157-160.
101. Kwakye GF, Jiménez J, Jiménez JA, Aschner M (2018) Atropa belladonna neurotoxicity: Implications to neurological disorders. *Food Chem Toxicol* 116: 346-353.
102. Glatstein M, Danino D, Wolyniez I, Scolnik D (2013) Seizures Caused by Ingestion of Atropa Belladonna in a Homeopathic Medicine in a Previously Well Infant: Case Report and Review of the Literature. *Am J Ther* 21: 196-198.
103. Panossian A, Seo EJ, Efferth T (2018) Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. *Phytomedicine* 50: 257-284.
104. Panossian A, Gabrielian E, Wagner H (1997) Plant adaptogens. II. Bryonia as an adaptogen. *Phytomedicine* 4: 85-99.
105. Park CS, Lim H, Han KJ, Baek SH, Sohn HO, et al. (2004) Inhibition of nitric oxide generation by 23,24-dihydrocucurbitacin D in mouse peritoneal macrophages. *J Pharmacol Exp Ther* 309: 705-710.
106. Ielciu I, Mouithys-Mickalad A, Franck T, Angenot L, Ledoux A, et al. (2019) Flavonoid composition, cellular antioxidant activity and (myelo) peroxidase inhibition of a Bryonia alba L. (*Cucurbitaceae*) leaves extract. *J Pharm Pharmacol* 71: 230-239.
107. Murali PM, Rajasekaran S, Paramesh P, Krishnarajasekar OR, Vasudevan S, et al (2006) Plant-based formulation in the management of chronic obstructive pulmonary disease: a randomized double-blind study. *Respir Med* 100: 39-45.
108. Abud AP, Cesar B, Cavazzani LF, de Oliveira CC, Gabardo J, et al. (2006) Activation of bone marrow cells treated with Canova *in vitro*. *Cell Biol Int* 30: 808-816.
109. Frass M, Linkesch M, Banyai S, Resch G, Dielacher C, et al. (2005) Adjunctive homeopathic treatment in patients with severe sepsis: a randomized, double-blind, placebo-controlled trial in an intensive care unit. *Homeopathy* 94: 75-80.
110. Shang A, Huwiler-Müntener K, Nartey L, Jüni P, Dörig S, et al (2005) Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 366: 726-732.
111. Mathie RT, Lloyd SM, Legg LA, Clausen J, Moss S, et al. (2014) Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev* 3: 142.
112. Mathie RT, Van Wassenhoven M, Jacobs J, Oberbaum M, Frye J, et al. (2016) Model validity and risk of bias in randomised placebo-controlled trials of individualised homeopathic treatment. *Complement Ther Med* 25: 120-125.
113. Mathie RT, Fok YYY, Viksveen P, To AKL, Davidson JRT (2019) Systematic Review and Meta-Analysis of Randomised, Other-than-Placebo Controlled, Trials of Non-Individualised Homeopathic Treatment. *Homeopathy* 108: 88-101.
114. Mathie RT, Van Wassenhoven M, Rutten ALB, Klein-Laansma CT, Eizayaga J, et al. (2017) Model validity of randomised placebo-controlled trials of non-individualised homeopathic treatment. *Homeopathy* 106: 194-202.
115. Hawke K, van Driel ML, Buffington BJ, McGuire TM, King D (2018) Homeopathic medicinal products for preventing and treating acute respiratory tract infections in children. *Cochrane Database Syst Rev* 4: CD005974.
116. Hahn RG (2013) Homeopathy: meta-analyses of pooled clinical data, *Forsch Komplementmed* 20: 376-381.

117. Siqueira CM, Homsani F, da Veiga VF, Lyrio C, Mattos H, et al. (2016) Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: blind, randomized, placebo-controlled clinical trial. *Homeopathy* 105: 71-77.
118. Fixsen A (2013) Should homeopathy be considered as part of a treatment strategy for otitis media with effusion in children? *Homeopathy* 102: 145-150.
119. Fixsen A (2018) Homeopathy in the Age of Antimicrobial Resistance: Is It a Viable Treatment for Upper Respiratory Tract Infections? *Homeopathy* 107: 99-114.
120. Kleijnen J, Knipschild P, ter Riet G (1991) Clinical trials of homeopathy. *BMJ* 302: 316-323.
121. Fisher P (2008) On the plausibility of Homeopathy. *Homeopathy* 97: 1-2.
122. Bellavite P (2012) On the plausibility of homeopathic 'similitude'. *Bioethics* 26: 506-507.
123. Rutten L, Mathie RT, Fisher P, Goossens M, van Wassenhoven M (2013) Plausibility and evidence: the case of homeopathy. *Med Health Care Philos* 16: 525-532.
124. Demangeat J-L (2010) NMR relaxation evidence for solute-induced nanosized superstructures in ultramolecular aqueous dilutions of silica-lactose. *J Mol Liquids* 155: 71-79.
125. Elia V, Ausanio G, Gentile F, Germano R, Napoli E (2014) Experimental evidence of stable water nanostructures in extremely dilute solutions, at standard pressure and temperature. *Homeopathy* 103: 44-50.
126. Bellavite P, Marzotto M, Oliosio D, Moratti E, Conforti A (2014) High-dilution effects revisited. I. Physicochemical aspects. *Homeopathy* 103: 4-21.
127. Jäger T, Scherr C, Shah D, Majewsky V, Wolf U, et al. (2015) The use of plant-based bioassays in homeopathic basic research. *Homeopathy* 104: 277-282.
128. Klein SD, Wolf U (2016) Comparison of homeopathic globules prepared from high and ultra-high dilutions of various starting materials by ultraviolet light spectroscopy. *Complement Ther Med* 24: 111-117.
129. Guedes JRP, Bonamin LV, Capelozzi VL (2018) Water-Related Mechanisms Proposed for Storing and Transmitting Homeopathic Information: Putative Links with Biological Responses. *Homeopathy* 107: 172-180.
130. Clausen J, van Wijk R, Albrecht H (2010) Infection models in basic research on homeopathy. *Homeopathy* 99: 263-270.
131. Fimiani V, Cavallaro A, Ainis O, Bottari C (2000) Immunomodulatory effect of the homeopathic drug Engystol-N on some activities of isolated human leukocytes and in whole blood. *Immunopharmacol Immunotoxicol* 22: 103-115.
132. Smit E, Oberholzer HM, Pretorius E (2009) A review of immunomodulators with reference to Canova. *Homeopathy* 98: 169-176.
133. Bellavite P, Conforti A, Pontarollo F, Ortolani R (2006) Immunology and Homeopathy. 2. Cells of the Immune System and Inflammation. *eCAM* 3: 13-24.
134. Bonamin LV, Bellavite P (2015) Immunological models in high dilution research following M Bastide. *Homeopathy* 104: 263-268.
135. Poitevin B (2015) Survey of immuno-allergological ultra high dilution research. *Homeopathy* 104: 269-276.
136. Mayer J, Williams RJ, Oppenheimer VA, He B, Tuckfield C, et al. (2016) The immunomodulatory effects of a commercial antiviral homeopathic compound in C57BL/6 mice, pre and post vaccine challenge. *Int Immunopharmacol* 39: 389-396.
137. Glatthaar-Saalmüller B, Fallier-Becker P (2001) Antiviral action of Euphorbium compositum and its components. *Forsch Komplementarmed Klass Naturheilkd* 8: 207-212.
138. Glatthaar-Saalmüller B (2007) *In vitro* evaluation of the antiviral effects of the homeopathic preparation Gripp-Heel on selected respiratory viruses. *Can J Physiol Pharmacol* 85: 1084-1090.
139. Mathie RT, Van Wassenhoven M, Jacobs J, Oberbaum M, Roniger H, et al. (2015) Model validity of randomised placebo-controlled trials of individualised homeopathic treatment. *Homeopathy* 104: 164-169.
140. Rutten LALB (2018) Flawed statistics and science confirming existing paradigms. *J Eval Clin Pract* 24: 1273-1276.



Journal of Anesthesia & Clinical Care
Journal of Addiction & Addictive Disorders
Advances in Microbiology Research
Advances in Industrial Biotechnology
Journal of Agronomy & Agricultural Science
Journal of AIDS Clinical Research & STDs
Journal of Alcoholism, Drug Abuse & Substance Dependence
Journal of Allergy Disorders & Therapy
Journal of Alternative, Complementary & Integrative Medicine
Journal of Alzheimer's & Neurodegenerative Diseases
Journal of Angiology & Vascular Surgery
Journal of Animal Research & Veterinary Science
Archives of Zoological Studies
Archives of Urology
Journal of Atmospheric & Earth-Sciences
Journal of Aquaculture & Fisheries
Journal of Biotech Research & Biochemistry
Journal of Brain & Neuroscience Research
Journal of Cancer Biology & Treatment
Journal of Cardiology & Neurocardiovascular Diseases
Journal of Cell Biology & Cell Metabolism
Journal of Clinical Dermatology & Therapy
Journal of Clinical Immunology & Immunotherapy
Journal of Clinical Studies & Medical Case Reports
Journal of Community Medicine & Public Health Care
Current Trends: Medical & Biological Engineering
Journal of Cytology & Tissue Biology
Journal of Dentistry: Oral Health & Cosmesis
Journal of Diabetes & Metabolic Disorders
Journal of Dairy Research & Technology
Journal of Emergency Medicine Trauma & Surgical Care
Journal of Environmental Science: Current Research
Journal of Food Science & Nutrition
Journal of Forensic, Legal & Investigative Sciences
Journal of Gastroenterology & Hepatology Research
Journal of Gerontology & Geriatric Medicine
Journal of Genetics & Genomic Sciences
Journal of Hematology, Blood Transfusion & Disorders
Journal of Human Endocrinology
Journal of Hospice & Palliative Medical Care
Journal of Internal Medicine & Primary Healthcare
Journal of Infectious & Non Infectious Diseases
Journal of Light & Laser: Current Trends
Journal of Modern Chemical Sciences
Journal of Medicine: Study & Research
Journal of Nanotechnology: Nanomedicine & Nanobiotechnology
Journal of Neonatology & Clinical Pediatrics
Journal of Nephrology & Renal Therapy
Journal of Non Invasive Vascular Investigation
Journal of Nuclear Medicine, Radiology & Radiation Therapy
Journal of Obesity & Weight Loss
Journal of Orthopedic Research & Physiotherapy
Journal of Otolaryngology, Head & Neck Surgery
Journal of Protein Research & Bioinformatics
Journal of Pathology Clinical & Medical Research
Journal of Pharmacology, Pharmaceutics & Pharmacovigilance
Journal of Physical Medicine, Rehabilitation & Disabilities
Journal of Plant Science: Current Research
Journal of Psychiatry, Depression & Anxiety
Journal of Pulmonary Medicine & Respiratory Research
Journal of Practical & Professional Nursing
Journal of Reproductive Medicine, Gynaecology & Obstetrics
Journal of Stem Cells Research, Development & Therapy
Journal of Surgery: Current Trends & Innovations
Journal of Toxicology: Current Research
Journal of Translational Science and Research
Trends in Anatomy & Physiology
Journal of Vaccines Research & Vaccination
Journal of Virology & Antivirals
Archives of Surgery and Surgical Education
Sports Medicine and Injury Care Journal
International Journal of Case Reports and Therapeutic Studies

Submit Your Manuscript: <http://www.heraldopenaccess.us/Online-Submission.php>