

# Homeopathy in the Age of Antimicrobial Resistance: Is It a Viable Treatment for Upper Respiratory Tract Infections?

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## Abstract

**Background** Acute upper respiratory tract infections (URTIs) and their complications are the most frequent cause of antibiotic prescribing in primary care. With multi-resistant organisms proliferating, appropriate alternative treatments to these conditions are urgently required. Homeopathy presents one solution; however, there are many methods of homeopathic prescribing. This review of the literature considers firstly whether homeopathy offers a viable alternative therapeutic solution for acute URTIs and their complications, and secondly how such homeopathic intervention might take place.

**Method** Critical review of post 1994 clinical studies featuring homeopathic treatment of acute URTIs and their complications. Study design, treatment intervention, cohort group, measurement and outcome were considered. Discussion focused on the extent to which homeopathy is used to treat URTIs, rate of improvement and tolerability of the treatment, complications of URTIs, prophylactic and long-term effects, and the use of combination versus single homeopathic remedies.

**Results** Multiple peer-reviewed studies were found in which homeopathy had been used to treat URTIs and associated symptoms (cough, pharyngitis, tonsillitis, otitis media, acute sinusitis, etc.). Nine randomised controlled trials (RCTs) and 8 observational/cohort studies were analysed, 7 of which were paediatric studies. Seven RCTs used combination remedies with multiple constituents. Results for homeopathy treatment were positive overall, with faster resolution, reduced use of antibiotics and possible prophylactic and longer-term benefits.

**Conclusions** Variations in size, location, cohort and outcome measures make comparisons and generalisations concerning homeopathic clinical trials for URTIs problematic. Nevertheless, study findings suggest at least equivalence between homeopathy and conventional treatment for uncomplicated URTI cases, with fewer adverse events and potentially broader therapeutic outcomes. The use of non-individualised homeopathic compounds tailored for the paediatric population merits further investigation, including through cohort studies. In the light of antimicrobial resistance, homeopathy offers alternative strategies for minor infections and possible prevention of recurring URTIs.

## Keywords

- ▶ homeopathy
- ▶ antimicrobial resistance
- ▶ upper respiratory tract infections
- ▶ clinical studies
- ▶ combination remedies

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## Introduction

With the emergence and proliferation of multi-resistant organisms, the prospect of an 'antimicrobial perfect storm'<sup>1</sup> in the approaching decades has become an urgent public health concern.<sup>1</sup> The excessive and indiscriminate use of these drugs in both human and veterinary practices has led to the emergence and dissemination of resistant organisms that endanger their efficacy.<sup>2-4</sup> Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics, and at least 23,000 people die as a direct result of these infections.<sup>5</sup> Warning of an approaching era in which antibiotics will no longer be effective, the World Health Organization (WHO) and other agencies<sup>6,7</sup> suggest alternative approaches, including the development of novel therapies to treat both mild and serious infections.<sup>7,8</sup> With a growing body of clinical evidence, a strong safety record and evidence of cost-effectiveness,<sup>9-11</sup> homeopathy represents one potential therapeutic solution that could lead to a reduction in the use of antibiotics. Acute upper respiratory tract infections (URTIs) account for 60% of antibiotic prescribing in primary care,<sup>12</sup> yet they provide little benefit for the large proportion of respiratory tract infections which are viral in origin. This review of the literature asks, firstly, whether the peer-reviewed literature on this topic is sufficiently robust for homeopathy to be seriously considered as an alternative to antibiotics for URTIs and their complications and, secondly, how this homeopathic intervention might take place, for example through more widespread use of particular homeopathic preparations.

## Literature Search Strategy

The literature review focuses on peer-reviewed clinical studies featuring homeopathic treatment of URTIs published after 1994. Due to the close association between URTIs and acute rhinopharyngitis and tonsillitis and their frequent treatment with antibiotics, several peer-reviewed studies in which homeopathy was used to treat these conditions were also reviewed. Although not rigorously following the format of a systematic review, the PRISMA guidelines (<http://www.prisma-statement.org>) and recommendations of PRISMA-P checklist (<http://www.prisma-statement.org/documents/PRISMA-P-checklist.pdf>) were utilised for the reporting of data in ► **Tables 1** and **2**. Searches were conducted in two phases. In phase one, the following electronic databases were searched: AMED, Embase, Cochrane Library, PubMed, ScienceDirect, Elsevier Health periodicals and CORE-Hom database. In phase two, additional searches were performed through Google Scholar, Mendeley literature search and the author's university library. Citation chaining was also utilised; however, studies for which the full article or key study details could not be later established were excluded from the final systematic analysis. Searches, although wide, were limited to published, peer-reviewed human trials reported in English. Key search terms were homeopathy, upper respiratory tract infections, rhinopharyngitis and mild viral infections. Studies

which included related conditions, such as bronchitis,<sup>13</sup> influenza,<sup>14</sup> otitis media and tonsillitis,<sup>15</sup> were considered only if URTI or viral infection involving the upper respiratory tract (URT) was mentioned in the title or aims, and where relevant to the study questions. Further exclusion criteria included studies deemed to be of poor quality, published before 1994 and where more than one complementary and alternative medicine (CAM) therapy was used. Case reports of homeopathic treatments for URTIs from books and journals were also not considered. To ensure that a broad body of evidence was considered, peer-reviewed published studies, whether randomised, controlled or cohort, were reviewed, but were considered separately in terms of study aims and design (see ► **Table 1**). Analysis of all studies focused on the following elements: trial design; treatment intervention, with particular reference to single/complex homeopathic medicaments (see ► **Table 2**); cohort group (paediatric/adult/both); measurement criteria, and outcome, with particular reference to reduction in antibiotic use.

## URTIs and Antibiotics

The upper respiratory tract (URT) consists of the nose, mouth, throat, larynx and trachea. URTI is the most common infectious illness in most populations and the primary reason people miss work or school.<sup>16</sup> Although generally short lived, symptoms of URTIs, such as fever, sore throat, headache and cough, are sources of distress for both adults and children and are costly in terms of time off work<sup>17,18</sup> and school.<sup>18</sup> The acute cough following a URTI can continue for several weeks.<sup>13</sup> Children are especially susceptible and may have as many as eight or even more episodes each year. Most URTIs are caused by a self-limiting viral illness (such as influenza and rhinoviruses) with symptoms lasting 7 to 10 days; however, complications such as otitis media,<sup>19</sup> pharyngitis,<sup>20</sup> tonsillitis<sup>21</sup> and sinusitis<sup>22</sup> are frequently treated with antibiotics.<sup>23-27</sup> In the United States, 23% of paediatric medical visits from 2004 to 2008 resulted in prescriptions for antibiotics<sup>9</sup> with otitis media, the most common reason for prescribing antibiotics in children. Other pharmacological treatments include antipyretics, anti-inflammatory drugs, expectorants, decongestants, and cough suppressants, either alone or in combination.<sup>28</sup> Respiratory complaints are also the most frequent reason for over-the-counter (OTC) purchases of homeopathic medicines,<sup>29</sup> suggesting a demand for alternatives to pharmaceutical OTC products.

Public health and medical stewardship programmes aim to alter patients' perceptions and doctors' prescribing behaviour.<sup>1</sup> Yet in many clinical contexts, antibiotic prescribing continues to elude best practice,<sup>1</sup> including in the treatment of URTIs and URTI-related conditions.<sup>23,30,31</sup> According to a recent US clinical report, up to 10 million antibiotic prescriptions per year directed towards respiratory conditions were unlikely to provide any benefit.<sup>32</sup> Fewer than 10% of sore throats are caused by bacterial infections, yet in around 60% of cases, antibiotics were prescribed for them.<sup>33</sup> In recent Cochrane reviews, the short-term effects of antibiotics on acute otitis media (AOM)<sup>34</sup> and URTIs<sup>35</sup> were moderate or negligible when compared with their potential risks.

One Cochrane study found antibiotics to be 'not very useful' in the treatment of AOM, only marginally decreasing the number of children with pain at 24 hours (when most children were better), only slightly reducing those with pain in the first few days following infection and having no effect on reducing the number of children with subsequent hearing loss.<sup>34</sup> In some patients with acute bronchitis, antibiotics had a modest beneficial effect; however, these benefits must be considered in the broader context of side effects, the self-limiting nature of the condition, the costs of antibiotic treatment and the increased resistance to respiratory pathogens.<sup>35</sup> Only in the case of pneumonia in the elderly were the benefits of antibiotics seen as significant;<sup>36</sup> however, the authors of this study concluded that the use of antibiotics for prophylaxis was still not justifiable. Another US study estimated the number of annual antibiotic prescriptions for acute respiratory conditions (including sinusitis, otitis media, and pharyngitis) as 221 per 1,000 people, yet only half of these prescriptions were considered appropriate for these conditions.<sup>37</sup> Understanding differential diagnosis is also important, as is ruling out more serious illness. For instance, while most cases of acute pharyngitis in children have a viral origin, are benign and self-limiting (and for which antibiotics are often unnecessarily prescribed), untreated streptococcal tonsillopharyngitis can result in serious complications, such as rheumatic fever and related cardiovascular disorders or post-streptococcal glomerulonephritis.<sup>38,39</sup>

In addition to efficacy, the immunological effects and safety of antibiotics are a concern. Studies confirm that pervasive changes occur within the human microbiome after antibiotic treatment and that resistant strains of bacteria can persist for years.<sup>40</sup> Individuals prescribed antibiotics in primary care for a respiratory infection develop bacterial resistance to that antibiotic, which not only increases the population carriage of organisms resistant to first-line antibiotics, but also leads to increased use of second-line antibiotics in the community.<sup>41</sup> According to one meta-analysis, the risk of acquiring methicillin-resistant *Staphylococcus aureus* increased by 1.8-fold in patients who had taken antibiotics.<sup>42</sup> Nevertheless, public awareness concerning the appropriate use and safety of antibiotics still appears to be lacking. In one Australian consumer study, over one-third of the 252 participants thought that taking antibiotics when suffering from a cold or flu would lead to more rapid recovery, while nearly one-fifth considered antibiotics as a cure for viral infections.<sup>43</sup> Links have been established between antibiotic use and paediatric asthma<sup>44,45</sup> and eczema<sup>46</sup> and less common but grave physical and psychoactive side effects associated with particular antibiotics. The class of antibiotics fluoroquinolones is known to cause tendonitis, central nervous system (CNS) effects, peripheral neuropathy,<sup>47</sup> and juvenile fluoroquinolone-induced joint/cartilage toxicity.<sup>48</sup> Severe side effects of the broad spectrum antibiotic clarithromycin include liver and renal failure<sup>49,50</sup> and psycho-neurological effects including hallucinations, depersonalisation, depression, insomnia and psychosis.<sup>51</sup>

## The Homeopathic Approach

As a CAM therapy, homeopathy has been subject to criticism for its use of infinitesimal doses to treat different ailments, with insufficient proof that such doses can have an effect.<sup>52</sup> Yet, despite a long history of scientific controversy, homeopathy has proved resilient, is geographically widespread,<sup>53</sup> and is an accepted part of the medical system in countries such as India,<sup>54</sup> France<sup>55</sup> and Switzerland.<sup>56</sup> Advantages of homeopathy include ease of application and safety, with few contraindications existing in the treatment of the very young<sup>9</sup> and old, beside the careful selection of remedy and dosage. Whereas using antibiotics and OTC medications does little to improve the body's future response to infection, homeopathy purports to do so.

When dealing with complex systems, a holistic medical approach, such as is frequently used in homeopathy, can offer therapeutic advantages over non-individualised reductionist methods.<sup>57,58</sup> In part, it is the person-focused approach of traditional homeopathy that distinguishes it from conventional approaches<sup>59</sup> and contributes to its appeal to certain population groups.<sup>60-62</sup> Unlike mainstream medicine, where treatment is based on the clinical diagnosis and the idiosyncratic symptoms of the patient are given less importance, in the 'classical' homeopathic tradition the prescription of a homeopathic medication or 'remedy' is based on the totality of symptoms and signs exhibited or expressed by an individual patient.<sup>63</sup> Thus, in homeopathic case-taking, the assessment of the medical situation may not be the principal reason for the choice of remedy,<sup>56</sup> and a spectrum of remedies based on different criteria may be considered.

There are, however, many variations to the homeopathic method of prescribing, especially in the treatment of chronic conditions. A particular distinction lies between individualised and clinically based homeopathic treatment protocols, the former being based on a 'total system approach' as described above and the latter on a more generic method, in which 'combination' or 'complex' homeopathic medicines may be prescribed for a particular condition or disease.<sup>64</sup> Another method, 'isopathy', refers to the use of diseased by-products or tissues, known as 'nosodes', and healthy animal tissue, referred to as sarcodes,<sup>65</sup> which may be prescribed individually or to a population group for preventative purposes.<sup>66,67</sup> All these methodologies have been employed in clinical studies, including for the treatment of URTIs. From the homeopathic perspective, patients with chronic conditions may require 'constitutional' remedies, emphasising the suitability of the in-depth individualised approach. Seeking a 'totality' of symptoms in a holistic sense<sup>68</sup> is resource and time consuming however, as it requires a detailed chronological history of the patient and their condition so that a single remedy can be prescribed to treat a range of symptoms. In acute conditions, the symptom picture is less complicated and the need to prescribe more urgent, strengthening the case for non-individualised prescribing.

## Homeopathy and Research

With an empirical tradition going back more than 200 years and homeopathic physicians trained in the scientific

method, research has always been the backbone of homeopathy. Homeopathic literature includes a vast number of published drug ‘provings’, case studies and practice reports; however, substantial areas of practice have remained uncharted. For instance, the treatment of large-scale epidemics has never been systematically and scientifically researched.<sup>56</sup> The problems of measuring the effects of homeopathic treatment through randomised controlled trials (RCTs) and other reductionist methods are considerable. A number of systematic reviews of the homeopathy RCT literature by Mathie et al<sup>64,69,70</sup> found significant inadequacies, with the majority of studies demonstrating uncertain or high risk of bias. Some studies were not properly randomised, with most studies addressing a different aspect of homeopathic care.<sup>71</sup> Practical problems of RCTs include selecting patients for participation, the insecurities caused by blinding and variations in the level of training of individual homeopathic physicians. Whereas conventional medicine examines the specific effect of a pharmaceutical substance, the effects of a homeopathic substance arise from its complex individual interaction with the organism and this limits the external validity and generalisability of placebo-controlled, blinded homeopathy studies.<sup>56</sup> As with all clinical trials, there are variations in size and outcome measures, with the limited number of homeopathic studies making these types of anomalies more significant.

The absence of positive or any RCT results does not necessarily mean that a treatment is ineffective, and a danger lies in eliminating treatments on the basis of no RCT proof of their efficacy.<sup>56</sup> Non-RCTs and patient reported surveys are considered by some to be inferior forms of research evidence, but are important adjuncts to RCTs that can measure key markers such as patient satisfaction, quality of life and functional health. Observational studies such as clinical outcome studies and case reports, monitoring the effects of homeopathy in real-life clinical settings, are a helpful adjunct to RCTs<sup>72</sup> and more closely reflect real-life experiences of patients and physicians than RCTs,<sup>73</sup> and are therefore considered in this study.

## Results

Searches of online libraries and bibliographical references found multiple peer-reviewed studies (in English and non-English) published between 1994 and 2017, in which homeopathy had been used to treat URTIs and associated symptoms (cough, pharyngitis, tonsillitis, otitis media, acute sinusitis, etc.). Both RCTs and observational/cohort studies were searched and screened to ensure that as many studies as possible were included in the review and its discussion. Non-English language studies, and those for which key study details could not be established, were later excluded from the final review, as were those that did not directly refer to URTIs in the title or content. For the final review, nine RCTs and eight observational/cohort studies were analysed, of which six of the RCTs and one observational/cohort trial were paediatric studies. Seven RCTs used combination remedies with multiple constituents. One of the RCTs in these tables is

featured twice as it measured treatment effects on two different cohorts. The first article<sup>74</sup> reports the effects and safety of standard treatment (ST) plus a homeopathic compound (Influcid [IFC]), or ST only, on a mixed age cohort with a URTI. The later article<sup>28</sup> reports the effects of ST plus IFC or ST only, on a paediatric cohort. Both articles have been included in the analysis. The two studies reported by Zanasi's team (RCT<sup>13</sup> and observational<sup>75</sup>) bear similarities in that the same homeopathic complex was used on both paediatric arms; however, in the observational study one arm received antibiotics in addition to the homeopathic cough medicine.

Full details of randomised and observational studies, including trial design, mode of homeopathic treatment (e.g. complex, individualised), cohort, outcome assessment, results and conclusions, are given in ►Table 1. ►Table 2 focuses on studies using complex homeopathic remedies, and a breakdown of the homeopathic constituents where this information was available.

The article's discussion focuses on the following areas of concern: extent to which homeopathy is used for URTIs, tolerability and rate of improvement of homeopathic treatment, complications of URTIs, prophylactic and long-term effects, and the use of combination versus single homeopathic remedies. As a literature review, rather than a systematic review, no attempt has been made to extract new data from the primary articles, or to assess the intrinsic quality of each study, including risk of bias.

## Use of Homeopathy for URTIs

Respiratory infections are a common reason for seeking homeopathic care.<sup>76,77</sup> For example, out of 551 paediatric patients treated at a homeopathic clinic in Rossi et al's observational study, 337 (61%) presented with respiratory infections, making this the most frequently observed disease in this population group.<sup>78</sup> Of the various clinical trials featuring the use of homeopathy for a specific condition, those concerning infectious diseases of the URT,<sup>13,28,79,80</sup> and complications such as AOM (ear infections)<sup>9,81</sup> contain some of the most positive evidence of the effectiveness of homeopathic interventions.<sup>56</sup> The evaluation of 27 studies for a Health Technology Assessment report on effectiveness, cost-effectiveness and appropriateness of homeopathy on URTIs and allergic reactions showed a positive overall result in favour of homeopathy, with six out of seven controlled studies showing at least equivalence to conventional medical interventions.<sup>56</sup>

## Tolerability

In the treatment of self-limiting acute conditions such as URTIs and mild infections, both treatment tolerability and the rate of improvement with a medical intervention are important, and several studies suggest that homeopathic treatment can fulfil both these prerequisites. Many participants in homeopathic studies are children<sup>9,14,79,81–84</sup> so it is significant that the safety and tolerability of homeopathic treatment in the trials reviewed was very good.<sup>28,74,79,85</sup> A good rate of improvement in the acute symptoms of URTIs in those

**Table 1** Reviewed URTI-related published studies (1994–2016)

Authors	Date/Journal	Description	Treatment	Cohort/Patients	Outcome assessment	Outcome	Conclusion
<b>Randomised Controlled Trials</b>							
de Lange et al	1994/ BMJ	Randomised, double-blind, placebo-controlled clinical trial	Homeopathy versus placebo Daily assessed symptom score	175 children with frequently recurring URTIs	Number of antibiotic courses, and number of adenoidectomies and tonsillectomies over 1 year of follow-up	Improvements in both groups, but fewer adenoidectomies in homeopathic treatment group	Homeopathy offers little more than careful counselling of children with URTIs, but some effects noted
Diefenbach et al	1997/ Z Allgemeinmed	Randomised, double-blind, placebo-controlled clinical trial	Homeopathic combination BRONCHISELECT versus placebo	258 patients presenting with acute URTI/ bronchitis	Number of days of coughing, and degree of expectoration and dysphagia	After 3 weeks, homeopathic group had < days of coughing than placebo Expectoration and dysphagia went better under verum	Therapy with BRONCHISELECT is effective
Steinsbekk et al	2007/ Preventive Medicine	Randomised controlled trial	Homeopathic care versus self-prescribed homeopathic medicine	208 children below the age of 10 years	Results of prescribed homeopathic medicine in the prevention of childhood URTIs	No significant differences in clinical effects between SPH and HC for primary outcomes	No evidence for clinically relevant effect of homeopathic care versus a homeopathic medicine prescribed by child's parents
Zanasi et al	2014/ Pulm Pharmacol Ther	Double blind, placebo controlled clinical trial	ST versus homeopathic cough syrup	80 patients	Cough severity and sputum viscosity	Cough diminished in all groups but at 4 and 7 days, cough severity was significantly lower in the homeopathic group than in the placebo	The homeopathic syrup is a valid remedy for the management of acute cough induced by URTIs
Thinnes-Mallwitz et al	2015/ Forsch Komplementärmed	Randomised, controlled, multinational clinical trial	ST plus IFC for 7 days	523 patients (1–65 years) 265 IFC group, 258 ST group, with febrile URTIs.	Effectiveness and safety of homeopathic IFC as add-on therapy to usual care in URTI patients	IFC group used less symptomatic medication; symptoms were alleviated 1–2 days earlier	IFC reduced used of SC medication accelerated resolution, and was safe in use

(Continued)

Table 1 (Continued)

Authors	Date/Journal	Description	Treatment	Cohort/Patients	Outcome assessment	Outcome	Conclusion
Van Haselen et al	2016/Glob Pediatr Health	Randomised, controlled, multinational clinical trial	ST plus a IFC for 7 days	261 children (<12 years) patients	Clinical effectiveness of homeopathic add-on therapy in paediatric group with URTIs	Less symptoms and faster symptoms resolution, fewer fevers from day 3 onwards in homeopathic group	IFC as add-on treatment reduced disease severity, shortened symptom resolution, and was safe in use
Jong et al	2016/Multidiscip Respir Med	Multi-centre randomised controlled trial	CalSuli-4-02 or a comparator homeopathic product for 3 weeks	200 children aged $\leq$ 6 years with ( $\geq$ three acute URTIs during previous 6 months	Frequency of acute URTIs 3 and 6 months post-treatment, Changes in symptoms, treatment satisfaction, antibiotic use, safety and tolerability also considered	Decrease in antibiotic use in both treatment groups. 'Appetite disorder' and 'child's activities' improved more in the CalSuli-4-02 group	Suggests potential of CalSuli-4-02 as antibiotic option
Siqueira et al	2016/Homeopathy	Randomised, placebo-controlled clinical trial	Homeopathic complex, placebo or InluBio	600 children	Number of flu and acute respiratory infection symptomatic episodes in 1 year	First year: 30.5% of children in the placebo group developed 3 or more flu and acute respiratory infection episodes, and no episodes in either homeopathic groups	Homeopathic prophylactic potential should be investigated in further studies
Jacobs and Taylor	2016/Comp Ther Med	Randomised, placebo-controlled clinical trial	Homeopathic cough syrup or placebo. medication given as needed by parents for 3 days	261 children 2-5 years with URTIs	Change in symptoms one hour after each dose	Improvements in sneezing, cough and the composite cold score significantly > at 1st and 2nd assessments for homeopathic group compared with placebo group	Homeopathic syrup appeared to be effective in reducing the severity of cold symptoms on first day after starting treatment

Table 1 (Continued)

Authors	Date/Journal	Description	Treatment	Cohort/Patients	Outcome assessment	Outcome	Conclusion
<b>Observational Studies</b>							
Herzberger and Weiser	1997/Biomed Ther	Prospective, multi-centre observational study	Engystol in combination with other therapies application, global evaluation	1,479 cases treated by 154 physicians	Application, effectiveness and tolerability of Engystol	Half of the patients improved in 1–4 days	Prophylactic effects of Engystol were very good, and tolerability was excellent
Riley et al	2001/J Altern Complement Med	Outcomes study	Homeopathy versus SC	456 patients	Clinical and subjective improvement in the complaints	Clinical and subjective improvement after 14 days in 82.6% of homeopathy group and 68% of conventional treatment group	Clear superiority of homeopathy over conventional treatment
Rabe et al	2004/Int J Clin Pract	Outcomes study	Homeopathic complex Gripp-Heel compared with SC	485 patients	Effectiveness of homeopathic remedy Gripp-Heel for mild viral infection	Success rate = 78.1% homeopathic group and 52.2% SC. 88.9% homeopathic group versus 38.8% SC rated 'very good'	Better satisfaction scores for Gripp-Heel therapy group than SC
Ammerschlager et al	2005/Res Complement Nat Class Med	Multi-centre, prospective, active-controlled study	Euphorbium complex compared with xylometazoline nasal drops	Patients with URTIs	To demonstrate non-inferiority of the homeopathic complex remedy to xylometazoline	Clinically relevant reductions disease-specific symptoms were observed with both therapies	Favorable outcomes for homeopathic Euphorbium. Tolerability was good with for both therapies
Schmiedel and Klein	2006/Explore	Observational study of 85 Gp practices Germany	Complex homeopathic Engystol versus conventional treatment	397 patients	A range of variables plus improvement time	Improvement in 77.1% patients using Engystol, versus 61.7% for control in 3 days	Engystol may be a useful component of an integrated symptomatic therapy for the common cold

(Continued)

**Table 1** (Continued)

Authors	Date/Journal	Description	Treatment	Cohort/Patients	Outcome assessment	Outcome	Conclusion
Haidvogel et al	2007/BMC Complement Altern Med	International, multi centre, comparative cohort outcome study	Homeopathic versus conventional treatment of acute respiratory and ear complaints	1,577 patients	Proportion of patients experiencing “complete recovery” or “major improvement” in each treatment group	Onset of improvement 7 days post treatment faster with homeopathic treatment in children ( $p = 0.0488$ ) and adults ( $p = 0.0001$ )	Homeopathic treatment of acute respiratory and ear complaints was not inferior to conventional treatment
Zanasi et al	2015/Multidiscip Respir Med	Prospective observational study	ST with homeopathic cough syrup versus cough syrup only	85 children	Whether antibiotics had a role in reducing the severity duration and resolution of cough, and safety of two treatments	Cough diminished in all groups, but adverse events were > in group on antibiotics	Antibiotics did not improve cough reduction but increased side effects
Beghi and Morselli-Labate	2016/Multidiscip Respir Med	Observational study longitudinal	Oscillocochinum	459 patients, followed up 1 and 10 years	Role of Oscillocochinum in preventing RTIs	Reduction in the frequency of onset of RTIs occurred in both groups, but homeopathic group improvement in first year was significantly better	Homeopathic medicine may have a positive effect in preventing RTIs

Abbreviations: IFC, Influcid; RTI, respiratory tract infection; SC, standard care; ST, standard treatment; URTI, upper respiratory tract infection.

**Table 2** URTI-related published studies using complex homeopathic remedies (1997–2016)

Authors	Description	Treatment	Cohort	Medical ingredients	Conclusion
Diefenbach M et al (1997)	RCT Acute URTI/bronchitis	BRONCHISELECT or placebo	258 patients	Drosera D3, Bryonia D4, Tartarus stibiatus D4, Spongia D6 Ipecacuanha D4	Therapy with BRONCHISELECT is effective
Zanasi A et al (2014)	RCT Acute cough arising from URTIs	Homeopathic syrup versus placebo in treating cough arising from URTIs	80 patients	Anemone pulsatilla 6 CH, Rumex crispus 6 CH, Bryonia dioica 3 CH, Ipecacuanha 3 CH, Spongia tosta 3 CH, Sticta pulmonaria 3 CH, Antimonium tartaricum 6 CH, Myocarde 6 CH, Coccus cacti 3 CH, Drosera MT	Homeopathic syrup was able to effectively reduce cough severity and sputum viscosity
Thinesse-Mallwitz et al (2016)	RCT Acute influenza + URTI	ST or ST plus homeopathic medication (Influcid) for 7 days	523 patients	Aconitum napellus D3 Gelsemium sempervirens D3 Cephaelis, Ipecacuanha D3 Phosphorus D5 Bryonia D2 Eupatorium perfoliatum D1	IFC reduced use of SC medication accelerated resolution and was safe in use
van Haselen et al (2016)	RCT Acute URTI (patients < 12 years)	ST or ST plus homeopathic medication (Influcid) for 7 days	261 children	Aconitum napellus D3 Gelsemium sempervirens D3 Cephaelis, Ipecacuanha D3 Phosphorus D5 Bryonia D2 Eupatorium perfoliatum D1	IFC treatment reduced disease severity, shortened symptom resolution, and was safe in use
Jong et al (2016)	RCT URTIs (prevention)	CalSuli-or another complex homeopathic product	200 children	Calcium carbonicum Hahnemanni D6, Calcium fluoratum D6, Calcium phosphoricum D6 and Sulfur jodatatum D12. Control = Gentiana D1, Aconitum D6, Bryonia D6, Ferrum phosphoricum D12, and Acidum sarcolacticum D12	Suggests potential of CalSuli-4-02 as antibiotic option
Taylor and Jacobs (2016)	RCT Severity and recovery time URTI/cold sxs	Homeopathic cough syrup (Hyland's cold and cough 4 kids) or placebo	261 children (2–5 years)	Allium Cepa 6X, Hepar Sulph Calc 12X, Natrum Muriaticum 6X, Phosphorus 12X, Pulsatilla 6X, Sulfur 12X, Hydrastis 6x	Homeopathic syrup appeared to be effective in reducing the severity of cold symptoms on first day after starting treatment

(Continued)

Table 2 (Continued)

Authors	Description	Treatment	Cohort	Medical ingredients	Conclusion
Siqueira et al (2016)	RCT Homeopathic prophylactic potential	InfluoBio homeopathic complex or placebo	600 children	Influbio = purified influenza virus × 30c Homeopathic complex = <i>Streptococcus</i> and <i>Staphylococcus</i> and inactivated influenza virus × 30c	Homeopathic prophylactic potential should be investigated in further studies
<b>Observational</b>					
Herzberger and Weiser (1997)	Prospective, multi centre observational study	Engystol in combination with other therapies	1479 cases treated by 154 physicians	Sulfur D4, D10, <i>Asclepias vincetoxicum</i> D6, D10, D30.	Prophylactic effects of Engystol were very good
Rabe et al (2004)	Cohort study	Homeopathic complex Gripp-Heel or standard care	485 patients	<i>Aconitum napellus</i> 4X, <i>Bryonia alba</i> 4X, <i>Lachesis mutus</i> 12X, <i>Eupatorium perfoliatum</i> 3X, <i>Phosphorus</i> 5X	Better satisfaction scores for Gripp-Heel therapy group than control
Ammerschlagler et al (2005)	Cohort study	<i>Euphorbium</i> complex or xylometazoline nasal drops	URTI patients	<i>Euphorbium</i> complex	Favourable outcomes for <i>Euphorbium</i> . Tolerability was good with for both therapies
Schmiedel and Klein (2006)	Observational study of 85 GP practices	Engystol versus conventional treatments	397 patients	See Herzberger and Weiser 1997	This homeopathic treatment may be a useful component of an integrated symptomatic therapy for the common cold
Beghi and Morselli-Labate (2016)	Observational study longitudinal	Role of the <i>Oscillocochin</i> in preventing RTIs	459 patients, followed up 1 and 10 years	<i>Oscillocochin</i> once a week for 8 months per year	Reduction in the frequency of onset of RTIs occurred in both groups, but homeopathic group improvement in first year was significantly greater

Abbreviations: IFC, Influcid; RCT, randomised controlled trial; SC, standard care; ST, standard treatment; URTI, upper respiratory tract infection.

receiving homeopathic treatment was reported in all the RCTs and observational trials in which this was measured; however, the timescale for symptom improvement varied, for example fever<sup>28</sup> improved/resolved faster than cough.<sup>13</sup>

In Rabe et al's study, treatment with the homeopathic remedy complex Gripp-Heel was perceived by patients with mild viral infections to be more successful, with greater tolerability and compliance than conventional treatment. About 67.9% of patients were considered by physicians to be asymptomatic at the end of Gripp-Heel therapy, compared with 47.9% in the control group.<sup>86</sup> In Zanasi et al's placebo-controlled RCT,<sup>13</sup> 80 patients were treated for acute cough with placebo or the homeopathic syrup. While cough scores decreased over time in each group, cough severity was significantly lower in the homeopathic group than in the placebo group after 4 and 7 days ( $p < 0.001$  and  $p = 0.023$ , respectively). A controlled multinational clinical trial conducted by Thinesse-Mallwitz et al<sup>74</sup> in Germany and the Ukraine compared the effectiveness, safety and tolerability of IFC as an add-on treatment, with standard care (SC) alone, in the prevention of recurrent acute URTIs. The IFC group (265 patients) that was given homeopathy experienced significantly faster improvement than those who had received conventional treatment alone.<sup>74</sup>

Another study by Jong et al<sup>79</sup> measured the effectiveness, safety and tolerability of a homeopathic medicinal complex in the prevention of recurrent acute URTIs in children. The trial, which took place in four outpatient paediatric clinics, involved children under six, with a known susceptibility to acute URTIs. Children were randomly divided into two groups, one group receiving the homeopathic combination remedy CalSuli-4-02 and the other (the control group) receiving another homeopathic product, for 3 weeks. The main outcome measure was frequency of acute URTIs occurring within 3 and 6 months following treatment. Another outcome measure was a reduction in antibiotic use. Both 'appetite disorder' and 'child's activities' improved in both arms of the trial, but more significantly in the CalSuli-4-02 group.

While results of the above studies are disadvantaged by limited cohort size, others such as the large-scale international comparative outcome study by Haidvoogl et al<sup>87</sup> of 1,577 adults and children from eight different countries are less disputable. In this study, individualised homeopathy and SC were compared in the treatment of acute respiratory and ear complaints. Treatment with homeopathy was associated with significantly faster onset of improvement in the first week, while adverse drug reactions occurred more frequently only in the adult group receiving conventional treatment. Results at 14 days were similar in both groups. The authors concluded that homeopathy was not inferior to conventional treatment in ear and acute respiratory infections.

### Complications of URTIs

Complications of URTIs are not the primary focus of this article; however, in clinical practice they remain the most common causes of antibiotic prescriptions<sup>21,37,88</sup> and as such warrant some attention in this review. Searches

revealed a good number of studies in which homeopathy had been used for the URTI-related disorders with promising outcomes, including AOM (ear infections),<sup>9,81,83,89</sup> rhinopharyngitis,<sup>90,91</sup> sinusitis,<sup>92-95</sup> and tonsillitis.<sup>15,96</sup> In a study by Trichard et al comparing homeopathic and antibiotic treatment strategies for rhinopharyngitis in children, homeopathy yielded significantly better results than antibiotics in terms of both medical effectiveness (reduced number of episodes and number of complications) and improved quality of life with significantly less time taken off work for parents.<sup>90</sup> A randomised, double-blind study by Friese and Zabalotny<sup>92</sup> investigated the efficacy and tolerability of a homeopathic combination remedy for the treatment of acute rhinosinusitis. One hundred and forty-four patients with acute rhinosinusitis were treated either with a homeopathic remedy ( $n = 72$ ) or placebo ( $n = 72$ ). In the treatment group, the average sum score dropped from initially  $12.1 \pm 1.6$  to  $5.9 \pm 2.0$  points after 7 days. In the placebo group, it decreased from  $11.7 \pm 1.6$  to  $11.0 \pm 2.9$  points ( $p < 0.001$ ). After 21 days, 90.3% of the homeopathic treatment group was free from complaints, whereas in 88.9% of the placebo group the complaints remained unchanged or became worse. The authors concluded that the homeopathic product allowed an effective and tolerable treatment of acute rhinosinusitis.

There have been several studies indicating the effectiveness of homeopathy for both acute and chronic tonsillopharyngitis. Friese et al<sup>97</sup> performed a multi-centre, randomised, placebo-controlled, double-blinded study on 158 paediatric patients affected by acute non-streptococcal tonsillitis. The study group received Tonsilotren hourly until onset of improvement, then three times a day, while the control group received placebo. Typical tonsillitis symptoms included swallowing difficulties, throat pain and redness, salivation and fever. By day 4, the study group showed a significantly higher rate of decrease in symptoms than the placebo group. By day 6, 92.4% of study patients showed full recovery or moderate improvement, compared with the 43.1% in the control group, with a deterioration rate of 3.8% in the study group against 22.8% in the control group.

A more recent, international, RCT of the homeopathic combination remedy SilAtro-5-90 (brand name: Tonsilotren) was performed in multiple settings by Palm et al.<sup>96</sup> Two hundred and fifty-six patients aged 6 to 60 years with moderate recurrent tonsillitis (RT) were given either the homeopathic preparation in addition to standard symptomatic treatment or ST alone. The test group received Tonsilotren for three treatment periods of 8 weeks, each treatment period being followed by an 8- to 12-week period without the homeopathic preparation. The primary outcome measure was the estimated rate of diagnosed acute throat infections per year, with other outcome measures being severity of RT symptoms and the antibiotics required due to acute throat infections. Occurrence of RT symptoms was seen in a significantly lower percentage of patients in the test group compared with the control group. There was also a reduction in antibiotics used due to acute throat infections. The authors conclude that an integrative treatment

approach, in which SilAtro-5-90 or Tonsilotren is given alongside mainstream symptomatic treatment, could be of therapeutic benefit to patients with a history of RT.

Both small- and large-scale studies suggest that homeopathy may reduce the prescribing of antibiotics for acute URTIs and their sequelae.<sup>28,83,98,99</sup> As part of an EPI3 nationwide survey of primary care practice in France, the progress of 518 adults and children with URTIs (79.3% with rhinopharyngitis) treated by either general practitioners (GPs) certified to use homeopathy (GP-Hom) or GPs who used conventional medicine only (GP-CM) was compared. Patients in the GP-Hom group showed significantly lower consumption of antibiotics (odds ratio [OR] = 0.43, 95% confidence interval [CI]: 0.27–0.68) and antipyretic/anti-inflammatory drugs (OR = 0.54, 95% CI: 0.38–0.76), with similar outcomes.<sup>91</sup>

### Prophylactic and Long-Term Effects

CAM therapies that are proven safe can be used to strengthen the self-healing capacities of the organism (preventive and curative health promotion).<sup>100</sup> Several studies examined for this review suggest prophylactic, as well as short-term, potential for the products or remedies under review. In Siqueira et al's<sup>14</sup> trial, 600 children aged 1 to 5 years were randomly distributed to three groups and prescribed either a homeopathic complex, placebo or InfluoBio. The number of flu and acute respiratory infections in each group in a year (2009–2010) was then recorded. While the number of episodes overall was small, 30.5% of the placebo group developed three or more acute infections in the post-intervention year, whereas there were no recorded episodes in those receiving the homeopathic complex and only one episode in the group receiving InfluoBio. A 2016 observational study by Beghi and Morselli-Labate,<sup>72</sup> conducted over a 10-year period in Italy, suggested that the regular use of the homeopathic medicine *Oscillococcinum* during the winter months could play a role in the prevention of respiratory tract infections. In comparison with the control group, patients who took *Oscillococcinum* once a week for 8 months per year had a greater reduction in the average infectious episodes during the study compared with the year before inclusion, independent of age and class.

An observational study from 1998 to 2008 by Rossi et al<sup>78</sup> assessed the outcome of homeopathic treatment in 551 children under 14 years of age. Respiratory infections (337 cases, 61%) were the most frequently observed diseases. The Glasgow Homeopathic Hospital Outcome Score (GHHOS) was used to assess outcome. After homeopathic treatment, 68% of children with respiratory disease showed a strong improvement or attained a resolution of their problems. The authors concluded that improvement or resolution of symptoms is more likely in patients with problems in the URT than other categories (e.g. dermatological, digestive, psychological) and in patients followed up for at least 12 months.

Another observational study, by Witt et al,<sup>95</sup> showed long-term improvements in patients seeking homeopathic treatment for sinusitis. The treatment group (a sub-group of a large multi-centred observational study) included 134 adults treated by 62 physicians. All patients had suffered

from chronic sinusitis (CS) for over 9 years, almost all (97.0%) of whom had previously been treated with conventional medicine. Self-reported scores showed both physical and mental improvements persisting for 8 years. The authors point to the need for more explanatory studies to establish the extent to which these effects could be due to lifestyle regulation, placebo, or context effects associated with the treatment. Also of interest is a multi-centre observational study, performed in India by Nayak et al,<sup>93</sup> which sought to test the therapeutic usefulness of homeopathic medicine in the management of CS in 550 patients. The chronic sinusitis assessment score (CSAS) was used to assess symptom severity. The authors of this study found statistically significant reductions in CSAS after 3 and 6 months of treatment, along with improved radiological appearance. No complications were observed during treatment. Their conclusion is that homeopathic treatment could be effective for patients with CS but controlled trials were required for further validation.

### Combination versus Single Homeopathic Remedies

The studies featured in this review adopt a range of approaches to prescribing, both from the perspective of control and selection of single or combination remedies with varying constituents (see ►Table 2). Of the seven RCTs in this review using combination remedies, four were placebo-controlled. The active controls used in the other two studies varied: Thinesse-Mallwitz et al's team<sup>28,74</sup> compared treatment with the homeopathic medication IFC with ST, while Jong et al<sup>79</sup> compared CalSuli with another complex homeopathic product. Siqueira et al<sup>14</sup> used placebo, but also compared the product InfluoBio (purified influenza virus × 30c) with a homeopathic nosode complex *Streptococcus*, *Staphylococcus* and inactivated influenza virus × 30c.

The constituents contained in the homeopathic complexes (most of them brand-named products) cover a wide range of remedies. Many of these remedies are derived from plant sources, and their propensity to alleviate or resolve the symptoms of URTIs and their complications have been discussed at length in the homeopathic clinical literature. Homeopathic compounds and syrups contained up to nine different constituents, generally in low potencies.<sup>13,14,74,79,101</sup> Despite wide variations in the remedies chosen, some clear 'favourites' emerged, the most commonly used remedies being *Bryonia* (6 studies), *Phosphorus* (4 studies), *Ipecacuanha* (4 studies) and *Sulfur* (3 studies).

The findings from this review suggest at least equivalence between complex homeopathy and conventional treatment for uncomplicated cases of URTIs. In all but one study, the homeopathic products under evaluation yielded favourable results by way of milder symptoms and shorter duration of acute illness, and several had led to reduced use of antibiotics. Given the ease and convenience of this type of prescribing, the distress associated with acute URTIs,<sup>97</sup> the need to reduce reliance on antibiotics and the known side effects of pharmaceutical OTC products, there is a case for using tried and tested combination remedies to treat uncomplicated cases of URTIs. On the other hand, the quality of the body of evidence on non-individualised homeopathic

treatment is low, and the risk of bias in existing RCTs is high.<sup>64</sup> The variable constituents of each product (some of which contained eight or more homeopathic ingredients) call into question the specific action of these products on URTIs, especially given the short-lived nature of this condition in otherwise healthy children and adults. In addition, some products such as Engystol have been tested in several studies with different results.<sup>64,85,102</sup> It is important that combination remedies continue to be subject to rigorous trials, which test the efficacy and safety of such compounds.<sup>28,74,79</sup> Dose frequency and duration of use also need to be considered to eliminate accidental provings or 'remedy exhaustion'.<sup>a</sup> Acute illnesses produce different symptoms in patients, and more research is required to establish which products suit particular scenarios and at which stage of illness they are most effective.

Mathie et al's recently published article suggests that the model validity of placebo-controlled trials of non-individualised homeopathic treatment is lower than that of individualised treatment.<sup>103</sup> In a follow-up article, the authors conclude that better designed and more rigorous RCTs are needed to develop an evidence base that can decisively provide reliable effect estimates of non-individualised homeopathic treatment;<sup>64</sup> however, neither individualised nor non-individualised RCTs featuring homeopathy score well in terms of model validity or risk of bias.

## Conclusion

With the emergence of antimicrobial resistance (AMR), respiratory infections have become more difficult to treat. Inappropriate use of antibiotics and other antimicrobials leads to the growth and spread of resistant bacteria, which colonise the airways and can affect the entire community.<sup>88</sup> The push to limit AMR requires a consolidated, concerted effort by multiple stakeholders.<sup>104</sup> Effective strategies are needed to restrict the use of antibiotics without harming those who truly need these medications. While lifestyle and nutrition play a significant part in their control, homeopathy presents a low cost, holistic adjunct or alternative for many common infections. The clinical trials examined in this article showed variations in size, location, cohort types, type of intervention and outcome measures, which make comparisons and generalisations problematic. Nevertheless, combined evidence from these and other studies suggests that homeopathic treatment can exert biological effects with fewer adverse events and broader therapeutic opportunities than conventional medicine in the treatment of URTIs.<sup>56,105</sup> Given the cost implications of treating URTIs and their complications in children, and the relative absence of effective alternatives without potential side effects, the use of non-individualised homeopathic compounds tailored for the paediatric population merits further investigation, including through large-scale cohort studies.

<sup>a</sup>The term 'remedy exhaustion' refers to the possibility that a remedy or compound might lose its initial efficacy if repeated too often and for too long.

The quantity of peer-reviewed homeopathic research is small when compared with conventional medicinal research. There are many gaps in evidence, but recent studies support the view that homeopathy could be at least as effective as an ST, with effects that can be differentiated from placebo<sup>106,107</sup> and can fill existing effectiveness gaps in the conventional medical treatment of URTIs and their complications.<sup>9</sup> Importantly for global health, studies such as those presented in this article suggest that patients given homeopathic treatment and who follow sensible disease avoidance measures may avoid infections or may be able to reduce reliance on conventional medication, including antibiotics.<sup>9,91</sup> In the meantime, the most important evidence still arises from practical clinical experience and from the successful treatment of millions of patients.

With the advent of AMR, homeopathy would appear to have a role to play both in offering alternative treatment for URTIs and the possibility of the prevention of recurring infections associated with the URT. Further research is required to establish the best means of achieving this; however, prioritising studies of paediatric and elderly populations would seem a path forward for the reduction in antibiotic use and the on-going risk of resistance.

## References

- 1 Broom A, Broom J, Kirby E. Cultures of resistance? A Bourdieusian analysis of doctors' antibiotic prescribing. *Soc Sci Med* 2014; 110:81–88
- 2 Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infect Dis* 2010;10:167–175
- 3 Carlet J. Multi-drug resistant bacteria and antibiotics [Article in French]. *Rev Infirm* 2013;192:17–19
- 4 Gottlieb T, Nimmo GR. Antibiotic resistance is an emerging threat to public health: an urgent call to action at the Antimicrobial Resistance Summit 2011. *Med J Aust* 2011;194:281–283
- 5 WHO. Fact sheet antimicrobial resistance. World Health Organization. 2011. Available at: <http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/antibiotic-resistance/factsheets/information-for-everyone>. Accessed 30 November 2015
- 6 WHO. Antimicrobial resistance [Internet]. World Health Organisation. 2016. Available at: <http://www.who.int/mediacentre/factsheets/fs194/en/>. Accessed December 2, 2017
- 7 European Medicines Agency (EMA) European Food Safety Authority. (EFSA). It's time to reduce, replace and re-think the use of antimicrobials in animals. 2017;(January). Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2017/01/news\\_detail\\_002683.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/01/news_detail_002683.jsp&mid=WC0b01ac058004d5c1). Accessed December 2, 2017
- 8 Roca I, Akova M, Baquero F, et al. The global threat of antimicrobial resistance: science for intervention. *New Microbes New Infect* 2015;6:22–29
- 9 Bell IR, Boyer NN. Homeopathic medications as clinical alternatives for symptomatic care of acute otitis media and upper respiratory infections in children. *Glob Adv Health Med* 2013; 2:32–43
- 10 Jain A. Does homeopathy reduce the cost of conventional drug prescribing? A study of comparative prescribing costs in general practice. *Homeopathy* 2003;92:71–76

- 11 Rossi E, Crudeli L, Endrizzi C, Garibaldi D. Cost-benefit evaluation of homeopathic versus conventional therapy in respiratory diseases. *Homeopathy* 2009;98:2–10
- 12 Tan T, Little P, Stokes T; Guideline Development Group. Antibiotic prescribing for self limiting respiratory tract infections in primary care: summary of NICE guidance. *BMJ* 2008;337. doi: 10.1136/bmj.a437
- 13 Zanasi A, Mazzolini M, Tursi F, Morselli-Labate AM, Paccapelo A, Lecchi M. Homeopathic medicine for acute cough in upper respiratory tract infections and acute bronchitis: a randomized, double-blind, placebo-controlled trial. *Pulm Pharmacol Ther* 2014;27:102–108
- 14 Siqueira CM, Homsani F, da Veiga VF, et al. Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: blind, randomized, placebo-controlled clinical trial. *Homeopathy* 2016;105:71–77
- 15 Malapane E, Solomon EM, Pellow J. Efficacy of a homeopathic complex on acute viral tonsillitis. *J Altern Complement Med* 2014;20:868–873
- 16 Morris PS. Upper respiratory tract infections (including otitis media). *Pediatr Clin North Am* 2009;56:101–117
- 17 Alsarraf R, Jung CJ, Perkins J, Crowley C, Alsarraf NW, Gates GA. Measuring the indirect and direct costs of acute otitis media. *Arch Otolaryngol Head Neck Surg* 1999;125:12–18
- 18 Neuzil KM, Hohlbein C, Zhu Y. Illness among schoolchildren during influenza season: effect on school absenteeism, parental absenteeism from work, and secondary illness in families. *Arch Pediatr Adolesc Med* 2002;156:986–991
- 19 Pichichero ME. Otitis media. *Pediatr Clin North Am* 2013;60:391–407
- 20 Hersh AL, Jackson MA, Hicks LA; American Academy of Pediatrics Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics* 2013;132:1146–1154
- 21 Jain N, Lodha R, Kabra SK. Upper respiratory tract infections. *Indian J Pediatr* 2001;68:1135–1138
- 22 Spurling GK, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for symptoms and complications of respiratory infections. *Cochrane Database Syst Rev* 2004;18:CD004417
- 23 Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2004
- 24 Viksveen P. Antibiotics and the development of resistant microorganisms. Can homeopathy be an alternative? *Homeopathy* 2003;92:99–107
- 25 Rosenfeld RM, Post JC. Meta-analysis of antibiotics for the treatment of otitis media with effusion. *Otolaryngol Head Neck Surg* 1992;106:378–386
- 26 McCormick DP, Chonmaitree T, Pittman C, et al. Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 2005;115:1455–1465
- 27 Zoorob R, Sidani MA, Fremont RD, Kihlberg C. Antibiotic use in acute upper respiratory tract infections. *Am Fam Physician* 2012;86:817–822
- 28 van Haselen R, Thinesse-Mallwitz M, Maidannyk V, et al. The effectiveness and safety of a homeopathic medicinal product in pediatric upper respiratory tract infections with fever: a randomized controlled trial. *Glob Pediatr Health* 2016;3. doi: 10.1177/2333794x16654851
- 29 Steinsbekk A, Bentzen N, Fønnebo V, Lewith G. 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* 2005;59:447–455
- 30 Kaushik V, Malik T, Saeed SR. Cochrane review: Interventions for acute otitis externa. *Evid Based Child Health* 2011;6:444–560
- 31 Coco AS, Horst MA, Gambler AS. Trends in broad-spectrum antibiotic prescribing for children with acute otitis media in the United States, 1998–2004. *BMC Pediatr* 2009;9. doi: 10.1186/1471-2431-9-41
- 32 Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics* 2011;128:1053–1061
- 33 Davies S, Sugden R. What if antibiotics stopped working? *Kings Fund*. 2017. Available at: <https://www.kingsfund.org.uk/reports/thenhsif/what-if-antibiotics-stopped-working/>. Accessed August 15, 2017
- 34 Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2013;1:CD000219
- 35 Smucny J, Fahey T, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2004:CD000245. doi:10.1002/14651858
- 36 Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007;335:982–982
- 37 Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA* 2016;315:1864–1873
- 38 Choby BA. Diagnosis and treatment of streptococcal pharyngitis. *Am Fam Physician* 2009;79:383–390
- 39 Gerber MA. Diagnosis and treatment of pharyngitis in children. *Pediatr Clin North Am* 2005;52:729–747
- 40 Sommer MOA, Dantas G. Antibiotics and the resistant microbiome. *Curr Opin Microbiol* 2011;14:556–563
- 41 Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;340. doi: 10.1136/bmj.c2096
- 42 Tacconelli E. Antimicrobial use: risk driver of multidrug resistant microorganisms in healthcare settings. *Curr Opin Infect Dis* 2009;22:352–358
- 43 Fredericks I, Hollingworth S, Pudmenzky A, Rossato L, Syed S, Kairuz T. Consumer knowledge and perceptions about antibiotics and upper respiratory tract infections in a community pharmacy. *Int J Clin Pharm* 2015;37:1213–1221
- 44 Risnes KR, Belanger K, Murk W, Bracken MB. Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. *Am J Epidemiol* 2011;173:310–318
- 45 Marra F, Marra CA, Richardson K, et al. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* 2009;123:1003–1010
- 46 Schmitt J, Schmitt NM, Kirch W, Meurer M. Early exposure to antibiotics and infections and the incidence of atopic eczema: a population-based cohort study. *Pediatr Allergy Immunol* 2010;21:292–300
- 47 Abramoicz M, Zuccotti G. Alternatives to fluoroquinolones. *JAMA* 2016;316:1404–1405
- 48 Leibovitz E. The use of fluoroquinolones in children. *Curr Opin Pediatr* 2006;18:64–70
- 49 Fox JC, Szyzkowski RS, Sanderson SO, Levine RA. Progressive cholestatic liver disease associated with clarithromycin treatment. *J Clin Pharmacol* 2002;42:676–680
- 50 Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005;41:291–300
- 51 Bandettini di Poggio M, Anfoso S, Audenino D, Primavera A. Clarithromycin-induced neurotoxicity in adults. *J Clin Neurosci* 2011;18:313–318
- 52 Ernst E. Homeopathy: what does the “best” evidence tell us? *Med J Aust* 2010;192:458–460

- 53 Fisher P. What is homeopathy? An introduction. *Front Biosci (Elite Ed)* 2012;4:1669–1682
- 54 Ghosh AK. A short history of the development of homeopathy in India. *Homeopathy* 2010;99:130–136
- 55 Piolot M, Fagot JP, Rivière S, et al. Homeopathy in France in 2011–2012 according to reimbursements in the French national health insurance database (SNIIRAM). *Fam Pract* 2015;32:442–448
- 56 Bornhöft G, Matthiessen PF. Homeopathy in Healthcare – Effectiveness, Appropriateness, Safety, Costs. An HTA report on homeopathy as part of the Swiss Complementary Medicine Evaluation Programme. Heidelberg: Springer-Verlag; 2011
- 57 Gao F, Li M. Systems Thinking: Creative Holism for Managers. [Internet]. Vol. 35, *International Journal of General Systems*. 2006:489–492. Available at: <https://login.e.bibl.liu.se/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=aph&AN=22056802&site=eds-live&scope=site>. Accessed December 2, 2017
- 58 Jackson MC. Systems Thinking: Creative Holism for Managers. Chichester, UK: John Wiley & Sons Ltd; 2003
- 59 Lewith G, Robinson N. Integrating complementary and alternative medicine (CAM) and conventional diagnoses. *Eur J Integr Med* 2016;8:879–880
- 60 Thomson P, Jones J, Evans J, Leslie SJ. Factors influencing the use of complementary and alternative medicine and whether patients inform their primary care physician [Internet]. 2012. Available at: <https://dspace.stir.ac.uk/handle/1893/3672>. Accessed December 2, 2017
- 61 Gagnon EM, Recklitis CJ. Parents' decision-making preferences in pediatric oncology: the relationship to health care involvement and complementary therapy use. *Psychooncology* 2003;12(05):442–452
- 62 Crawford NW, Cincotta DR, Lim A, Powell CV. A cross-sectional survey of complementary and alternative medicine use by children and adolescents attending the University Hospital of Wales. *BMC Complement Altern Med* 2006;6. doi: <http://www.ncbi.nlm.nih.gov/pubmed/16670012>
- 63 Homeopathy in Healthcare [Internet]. 2012. Available at: <http://www.springer.com/medicine/complementary+&+alternative+medicine/book/978-3-642-20637-5>. Accessed November 4, 2017
- 64 Mathie RT, Ramparsad N, Legg LA, et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev* 2017;6. doi: <http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-017-0445-3>. Accessed December 14, 2017
- 65 Sankar K, Jadhav AP. Nosodes and sarcodes. *Indian J Tradit Knowl* 2017;16:158–163
- 66 Joshi S, Mukerjee S, Vaidya S, Talele G, Chowdhary A, Shah R. Preparation, standardization and in vitro safety testing of Mycobacterium nosodes (Emtact- polyvalent nosode). *Homeopathy* 2016;105:225–232
- 67 Mathie RT, Frye J, Fisher P. Homeopathic Oscilloccinum® for preventing and treating influenza and influenza-like illness. *Cochrane Database of Systematic Reviews*. 2015:CD001957. doi: 10.1002/14651858.CD001957.pub6
- 68 Flood RL. The relationship of “systems thinking” to action research. *Syst Pract Action Res* 2010;23:269–284
- 69 Mathie RT. Systematic reviews of RCTs in homeopathy a focused appraisal. *Focus Altern Complement Ther* 2010;15:104–106
- 70 Mathie RT, Lloyd SM, Legg LA, et al. Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev* 2014;3. doi: 10.1186/2046-4053-3-142
- 71 Mathie RT, Hacke D, Clausen J, Nicolai T, Riley DS, Fisher P. Randomised controlled trials of homeopathy in humans: characterising the research journal literature for systematic review. *Homeopathy* 2013;102:3–24
- 72 Beghi GM, Morselli-Labate AM. Does homeopathic medicine have a preventive effect on respiratory tract infections? A real life observational study. *Multidiscip Respir Med* 2016;11. doi: 10.1186/s40248-016-0049-0
- 73 Van Wassenhoven M, Goossens M, Anelli M, et al. Pediatric homeopathy: a prospective observational survey based on parent proxy-reports of their children's health-related quality of life in six European countries and Brazil. *Homeopathy* 2014;103:257–263
- 74 Thinesse-Mallwitz M, Maydannik V, Keller T, Klement P. A homeopathic combination preparation in the treatment of febrile upper respiratory tract infections: an international randomized controlled trial. *Forsch Komplement Med* 2015;22:163–170
- 75 Zanasi A, Cazzato S, Mazzolini M, et al. 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* 2015;10:25
- 76 Buskin S, Pilar M, Huckstadt R, Salatino S. Use of natural and homeopathic remedies in children ailments. *Clin Manag Issues* 2016;10:33–48
- 77 Ekins-Daukes S, Helms PJ, Taylor MW, Simpson CR, McLay JS. Paediatric homeopathy in general practice: where, when and why? *Br J Clin Pharmacol* 2005;59:743–749
- 78 Rossi E, Bartoli P, Panozzo M, Bianchi A, Da Frè M. Outcome of homeopathic treatment in paediatric patients: an observational study from 1998 to 2008. *Eur J Integr Med* 2010;2:115–122
- 79 Jong MC, Buskin SL, Ilyenko L, et al. 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* 2016;11:19
- 80 Ramchandani NM. Homeopathic treatment of upper respiratory tract infections in children: evaluation of thirty case series. *Complement Ther Clin Pract* 2010;16:101–108
- 81 Fixsen A. Should homeopathy be considered as part of a treatment strategy for otitis media with effusion in children? *Homeopathy* 2013;102:145–150
- 82 Steinsbekk A, Fønnebo V, Lewith G, Bentzen N. 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* 2005;13:231–238
- 83 Taylor JA, Jacobs J. Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media. *Homeopathy* 2011;100:109–115
- 84 Frei H, Thurneysen A. Homeopathy in acute otitis media in children: treatment effect or spontaneous resolution? *Br Homeopath J* 2001;90:180–182
- 85 Herzberger G, Weiser M. Homeopathic treatment of infections of various origins: a prospective study. *Biomed Ther* 1997;15:123–127
- 86 Rabe A, Weiser M, Klein P. Effectiveness and tolerability of a homeopathic remedy compared with conventional therapy for mild viral infections. *Int J Clin Pract* 2004;58:827–832
- 87 Haidvogel M, Riley DS, Heger M, et al. Homeopathic and conventional treatment for acute respiratory and ear complaints: a comparative study on outcome in the primary care setting. *BMC Complement Altern Med* 2007;7:7
- 88 Sih TM, Bricks LF. Optimizing the management of the main acute infections in pediatric ORL: tonsillitis, sinusitis, otitis media. *Rev Bras Otorrinolaringol (Engl Ed)* 2008;74:755–762
- 89 Bellavite P. Homeopathic treatment of otitis media: a literature review. *Altern Complement Ther* 2008;14:246–247
- 90 Trichard M, Chafferin G, Dubreuil C, Nicoloyannis N, Duru G. Effectiveness, quality of life, and cost of caring for children in France with recurrent acute rhinopharyngitis managed by

- homeopathic or non-homeopathic general practitioners: a pragmatic, prospective observational study. *Dis Manag Health Outcomes* 2004;12:419–427
- 91 Grimaldi-Bensouda L, Bégaud B, Rossignol M, et al. 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* 2014;9:e89990. doi: 10.1371/journal.pone.0089990
  - 92 Friese KH, Zabalotnyi DI. Homeopathy in acute rhinosinusitis: a double-blind, placebo controlled study shows the efficiency and tolerability of a homeopathic combination remedy [Article in German]. *HNO* 2007;55:271–277
  - 93 Nayak C, Singh V, Singh VP, et al. Homeopathy in chronic sinusitis: a prospective multi-centric observational study. *Homeopathy* 2012;101:84–91
  - 94 Sharma SR, Murty KB, Sahagal GC, Sharma B, Bharatalaxmi KSV. Clinical evaluation of homoeopathic medicines in sinusitis. *Indian J Res Homoeopath* [Internet]. 2008;2:26–37
  - 95 Witt CM, Lüdtke R, Willich SN. Homeopathic treatment of patients with chronic sinusitis: a prospective observational study with 8 years follow-up. *BMC Ear Nose Throat Disord* 2009;9:7
  - 96 Palm J, Kishchuk VV, Ulied Å, et al; TocTo Research Group. 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* 2017;28:181–191
  - 97 Friese K, Timen G, Zabalotnyi D. Homeopathy in children with nonstreptococcal tonsillitis. Study proves efficacy and tolerability of a homeopathic combination medicine. *Der Kassenarzt* 2006;6:4042
  - 98 Sinha MN, Siddiqui VA, Nayak C, et al. Randomized controlled pilot study to compare homeopathy and conventional therapy in acute otitis media. *Homeopathy* 2012;101(01):5–12
  - 99 Jong MC, Verwer C, van de Vijver L, Klement P, Burkart J, Baars E. A randomized open comparative clinical trial on the effectiveness, safety and tolerability of a homeopathic medicinal product for the treatment of painful teething in Children. *Altern Integr Med* 2015;4:1–9
  - 100 Kok ET, Jong MC, Gravendeel B, Van Leeuwen WB, Baars EW. Resistance to antibiotics and antifungal medicinal products: can complementary and alternative medicine help solve the problem in common infection diseases? The introduction of a Dutch research consortium. *Evid Based Complement Altern Med*. 2015. doi: <http://dx.doi.org/10.1155/2015/521584>
  - 101 Jacobs J, Taylor JA. A randomized controlled trial of a homeopathic syrup in the treatment of cold symptoms in young children. *Complement Ther Med* 2016;29:229–234
  - 102 Schmiedel V, Klein P. A complex homeopathic preparation for the symptomatic treatment of upper respiratory infections associated with the common cold: An observational study. *Explore (NY)* 2006;2:109–114
  - 103 Mathie RT, Van Wassenhoven M, Jacobs J, et al. Model validity and risk of bias in randomised placebo-controlled trials of individualised homeopathic treatment. *Complement Ther Med* 2016;25:120–125
  - 104 Access to Medicine Foundation. Antimicrobial Resistance Benchmark 2018. Methodology 2017. Available at: <http://accessto-medicinesfoundation.org>. Accessed October 12, 2017
  - 105 Mathie RT, Fisher P. Homeopathy is safe and does not lack positive evidence in clinical trials. *Br J Clin Pharmacol* 2007; 64:396–397, author reply 398–399
  - 106 Fisher P, Berman B, Davidson J, Reilly D, Thompson T. Are the clinical effects of homoeopathy placebo effects? *Lancet* 2005; 366:2082–2083, author reply 2083–2086
  - 107 Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350:834–843