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Homeopathy in the age of antimicrobial resistance: Is it a viable treatment for upper respiratory tract infections?

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Introduction

With the emergence and proliferation of multi-resistant organisms, the prospect of an 'antimicrobial perfect storm' ¹ in the approaching decades has become an urgent public health concern. ¹ 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. ^{2,3,4} 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. ⁵ Warning of an approaching era in which antibiotics will no be longer effective, the World Health Organisation (WHO) and other agencies ^{6,7} suggest alternative approaches, including the development of novel therapies to treat both mild and serious infections. ^{7,8} With a growing body of clinical evidence, a strong safety record and evidence of cost-effectiveness, ⁹⁻¹¹ 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, ¹² 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 review literature on this topic is sufficiently robust for homeopathy to be seriously considered as an alternative to antibiotics for upper respiratory tract infections (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 upper respiratory tract infections published after 1994. Due to the close association between URTIs and acute rhino-pharyngitis and tonsillitis and their frequent treatment with antibiotics, a number of peer review studies in which homeopathy was used to treat these conditions were also reviewed. Although not rigorously following format of a systematic review, the PRISMA guidelines (<http://www.prisma->

[statement.org](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 on tables one and two. 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 utilized, however studies for which the full paper 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,¹³ influenza,¹⁴ otitis media and tonsillitis¹⁵ were considered only if upper respiratory tract infection, or viral infection involving the upper respiratory tract 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 CAM therapy was used. Case reports of homeopathic treatments for upper respiratory tract infections 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 one). Analysis of all studies focused on the following elements: trial design; treatment invention, with particular reference to single/complex homeopathic medicaments (see table two); 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. Upper respiratory tract infection (URTI) it is the most common infectious illness in most populations and the primary reason people miss work or school.¹⁶ 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

^{17,18} and school. ¹⁸ The acute cough following a URTI can continue for several weeks.¹³ Children are especially susceptible, and may have as many as 8 or even more episodes each year. Most URTIs are caused by a self-limiting viral illness (such as influenza and rhinoviruses) with symptoms lasting 7-10 days however complications such as otitis media,¹⁹ pharyngitis,²⁰ tonsillitis²¹ and sinusitis²² are frequently treated with antibiotics.²³⁻²⁷ In the US, 23% of paediatric medical visits from 2004-8 resulted in prescriptions for antibiotics²⁸ 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.²⁹ Respiratory complaints are also the most frequent reason for over the counter (OTC) purchases of homeopathic medicines,³⁰ suggesting a demand for alternatives to pharmaceutical OTC products.

Public health and medical stewardship programs aim to alter patients' perceptions and doctors' prescribing behaviour.¹ Yet in many clinical contexts, antibiotic prescribing continues to elude best practice,¹ including in the treatment of URTIs and URTI related conditions.^{31,32,33} According to a recent US clinical report, up to 10 million antibiotic prescriptions per year directed toward respiratory conditions were unlikely to provide any benefit.³⁴ Fewer than 10% of sore throats are caused by bacterial infections, yet in around 60% of cases, antibiotics were prescribed for them.³⁵ In recent Cochrane reviews the short-term effects of antibiotics on acute otitis media (AOM)³⁶ and URTIs³⁷ were moderate or negligible when compared to their potential risks. One Cochrane study found antibiotics 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 few days following infection and having no effect on reducing the number of children with subsequent hearing loss.³⁶ 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.³⁷ Only in the case of pneumonia in the elderly were the benefits of antibiotics seen as significant,³⁸ 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 1000 people, yet only half of these prescriptions were considered appropriate for these conditions.³⁹ 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.^{40,41}

In addition to efficacy, the immunological effects and safety of antibiotics is 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.⁴² Individuals prescribed antibiotics in primary care for a respiratory infection develop bacterial resistant to that antibiotic, which not only increases the population carriage of organisms resistant to first line antibiotics, but leads to increased use of second line antibiotics in the community.⁴³ According to one meta-analysis, the risk of acquiring methicillin-resistant *Staphylococcus aureus* increased by 1.8-fold in patients, who had taken antibiotics.⁴⁴ Nevertheless, public awareness concerning the appropriate use and safety of antibiotics still appears to be lacking. In one Australian consumer study, over a 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.⁴⁵ Links have been established between antibiotic use and paediatric asthma^{46,47} and eczema⁴⁸ and less common but grave physical and psychoactive side effects associated with particular antibiotics. The class of antibiotics fluoroquinolones are known to cause tendonitis, CNS effects, peripheral neuropathy,⁴⁹ and juvenile fluoroquinolone-induced joint/cartilage toxicity.⁵⁰ Severe side effects of the broad spectrum antibiotic Clarithromycin include liver and renal failure^{51,52} and psycho-neurological effects including hallucinations, depersonalization, depression, insomnia and psychosis.⁵³

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.⁵⁴ Yet, despite a long history of scientific controversy, homeopathy has proved resilient, is geographically widespread⁵⁵ and is an accepted part of the medical system in countries such as India,⁵⁶ France⁵⁷ and Switzerland.⁵⁸ Advantages of homeopathy include ease of application and safety, with few contraindications existing in the treatment of the very young²⁸ and old, beside the careful selection of remedy and dosage. Whereas using antibiotics and over the counter 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.^{59,60} In part it is the person focused approach of traditional homeopathy that distinguishes it from conventional approaches⁶¹ and contributes to its appeal to certain population groups.⁶²⁻⁶⁴ 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.⁶⁵ Thus in homeopathic case-taking the assessment of the medical situation may not be the principle reason for the choice of remedy⁵⁸ 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.⁶⁶ Another method, 'isopathy,' refers to the use of diseased byproducts or tissues known as 'nosodes,' and healthy animal tissue, referred to as sarcodes,⁶⁷ which may be prescribed individually or to a population group for

preventative purposes.^{68,69} All of these methodologies have been employed in clinical studies, including for the treatment of UTRIs. 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 sense⁷⁰ 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 as 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 have never been systematically and scientifically researched.⁵⁸ 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^{66,71,72} 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.⁷³ 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 generalizability of placebo-controlled, blinded homeopathy studies.⁵⁸ As with all clinical trials, there are variations in size and outcome measures with the limited number of homeopathic studies making these types of anomaly 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.⁵⁸ Non-randomised controlled trials and patient reported surveys are considered by some to be inferior forms of research evidence, but are important adjuncts to RCTs which 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 randomised controlled trials⁷⁴ and more closely reflect real life experiences of patients and physicians than RCTs,⁷⁵ and are therefore considered in this study.

Results

Searches of online libraries and bibliographical references found multiple peer review studies (in English and non-English) published between 1994 and 2017, in which homeopathy had been used to treat upper respiratory tract infections and associated symptoms (cough, pharyngitis, tonsillitis, otitis media, acute sinusitis etc.). Both randomised control trials (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 UTRIs in the title or content. For the final review, 9 RCTs and 8 observational/ cohort studies were analysed, of which 6 of the RCTs and one observational/ cohort trial were paediatric studies. 7 RCTs used combination remedies with multiple constituents. One of RCTs in these tables is featured twice as it measured treatment effects on two different cohorts. The first paper (Thinesse-Mallwitz et al (2015))⁷⁶ reports the effects and safety of standard treatment (ST) plus a homeopathic compound (Iflucid), or ST only, on a mixed age cohort with a URTI. The later paper (Van Haselen et al (2016))²⁹ reports the effects of ST plus a homeopathic compound (Iflucid), or ST only, on a paediatric cohort. Both papers have been included in the analysis. The two studies reported by Zanasi's team (RCT¹³ and observational⁷⁷) 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 on table 1. Table 2 focuses on studies using complex homeopathic remedies, and a breakdown of the homeopathic constituents where this information was available.

Insert tables here:

The paper'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; 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 papers, or to assess the intrinsic quality of each study, including risk of bias.

Use of Homeopathy for UTRIs

Respiratory infections are a common reason for seeking homeopathic care.^{78,79} For example, out of 551 paediatric patients treated at a homeopathic clinic in Rossi et al's (2010) observational study, 337 presented (61%) presented with respiratory infections, making this the most frequently observed disease in this population group.⁸⁰ Of the various clinical trials featuring the use of homeopathy for a specific condition, those concerning infectious diseases of the upper respiratory tract,^{13,29,81,82} and complications such as acute otitis media (ear infections)^{9,83} contain some of the most positive evidence of the effectiveness of homeopathic interventions.⁵⁸ The evaluation of 27 studies for a Health Technology Assessment report on effectiveness, cost effectiveness and appropriateness of homeopathy on upper respiratory tract infections and allergic reactions showed a positive overall result in favour of homeopathy, with 6 out of 7 controlled studies showing at least equivalence to conventional medical interventions.⁵⁸

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 a number of studies suggest that homeopathic treatment can fulfil both these prerequisites. Many participants in homeopathic studies are children^{9,81,83-87} so it is significant that the safety and tolerability of homeopathic treatment in the trials reviewed was very good.^{29,76,81,88} A good rate of improvement in the acute symptoms of URTI in those 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 fever²⁹ improved/ resolved faster than cough.¹³

In Rabe et al's (2004) 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. 67.9% of patients were considered by physicians to be asymptomatic at the end of Gripp-Heel therapy, compared to 47.9% in the control group.⁸⁹ In Zanasi' et al's (2014) placebo controlled RCT⁸⁷, 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 (2015) in Germany and the Ukraine compared the effectiveness, safety and tolerability of Influcid®(IFC) as an add-on treatment, with standard care (SC) alone, in the prevention of recurrent acute URTIs. The IFC group (265 patients) given homeopathy experienced significantly faster improvement than those who had received conventional treatment alone.⁷⁶

Another study by Jong et al (2016)⁸¹ measured the effectiveness, safety and tolerability of a homeopathic medicinal complex in the prevention of recurrent acute upper respiratory tract infections 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) 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 Haidvogel et al (2007)⁹⁰ of 1,577 adults and children from 8 different countries are less disputable. In this study, individualised homeopathy and standard care 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 paper, however in clinical practice they remain the most common causes of antibiotic prescriptions^{21,91,39} 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 acute otitis media (ear infections)^{9,83,92,93}, rhinopharyngitis,^{94,95} sinusitis,^{96,97,98,99} and tonsillitis.^{100,101} In a study by Trichard et al (2004) 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.⁹⁴ A randomised, double-blind study by Friese and Zabalotnyi (2007)⁹⁶ investigated the efficacy and tolerability of a homeopathic combination remedy for the treatment of acute rhinosinusitis. 144 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+/-1.6 to 5.9+/-2.0 points after 7 days. In the placebo

group it decreased from 11.7+/-1.6 to 11.0+/-2.9 points ($p < 0.0001$). After 21 days, 90.3% of the homeopathic treatment group were 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.¹⁰² (2006) performed a multicentre, randomised, placebo-controlled, double-blinded study on paediatric 158 patients affected by acute non-streptococcal tonsillitis. The study group received Tonsilotren® hourly until onset of improvement, then 3 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 and than the placebo group. By day 6, 92.4% of study patients showed full recovery or moderate improvement, compared to 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 randomised, controlled, clinical trial of the homeopathic combination remedy SilAto-5-90 (brand name Tonsilotren®) was carried out in multiple settings by Palm et al (2017).¹⁰¹ 256 patients aged 6-60 years with moderate recurrent tonsillitis (RT) were given either the homeopathic preparation in addition to standard symptomatic treatment, or standard treatment alone. The test group received Tonsilotren® for 3 treatment periods of 8 weeks, each treatment period being followed by an 8 to 12 weeks 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 to 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 SilAto-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.^{29,85,103,104} 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 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.⁹⁵

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).¹⁰⁵ A number of 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 (2016)⁸⁷ trial, 600 children aged 1-5 years were randomly distributed to three groups and prescribed either a homeopathic complex, placebo or InluBio. 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 InluBio. A 2016 observational study by Beghi et al (2016)⁷⁴ conducted over a 10-year period in Italy suggested that the regular use of the homeopathic medicine Oscillocoquinum® during the winter months could play a role in the prevention of respiratory tract infections. In comparison with the control group, patients who took Oscillocoquinum® once a week for 8 months per year had a greater reduction in the average infectious episodes during the study compared to the year before inclusion independent of age and class.

An observational study from 1998 to 2008 by Rossi et al (2010)⁸⁰ 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. They conclude that improvement or resolution of symptoms is more likely in patients with problems in the upper respiratory tract than other categories (e.g. dermatological, digestion psychological) and in patients followed up for at least 12 months.

Another observational study by Witt et al (2009)⁹⁹ showed long term improvements in patients seeking homeopathic treatment for sinusitis. The treatment group (a subgroup of a large multi-centred observational study) included 134 adults treated by 62 physicians. All patients had suffered from chronic sinusitis for over 9 years almost all (97.0%) of who 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 life-style regulation, placebo, or context effects associated with the treatment. Also of interest is a multicentre observational study carried out in India by Nayak et al (2012)⁹⁷ which sought to test the therapeutic usefulness of homeopathic medicine in the management of chronic sinusitis (CS) on 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 CS patients 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 7 RCTs in this review using combination remedies, 4

where placebo controlled. The active controls used in the other two studies varied; Thinesse-Mallwitz et al's team ^{29,76} compared treatment with the homeopathic medication Influcid with standard treatment, while Jong et al ⁸¹ compared CalSuli with another complex homeopathic product. Siqueira et al ⁸⁷ used placebo, but also compared the product InluBio (purified influenza virus x 30c) with a homeopathic nosode complex Streptococcus, Staphylococcus and inactivated influenza virus x 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. ^{76,81,106-108} Despite wide variations in the remedies chosen, some clear 'favourites' emerged, the most commonly used remedies being Bryonia (6 studies), Phosphorus (4 studies), Ipecachuana (4 studies) and Sulphur (3 studies).

The findings from this review suggest at least equivalence between complex homeopathy and conventional treatment for uncomplicated cases of URTI. 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, ¹⁰² 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. ⁶⁶ The variable constituents of each product (some of which contained 8 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. ^{66,88,109} It is important that combination remedies continue to be subject to rigorous trials, which test the efficacy

and safety of such compounds.^{29,76,81} Dose frequency and duration of use also need to be considered to eliminate accidental provings or remedy ‘exhaustion’.¹ 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 paper suggests that the model validity of placebo-controlled trials of non-individualised homeopathic treatment is lower than that of individualised treatment.¹¹⁰ In a follow up paper, the authors conclude that better designed and more rigorous RCTs are needed in order to develop an evidence base that can decisively provide reliable effect estimates of non-individualised homeopathic treatment⁶⁶, however neither individualised nor non-individualised RCT trials featuring homeopathy score highly in terms of risk of model validity and risk of bias.

Conclusions

With the emergence of 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.⁹¹ The push to limit AMR requires a consolidated, concerted effort by multiple stakeholders.¹¹¹ Effective strategies are needed to restrict the use of antibiotics without harming those who truly need these medications. While life style 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 paper showed variations in size, location, cohort types, type of intervention and outcome measures, which makes comparisons and generalisations problematic. Nevertheless, combined evidence from these and other studies suggest that homeopathic treatment can exert biological effects with fewer adverse events and broader therapeutic opportunities than conventional medicine in the treatment of URTIs.^{58,112} Given the cost implications of treating UTRIs and their complications in children, and the relative absence of effective alternatives without potential side effects, the use of non-individualised homeopathic compounds

¹ 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.

tailored for the pediatric population merits further investigation, including through larger scale cohort studies.

The quantity of peer reviewed homeopathic research is small when compared to conventional medicinal research. There are many gaps in evidence, but recent studies support the view that homeopathy could be at least as effective as a standard treatment, with effects which can be differentiated from placebo ^{113,114} and can fill existing effectiveness gaps in the conventional medical treatment of URTIs and their complications. ⁹ Importantly for global health, studies such as those presented in this paper 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. ^{9,95} 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 antimicrobial resistance, 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 upper respiratory tract. Further research is required to establish the best means of achieving this, however prioritizing studies of pediatric and elderly populations would seem a path forward for the reduction of antibiotic use and the on-going risk of resistance.

1. Broom A, Broom J, Kirby E. Cultures of resistance? A Bourdieusian analysis of doctors' antibiotic prescribing. *Soc Sci Med.* 2014;110:81–8.
2. Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. Vol. 10, *The Lancet Infectious Diseases.* 2010. p. 167–75.
3. Carlet J. [Multi-drug resistant bacteria and antibiotics]. *Rev Infirm.* 2013;192:17–9.
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(6):281–3.
5. WHO. Fact sheet antimicrobial resistance. World Health Organization. 2011.

<http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/antibiotic-resistance/factsheets/information-for-everyone>. Accessed 30 november 2015. [Internet]. Available from: <http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/antibiotic-resistance/factsheets/information-for-everyone>

6. WHO. Antimicrobial resistance [Internet]. World Health Organisation. 2016. Available from: <http://www.who.int/mediacentre/factsheets/fs194/en/>
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 from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/01/news_detail_002683.jsp&mid=WC0b01ac058004d5c1
8. Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S. 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 Heal Med* 2013; 2(1) 32-43.
10. Asha J. Does homeopathy reduce the cost of conventional drug prescribing?: A study of comparative prescribing costs in General Practice. *Homeopathy* 2003 92(2):71–6.
11. Rossi E, Crudeli L, Endrizzi C, Garibaldi D. Cost–benefit evaluation of homeopathic versus conventional therapy in respiratory diseases. *Homeopathy* 2009;98(1):2–10.
12. Tan T, Little P, Stokes T. Antibiotic prescribing for self limiting respiratory tract infections in primary care: summary of NICE guidance. *BMJ.* 2008;337: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* [Internet]. 2014;27(1):102–8. Available from: <http://dx.doi.org/10.1016/j.pupt.2013.05.007>
14. Siqueira CM, Homsani F, da Veiga VF, Lyrio C, Mattos H, Passos SRL, et al. Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: Blind, randomized, placebo-controlled clinical trial. *Homeopathy.* 2016;105(1):71–7.
15. Malapane E, Solomon EM, Pellow J. Efficacy of a Homeopathic Complex on Acute Viral Tonsillitis. *J Altern Complement Med.* 2014;20(11).
16. Morris PS. Upper Respiratory Tract Infections (Including Otitis Media). Vol. 56, *Pediatric Clinics of North America.* 2009. p. 101–17.
17. Alsarraf R, Jung CJ, Perkins J et al. Measuring the Indirect and Direct Costs of

- Acute Otitis Media. *Arch Otolaryngol Head Neck Surg.* 1999;125:12–8.
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;156:986–91.
 19. Pichichero ME. Otitis Media. Vol. 60, *Pediatric Clinics of North America.* 2013. p. 391–407.
 20. Hersh AL, Jackson MA, Hicks L a. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics* 2013;132(6):1146–54.
 21. Jain N, Lodha R, Kabra SK. Upper respiratory tract infections. *Indian J Pediatr.* 2013;68(12):1135–8.
 22. Spurling G, Del Mar C, Dooley L, Foxlee R. Delayed antibiotics for symptoms and complications of respiratory infections. In: *Cochrane Database of Systematic Reviews* 2004; 18(4):CD004417.
 23. Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. In: *Collaboration TC, Sanders S, editors. 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(2):99–107.
 25. RM R, JC P. Meta-analysis of antibiotics for the treatment of otitis media with effusion. *Otolaryngol Head Neck Surg.* 2011;27;106(4).
 26. McCormick DP, Chonmaitree T, Pittman C, Saeed K, Friedman NR, Uchida T, et al. Nonsevere Acute Otitis Media: A Clinical Trial Comparing Outcomes of Watchful Waiting Versus Immediate Antibiotic Treatment. *Pediatrics* 2005 115(6):1455–65.
 27. Zoorob R, Sidani MA, Fremont RD, Kihlberg C. Antibiotic use in acute upper respiratory tract infections. *Am Fam Physician.* 2012;86(9):817–22.
 28. 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(1):32–43.
 29. van Haselen R, Thinesse-Mallwitz M, Maidannyk V, Buskin SL, Weber S, Keller T, 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 Heal* 2016 4;3:2333794X16654851.
 30. Steinsbekk A, Bentzen N, Fonnebo 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.
 31. Kaushik V, Malik T, Saeed SR. Cochrane review: Interventions for acute otitis externa. *Evidence-Based Child Heal A Cochrane Rev J.* 2011 Nov 22;6(2):444–

560.

32. Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. In: Collaboration TC, Sanders S, editors. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2004.
33. 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 Mar 12;9. DOI: 10.1186/1471-2431-9-41.
34. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic Prescribing in Ambulatory Pediatrics in the United States. Vol. 128, *Pediatrics*. 2011. p. 1053–61.
35. Davies S, Sugden R. What if antibiotics stopped working? Kings Fund. 2017. Available from: <https://www.kingsfund.org.uk/reports/thenhsif/what-if-antibiotics-stopped-working/> (last accessed 150817).
36. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2013;1(1):CD000219.
37. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev*. 2004; March 1: (3): CD000245. doi: 10.1002/14651858.
38. 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. Vol. 335, *BMJ*. 2007. p. 982–982.
39. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *Jama* 2016;315(17):1864.
40. Choby BA. Diagnosis and treatment of streptococcal pharyngitis. Vol. 79, *American Family Physician*. 2009. p. 383–90.
41. Gerber MA. Diagnosis and treatment of pharyngitis in children. Vol. 52, *Pediatric Clinics of North America*. 2005. p. 729–47.
42. Sommer MOA, Dantas G. Antibiotics and the resistant microbiome. Vol. 14, *Current Opinion in Microbiology*. 2011. p. 556–63.
43. 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:c2096
44. Tacconelli E. Antimicrobial use: risk driver of multidrug resistant microorganisms in healthcare settings. *Curr Opin Infect Dis*. 2009;22(4):352–8.
45. 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(6):1213–21.
46. 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(3):310–8.
47. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, Patrick DM, et al. Antibiotic Use in Children Is Associated With Increased Risk of Asthma. Vol. 123, *PEDIATRICS*. 2009. p. 1003–10.
 48. 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(2 PART 1):292–300.
 49. Abramoicz M, Zuccotti G. Alternatives to Fluoroquinolones. *JAMA J Am Med Assoc*. 2016;316(13):1404–5.
 50. Leibovitz E. The use of fluoroquinolones in children. *Curr Opin Pediatr* [Internet]. 2006;18(1):64–70. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16470165>
 51. Fox JC, Szyjkowski RS, Sanderson SO, Levine RA. Progressive Cholestatic Liver Disease Associated with Clarithromycin Treatment. *J Clin Pharmacol* [Internet]. 2002;42(6):676–80. Available from: <http://doi.wiley.com/10.1177/00970002042006011>
 52. Hung IFN, Wu a KL, Cheng VCC, Tang BSF, To KW, Yeung CK, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis*. 2005;41(3):291–300.
 53. Bandettini Di Poggio M, Anfosso S, Audenino D, Primavera A. Clarithromycin-induced neurotoxicity in adults. Vol. 18, *Journal of Clinical Neuroscience*. 2011. p. 313–8.
 54. Ernst E. Homeopathy: What does the “best” evidence tell us? Vol. 192, *Medical Journal of Australia*. 2010. p. 458–60.
 55. Fisher P. What is homeopathy? An introduction. *Front Biosci (Elite Ed)*. 2012;4:1669–82.
 56. Ghosh AK. A short history of the development of homeopathy in India. *Homeopathy*. 2010;99(2):130–6.
 57. Piolot M, Fagot J-P, Rivière S, Fagot-Campagna A, Debeugny G, Couzigou P, et al. Homeopathy in France in 2011-2012 according to reimbursements in the French national health insurance database (SNIIRAM). *Fam Pract* [Internet]. 2015;32(4):442–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25921648>
 58. 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. Berlin Heidelberg: Springer-Verlag; 2011.
 59. Gao F, Li M. Sy thinking: Creative Holism for Managers. [Internet]. Vol. 35, *International Journal of General Systems*. 2006. 489-492 p. Available from:

<https://login.e.bibli.liu.se/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=aph&AN=22056802&site=eds-live&scope=site>

60. Jackson MC. *Systems thinking: Creative holism for managers*. Chichester, UK: John Wiley & Sons Ltd; 2003.
61. Lewith G, Robinson N. Integrating complementary and alternative medicine (CAM) and conventional diagnoses. *Eur J Integr Med* [Internet]. 2016;8(6):879–80. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1876382016304243>
62. 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 from: <https://dspace.stir.ac.uk/handle/1893/3672>
63. Gagnon EM, Recklitis CJ. Parents’ decision-making preferences in pediatric oncology: the relationship to health care involvement and complementary therapy use. *Psychooncology* [Internet]. 2003 Jul 4;12(5):442–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12833557>
64. Crawford NW, Cincotta DR, Lim A, Powell CVE. A cross-sectional survey of complementary and alternative medicine use by children and adolescents attending the University Hospital of Wales. *BMC Complement Altern Med* [Internet]. 2006 Jul 4;6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16670012>
65. *Homeopathy in Healthcare* [Internet]. 2012. Available from: <http://www.springer.com/medicine/complementary+&+alternative+medicine/book/978-3-642-20637-5>
66. Mathie RT, Ramparsad N, Legg LA, Clausen J, Moss S, Davidson JRT, et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev* [Internet]. 2017;6(1):63. Available from: <http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-017-0445-3>
67. Sankar K, Jadhav AP. Nosodes and sarcodes. *Indian J Tradit Knowl*. 2017;16(1):158–63.
68. 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(3):225–32.
69. Mathie RT, Frye J, Fisher P. Homeopathic Oscilloccinum[®] for preventing and treating influenza and influenza-like illness. In: *Cochrane Database of Systematic Reviews*. 2015.
70. Flood RL. The relationship of “systems thinking” to action research. *Syst Pract Action Res*. 2010;23(4):269–84.
71. Mathie RT. Systematic reviews of RCTs in homeopathy A focused appraisal.

- Focus Altern Complement Ther [Internet]. 2010 Mar 9;15(2):104–6. Available from: <http://onlinelibrary.wiley.com/doi/10.1211/fact.15.2.0006/abstract>
72. Mathie RT, Lloyd SM, Legg LA, Clausen J, Moss S, Davidson JRT, et al. Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis. *Syst Rev* [Internet]. 2014;3:142. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4326322&tool=pmcentrez&rendertype=abstract>
 73. Mathie RT, Hacke D, Nicolai T, Riley DS, Fisher P. Randomised controlled trials of homeopathy in humans □: characterising the research journal literature for systematic review. 2013;(October 2012):3–24.
 74. 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.
 75. Wassenhoven M, Goossens M, Anelli M, Sermeus G, Kupers P, Morgado C. 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* [Internet]. 2014;103. Available from: <http://dx.doi.org/10.1016/j.homp.2014.05.003>
 76. Thinesse-Mallwitz M, Maydannik V, Keller T, Klement P. A homeopathic combination preparation in the treatment of feverish upper respiratory tract infections: an international randomized controlled trial. *Forsch Komplementmed* [Internet]. 2015;22. Available from: <http://dx.doi.org/10.1159/000430762>
 77. Zanasi A, Cazzato S, Mazzolini M, Ierna CMS, Mastroroberto M, Nardi E, 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(1).
 78. Buskin S, Pilar M, Huckstadt R, Salatino S. Use of natural and homeopathic remedies in children ailments. *Clin Manag Issues*. 2016;10(2).
 79. Ekins-Daukes S, Helms PJ, Taylor MW, Simpson CR, McLay JS. Paediatric homoeopathy in general practice: where, when and why? *Br J Clin Pharmacol* [Internet]. 2005;59(6):743–9. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884867/>
 80. 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* [Internet]. 2010 Jan 7;2(3):115–22. Available from: <http://www.sciencedirect.com/science/article/pii/S1876382010000430>
 81. Jong MC, Buskin SL, Ilyenko L, Kholodova I, Burkart J, Weber S, 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 [Internet]. 2016;11(1):1–13. Available from:
<http://dx.doi.org/10.1186/s40248-016-0056-1>
82. Ramchandani NM. Homeopathic treatment of upper respiratory tract infections in children: Evaluation of thirty case series. *Complement Ther Clin Pract* [Internet]. 2010 Jul 23;16(2):101–8. Available from:
<http://www.sciencedirect.com/science/article/pii/S1744388109001017>
 83. Fixsen A. Should homeopathy be considered as part of a treatment strategy for otitis media with effusion in children? *Homeopathy*. 2013;102(2):145–50.
 84. Steinsbekk A, Fønnebø 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(4):231–8.
 85. Taylor JA, Jacobs J. Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media. *Homeopathy*. 2011;100(3):109–15.
 86. Frei H, Thurneysen A. Homeopathy in acute otitis media in children: treatment effect or spontaneous resolution? *Br Homeopath J* [Internet]. 2001 Apr 9;90(4):180–2. Available from:
<http://www.sciencedirect.com/science/article/pii/S1475491699905052>
 87. Siqueira CM, Homsani F, da Veiga VF, Lyrio C, Mattos H, Passos SRL, et al. Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: blind, randomized, placebo-controlled clinical trial. *Homeopathy* [Internet]. 2016;105(1):71–7. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/26828000>
 88. Herzberger, G., Weiser M. Homeopathic treatment of infections of various origins: a prospective study. *Biomed Ther*. 1997;15:123–7.
 89. 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(9):827–32.
 90. Haidvogel M, Riley DS, Heger M, Brien S, Jong M, Fischer 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* [Internet]. 2007 Mar 31;7(1). Available from:
<http://www.audesapere.in/researchstudies/db/db14.html>
 91. Sih TM, Bricks LF. Optimizing the management of the main acute infections in pediatric ORL: tonsillitis, sinusitis, otitis media. *Braz J Otorhinolaryngol*. 2008;74(5):755–62.
 92. Bellavite P. Homeopathic Treatment of Otitis Media: A Literature Review. *Altern Complement Ther* [Internet]. 2008 Nov 2;14:246–7. Available from:
<http://www.liebertonline.com/doi/abs/10.1089/act.2008.14509>
 93. Taylor JA, Jacobs J. Homeopathic ear drops as an adjunct to standard therapy in

children with acute otitis media. *Homeopathy* [Internet]. 2011 Feb 16;100(3):109–15. Available from:
<http://www.sciencedirect.com/science/article/pii/S1475491611000361>

94. Trichard M, Chaufferin 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 Heal Outcomes*. 2004;12(6):419–27.
95. Grimaldi-Bensouda L, Begaud B, Rossignol M, Avouac B, Lert F, Rouillon F. 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* [Internet]. 2014;9. Available from:
<http://dx.doi.org/10.1371/journal.pone.0089990>
96. Friese K-H, Zabalotnyi DI. [Homeopathy in acute rhinosinusitis: a double-blind, placebo controlled study shows the efficiency and tolerability of a homeopathic combination remedy]. *HNO* [Internet]. 2007;55(4):271–7. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/17180695>
97. Nayak C, Singh V, Singh VP, Oberai P, Roja V, Shitanshu SS, et al. Homeopathy in chronic sinusitis: A prospective multi-centric observational study. *Homeopathy*. 2012;101(2):84–91.
98. Sharma SR, Murty KB, Sahagal GC, Sharma B, Bharatalaxmi KS V. Clinical evaluation of homoeopathic medicines in sinusitis. *Indian J Res Homoeopath* [Internet]. 2008;2(1):26–37. Available from: [http://ccrhindia.org/ijrh/2\(1\)/5.pdf](http://ccrhindia.org/ijrh/2(1)/5.pdf)
99. 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* [Internet]. 2009;9(1):7. Available from:
<http://bmcearthroatdisord.biomedcentral.com/articles/10.1186/1472-6815-9-7>
100. Malapane E, Solomon EM, Pellow J. Efficacy of a Homeopathic Complex on Acute Viral Tonsillitis. *J Altern Complement Med* [Internet]. 2014;20(11):868–73. Available from: <http://online.liebertpub.com/doi/abs/10.1089/acm.2014.0189>
101. Palm J, Kishchuk VV, Uljed À, Fernández JP, De Jaegere S, Jong MC, et al. Effectiveness of an add-on treatment with the homeopathic medication SilAtró-5-90 in recurrent tonsillitis: An international, pragmatic, randomized, controlled clinical trial. *Complement Ther Clin Pract*. 2017;28.
102. Friese K, Timen G, Zabalotnyi D. Homeopathy in children with non-streptococcal tonsillitis. Study proves efficacy and tolerability of a homeopathic combination medicine. *Der Kassenarzt*. 2006;6:4042.
103. Sinha MN, Siddiqui VA, Nayak C, Singh V, Dixit R, Dewan D, et al. Randomized controlled pilot study to compare Homeopathy and Conventional therapy in Acute Otitis Media. *Homeopathy* [Internet]. 2012 Feb 12;101(1):5–12. Available from:
<http://www.sciencedirect.com/science/article/pii/S1475491611001147>

104. 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* [Internet]. 2015;4(1):1–9. Available from: http://www.omicsgroup.org/journals/internal-medicine-abstract.php?abstract_id=40740
105. Kok ET, Jong MC, Gravendeel B, 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* [Internet]. 2015;2015. Available from: <http://dx.doi.org/10.1155/2015/521584>
106. 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(1):102–8.
107. 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;29:229–34.
108. Siqueira CM, Homsani F, Veiga VF, Lyrio C, Mattos H, Passos SR. Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: blind, randomized, placebo-controlled clinical trial. *Homeopathy* [Internet]. 2016;105. Available from: <http://dx.doi.org/10.1016/j.homp.2015.02.006>
109. 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(2):109–14.
110. Mathie RT, Wassenhoven M Van, Jacobs J, Oberbaum M, Frye J, Manchanda RK, et al. Model validity and risk of bias in randomised placebo-controlled trials of individualised homeopathic treatment. *Complement Ther Med*. 2016;25:120–5.
111. Access to Medicine Foundation. *Antimicrobial Resistance Benchmark 2018: Methodology 2017*. 2018.
112. Mathie RT, Fisher P. Homeopathy is safe and does not lack positive evidence in clinical trials. *Br J Clin Pharmacol* [Internet]. 2007;64(3):396–7. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2000659/pdf/bcp0064-0396.pdf>
113. Fisher P, Berman B, Davidson J, Reilly D, Thompson T. Are the clinical effects of homeopathy placebo effects? *Lancet* [Internet]. 2005 Mar 9;366(9503):2082–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16360780>
114. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges L V, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* [Internet]. 1997 Mar 9;350(9081):834–43. Available from: [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(97\)02293-](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(97)02293-)

9/abstract