



**The role of
Complementary and Alternative
Medicine (CAM)
in reducing the problem
of antimicrobial resistance**

This document reflects the position of EUROCAM, the alliance of European umbrella organisations of patients, physicians and practitioners in the field of Complementary and Alternative Medicine.

The objective of EUROCAM is to promote and facilitate CAM's role in maintaining citizens' health, highlight the health promotion and illness prevention aspects of CAM for EU public health policy and programmes, to advance the accessibility, affordability and availability of CAM, and generally promote CAM at European level.

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1. Introduction

Antimicrobial resistance (AMR) – the resistance of bacteria, parasites, viruses and fungi to antimicrobial drugs previously effective for treatment of infections they caused – is now a serious worldwide threat to public health. Dr Keiji Fukuda, WHO's Assistant Director-General for Health Security recently said that AMR is occurring in every region of the world, potentially affecting anyone, of any age, in any country. He warned that, if measures were not taken immediately to counter AMR, the implications will be devastating. Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill'.^a In the light of this, this paper describes how the sector of Complementary and Alternative Medicine (CAM) can make a significant contribution to reducing the problem of AMR.

The CAM perspective on health and disease is essentially different from the conventional biomedical perspective. It is not just a difference in the technology and instruments used, but in the underlying paradigms, basic concepts and philosophical perspective. Although CAM represents a variety of different medical systems and therapies, the CAM modalities have a common denominator, i.e. their individualised holistic approach and their focus on promoting the individual's health by assisting the person's innate self-healing and health-maintaining capacity.

The CAM perspective on infectious disease also differs from the biomedical one. A short retrospective of the different scientific positions in the 19th century on the role of pathogens in infectious disease is helpful to understand this.

The German physician Robert Koch (1843-1910) argued that bacteria are the smallest but most dangerous enemies of mankind. His critic Max Josef von Pettenkofer (1818-1901) a chemist and hygienist, maintained that pathogens infect only the most susceptible (those with poor diet, constitution, etc.) and, proving his point, he drank a large cholera cocktail without falling ill.

In France a similar controversy existed between Louis Pasteur and Claude Bernard. Louis Pasteur (1822-1885), a chemist and microbiologist, took the position that microorganisms infecting animals and humans cause disease. Physiologist Claude Bernard (1813-1878) argued on the other hand that the body becomes susceptible to infectious agents only if the internal balance – or homeostasis as we now call it – is disturbed. After all, there are billions of microbes and bacteria inhabiting our gut, our blood, in fact our whole system most of which are essential to good health. Pathological bacteria, fungi and viruses take root as disease when the terrain is weakened and susceptible to them. This explains why when a bacterial or viral agent is “doing the rounds,” some people become sick while others remain healthy.

History shows that the perspectives of Pasteur and Koch that focused on combating disease by directly killing germs have prevailed. There is no question that antibiotics have dramatically and successfully reduced illness and death from serious infectious

^a World Health Organisation, 2014. *WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health*. Available from: <http://www.who.int/mediacentre/news/releases/2014/amr-report/en/>

diseases. However, the vital role of the host's ability to repel invaders based on a properly functioning immune system, has been neglected. In reality, infection is always the result of two factors: exposure to a pathogen *and* the person's susceptibility.

This one-eyed approach which focuses only on the infecting organism is also reflected in research, which has been directed at finding the most potent way to kill the germs, whereas hardly any research investigates ways and means to raise the effectiveness of the immune system.

In fact, both approaches have their merits. In a patient who is seriously ill and affected by highly virulent bacteria, there is no argument, that antibiotics can be life saving. On the other hand, antibiotics do not offer an adequate solution for a patient who has had recurrent infections and taken several courses of antibiotics, because in this case it is the patient's susceptibility that needs to be addressed.

Lastly there is a growing awareness of the importance to health of the microbiome – the collective genomes of the microbes (composed of bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body. The human body has about 10 times as many microbial cells as human cells. The microbiome plays an essential part in the immune system protecting us against infection, breaking down food in the digestive system to release energy and producing vitamins and helping in the elimination of waste. What is also now being understood is that antibiotics can have a disrupting and disturbing effect on the microbiome and may be causatively involved a number of the widespread chronic illnesses that currently affect us such as obesity, diabetes and cancer, e.g. a recent study revealed a connection between early antibiotic exposure in infants and the development of a tendency to obesity by the age of three^b. A large population-based study carried out in Finland showed a clear statistical correlation between the level of antibiotic exposure in early life and the likely development of cancer later in life^c.

This growing awareness of the how the microbiome is impacted by antibiotics adds another extremely important reason for why antibiotic use must be dramatically reduced to when they are absolutely essential. It also calls for other ways to treat and prevent illness that support and strengthen the health and resilience of the terrain of the microbiome which is being increasingly understood to be so essential to our immune system and health generally.

2. The role of CAM in increasing the resilience of individuals

When it comes to the host's ability to repel invaders, basic requirements to keep the immune system strong include quality sleep, regular exercise, healthy food, relaxation practice and healthy relationships. In building and maintaining resistance to infectious illness, CAM therapies have an important role to play because they mobilise and stimulate the self-regulating capacity of the organism, thus increasing its resilience.

^b Trasande L et al (2013). Infant antibiotic exposures and early-life body mass. *International Journal of Obesity* (London), 37(1):16-23

^c Kilkkinen A et al. (2008). Antibiotic use predicts an increased risk of cancer. *International Journal of Cancer*, 123(9):2152-2155

Greater resilience means

- a swift and sustained recovery from infections
- a reduced susceptibility to future infections
- less reliance on antibiotics

Moreover, herbal medicinal products in particular, as used in CAM, can be used as an alternative means to fight infection based on their own antimicrobial properties.

The following sections describe the role herbal, homeopathic and anthroposophic medicine and their associated medicinal products can play to reduce the problem of antimicrobial resistance both in humans and animals. These strategies to reduce our reliance on antibiotics or to make antibiotics that have now lost their efficacy viable once again are backed by convincing research.

Below we provide tables reviewing some promising evidenced-based research on herbal, anthroposophic and homeopathic medicines demonstrating their potential to help combat the growing threat of antibiotic resistance. This presentation is a selective review illustrating the way in which these medicines might make a useful contribution; it is not a completely comprehensive and systematic evaluation of the evidence. To produce this review searches were performed in October 2013 in AltHealthWatch, AMED, Embase, Estar, Cinahl, the Cochrane Library and PubMed.

To provide a practical evaluation of the evidence presented in this review we have adapted a version of the widely used GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation)¹. This allows for 4 levels of rating of the research evidence – High/Strong, Moderate, Low and Very Low. For simplicity, we have amalgamated Low and Very Low grades into a single category of Preliminary evidence. This selective review highlights potentially fruitful areas for future research.

3. Herbal medicine in humans

Herbal medicine – also called botanical medicine, phytomedicine or phytotherapy – refers to using a plant's seeds, berries, roots, leaves, bark, or flowers at therapeutic doses in the maintenance of optimal health, and in the treatment and prevention of disease. Whole herbs contain many chemical constituents working synergistically together to treat disease and support the body's own healing mechanisms (e.g. its immunity).

Herbal medicines may play a role as autonomous anti-bacterial agents or as adjuvant treatments used to potentiate conventional drugs. This section selectively reviews the evidence for herbal medicine as a valuable resource to combat bacterial resistance to antibiotics and suggests that further research is warranted.

Synergy is an important characteristic determining the medicinal action of many herbal medicines occurring at pharmacodynamic and pharmacokinetic level^{2,3} and a number of papers have been published investigating potential benefits conferred by the synergism of phytoconstituents^{4,5,6,7}. In particular, researchers have demonstrated that combining antibiotics with plant medicines can enhance the action of antibiotics thereby overcoming antibiotic resistance⁸.

This is achieved in three main ways: firstly by means of a combined phytochemical and antibiotic attack on the bacterial cell wall - epigallocatechin gallate (EGCG) as found in green tea and carob powder is effective in this regard. Secondly, antibiotic resistance can be overcome by inhibition of enzymes that are generated by bacteria for the deactivation of antibiotics (again EGCG is active here) or, thirdly, by disabling an efflux pumping system developed by several bacteria in order to prevent potentially destructive compounds such as antibiotics from penetrating into the bacteria, or to expel the antibiotics out of the bacteria cell once they have invaded it⁹, for example the flavonoids in *Hydrastis canadensis*. Further examples are that thymol and carvacrol, two compounds in the essential oil of thyme (*Thymus vulgaris*), act as so-called 'membrane permeabilizers' enabling antibiotics to penetrate into Gram-negative bacteria¹⁰. Thyme also contains baicalein also present in the *Scutellaria* species (Lamiaceae family) and baicalein has shown significant ability to reverse MRSA resistance to the antibiotic ciprofloxacin by inhibiting the bacteria's defensive efflux pump¹¹.

Most research to find agents to support antibiotics which have become ineffective against common bacteria has been lab-based rather than on human populations. A recent review provided evidence of 34 different herbs containing constituents known to inhibit the bacterial efflux pumps¹². For example, *E. coli* is currently demonstrating resistance to several antibiotics but, combined with extracts of *Sophora alopecuroides*, isolates of the bacteria were found susceptible to ciprofloxacin¹³. Similarly, Klančnik et al. (2013) found that extracts of *Rosmarinus officinalis* inhibited drug resistant strains of *Campylobacter*¹⁴. Extracts from several other plants in this study, have shown similar inhibitory effects on *Campylobacter* as have extracts of green tea¹⁵.

Another major concern is the drug resistant bacterium, Methicillin-resistant *Staphylococcus aureus* (MRSA). Exposure to berberine, a compound found in many medicinal plants (e.g. *Coptis chinensis* and *Phellodendron amurense*) together with antibiotics such as levofloxacin and azithromycin¹⁶ (which had recently proved ineffective against MRSA), resulted in the reactivation of the efficacy of the antibiotic drugs. Similar results were found employing *Scutellaria baicalensis* against *Staphylococcus aureus* to restore the antibacterial actions of ciprofloxacin via similar mechanisms of efflux pump inhibition¹⁷. Indirubin, extracted from the leaves of *Wrightia tinctoria*, used in Ayurvedic medicine, has also been found to have an inhibitory effect on *Staphylococcus aureus*¹⁸. Nineteen herbs commonly used in Chinese medicine have inhibitory effects of which *Dendrobenthamia capitata*, *Elsholtzia rugulosa*, *Elsholtzia blanda*, *Geranium strictipes*, *Polygonum multiflorum* offer promising anti-MRSA possibilities¹⁹. Zuo et al. investigated the antimicrobial effects of 30 plants traditionally used to treat skin infection focusing on their potential to inhibit *Staphylococcus aureus*. Of these, 21 extracts were found to have anti-MRSA effects with *Mallotus yunnanensis* and *Skimmia arborescens* being the most active²⁰.

Herbal medicines may help to resolve the problem of antibiotic resistance more directly. Doctors faced with relatively minor, often self-limiting, but common infections e.g. pharyngitis, laryngitis and tonsillitis or mild urinary tract infections (UTIs) have little to offer except advice on how to manage the condition or otherwise prescribe an antibiotic which may not be appropriate.

Herbal medicines may fill this therapeutic gap, providing effective treatment that reduces antibiotic prescribing and does not contribute to microbial resistance. For

example, a number of herbal medicines are traditionally used to treat sore throat such as sage (*Salvia officinalis*)^{21,22}, dyers woad (*Isatis tinctoria*)²³, echinacea (*Echinacea purpurea* or *angustifolia*)^{24,25} and burdock (*Arctium lappa*)^{26,27}. Herbal medicine can also help to ease UTIs employing remedies such as *Arctostaphylos uva ursi*^{28,29,30,31} and *Zea mays*³². *Nigella sativa* shows promise in treating drug resistant H-pylori (see Table 1, page 17).

Several studies suggest that certain Indian and Chinese medicinal plants used in Ayurvedic medicine^{33,34,35,36} and traditional Chinese medicine³⁷ respectively have significant antimicrobial activity. The systems of herbal medicine that developed in India and China differ in several significant ways from European herbal medicine. The most obvious difference is that the Western herbal tradition often, but not always, focuses on 'simples', that is a single herb taken by itself. In contrast, traditional Indian (Ayurvedic) and traditional Chinese herbal medicine (TCHM) make almost exclusive use of herbal combinations. More importantly, these formulas are not designed to treat symptoms of a specific illness; rather, they are tailored specifically to the individual according to the complex principles of traditional Indian (Ayurvedic) and traditional Chinese medicine.

Herbal medicines form a potentially rich territory worth exploring as a practical way of combating microbial resistance to conventional antibiotics. Herbal medicines have been used as antibiotics for thousands of years, yet remain effective, suggesting that bacteria have a reduced ability to adapt to a plant derived antibacterial regimen.

4. Homeopathic medicine in humans

Homeopathic treatment is based upon the similarity principle referred to as 'like cures like'. This principle suggests that a substance that causes symptoms at a large dose in a healthy person can be used at lower doses to treat very similar symptoms in a person who is unwell. In practical, clinical terms, a homeopath aims to match an appropriate homeopathic remedy with the patient's symptom picture as closely as possible. In this way, two individuals presenting with tonsillitis, for example, may be prescribed different homeopathic remedies according to their individualised symptoms rather than according to the infectious agent. However, in many published trials and tests of the efficacy of homeopathy the methodology used to investigate the treatment being applied rarely reflects this central homeopathic principle, thus hampering the ability to demonstrate homeopathy's effectiveness in a real-world context.

Homeopathy is considered to be safe with minimal side effects. Adverse events have only occurred when homeopathic medicines have been improperly self-administered in inappropriate amounts, or when patients taking homeopathic medicines have not been receiving concomitant conventional medical treatment where appropriate.^{51, 52, 53, 54}

Homeopathic philosophy holds that homeopathic treatments improve functionality of an individual's immune system so that they can deal with infection efficiently, and restore wellness without lasting damage or complications.

There is no risk of resistance developing with homeopathic medicines: homeopathic

medicinal treatment is aimed at stimulating a homeostatic response in an affected individual, supporting the efficient endogenous management of infections e.g. such as those in the respiratory and urinary tracts without the need for antimicrobial treatments. In this way, homeopathic treatment focuses on supporting the resistance of the individual patient and not on the infecting microbe, removing the risk of microbial resistance developing to homeopathic medicines and leaving current conventional antimicrobial treatments to be safeguarded for essential usage in serious and life-threatening infections.

Upper respiratory tract infections (URTIs) represent one of the most common reasons for antibiotic prescriptions in primary care, with these prescriptions often being unnecessary or inappropriate, because only approximately one-quarter of URTIs are of bacterial origin^d. Thus, any novel therapy that can be used effectively instead of unnecessary antibiotic prescriptions in these acute conditions would help support the EU strategy to combat antimicrobial resistance.

The balance of moderate and strong evidence is considered positive for the effectiveness of homeopathy in URTIs, particularly for the following specific infectious conditions that are commonly treated with antimicrobials: otitis media^{55, 56, 57}, sinusitis^{58, 59, 60, 61}, common cold^{62, 63}, influenza-like syndromes^{64, 65, 66, 67} and (unspecified) upper respiratory tract infections^{68, 69, 70} (see Table 2, page 20). Also an HTA report on homeopathy as part of the Swiss Complementary Medicine Evaluation Programme⁶⁸ concluded that [...] “the trial results showed probable effectiveness of homeopathy for allergies and infectious diseases of the upper respiratory tract. Tolerability of the treatment is very good and is not reduced through combination with conventional treatment. Economic advantages are possible due to the fact that homeopathic treatment can lessen the need for conventional medication.” That means that homeopathy may be effective in reducing excessive antibiotic prescribing in primary care.

At the moment there are only two choices in managing acute otitis media and sinusitis: either immediate antibiotic treatment in case it is the uncommon bacterial form of the condition, or delaying antibiotic therapy for 2-3 days on the basis that it is more likely to be a viral infection (known as ‘watchful waiting’). The former approach can lead to widespread inappropriate use of antibiotics, whilst the latter may increase the risk of complications from delayed treatment of a bacterial infection.

In these conditions homeopathy offers an additional choice. In cases where watchful waiting would currently be recommended, homeopathy could be given immediately instead. Any patients who did not respond to homeopathic treatment by day 3 would be given antibiotics (just as they would with watchful waiting).

As there are virtually no side effects from homeopathic medicines and they do not contribute to antimicrobial resistance, there is no expected negative impact from this proposed additional intervention. However, if homeopathy proved to be an effective treatment by day 3 of the disease, the potential benefits would include the reduced use

^d Lingard H et al (2008). Bacterial superinfection in upper respiratory tract infections estimated by increases in CRP values: A diagnostic follow-up in primary care. *Scandinavian Journal of Primary Health Care*, 26(4): 211–215.

of antibiotics and delivery of prompt treatment.

In conclusion, there is some evidence to support the suggestion that homeopathy could provide an effective treatment option to support the EU strategy for combating antimicrobial resistance, especially in URTIs where antibiotics are commonly used.

5. Anthroposophic medicine

Anthroposophic Medicine is an integrative medicine system originated in Europe in the early 1920's, established nowadays in 80 countries worldwide, most significantly in central Europe.^e Anthroposophic medicine is integrated with conventional medicine in hospitals and medical practices. It applies medicines derived from plants, minerals, and animals; art therapy, eurythmy therapy, and rhythmical massage; counseling; psychotherapy; and specific nursing techniques such as external embrocation. Anthroposophic healthcare is provided by medical doctors, therapists, and nurses. A Health-Technology Assessment Report and its recent update identified 265 clinical studies on the efficacy and effectiveness of anthroposophic medicine.

Over decades, anthroposophic doctors practising within the primary health care sector have accumulated a large expertise in the treatment of bacterial infections using AM remedies alone or, if needed, in combination with antibiotics. The International Integrative Primary Care Outcomes Study (IIPCOS) on anthroposophic medicine was conducted in four European countries and the United States and compared primary care patients who were treated by anthroposophic or conventional physicians for acute respiratory and ear infections⁷². [For more details of AM trials see Table 3, page 25]. Compared to conventional therapy, anthroposophic treatment was associated with much lower use of antibiotics and antipyretics as well as quicker recovery, fewer adverse reactions, and greater therapy satisfaction. These differences remained after adjustment for country, age, gender, and four markers of baseline severity.

Improvement within 24 hours occurred in 30.9% (221/715) of patients treated by AM doctors and 16.6% (50/301) of patients treated by conventional doctors. Antibiotics were used in 5.5% of patients in the anthroposophic doctors group compared to 33.6% in the conventional group. Day 7 complete recovery or major improvement was reported by 77.1% (AM doctors) vs. 66.1% of patients (conventional doctors), respectively. Adverse drug reactions were reported in 2.7% patients treated by AM doctors compared to 6.0% within the other group. The safety analysis of the AM medicines used showed that adverse drug reactions were rare (2/715 patients) and mild.

In another multicentre prospective observational study in AM primary care centres in Germany⁷⁴, 12,081 patients with 19,050 acute upper airway infections occurring during one year of observation were enrolled. The infections included most often common cold (63.3%) and acute tonsillitis (12.9%). 73.7% of patients were children. In 63% of all cases, treatment was purely anthroposophic. In only 6.3% antibiotics were used. Within

^e Kienle GS, Albonico HU et al. (2013): Anthroposophic Medicine: An Integrative Medical System Originating in Europe. *Global Advances in Health and Medicine* 2,6: 20-31

the group of the 8,900 children with 14,945 respiratory tract infections, antibiotic prescriptions occurred in only 5.8%. The prescription rate of antibiotics was much lower than the mean in Germany.

Antibiotic and antipyretic use in early childhood are known today as putative risk factors for the development of allergic and autoimmune diseases like asthma, atopic eczema and chronic inflammatory bowel disease. Thus, a reduced prescription rate of antibiotics and antipyretics is of use not only to reduce AMR but to increase health performance in children, which could be demonstrated in a well-controlled paediatric epidemiological study.^f

A recent study in an anthroposophic hospital⁷³ demonstrated that 16/18 patients with community-acquired pneumonia were successfully treated with anthroposophic medicine only and 2/18 needed additional antibiotic therapy (both of risk class IV). Thus, it was shown that even severe infectious diseases can be cured by means of AM lowering the need for antibiotics significantly.

A recent surveillance on multi-resistant bacteria at the Paracelsus hospital in Bad Liebenzell, Germany, executed by the Department of Environmental Health Sciences of the Freiburg University revealed that the percentages of most multi-resistant bacteria in the anthroposophic medicine hospital were much lower than in the average conventional hospital. Patients mostly have CAM family doctors in their primary care prescribing antibiotic less often and they received fewer antibiotics during their hospital stay. The data showed frequencies for Vancomycin-resistant Enterococci of 0.4% (Paracelsus-Hospital) vs. 12.6% (group of comparable German hospitals of same size and patient structure), imipenem-resistant *Pseudomonas aeruginosa* 7.7% vs. 16.8% and multi-resistant gram-negative bacilli (ESBL) 1.2% vs. 10.4% (the percentages of MRSA in anthroposophic medicine hospital vs. conventional hospitals were almost equal: 19% vs. 21.3%). This can be regarded as proof of principle: overall low prescription rates of antibiotics by family doctors and during hospital stays will lead to a significantly reduced prevalence of AMR in hospitals.

6. Antibiotics in the farming industry

It is estimated that more than half of the worldwide production of antibiotics is used by the farming industry^g. Animals are routinely put on a course of antibiotics to treat common bacterial infections and it is now common practice to treat the whole herd prophylactically (metaphylaxis) to stop the infection spreading. In addition, low, sub-therapeutic doses of antibiotics may be given to animals en masse over periods of weeks when they are considered to be at risk of infection. Although the practice of using low doses of antibiotics to promote growth in animals is banned in the EU, in practice growth-promoting effects are achieved through the low doses administered as chemoprophylaxis, thereby blurring the boundaries between the two uses.

^f Alm JS, Swartz J et al 1999: Atopy in children of families with an anthroposophic lifestyle. *Lancet*, 353 (9163):1485-1488

^g Urgent action necessary to safeguard drug treatments, WHO (2011) at http://www.who.int/mediacentre/news/releases/2011/whd_20110406/en/

This extensive usage of veterinary antibiotics necessitates the development of sustainable alternatives. The basis for sustainable animal husbandry lies with a goal-oriented and responsible breeding policy, appropriate nutrition and housing and professional care with an eye for the individual animal. Health and wellbeing are intrinsically connected. Measures that improve animal welfare will also have a positive influence on health and productivity.

Natural feed components and herbal and homeopathic medicinal products can help sustain animal health. Using these products can diminish the number of disease outbreaks on a farm and can help to restrict the use of antibiotics to a limited number of severely diseased animals. The greatest added value of the use of natural products is disease and problem prevention.

7. Recent policy of the European Commission in this area

In June 2007 the European Council of Agricultural Ministers agreed on a new Council Regulation^h on organic production and labelling of organic products. This Council Regulation contains defines goals, principles and general rules for organic production.

The goal of this legal framework was to set a new course for the continued development of organic farming. Sustainable cultivation systems and a variety of high-quality products are the aim. In this process, even greater emphasis is placed on environmental protection, biodiversity and high standards of animal protection. In addition, the legislation aims at ensuring consumer confidence and protecting consumers' interests.

The European Commission funded ANIPLANⁱ ran from 2007 to 2010 and was aimed to minimise medicine use in organic dairy herds through active and well-planned animal health and welfare promotion and disease prevention. The process having been implemented on the farms appeared to be a feasible approach to improve udder health and minimise use of antibiotics without impairment of productivity.

A more recent project, funded by the European Commission under the 7th Research Framework Programme is the IMPRO project - Impact matrix analysis and cost-benefit calculations to improve management practices regarding health status in organic dairy farming.^j This project aims to substantially overcome weak points in current health management strategies on organic dairy farms and to increase the implementation of evidence-based measures and to improve practice of health management. It includes, among other things, (1) the development of a pro-active monitoring protocol aiming for improved effectiveness of preventive and treatment strategies and for a reduction in the use of allopathic drugs, and (2) the assessment of the manageability of alternative treatments (CAM) according to the state-of-the-art. It runs until 30 September 2016.

^h Council Regulation (EC) No 834/2007 of 28 June 2007 on organic production and labelling of organic products and repealing Regulation (EEC) No 2092/91

ⁱ http://www.coreorganic.org/research/projects/aniplan/ANIPLAN_final_report_dec2011.pdf

^j http://cordis.europa.eu/project/rcn/104247_en.html

<http://www.dev.impro-dairy.eu/index.php/en/>

8. Herbal medicine in animal husbandry

After the ban of antibiotic growth promoters in the European Union many alternative substances have been investigated for their potential to replace them. An interesting project was initiated in 2006 by the Dutch Ministry of Agriculture, Nature and Food Quality. The project *Development of phytotherapy as a tool for reducing and/or prevention of diseases in farm animals* was carried out by the Institute of Food Safety (RIKILT) in cooperation with the Universities of Wageningen and Utrecht, the Institute for Ethnobotany and Zoopharmacognosy among others. The goal of the project was to increase the number of available herbal medicines for organic farmers, but also regular animal husbandry is interested in products that may reduce the need for antibiotics.

The project showed that there are many herbal products (compounds of several herbs) available that can be primarily recommended for the promotion of health, both in organic and regular animal husbandry. Herbal products are mainly used for prevention, particularly in periods in which animals are more vulnerable to diseases, for example, in case of changing diet, housing or environment. Almost all herbal products selected for this project showed that the quality could be substantiated and the declared composition could be confirmed. This shows that reliable quality products are put on the market. In a number of these herbal products, the claimed effect has been made plausible by laboratory tests and / or animal studies.

Because registration as veterinary medicine is expensive and often not feasible due to the complex nature of the products, most of these herbal products are sold as supplementary feed or feed additive. Even though they are not registered as veterinary medicinal products it is advisable to determine the effects of these herbal products on animal health in an objective manner, making it possible for farmers to rationally apply these products to their animals and for veterinarians to take account of these products when treating the animals.

During this project some animal experiments have been performed relating to current health problems in organic farming. They included animal experiments in proven animal study models where animals fed with herbal products were compared with untreated control animals. In addition field experiments were performed both on organic and conventional farms. Experiments were performed with organic layer hens, grower pigs and dairy cows.

The project produced two databases, one on products and one on background literature, which can be accessed at the website (www.fyto-v.nl). The product database includes 142 herbal products, broken down by sectors: 86 in cattle, 74 in pigs, 54 in poultry and 41 in small ruminants (a large number of products is used in several animal species). The literature database covering each single herb has about 500 entries^k.

Currently, veterinary and animal herbalists throughout the world use herbs from several systems of medicine, including Ayurvedic medicine, Western herbal medicine, Traditional Chinese Medicine as well as Kampo (traditional Japanese medicine). A veterinarian need not adopt any or all of the principles and practices of these systems of medicine to benefit from its use.

^k http://www.fyto-v.nl/pub_data/table_summary.php?table=literatuur

In India a considerable amount of literature on veterinary herbal drug research, clinical trials, pharmacology, and basic research has been generated with a view to scientifically systematising the ethnoveterinary medical practices and folklore claims on herbal treatments. Research efforts by the National Laboratories and Veterinary, Medical, Pharmacy, and Science Colleges in India have established detailed data regarding herbs—their effects, effectiveness and safety. The most investigated Ayurvedic herbs and the most commonly used Ayurvedic herbs in veterinary practice are listed in Wynn & Fougere's textbook of Veterinary Herbal Medicine¹.

Also phytogenic feed additives or phytobiotics are a promising alternative. These are plant-derived products (extracts or essential oils) added to feed in order to improve performance. They comprise of a very wide range of substances with respect to biological origin, formulation, chemical description and purity. They act mainly in the direction of improving gut health, immune system and well-being. A great number of in vitro and in vivo studies have confirmed a wide range of activities of phytobiotics in animal nutrition like stimulation of feed intake, antimicrobial, coccidiostatic, anthelmintic and immunostimulating^m action.

Phytobiotics produce their beneficial effects in several waysⁿ: (1) stimulation of feed intake and digestive secretions (e.g. *Sanguinaria canadensis*, garlic, horseradish, turmeric), (2) antimicrobial and coccidiostatic activity (e.g. oregano, cloves, cinnamon) (3) stimulation or moderation of the immune system (e.g. *Astragalus membranaceus*), and (4) antioxidant activity (e.g. rosemary).

9. Homeopathic medicine in animal husbandry

Homeopathic medicine or homeopathy has traditionally been used for the treatment of animals as well as humans. In animal husbandry it is used for pigs, calves, chickens, turkeys, sheep, and cattle. The most common diseases treated include diarrhoea, pneumonia, infertility, mastitis, and birthing problems.

Mastitis is an economically important disease of dairy animals throughout world, due to its long-term effects on milk yields. Huge economic losses are also incurred due to unmarketable milk or milk-products contaminated with antibiotic residues. Conventional treatment depends on the use of antibiotics, which are not only costly but residues in milk and meat pose human health risks. Indiscriminate use of antibiotics results in the emergence of resistant bacterial strains causing an increase in treatment failures.

Diarrhoea became a disease with significant economic impact in the production of swine due to the systems of intensive farming adopted. Enteritis can appear in three different stages: neonatal diarrhoea, appearing during the first days of life; piglet diarrhoea, when it appears from the first week of life to weaning; and diarrhoea after weaning. Generally, 50-60% of deaths during the suckling stage happen during the first

¹ Wynn SG & Fougere B (2006) Veterinary Herbal Medicine, Mosby Elsevier, USA

^m Jacela JY, DeRouchey JM, Tokach MD, et al (2010). Feed additives for swine: Fact sheets – prebiotics and probiotics, and phytogenics. J Swine Health Prod., 18(3):132–136.

ⁿ Vidanarachchi JK et al (2005). Phytobiotics: alternatives to antibiotic growth promoters in monogastric animal feeds, Recent Advances in Animal Nutrition in Australia, 15, 131-144

week of life mainly due to crushing by the sow or neonatal diarrhoea. Neonatal diarrhoea, mostly caused by *Escherichia coli*, is the disease with highest impact in production of swine. If left untreated, it leads to weight loss and, not uncommonly, to death of the piglet, resulting in significant financial losses to the farmer. Conventional treatments of *E. coli* diarrhoea is administration of antibiotics to affected piglets, or preventive vaccination of the sows. A recent study involving the use of homeopathy in the treatment of *E. coli* diarrhoea in neonatal piglets showed promising results⁸¹

Antimicrobial use in animals contributes less to the rising problem of resistance and it is obvious that any non-essential usage of antimicrobials in animals should be curtailed: homeopathy may therefore offer an appropriate alternative. Homeopathy is emerging as an alternative therapy in veterinary medicine for its ability to prevent recurrence of diseases without leaving residues in animal products. Homeopathy depends on the totality of physical and psychological symptoms of the diseased animals and aiming to augment the body's immune defences, supporting these rather than treating, inhibiting, or suppressing symptoms. Homeopathy can be effective in both bacterial and viral diseases, and can prevent progress to serious diseases by use in the early stages of discomfort. In addition, epidemic diseases in animals can be addressed with homeopathy, both in a preventive as well as a curative way. With one remedy often a whole epidemic within a herd can be treated.

Both mastitis in cattle^{76, 77, 78, 79, 80} and *Escherichia coli* diarrhoea in swine^{81, 82} have been identified as clinically relevant issues for which homeopathy could be efficacious and some research has been conducted to begin evaluating these approaches (see Table 4, page 27).

The most recent trial on *Escherichia coli* diarrhoea⁸¹ is a very good example of how a trial would be relatively easy and inexpensive to carry out, yet in return for this small investment, the potential rewards could be significant. It was a robust observer-blind, randomised placebo-controlled trial (triple-blinded, i.e. as to administration, scoring, and analysis) carried out by researchers at the University of Wageningen in the Netherlands. It explored the use of a homeopathic medicine derived from *Escherichia coli* bacteria (*Coli 30K*) instead of antibiotics at the prevention of *E. Coli* diarrhoea in piglets. 52 sows were randomly allocated into either the homeopathy group or the placebo group. The sows gave birth to 525 piglets that were scored for occurrence and duration of diarrhoea. The results clearly showed an effect of the homeopathic medicine with only 3.8% of the homeopathy group suffering from diarrhoea compared to 23.8% in the control group ($p < 0.0001$).

This study and others⁸⁰ indicates that potential benefits of the use of homeopathy in the treatment of neonatal diarrhoea in piglets is considerable; furthermore it does not carry the risk of AMR. EUROCAM recommends that a replication of this study be conducted. Given the size of the pig industry, a large-scale multi-centred approach would allow firm conclusions to be reached as to whether this form of homeopathic treatment is efficacious for prevention of *E.coli* diarrhoea in piglets in the EU and could therefore significantly replace the use of antibiotics for this purpose.

We believe that the evidence mentioned here indicates an area of novel antimicrobial treatment options in animal care that deserve further investment and investigation with adequately sized and appropriately designed trials.

10. Concluding remarks and suggestions

EUROCAM supports and encourages integrated and fully informed healthcare choices for patients and recognises that conventional antimicrobial treatment, when appropriately prescribed, plays a vital role in managing public health. However, the severity of the threat posed by AMR to global health means that all potential measures, particularly novel solutions, must be explored as a matter of urgency.

EUROCAM therefore recommends that the potential of CAM in reducing the problem of AMR is given serious consideration and that further research is carried out in this area to determine in which conditions, both in human and veterinary healthcare, specific CAM modalities are particularly effective. Compared with other avenues of such as the identification and development of new antibiotics, such trials would be relatively easy and inexpensive to carry out, yet in return for this small investment, the potential rewards could be highly significant.

To date, there has been a huge disparity between public funding for conventional drug research and that for CAM research. Whilst CAM may improve health, reduce disease, reduce health costs and help reduce the problem of antimicrobial resistance, the CAM sector alone cannot be expected to fund the research to investigate these possibilities. The CAM industry is small and there are no major financial and/or industrial interests driving research efforts in this field. Like mainstream medical research, there is a social responsibility for government to fund such research. As for conventional medicine there should be industry-independent funded research.

Complementary and Alternative Medicine can support the EU strategy to conserve and steward the effectiveness of existing antimicrobial treatments and offer an avenue for the development of novel future therapies. It is time for serious consideration and investment to be given to it.

Table 1: Herbs to help combat growing antibiotic resistance (randomised controlled trials only)

Study Design	Publication Details	Main Findings	Possible Mechanisms	Strength of Evidence
An evidence-based systematic review of umckaloabo (<i>Pelargonium sidoides</i>) by the US Natural Standard Research Collaboration.	Ulbricht C et al. (2010) An evidence-based systematic review of umckaloabo (<i>Pelargonium sidoides</i>) by the Natural Standard Research Collaboration. <i>Journal of Dietary Supplements</i> , 7(3):283-302. ³⁸	This comprehensive systematic review concluded that there was strong scientific evidence (Grade A) - including 4 good quality RCTs involving 933 participants - to support the use of pelargonium for acute bronchitis and good scientific evidence (Grade B) for the its use in acute pharyngitis and the common cold. No serious toxic effects have been observed in any trial relating to pelargonium.	Pelargonium has exhibited a marked antibacterial action against a wide range of pathogenic bacteria.	Strong
Efficacy and safety of a combination herbal medicinal product containing nasturtium (<i>Tropaeoli majoris herba</i>) and Horseradish (<i>Armoracia rusticana</i>) for the prophylactic treatment of patients with respiratory tract diseases: a randomised, prospective, double-blind, placebo-controlled phase III trial.	Fintelmann V et al. (2012). Efficacy and safety of a combination herbal medicinal product containing nasturtium (<i>Tropaeoli majoris herba</i>) and Horseradish (<i>Armoracia rusticana</i>) for the prophylactic treatment of patients with respiratory tract diseases: a randomised, prospective, double-blind, placebo-controlled phase III trial. <i>Current Medical Research Opinion</i> , 28(11):1799-1807. ³⁹	351 participants were randomly allocated to either active treatment (Group 1), a lower dose of active herbs + placebo (Group 2), or just placebo (Group 3). The maximum duration of treatment was 84 days. In the intention to treat (ITT) population excluding early infections (n = 344) the infection rates were 13.3% for Group 1, 18.4% for Group 2 and 25.6% for placebo Group 3. The statistical trend test showed significant results (p = 0.0171). The herbal combination appears to offer a prophylactic advantage which could help reduce antibiotic	These herbs contain several isothiocyanates which have a marked in vitro broad spectrum anti-bacterial action. ⁴⁰	Moderate

		prescription.		
A double blind randomised control trial where 107 participants were randomised to receive either licorice root (<i>Glycyrrhiza glabra</i>) - trade name <i>gutgard</i> - or placebo for 60 days	Puram et al. (2013) Effect of GutGard in the Management of Helicobacter pylori: A Randomized Double Blind Placebo Controlled Study, <i>Evidence-Based Complementary and Alternative Medicine</i> , Article ID 263805. ⁴¹	The results showed that 56% (n=28) were <i>H.pylori</i> negative compared to 4% (n=2) in the placebo group. In other work by the same team, the herb extract reduced symptoms of dyspepsia and there were no adverse events reported.	<i>Glycyrrhiza glabra</i> showed antimicrobial activity in vitro and anti-adhesive properties against <i>H.pylori</i> . ⁴²	Moderate
A randomised, double-blind, placebo-controlled trial of a herbal medicinal product Angocin Anti-Infekt N containing nasturtium (<i>Tropaeoli majoris herba</i>) and horseradish (<i>Armoraciae rusticana</i>) for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections (RUTIs).	Albrecht U et al. (2007). A randomised, double-blind, placebo-controlled trial of a herbal medicinal product containing Tropaeoli majoris herba (Nasturtium) and Armoraciae rusticanae radix (Horseradish) for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections. <i>Current Medical Research Opinion</i> , 23(10):2415-2422. ⁴³	129 patients with RUTIs were randomised to active herbal or placebo treatment for 90 days. The primary outcome was the number of laboratory confirmed urinary tract infections. The per protocol mean number of recurrent UTIs in the study period was 0.43 versus 0.77 for the placebo group. This result is statistically significant (p = 0.035). A total of 36 patients in the test group and 37 patients in the placebo group reported adverse events. Two serious adverse events were reported in the placebo group and one serious adverse event in the treatment group (not associated with the study medication). This herbal product appears to be effective and safe as a prophylaxis for RUTIs.	Mustard oils (including isothiocyanates) found in these two herbs have been shown to have a broad spectrum antibacterial action. ⁴⁴	Preliminary (This trial needs to be repeated by independent researchers using an intention to treat analysis.)
A randomised control trial of a complex Chinese herbal medicine (San Ling Jie Du Tang) in the treatment of women with recurrent lower urinary tract	Huang MJ. (2007). A randomised control trial of a complex Chinese herbal medicine (San Ling Jie Du Tang) in the treatment of women with recurrent lower urinary tract	300 women were randomised in a 2:1 ratio to the Chinese herbal remedy or an antibiotic. Treatment was administered for 7 days with a	Several of the included herbs, such as tree peony bark (<i>Paeonia suffruticosa</i>), have been shown to have a broad	Preliminary (Due to a lack of detail relating to the trial methodology.)

infections (RUTIs)	infections (RUTIs), <i>Hubei Journal of Traditional Chinese Medicine</i> ;29:38-39. ⁴⁵	6 month follow up. 79.5% of the herbal group reported no infection in the follow up period compared with 49% in the antibiotic group. This was statistically significant (p<0.05).	spectrum antibacterial action. ⁴⁶	
A Cochrane systematic review of Chinese herbs for sore throat.	Huang Y et al. (2012). A Cochrane systematic review of Chinese herbs for sore throat, <i>Cochrane Database Systematic Review</i> . 14;3:CD004877. ⁴⁷	12 studies involving 1954 participants were included in this systematic review. 6/12 studies were shown to be more effective than the control with 3 herbal remedies appearing more effective than antibiotics. The remaining 6 studies showed equivalent effectiveness to the controls.	Several of the included herbs such as Japanese Honeysuckle (<i>Lonicera japonica</i>), have been shown to have a broad spectrum anti-bacterial action. ⁴⁸	Preliminary (Due to the poor methodological quality of the included trials.)
Comparative study of <i>Nigella sativa</i> and triple therapy in eradication of <i>Helicobacter pylori</i> in patients with non-ulcer dyspepsia. 88 adults with dyspeptic symptoms and positive <i>H.pylori</i> test were randomised to four groups: receiving i) triple therapy (TT) comprising of clarithromycin, amoxicillin, omeprazole [n= 23], ii) 1 g <i>Nigella sativa</i> + 40 mg omeprazole (OM) [n= 21], iii) 2 g NS + OM [n= 21] or iv) 3 g NS + OM [n= 23]. Main outcome was eradication of <i>H.pylori</i> .	Salem et al. (2010). Comparative study of <i>Nigella sativa</i> and triple therapy in eradication of <i>Helicobacter pylori</i> in patients with non-ulcer dyspepsia. <i>Saudi Journal of Gastroenterology</i> . 16(3):207-214. ⁴⁹	<i>H.pylori</i> eradication was 82.6% in the antibiotic triple therapy group, 47.6 with 1g of <i>Nigella sativa</i> , 66.7% with 2g and 47.8% with 3g <i>Nigella sativa</i> . Eradication rates with 2 g <i>Nigella sativa</i> and antibiotics were statistically similar. <i>Nigella sativa</i> seeds possess clinically useful anti- <i>H.pylori</i> activity, comparable to antibiotic triple therapy.	In vitro study showed that <i>Nigella sativa</i> inhibited growth in all strains of <i>H.pylori</i> within 60 minutes of exposure. ⁵⁰	Preliminary

Table 2: Homeopathy to help combat growing antibiotic resistance (randomised controlled trials only)

Study Design	Publication Details	Main Findings	Strength of Evidence
A randomized double-blind placebo control pilot study of individualized homeopathy.	Jacobs J, Springer DA, Crothers D (2001). Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. <i>Pediatric Infectious Disease Journal</i> , 20:177-183.	There were fewer treatment failures in the group receiving homeopathy after 5 days, 2 weeks and 6 weeks, with differences of 11.4, 18.4 and 19.9%, respectively, but these differences were not statistically significant. Diary scores showed a significant decrease in symptoms at 24 and 64 h after treatment in favour of homeopathy ($P < 0.05$).	Strong
Children with acute otitis media were enrolled in the study at the time of diagnosis and randomized to receive either standard therapy alone or standard therapy plus a homeopathic ear drop solution that was to be used on as needed basis for up to 5 days.	Taylor JA, Jacobs J (2011). Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media . <i>Homeopathy</i> , 100(3):109-15.	A total of 119 eligible children were enrolled in the study; symptom diaries were received from 94 (79%). Symptom scores tended to be lower in the group of children receiving ear drops than in those receiving standard therapy alone; these differences were significant at the second and third assessments ($P = 0.04$ and $P = 0.003$, respectively). In addition, the rate of symptom improvement was faster in children in the ear drop group compared with children in standard therapy alone group ($P = 0.002$).	Strong
A randomized placebo-controlled parallel group pilot study of homeopathic vs conventional treatment for acute otitis media. Patients were randomized by a computer generated random number list to receive either individualized homeopathic medicines in fifty millesimal (LM) potencies, or conventional treatment including analgesics, antipyretics and anti-inflammatory drugs. Patients who did not improve were prescribed	Sinha MN, Siddiqui VA, Nayak C, Singh V, Dixit R, Dewan D, Mishra A (2012). Randomized controlled pilot study to compare homeopathy and conventional therapy in acute otitis media . <i>Homeopathy</i> , 101: 5-12.	81 patients were included, 80 completed follow-up: 41 for conventional and 40 for homeopathic treatment. In the conventional group, all 40 (100%) patients were cured, in the homeopathy group, 38 (95%) patients were cured while 02 (5%) patients were lost to the last two follow-up. By the 3rd day of treatment, 4 patients were cured in Homeopathy group but in conventional group only one patient was cured. In the conventional group antibiotics were prescribed in 39 (97.5%), no antibiotics were required in the homeopathy group. 85% of patients were prescribed six	Non-conclusive

antibiotics at the 3rd day. Outcomes were assessed by the Acute Otitis Media-Severity of Symptoms (AOM-SOS) Scale and Tympanic Membrane Examination over 21 days.		homeopathic medicines.	
A prospective randomized, double-blind study including 144 patients with acute rhinosinusitis. They received either a homeopathic remedy (n=72) or placebo (n=72). At the control examinations after 7, 14 and 21 days, five sinusitis-typical symptoms were measured with scores from 0 (absent) to 4 (very strong).	Friese K-H, Zabalotnyi DI (2007) Homöopathie bei akuter Rhinosinusitis. Eine doppelblinde, placebokontrollierte Studie belegt die Wirksamkeit und Verträglichkeit eines homöopathischen Kombinations-arzneimittels [Homeopathy in acute rhinosinusitis . A double-blind, placebo controlled study shows the effectiveness and tolerability of a homeopathic combination remedy]. <i>HNO</i> , 55: 271-7.	In the homeopathic 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). The homeopathic treatment resulted in freedom from complaints in 90.3% of the patients and improvement in a further 8.3%, whereas in the placebo group, the complaints remained unchanged or became worse in 88.9% of the patients.	Strong
A prospective, randomized, double-blind, placebo-controlled, phase III clinical trial was conducted for a treatment period of 22 days, followed by an eight-week post-treatment observational phase. 113 patients with radiography-confirmed AMS participated in the trial.	Zabolotnyi DI, Kneis KC, Richardson A et al (2007). Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis : a prospective, randomized, double-blind, placebo-controlled, multicentre clinical trial. <i>Explore (NY)</i> , 3: 98-109.	From day zero to day seven, Sinfrontal caused a significant reduction in the SSS total score compared with placebo (5.8 +/- 2.3 [6.0] points vs 2.3 +/- 1.8 [2.0] points; P < .0001). On day 21, 39 (68.4%) patients on active medication had a complete remission of AMS symptoms compared with five (8.9%) placebo patients. All secondary outcome criteria displayed similar trends. Eight adverse events were reported that were assessed as being mild or moderate in intensity. No recurrence of AMS symptoms occurred by the end of the eight-week post-treatment observational phase.	Strong
A randomized placebo-controlled double-blind study over a 5-month period including 173 patients with chronic sinusitis, 155 of whom were included in the final evaluation (89.6%)	Weiser M, Clasen B (1994). Randomisierte plazebo-kontrollierte Doppelblindstudie zur Untersuchung der klinische Wirksamkeit der homöopathischen Euphorbium compositum-Nasentropfen S bei chronischer Sinusitis [Randomised, placebo-controlled, double-blind study of the clinical efficacy of the homeopathic Euphorbium compositum-S nasal spray in cases of chronic sinusitis].	Statistical comparison of the therapeutic collectives demonstrates a significant superiority of Euphorbium compositum S nasal spray (5% significance level, p=0.016). Improvement was most evident within the subjective criteria of respiratory obstruction, sensation of pressure and headache.	Strong

	<i>Forschende Komplementärmedizin</i> , 1:251-259.		
A randomized double-blind controlled trial including 152 patients with sinusitis. The effect of one single homeopathic medicine and two fixed combinations of homeopathic medicines were compared with a placebo group.	Wiesenauer M, Gaus W et al (1989). Wirksamkeitsprüfung von homöopathische Kombinationspräparaten bei Sinusitis. Ergebnisse einer randomisierten Doppelblindstudie unter Praxisbedingungen [Efficiency of homeopathic preparation combinations in sinusitis . Results of a randomized double blind study with general practitioners]. <i>Arzneimittel Forschung</i> , 39:620–625.	No remarkable difference in the therapeutic success could be found among the various groups.	Non-conclusive
Controlled clinical trial including 53 outpatients suffering from common cold (flu) who were randomly assigned to either a therapy with acetylsalicylic acid (ASA) or the homeopathic drug Eupatorium perfoliatum D2 in a controlled clinical trial.	Gassinger CA, Wünstel G, Netter P (1981). Klinische Prüfung zum Nachweis der therapeutischen Wirksamkeit des homöopathischen Arzneimittels Eupatorium perfoliatum D2 (Wasserhanf composite) bei der Diagnose "Grippaler Infekt". [A controlled clinical trial for testing the efficacy of the homeopathic drug Eupatorium perfoliatum D2 in the treatment of common cold]. <i>Arzneimittel Forschung</i> , 31:732–736.	The efficacy of the drugs was assessed on day 1, 4 and 10 of the infection by symptom check lists and physical examinations. Neither subjective complaints nor body temperature or laboratory findings showed any significant differences between groups which was taken as evidence that both drugs were equally effective.	Moderate
A randomized double-blind clinical study including 170 army soldiers suffering from common cold. The test was conducted on a monocentric, randomized, non-sequential, and inter-individual basis, comparing the effectiveness of a combination homeopathic preparation (Gripp-Heel) with that of acetylsalicylic acid.	Maiwald VL, Weinfurtnner T et al (1988). Therapie des grippalen Infekts mit einem homöopathischen Kombinationspräparat im Vergleich zu Acetylsalicylsäure. Kontrollierte, randomisierte Einfachblindstudie [Treatment of common cold with a combination homeopathic preparation compared with acetylsalicylic acid. A controlled, randomized single-blind study]. <i>Arzneimittel Forschung</i> , 38:578-582	On the 4th and 10th treatment days, no significant difference was determined with respect to changes in clinical findings, subjectively assessed complaints, or length of time the patients were unable to work. Thus the two preparations possess comparative effectiveness in the treatment of the common cold.	Moderate
A randomized double-blind controlled trial including 124 chronically ill residents (73 in the verum group, 51 in the control group). Antibody production was determined in serum samples collected before and three and four weeks after treatment with Gripp-Heel. The same procedures were carried out in the control group.	Brydak LB, Denys A (1999). The evaluation of humoral response and the clinical evaluation of a risk-group patients' state of health after administration of the homeopathic preparation Gripp-Heel during the influenza epidemic season 1993 to 94. <i>International Review of Allergology and Clinical Immunology</i> , 5:223-227.	Three weeks after administration of Gripp-Heel Geometric Mean Antibody Titers for hemagglutinins H1, H3 and HB were about 2 times higher than before treatment. Geometric Mean Titers for neuroaminidase N1 was 9.5 times higher than before drug administration, while for neuraminidase N2 it was 15.4 times higher and for neuraminidase NB it was 8.0 times higher. In the control group GMTs were nearly on the same	Strong

		level.	
A randomized placebo-controlled clinical trial to assess the effectiveness of a homeopathic preparation in the treatment of influenza-like syndromes. 237 cases in verum group, 241 in placebo group.	Ferley JP, Zmirou D et al (1989). A controlled evaluation of a homeopathic preparation in the treatment of influenza like syndromes . <i>British Journal of Clinical Pharmacology</i> , 27:329-335.	The proportion of cases who recovered within 48 hours of treatment was greater among the active drug group than among the placebo group (17.1% against 10.3%, P = 0.03).	Strong
A randomized placebo-controlled clinical trial to assess the effectiveness of a homeopathic preparation in the treatment of influenza-like syndromes, including 372 patients.	Papp, R, Schuback G et al (1998). Oscillococcinum® in patients with influenza-like syndromes : a placebo-controlled double-blind evaluation. <i>British Homeopathic Journal</i> , 87:69-76.	After 48 hours the symptoms of the patients in the verum group were significantly milder (p=0.023) than in the placebo group. The number of patients with no symptoms was significantly higher in the verum group from the second day onwards (verum: 17.4%, placebo: 6.6%) until the end of the patients' recording (day 5 in the evening: verum: 73.7%, placebo: 63.7%). The biggest group difference was recorded for the time between the evening of the second day (10.6% more patients with no symptoms) and the morning of the fourth day (10.2% more patients with no symptoms).	Moderate
A multicenter, prospective, randomized, triple-arm placebo controlled trial conducted at nine Institutes and Units of Central Council for Research in Homoeopathy (CCRH) from June 2009 to December 2010. The patients fulfilling the inclusion criteria were randomized to LM, centesimal and placebo groups.	Chakraborty PS, Lamba CD et al (2013). Effect of individualized homoeopathic treatment in influenza-like illness : A multicenter, single blind, randomized, placebo-controlled study. <i>Indian Journal of Research in Homoeopathy</i> , 7: 22-30.	Out of 739 screened cases, 447 cases were eligible for enrolment comprising LM (n=152), centesimal (n=147) and placebo (n=148) cases. There was a significant difference in temperature from 2 nd day onwards in LM and centesimal groups. Conclusion: The study revealed the significant effect of individualized homoeopathic treatment in the patients suffering from influenza like illness with no significant difference between LM and centesimal groups. The complication/sequel rate was also significantly less in the intervention groups compared to the placebo group.	Moderate
A randomized double blind placebo controlled study including 175 children with frequently recurring upper respiratory tract infections. Of the 170 children evaluable, 86 were randomized	de Lange de Klerk ESM, Blommers J et al (1994). Effects of homoeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections . <i>British Medical Journal</i> , 309:1329-1332.	The mean daily symptom score was 2.61 in the placebo group and 2.21 in the treatment group (difference 0.41; 95% confidence interval -0.02 to 0.83). In both groups the use of antibiotics was greatly reduced compared with that in the year	Non-conclusive

to homeopathic medicines and 84 to placebo.		before entering the trial (from 73 to 33 in the treatment group and from 69 to 43 in the placebo group). The proportion of children in the treatment group having adenoidectomies was lower in the treatment group (16%, 8/50) than in the placebo group (21%, 9/42). The proportion having tonsillectomies was the same in both groups (5%).	
A double-blind randomized parallel group placebo controlled trial in 251 children below the age of 10 years, recruited by post from those previously diagnosed with URTI when attending a casualty department. The children received either placebo or ultramolecular homeopathic medicines in C-30 potency (diluted 10-60) administered twice weekly for 12 weeks. Parents chose the medicine based on simplified constitutional indications.	Steinsbekk A, Bentzen N, Fønnebø V, Lewith G (2005). Self treatment with one of three self selected, ultramolecular homeopathic medicines for the prevention of upper respiratory tract infections in children. A double-blind randomized placebo controlled trial. <i>British Journal of Clinical Pharmacology</i> , 59:447–455.	There was no difference in the predefined primary outcome between the two groups ($P = 0.733$). Median URTI scores over 12 weeks in the homeopathic medicine group were 26.0 (95% confidence interval (CI) 16.3, 43.7) and for placebo 25.0 (95% CI 14.2, 38.4). There was no statistical difference between the two groups in median number of days with URTI symptoms or in the use of conventional medication/care.	Non-conclusive
Open, pragmatic, randomised parallel-group trial with waiting-list group as control, including 169 children below the age of 10 years, recruited by post from children previously diagnosed with URTI. They received either pragmatic homeopathic care from one of five homeopaths for 12 weeks or were assigned to a waiting-list control using self-selected, conventional health care.	Steinsbekk A, Fønnebø V, Lewith G, Bentzen N (2005). Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomized, controlled trial comparing randomized homeopathic care and waiting-list controls. <i>Complementary Therapies in Medicine</i> , 13:231–238.	There was a significant difference in median total symptom score in favour of homeopathic care (24 points) compared to the control group (44 points) ($p = 0.026$). The difference in the median number of days with URTI symptoms was statistically significant with 8 days in the homeopathic group and 13 days in the control group ($p = 0.006$). There was no statistical difference in the use of conventional medication or care between the two groups.	Moderate

Table 3: Anthroposophic medicine to help combat growing antibiotic resistance

Study Design	Publication Details	Main Findings	Strength of Evidence
Observational case series from an Integrative-Medicine unit using anthroposophic medicines within a university teaching hospital.	Geyer U, Diederich K, Kusserow M, Laubersheimer A, Kramer K (2013). Inpatient treatment of community-acquired pneumonias with integrative medicine. <i>Evidence Based Complementary Alternative Medicine</i> , 2013: 578274.	<p>16/18 patients with community-acquired pneumonia could be cured successfully by application of AM medicine only, using AM medicines and external applications like compresses and embrocations.</p> <p>The pneumonia severity index (PSI) was used to estimate the severity of pneumonia. 2/18 patients needed antibiotic therapy in addition. 15/16 patients without antibiotic treatment belonged to risk groups I-III (low and moderate risk) and one patient to risk group V (high risk). Both patients with antibiotic treatment belonged to risk group IV.</p> <p>Thus, it was shown that in specialized units treatment of severe infectious conditions like pneumonia by AM is possible and will lead to a significantly reduced need for antibiotics.</p>	Moderate
GCP-conform prospective observational nonrandomised comparative outcomes study including 21 primary care centres in 4 European countries and the US. 715 patients with acute respiratory and ear infections treated by 27 anthroposophic physicians were compared to 301 patients treated by 16 conventional physicians.	Hamre HJ, Fischer M et al. (2005). Anthroposophic vs. conventional therapy of acute respiratory and ear infections: a prospective outcomes study. <i>Wiener klinische Wochenschrift</i> , 117, 256–268	Improvement within 24 hours occurred in 30.9% (221/715) of patients treated by AM doctors and 16.6% (50/301) of patients treated by conventional doctors. Day 7 complete recovery or major improvement was reported by 77.1% (AM doctors) vs. 66.1% of patients (conventional doctors), respectively. Antibiotics were used in 5,5% of patients in the anthroposophic doctors group compared to 33,6% in the conventional group.	Strong
GCP-conform prospective observational nonrandomised comparative cohort study including 21 primary care centres in 4	Hamre HJ, Fischer M et al. (2007). Use and Safety of Anthroposophic Medications for Acute Respiratory and Ear Infections: A Prospective	The safety analysis of the AM medicines used showed that ADR's were rare (2/715 patients) and mild. In one case, there was sleeplessness at	Strong

European countries and the US.	Cohort Study. <i>Drug Target Insights</i> , 2, 209–219.	night, in the other case local swelling due to subcutaneous injection of an AM remedy. ADR's thus occurred at a significantly lower percentage than with conventional treatment.	
Large multi-centre prospective observational study in AM primary care centres in Germany including 12,081 patients with 19,050 acute upper airway infections including common cold (63,3%) and tonsillitis (12,9%). 73,7% of patients were children.	Jeschke E, Lüke C et al. (2007). Verordnungsverhalten anthroposophisch orientierter Ärzte bei akuten Infektionen der oberen Atemwege [Prescribing practices in the treatment of upper respiratory tract infections in anthroposophic medicine]. <i>Forschende Komplementärmedizin</i> , 14, 207-215.	In 63%, treatment was purely anthroposophic. In only 6,3% of cases antibiotics were used. Within the group of the 8,900 children showing 14,945 respiratory tract infections, antibiotic prescriptions occurred in only 5,8%.	Strong

Table 4: Homeopathy in animals to help combat growing antibiotic resistance (randomised controlled trials only)

Study Design	Publication Details	Main Findings	Strength of Evidence
Randomised placebo-controlled trial on 104 cows with subclinical mastitis. Six different homeopathic medicines were compared with placebo. Intra-mammary application of 1 ml of the homeopathic medicine or isotonic saline solution as placebo.	Andersson R, Morcillo LL, Sommer H (1997). Untersuchungen über den Einsatz von homöopathischen Arzneimitteln bei der Behandlung und Prophylaxe subklinischer Mastitiden von Milchkühen [Treatment and prophylaxis of subclinical mastitis with homeopathic drugs]. <i>Tierärztliche Umschau</i> , 52: 407–412.	None of the homeopathic drugs showed a prophylactic effect. Four of the six homeopathic medicines did not show a therapeutic effect. Only Lachesis D8 and Silicea D6 in mastitis caused by <i>Staphylococcus aureus</i> had a therapeutic effect, i.e. a significant decrease of cells in the milk and LDH (lactate dehydrogenase) blood level.	Preliminary
Randomized placebo-controlled trial including 26 cows, divided in 2 groups, pairing on clinical and subclinical mastitis status, milk production and number of lactations.	Searcy R, Reyes O, Guajardo G (1995). Control of subclinical bovine mastitis. Utilization of a homeopathic combination. <i>British Homeopathic Journal</i> , 84: 67-70.	The proportion of affected quarters (a cow's udder is divided up into four quarters) according to the California Mastitis Test was 32% in the treated group, and 68% in the control group. The odds ratio of the difference shows that animals receiving placebo presented 4.5 (1.78-11.73) times more subclinical mastitis than those under homeopathic treatment ($p < 0.05$). Average milk production in the treated group did not differ significantly from that of the control group.	Preliminary
Ninety-six mastitic quarters (non-fibrosed 67 and fibrosed 29) were treated with a homeopathic combination medicine Healwell VT-6 (consisting of <i>Phytolacca</i> , <i>Calcarea fluoric.</i> , <i>Silica</i> , <i>Belladonna</i> , <i>Bryonia</i> , <i>Arnica</i> , <i>Conium</i> and <i>Ipecacuanha</i>). Another 96 quarters with acute mastitis (non-fibrosed) treated with different antibiotics were included in the study.	Varshney JP, Naresh R (2005). Comparative efficacy of homeopathic and allopathic systems of medicine in the management of clinical mastitis of Indian dairy cows. <i>Homeopathy</i> , 94: 81-85.	The overall effectiveness of homeopathic combination medicine in the treatment of acute non-fibrosed mastitis was 86.6% with a mean recovery period of 7.7 days (range 3–28), and total cost of therapy as Indian Rupees 21.4 (€0.39, US\$0.47). The corresponding cure rate for the antibiotic group was 59.2% with a mean recovery period of 4.5 days (range 2–15) and an average treatment cost of Rs.149.20 (€2.69, US\$3.28). The authors conclude that the homeopathic combination medicine Healwell VT-6 was effective and economical in the management of mastitis in	Preliminary

Randomized controlled trial comparing the effectiveness of homeopathic treatment with antibiotic and placebo treatments in cases of mild and moderate bovine clinical mastitis. A total of 136 lactating dairy cows with 147 affected quarters from four herds in Germany were randomly allocated to three treatment groups. The cows were examined on days 0, 1, 2 and on days 7, 14, 28 and 56 post initial infection to assess clinical signs. Simultaneously, with the exception of days 1 and 2, quarter milk samples for laboratory examinations (bacteriology, somatic cell count) were collected to assess bacteriological and cytological cure rates.	Werner C, Sobiraj A, Sundrum A (2010). Efficacy of homeopathic and antibiotic treatment strategies in cases of mild and moderate bovine clinical mastitis. <i>Journal of Dairy Research</i> , 77: 460-467.	lactating dairy cows. On days 28 and 56, treatment strategies did not differ significantly with respect to the clinical outcomes and the total cure rate in cases of bacteriological negative mastitis (n=56). In cases of pathogen-positive mastitis (n=91), the cure rate after 4 and 8 weeks was similar between the two treatment strategies, homeopathy and antibiotic treatment, but the difference between the homeopathic and the placebo treatment at day 56 was significant (P<0.05). The results indicate a therapeutic effect of homeopathic treatment in cases of mild and moderate clinical mastitis.	Preliminary
A field trial with 102 dairy cows from 13 Swiss organic dairy farms was conducted. Cows were randomly assigned to one of three groups within a herd. In the Internal Teat Sealer group (ITS; 36 cows) cows were treated with the commercial ORBESEAL (Pfizer) in all four quarters immediately after the last milking. In the homeopathy group (HDT; 32 cows) the cows were treated per-orally by a herd-specific homeopathic formulation consisting of two remedies in 1:10(6) dilution over 5 days before and after drying-off. The untreated group received no therapy (U; 34 cows).	Klocke P, Ivemeyer S, Butler G, Maeschli A, Heil F (2010). A randomized controlled trial to compare the use of homeopathy and internal Teat Sealers for the prevention of mastitis in organically farmed dairy cows during the dry period and 100 days post-calving. <i>Homeopathy</i> , 99: 90-98.	For ITS, HDT and U the clinical mastitis incidence rates for the first 100 days post-calving were 11%, 9% and 3%, respectively, and the proportion of normally secreting quarters was (quarter somatic cell count (SCC) [QSCC]<100,000/ml) 70%, 68%, and 65%, respectively. Power analysis indicates that a proportion of 75% would support the rejection of null hypothesis in the HDT, and 74% in the ITS group against untreated control. Quarters of cows with SCC<200,000/ml at drying-off showed significantly higher normal secretion in HDT group (odds ratio [OR] 9.69) compared to untreated control, whereas Teat Sealing lead to an OR of 3.09 (not significant, post hoc power 31.3%). Under the studied conditions herd-specific homeopathic dry cow therapy was effective in increasing the number of animals with normal milk secretion after subsequent parturition, compared to untreated control. It may be an effective alternative to Teat Sealing, particularly in animals	Preliminary

Randomized controlled trial in which newborn piglets were divided into 4 groups (n= 11 or 12): 1) control, subjected to antibiotic treatment against diarrhea; 2) homeopathic Phosphorus 30CH according to the symptoms collected; 3) homeopathically prepared Escherichia coli 30CH prepared from the locally obtained bacteria; 4) a combination of Phosphorus 30CH and Escherichia coli 30CH.	Coelho C de P, Soto FRM et al. (2009). Evaluation of preventive homeopathic treatment against colibacillosis in swine production. <i>International Journal of High Dilution Research</i> , 8: 183-190.	with relatively low SCCs. Group 2, 3 and 4 presented a significant reduction of diarrhea compared to the control group (p=0.02); the group treated with Phosphorus 30CH + Escherichia coli 30CH presented the highest weight gain which was significant by comparison to all other groups (p=0.001).	Preliminary
Randomised, observer blind, placebo-controlled clinical trial. On a commercial pig farm 52 sows of different parities, in their last month of gestation, were treated twice a week with either the homeopathically prepared Escherichia Coli 30K or placebo. The 525 piglets born from these sows were scored for occurrence and duration of diarrhoea.	Camerlink I, Ellinger L et al (2010). Homeopathy as replacement to antibiotics in the case of Escherichia coli diarrhoea in neonatal piglets. <i>Homeopathy</i> , 99: 57-62.	Piglets of the homeopathic treated group had significantly less E. coli diarrhoea than piglets in the placebo group (p< 0.0001). Especially piglets from first parity sows gave a good response to treatment with Escherichia Coli 30K. The diarrhoea seemed to be less severe in the homeopathically treated litters, there was less transmission and duration appeared shorter.	Strong

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