Antimicrobial resistance: Also think like patients – ‘outside the box’
Supplement to the RAND questionnaire by ECH, December 2015

The RAND survey about antimicrobial resistance (AMR) enquires about the opinion of and the effectiveness of the EU action plan on AMR. The users and professionals involved in complementary/alternative medicine (CAM), including homeopathy, had no part in this action plan. Therefore, our response to the RAND survey requires extensive explanation. In our opinion homeopathy is, and has been for a long time already, a relevant solution for AMR, highly valued by patients, but neglected by governments.

At the Commission’s Joint Conference on AMR of December 2013 experts agreed that key elements in fighting AMR are taking a holistic approach, ensuring that all key players carry out their responsibilities, and global cooperation. Reading the ‘Progress report on the Action plan against the rising threats from Antimicrobial Resistance’, however, we notice that the Commission does not think ‘outside the box’, while millions of patients use complementary and alternative medicine (CAM), also for their problems with AMR. In that respect the action plan is not holistic. We have known about the threat of antimicrobial resistance (AMR) for decades now, in this short history of 70 years of antibiotics. Still, solutions like new antibiotics and reduction of improper use of antibiotics are so far not very successful. Of course, such efforts should continue, but the immense threat of AMR and the slow progress of the evident solutions are reasons to think ‘outside the box’ too. This may meet considerable practical and emotional hurdles, but there is a compass available in the form of practical experience in millions of patients and tens of thousands of doctors.

Millions of patients use CAM for complaints that do not respond well to conventional medicine, like recurrent infections. In Europe about 145,000 doctors follow this need and practice CAM. The large majority of these doctors practice acupuncture and homeopathy. There are 45,000 doctors practicing homeopathy in Europe and Respiratory Tract Infections (RTI) is one of the most frequently treated conditions in homeopathy. RTI is also one of the most frequent reasons for prescribing antibiotics. Other recurrent infections – not responding to conventional medicine - are also a frequent reason for consulting a homeopathic practitioner.

Homeopathy is indeed ‘outside the box’ of conventional medicine because we do not yet understand how it works. Some say it cannot work. That is incorrect: it cannot work like conventional medicines via a medicine-receptor model, because homeopathic medicines are stepwise diluted (also applying succussion) to a degree that makes this mechanism of action highly improbable. Another mechanism of action though may be possible. Such an unknown mechanism of action may lead to new opportunities. In the experience of doctors and patients using homeopathy it indeed works differently in several respects:
• In a chronic condition the effect builds up slowly over weeks to months.
• A homeopathic medicine cannot be prescribed solely by medical condition; it has to fit the patient, not only the specific complaint.
• The effect of a homeopathic medicine extends to several complaints in the same patient.
• There may be an initial aggravation of complaints, but serious adverse effects are rare.
• The same homeopathic medicines have been used for infections all over the world for two centuries; no resistance has developed as yet.

Observational research confirms that homeopathy is often applied after conventional medicines have failed for several years and in conditions where antibiotics are used. Despite the chronicity of complaints there is considerable satisfaction and long-term benefit. Observational studies and randomised controlled trials confirm that the method is safe despite its effectiveness.

The critic on homeopathy refers mainly to implausibility, has hardly changed over two centuries and ignores scientific developments in the fields of thermodynamics, biology and information science which occurred in the second half of the twentieth century. The fact that homeopathy is often applied after conventional medicine failed and the differences mentioned above indicate that homeopathy is complementary to conventional medicine. It does not seem to fit in the conventional paradigm. The present infrastructure for research is strongly connected to the conventional paradigm, but AMR is a good reason to question the completeness of this paradigm.

The Progress report on the Action plan against the rising threats from Antimicrobial Resistance (2015) states: “The up-to-date and evidence-based medicinal product information should be one of the key elements supporting an appropriate use of antimicrobials”. In this answer to the RAND consultation we want to present the evidence for homeopathy and our suggestions to apply homeopathy to fight AMR.

Medical doctors with additional qualification in homeopathy use less antibiotics (Grimaldi-Bensouda et al., 2014). There is also evidence that homeopathy reduces the use of antibiotics in farming (Camerlink, Ellinger, Bakker, & Lantinga, 2010). It is stated that the effect of homeopathy is solely due to context effects, because of implausibility, but there is evidence from randomised controlled trials (RCTs) that homeopathy works better than placebo (context). This evidence is contested, but so is much evidence in conventional medicine. At first, several independent scientists acknowledged that proof for homeopathy by RCT is not inferior to proof for conventional medicine (Kleijnen, Knipschild, & ter Riet, 1991)(Linde et al., 1997)(Vandenbroucke, 1998). There is one review comparing homeopathy trials with conventional trials that does not disprove this (Shang et al., 2005). Later reviews concluded negatively; this was based on post-hoc selection of trials, see appendix. Hitherto there is no evaluation of all combined evidence (RCT, fundamental research, observational research). Only the RCT evidence is evaluated repeatedly and subjective circular reasoning is apparent: “It does not work because it cannot work”. Nobody can tell what and how much evidence is needed for ‘recognition’, resulting in acceptance by the majority of doctors and the usual infrastructure for research.

CAM and homeopathy are not included in the ARNA and ARPEC projects. It would be a waste to ignore the vast amount of information (practical experience, clinical and fundamental research) about treating infections with homeopathy that already lies on the shelf.
The reproducibility of homeopathy offers an interesting opportunity to explore other ways of thinking. Recent developments in genetics result in personalised medicine: the therapy should not only fit the medical condition, but also the genotype. It is acknowledged that all personal characteristics and symptoms can influence outcome of disease and therapy. Homeopathy has a long tradition exploring the relationship between phenotype and medicine: the homeopathic medicine should fit the personal characteristics and symptoms, not only the complaint.

Homeopathy can be applied to reduce the use of antibiotics, but also in treating the patients with drug-resistant bacteria (causing about 25,000 human deaths annually). Even in severe sepsis additional value of homeopathy has been proven (Frass et al., 2005). For the patients with drug-resistant bacteria there is no solution in the near future, except CAM solutions like homeopathy.

Applying homeopathy to reduce the use of antibiotics opens new perspectives, but also introduces new challenges because of the ‘outside the box’ elements in the method. The most important challenge is to meet the individualised character of the prescription of a homeopathic medicine. This should be expressed in research and in the skill of prescribers. Developing methods for research in individualised medicine is necessary for the recently developed need for individualised (personalised) conventional medicine. Another challenge is to spread the use of homeopathy.

In daily practice homeopathy may offer the following solutions for reducing AMR:

1. Medical doctors with additional qualification in homeopathy often treat patients with recurrent infections to reduce the number of episodes.
2. Involve doctors with additional qualification in homeopathy in the treatment of infections with drug-resistant bacteria.
3. Assist doctors in applying homeopathy for delayed prescription of antibiotics by computer algorithms to make a personalised homeopathic prescription.
4. Develop and evaluate the applicability of homeopathic medicinal products in daily practice to prevent non-prudent use of antibiotics and to assist delayed prescribing of antibiotics.
5. Promote homeopathic medicinal products as a safe alternative for self-medication to prevent non-prudent use of antimicrobial agents in self-medication.
6. Apply homeopathy in farming by training farmers in using homeopathy.

On behalf of ECH,

Dr. Thomas Peinbauer, President
Dr. Lex Rutten, scientific committee

About ECH:

The European Committee for Homeopathy (ECH) represents all medical doctors with an additional qualification in homeopathy, organized in 40 associations in 25 European countries.
The aim of the ECH is to achieve full integration of homeopathy within the European healthcare system, which will meet the growing demand among European citizens for homeopathic care within a safe medical context.

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Appendix 1: Plausibility

Plausibility rightfully has an important role in medicine; if we understand how the organism works we can better predict illness and cure. We will not send a human being to Mars before we understand all processes that could influence this trip. But many ill people cannot wait until conventional medicine has understood their illness, let alone found a cure for it. In AMR plausibility may play a negative role: patients with an infection go to the doctor to be cured and antibiotics are the logical expectation.

Patients with complaints that cannot be cured by conventional medicine have to consider ‘outside the box’ methods. They talk about their illness with others and they get all sorts of well-meant advice, many times irrelevant, but sometimes helpful. This is the way many patients arrive at complementary and alternative medicine (CAM); only a few of the hundreds of described CAM methods survive over centuries and worldwide, like acupuncture, anthroposophical medicine, herbal medicine and homeopathy. The reason that they survive is probably their reproducibility.

Reproducibility is one of the other pillars of evidence based medicine, besides plausibility. In homeopathy all doctors use the same descriptions of their medicine (materia medica) and the same index to this knowledge base (repertory). Many conventional doctors are made aware of homeopathy by their patients, who report their experience with this method, like mothers that report that their child has been cured of recurrent otitis media by homeopathy after several interventions with antibiotics and surgery failed.

When a doctor follows his patient and prescribes homeopathic Chamomilla for that child with otitis media he will notice that this medicine works only in a limited number of cases. Studying and following the literature about this medicine he will experience more success in children with otitis media that are quiet when carried by the mother, but start to scream loudly when laid down for examination. He will also learn that the homeopathic medicine Belladonna is a better option if the child with otitis media grinds his teeth during the night. The more the doctor knows about homeopathic medicines, the more children with otitis media he can help. These rules of personalised medicine existed long before antibiotics came up and are still valid in this time of AMR.

Following his patients treated with homeopathy the doctor will see a different course of cure: the child treated with Chamomilla will become less irritable (also when not ill) and the child treated with Belladonna will grind his teeth less and have less night sweats. If the child treated with Belladonna develops headaches as he gets older, Belladonna will also work for these headaches.

Doctors learn from experience: how to diagnose pneumonia and appendicitis, about adverse effects of medicines, etcetera. The same way they learn that homeopathy works differently, and that is plausible: it cannot work like conventional medicines. And it is also plausible why homeopathy can work after antibiotics failed, precisely because it does not work like antibiotics. Like Einstein said: “We can’t solve problems by using the same kind of thinking we used when we created them”.
**Fundamental research in homeopathy**
The HomBRex Database on Fundamental Research in Homeopathy ([www.carstensstiftung.de/hombrex](http://www.carstensstiftung.de/hombrex)) includes details of more than 2100 basic research experiments in homeopathy. A meta-analysis evaluated 67 in-vitro biological experiments in 75 research publications and found high-potency effects were reported in nearly 75% of all replicated studies; however, no positive result was stable enough to be reproduced by all investigators (Witt et al. 2007). The infrastructure and funding of fundamental research in homeopathy is still poor. Below we describe the most important programs so far, but we cannot yet draw firm conclusions.

The most repeated series of in-vitro experiments in homeopathy is the model of the allergic response to antibody using the human basophil degranulation test. There are now 17 publications on inhibition of basophil activation by high dilutions of histamine, spanning over 25 years and including multi-centre and independent replications. There has been steady refinement of the method, including improved markers and the introduction of flow cytometry (Sainte Laudy and Belon 2009; Endler et al. 2010). There is a consistent peak at 16C (10^{-32}M), well into the ultramolecular range. These experiments have also yielded insights into possible mechanisms of action, for instance the response is highly specific to histamine; it is not induced by the structural analogue histidine, it appears to be mediated by H2 receptor-mediated inhibition of basophil activation and it is partly blocked by the H2 receptor antagonists ranitidine and cimetidine (Belon et al. 2004; Chirumbolo et al. 2009).

Another cellular system that has been the subject of repeated experiments over a long period of time is the effect of ultramolecular dilutions of aspirin on blood clotting (Eizayaga 2007). Experiments with ‘knock-out’ mice suggests that the effect is due to inhibition of COX-2 mediated PGI2 production in vascular endothelium (Aguejouf et al. 2008).

The most repeated whole animal model is the effect of thyroxine on the rate of metamorphosis of frogs. This effect has been reproduced in multi-centre experiments (Welles et al. 2007) and by independent workers with different species of frog and with different outcome measures (Guedes et al. 2004).

**Possible mechanisms of action**
Fundamental research indicates that there is a difference between just water and a homeopathically prepared ultra-high (beyond the Avogadro-Loschmidt number) dilutions, but there is not yet a satisfactory explanation. The following concepts for a theoretical basis of homeopathy are being explored:

**Hormesis** has a longstanding but disputed link to homeopathy (Calabrese, 2015). The principle of hormesis means that a substance can be toxic in high doses, but enhance the recovery of the metabolism in low doses: a biphasic dose-response curve. This is similar to homeopathic theory, but hormesis is problematic as an explanation for ultra-high dilutions above the Avogadro-Loschmidt number. Hueppe reported the biphasic dose-response with bacteria already in the end of the nineteenth century (Hueppe, 1896). Hormesis has been identified with homeopathy for a long time and was therefore repressed by the scientific community on ideological instead of scientific grounds. The paradigm of a linear dose-response relationship persisted until it became problematic in the regulation of carcinogens: a low dose carcinogen is still a carcinogen in a linear model. In the last decades the hormesis model is gaining rapid recognition. But we must still be careful not to identify
hormesis with homeopathy: there are similarities with (low potency) homeopathy, but the response to a homeopathic medicine is more complex than hormesis can explain (Oberbaum, Frass, & Gropp, 2015).

**Nanobubbles.** The succussion process involved in preparing a homeopathic solution may well cause the formation of nanobubbles (Demangeat, 2015). It is still unclear if nanobubbles can fully explain how homeopathy works, especially in ultra-high dilutions.

**Microarrays.** Recently investigations on DNA-microarrays suggest that ultrahigh dilutions can have an effect on gene expression (Dei & Bernardini, 2015)(Khuda-Bukhsh et al., 2011). Gene expression might explain the complex and gradually building up effects of homeopathic medicines observed in daily practice.

**Allostery and allostasis.** While many common drugs act through orthostatic chemical interactions aimed at blocking undesired activities of enzymes or receptors, allosteric interactions are associated with dynamic conformational changes and functional transitions in target proteins, which enhance or inhibit specific cellular actions in normal or disease states (Bellavite et al., 2015). The concept of allostery and the way it controls physiological activities can be broadened to include diluted/dynamized compounds, and may constitute a working hypothesis for the study of molecular mechanisms underlying the inversion of drug effects.

**Quantum inference** is another model that is explored because it could explain an effect without physical-chemical reactions in homeopathy (Conte, Licata, & Alelú-paz, 2015).
Appendix 2: Safety

RCT Evidence for homeopathy is not inferior to evidence in conventional medicine, see later. A different mechanism of action may also explain that the apparent safety of homeopathy is not due to inefficacy.

Safety of homeopathy is repeatedly confirmed. A systematic review on adverse effects of homeopathic medicines published in English from 1970 to 1995 was performed using electronic databases, hand searching, searching reference lists, reviewing the bibliography of trials, and other relevant articles, contacting homeopathic pharmaceutical companies and drug regulatory agencies in UK and USA (Dantas & Rampes, 2000). The mean incidence of adverse effects of homeopathic medicines was greater than placebo in controlled clinical trials (9.4/6.1) but effects were minor, transient and comparable.

An Italian observational study recorded 9 adverse effects in 335 patients (2.68%) (Rossi, 2014).

A German observational study recorded 7% adverse effects in 852 patients (Güthlin, Lange, & Walach, 2004).

In five European countries and Brazil 6% adverse effects were recorded in 444 patients (van Wassenhoven et al, 2014).

There are no clear recordings of serious adverse effects. Posadzki et al performed an extensive search in the literature and hand-searched their own archive (Posadzki, Alotaibi, & Ernst, 2012). They stated that sometimes serious adverse effects might occur, but the paper was heavily criticised. Tournier et al checked the original papers and found numerous errors (Tournier et al. 2013). They found misreporting, intermingling of adverse effects and clinical negligence and of homeopathy and other forms of CAM, like phytotherapy. One report mentioning 4 serious aggravations of atopic dermatitis appeared to be an incorrect translation from Danish where ‘alternative treatment’ is translated as ‘homeopathy’. Another case reported ‘heart disease and bladder cancer’ as adverse effects of homeopathy, but this illness appeared 7 years after homeopathic treatment. Another case was interpreted by Posadzky et al as ‘certain’ adverse effect, while the authors of the original paper stated that homeopathy was certainly not the cause of the adverse effect. Posadzky et al included cases regarding phytotherapy/low potencies (more than 10 cases) - which should not be confused with professional homeopathy - and clinical negligence (16 cases). In 9 out of 41 cited reports the medicines were not specified. In 4 reports patients died. In these 4 fatal cases one expects precise descriptions, but in none of these cases the medicine was specified, nor the use of any instrument to ascertain a causal relationship, like the Naranjo algorithm. In two of the fatal cases there was clinical negligence. In one other fatal case there was Arsenic poisoning by an unspecified medicine (unlikely to be caused by a real homeopathic dilution), but by the authors interpreted as “likely caused by an unspecified homeopathic medicine”. In the fourth fatal case the patient also used Glimepiride, a more likely cause of death than the homeopathic medicine. One cited report mentioned 1070 “mostly mild symptoms (no details provided)”. Such reactions are most likely initial aggravations, well known in homeopathy, but not known to have long-lasting effects. The total number of patients with adverse effects found by Posadzki et al was 1159. If we subtract mild symptoms, misreporting, phytotherapy/low potencies, negligence and unspecified medicines, there remain some 40 cases that deserve better analysis. This is the outcome of an extensive search in all languages concerning reports from 1978 until 2011. There is no substantial evidence for serious adverse effects despite
billions of prescriptions of homeopathic medicines in this period of more than 30 years. The only valid concern is about allergic reactions to low potencies (dilutions) of homeopathic medicines. Homeopathy is safe if practiced by doctors qualified in medicine and in homeopathy: they know their limitations and they don’t prescribe low potencies that can cause allergic reactions.
Appendix 3: Observational research

Observational research confirms the firm position of homeopathic medicine in the society. The CORE-Hom database for clinical research (http://www.carstens-stiftung.de/core-hom/index.php) contains over 270 observational studies. From this database we select the studies that inform about the societal position, see Table 1. One additional study concerning dairy farming is added at the end.

Table 1: Summary of some observational studies, indicating some reasons for consultation and results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Data</th>
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<tbody>
<tr>
<td>Duration of complaints</td>
<td>Witt 2005 79% duration &gt; 8 years</td>
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<td></td>
<td>v.Wassenhoven 2007 53.1% &gt;3 years</td>
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<td>After conventional treatment failed</td>
<td>v Wassenhoven 2007 77%</td>
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<td>Güthlin 2004 65%</td>
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<td>Rossi 2009 70%</td>
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<td>‘antibiotics-conditions’</td>
<td>Clover 2000 22% respiratory and ENT complaints</td>
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<td></td>
<td>Güthlin 2004 16% respiratory complaints</td>
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<td>Mathie 2006 25% infectious conditions</td>
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<td></td>
<td>v.Wassenhoven 2007 8.4% respiratory complaints</td>
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<td></td>
<td>v. Wassenhoven 2004 21.6% respiratory complaints</td>
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<td></td>
<td>Rossi 2009 32% respiratory complaints</td>
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<td></td>
<td>Danno 2014 25.3% self-medication with homeopathy in RTI/ENT</td>
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<tr>
<td>Antibiotics reduction</td>
<td>Grimaldi 2014 OR 0.43 (95% CI 0.27-0.68)</td>
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<td></td>
<td>v.Wassenhoven 2004 79.5% compared to conventional GPs</td>
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<tr>
<td>Satisfaction</td>
<td>Rossi 2009 74% improved</td>
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<td></td>
<td>Clover 2000 77% improved in respiratory/ENT infections</td>
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<td>Güthlin 2004 77% improved</td>
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<td></td>
<td>Mathie 2006 75.9% improved</td>
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<tr>
<td>Long-term benefit</td>
<td>Güthlin 2004 Improvement lasted &gt;30 months. Work days lost decreased gradually during 5 years.</td>
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<td></td>
<td>Witt 2005 Disease severity decreased &gt; 24 months (p&lt;0.001)</td>
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<tr>
<td></td>
<td>Rossi 2009 85% improvement &gt; 24 months</td>
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1. Clover 2000, UK: Survey in Tunbridge Wells Homeopathic Hospital (UK) in 1997 comprised 1372 questionnaires (Clover, 2000). Respiratory and ear-nose-throat complaints were together the most frequent conditions (22%, 280 patients). For 39 patients with chronic sinusitis, Recurrent upper respiratory tract infections and glue ears/otitis media results were recorded; in 30 of them (77%) complaints were improved.

2. Mathie 2006, UK: Recorded clinical conditions and outcome in 14 practices in the UK over 6 months (R. T. Mathie & Robinson, 2006). The 24 most recorded (out of 416) different conditions accounted for 851 cases; 209 (25%) of these cases had conditions often associated with antibiotics (cough, catarrh, URTI, otitis media, cystitis, sinusitis). In comparison: the most treated condition was depression with 88 cases.
3. Güthlin 2004, Germany: Prospective assessment of effect of homeopathy in General Practice settings on 900 patients, satisfaction with treatment and work absenteeism (Güthlin et al., 2004). Middle to large sized effect on wellbeing and a long-lasting decline of work absenteeism in comparison with comparable data of an insurance company, see Figure 1.

Figure 1: Work days lost before and after homeopathic treatment based on health insurance company data. The flat line below is the reference population.

![Figure 1: Work days lost before and after homeopathic treatment based on health insurance company data. The flat line below is the reference population.](image)

4. Witt 2005, Germany/Switzerland: Prospective, multicentre cohort study with 103 primary care practices with additional specialisation in homeopathy (Witt, Lüdtke, Baur, & Willich, 2005). RESULTS: A total of 3,981 patients were studied including 2,851 adults and 1,130. Ninety-seven percent of all diagnoses were chronic with an average duration of 8.8 +/- 8 years. Disease severity decreased significantly (p < 0.001) between baseline and 24 months (adults from 6.2 +/- 1.7 to 3.0 +/- 2.2; children from 6.1 +/- 1.8 to 2.2 +/- 1.9). For adults and young children, major improvements were observed for quality of life, whereas no changes were seen in adolescents.

4. v. Wassenhoven 2004, Belgium: Observational study in 80 Belgian general practices evaluating 782 patients (Van Wassenhoven & Ives, 2004). Respiratory problems constituted 21.6% of all complaints. GPs with homeopathic training used 20.5% of the amount of antibiotics compared to conventional GPs.

5. v. Wassenhoven 2014, six European countries (Belgium, France, Germany, Italy, Portugal and Spain) and Brazil. Survey evaluated reasons for consultation and satisfaction of 919 adults receiving homeopathic treatment (van Wassenhoven M et al, 2014). Results: 77% patients had initially used
conventional treatments. Satisfaction of patients with the medical homeopathic consultation is high. The difference between the final QoL scores after six months and the baseline are positive. Reported differences between baseline and final index range from 3.87 to 10.41 depending on diagnosis. Taking 7% as a reference value for ‘minimal clinically significant difference’, this is reached for 3 of 8 conditions. 6% of the patients experienced side-effects which they attributed to homeopathic treatment.

6. Rossi 2009, Italy: Response to homeopathic treatment in a public homeopathic clinic (LUCA) of all patients attending between September 1998 until December 2005 (Rossi, Endrizzi, Panozzo, Bianchi, & Da Frè, 2009). Longitudinal observational study. Results: Overall 74% of patients reported at least moderate improvement. Outcomes were better with longer treatment duration and younger age of patients. Respiratory, followed by dermatological and gastrointestinal pathologies responded best, psychological problems relatively poorly.

7. Grimaldi 2014, France: The EPI3 survey was a nationwide population-based study of a representative sample of 825 GPs and their patients in France (2007-2008) (Grimaldi-Bensouda et al., 2014). Objectives: To describe and compare antibiotic and antipyretic/anti-inflammatory drugs use, URTI symptoms’ resolution and occurrence of potentially-associated infections in patients seeking care from general practitioners (GPs) who exclusively prescribe conventional medications (GP-CM), regularly prescribe homeopathy within a mixed practice (GP-Mx), or are certified homeopathic GPs (GP-Ho). RESULTS: 518 adults and children with URTI (79.3% rhinopharyngitis) were included. As opposed to GP-CM patients, patients in the GP-Ho 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 evolution in related symptoms (OR = 1.16, 95% CI: 0.64-2.10). An excess of potentially-associated infections (OR = 1.70, 95% CI: 0.90-3.20) was observed in the GP-Ho group (not statistically significant). No difference was found between GP-CM and GP-Mx patients.

8. Danno 2014, France: Socio-demographic and clinical characteristics of patients who seek direct therapeutic advice from a pharmacist for influenza-like illness (ILI) or ear, nose and throat (ENT) disorders, the types of medicines dispensed and patient satisfaction with the advice received (Danno et al., 2014). METHODS: prospective, observational study was carried out on a random sample of French pharmacies between November 2010 and March 2011. Patients (>=12-years) with early symptoms of ILI or ENT disorders (<36 h duration) who received treatment were included. RESULTS: 573 patients (mean age: 42.5 ± 16.2 years; 61.9% female) were recruited by 133 pharmacies. Two-thirds of patients (63.2%) visited the pharmacy early (<24 h) after symptom onset. The most common symptoms were runny nose (56.4%), sore throat (54.6%) and cough (49.0%). Patients were given 2.6 ± 1.2 medications; 98.4% of patients received allopathic (usually paracetamol, 33.5%) and 25.3% homeopathic (Oscillococcinum, 56.6%) treatment, usually combined with allopathy. Compliance was good and 77.2% of patients continued treatment for 3 days. Most symptoms improved significantly after 3 days and quality of life was enhanced. 85.9% of patients were satisfied with the advice received.

9. Orjales 2015, Spain: Survey about homeopathy in dairy farming in Spain (Orjales et al., 2015). Fifty-six Spanish organic dairy farmers were interviewed to obtain what we believe to be the first data on the use of homeopathy in organic dairy cattle in Spain. Only 32% of farms use some sort of
alternative therapy (16.1% homeopathy, 10.7% phytotherapy and 5.3% using both therapies) and a clear geographical pattern showing a higher use towards the East (similar to that in the human population) was observed. The main motivation to use homeopathy was the need to reduce chemical substances promoted by organic regulations, and the treatment of clinical mastitis being the principal reason. The number of total treatments was lower in farms using homeopathy compared with those applying allopathic therapies (0.13 and 0.54 treatments/cow/year respectively) and although the bulk SCC was significantly higher (p < 0.001) in these farms (161,826 and 111,218 cel/ml, respectively) it did not have any negative economical penalty for the farmer and milk quality was not affected complying with the required standards; on the contrary homeopathic therapies seems to be an alternative for reducing antibiotic treatments, allowing farmers to meet the organic farming principles.
Appendix 4: Reviews and meta-analyses of homeopathy

RCT in human homeopathy
To the surprise of many, three independent systematic reviews and meta-analyses of homeopathy published in leading medical journals between 1991 and 2000 reached essentially positive conclusions (Kleijnen et al. 1991) (Linde et al. 1997) (Cucherat et al. 2000). More recent reports concluded that there is no proof of its effectiveness (Shang et al 2005)(De Gendt et al, 2011)(House of Commons, 2010) (Optum, 2014). This shift in conclusions is not accounted for by the impact of more recently published RCTs. New systematic reviews of homeopathy addressing different modalities of homeopathy (like individualised and not-individualised homeopathy) are in progress (R. Mathie, Legg, & Clausen, 2014b).

The first systematic review of homeopathy concluded: “Based on this evidence we would readily accept that homeopathy can be efficacious, if only the mechanism of action were more plausible” (Kleijnen et al. 1991). In 1997 Linde et al published a new independent meta-analysis, concluding that the results were not compatible with the hypothesis that the clinical effects of homeopathy are merely due to placebo (Linde et al. 1997). Vandenbroucke challenged the medical community to compare the funnel plot of homeopathy trials in this analysis with a similar plot of conventional trials (Vandenbroucke 1998). Sterne et al postulated quality bias as an explanation for a difference in efficacy despite similar forest plots (Sterne, Egger, & Smith, 2001). The review of existing reviews by the Australian National Health and Medical Research Council (NHMRC) concluded (Optum 2014): “There is a paucity of good-quality studies of sufficient size that examine the effectiveness of homeopathy as a treatment for any clinical condition in humans. The available evidence is not compelling and fails to demonstrate that homeopathy is an effective treatment for any of the reported clinical conditions in humans”. But Shang et al (2005) concluded that the quality of homeopathy trials was better than of comparable conventional trials: 21 out of 110 (19%) good quality homeopathy trials versus 9 out of 110 (8%) good quality conventional trials, see below. Shang et al found also: “... for the eight trials of homeopathic remedies in acute infections of the upper respiratory tract that were included in our sample, the pooled effect indicated a substantial beneficial effect (odds ratio 0.36, [95% CI 0.26-0.50]) and there was neither convincing evidence of funnel-plot asymmetry nor evidence that the effect differed between the trials classified as of higher reported quality and the remaining trials”. From recent meta-analysis data, Mathie et al concluded: “Medicines prescribed in individualised homeopathy may have small, specific treatment effects” (R. Mathie, Legg, & Clausen, 2014a).

There seem to be opposite opinions about the same proof for homeopathy: ‘not inferior to conventional medicine’ and ‘no proof for any clinical condition’. However, opinions about proof for conventional medicine can also diverge. Therefore we concentrate on the one single systematic review that compared homeopathy and conventional medicine, the review by Shang et al. The funnel plots of homeopathy and conventional medicine showed no significant differences (see Figure 2). For both plots there was a clear majority of trials suggesting an effect of verum over placebo and the proportions of positive results were similar. The hypothesis of this review was that positive results were due to quality bias, especially in smaller trials, leading to increased asymmetry of the plot. This hypothesis was falsified: the quality of homeopathy trials was, in fact, superior to that of
matched trials of conventional medicine: 19% trials of homeopathy compared to 8% of conventional medicine were of high quality.

The divergence of interpretation can be visualised from the plots of the results of RCTs for homeopathy and conventional medicine, which formed the basis of the negative Shang meta-analysis (Shang et al, 2005). As figure 2 shows, the plots for homeopathy and conventional medicine are very similar; this is compatible with the conclusion of a previous systematic review that the evidence for homeopathy is not inferior to that for conventional medicine (Kleijnen et al. 1991; Vandenbroucke. 1998). The hypothesis that this was due to quality bias (i.e. that the evidence for homeopathy is positively skewed by low quality positive RCTs) has been disproved (see above).

Apart from quality there are other aspects invisible in the funnel plot, like publication bias. The conventional trials in this comparison were all published (L. Rutten, Mathie, Fisher, Goossens, & van Wassenhoven, 2013).

In former reviews (included in the Shang review) much effort was made to retrieve unpublished trials and because of this there are 16 unpublished trials in the homeopathy set. The comparison of homeopathy and conventional medicine is biased by publication bias in favour of conventional medicine. There was also selection bias in this comparison: four trials that were in the left upper quadrant of the funnel plot in former homeopathy reviews were excluded “because no matching conventional trial could be found”. Furthermore, safety was not considered, while homeopathy is generally acknowledged as a safe method. Numerous authors, like Gøtsche and Goldacre (Gøtsche, 2013)(Goldacre, 2012), demonstrated serious underreporting of adverse effects in conventional trials. If we consider only reported adverse effects, several conventional trials with strong effects, and serious adverse effects, influenced the Shang comparison in favour of conventional medicine. Dexfenfluramine for weight loss showed a strong effect and the trial was in the upper-left part of the conventional plot because of the sample size. This medicine was retracted in 1997 by the American Food and Drugs Administration because of serious cardiac adverse effects. Two other larger studies, Deladumone (androgen–estrogen) in breastfeeding and Piroxicam for soft tissue injury suffered from the same problem. Moreover, compared to placebos in conventional medicine placebos in homeopathy are much less distinguishable because of the lack of adverse effects (Hróbjartsson et al., 2013). There is a (statistically not significant) difference between the asymmetry of the homeopathy
plot and the conventional plot, but a comparison of asymmetry is not valid because of differences in quality, publication bias and safety.

The final conclusion of Shang et al ("weak evidence for homeopathy and strong evidence for conventional medicine") was based on subsets (‘larger high quality trials’) of 8/110 homeopathy trials compared with 6/110 conventional trials. After publication of the review it became clear that similar medical conditions had not been compared (Table 2). And the criteria for ‘good quality’ were changed, resulting in the exclusion of a larger high-quality trial on seasonal allergic rhinitis showing considerable effect (Reilly et al. 1986)(A. L. B. Rutten & Stolper, 2008).

It was known that better homeopathy trials yield less positive results (Linde et al. 1999), but this is also true for conventional medicine (Shang et al. 2005)(Schulz et al. 1995). This review concluded that larger high-quality studies show less effect than comparable conventional studies, but in fact it could not rightly reach such conclusion, because the trials were not comparable: they were in different conditions (table 2). Regrettably, these important facts were not revealed until well after publication. There is much heterogeneity and the outcome is highly sensitive to excluding trials previously classified as high quality and strongly influenced by a single indication (muscle soreness after marathon running) and the definition of ‘larger trial’ (Lüdtke & Rutten, 2008).

Shang et al did, however, identify a subset of 8 trials of homeopathy for acute upper respiratory tract infections (URTI) with a “substantial beneficial effect (odds ratio 0.36, [95% CI 0.26-0.50])” and no evidence of bias. But they went on to dismiss this because of “biases ... shown by our study” – a surprising conclusion given that they had also shown that homeopathy studies were of higher quality and therefore less biased than those of conventional medicine.

When we look at the whole set of homeopathy trials we cannot conclude that the evidence for homeopathy is inferior to comparable evidence for conventional medicine. Negative conclusions
regarding the efficacy of homeopathy are based on subjective selection of trials. While Shang concluded from meta-analysis of 8 trials that there was a substantial beneficial effect without evidence of bias for homeopathy in URTI the NHRMC concluded: “Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with upper respiratory tract infection” (Optum). The NHRMC performed no meta-analysis, did not include Shang’s meta-analysis and based his conclusion on 3 trials and especially “… one medium-sized, good-quality trial (251 participants) did not detect a difference between homeopathy and placebo”. In this trial the choice of the homeopathic medicine was made by the parents of the included children, not by qualified practitioners. This was trial nr. 16 in Table 3 in Appendix 5: ‘Scientific evidence of homeopathy in (upper) respiratory tract infections’. The other two trials leading to the conclusion of the NHRMC were trial nr. 15 (de Lange-de Klerk) and trial nr. 18 (also Steinbekk). The NHRMC did not include another trial by Steinsbekk (trial nr. 17) with positive outcome for homeopathy. We identified 21 randomised trials in (upper) respiratory tract infections in the Appendix 5: ‘Scientific evidence of homeopathy in (upper) respiratory tract infections’. In this set of 21 trials 16 reported a statistically significant effect of homeopathy over control, 4 no statistically significant difference between homeopathy and placebo, 1 no statistically significant difference with conventional medicine, and no trials reported a statistically significant effect of control over homeopathy.

This example clearly demonstrates the subjectivity of the review process. Hahn stated that more than 90% of the clinical trials of homeopathy must be discarded, or flawed statistical methods had to be applied to reach a negative conclusion (Hahn, 2013). About himself Hahn stated that he “… has never practiced, received, or studied homeopathy, but has worked in clinical medicine and performed traditional medical research in anesthesiology and surgery for the past 30 years”.

We conclude that the RCT evidence for homeopathy cannot be dismissed. The limitations of RCT and reviews are well known and no reason to ignore this evidence. This evidence has not yet been combined with other evidence. The RCT evidence for homeopathy alone is reason enough to be considered for the struggle against AMR.

Appendix 5, Table 3 summarises the randomised controlled trials for homeopathy in respiratory tract infections. However, homeopathy can also be effective in severe sepsis, like Frass et al showed (Frass et al., 2005): Seventy patients with severe sepsis received homeopathic treatment (n=35) or placebo (n=35). On day 180, survival was statistically significantly higher with verum homeopathy (75.8% vs 50.0%, P=0.043). No adverse effects were observed.

**RCT in veterinary homeopathy**

The EU Council Regulation (EC)834/2007 on organic production and labelling of organic products states: “Chemically synthesised allopathic veterinary medicinal products including antibiotics may be used where necessary and under strict conditions, when the use of phytotherapeutic, homeopathic and other products is inappropriate”.

There is one meta-analysis of veterinary homeopathy (RT Mathie; J Clausen, 2015). Nine of 15 trials with extractable data displayed high risk of bias; low or unclear risk of bias was attributed to each of the remaining six trials, only two of which comprised reliable evidence without overt vested interest. For all N=15 trials, pooled OR=1.69 [95% confidence interval (CI), 1.12 to 2.56]; P=0.01. For the N=2 trials with suitably reliable evidence, pooled OR=2.62 [95% CI, 1.13 to 6.05]; P=0.02). Conclusions:
Meta-analysis provides some very limited evidence that clinical intervention in animals using homeopathic medicines is distinguishable from corresponding intervention using placebos. The low number and quality of the trials hinders a more decisive conclusion. The randomised controlled trials in animals are described in Table 4.
Appendix 5: RCT evidence of homeopathy in (upper) respiratory tract infections (humans)

Table 3: Homeopathy in upper and lower respiratory tract infections (randomised controlled trials only)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Publication Details</th>
<th>Main Findings</th>
<th>Outcome</th>
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</thead>
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<tr>
<td>1. A randomized double-blind placebo control pilot study of individualized homeopathy. N=75.</td>
<td>Jacobs J, Springer DA, Crothers D (2001). Homeopathic treatment of <em>acute otitis media</em> in children: a preliminary randomized placebo-controlled trial. <em>Pediatric Infectious Disease Journal</em>, 20:177-183.</td>
<td>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 &lt; 0.05).</td>
<td>Positive</td>
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<td>2. 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.</td>
<td>Taylor JA, Jacobs J (2011). Homeopathic ear drops as an adjunct to standard therapy in children with <em>acute otitis media</em>. <em>Homeopathy</em>, 100(3):109-15.</td>
<td>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).</td>
<td>Positive</td>
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<tr>
<td>3. 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</td>
<td>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 <em>acute otitis media</em>. <em>Homeopathy</em>, 101: 5-12.</td>
<td>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</td>
<td>No difference between homeopathy and conventional treatment in primary outcome, but less use of antibiotics in homeopathy</td>
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prescribed 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.

<table>
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<th>Study Description</th>
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<td>4. 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).</td>
<td>Friese K-H, Zabolotnyi 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]. HNO, 55: 271-7.</td>
</tr>
<tr>
<td>6. 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%)</td>
<td>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]. Forschende Komplementärmedizin, 1:251-259.</td>
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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.

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.

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.
<table>
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<tr>
<th>Study</th>
<th>Authors</th>
<th>Results</th>
<th>Outcome</th>
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<tr>
<td>7. A randomised 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.</td>
<td>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]. Arzneimittel Forschung, 39:620–625.</td>
<td>No remarkable difference in the therapeutic success could be found among the various groups.</td>
<td>Non-conclusive</td>
</tr>
<tr>
<td>8. A randomised, double-blind, placebo-controlled, 6-day pilot study including 30 children, age 6 to 12 years, with acute viral tonsillitis</td>
<td>Malapane E et al (2014). Efficacy of a homeopathic complex on acute viral tonsillitis. Journal of Alternative and Complementary Medicine, 20(11):868-873.</td>
<td>The treatment group had a statistically significant improvement in the following symptoms compared with the placebo group: pain associated with tonsillitis, pain on swallowing, erythema and inflammation of the pharynx, and tonsil size.</td>
<td>Positive</td>
</tr>
<tr>
<td>9. 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.</td>
<td>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 &quot;Grippaler Infekt&quot;. [A controlled clinical trial for testing the efficacy of the homeopathic drug Eupatorium perfoliatum D2 in the treatment of common cold]. Arzneimittel Forschung, 31:732–736.</td>
<td>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.</td>
<td>Positive</td>
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<tr>
<td>10. 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 interindividual basis, comparing the effectiveness of a combination homeopathic preparation (Gripp-Heel) with that of acetylsalicylic acid.</td>
<td>Maiwald VL, Weinfurtner 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]. Arzneimittel Forschung, 38:578-582</td>
<td>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.</td>
<td>Positive</td>
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<td>11. A randomized double-blind controlled trial including 124 chronically ill residents (73 in the verum group, 51 in the control group). Antibody production was measured.</td>
<td>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</td>
<td>Three weeks after administration of Gripp-Heel Geometric Mean Antibody Titers for hemagglutinins H1, H3 and H8 were about 2 times higher than before treatment. Geometric Mean Titers for</td>
<td>Positive</td>
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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.


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 level.

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%, $P = 0.03$).

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).

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 2nd 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.
15. 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 to homeopathic medicines and 84 to placebo.


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 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%).

16. 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.


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.

17. 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.


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.

18. Randomised parallel group trial with

Steinsbekk A, Lewith G, Fønnebø V, Bentzen N

No significant differences in clinical effects between

Non-conclusive
208 children below the age of 10. The children were randomly assigned to receive either homeopathic care (HC: individual homeopathic consultations with any homeopathic medicine in any potency being prescribed) or one of three self-prescribed homeopathic medicines (SPH) in C-30 administered twice weekly, for 12 weeks.


SPH and HC for primary outcomes. Mean URTI scores over 12 weeks were 39.0 in the HC group and 43.9 in the SPH group (p=0.782, difference -5.0 points (95% C.I.; -20.5 to +10.5)). The mean number of days where the parents rated their child as ‘ill with URTI’ was 10.0 in the HC group and 13.7 in the SPH group (p=0.394). There was a trend in favour of HC for other outcomes. CONCLUSIONS: In this innovative and exploratory study, there was no evidence for a clinically relevant effect of homeopathic care vs. a homeopathic medicine given by the child’s parents and based on a pre-agreed homeopathic treatment protocol.

19. Double-blind randomised placebo controlled trial in 80 patients, 40 received placebo, 40 the homeopathic syrup. Patients were treated with either the homeopathic complex syrup or a placebo for a week, and recorded cough severity in a diary by means of a verbal category-descriptive score for two weeks. Sputum viscosity was assessed with a viscosimeter before and after 4 days of treatment; patients were also asked to provide a subjective evaluation of viscosity.


In each group cough scores decreased over time, however, after 4 and 7 days of treatment, cough severity was significantly lower in the homeopathic group than in the placebo one (p < 0.001 and p = 0.023, respectively). Sputum was collected from 53 patients: in both groups its viscosity significantly decreased after 4 days of treatment (p < 0.001); however, viscosity was significantly lower in the homeopathic group (p = 0.018). The subjective evaluation did not significantly differ between the two groups (p = 0.059). No adverse events related to any treatment were reported.

20. A randomised, double blind, placebo controlled study was conducted from 2003 to 2008. 120 diagnosed MDR-TB patients (both culture positive and negative) were enrolled and randomized to receive Standard Regimen + individualized homeopathic medicine (SR + H) or Standard Regimen + identical placebo (SR + P). The medicines have been used in infrequent doses. The outcome measures were sputum


There was an improvement in all the outcome measures as per intention to treat (ITT) and per protocol (PP) analyses. iTT analyses revealed sputum culture conversion from positive to negative in 23 (38.3%) in SR + H; 23 (38.3%) patients in SR + P group; (p = 0.269) and 27 (55.1); 21 (42.8%), p = 0.225 as PP analyses. The mean weight gain in SR + H group was 2.4 ± 4.9 and in SR + P was 0.8 ± 4.4; [p = 0.071], reduction in ESR in SR + H was -8.7 ± 13.2; SR + P was 3.9 ± 15.4 [p = 0.068]. The mean increase in hemoglobin was by 0.6 ± 1.7 in SR + H & 0.3 ± 2.3 [p
conversion, changes in chest X-ray (CXR), hemoglobin, erythrocyte sedimentation rate (ESR), weight gain, and clinical improvement.

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<td>Out of the 600 children recruited, 445 (74.17%) completed the study (149: Homeopathic complex; 151: Placebo; 145: InfluBio). The number of flu and acute respiratory infection symptomatic episodes detected in this clinical trial was low; however, it was different between homeopathic groups and placebo (p &lt; 0.001). In the first year post-intervention, 46/151 (30.5%) of children in the placebo group developed 3 or more flu and acute respiratory infection episodes, while there was no episode in the group of 149 children who used Homeopathic Complex, and only 1 episode in the group of 145 (1%) children who received InfluBio.</td>
<td>Positive</td>
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# Appendix 6: Homeopathy in infectious diseases in animals

## Table 4: Homeopathy in animals in infectious diseases (randomised controlled trials only)

<table>
<thead>
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<th>Study Design</th>
<th>Publication Details</th>
<th>Main Findings</th>
<th>Outcome</th>
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<td>Randomised placebo-controlled trial on 104 cows with subclinical mastitis. Six different homeopathic medicines were compared with placebo. Intramammary application of 1 ml of the homeopathic medicine or isotonic saline solution as placebo.</td>
<td>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]. <em>Tierärztliche Umschau</em>, 52: 407–412.</td>
<td>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 <em>Staphylococcus aureus</em> had a therapeutic effect, i.e. a significant decrease of cells in the milk and LDH (lactate dehydrogenase) blood level.</td>
<td>Preliminary</td>
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<td>Randomized placebo-controlled trial including 26 cows, divided in 2 groups, pairing on clinical and subclinical mastitis status, milk production and number of lactations.</td>
<td>Searcy R, Reyes O, Guajardo G (1995). Control of subclinical bovine mastitis. Utilization of a homeopathic combination. <em>British Homeopathic Journal</em>, 84: 67-70.</td>
<td>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&lt;0.05). Average milk production in the treated group did not differ significantly from that of the control group.</td>
<td>Preliminary</td>
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<td>A three-armed, stratified, semi-crossover design comparing individualised homeopathy, placebo and a standardised antibiotic treatment was used. 57 dairy cows were included. Evaluation was made by two score scales, with score I measuring acute symptoms and score II measuring chronic symptoms, and by recording the frequencies of responders to treatment based on four different responder definitions.</td>
<td>Hektoen L1, Larsen S, Odegaard SA, Løken T. Comparison of homeopathy, placebo and antibiotic treatment of clinical mastitis in dairy cows - methodological issues and results from a randomized-clinical trial. <em>J Vet Med A Physiol Pathol Clin Med</em>. 2004 Dec;51(9-10):439-46.</td>
<td>Significant reductions in mastitis signs were observed in all treatment groups. Homeopathic treatment was not statistically different from either placebo or antibiotic treatment at day 7 (P = 0.56, P = 0.09) or at day 28 (P = 0.07, P = 0.35). The antibiotic treatment was significantly better than placebo measured by the reduction in score I (P &lt; 0.01). Two-thirds of the cases both in the homeopathy and placebo groups responded clinically within 7 days. The outcome measured by frequencies of responders at day 28 was poor in all treatment groups. Evidence of efficacy of</td>
<td>Non-conclusive</td>
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Ninety-six mastitic quarters (non-fibrosed 67 and fibrosed 29) were treated with a homeopathic combination medicine Healwell VT-6 (consisting of Phytolacca, Calcarea fluorica, Silica, Belladonna, Bryonia, Arnica, Conium and Ipecacuanha). Another 96 quarters with acute mastitis (non-fibrosed) treated with different antibiotics were included in the study.


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 lactating dairy cows.

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.


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


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%.

Preliminary
ORBESAL (Pfizer) in all four quarters immediately after the last milking. In the homeopathy group (HDT; 32 cows) the cows were treated per-oraly 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).

during the dry period and 100 days post-calving. Homeopathy, 99: 90-98.

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 with relatively low SCCs.

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Coelho C de P, Soto FRM et al. (2009). Evaluation of preventive homeopathic treatment against colibacillosis in swine production. International Journal of High Dilution Research, 8: 183-190.</td>
<td>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</td>
</tr>
<tr>
<td>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.</td>
<td>Camerlink I, Ellinger L et al (2010). Homeopathy as replacement to antibiotics in the case of Escherichia coli diarrhoea in neonatal piglets. Homeopathy, 99: 57–62.</td>
<td>Piglets of the homeopathic treated group had significantly less E. coli diarrhoea than piglets in the placebo group (p&lt; 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. Positive</td>
</tr>
</tbody>
</table>
Appendix 7: Personalised prescription, optimising choice of medicine

The most characteristic element of homeopathic treatment is the personalised prescription. Thanks to genomics the personalised prescription is recently gaining a larger scientific focus in conventional medicine. The outcome of RCT gives insufficient information for the individual patient; the fact that a medicine works better than placebo gives no prognosis for the individual. Croft et al state: “a model of clinical practice focused on patient prognosis and predicting the likelihood of future outcomes may be more useful” (Croft et al., 2015). Individualised outcome is already provided for in diagnosis research. There is growing awareness that, in addition to diagnosis research, a renewed focus on prognosis research is needed (Dinant, Buntinx, & Butler, 2007). The diagnostic process can be described as a Bayesian updating of probability of a specific considering several subsequent symptoms and clinical investigations (Gill, Sabin, & Schmid, 2005). The PROGRESS working group states that biomarkers, but also symptoms and behavioural and psychosocial characteristics may be prognostic factors (Riley et al. 2013). These symptoms and characteristics are essential in prescribing homeopathic medicines.

The decision process in choosing a homeopathic medicine is similar to the diagnostic process: the probability that a specific homeopathic medicine will work is step-by-step increased by adding subsequent symptoms. In diagnosis a symptom is known to be related to specific diagnoses because the symptom occurs more frequently in the population with that diagnosis than in other populations. The higher the difference of the prevalence in the target population and in the remainder of the population, the more indicative the symptom. This difference is expressed as Likelihood Ratio (LR = (prevalence in the target population) / (prevalence in the remainder of the population)).

Table 5 describes a hypothetical example how the diagnosis of pneumonia is build up considering clinical signs, physical examination and laboratory testing. Traditionally this ‘algorithm’ of clinical reasoning is mostly based on expert opinion and consensus estimates. There is a growing tendency to corroborate this expert knowledge by diagnostic/prognostic factor research (Thompson et al., 2012). Likewise, the prognostic reasoning in homeopathy is also described in Table 5. In homeopathy some symptoms are also assessed by prognostic factor research (A. L. B. Rutten & Stolper, 2009). In Table 5 one assessed diagnostic factor for pneumonia (CRP) and one assessed prognostic factor for the homeopathic medicine Belladonna are included.

Table 5: hypothetical example of the diagnostic process in pneumonia and the prognostic process in selecting the homeopathic medicine Belladonna. Most chances are based on expert’s estimates. The tests/symptoms marked with * are assessed by diagnostic/prognostic factor research.

<table>
<thead>
<tr>
<th>Diagnosis pneumonia</th>
<th>chance</th>
<th>Prognosis Belladonna</th>
<th>chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>5%</td>
<td>Cough</td>
<td>5%</td>
</tr>
<tr>
<td>Cough</td>
<td>10%</td>
<td>High fever</td>
<td>15%</td>
</tr>
<tr>
<td>Rapid breathing</td>
<td>30%</td>
<td>Painful cough</td>
<td>25%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>50%</td>
<td>Dry barking cough</td>
<td>30%</td>
</tr>
<tr>
<td>Auscultation</td>
<td>60%</td>
<td>Hot face with cold extremities</td>
<td>40%</td>
</tr>
<tr>
<td>*CRP + (LR = ± 3)</td>
<td>80%</td>
<td>*Grinding teeth during sleep (LR = 5.4)</td>
<td>75%</td>
</tr>
</tbody>
</table>

Diagnostic reasoning, intuitively applying Bayes’ theorem and expert opinion, has formed the pillar of medicine along its entire history, and it provides for a reproducible choice of homeopathic medicines.
for two centuries. Bayes’ theorem provides an instrument for scientific assessment of diagnostic/prognostic factors.

**Prognostic factor research**

RCT evidence is the gold standard in proving that homeopathy is not a placebo effect, but, even with more than 110 RCTs, RCT evidence cannot resolve the plausibility question in homeopathy. More RCT evidence will be of limited value, especially for the patient.

The patient will benefit most from research that indicates the best medicine for him. In homeopathy that is the medicine that fits the person in the first place, and the condition in the second place. Table 5 shows that the condition is only one of the six parameters indicating the eligible medicine.

The condition can also be regarded as a prognostic factor. Scientific improvement of homeopathy can be achieved by replacing expert knowledge about prognostic factors by prospective assessment. If we know the LR of prognostic factors related to infectious diseases we can optimise the choice of eligible homeopathic medicines.

Scientific assessment and expert knowledge of prognostic factors can be applied in prescription algorithms. Such an algorithm is presently tested for premenstrual syndrome (Klein-Laansma et al. 2014).

Scientific assessment should also be applied in complex homeopathic medicines, to select the best indications, the best constituents and assess effectiveness.
Appendix 8: Personalised prescription, optimising daily practice

To optimise success of homeopathy in combatting AMR the personalised character of the method should be reflected in applying the method by various groups of professionals and in self-medication.

**Homeopathic doctors / Homeopathic veterinary surgeons**
Doctors with additional training in homeopathy are the best qualified to prescribe homeopathy, but they are not always available for immediate consultation, like in acute infections. They often treat recurrent infections and complaints that do not respond to conventional treatment. The role of homeopathy in treating infections in case of AMR has not yet been evaluated.

Improved diagnostic/prognostic tools for prescribing homeopathy should enhance the evidence base for prescribing of homeopathic medicines.

**Conventional doctors / Conventional veterinary surgeons**
Doctors with additional training in homeopathy could apply homeopathy in delayed prescribing of antibiotics (Spurling et al, 2013).

Conventional doctors without additional training are not able to make a reliable homeopathic prescription. However, with the help of a computerised algorithm and some additional training to use it, they can make personalised prescriptions in specific cases. Such an algorithm is presently being tested for premenstrual syndrome.

Complex homeopathic medicines (combinations of several homeopathic medicines suited for the condition) can also be applied in delayed prescribing of antibiotics.

**Farmers**
Proper education in homeopathy of farmers is required if homeopathy is to be introduced in farms. Initially this will lead the way for veterinary surgeons to become interested in homeopathy due to demand. Secondly, farmers need to be trained for the successful implementation of homeopathy in farms with the help of homeopathic veterinary surgeons. This could reduce inappropriate use of antibiotics in animals.

**Patients**
Patients could apply (complex) homeopathic medicines for self-medication, possibly with assistance of pharmacists (Danno et al., 2014). This could reduce inappropriate use of antibiotics, but self-medication should not lead to patient-delay.
Appendix 9: References


Thompson, M., van den Brule, a., Verbakel, J., Lakanpaul, M., Haj-Hassan, T., Stevens, R., ... Mant,


van Wassenhoven, M;Goossens, M; Anelli, M;Sermeus, G;Kupers, P;Morgado, C;Martin, E;Bezerra, M. (2014). Homeopathy and health related Quality of Life: a survey in six European countries. Homeopathy, 103(4), 250–256. http://doi.org/10.1016/j.homp.2014.08.005
