



# Comparative effectiveness of individualised homeopathy and antibiotics in the treatment of bovine clinical mastitis: randomised controlled trial

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Based on the widespread use of homeopathy in dairy farm practice when treating mastitis, a blind randomised controlled trial (RCT) was conducted to assess the effectiveness of homeopathic treatment of clinical mastitis on four dairy farms. The study considered specific guidelines for RCTs as well as the basic principles of individualised homeopathy and involved 180 lactating dairy cows. Evaluation of cure rates was based on clinical investigation of the udder and on laboratory analysis of milk samples. In culture-positive cases, the antibiotic treatment provided suboptimal bacteriological cures (60–81 per cent) but was more effective than individualised homeopathy (33–43 per cent) whose effects appeared little different to those of placebos (45–47 per cent) ( $P \leq 0.05$ ). On the cytological cure level, all three treatment methods were similarly ineffective: antibiotic being 2–21 per cent, individualised homeopathy 0–8 per cent and placebo 3–13 per cent ( $P \leq 0.05$ ;  $P = 0.13$ ). Antibiotics, individualised homeopathy and placebo had similar effects on bacteriological and cytological cure in cases of culture-negative milk samples ( $P > 0.4$ ) and *Escherichia coli* infections ( $P = 1.0$ ). The study results implied that the effectiveness of individualised homeopathy does not go beyond a placebo effect and successful treatment is highly dependent on the specific mastitis pathogen. Thus, antimicrobial or alternative remedies used should be based on the bacterial culture of the milk sample.

Trial registration number NTP-ID: 00008011-1-9, Pre-results.

## Introduction

Mastitis is the main reason for antimicrobial use in dairy production worldwide<sup>1–3</sup> and the cause of high economic losses on dairy farms.<sup>3,4</sup> On the other hand, overuse of antibiotics is responsible for a significant increase in the prevalence of antibiotic resistance.<sup>5–7</sup> Finding alternative treatments is often seen as a way of combating antimicrobial resistance. In this context, homeopathy is enjoying increasing popularity as an alternative mastitis treatment method, particularly on organic farms. On-farm studies (organic farms in Germany and in the south of England and Wales) showed that 34–51 per cent of clinical mastitis cases

were treated homeopathically.<sup>8,9</sup> The European Regulations on organic agriculture also promote the use of homeopathy: homeopathic products shall be used in preference to chemically synthesised veterinary products.<sup>10</sup> However, only remedies with positive therapeutic effect for the species of animal, and the condition for which the treatment is intended should be administered. In order to ensure that only effective remedies are administered to diseased animals, medicinal products need proven therapeutic efficacy. Randomised controlled trials (RCTs) are widely accepted as the gold standard for clinical research on the efficacy or effectiveness of medicinal products.<sup>11–13</sup> A recent review by Doehring and Sundrum<sup>14</sup> revealed that various clinical studies testing the efficacy or effectiveness of homeopathy returned heterogeneous results. Due to differing scientific approaches and study qualities, some of these studies supported the use of homeopathy while others showed no positive effects. The authors concluded that there was a need to repeat RCTs under various farm conditions before final conclusions on the efficacy

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of homeopathic remedies could be drawn. However, when repeating such clinical trials, particular attention should be paid to the study quality. Other authors<sup>15–17</sup> also noted the low number and quality of studies available and strongly indicated new and substantially improved research in both individualised and non-individualised veterinary homeopathy. The present study could contribute to extending current knowledge on the effectiveness of homeopathy by creating one additional high-quality RCT. While considering weak points identified in previous study designs (risk of bias according to Cochrane's evidence-based medicine principles, basic principles of classical homeopathy or small sample size), the aim of the trial (conducted as an RCT) was to examine the comparative effectiveness of treatments for bovine clinical mastitis treated with homeopathic, antimicrobial and placebo remedies on four dairy farms, following homeopathic principles (individualised treatment) and including the best possible treatment conditions (experienced veterinarians in homeopathy, timely and regular follow-up checks and laboratory analyses) in practice.

## Materials and methods

### Study sample

The RCT was conducted from June 2016 until the end of December 2016. In total, 180 lactating dairy cows were examined, derived from one organic herd and three conventional herds located in the eastern part of Germany. Herd size varied from 240 to 1500 lactating cows, with a milk yield range from 6.500 to 10.000 kg milk per cow per year. All cows were kept in loose stalls, and the milking routine was conducted in different milking systems (herringbone milking parlour, side-by-side milking parlour, carousel (an internal rotary milking parlour and an external one)). Both pre-milking and post-milking teat disinfection was integrated into the daily milking routine on all farms. Cows were recruited suffering from mild or moderate clinical mastitis according to the definition from the International Dairy Federation.<sup>18</sup> Cows exhibiting severe mastitis (presence of fever and/or disturbances of general behaviour) or cows suffering from mastitis in more than one mammary gland were excluded from the study. All animals considered in the study were not suffering from any other clinical disease during the trial period. Furthermore, cows with mastitis caused by *Streptococcus agalactiae* and *Trueperella pyogenes* or with injuries to the teats were excluded because unsuccessful treatment could create long-term damage to the udder. Cows treated with antimicrobial or anti-inflammatory products within the previous 30 days and those with recurrent mastitis were also excluded from the study.

### Study design

The study was performed as a randomised and placebo-controlled trial which compared the effectiveness of

two different treatment strategies (individualised homeopathy and use of antibiotics), taking into account the specific guidelines for RCTs<sup>19</sup> as well as the basic principles of classical homeopathy.<sup>20 21</sup> The clinical study tried to avoid weak points in study design (blinding or other bias) mentioned by Mathie and Clausen.<sup>15</sup>

Farmers on four farms, three local veterinarians from one veterinary practice with frequent use of homeopathy, a laboratory assistant and the supervising scientist were involved in the trial. The study enrolled 180 lactating cows using the defined inclusion and exclusion criteria, each with one affected udder quarter. Each case of mild or moderate clinical mastitis was randomly allocated to one of the three treatment strategies: individualised homeopathic (n=60), use of placebo (n=60) or antimicrobial treatment (n=60). Randomisation was ensured by drawing out lots in the form of coloured sticks, stored in opaque boxes. Each stick represented a treatment group and one was drawn before each treatment. In order to keep the number of cows in each treatment group balanced, a total of 60 sticks of each colour were used; 15 sticks of each colour were thus allocated per farm. In comparison with previous studies, the authors implemented standardised homeopathic remedy selection using a predefined procedure, which reduced a possible selection bias towards a favoured remedy to a minimum. The veterinarians' task was the clinical examination of cows suffering from clinical mastitis, reporterisation of symptoms and the assignment of a homeopathic, placebo or antibiotic remedy in each mastitis case, and undertaking the follow-up checks. A pre-test served for the unification of assessment criteria for clinical symptoms and treatment procedures. The farmers were responsible for the administration of the remedies selected, randomisation and observation of animals' health status. The scientist, veterinarians and laboratory assistant were blinded to the type of treatment over the whole observation period so as to avoid biased evaluations of treatment success. Farmers were blinded to the homeopathic and the placebo remedies. Knowledge of the antimicrobial products (udder infusions) and the homeopathic/placebo treatments was allowed deliberately for the sake of protection against injuries to the teats or new iatrogenic infections when administering the placebo or homeopathic remedy intracisternally. Differing means of treatment administration were not an issue as the veterinarian was only brought in at the end to evaluate treatment outcome and was blinded beforehand. Correspondingly, the farmers were aware of an antimicrobial treatment when they had to administer the remedies.

### Remedies

Twenty-one homeopathic remedies were selected on the basis of the most frequently used pure remedies dedicated for the treatment of animals with mastitis. The selection was made by a software repertory

(RadarOpus) and input from a professional veterinary homeopath with long-standing experience in the homeopathic treatment of food-producing animals: *Aconitum napellus* C30, *Apis mellifica* C30, *Belladonna* C30, *Bryonia alba* C30, *Calcium fluoratum* C30, *Calendula officinalis* C30, *Carbo vegetabilis* C30, *Cistus Canadensis* C30, *Conium* C30, *Hepar sulphuris calcareum* C30, *Kalium bichromicum* C30, *Lachesis muta* C30, *Mercurius solubilis* C30, *Phellandrium aquaticum* C30, *Phytolacca decandra* C30, *Pulsatilla pratensis* C30, *Pyrogenium* C30, *Silicea* C30, *Sulphur* C30, *Tuberculinum Koch* C30 and *Urtica urens* C30. All homeopathic remedies (including their clinical remedy picture) were saved in a specially developed software tool which served for standardised repertorisation. Nevertheless, other individual homeopathic remedies which did not appear on the above list were permitted if the veterinarian deemed it necessary. All homeopathic remedies used in the study were produced by Deutsche Homöopathie-Union in Germany. Sugar-based globules without an active ingredient (Globuli Sacchari HAB Gr. 3, Caelo, Germany) were used for the placebo treatment. Both homeopathic and placebo globules—administered in a dosage of 10 globules per day, dissolved in water and administered via syringe (either orally or vaginally), for a period of five days—were identical in their packaging, physical appearance and labelling.

Cows allocated to the antibiotic group received the most appropriate antimicrobial product selected by the veterinarian: *Synulox LC Plus*, *Cloxacymycin L*, *Oxacillin-Na 1000mg-Euter-Injektor*, *Vetriclox L*, *Peracef*, *Ubrolexin*, *Procain-Penicillin-G Injektor* and *Wedeclox Mastitis*. This was administered aseptically via udder infusion at the dosage recommended by the manufacturer. The national guidelines for prudent use of antimicrobials in veterinary medicine<sup>22</sup> were adhered to. Additional remedies such as NSAIDs or udder ointments were not used during the trial.

### Treatment procedure

Cows suffering from clinical mastitis as identified by farmers during the daily milking routine (occurrence of clinical symptoms) were subsequently examined by the consultant veterinarian. Those cows which met the inclusion criteria had a milk sample taken from all four udder quarters before the initial treatment. Both clinical and homeopathic symptoms were documented and repertorised individually according to Hahnemann's theory (cross-check of clinical symptom picture with remedy picture) by using a previously developed software tool containing the above-mentioned 21 homeopathic remedies and their corresponding symptoms. The software tool aided standardisation and transparency of the repertorisation procedure. One remedy for each treatment method was allocated to the diseased animal by the veterinarian. Farmers randomised and administered

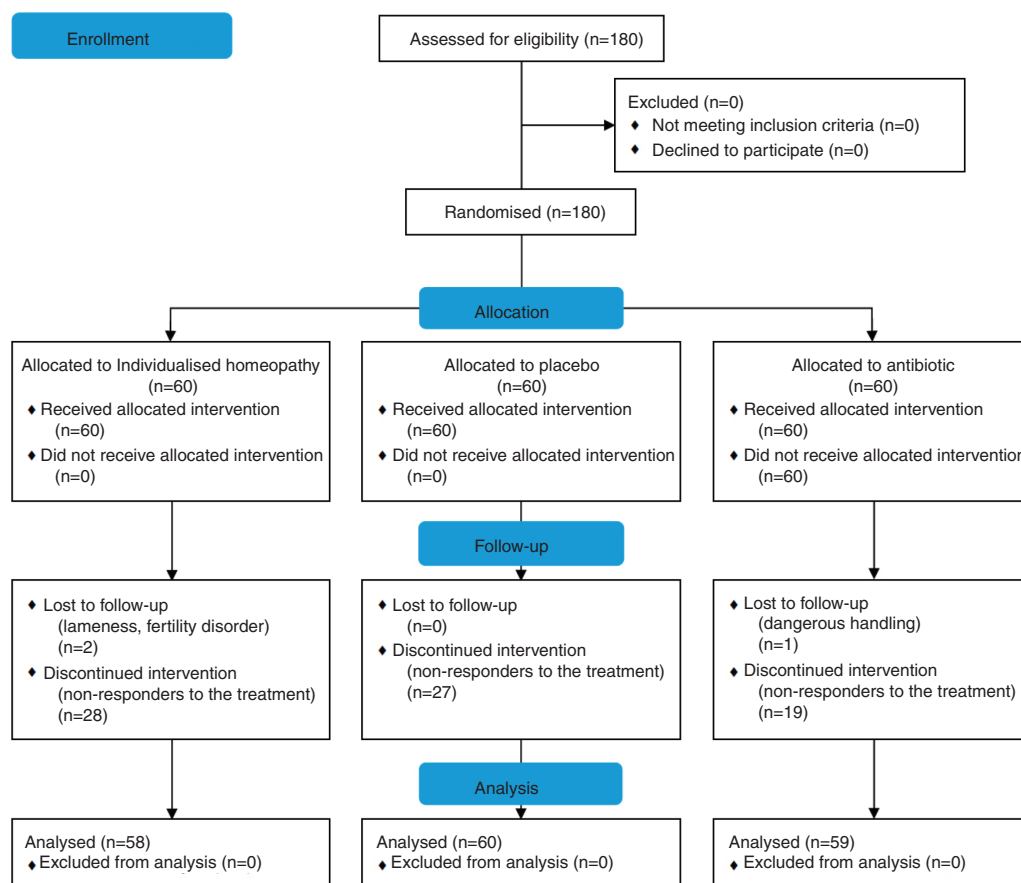
then the allocated remedy—previously determined by the veterinarian—to animal. In order to assess treatment outcomes, the veterinarian, who was completely unaware which treatment method was being used, performed a clinical examination and kept taking milk samples on the 7th, 14th and 28th days post onset of the infection. If the farmer observed a worsening of clinical symptoms or the development of new symptoms during the trial period, the veterinarian examined the affected cow thoroughly and classified the animal as either responsive or non-responsive to the treatment given. The decision whether or not an animal should be excluded from the trial was based on predefined exclusion criteria: body temperature >40°C, considerably reduced thirst or appetite, infection of a second udder quarter, major changes in udder health (occurrence of mammary gland abscesses, gangrenous mastitis) and recumbency. If homeopathic symptoms changed within four days after inclusion or the laboratory results indicated a pathogenic resistance to the antimicrobial agent administered, the veterinarian was allowed to change the remedy while retaining the treatment method. A Consolidated Standards of Reporting Trials flow diagram (Fig 1) displays the progress of all animals through the trial.

### Milk samples and laboratory procedure

According to good clinical practice, milk samples were taken aseptically from all four udder quarters by the veterinarian<sup>23</sup> and cyto-bacteriologically analysed by a certified milk laboratory (bovicare, Potsdam, Germany) at days 0, 7, 14 and 28. Pathogens were identified by using a standard mastitis diagnostic test, which included bacteriological culture on aesculin blood agar followed by sensory, microscopic and (if necessary) biochemical or serological evaluation of the pathogens. The milk laboratory always ascertained the major pathogen suspected to have caused the clinical mastitis. The somatic cell count (SCC) was also measured by the milk laboratory using a fluorescence method (Integrated Milk Testing MilkoScan FT 6000; Foss, Hamburg). For technical reasons, the SCC could not be determined when the milk deviated significantly from normal (eg, flocks or clots). In this case, the SCC was assessed with FL+, FL++ or FL+++ , depending on the degree of deviation from normal: low, medium or high, respectively.

### Classification of outcome

Assessment of the effectiveness of different medical mastitis treatment methods was based on criteria from the European Agency for the Evaluation of Medicinal Products (EMA).<sup>19</sup> Despite displaying clinical mastitis symptoms, pathogens were not always identified in routine clinical culture, and in these cases, cows were classified as 'culture-negative'.



**FIG 1: Consolidated Standards of Reporting Trials flow diagram.**

Cure rates were accordingly calculated separately for culture-positive and culture-negative pretreatment milk samples. Cure at a clinical level was ascertained via visual examination of milk and udder palpation and defined as an absence of visible changes in milk and inflammation of the udder. Cows exhibiting no clinical cure were rated as non-responsive to the treatment given. According to the EMEA criteria, bacteriological cure was determined as the elimination of the pathogen present on day 0. Udder quarters were rated as ‘newly infected’ when a new mastitis pathogen (different from the one on day 0) appeared. A newly infected udder quarter was also considered as bacteriological cure. However, from a medical point of view, a newly infected udder quarter cannot be classified as a clinical or bacteriological cure; therefore, criteria for a healthy udder defined by the German Veterinary Association (DVG)<sup>24</sup> were also considered. The DVG assessed a bacteriological cure as the elimination of any mastitis pathogens (culture-negative milk sample) but a new udder infection was absence of bacteriological cure. Using DVG’s criteria for a healthy udder quarter, a cytological cure was defined when the SCC was below the threshold of 100,000 cells/ml milk (German standard, in other European countries the threshold is below 200,000 cells/ml milk). For the purpose of SCC evaluation, three categories were used: ‘SCC was higher’ (increase of SCC compared with day 0), ‘SCC was lower’ (decrease of SCC until 100,000 cells/ml compared with day 0)

and ‘SCC <100,000 cells/ml’ (decrease of SCC below 100,000 cells/ml compared with day 0). The evaluation criteria ‘total cure’ (primary endpoint) was only awarded when a bacteriological, clinical and cytological (SCC <100,000 cells/ml) cure was present at the same time. The primary outcome measure was the elimination of the initial pathogen and a reduction in SCC.

### Statistical analysis

SPSS Statistics V.24 (IBM) was used for statistical analysis. All analyses of cure rates were based on udder quarter values and on the intention-to-treat (ITT) principle. Following Gupta,<sup>25</sup> the ITT analysis included all randomised animals in the groups to which they were randomly assigned, regardless of the treatment they actually received and regardless of subsequent withdrawal from treatment. ITT analysis avoids the problems created by omitting dropouts, which can negate randomisation, introduce bias and overestimate clinical effectiveness.<sup>26,27</sup> This means that all 180 animals entered into the study were analysed according to the group they were randomly allocated to at the time of each follow-up check, regardless of whether or not they were excluded from the study before it ended. The evaluation of nominal or categorical parameters was performed by using frequency distribution (contingency table). Significant differences in categorical variables for cure rates within the three treatment groups were tested by chi-squared test and, in case of a frequency

**TABLE 1: Initial condition of udder quarters suffering from mild or moderate mastitis by treatment strategy**

Initial condition		P value	Treatment strategy			All patients (n=180)
			Individualised homeopathy (n=60)	Placebo (n=60)	Antibiotic (n=60)	
Affected udder quarter*	LF	0.55	11	15	15	41
	RF		20	17	15	52
	RR		10	9	16	35
	LR		19	19	14	52
Lactation number		0.44	2.7±1.6†	2.9±1.7	3.0±1.6	2.9±1.6
Days in milk		0.32	125±94†	122±89	106±80	117±88
Bacterial isolates‡	Yes	0.74	40	38	42	120
	No		20	22	18	60

\*The udder quarter position is indicated as RF, RR, LF and LR.

†Mean value and corresponding SD.

‡The presence of mastitis pathogens in milk samples from infected udder quarters at day 0 before treatment.

LF, left front; LR, left rear; RF, right front; RR, right rear.

distribution of less than five, by using Fisher's exact test. For all comparisons,  $P \leq 0.05$  was considered to be significant.

## Results

Cure rates were recorded separately for each follow-up check on days 7, 14 and 28, followed by an analysis of the specific findings. Table 1 shows the initial conditions for mastitis treatment. These did not differ significantly ( $P > 0.30$ ) among treatment groups.

In total, 120/180 (66 per cent) pretreatment milk samples showed positive for bacterial growth whereas no bacteria culture could be detected in 60/180 (33 per cent) of cases. Isolated mastitis pathogens were identified as *Streptococcus uberis* (n=45), *Escherichia coli* (n=16) and *Streptococcus dysgalactiae* (n=13), *Klebsiella* species (n=9), other aesculin-positive streptococci (n=8), coagulase-negative staphylococci (n=7), *Staphylococcus aureus* (n=7), coliform bacteria (n=5), *Enterococci* species (n=5), *Corynebacterium bovis* (n=2), yeasts (n=2) and *Serratia* species (n=1).

### First follow-up check (day 7)

At the time of the first check-up (Table 2), the antibiotic treatment method showed an 81 per cent elimination rate of mastitis pathogens which had been found on day 0 (EMEA criteria). This was almost twice as high as those receiving the homeopathic treatment (43 per cent) or the placebo treatment (45 per cent) ( $P < 0.05$ ). If using the DVG criteria, the antibiotic treatment was 2.3 or 2.9 times more efficient as either the homeopathic or the placebo treatment. Cows in the homeopathic (15 animals) and placebo groups (17 animals) were more often assessed as non-responsive to the administered remedy than cows in the antibiotic treatment group (3 animals). Where no mastitis pathogen was found at day 0, there was no difference observed in the bacteriological cure rates ( $P = 0.63$ ) between the three treatment groups (Table 2).

The SCC of one milk sample could not be measured because the milk production from the infected udder quarter ceased almost completely. Cytological

cure rate results were similar to those for the bacteriological cure (Table 3). In general, SCC decreased after mastitis treatment in 124/179 cases (69 per cent). The largest decrease in SCC (including SCC  $< 100,000$  cells/ml) was recorded in the antimicrobial remedies group (85 per cent), followed by the placebo (55 per cent) and homeopathic treatment groups (45 per cent). In contrast, the SCC was more often higher after a homeopathic treatment on the seventh day post onset of the infection compared with the other treatment methods. A decrease in SCC below the threshold of 100,000 cells/ml milk was detected in 13/180 mastitis cases (7 per cent). For culture-negative milk samples on the day of inclusion (day 0), no significant differences in cytological cure could be found ( $P = 0.69$ ). Where a mastitis pathogen was found on day 0, cytological cure rates differed significantly ( $P < 0.01$ ) (Table 3).

### Second follow-up check (day 14)

Bacteriological cure rates measured 14 days after the initial treatment (second follow-up check) were similar to those observed at day 7 (Table 2). The antibiotic treatment method was significantly more effective in eliminating mastitis pathogens found on the day of inclusion than the placebo and homeopathic treatment methods ( $P < 0.05$ ). Again, the homeopathic treatment method had the highest number of cases in which the mastitis pathogen identified on day 0 was still present in the milk sample. Although a good proportion of cows in the antibiotic treatment group were evaluated as non-responsive during the second trial week (Table 2), at the same time, the homeopathic and placebo treatment groups made up the majority of all non-responsive cows. For those cases with a negative result for bacterial growth in the pretreatment milk sample, all three treatment methods came out as equally effective ( $P = 0.72$ ; Table 2).

Two weeks following the initial treatment, the antimicrobial treatment group had achieved the best cytological cure rates with an SCC decrease evident in 45/60 (75 per cent) of quarters (Table 3), but only 14/60 (23 per cent) of quarters fell below the threshold of

**TABLE 2: Bacteriological cure rate by treatment strategy, time of examination and evaluation criteria by EMEA and DVG**

Day of examination and bacteriological status at day 0	Treatment strategy											
	Individualised homeopathy (n = 60)				Placebo (n = 60)				Antibiotic (n = 60)			
	EMEA*		DVG *		EMEA		DVG		EMEA		DVG	
	n/n	%	n/n	%	n/n	%	n/n	%	n/n	%	n/n	%
Day 7												
Positive (n=120)												
BacC	17/40	42.5	10/40	25.0	17/38	44.7	12/38	31.6	34/42	81.0	30/42	71.4
NoBacC	8/40	20.0	8/40	20.0	4/38	10.5	4/38	10.5	5/42	11.9	5/42	11.9
NewInf	–	–	7/40	17.5	–	–	5/38	13.2	–	–	4/42	9.5
Non-responders	15/40	37.5	15/40	37.5	17/38	44.7	17/38	44.7	3/42	7.1	3/42	7.1
Negative (n=60)												
BacC	19/20	95.0	12/20	60.0	22/22	100.0	17/22	77.3	18/18	100.0	13/18	72.2
NewInf	–	–	7/20	35.0	–	–	5/22	22.7	–	–	5/18	27.8
Non-responders	1/20	5.0	1/20	5.0	0/22	0.0	0/22	0.0	0/18	0.0	0/18	0.0
Day 14												
Positive (n=120)												
BacC	14/40	35.0	12/40	30.0	18/38	47.4	13/38	34.2	28/42	66.7	23/42	54.8
NoBacC	5/40	12.5	5/40	12.5	0/38	0.0	0/38	0.0	4/42	9.4	4/42	9.4
NewInf	–	–	2/40	5.0	–	–	5/38	13.2	–	–	5/42	11.9
Non-responders	21/40	52.5	21/40	52.5	20/38	52.6	20/38	52.6	10/42	23.8	10/42	23.8
Negative (n=60)												
BacC	17/20	85.0	13/20	65.0	18/22	81.8	11/22	50.0	16/18	88.9	13/18	72.2
NewInf	–	–	4/20	20.0	–	–	7/22	31.8	–	–	3/18	16.7
Non-responders	3/20	15.0	3/20	15.0	4/22	18.2	4/22	18.2	2/18	11.1	2/18	11.1
Day 28												
Positive (n=120)												
BacC	13/39†	33.3	9/39	23.1	17/38	44.7	13/38	34.2	25/42	59.5	23/42	54.8
NoBacC	2/39	5.1	2/39	5.1	0/38	0.0	0/38	0.0	2/42	4.8	2/42	4.8
NewInf	–	–	4/39	10.2	–	–	4/38	10.5	–	–	2/42	4.8
Non-responders	24/39	61.5	24/39	61.5	21/38	55.3	21/38	55.3	15/42	35.7	15/42	35.7
Negative (n=60)												
BacC	15/19†	78.9	13/19	68.4	16/22	72.7	14/22	63.6	13/17†	76.5	10/17	58.8
NewInf	–	–	2/19	10.5	–	–	2/22	9.1	–	–	3/17	17.6
Non-responders	4/19	21.1	4/19	21.1	6/22	27.3	6/22	27.3	4/17	23.5	4/17	23.5

Results are given in number of total cures out of cases treated (n/n) and in % of all cases treated.  
 \*Evaluation criteria according to EMEA or DVG.  
 †Early culling of one cow due to different reasons (dangerous handling, lameness, fertility disorder).  
 BacC, bacteriological cure (elimination of the pathogen present on day 0); DVG, German Veterinary Association; EMEA, European Agency for the Evaluation of Medicinal Products; NewInf, newly infected udder quarter (pathogen was different from the one on day 0); NoBacC, no bacteriological cure (the pathogen on day 0 was still present in the udder); non-responders, cows with no clinical cure were rated as non-responsive to the treatment given.

100,000 cells/ml milk. A decrease in SCC was observed in 33/60 (55 per cent) after a homeopathic treatment and in 30/60 (50 per cent) after use of placebo remedies. Furthermore, an increase in SCC had occurred in 12 cases by the time of the second follow-up check; most in the placebo treatment group. When breaking down the cytological cure rates by bacteriological status at day 0, it became evident that significant differences only occurred when an actual mastitis pathogen had been identified on day 0 ( $P < 0.05$ ) (Table 3). The cytological cure rates for the different treatment methods in a culture-negative pretreatment sample did not differ ( $P = 0.43$ ).

### Third follow-up check (day 28)

The antibiotic treatment method had achieved the highest bacteriological cure rates at the time of the

third check-up (Table 2). In contrast, treatment to eliminating mastitis pathogens using a homeopathic or a placebo remedy at day 28 was significantly less successful compared with the antibiotic treatment ( $P = 0.05$ ). The pathogen present on day 0 was still found in four udder quarters, which were treated with antibiotic and placebo remedies (each two animals). Cows categorised as non-responsive at the time of the final check-up on day 28 were mostly those treated with antimicrobial remedies (five out of nine animals). Both the lowest non-responsive and highest bacteriological cure rates for the whole observation period were found after antibiotic treatment. The final check-up revealed no significant differences in treatment success in the three treatment groups where no mastitis pathogen had been found on the day of inclusion ( $P = 0.93$ ; Table 2).

**Table 3** Cytological cure compared with day 0 by treatment strategy and time of examination

Day of examination and bacteriological status at day 0	Treatment strategy					
	Individualised homeopathy (n=60)		Placebo (n=60)		Antibiotic (n=60)	
	n/n	%	n/n	%	n/n	%
<b>Day 7</b>						
Positive (n=120)						
SCC<100,000 cells/ml	0/40	0.0	1/38	2.6	1/41*	2.4
SCC was lower	18/40	45.0	20/38	52.6	34/41	82.9
SCC was higher	7/40	17.5	0/38	0.0	3/41	7.3
Non-responders	15/40	37.5	17/38	44.7	3/41	7.3
Negative (n=60)						
SCC<100,000 cells/ml	2/20	10.0	6/22	27.3	3/18	16.7
SCC was lower	13/20	65.0	13/22	59.1	13/18	72.2
SCC was higher	4/20	20.0	3/22	13.6	2/18	11.1
Non-responders	1/20	5.0	0/22	0.0	0/18	0.0
<b>Day 14</b>						
Positive (n=120)						
SCC<100,000 cells/ml	3/40	7.5	1/38	2.6	7/42	16.7
SCC was lower	13/40	32.5	15/38	39.5	23/42	54.8
SCC was higher	3/40	7.5	2/38	5.3	2/42	4.8
Non-responders	21/40	52.5	20/38	52.6	10/42	23.8
Negative (n=60)						
SCC<100,000 cells/ml	5/20	25.0	6/22	27.3	7/18	38.9
SCC was lower	12/20	60.0	8/22	36.4	8/18	44.4
SCC was higher	0/20	0.0	4/22	18.2	1/18	5.6
Non-responders	3/20	15.0	4/22	18.2	2/18	11.1
<b>Day 28</b>						
Positive (n=120)						
SCC<100,000 cells/ml	2/39†	5.1	5/38	13.2	9/42	21.4
SCC was lower	13/39	33.3	11/38	28.9	17/42	40.5
SCC was higher	0/39	0.0	1/38	2.6	1/42	2.4
Non-responders	24/39	61.5	21/38	55.3	15/42	35.7
Negative (n=60)						
SCC<100,000 cells/ml	6/19†	31.6	8/22	36.4	7/17†	41.2
SCC was lower	7/19	36.8	5/22	22.7	6/17	35.3
SCC was higher	2/19	10.5	3/22	13.6	0/17	0.0
Non-responders	4/19	21.1	6/22	27.3	4/17	23.5

Results are given in number of total cures out of cases treated (n/n) and in % of all cases treated.  
 \*Low quantity of milk: SCC measurement was not possible.  
 †Early culling of one cow due to different reasons (dangerous handling, lameness, fertility disorder).  
 Non-responders, cows with no clinical cure were rated as non-responsive to the treatment given; SCC, somatic cell count.

Table 3 shows the cytological results from 177 milk samples (three animals were previously culled) 28 days after the initial treatment. As already found in the previous check-ups, the antimicrobial treatment method led more often to a decrease in SCC (39 per cent) than the homeopathic (34 per cent) and the placebo treatment strategies (27 per cent) ( $P=0.13$ ). A total of only 37/177 (21 per cent) quarters saw the SCC drop under the desired threshold value of 100,000 cells/ml milk and most (16 animals) were treated with antimicrobial remedies. An increase in SCC occurred in seven mastitis cases; mainly those treated with placebo remedies (four animals). Significant differences in cytological cure rates between treatments were found neither for culture-negative ( $P=0.81$ ) nor for culture-positive pre-treatment samples ( $P=0.13$ ).

### Additional findings

#### Bacteriological cure rate at pathogen level

An assessment of the results of the bacteriological cure rates at pathogen level showed that the homeopathic and the placebo treatment strategies were less effective in curing mastitis caused by *S uberis* ( $P=0.01$ ) and *S dysgalactiae* ( $P=0.03$ ) than the antibiotic treatment method. In contrast, all treatment methods showed similar bacteriological cure rates when treating an *E coli* infection ( $P=1.0$ ) (Table 4).

#### Total cure rate

The total cure rate (Table 5) generally did not differ between the treatment methods ( $P>0.05$ ), except on 28th day post onset of the infection ( $P<0.05$ ). A total cure in udder health (DVG criteria) was only identified

**Table 4 Bacteriological cure at pathogen level by treatment strategy at the time of the first follow-up check (day 7\*)**

Mastitis pathogens	Treatment strategy					
	Individualised homeopathy		Placebo		Antibiotic	
	n/n	%	n/n	%	n/n	%
<i>Streptococcus uberis</i> (n=45)						
BacC	1/12	8.3	3/16	18.7	11/17	64.7
Pathogen change	1/12	8.3	1/16	6.3	2/17	11.8
NoBacC	3/12	25.0	3/16	18.7	2/17	11.8
Non-responders	7/12	58.3	9/16	56.3	2/17	11.8
<i>Escherichia coli</i> (n=16)						
BacC	3/6	50.0	3/5	60.0	4/5	80.0
Pathogen change	2/6	33.3	2/5	40.0	1/5	20.0
NoBacC	1/6	16.7	0/5	0.0	0/5	0.0
Non-responders	0/6	0.0	0/5	0.0	0/5	0.0
<i>Streptococcus dysgalactiae</i> (n=13)						
BacC	0/3	0.0	2/3	66.7	6/7	85.7
Pathogen change	0/3	0.0	0/3	0.0	1/7	14.3
NoBacC	1/3	33.3	0/3	0.0	0/7	0.0
Non-responders	2/3	66.7	1/3	33.3	0/7	0.0

Results are given in number of total cures out of cases treated (n/n) and in % of all cases treated.  
 \*An evaluation of bacteriological cure rates at the time of the second/third follow-up check has not been performed due to low sample sizes (occurrence of non-responders and new infections at subsequent follow-up checks).  
 BacC, bacteriological cure (elimination of the pathogen present on day 0); NoBacC, no bacteriological cure (the pathogen on day 0 was still present in the udder); non-responders, cows with no clinical cure were rated as non-responsive to the treatment given.

in a few cases: 13 cows (homeopathy: 2, placebo: 7, antibiotic: 4) at the time of the first follow-up check, 26 animals (homeopathy: 8, placebo: 7, antibiotic: 11) at the second and 33 cows (homeopathy: 6, placebo: 13, antibiotic: 14) at the third. Over the whole observation period (28 days), a total cure was only observed in seven cases, mainly after a placebo treatment (five cows). Only one animal in the homeopathic treatment group and one animal in the antibiotic group were declared to be totally cured from mastitis.

### Changes in SCC

The change in SCC trends by treatment strategy is illustrated in Table 3. The SCC analysis showed that a rapid return to a normal SCC below 100,000 cells/ml milk was more likely when no mastitis pathogen was found in the pretreatment milk sample than when the milk sample on day 0 indicated positive bacterial growth.

Even 28 days after the initial treatment (independent of the treatment strategy), only 37 animals had achieved the target value 100,000 cells/ml needed in order to be considered as having achieved a cytological cure.

### Differences in cure rates by using DVG or EMEA criteria

Table 2 illustrates that bacteriological cure rates assessed with DVG criteria were always lower than those determined by using the EMEA criteria.

### Discussion

#### Methodological issues

The present study design fulfilled the RCT criteria required for a comparison of different treatment strategies, including definition of inclusion and exclusion criteria, randomisation and blinding.<sup>19</sup>

All bacteriological and cytological cure rates evaluated in the current study for the homeopathic treatment

**Table 5 Total cure rate by treatment strategy and time of examination**

Day of examination and bacteriological status at day 0	Treatment strategy					
	Individualised homeopathy (n = 60)		Placebo (n=60)		Antibiotic (n=60)	
	n/n	%	n/n	%	n/n	%
Positive (n=120)						
Day 7	0/40*	0.0	1/38	2.6	1/42	2.4
Day 14	3/40	7.5	1/38	2.6	5/42	11.9
Day 28	1/40†	2.5†	5/38†	13.2†	9/42†	21.4†
Negative (n=60)						
Day 7	2/20	10.0	6/22	27.3	3/18	16.7
Day 14	5/20	25.0	6/22	27.3	6/18	33.3
Day 28	5/20	25.0	8/22	36.4	5/18	27.8

Results are given in number of total cures out of cases treated (n/n) and in % of all cases treated.  
 \*Values in roman font did not differ significantly in total cure rates (P>0.05).  
 †Values in italics show significant differences in total cure rates (P<0.05).



method were below those of the antimicrobial treatment method, with one exception at day 28 (Tables 2 and 3). This might be due to various reasons. The lack of an individualised homeopathic treatment (repertorisation) is often claimed to be a major obstacle in clinical studies concerning the effectiveness of homeopathy. The methodological approach of the present study, however, followed the basic principles of classical homeopathy (individualised treatment and repertorisation) as far as possible and reduced possible personal bias using a software repertory. Nevertheless, detection and assessment of individual homeopathic symptoms (such as modalities or peculiar symptoms) can be challenging under practical conditions and can be the cause of uncertainty, even for a veterinary expert in homeopathy. Despite the veterinarian's expertise and the use of the digital repertory, it is possible that an inappropriate homeopathic remedy was selected, resulting in negative influences on cure rates.

Another questionable point might be the standardised dosage of homeopathic remedies. All animals were treated with the same dosage (number of globules and potency) during the milking routine in the milking parlour. This kind of standardisation was used to streamline the treatment procedures which may have had some influence on cure rates. The question of the appropriate potency has often triggered discussions. Some authors<sup>28,29</sup> recommend the use of high potencies, while other authors used both low and high potencies for acute diseases.<sup>30,31</sup> It is reported in literature that the correct remedy will act curatively in any dosage or potency.<sup>21,32</sup> According to Day,<sup>21</sup> a correct remedy at high potency reaches the centre of the disease and has the potential to result in total cure.

Shang and others<sup>33</sup> assumed that any beneficial effects of homeopathic treatment are primarily due to a placebo effect or a non-specific stimulus. For this reason, the authors considered it essential to employ a placebo control group during the clinical trial. While some authors included two control groups,<sup>34-36</sup> others had only one control group to compare treatment outcomes.<sup>37,38</sup> However, implementing a control group creates new challenges (blinding and evaluation). Thus, the partial blindness between homeopathic or placebo remedies (globules) and antimicrobial remedies (udder infusions) must be seen critically. In the current study, farmers were aware of the antibiotic treatment, so a possible consequence of farmers' partial impartiality is the risk they may have stopped a homeopathic or placebo treatment at an earlier stage. However, this minor impartiality was deliberately accepted to prevent the risk of iatrogenic harm to animals (injuries of the teats or new infections).

### Effectiveness of treatment

In general, a direct comparison of the cure rates achieved in the present study with other clinical mastitis studies

is barely meaningful because of large variations in study design, treatment procedure, definition of cure, implementation of homeopathic principles and the use of appropriate control groups.<sup>14</sup> Only two other studies<sup>34,36</sup> conducted a placebo-controlled trial while taking the individual treatment principle into account.

The present study also demonstrates how different evaluation criteria influence cure rates when a mastitis pathogen was identified on the day of inclusion. The bacteriological cure rates also differed widely (up to 17.5 percentage points) when using EMEA instead of DVG criteria. Both treatment strategies achieved higher cure rates when taking EMEA criteria into account, but the results were inadequate, as the true udder health status was concealed (new udder infections were regularly evaluated as cured). On the contrary, the DVG criteria were not intended to be used for evaluation in scientific studies, but they were seen as more important for udder health and had higher clinical relevance than the EMEA criteria, as they considered the SCC (threshold <100,000 cells/ml) and new udder infections.

In this study, the frequency of non-responsive animals was generally higher in the homeopathy and placebo groups than in the antibiotic group. This supports the findings of other studies<sup>37-39</sup> which found higher clinical cure rates after an antibiotic mastitis treatment. However, in the course of the study, the frequency of non-responsive animals after an antibiotic treatment increased steadily. Cows treated with antibiotics were assessed as non-responsive at a later stage of the study; mainly at the time of the second and third check-up. A reason for this could be that many farmers had administered a well-known effective treatment; they believed in the efficacy of antibiotic remedies. It could therefore be assumed that they waited longer before changing the remedy. At the time of the first follow-up check, animals within the homeopathic treatment group were classified as non-responsive five times as often as those after an antibiotic treatment. An explanation could be the 'initial worsening': according to homeopathic philosophy, it is a signal that the healing process is under way, generally seen as a favourable response to treatment and is expected to be followed by an improvement of clinical symptoms.<sup>20,40,41</sup> This type of aggravation is described as the optimal reaction to a correct homeopathic remedy.<sup>42</sup> The difficulty is distinguishing whether the worsening of the diseased animals' symptoms are homeopathic aggravations or adverse effects. An incorrect estimate of these symptoms as adverse effects can lead to an early exclusion of animals within the homeopathic treatment group. As the animals' health and welfare was a priority during the clinical study, animals whose symptoms worsened without clearly being linked to homeopathy were therefore excluded. This procedure could have contributed to the high number of non-responsive animals within the homeopathic treatment group.

In terms of the cure rates of mastitis pathogens found on day 0, subsequent follow-up checks found that the antibiotic treatment method was the most effective. This outcome compares well with results found in previous mastitis studies. However, the bacteriological cure rates for all three treatment methods were higher than those reported by Hektoen and others<sup>34</sup> and lower than those reported by Werner and others.<sup>36</sup>

In the present study, a high rate of culture-negative mastitis cases was found, which compares well with study results of Krömker and others.<sup>43</sup> In approximately 10–40 per cent of samples, pathogens are not identified in routine clinical culture assays.<sup>44–46</sup> Culture-negative cases cannot be detected from a change in milk appearance or from clinical symptoms. They cannot thus be excluded *a priori* and were therefore included in the analysis. As the trial was a clinical study under practical conditions, culture-negative mastitis cases were also treated as is usual in agricultural practice. Independent of the treatment method, almost all culture-negative mastitis cases treated were successfully cured. The study results indicated that the use of antimicrobial remedies in cases of culture-negative pretreatment milk samples is unnecessary and must be seen as contraindicated. The study also confirmed that cure rates are dependent on the pathogen species. As already shown by other authors,<sup>35 47–49</sup> the use of antibiotic remedies in case of mastitis caused by *E coli* is often contraindicated. In the current study, the cure rates of *E coli* infections showed no significant differences after a homeopathic, placebo or antibiotic treatment. However, it should be taken into account that the evaluation of *E coli* infections is based on a small sample size, thus the results may not be representative.

Previous studies on homeopathy provided total cure rates after a homeopathic treatment from 19 up to 34 per cent; from 6 to 16 per cent for a placebo treatment and from 20 to 34 per cent for an antimicrobial treatment.<sup>34 36 37 50</sup> While total cure rates for the placebo and antibiotic treatment method revealed in the present study were on a slightly lower level compared with those from other authors, total cure rates of mastitis cases treated with placebos were similar. In general, the homeopathic treatment method returned a lower effectiveness in treating clinical mastitis than the antibiotic treatment strategy. The mechanism by which homeopathy might work is unknown. Hahnemann believed that the process of dilution released a spirit-like healing power that is particularly adapted to work on the equally vital force in animal,<sup>51</sup> resulting in stimulating the body's own healing responses and restoring its inner balance.<sup>21</sup> It was also notable that when using homeopathic remedies the SCC in 17 per cent of mastitis cases was higher at the time of the first follow-up check than on day 0. Compared with that, an increase in SCC after an antibiotic treatment was found in only 7 per cent of cases and no increase was found after administering a

placebo. Somatic cells are a mixture of milk-producing cells shed from the udder tissue (about 2 per cent) and cells from the immune system (leucocytes; 98 per cent). Leucocytes are the cells responsible for identifying bacteria and killing them and are transferred to the udder during infection, resulting in an increase in SCC. As homeopathic remedies are intended to stimulate vital force, it cannot be ignored that the increase of SCC after a homeopathic treatment could be stimulated by this kind of activation. A direct correlation between an increase in SCC and new infection rate was not observed.

## Conclusion

Before homeopathy can be recommended as a serious alternative for the treatment of bovine clinical mastitis, its effectiveness has to be proven. Despite designing the study carefully around the correct use of homeopathy in the current RCT, the homeopathic treatment method was significantly less successful in curing clinical mastitis compared with antibiotic treatment strategy. In culture-positive cases, the antibiotic treatment provided suboptimal bacteriological cures but was more effective than individualised homeopathy whose effects appeared little different to those of placebos. However, on the cytological cure level, all three treatment methods were similarly ineffective. The results of the present study imply that the effectiveness of individualised homeopathy does not go beyond a placebo effect. In more than one-third of all mastitis cases (culture-negative milk samples and *E coli* infections), antibiotic treatment was contraindicated retrospectively, as antibiotics, individualised homeopathy and placebo had similar effects on bacteriological and cytological cure. In contrast, the antibiotic treatment of mastitis caused by specific mastitis pathogens (except *E coli*) seems best at promoting successful udder recovery. The study results emphasise the need for bacteriological analysis of milk samples as successful treatment is highly dependent on the specific mastitis pathogen. Homeopathy does not appear to be a universal treatment alternative for cases of mastitis. Instead, good preventive measures (avoiding mastitis) and target-oriented treatment procedures based on bacteriological culture should be implemented in dairy practice. The use of individualised homeopathy is therefore only recommended under specific conditions *inter alia*: treatment of mastitis caused by specific mastitis pathogens in combination with antibiotics (complementary therapy), timely and regular follow-up checks, enough time for a homeopathic clinical examination, knowledge of homeopathic principles and use of homeopathic remedies as an initial treatment until culture results suggest other treatment methods. For a target-oriented treatment approach, a reduction in the use of antimicrobial remedies and in order to promote animals' health and welfare (as Roberson and others<sup>35</sup> also recommend) culture analyses of milk samples should be made

mandatory and be performed regularly before any treatment is undertaken.

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