Impact matrix analysis and cost-benefit calculations to improve management practices regarding health status in organic dairy farming

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- Deliverable -

D4.3 - Comparison of allopathic and homeopathic treatments in cases of bovine mastitis

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Executive Summary

A randomised clinical control trial (RCT) and a field trial were conducted to assess the effectiveness of the homeopathic treatment strategy.

In the RCT, three treatment strategies (use of allopathy, homeopathy, and placebo) in cases of bovine clinical mastitis were assessed by using a total number of 180 cases of clinical mastitis. The clinical control study revealed that homeopathic treatment achieved clearly lower cure rates in comparison to those of the antimicrobial treatment and similar results in comparison to the placebo treatment strategy. The highest bacteriological and cytological cure rates were achieved by the antimicrobial treatment throughout the whole study period. Despite of the relatively high cure rates of the antimicrobial treatment method, none of the treatment strategies achieved satisfactory treatment results in total cure. A total cure in udder health was identified in only few cases: 13 cows (homeopathy: 2, placebo 7, antibiotic: 4) at the time of the first, 26 animals (homeopathy: 8, placebo 7, antibiotic: 11) at the time of the second and 33 cows (homeopathy: 6, placebo 13, antibiotic: 14) at the time of the third follow-up check. In only seven mastitis cases (2.8%) a continuous total cure throughout the period of 28 days was found; the majority of them occurred after a placebo treatment (5 cases).

An additional study took place on 63 dairy farms in Germany, Spain and France which have been preselected from the group of farmers in WP2. The farmers were asked to keep comprehensive records of their treatments for mastitis with conventional and homeopathic remedies over a time period of a year. The one-year-mastitis-study on organic dairy farms revealed curing rates which ranged between 20.8% up to 44.8% among the farms for a successful therapy of clinical mastitis when a homeopathic remedy was used.

Despite the fact that according to the current state of the art the best possible conditions for the use of homeopathy have been implemented in the RCT, no positive therapeutic effect of homeopathic remedies could be evidenced. The clinical control study showed that a successful treatment depends to a high degree on the pathogen species that might have caused the clinical mastitis. For the responsible use of antimicrobial remedies, it should be mandatory to take milk samples for microbiological analysis before starting the mastitis treatment. The choice of whether or not to use antimicrobial or other remedies should in the first place be made on the basis of laboratory results.

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1. Introduction

Mastitis is one of the most common reasons for the culling of dairy cows (Bradley 2002; Kuwan 2012) and causes high economic losses on dairy farms (Wilson and others 1999; Suriyasathaporn and others 2000; McCarron and others 2009; Mansion-de Vries and others 2015). Moreover, mastitis treatment is the most frequent reason for the use of antimicrobials in dairy production world-wide (Erskine and others 2002; Roberson and others 2004; Lago and others 2011; Mansion-de Vries and others 2014; Mansion-de Vries and others 2015). Significant increases in the prevalence of antibiotic resistance have been observed worldwide (ECDC/EFSA/EMA 2015; Kuipers and others 2016). A fundamental cause of the development and spread of antimicrobial resistance has been the increasing use of antimicrobials (CDC 2013; Read and Woods 2014; ECDC/EFSA/EMA 2015). Finding alternative treatments are one of the methods of combatting antimicrobial resistance. For various reasons, homeopathy is enjoying increasing popularity as an alternative treatment method, particularly on organic farms. The increasing expectations of consumers concerning food without antimicrobial residues, no unintended side-effects and no or very short withdrawal periods📖 might also be contributing to an increase in the use of homeopathy in food-producing animals (Leon and others 2006). Furthermore, homeopathic remedies can be used without consulting a veterinary practitioner. The price of homeopathic remedies is also considerably lower than that of conventional remedies.

The European Regulation on organic agriculture promotes the use of homeopathy*: homeopathic products shall be used in preference to chemically-synthesized veterinary products provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended* (European Commission 2008). However, homeopathy is discussed controversially in medical science (Shang and others 2005; Rostock and others 2011). According to European law (European Commission 2008) only remedies with proven therapeutic efficacy should be administered to diseased. The use of ineffective remedies is a risk to animals' welfare; an ineffective treatment can lead to prolonging the suffering of diseased animals or to the development of a chronic disease. In order to ensure that only effective remedies are administered to diseased animals, medicinal products need proven therapeutic efficacy both from clinical trials and in farm practice. Randomised Control Trails (RCTs) are widely accepted as the gold standard for clinical research on the efficacy of medicinal products (Pocock 1983; Kaptchuk 2001; Kabisch and others 2011).

Although various clinical trials concerning the efficacy of homeopathic remedies have been conducted in the past (recently reviewed by Doehring and Sundrum (2016)), a clear indication of whether homeopathy is effective or not could not be provided. Apart from inappropriate study designs often found in the reviews, homeopathic principles were hardly followed adequately. In trying to avoid weak points identified in previous study designs, a randomised clinical control trial (RCT) on the use of homeopathy was conducted to compare the effectiveness of treatments of bovine clinical mastitis treated with homeopathic remedies, conventional antimicrobial remedies and a placebo on dairy farms while following homeopathic principles and considering best possible treatment conditions.

An additional mastitis study took place on 63 farms in Germany, Spain and France over a period of one year. The on-farm study was performed to find out how curing rates of bovine mastitis will develop when farmers treat their animals on their own criteria (no external input). Farmers, who already participated in task 4.2 and from which is known that they use homeopathic remedies in case of clinical mastitis, were asked to keep comprehensive records regarding their mastitis treatments.

2. What is the difference between Homeopathy and Allopathy?

The term “homeopathy” is derived from the Greek words for "like/similar" and "suffering" and it is a complementary and alternative or regulatory medicine which was developed by Samuel Hahnemann (*1755 - 1843†, a German physician and philosopher) more than 200 years ago. This alternative treatment has a wide field of applications: acute and chronic diseases, infections, metabolic disorders, preventive health care and mental illness etc. Hahnemann (Schmidt 1992) developed three basic principles of homeopathy:

a) 1st principle: “similia similibus curentur” (“like cures like):

This central principle is that a disease can be cured by a substance that produces similar symptoms in healthy people. For example an onion causes nasal or ocular discharge and is used in the treatment of acute rhinitis (runny nose).

b) 2nd principle: Homeopathic testing & principle of individualisation:

An initial step in the similarity rule is testing the substances on healthy people. The resulting symptoms caused by the substances administered are compiled into a homeopathic “drug picture”. The most important characteristics of a remedy are determined as leading symptoms, summarised in the “Materia Medica”📖. Treatments are “individualized” for each animal. Thus, it is not uncommon to treat different animals with the same disease differently, depending on the totality of symptoms expressed by the animal. Contrary to conventional treatments, the aim of a homeopathic consultation is to find the “totality of symptoms” on a physical and mental level. This closest match is called the “simillimum”.

c) 3rd principle: Potentiation - “law of minimum dose”:

While a substance in the mother tincture causes certain symptoms, it might have the potential to cure these symptoms in small doses. Many practitioners believe that the more a substance is diluted, the greater its power to treat diseases. The substance need to be shaken between each dilution in order to activate the properties of the homeopathic remedy. Homeopaths claim that water molecules can form a structure that contains physical information from the homeopathic drugs. Today, dilutions of 1:100 repeated 6 or 30 times are commonly used, but it goes up to 10,000 consecutive dilutions.

The effect of homeopathy is based on the principle of resonance. According to Hahnemann, homeopathic remedies aim to stimulate the body's ability to heal and result in “the complete restoration of perfect health” (physically, mentally and emotionally). By contrast, the allopathic approach relies on treating an animal’s physical symptoms. In general, conventional medicine starts with an organotroph medical approach, which means focusing on the affected organ. Allopathic remedies were chosen according to the diagnosis (name of disease) because it is a predictable entity. Therefore, it is possible to treat every patient with the same diagnosis / disease with the same remedy. Similar diagnoses might thus lead to the same prescription, regardless of individual or unique symptoms. Another difference between both treatment methods is that homeopathic remedies derived from Nature are highly diluted whereas conventional remedies are often produced synthetically and are usually in higher dosages.

Part A - Randomised Control Trial

3. Material and Methodology

An RCT was performed, taking into account specific guidelines for RCTs as well as the basic principles of homeopathy, in order to compare the effectiveness of homeopathy, antimicrobial treatment and placebo in cases of bovine clinical mastitis in dairy cows.

3.1.1 Study population

The clinical study was conducted from June 2016 until the end of December 2016. In total, a number of 180 lactating dairy cows were enclosed, deriving from four herds located in the eastern part of Germany. Recruited were cows suffering from mild or moderate clinical mastitis. According to the International Dairy Federation (1999), a mild case of mastitis is defined as a case where there are only visible changes in milk secretion (e.g. flakes, discoloration, change in consistency) and by the absence of localised udder symptoms. Moderate mastitis is additionally characterised by the presence of inflammatory signs (swelling, pain, redness and/or heat). Cows exhibiting severe mastitis, which is defined by the presence of fever or disturbances of general behaviour, were excluded from the study. All animals considered in the study did not suffered from any other disease during the trial period. Animals affected in more than one mammary gland quarter were also excluded. In addition, cows with mastitis caused by *Streptococcus agalactiae* and *Trueperella pyogenes* or with injuries to the teats were not considered either, because an unsuccessful treatment could create long-term damage to the udder. Furthermore, to avoid a treatment of recurrent mastitis, cows treated with antimicrobial or anti-inflammatory products within the previous 30 days were also not recruited to the study.

3.1.2 Study design

Concerning the assessment of remedies' efficacy, the study was performed as a randomized, double-blind and placebo-controlled trial, following the gold standard in clinical research for the assessment of a remedy's efficacy (Pocock 1983; Kaptchuk 2001; Kabisch and others 2011). Randomisation was ensured by using a "lucky dip", containing coloured sticks in white, red and green; each of the colours representing one treatment group. In order to keep the number of cows in each treatment group balanced, 15 sticks of each colour were used per farm. All participants were blind to the treatment method as far as possible. The veterinarian and the laboratory assistant were blind to the type of treatment in order to avoid biased evaluations of treatment success and farmers were blind to the homeopathic and the placebo treatment to prevent an early stop of the clinical trial. Homeopathic and placebo remedies were administered in the form of globules and antimicrobials in the form of udder injectors. A non-blindness between the antimicrobial and homeopathic / placebo treatment was allowed deliberately for the sake of protection against injuries of the teats or new udder infections when administering the remedy intracisternal.

3.1.3 Remedies

The selection of homeopathic remedies was based on a list of 21 homeopathic remedies, dedicated for the treatment of animals with mastitis (*Aconitum* C30, *Apis* C30, *Belladonna* C30, *Bryonia* C30, *Calcium floratum* C30, *Calendula* C30, *Carbo vegetabilis* C30, *Cistus* C30, *Conium* C30, *Hepar sulphuris* C30, *Kalium bichromicum* C30, *Lachesis* C30, *Mercurius solubilis* C30, *Phelandrinum* C30, *Phytolacca* C30, *Pulsatilla* C30, *Pyrogenium* C30, *Silicea* C30, *Sulphur* C30, *Tuberkulinum Koch* C30, *Urtica urens* C30). The pre-selection - performed by a software-repertory📖 when inputting "mastitis" in the entry field "disease" and by a professional veterinary homeopath, with longstanding experience in the homeopathic treatment of food producing animals - was based on the frequency of use for the

treatment of mastitis. Nevertheless, it was possible to use any other homeopathic single remedy when 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 were of the same size. Correspondingly, the person administering the remedies cannot distinguish between a homeopathic and a placebo treatment (see Annex III). Both types of globules were administered in a dosage of 10 globules per day dissolved in water and drawn up in a syringe (either orally or vaginally) for a period of five days. The antimicrobial treatment was carried out according to the national antibiotic guidelines and the farm protocol relating to the use of antimicrobials in case of mastitis. Antibiotics were applied via udder injector in the dosage recommended by the manufacturer (see Table 1).

Table 1: Antimicrobial remedies used in the clinical trial on farms

Antimicrobial remedy	Active substance per injector	Dosage per day	Duration of administration
Synulox™ LC Plus	Amoxicillin (200mg), Clavulanic acid (50mg), Prednisolone (10mg)	1 injector every 12 hours	1,5 days
Oxacillin-Na 1000mg-Euter-Injektor	Oxacillin-Natrium (1043mg)	1 injector per 24 hours	3 days
Vetriclox® L	Cloxacillin-Natrium (1000mg)	1 injector per 24 hours	3 days
Ubrolexin®	Cefalexin (200mg) Kanamycin (100.000 I.U.)	1 injector per 24 hours	2-3 days
Procain-penicillin-g injector	Procain-Benzylpenicillin (3000mg)	1 injector per 24 hours	3 days
Wedeclox® Mastitis	Oxacillin-Natrium (1000mg)	1 injector per 24 hours	2-3 days
Peracef®	Cefoperazon (100mg)	1 injector per 24 hours	2 days
Cloxamycin L®	Cloxacillin-Natrium (1000mg)	1 injector per 24 hours	3 days

3.1.4 Treatment procedure

After the identification of clinical mastitis by the farmer during the milking routine, the consulted veterinarian decided - on the basis of the defined inclusion and exclusion criteria - whether or not to include the cow in the study. On the day of inclusion (day 0), a clinical examination and milk sampling were performed. Clinical and homeopathic symptoms were documented in a previously developed anamnesis book and software tool for the purpose of selecting a homeopathic remedy. Every case of mastitis was repertorised (cross-check of clinical symptom picture with remedy picture; see chapter 3) individually by the veterinarian experienced in homeopathy (see Annex II). The tools were used to standardise the repertorisation and to avoid any personal preferences the veterinarian might have had for a particular remedy. Independently of the future treatment method, a homeopathic, placebo and antimicrobial remedy was allocated to each cow. After the clinical examination and selection of remedies, the cows were randomly allocated to different treatment strategies (homeopathic, placebo or antibiotic treatment) by the farmers using the aforementioned lucky dip. The homeopathic and placebo remedies were identical in their packaging, physical appearance and labelling. Implementing this additional level of blinding in the trial ensured that the farmer does not end the placebo treatment prematurely. The farmer administered the remedy determined in the previous randomisation to the diseased animal. In order to verify treatment outcome, the veterinarian, who was completely unaware

which treatment method was being set, performed a clinical examination and took milk samples again on the 7th, 14th and 28th day after the initial treatment (see Annex I). If the farmer observed a worsening of symptoms or new symptoms developing during the trial period, the veterinarian performed a thorough clinical examination of the diseased cow and classified the animal as either responsive or non-responsive to the treatment given, followed by deciding whether or not the animals should be excluded from the trial. In the case of exclusion, the cow was immediately treated with conventional remedies. When homeopathic symptoms changed within the first seven days after inclusion or the laboratory results indicated a pathogenic resistance to the antimicrobial agent administered, the veterinarian was allowed to change the remedy whilst staying with the same treatment method. Additional remedies such as non-steroidal anti-inflammatory drugs (NSAIDs) or udder ointments were not used.

3.1.5 Milk samples

Milks samples were taken by the veterinarian according to the good manufacturing practice (Baumgartner 2014) which were cyto-bacteriologically analysed by a certified milk laboratory (bovicare GmbH, Potsdam, Germany). Pathogens were identified by using a common mastitis diagnostic test: bacteriological culture on blood agar plates followed by sensory, microscopic and - if necessary- by 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 determined by the aforementioned milk laboratory using the Integrated Milk Testing™ MilkoScan FT 6000 (Foss GmbH, Hamburg) device. For technical reasons, SCCs could not be determined when milk deviates significantly from normal (e.g. flocks or clots). In this case, the SCCs are assessed with FL+, FL++ or FL+++, depending on the degree of deviation from normal: low, medium or high, respectively.

3.1.6 Evaluation criteria for the therapeutic success

For the purposes of evaluation, the following hypotheses for the effectiveness of allopathic and homeopathic remedies for treating clinical mastitis in dairy cows were formulated beforehand:

- *The homeopathic treatment procedure is more effective than the placebo treatment for curing mastitis completely.*
- *The antibiotic treatment is more effective than the placebo treatment for curing mastitis completely.*
- *The homeopathic and the antibiotic treatment procedure are just as effective as one another in curing mastitis completely.*

The assessment of effectiveness was based on well-established criteria for determining cure rates for different medical mastitis treatment methods (EMEA 2003) and on the criteria for an healthy udder defined by the German Veterinary Association (DVG 2012):

- Bacteriological cure: Elimination of the pathogens present on the day of inclusion (day 0),
- Cytological cure: SCC is ≤ 100.000 cells / ml milk and no visible changes in the milk,
- No external pathological changes in the udder,
- Cow's general condition is normal.

The category "full recovery" was only awarded when the following criteria were fulfilled:

- Negative for bacteriological growth in laboratory analysis of milk samples and

- SCC is ≤ 100.000 cells / ml milk

Udder quarters were defined as “newly infected” when a new pathogen (unlike the one on day of inclusion) appeared and at least one follow-up milk sample was culture-negative in between. If the initial pathogen occurred again within the investigation period of 28 days, it was classified as a recurrence. Relapses of the same pathogen within the observation period are considered as unsuccessful in pathogen elimination.

In approximately 10 - 40% of analysed milk samples, pathogens are not usually identified in routine clinical culture assays (Makovec and Ruegg 2003; Kuehn and others 2013; Ganda and others 2016). When this happened on the day of inclusion, the follow-up milk sample also needed to be culture-negative in order to evaluate the treatment as successful in curing the bacterial infection. To calculate cure rates, a comparison of treatment results at the time of each follow-up check on day 7, 14 and 28 with the result of the milk analysis on day 0 was made. When a cow’s general condition deteriorated or there was no improvement of clinical symptoms within seven days after the first treatment (day of inclusion) or after medical prescription was altered, these animals were grouped as non-responsive.

4. Results

In the present study, a total number of 180 cases of clinical mastitis were assessed. From these, 60 cows suffering from mastitis were randomly allocated to homeopathic treatment, 60 got placebo and 60 received antimicrobial treatment. Infections were identified in the following udder quarters: 29% rear left (RL), 29% rear right (RR), 23% front right (FR) and 19% front left (FL). Figure 1 and Table 2 show the distribution of frequency of the pathogens identified in pre-treatment milk samples within the treatment groups. In total, 13 pathogen species were found in milk samples on the day of first examination. The majority of the isolated mastitis pathogens were identified as *Streptococcus uberis* (n=45), *Escherichia coli* (n=16) and *Streptococcus dysgalactiae* (n=13), Klebsiella spp. (n=9) and other aesculin-positive streptococci (n=8). The distribution of the remaining identified pathogens between the bacteria species is as follows: coagulase-negative staphylococci (n=7), *Staphylococcus aureus* (n=7), coliform bacteria (n=5), Enterococci spp. (n=5), *Corynebacterium bovis* (n=2), yeasts (n=2) and Serratia spp. (n=1). In 33% of milk samples a mastitis pathogen could not be found.

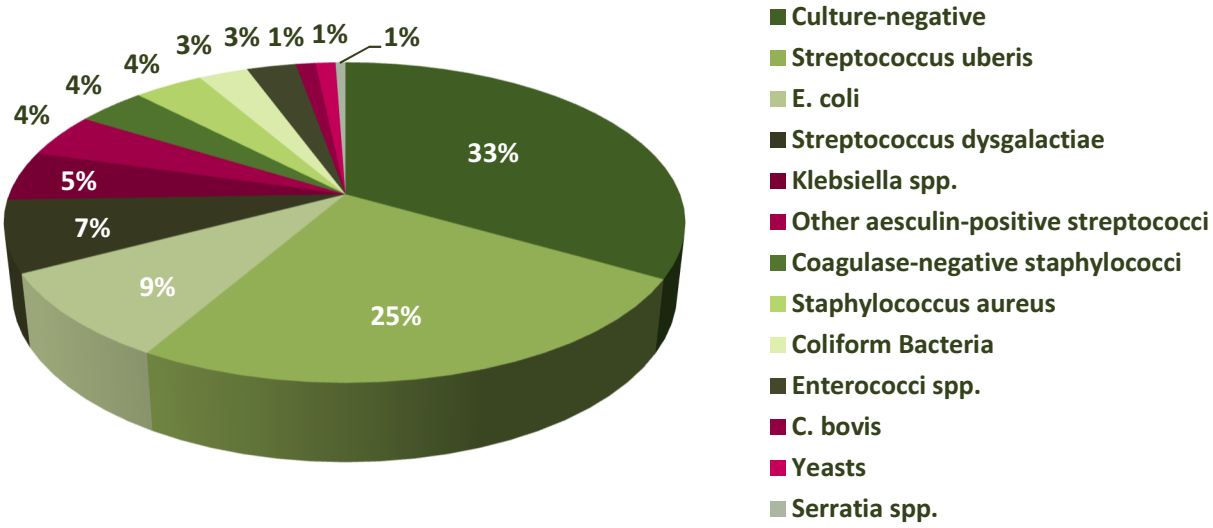


Figure 1: Pathogens identified in the milk samples on the day of inclusion before mastitis treatment commenced

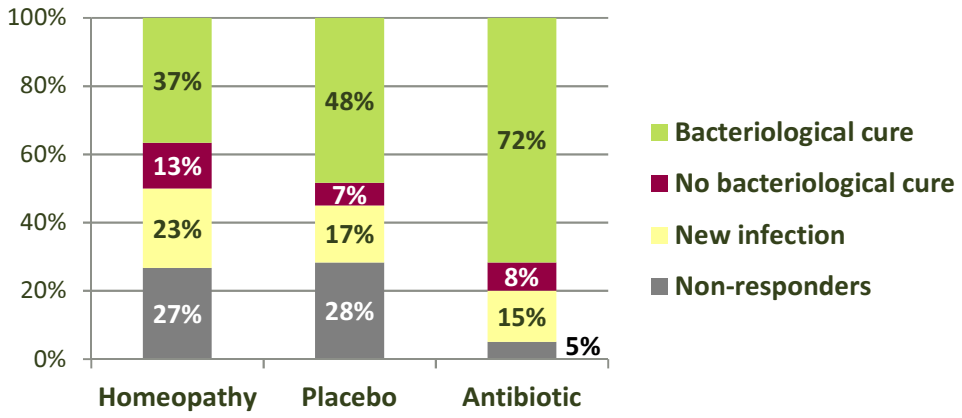
Table 2: Frequency distribution of pathogens identified on day of inclusion by treatment strategy

Pathogen species	Treatment strategy

	Homeopathy	Placebo	Antibiotic
Culture-negative	**20**	**22**	**18**
Streptococcus uberis	**12**	**16**	**17**
E. coli	**6**	**5**	**5**
Streptococcus dysgalactiae	**3**	**3**	**7**
Klebsiella spp.	**5**	**1**	**3**
Other aesculin-positive streptococci	**4**	**3**	**1**
Coagulase-negative staphylococci	**3**	**2**	**2**
Staphylococcus aureus	**1**	**2**	**4**
Coliform Bacteria	**1**	**2**	**2**
Enterococci spp.	**4**	**0**	**1**
C. bovis	**0**	**2**	**0**
Yeasts	**1**	**1**	**0**
Serratia spp.	**0**	**1**	**0**
In total	**60**	**60**	**60**

4.1.1 Evaluation of therapeutic success one week after the initial treatment started

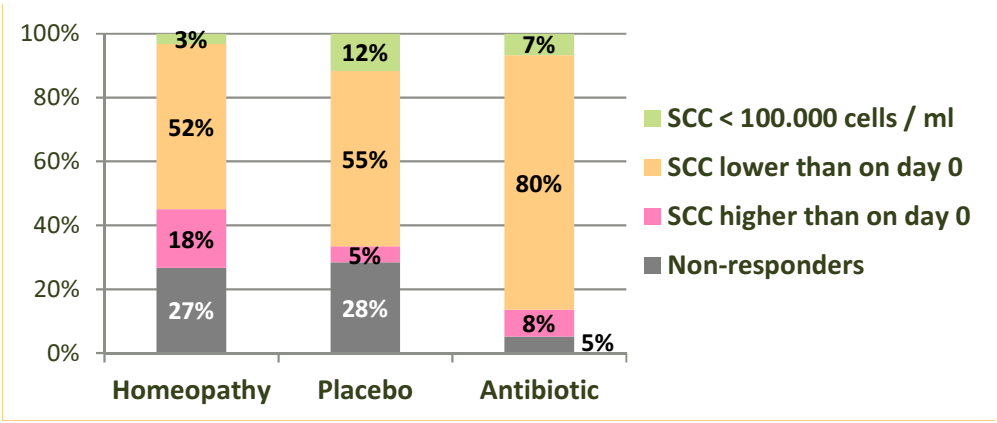
One week after the initial treatment, the therapeutic success was evaluated with a laboratory analysis of milk samples and examination of clinical symptoms. Whether treatment was successful in effecting a bacteriological cure is presented in Figure 2. In total, 94 out of 180 treatments (52.2%) were rated as successful while 53 treatments (29.4%) were seen as unsuccessful (non-responders and no bacteriological cure). New infections were detected in 33 out of 180 cases (18.3%). The pathogens identified before the initial treatment were still present in the udder quarter at the time of the first follow-up check in 9.4% of all cases of mastitis investigated. 36 of all 180 cows (20.0%) suffering from mastitis were excluded from the clinical trial within one week after the day of inclusion. The majority of animals excluded belonged to the placebo treatment (17 cows; 47.2%), followed by 16 cows from the homeopathic (44.4%) and three animal from the antibiotic treatment group (8.3%). Reasons for exclusion from the study were either the deterioration of a cow's general condition or the fact that no visible positive changes in milk character had appeared in comparison to the beginning of the clinical trial. The antimicrobial treatment achieved the highest bacteriological cure rate compared to the other treatment groups: 45.7% of all successful treatments in bacteriological cure took place as part of the antibiotic treatment. In contrast, 47.1% of all cows which failed to be cured were treated with homeopathic remedies. Regarding the ratio of successful treatment to unsuccessful treatment of the bacteriological infection (no bacteriological cure and exclusion), the antimicrobial treatment appeared to be the most promising method for eliminating pathogens within the first week after the initial treatment.



	Bacteriological cure	No bacteriological cure	New infection	Non-responders	
Homeopathy (n=60)	22	8	14	16	
Placebo (n=60)	29	4	10	17	
Antibiotic (n=60)	43	5	9	3	
In total	94	17	33	36	180

Figure 2: Bacteriological cure rates in comparison with results of day 0, showing treatment groups at the time of the first follow-up check. (Data table contains number of cases)

Similar results to the bacteriological cure rates were found for cytological curing (see Figure 3). Placebo and antimicrobial treatments were superior to the homeopathic treatment when evaluating the cytological cure rates. In general, SCCs decreased (124 out of 179 cases of mastitis; 69.3%) after mastitis treatment, especially after the treatment with the antimicrobial remedies. A full recovery in SCCs (<100.000 cells per ml milk) only took place in 13 cases of mastitis (7.3%); mainly after a placebo treatment. In contrast, after a treatment with homeopathic remedies the SCC was more often higher than on day 0 in comparison to the placebo- and antimicrobial treatments. The antimicrobial treatment showed the best development in cytological cure. The SCC of one milk sample could not be measured because the milk production of the infected udder quarter ceased almost completely.



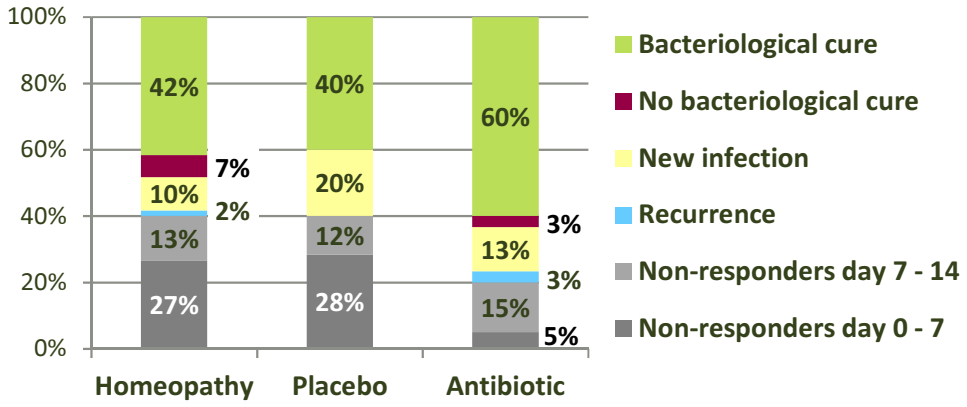
	SCC < 100.000 cells / ml	SCC lower than on day 0	SCC higher than on day 0	Non-responders	
Homeopathy (n=60)	2	31	11	16	
Placebo (n=60)	7	33	3	17	
Antibiotic (n=59)	4	47	5	3	
In total	13	111	19	36	179

Figure 3: Cytological cure rates in comparison with results of day 0, showing treatment groups at the time of the first follow-up check. (Data table contains number of cases)

Restitutio ad integrum (full recovery) was only awarded when bacteriological and cytological cures appeared simultaneously. Only 13 out of 180 udder quarters (7.2%) fully recovered one week after the initial treatment; mainly after a placebo treatment (7 animals), followed by the antibiotic (4 animals) and homeopathic treatment (2 animals).

4.1.2 Evaluation of therapeutic success two weeks after the initial treatment started

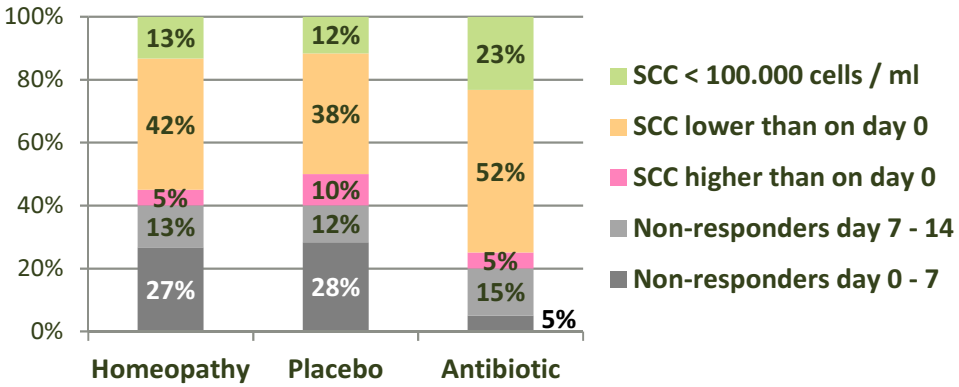
At the time of the second follow-up check, 85 out of the 180 animals (47.2%) were successfully cured of the pathogens (elimination) and in nine udder quarters the initial pathogen was still found (including recurrences; 5.0%). Further 24 cows (in total 60 out of 180 animals) were excluded from the clinical trial due to deterioration of the cows' general condition and/or no positive changes in milk character within the previous week. The majority of cows excluded within the second trial week were mainly treated with antibiotic remedies (9 animals), closely followed by the homeopathic (8 animals) and the placebo treatment (7 animals). 42.4% of all cows categorised as bacteriological cured received an antimicrobial, 29.4% a homeopathic and 28.2% a placebo remedy. Only six out of 180 udder quarters (3.3%) were still infected with the same pathogen as on day 0: four in the homeopathic- and two in the antibiotic-group. Despite the relatively high bacteriological cure rate, 26 cases of new udder infections appeared which had been culture-negative before; mainly in the case after a placebo-treatment (46.2%). A pathogen occurred again (recurrence) in the three udder quarters which had been treated and evaluated as bacteriological cured before. Overall, the antimicrobial treatment achieved the highest therapeutic success when considering the ratio of success (bacteriological cure) and failure in bacteriological cure (no bacteriological cure, new infections and exclusion) (see Figure 4).



	Bacteriological cure	No bacteriological cure	New infection	Recurrence	Non-responders	
Homeopathy (n=60)	25	4	6	1	24	
Placebo (n=60)	24	-	12	-	24	
Antibiotic (n=60)	36	2	8	2	12	
In total	85	6	26	3	60	180

Figure 4: Bacteriological cure rates in comparison with results on day 0, showing treatment groups at the time of the second follow-up check. (Data table contains number of cases)

The SCC decreased in 108 out of 180 udder quarters (60.0%) within the last two weeks after the initial treatment. Despite the decrease in SCCs, the values seldom fell below the threshold for a healthy udder quarter of 100.000 cells per ml milk. Only 29 from 180 udder quarters (16.1%) could comply with this goal. Furthermore, an increase of the SCC appeared in 12 cases at the time of the second follow-up check, which was mainly observed after a placebo treatment. Figure 5 shows the comparison of cytological curing rates for each treatment method in detail 14 days after the initial mastitis treatment. Even after two weeks the antimicrobial treatment seems to be the method of choice in order to gain the best cytological curing rates.



	SCC < 100.000 cells / ml	SCC lower than on day 0	SCC higher than on day 0	Non-responders	
Homeopathy (n=60)	8	25	3	24	
Placebo (n=60)	7	23	6	24	
Antibiotic (n=60)	14	31	3	12	
In total	29	79	12	60	180

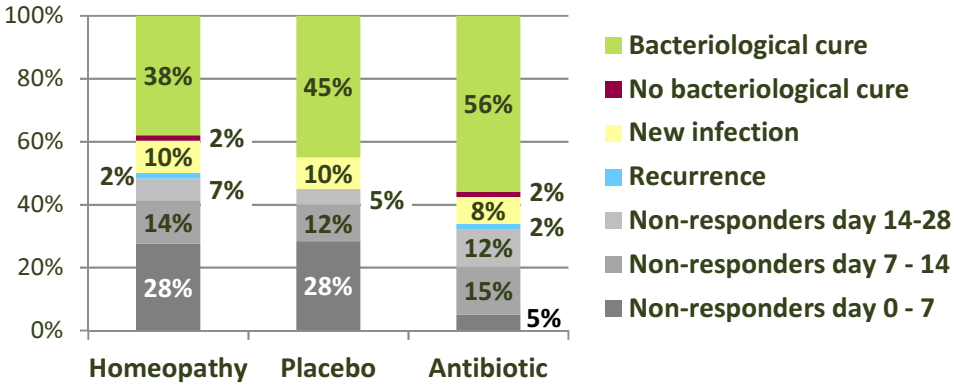
Figure 5: Cytological cure rates in comparison with results of day 0, showing treatment groups at the time of the second follow-up check. (Data table contains number of cases)

At the time of the second follow-up check, only 26 out of 180 udder quarters (14.4%) were classified as fully recovered (bacteriological and cytological cure appeared at the same time). The majority of them (11 cows) were treated with antimicrobial remedies, followed by the homeopathic treatment method (8 animals). Seven out of 26 animals were classified as totally cured after administering a placebo remedy.

4.1.3 Evaluation of therapeutic success four weeks after the initial treatment started

Three animals did not receive a third follow-up check due to involuntary culling (culling reasons: dangerous handling, lameness and fertility disorder). At the time of the last follow-up check (28 days after the day of inclusion), further 14 animals suffered a new infection or a relapse for which an improvement in udder health was not foreseeable. They were therefore also classified as no-responders and were excluded from the study. A total of 74 animals (41.8%) were excluded from since the beginning of the clinical trial, mainly after a homeopathic and placebo treatment (each 27 animals). Despite of the expected superior treatment success of the antibiotic treatment method, it has to be mentioned, that only eight animals were less excluded from the antibiotic treatment group than from the other two treatment strategies within the whole trial period of 28 days. In total, 82 out of the 177 animals (46.3%) were successfully cured in a bacteriological point of view; mainly after the antibiotic therapy (55.9%),

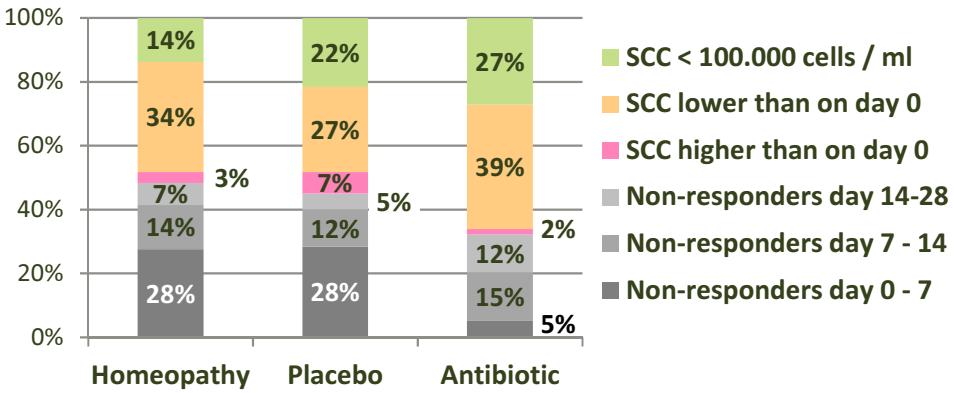
followed by the placebo treatment (45.0%). The cure rate after a homeopathic treatment was again the lowest: 37.9%. In three mastitis cases, the pathogen found in the pre-treatment milk sample was still present. Furthermore, 17 udder quarters (9.6%) were evaluated as newly infected. New infections occurred with an approximately equal frequency within all three treatment strategies: each six animals within the homeopathic and placebo group and five animals within the antibiotic one. Two cows experienced a recurrence at the time of the third check-up. Figure 6 shows the cure rates in detail for all three treatment methods.



	Bacteriological cure	No bacterio-logical cure	New infection	Recurrence	Non-respond-ers	
Homeopathy (n=58)	22	2	6	1	28	
Placebo (n=60)	27	0	6	0	27	
Antibiotic (n=59)	33	1	5	1	19	
In total	82	3	17	2	73	177

Figure 6: Bacteriological cure rates in comparison with results on day 0, showing treatment groups at the time of the third follow-up check. (Data table contains number of cases)

Figure 7 shows the cytological results of milk samples' analysis 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 than the homeopathic and the placebo treatment strategy. In total, only in 37 out of 177 udder quarters (20.9%) the SCCs dropped under the envisaged threshold value of 100.000 cells per ml milk; almost half of them were treated with antimicrobial remedies (43.2%). An increase in SCC occurred in seven mastitis cases, which were mainly treated placebo remedies (4 animals).



	SCC < 100.000 cells / ml	SCC lower than on day 0	SCC higher than on day 0	Non-responders	
Homeopathy (n=58)	8	20	2	28	
Placebo (n=60)	13	16	4	27	
Antibiotic (n=59)	16	23	1	19	
In total	37	59	7	74	177

Figure 7: Cytological cure rates in comparison with results of day 0, showing treatment groups at the time of the third follow-up check. (Data table contains number of cases)

A full recovery *(Restitutio ad integrum*) was only identified when bacteriological and cytological cures appeared simultaneously. Only 36 out of 177 udder quarters (20.3%) had fully recovered within 28 days; mainly after an antibiotic treatment (44.4%), closely followed by the placebo (36.1%). The homeopathic treatment method achieved in only 19.4% of all mastitis cases treated a total cure at the time of the third follow-up check.

4.1.4 Specific findings

In addition, an evaluation of bacteriological cure rates on pathogen level was performed in order to find out how effective the different treatment methods in elimination of specific pathogen species have been (see Figure 8). For the purpose of evaluation the bacteriological laboratory results of the first follow-up check were used for comparison, because a lower recurrence and new infection rate in treated udder quarters were expected than in the other follow-up checks. An analysis of bacteriological cure rates at pathogen lever was only carried out for culture-negative milk samples and bacteria species *Streptococcus uberis, E. coli, Streptococcus dysgalactiae and* Klebsiella spp.. Due to very low sample sizes of other pathogen species identified on day 0, the evaluation of those species was done in a summarised category “Other pathogens”. Particularly for unspecific infections (culture-negative pre-treatment milk samples) and *E. coli*-infections high cure rates were found; independently of the treatment method. A mastitis caused by specific pathogens species were more likely successfully treated with antimicrobial remedies. For instants, the present study shows that low cure rates were achieved by a homeopathic or placebo treatment when treating a mastitis caused by *Streptococcus uberis, Streptococcus dysgalactiae,* Klebsiella spp. and other bacteria species.

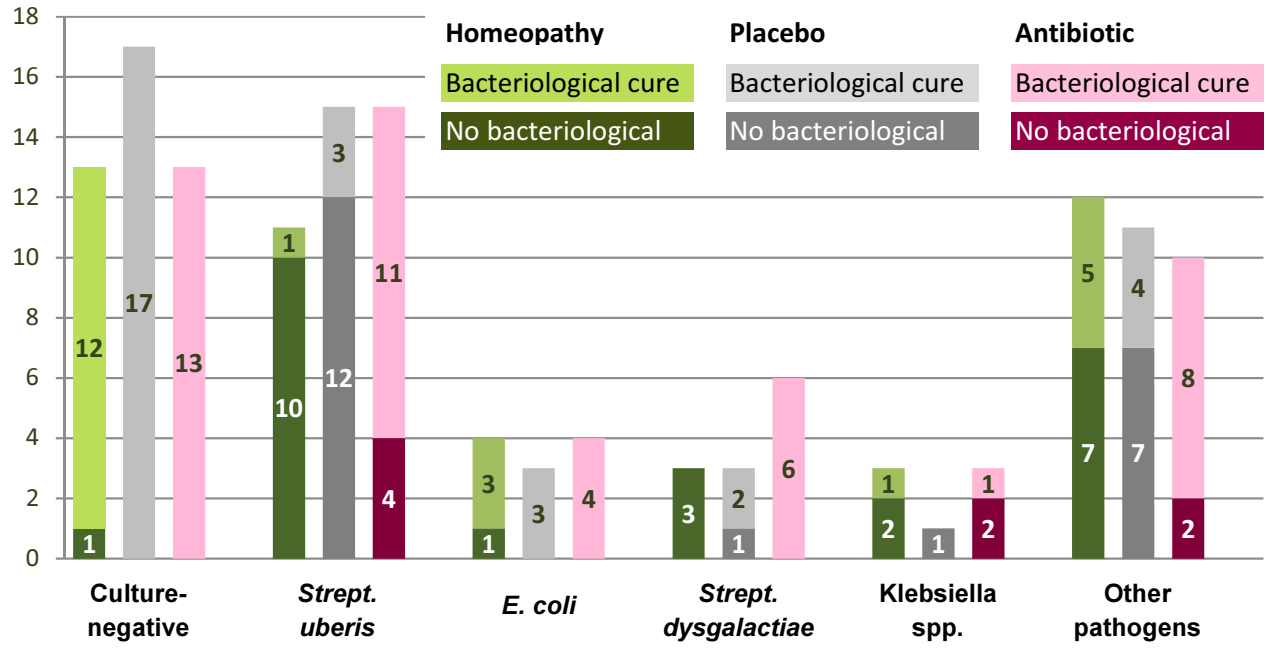


Figure 8: Bacteriological cure rates by treatment methods on pathogen level. Number of animals who has or has not eliminated the initial pathogen identified on the day of inclusion at the time of the first follow-up check (day 7).

Figure 9 shows the bacteriological cure course of udder quarters treated with homeopathic, placebo and antimicrobial remedies over a period of 28 days. The overview confirms the results of the case-by-case analysis: the antimicrobial treatment method showed continuous high cure rates and low non-responder rates. The homeopathic treatment strategy showed similar cure rates compared to the placebo treatment method. Concerning the development of SCC, the antimicrobial treatment was superior to placebo and homeopathic treatment (see Figure 10). A continuous decline in SCCs was observed after each treatment method. Although, the best results in cytological cure achieved the antibiotic treatment method. A presence of high SCCs by some cows was mainly found after a homeopathic and placebo treatment. However, over the total observation period the number of high SCCs declined steadily after the use of homeopathic and placebo remedies.

A continuous total cure throughout the period of 28 days was found in only seven out of 177 cases (2.8%). The majority of them occurred after a placebo treatment (5 cases) and each one total cure was achieved by a homeopathic and antibiotic treatment.

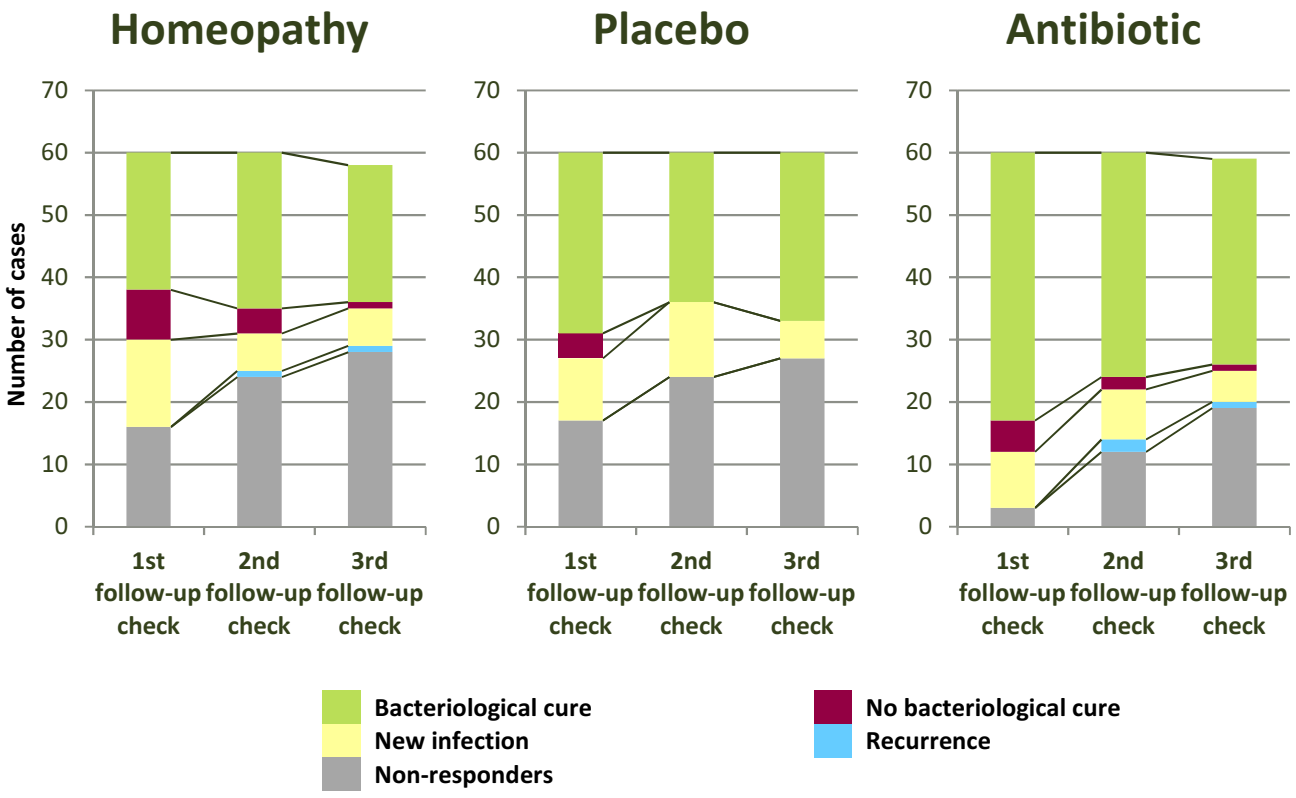


Figure 9: Development of bacteriological cure rates at the time of the 1st, 2nd and 3rd follow-up check.

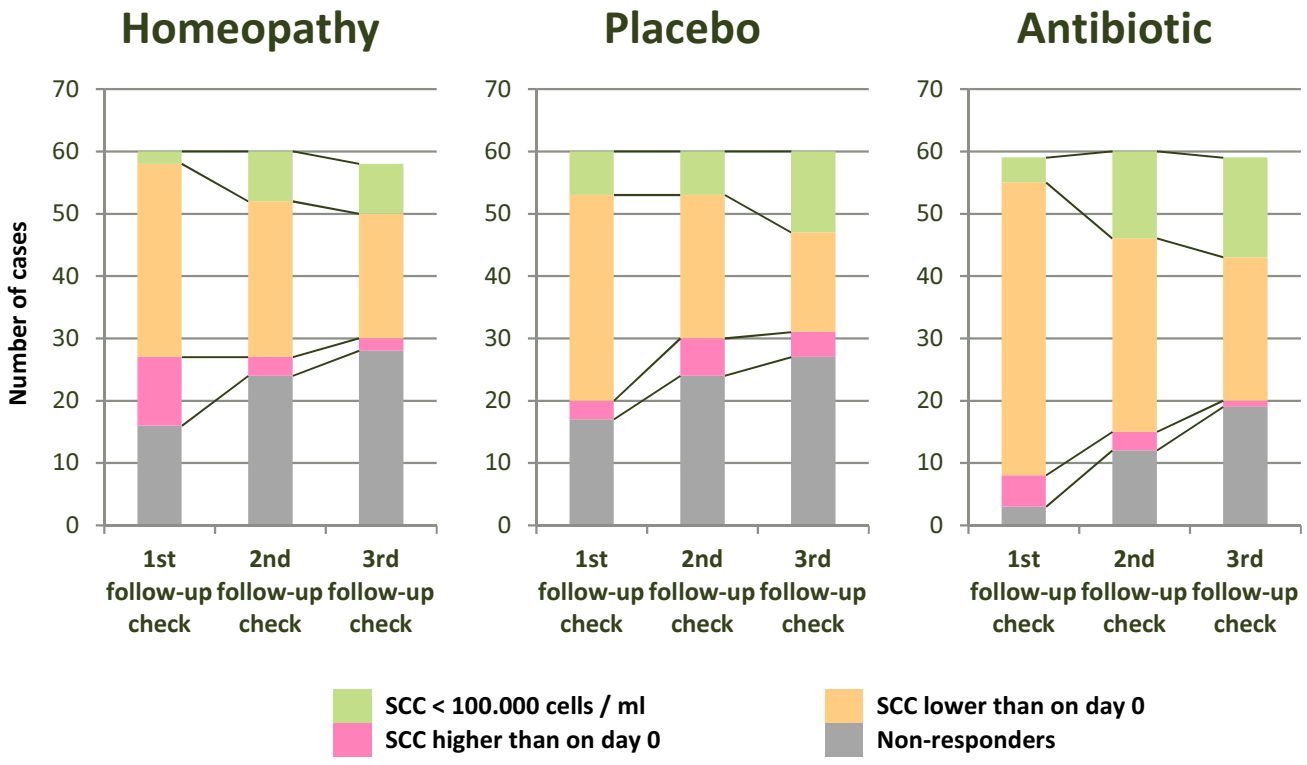


Figure 10: Development of cytological cure rates at the time of the 1st, 2nd and 3rd follow-up check.

5. Discussion

In general, a direct comparison of cure rates revealed in the present study with other clinical mastitis studies is barely meaningful, because of large variations in study design, treatment procedure, definition for cure, implementation of homeopathic principles and in control groups (Doehring and Sundrum 2016).

The cure rates of the homeopathic treatment method were regularly below those of the antimicrobial and similar to the placebo treatment method. This might be due to various reasons:

The methodological approach of the study made an attempt to consider the homeopathic principles as far as possible. Dairy cows were treated as a unique individual and received the remedy which matched best according to the clinical symptoms. The appropriateness of selection of a remedy cannot be verified, because there are no standard treatments in classical homeopathy. The accuracy of the selected homeopathic remedy depends to a high degree on the homeopathic expertise of the veterinarian. To reduce possible bias and to consider the principle of an individualised homeopathic treatment as much as possible, a software-repertory was used. Despite of the veterinarians' expertise and the use of the digital repertory, it might have happened that an inappropriate homeopathic remedy was selected resulting in negative influences on curing rates. Some homeopathic symptoms (e.g. modalities or striking symptoms) are difficult to detect under practical conditions, even for a homeopathic expert. It could also have been the case that some homeopathic symptoms were not properly detected, a consequence of this could be an inappropriate selection of a homeopathic remedy. Another point of critic 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 for the sake of smooth functioning of the treatment procedures and for elimination of troublesome factors which may have some influence on curing rates. Furthermore, it is reported in literature that if the correct remedy is selected, then it will act curatively in any dosage or potency (Vithoulkas 2002). A critically view must also be taken to the incomplete blindness between homeopathic or placebo remedies (globules) and antimicrobial remedies (udder injectors). Animals of the homeopathic and placebo treatment were excluded more often at the time of the first and second follow-up check than those of the antibiotic treatment. This kind of farmers' incomplete blindness implied the risk that farmers might have stopped a homeopathic or placebo treatment at an earlier stage than an antimicrobial treatment. Many farmers believe in the efficacy of antibiotic remedies, it could therefore be possible, that they wait longer until they change the remedy. This could be the reason why animals within the antibiotic-group were excluded mainly at the time of the second and third follow-up check. However, the bias was deliberately accepted in order to prevent the risk of iatrogenic harm to animals diseased. The placebo treatment often achieved similar levels of cure rates than the homeopathic treatment method. Shang and others (2005) assumed that any beneficial effects of homeopathic treatment are primarily due to a placebo effect or a non-specific stimulus. Another reason could also be, that the placebo-group had the most culture-negative cases of mastitis that the antibiotic treatment group, which may have contributed positively to the therapeutic success. The problem is that culture-negative milk samples cannot be detected from change in milk character or from clinical symptoms and therefore they cannot be excluded a priori. Furthermore, these cases were treated in agricultural practice as well, culture-negative milk samples were thus not excluded from the analysis. Independently of the treatment method, the majority of all culture-negative mastitis cases treated were successfully cured. The study results indicate that the use of antimicrobial remedies in case of culture-negative pre-treatment milk samples is unnecessary and must be evaluated as contra-indicted. Secondly, other studies have also determined high curing rates when a placebo treatment was used in case of bovine clinical mastitis (0-87%) (Morin

and others 1998; Hillerton and Kliem 2002; Hektoen and others 2004; Werner 2006). A further explanation for relatively high cure rates within the homeopathic and placebo treatment group could also be the fact, that most animals were excluded from these groups at an early stage of the clinical trial. Hence, it is possible that animals affected by the most acute symptoms were prematurely excluded and those suffered from mild symptoms were evaluated. This could have also contributed to positive results. However, the positive results of the placebo treatment should not lead automatically to refrain a mastitis treatment. Mastitis is a painful disease and needs to be treated with the best possible treatment method. Otherwise, a non-treatment increases the risk of extended suffering for diseased animals. In general, the SCCs after a homeopathic treatment were often higher than those after an antimicrobial treatment. Somatic cells (or "body" cells) are a mixture of milk-producing cells shed from the udder tissue (about 2%) and cells from the immune system (leukocytes; the other 98%). Leukocytes are the cells responsible for identifying bacteria and killing them. When leukocytes are transferred to the udder during infection, this results in an increase in SCC. As homeopathic remedies are intended to stimulate the immune system, it cannot be excluded that the increase of SCCs after a homeopathic treatment was stimulated by this kind of activation of the immune system ("initial worsening"). This type of aggravation is described as the optimal reaction from a correct homeopathic remedy (Vithoulkas 1996). The difficulty is to distinguish whether worsening of the diseased animals' symptoms are homeopathic aggravations or a non-response to the remedy administered. A misinterpretation can lead to a prolonged animals' suffering, thus animals with unclear symptoms of aggravation were precautionary excluded for the sake of animals' welfare and health. Also worth mentioning is the low cure rate for a full recovery. None of the treatment groups achieved satisfactory treatment results in this category. Moreover, the study revealed that not every case of mastitis necessarily is in need of an antimicrobial treatment. For a responsible use of antimicrobial remedies in future, it is mandatory necessary to take milk samples before a mastitis treatment. The choice of whether or not to use antimicrobial remedies should only be made on the basis of laboratory results.

6. Conclusion

Some clinical studies showed positive treatment effects when using homeopathy, but the effectiveness of homeopathic remedies must be reconsidered. The clinical study has shown that a homeopathic treatment achieved only moderate cure rates, which were similar to those of a placebo treatment and far beyond those of the antimicrobial treatment strategy. Despite best possible conditions for a homeopathic treatment, no positive therapeutic effect could be evidenced. It can be expected, that a homeopathic treatment in daily farm practice will obtain even worse results. On the basis of these current results, an exclusively treatment with homeopathic remedies for each case of mastitis cannot be recommended. Despite the present study also revealed high cure rates for a placebo treatment, particularly for curing of unspecific mastitis and E.-coli-infections, a general non-treatment of all cases of mastitis cannot be recommend. A non-treatment of diseased animals often led to a deterioration of animals' health (high non-responder rate). A laboratory analysis of milk sample provides detailed information about pathogens present when a mastitis occurred. On the basis of the laboratory results of the milk sample, a target-oriented treatment should be mandatory implemented in daily farm practice in order to achieve a reduce in the use of antimicrobial remedies.

Part B - On-farm mastitis study

7. Material and Methodology

The one-year-mastitis-study took place on 63 farms in Germany, Spain and France who already participated in task 4.2 and from which it was known that they use homeopathic remedies in cases of clinical mastitis (see Deliverable 4.2). The farmers were asked to keep comprehensive records regarding their treatments in cases of mastitis with allopathic and homeopathic remedies during a time period of one year. Farmers are receiving a monthly allowance of 10 Euro when the cases recording has been completed. For the sake of documentation, a template inspired by the decision tree developed in task 4.1 was developed (see annex IV & V). Farmers received a reminder at regular intervals with the request to return complete documentation sheets. For a period of one year scientists recorded the data received from farmers in an excel sheet. At the end of the documentation phase all data collected in Germany, Spain and France were summarised in one excel file, which was analysed by a scientist step by step beginning with checking data completeness and assessing the number of cases of mastitis per treatment method followed by analysing of treatments' curing rates.

A mastitis case was defined from the moment of discovery of clinical signs by the farmers (day of initial treatment) until the cows' full recovery (last follow-up check without clinical signs of mastitis). In case a cow has relapsed within seven days after full recovery, it was classified and evaluated as a new case of mastitis. Within these seven days the mastitis case was determined as a recurrence. For the purpose of evaluating the treatment success, the somatic cell count (SCC) and clinical symptoms were used. According to the International Dairy Foundation, a cut-off of 200.000 cells per ml at cow level (International Dairy Federation 2013) was used for identification an udder infection. A full recovery was determined when the SCC was less than 200.000 cells / ml for three consecutive milk recordings after the end of treatment.

8. Results

Over a period of one year, a total of 175 cases of mastitis were received from the farmers of all three countries and documented: 109 cases from seven German farms, 51 cases from 11 farms in France and 18 cases from five Spanish farms (see Table 3). In total, 62 cases were excluded from the evaluation due to different reasons. On the one hand, the data received were not complete in some cases. Either the data of initial treatment or for checking the treatment success were missing or the somatic cell counts, which were used for evaluating the treatment success, were not available. On the other hand, in some cases farmers administered homeopathic and conventional remedies at the same time, thus it was impossible to evaluate which therapeutic method has contributed to animal's cure. Furthermore, only very few cases were documented by farmers although several reminders via email and post were sent. The study also confirmed the results of the on-farm assessment on the use of homeopathy (see Deliverable 4.2): Despite the prospect of receiving a monthly allowance, farmers neglected any kind of documentation regarding treatment procedures. This contradicted with the expectations at the beginning of the study. Due to the lack of an appropriate sample size and data incompleteness of mastitis cases, an analysis of curing rates could not be undertaken for French and Spanish farms. Particularly in France, information about the SCC were not available. For German farms, an analysis of farmers' therapeutic success in treatment clinical mastitis with homeopathic remedies was conducted as far as possible; however, treatment data with regard to the antimicrobial treatment were also missing.

Table 3: Cases of mastitis received from farmers over a period of year

Cases received	Germany	France	Spain
In total	**109**	**51**	**18**
Min per farm	1	2	1
Mean per farm	16	5	4
Max per farm	29	10	6
Cases excluded from the evaluation	21	51	13
Cases analysed	**88**	**0**	**5**

The estimation of cure rates is based on the evaluation of five out of seven German farms which provided almost completely treatment data required for calculation. Ranges for curing rates from 20.8% up to 44.8% were calculated for a successful therapy of clinical mastitis when a homeopathic remedy was used. Following Table 4 shows an overview about the achieved curing rates after a mastitis treatment with homeopathic remedies on five German dairy farms.

Table 4: Curing rates of mastitis treatments by five German farmers over a period of one year

Farm Number	Recovery in udder health	No recovery in udder health	Non-evaluable cases
1	**44.8 %**	**37.9 %**	**17.2 %**
2	**20.8 %**	**41.7 %**	**29.2 %**
3	**25.0 %**	**25.0 %**	**50.0 %***
4	**39.3 %**	**53.6 %**	**28.8 %***
5	**36.4 %**	**36.4 %**	**27.3 %**
* value contains 16.7% successful treated cases with combination therapy (homeopathic & antibiotic remedies)			

9. Discussion

The calculated curing rates have to be treated with caution and can only provide a rough estimation about the treatment success since a reliable calculation could not be conducted for various reasons. On the one hand, a completeness of treatment records by farmers cannot be ensured. Experiences from the clinical trial have shown that changes in therapy, especially changes in remedies, were not documented very well. This might have resulted in false-positive results in favour for the homeopathic treatment method. On the other hand, the sample size is very low. Despite of sending repeated reminders to farmers, the number of received documentation sheets was not satisfactory. The reluctant behaviour of farmers to provide reliable documentation data corresponds with results previously obtained and described in Deliverable 4.2. Also the results of D4.2 revealed that a comprehensive documentation and follow-up checks were rarely performed by farmers. Without a solid data base, a reliable calculation of treatment success and concrete conclusions about the effectiveness of treatment methods in agricultural practice are de facto not feasible. Therefore, the first step for a target-oriented treatment should be implementing complete treatment documentation. On that data base a success or a failure in cure can be thereby made visible and effects of treatment methods (positive or negative) can be measured.

10. Acknowledgement

The study was supported by Christian Fidelak (bovicare GmbH, Germany, Potsdam), who was partly responsible for the clinical examination and analysis of milk samples. Furthermore, the authors would like to thank the farmers for their dedication to the study.

11. Glossary

Homeopathic potencies	The potency defines to which extent the original substance or mother tincture is diluted (= homeopathic dilution).
Materia medica	The Materia medica is a complete published list of homeopathic remedies; a collection of remedy pictures of different substances (Steingassner, 2007; Murphy and Klendauer, 2010).
Potentiation	Potentiation in homeopathy is the process of making a remedy more potent by serial dilution (even to extent that it is unlikely to contain a single molecule of the original substance)
Repertorisation	This is not only a mechanical process of counting rubrics and totality marks obtained by a remedy; it also includes the logical steps to reach the proper repertory and finally differentiating the remedies with the help of Materia medica.
Repertory	A reference book which lists homeopathic symptoms in alphabetic order and the remedies used to treat them (Kent and Holzapfel, 2008; Schroyens, 2014).
Withdrawal period/time	Withdrawal period is the time required after administration of a drug to a food-producing animas needed to assure that the pharmaceutical residues in food (meat, milk, egg) is below a determined maximum residue limit (MRL).

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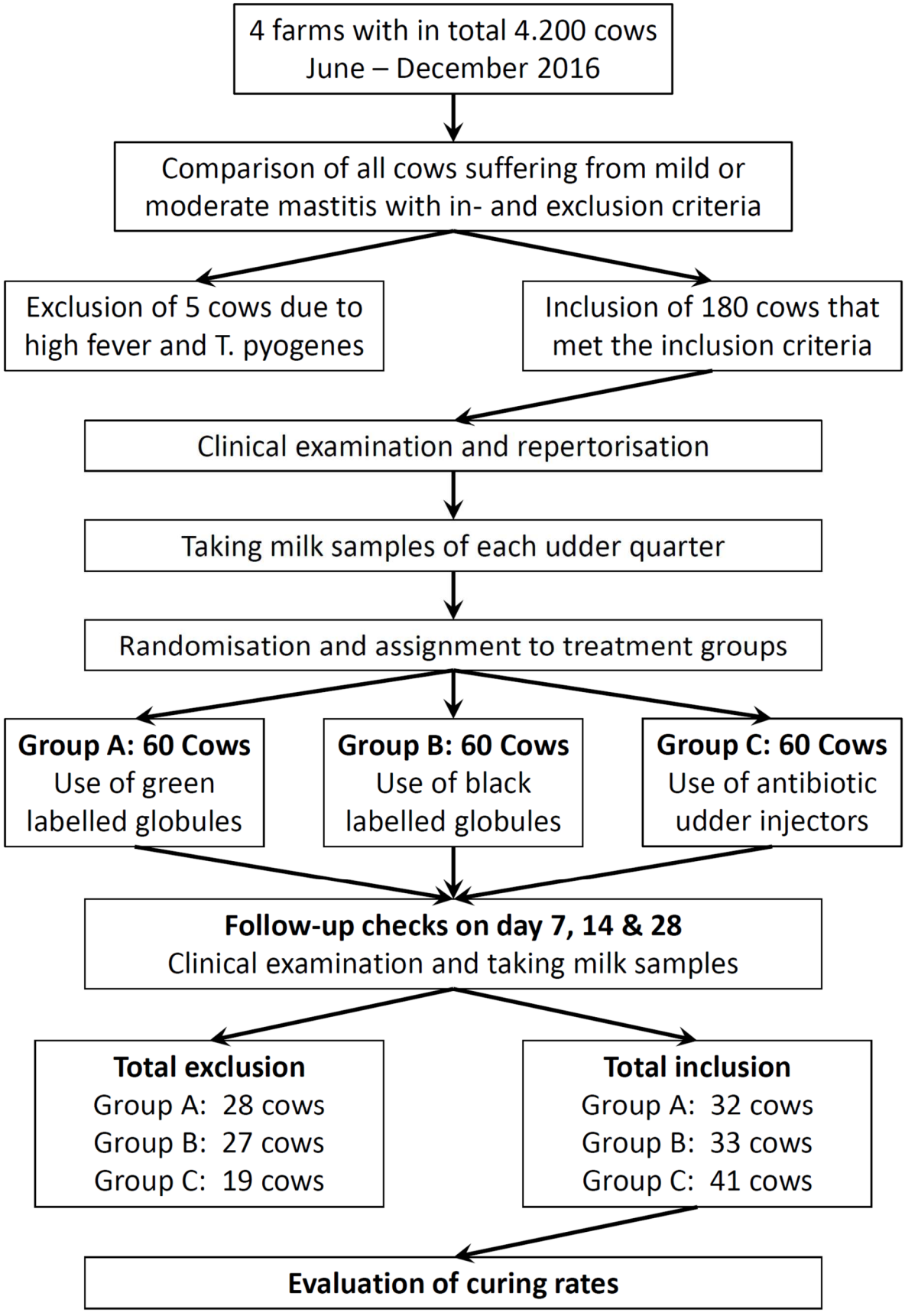
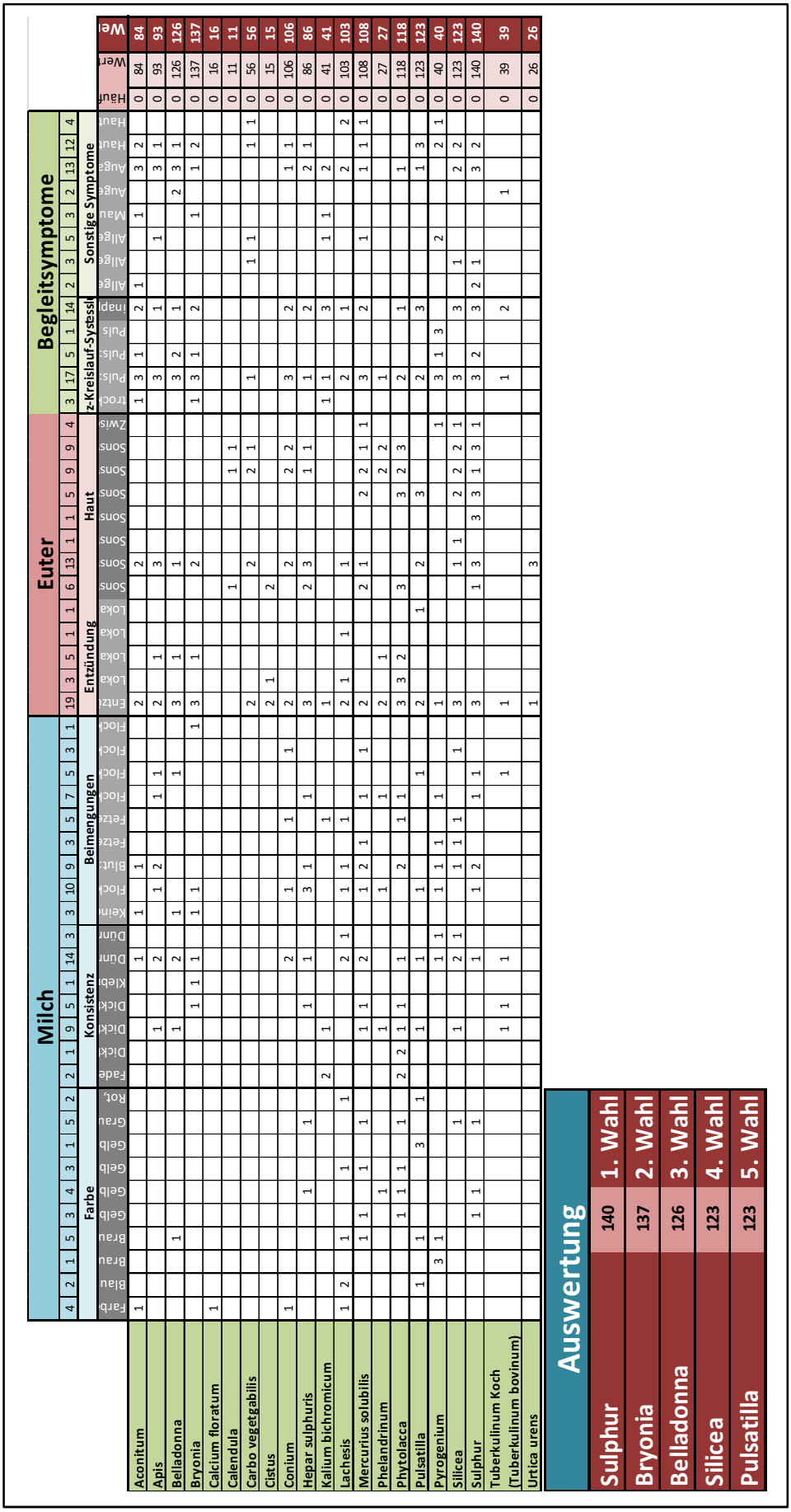
13. Annex

13.1 Annex I - Treatment and evaluation procedure

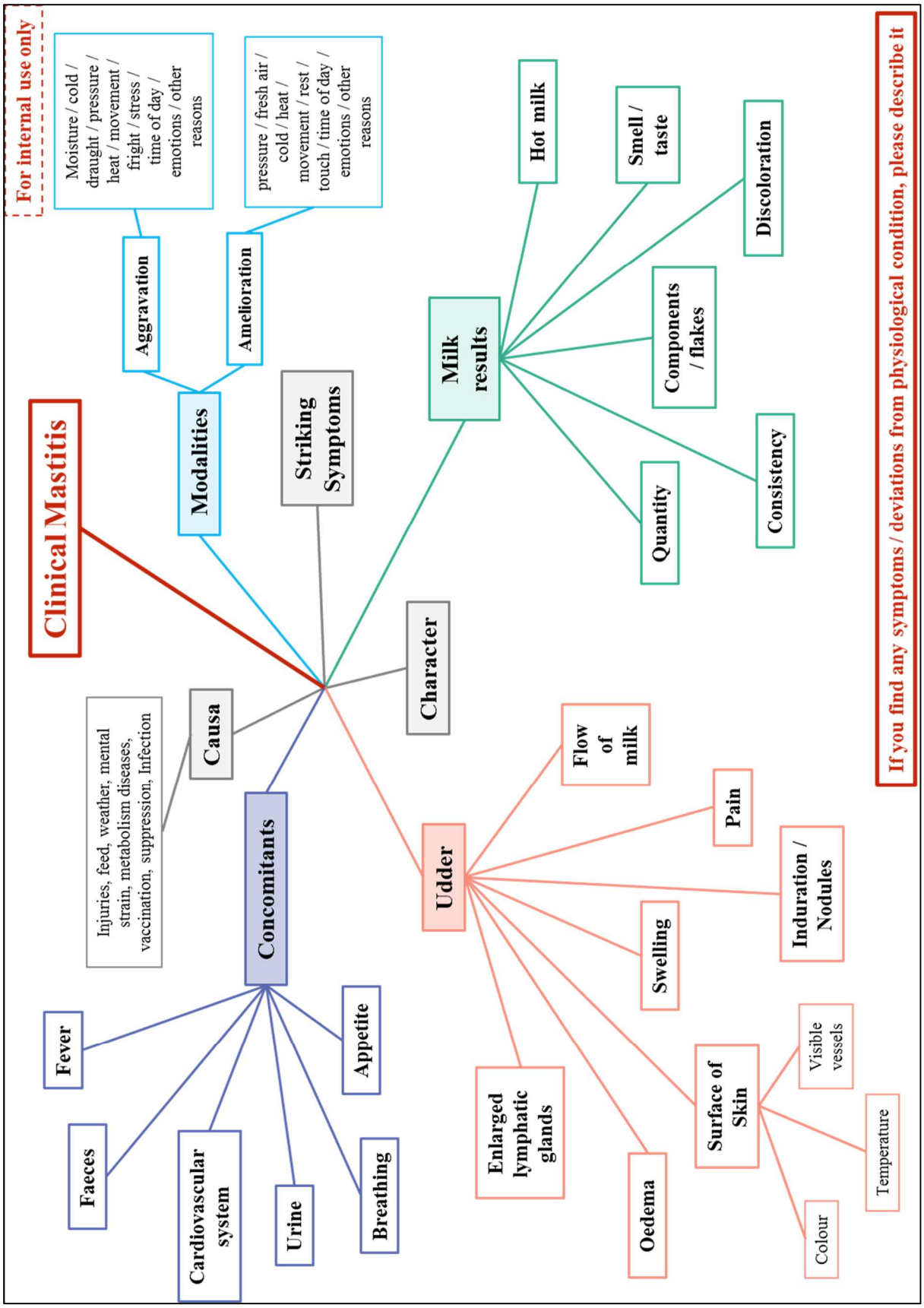


13.2 Annex II - Repertorisation tool (small excerpt)



13.3 Annex III - Blindness for homeopathic and placebo remedies

13.4 Annex IV - Documentation sheet for one year mastitis study (front)



13.5 Annex V - Documentation sheet for one year mastitis study (back)

For internal use only

Ear tag / Cow Identity: ____________________

Initial treatment: ☐ **Success control:** ☐

Date of treatment / control: ____________________

Affected udder quarter: ☐ FR ☐ FL ☐ RL ☐ RR

Consultation of a vet: ☐ Yes ☐ No

Milk samples ☐ No milk samples were taken

Date of sampling: ____________________

Reason of sampling: ☐ Flocks / SCC ☐ Sensitivity testing ☐ Success control ☐ Identification of pathogens

Therapy

Homeopathy		Conventional treatment
	Remedy	
	Way of application	
	Period of application	
	Potency	
	Waiting time	