Outcomes and effects of homeopathic treatment of malaria in Kenya, a multi-centre study

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Abstract

Background In Kenya malaria is the leading cause for illness and death; homeopathy is used for many years to treat this disease. A previous study in Ghana in 1996, showed comparable effects of homeopathy and chloroquine. Methods In three studies we documented homeopathic treatment in a retrospective qualitative study, a prospective single arm study, and a comparison between one cohort receiving homeopathic treatment and the other artemether. Results In the qualitative retrospective study (2014) (n=54), we related typical malaria and individual symptoms, with remedy prescriptions and affected organs. Principal Component Analysis (PCA) showed, that specific remedies were prescribed for patterns of affected organs. In the prospective study (2014) (n=70), the primary outcome was the parasitological status at the first follow up (median 8 days), secondary outcome was the quality of life measure with Outcome Related to Impact on Daily Life. In the third study, of the group (n=79) (b) exposed to homeopathy, n=6 (a) were still parasite-positive after one week, in the control (co-artem) group of n=35 (c) no patient was positive (d). The odds ratio was 5.8068 (95% CI 0.3183 – 105.8794), with z = 1.187 and P = 0.2352. The difference was not statistically significant; homeopathic remedies and coartem tablets had similar effect for uncomplicated malaria in that region. Co-morbidity was treated with different remedies. Conclusion Homeopathic treatment can be used as a valuable option, also when other treatments are ineffective by microbial resistance, not indicated (as in pregnancy) and financially not affordable.

Keywords: malaria, homeopathy, artemether, comparative study, cohort study, plasmodium, ORIDL

Introduction

Background and scientific relevance

Malaria remains globally a major cause of morbidity and mortality. And this is despite public health measures in water management, prevention and prophylaxis.

The Kenyan medical research Institute [1] mentions the burden of malaria on society:
- 25 million of Kenya’s 44 million people are at risk for malaria,
- it is the leading cause for illness and death;
- it accounts for 20% of the mortality of children under five,
- and for 30-50% of outpatient attendance and 20% of hospital admissions.
- And, it leads to a large amount of sickness leave.

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Therefore, malaria forms a major threat both for the country’s work force as well as for vulnerable groups such as young children and pregnant women who bear the future generation. These make a study in this disease relevant, and also as we were informed of the successful cases in homeopathic clinics during the Pan-African homeopathic conference in 2012 in Kwale, Kenya. Individual case reports are usually considered to be the lowest grade of evidence. Therefore, we aimed at a more systematic, open study of one cohort and a comparison between two cohorts.

The literature shows, effects of single remedies both in animal studies [2-4], and in case-series and open studies, in humans; in pregnant women in Benin [5-6], other studies in India [7-9]. The use of limited number of remedies runs counter to the individualized homeopathic treatment. These data suggest that some remedies have a preferential use in malaria treatment, such as *Lachesis* [10], *Ipecacuanha* [11], *Arsenicum album* [12]. This corresponds to the homeopathic concept of *genus epidemicus*, i.e. a limited number of remedies is used for the treatment of endemic and epidemic diseases– e.g. malaria in rainy seasons. Master [8-9] recorded *China officinalis, Natrum muriaticum, Nux-vomica* and *Opium* in a case series of patients with malaria, they constitute then the *genus epidemicus*. Appropriate training for community health workers may assist them to apply this for specific epidemics.

Homeopathy is used, too, in several large countries such as India and Brazil where it is integrated in the health care system and used in primary care; in India about 10% of the population (120 million) uses homeopathy as preferential treatment [13], with similar numbers in Brazil. In Bahia and the South regions its use is most prevalent [14-15]. The plausibility of homeopathic treatment is discussed in Western countries.

We will present a model which is based on systems theory that may account for both the use of minute doses and larger ones as in conventional pharmacology. Worldwide homeopathy is estimated the second or third choice of treatment for many patients (more than 300 million). We advocate the respect of many patients and to develop cooperation on a solid basis between conventional and complementary medicine.

Antibiotic and systemic treatments

A sustainable public health policy seeks to combine therapeutic approaches in order to provide the best possible care to patients. Moreover, the World Health Organization and the US Infectious Diseases Society have requested to develop innovative strategies for antibiotic treatments due to the rise of microbial resistance [16].

To make cooperation feasible we use systems theory as the ‘bridging’ model between the conventional and homeopathic approach. This enables the distinction of a hierarchy of increasingly complex living systems, from cells, to organs and networks of messengers (neurotransmitters, hormones and immune-agents). These messengers create coherence by exchange of information between networks of cells and organs.

The implicit hypothesis in conventional pharmacology is that distinct cellular mechanisms in specific organs create disease. Systems biology shows clinical effects occur with simultaneous changes in the pattern of biomarkers [17]. They are part of messenger networks. Parallel to this, immunological studies with homeopathic preparations have shown their effect of these networks. Bellavite et al [18] reviewed these effects in herbal, animal and human-immunological models. The interaction appears to occur as the low doses of homeopathic remedies are in the same range of the concentrations of the messengers. Actions through the immune system have a systemic character.
due to the multiple immune-active agents. These empirical results explain an effect of low doses, instead of the conventional drugs which act through one single mechanism.

Another theory is the placebo or context effect of homeopathy, supposed to develop through a lengthy consultation, as carried out in urban upscale, Western clinics. Practices of short consultations exist in many busy primary care clinics worldwide, as well for small children. Malaria is not an innocent, self-limiting disease that might be treated by an empathic doctor-patient relationship alone.

Together, given the burden of disease, it seems a patient-centered approach to combine therapeutic modalities in a complex health care system.

Scientific evidence

Both parasitic and clinical data need to be collected to establish a solid outcome. Further, the nature of homeopathic substances themselves has been clarified the last decade using conventional physico-chemical methods. The combination of serial dilution and agitation (SDA), shows a change in physical properties. The techniques fit the general framework of non-linear, complex systems – in which small changes in stimuli may create a whole systems effect [19].

As mentioned above, the target, the bio-messengers - neurotransmitters, cytokines and hormones – act as a sensitive system not as an organ-bound local reaction mechanism [20]. This sensitivity is due to that the system is far from equilibrium and in this state it can respond to minute stimuli [21-22]. In this way, homeopathic medicines are capable of influencing a complex disease process such as malaria. Therefore, we chose a design that, in order to have model validity, involves both the main clinical complaints, and the overall effect on the organism as a systemic indicator of the impact of homeopathic medicines, the ‘outcome’. The resulting change in immune function, in this model, is supposed to neutralize the parasites, which can be measured as a primary outcome, the ‘effect’. This road is followed in the design, where the outcomes of the immune process are both clinical change and parasite presence in the blood.

Methods

Choice of approach

Homeopathic treatment is an option to consider in case of 1) ineffectiveness of antimicrobial drugs due to resistance of plasmodium 2) safety concerns (pregnant women, young children), 3) unaffordability (price of conventional malaria drugs) or 4) distribution problems (access from remote rural settlements to conventional health clinics).

Previously, a systematic study has been done by the first author in Ghana, showing comparable effects of homeopathy and the standard treatment of that time, chloroquine [23]. Now it is relevant to compare homeopathy with current antiparasitical treatments such as artemisin-lumefantrin (co-artem), we did this in the third study.

Study context description

As our emphasis was on the utility for public health policies rather than only the efficacy of homeopathic medicines which have been used for many years in tropical countries, we made a systematic assessment of daily practices in several homeopathic clinics. These were located both in
areas where malaria is endemic (Homa Bay County in the former Nyanza province) close to Lake Victoria, and in areas where malaria epidemics occur during rainy season episodes (Makueni County).

All clinics contain experienced staff trained in classical homeopathy, so they prescribe both single remedies following the individual method, as well as problem-oriented composed ‘complex’ remedies that contain several remedies targeted for a specific disease.

In June 2012, the first author made a feasibility study of the existing health services provided by the above-mentioned homeopathic clinics. The question was whether a good quality study could be carried out that meets general methodological standards along with individualized homeopathic treatment. The following aspects were addressed: the quality of practice and the medicines, and the methodology to be used.

For quality of practice were assessed:
- the experience and training of the practitioners involved,
- the suitability and privacy of the consultation rooms,
- the quality and storage of the medicines administered,
- the quality of the laboratory equipment for hematology (Hb and differentiation), thick blood smear and parasite counts, as well as other microbial diagnostics
- the accessibility of care regarding the fees asked from patients

Consultation rooms, lab facilities and stocks conformed to the requirements of good practice. The practitioners were experienced, most of them with 10 or more years of practice. They had all followed the 3-year education program of Abha Light Foundation in Nairobi.

With regards to the medicines, most remedies used were produced by Indian manufacturers that had submitted toxicity and stability tests to the Indian Ministry of Health, department of Homeopathy. Subsequently they had been approved by the Pharmacy and Poisons Board in Kenya. The effect of these remedies have been assessed in several clinical case-studies [7-9]. Also, the Deutsche Homoeopathische Union (DHU Arzneimittel GmbH & Co. KG) provided for the comparative study n° 3, six remedies (Arsenicum album 30 and 200C, China Officinalis 3X, Eupatorium perfoliatum 30C, Natrium muriaticum 30 and 200 C).

Additionally, several complex or composed remedies were used. The ‘Malaria mix 30’ contains in 30C potencies of the homeopathic medicines Arsenicum album, Quinine, Natrium muriaticum, Eupatorium perfoliatum, and Malaria Officinalis. ‘Malaria Mix 200’ contains the same remedies, except that it does not contain Natrium muriaticum, and has the addition of the Malaria Co Nosode; a nosode is a homeopathic remedy produced from the original microorganisms, in this case from a mixture of Plasmodium species, vivax and falciparum.

The storage of medicines was in stocks, dry and dark with constant temperature, in accordance with Good Manufacturing Homeopathic Practice in the German Homeopathic Pharmacopeia.

Prescription

Remedies are made from a herbal, animal and mineral substances. Their effects are tested in experiments with healthy volunteers. The resulting patterns are classified as ‘remedy pictures’. And patients are compared in their symptom pattern with them.
Then the remedy with the highest analogy or best matching picture of the patient pattern is chosen and administered.

The elements of the picture include symptoms and features, the latter represent functions regulated by the endocrine and autonomous nervous systems.

As features can differ between patients, patients within one disease category may be given different remedies. At the same time, patients sharing similar feature patterns but with different diseases, may find an overlap in classification. This is the reasons that the same remedies have been used in three studies of another major microbial disease, childhood diarrhea [24].

Data collection

Recruitment of patients.

We conducted two studies in 2014:

- A retrospective study of n=54 patients who had attended for confirmed malaria the rural Toru clinics in central Kenya, Makueni County: in Manyanga (next to Kibwezi) and Kambi Mawe, in the rainy season of December 2013- January 2014.

- A prospective study of n=86 patients who the two mentioned clinics plus the clinic in Kendu Bay (West Kenya, Homa County), during the rainy season of March-June 2014.

In 2015, we compared two cohorts of new patients; the first cohort of n=70 consisted of three groups of patients attending the homeopathic clinics in Manyanga and Kambi Mawe as well as in Matuu (Makueni County). The second cohort of n =35 consisted of the patients attending the governmental out-patient clinic of the regional hospital in Kibwezi, two km from Manyanga. All patients gave informed consent to participate. Ethical clearance was given by the Kenyatta University, Nairobi, under the protocol number KU/R/Comm/51/396, date February 4, 2015.

All patients that attended were diagnosed following the classical method of diagnosis in homeopathy, and special attention was paid to the main symptoms of malaria. Based on the clinical experience and previous study in Ghana, several key-symptoms were considered important for malaria: headache, fever, chills, joint pain, paravertebral lumbar pain.

Data collection and processing

All data were recorded by the practitioners in the three studies using a preformatted malaria record, and transferred by the researchers to excel spreadsheets. This format contained the following data (table 1).

The patients narrated in their own words their illness history, including their specific sensations and modifying factors (the 'modalities' see below). Moreover, comorbidity of the other systems involved (tracts) and potential factors contributing to the onset of disease (lowering general resistance) were recorded.

Follow up

The main symptoms were reviewed 1 week (study 3) or 2 weeks (study 2) later to assess eventual change, using the same format.
Parasitology tests were repeated. For the general health, the ORIDL score was used, indicating the impact on daily living which is patient-oriented information about the experience of change in main complaint and general health (table 2).

**Table 1: Patient file rubrics to record Acute episodes of malaria**

| Patient file rubric              | Specification                                                                                                                                                                                                 |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Classical malaria symptoms      | Headache, fever, chill, joint pain, lumbar paravertebral pain; with personal details of each symptom                                                                                                           |
| Individual symptoms             | What? - sensations (type of pain or whole body sensations)                                                                                                                                                     |
|                                 | When? – modalities (factors that ameliorate /aggravate the main complaint such as headache etc.)                                                                                                              |
|                                 | With what? Co-morbidity symptoms next to the malaria symptoms                                                                                                                                                 |
|                                 | Since when? The context of beginning of symptoms/causality                                                                                                                                                     |

*If required for a more precise classification, the next questions are added:*

| Individual features:            |                                                                                                                                                                                                            |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mental level                    | I.e. :expression of emotions; fears, dreams; memory, concentration                                                                                                                                            |
| General/ autonomous functions   | I.e. : sleep, menses, sexuality, food preferences and aversions, sensitivity for climate and weather, temperature, movement, exercise                                                                        |
| functions level                 |                                                                                                                                                                                                            |
| Local                           | longer-term localized complaints                                                                                                                                                                             |

*Added in the follow up: ORIDL (Outcome Related to Impact on Daily Life)*

Two questions are posed about the effect of treatment on the main complaint and the overall well-being of the patient.
Table 2 - ORIDL - Outcome Related to Impact on Daily Living

| Score | Description                                      |
|-------|--------------------------------------------------|
| +4    | Cured / Back to normal                           |
| +3    | Major Improvement                                |
| +2    | Moderate improvement, affecting daily living     |
| +1    | Slight improvement, no effect on daily living    |
| 0     | No change / Unsure                               |
| -1    | Slight deterioration, no effect on daily living  |
| -2    | Moderate deterioration, affecting daily living   |
| -3    | Major deterioration, affecting daily living      |
| -4    | Critical deterioration, emergency situation      |

Ask every follow-up patient:

1. Compared to how you were before your initial appointment, what has been the overall effect of your treatment at this clinic on your **Main Complaint** (the one you came to get treated)?

   *(please select one option from the scale below)*

   | Score | Description |
   |-------|-------------|
   | -4    | -3 | -2 | -1 | 0 | +1 | +2 | +3 | +4 |

2. Compared to how you were before your initial appointment, what has been the overall effect of your treatment at this clinic on your **general well-being**?

   *(please select one option from the scale below)*

   | Score | Description |
   |-------|-------------|
   | -4    | -3 | -2 | -1 | 0 | +1 | +2 | +3 | +4 |

Study 1

Records of 54 patients from December 2013-January 2014 were screened for diagnostic and therapeutic interventions: type of remedies, potency and posology (frequency and duration of dosage). Follow up data on the parasitology were not included as they were not available in all cases. This assessment was made as a pilot for the second study, including patients’ symptom combinations related to remedies.
Study 2

From the patients presented in the second study, were recorded: clinical parameters of malaria and symptoms indicating other pathologies. Malaria parasites were screened in thick blood smears, coupled with blood examination for typhoid fever, brucellosis, and of faeces for amebiasis (cysts, eggs) and hookworm. All these diseases have a high prevalence in the rural regions of the clinics’ locations.

Drop out risk management: no charges were made for follow up lab fees and travel was refunded on follow up, to promote return for check up. Because, patients, mainly farmers in the region of the clinics, were known from previous years not to return when well again after the first treatment, but only for a new disease episode. Follow up shows that patients only return if their health has not improved.

Inclusion criteria were:

- all patient older than three years, presenting malaria-like symptoms that were confirmed by a positive parasite count, at the three homeopathic clinics.
- Also those which had co-morbidity such as amebiasis, typhoid fever, hookworm and brucellosis, all major pathologies in that region.

The latter group was included as multi-morbidity next to malaria is quite common here and our aim was to record actual, not best practice homeopathic treatment,

Excluded from participation were patients with

- serious symptoms suggesting cerebral malaria; they were to be referred to two nearby hospitals (located respectively at 2 and 12 kms distance).
- febrile conditions but with confirmed absence of malaria.

Study 3

Two cohorts were compared, one of the patients attending the homeopathic clinics in Makueni county (in Manyanga (nearby Kibwezi), Kambi Mawe and Matuu), and the other of the outpatient department of the Kiwezi hospital, during the same rainy season. Inclusion and exclusion criteria were the same as in study 2.

Diagnostic procedures for malaria were identical with those in study 2. The treatments were performed as usual, no changes in diagnostic and therapeutic interventions were made. Homeopathic remedies were administered in the homeopathic clinics, artemether-lumefantrine was administered in the government out-patient department.

Data processing

1. extraction from the clinical files of the data, recorded in Excel data base
2. data: demographic, clinical, laboratory, remedies prescribed (table 1 and 2)
3. follow up data after one week – and if still positive for parasites, repeated after again one week: clinical data and ORIDL data
Results

Study 1 (retrospective, 2014)

Previous studies [8,9,22], showed a preferential use of certain remedies for malaria. In general, homeopathic treatment is focused on the individual patient by combining patterns of symptoms and features. Limitations to this practice were:

Due to a limited duration of the consultations, not all features required for a highly individual analysis could be obtained; therefore, practitioners did not select one single remedy covering all data (table 3).

Table 3 - Diversity in type of remedies – frequency of use (retrospective study 2014)

| Type of remedy          | Number of patients | Patients in % |
|-------------------------|--------------------|---------------|
| Single remedy           | 52                 | 96%           |
| Complex remedy (MIX)    | 35                 | 54%           |
| Nosodes (NOS)           | 22                 | 41%           |
| Narayani remedy (NAR)   | 15                 | 28%           |
| Single remedy only      | 8                  | 15%           |

Types of symptoms used for diagnosis:

A - Classical malaria symptoms

- Individual differences within the set of classical malaria symptoms (figure 1) with the other individual symptoms, provided enough variation to prescribe individual remedy combinations. Fever is not the most common symptom in this series, but headache - which leads patients suspect they have contracted malaria. Fever may be in patients’ experience an overlapping sign for the presence of other diseases.

- Pain in extremities is frequently recorded as a malaria symptom.

Figure 1 - Frequency of classical malaria symptoms
B - Co-morbidity

Additionally, co-morbidity symptoms due to the presence of other diseases led to the choice of remedies that included symptoms from those diseases as well (table 3 and 4).

Types of remedies

96% of all patients received a single remedy, joined for 54% with complex remedies, and for 41% by nosodes. The variation in malaria symptom patterns and comorbidity of other diseases led to no more than 15% of patients receiving a single remedy, only.

Frequent systemic involvement or organs (table 4), led to, besides the individual prescribing, the use of combination of single remedies in one patient, due to the limited time for a consultation. So there was variation in the types of remedies (table 3). This variation is also visible in the ten most used remedies, including both single and complex remedies (table 5).

Table 4 - Involvement of organs and general functions (retrospective study 2014)

| Organs and general functions | Number of patients | Patients in % |
|------------------------------|--------------------|---------------|
| Extremities                  | 31                 | 57%           |
| Abdomen                      | 30                 | 56            |
| Stomach                      | 23                 | 43            |
| Stool                        | 20                 | 37            |
| Chest                        | 17                 | 31            |
| Mouth                        | 17                 | 31            |
| Sleep                        | 16                 | 30            |
| Thirst                       | 15                 | 28            |
| Appetite                     | 13                 | 24            |
| Cough                        | 11                 | 20            |
| Expectoration                | 9                  | 17            |
| Eyes                         | 7                  | 13            |

The second position in frequency for abdominal complaints, is due to the cases with typhoid fever.

An example of a comprehensive prescription in study 1 was:

- REM China-off 5x dd in drops
- REM Calc-phos 200 2dd1 1w (starting after 10 days)
- MIX typhoid nr. 30 2dd1 1w, (complex remedy for typhoid treatment)
- NOS brucellosis nosode 10m 2dd1 1w,
  - and
- NAR Malaria Blood nr. 37 3dd1 1w (complex remedy)
Diagnostic prescription patterns in the study sample 1

The insertion of individual symptoms in SPSS (Statistical Package for Social Sciences), did not provide patterns which we could link to the remedy choices for each patient, as the number of different symptoms was too large compared with the relative small number of patients. Therefore, we reduced the data to discover a common factor behind the actual variation, by performing Principal Component Analysis. (PCA) [25].

| Top 10 remedies - frequency of use (N=54) |
|------------------------------------------|
| 1 | MIX typhoid | 29 | 54% |
| 2 | REM China | 28 | 52% |
| 3 | REM China-S | 16 | 30% |
| 4 | NOS Amoebe | 15 | 28% |
| 5 | REM Belladonna | 13 | 24% |
| 6 | NAR malaria blood | 11 | 20% |
| 7 | NOS brucella | 6 | 11% |
| 8 | MIX malaria | 5 | 9% |
| 9 | REM Nux-V | 5 | 9% |
| 10 | REM Ars. / REM Nat-m | 4 | 7% |

Figure 2 - study 1; Example of a Principal component analysis; (Malaria, Organsystems >4%, 19 vars, Remedies >4%, 11 vars, RefCA biplot); showing association of use of remedy natrium muriaticum for a patient with a cluster of symptoms in respiratory and sleep disturbances.
Data of affected organ systems, instead of single symptoms, were coupled with the remedies prescribed. This led to a two-component preliminary graph that indicates the relationship between a remedy and a set of affected organs/systems.

Figure 2 shows in the far right corner the co-variation in principal components (as mathematical factors) between the prescription of the remedy *Natrum Muriaticum* (sodium chloride) and the pattern of symptoms in the categories of Nose, Ear and Sleep disturbance. This may facilitate ‘pattern prescribing’ in similar cases.

**Study 2 (prospective 2014)**

**Demography**

**Table 6: study 2 - Age distribution in the three clinics**

| Age distribution in numbers | Manyanga | Kendu Bay | Kambi Mawe |
|-----------------------------|----------|-----------|------------|
| 0-10                        | 3        | 3         | 0          |
| 11-20                       | 5        | 1         | 2          |
| 21-30                       | 5        | 0         | 5          |
| 31-40                       | 9        | 0         | 6          |
| 41-50                       | 6        | 1         | 6          |
| 51-60                       | 4        | 0         | 9          |
| 61-70                       | 4        | 0         | 1          |
| 71-80                       | 3        | 0         | 1          |

A slight difference in age distribution is visible between Manyanga and KambiMawe (table 6); the emphasis in Kambi Mawe is on the older age group, and in Manyanga the majority of sample is female (table 7).

**Table 7: Study 2 - Gender distribution (prospective study 2014)**

| Demography – malaria patients | Gender |
|-------------------------------|--------|
| Clinic                        | Gender |
|                               | Male % | Female % |
| Manyanga clinic               | 45     | 40 %     | 60 %     |
| Kendu Bay (mobile clinic)     | 11     | 45 %     | 55 %     |
| Kambi Mawe clinic             | 30     | 20 %     | 80 %     |
| Patients total                | 86     |          |          |
Only in the third clinic the gender distribution was fairly skewed.

**Table 8**: study 2 - Cured cases, parasitologically confirmed, with dropout rates

| Clinic          | 1st consultation | 2nd consultation – test (negative) | Drop-out rate      |
|-----------------|------------------|-----------------------------------|--------------------|
| Manyanga        | 45               | 29                                | 35% (16 persons)   |
| Kambi Mawe      | 30               | 29                                | 3% (1 person)      |
| Kendu Bay       | 11               | 11                                | None               |

**Table 9**: study 2 - Drop out analysis

| Manyanga          | Kambi Mawe | Kendu Bay |
|-------------------|------------|-----------|
| • 8 due to logistics (truck drivers) | No drop-outs | 1 unknown |
| • 2 students: school obligations |           |           |
| • 2 old persons   |           |           |
| • 2 unknown       |           |           |
| • 2 not motivated on check |       |           |

The primary outcome was the parasitological status (table 8) at the first follow up visit, with a median follow up time of 8 days. There was a considerable dropout rate in one of the clinics. Table 9 lists the reasons.

Next to the clinical effect, the ORIDL indicated the impact of treatment on daily life (table 10)

**Table 10**: ORIDL scores, in follow–up parasite negative cases

| ORIDL score | 1. Main complaint | 2. General quality of life |
|-------------|-------------------|---------------------------|
| -1          | 1                 | 1                         |
| 0           | 1                 | 1                         |
| 1           | 1                 | 2                         |
| 2           | 10                | 6                         |
| 3           | 32                | 32                        |
| 4           | 11                | 10                        |
| Total: 56   |                   | Total: 52                  |
Study 3

The context of this study was different: on the invitation of the Ministry of Health, Makueni County, we were allowed to also assess malaria patients in the nearby government clinics. This led to that we followed two cohorts, the patients treated in the three homeopathic clinics, and one in the hospital in Kibwezi, in proximity to the Manyanga clinic (table 11). The planned provision of data in the government clinic in Kambi Mawe did not materialize, but in Kibwezi hospital the patients presenting with malaria were examined in the Out Patient Department, by the nurse and lab technician; they also attended the follow up session for clinical and parasitological assessment.

Demography

| Clinic       | Male % | Female % |
|--------------|--------|----------|
| Manyanga clinic | 53     | 66.6     |
| Matuu        | 10     | 40       |
| Kambi Mawe clinic | 33     | 82       |
| Hospital     | 35     | 66       |
| Total/ mean %| 131    | 68.5     |

Also in this study, proportionally more women seek help for malaria treatment than men (Table 12), which is in line with other morbidities without a different attack rate between men and women. This confirms the trend that women more actively seek help for their health conditions.

Severity of existing illness on presentation would be an interesting covariable for comparison between the two cohorts. But lack of quantitative laboratory data (plasmodium counts) did not permit further analysis. And the comprehensive co-morbidity in this sample (Fig. 3) makes the overlapping clinical criteria unreliable for the comparison of specific malaria symptoms.
As in the 2014 study 2, this time again there was a considerable drop out for the clinic in Manyanga, mainly for logistic reasons similar with study 2; the patients who improved did not return for check-up (table 13).

Figure 3: study 3 - Comorbidity in homeopathic clinics

Table 13: study 3 – Dropout percentages

| Homeopathic clinics | Hospital Kibwezi |
|---------------------|------------------|
| Manyanga            | 15/53 =28%       | 3/35 = 8%       |
| Kambi Mawe          | 1/33 = 6 %       |                |
| Matuu               | 0/10 = zero %    |                |

Statistical comparison

We measured the positive presence of malaria parasites after one week in both cohorts. In the homeopathically treated cohort, of the patients who returned, only one patient still had parasites after one week, after two weeks this patient was negative too.

As all patients that returned in the artemether-lumefantrine (co-artem) group were negative after one week, we compared the odds of having positive parasite count for the two groups, after one week only.

We compared homeopathy with the standard treatment for malaria, co-artem, therefore we considered as ‘exposed’ group those patients who followed homeopathic treatment, and as ‘control’ group those who received artemether.

Given the dangerous nature of malaria we wanted to monitor the results after one week's treatment and demanded all patients to return then. Therefore, we included for analysis all patients who returned, and checked whether they were positive or negative for parasites. Of the ‘exposed’ (homeopathy) group of n=79 (b) who came for follow up, there were 6 positive (a) after one week, and in the ‘control’ (co artem) group of n=35 (d) there was no patient positive (c) for parasites.
The odds ratio was \((a:b) : (c:d) = 5.8068\), within the 95% Confidence interval (CI 0.3183 – 105.8794), with \(z = 1.187\) and \(P = 0.2352\). The difference was not statistically significant, which implies that homeopathic remedies and coartem tablets had a similar effect on the treatment of patients with uncomplicated malaria in that region (table 14).

We also compared the satisfaction of patients regarding the effect on their main complaint and general quality of life, using the scores on the ORIDL (table 15).

- The difference between the three homeopathic clinics in the satisfaction regarding the main complaint is statistically significant, with \(P < .002175\), and chi-square 16.7362.
- There was no significant difference for all homeopathic clinics in satisfaction compared between main complaint and quality of life, \(P = .820173\) and chi-square .9218.
- And the difference between the homeopathic clinics and hospital in satisfaction for the main complaint was significant, with \(P = .017414\) and chi-square 10.1399.

Table 14: Study 3: Odds ratio for negative parasite cases in two cohorts

|                | Exposed group (homeopathy) | Control group Artemether |
|----------------|---------------------------|-------------------------|
| Positive for parasites | 6 (a)                     | 0 (c)                   |
| Negative for parasites | 79 (b)                    | 35 (d)                  |
| Odds ratio      | \(\frac{a}{b}\) = 5.8068  |                          |
|                 | \(\frac{c}{d}\)           |                          |
| 95% CI          | 0.3183 – 105.8794         |                          |
| \(P\)           | 0.2352                    |                          |

*with 0.5 added to each number as \(c = 0\) (26)

These results suggest that improvement in main complaint was generally paralleled by a better quality of life, while between homeopathic clinics there was a difference in the rapidity of the improvement of the main complaint. And the improvement of the main complaint (fever, headache, limb pain etc) was larger after one week in the homeopathic cohort than in the hospital cohort. Which suggests a symptomatic difference in clinical improvement in favour of homeopathic treatment.
Table 15: ORIDL scores for impact of treatment on daily life (Open cohort 2015). *2 patient’s data missing (26).

| Score | Main complaint               | In total | Hospital | General quality of life (no data from hospital) | In total | Hospital |
|-------|------------------------------|----------|----------|--------------------------------------------------|----------|----------|
|       |                              | Homeopathic clinics |          |                                                  |          |          |
| -1    |                              | Manyanga (n=38) | Matuu (n=10) | Kambi Mawe (n=29) | Homeopathic clinics | Manyanga | Matuu | Kambi Mawe | Homeopathic clinics |
| 0     |                              | 0         | 0        | 0                                                | 0        | 0        | 0        | 0 |
| +1    |                              | 1         | 0        | 0                                                | 1        | 0        | 0        | 1 |
| +2    |                              | 13        | 5        | 0                                                | 18       | 0        | 14       | 3 |
| +3    |                              | 22        | 3        | 21                                               | 46       | 22       | 20       | 6 |
| +4    |                              | 2         | 2        | 8                                                | 12       | 13       | 3        | 4 |
| 38    |                              |           |          | 10                                               | 29       |          | 38       | 10 |
| 77*   |                              | 35        |          | 77                                               | No data  |          | 77       | No data |

*2 patient’s data missing (26).
Discussion

The effects of homeopathic treatment were documented in three types of studies:

- A retrospective study of n = 54 patients with checked malaria, of which the follow up is not documented with objective outcomes;
- A prospective single arm study, of n = 69 confirmed cases with negative parasitology on follow-up.

A comparative open label study of two cohorts of n = 35 treated with co-artem and n = 79 with homeopathic remedies, with an effective parasite elimination after one week in both groups, with no significant difference – an odds ratio within 95% CI. Within the homeopathic group of remedies, two remedies accounted for 82% of all cases: chin and chins.

Together, these results indicate an measured effect of homeopathic remedies in 148 patients of whom 79 were compared with a cohort of n=35 treated with co-artem. We have in this open label design checked for certain potential confounders, both at the diagnostic and the therapeutic level.

Selection bias [27]: all patients were seen in the rainy season where malaria has a high incidence and prevalence in the regions studied. Study 3 occurred in the course of several weeks in the same semi-arid region, with patients mainly coming from small villages in a rural area. We did not find major differences in age or gender distribution between the two cohorts in study 3. The interventions we studied were not different from the usual care delivery in the respective health settings, homeopathic and hospital outpatient services. We took care not to introduce special modifications of treatment for the purpose of the study.

Confounding bias: we compared two samples with uncomplicated malaria, the same level of disease severity, by excluding cases of cerebral malaria that would lead to different therapeutic regimens than the usual case management – all patients in that category are always referred to the hospital.

Information bias: below we detail the diagnostic question strategies for the homeopathic clinics, while the government clinic followed one therapy for all cases, the guideline for co-artem treatment.

Prescription strategies.

In study 1, 82% of all cases had received the homeopathic form of quinine. Which is an indication of its value in homeopathic treatment of malaria. This was confirmed in studies 2 and 3 where this remedy was used, too, and a parasite check validated the correctness of prescription.

‘Typhoid mix’, a complex remedy was used frequently on the basis of clinical symptoms – that overlap with those of malaria, typhoid was not confirmed. Also, amoebiasis and brucellosis overlapped typhoid symptom patterns.

Heterogeneity of samples

Recorded symptom patterns were heterogeneous enough to apply and combine many remedies. Yet, a relative small number of remedies was used, confirmed in studies 2 and 3 by parasite
disappearance. From this small set of remedies, we may construct the ‘genus epidemicus’. In this study these were:

- **China, China sulphuricum**, both derived from quinine, and **Arsenicum album, Belladonna, Natrium muriaticum, Nux vomica**, as well as two complex remedies, malaria mix and malaria blood. These confirm the remedies frequently used in the study of van Erp and Brands in Ghana [22]; as well with the ones found in the reviewed literature in the Introduction. Use of Belladonna reflects the high prevalence of headache complaints in this sample (see table 3). A differential diagnostic module of these principal remedies will facilitate the choice for community health workers.

In the Ghana study during the rainy season, were prescribed additionally **Eupatorium perfoliatum** (a marshland flower) and **Rhus toxicodendron** (poison ivy), - as they have been recorded to apply to people sensitive to humid weather conditions. The case reports of Master [8-9] confirm our results with the same remedies.

Confirmation from different sources supports the use of a limited number of remedies, which serves focused training for CHW with little education in homeopathy, what makes treatment of malaria outbreaks effectively, and affordably by low costs.

**Posology**

- **Artemether** was used in the control group according to guidelines.

The homeopathic posology was for most remedies, in low potencies such as 6X and 12 X (below Avogadro’s number, 24 X, (1024 mmol/l), frequent administration for 5-7 days was made to stimulate repeatedly persons with compromised immune system after recurrent infections with different microorganisms. This prescription for acute cases does not exclude chronic approach for those with a tendency to acquire frequent malaria. This may indicate a genetic difference in sensitivity to infestation by plasmodium species – a lower sensitivity has been related to T regulatory cell deficit [28], and before to FyFy blood-group presence [29].

Single remedy prescription (SRP), the standard in classical homeopathy, was on average in 15% of cases in study 1 (table 5). The question arises whether SRP as best practice corresponds with the actual practices in many countries.

Limiting factors for SRP are 1. large numbers of patients in busy clinics 2. Short consultation, 3. inaffordability for low income groups, 4. Risk of selecting an incorrect single remedy when multi-morbidity is present. Therefore, in these cases, complex remedy use composed of the **genus epidemicus remedies** may be a pragmatic choice.

Given the promising outcome of this Problem Oriented (P-O) approach in the comparative study, it may have implications for homeopathic case management in primary health care (PHC).

**Short term effects: ORIDL in study 2 and 3**

We had some doubts about the reliability of the ORIDL in study 2, as we received consistently very high ratings for the general improvement; and when we compared this with the remaining clinical symptoms on the first week’s follow up, there seems to be a positive bias of the ORIDL scores. Therefore, we questioned the patients’ subjective interpretation of the concept ‘impact on daily life’: in study 3 we advised the practitioners to specify their questions for key rehabilitation aspects: energy, exertion, mobility, work. This led to a wider variation in scores, which is probably a more realistic representation of the actual inter-patient variation.
Long term effects

Longer term protection to malarial attacks by stimulating the immune system is the ideal outcome. To assess this, we would need a longer follow up period and a longer presence of research personnel in the region, which was financially not feasible. Preceding the randomized clinical trial of the study in Ghana [22], an open pilot study had been done with the staff of the hospital; they reported less frequent and milder attacks of malaria after homeopathic treatment. Treatment of acute symptoms does not imply definite increase of resilience to a communicable recurrent disease. To date, there are no data on acute episode treatment for secondary prevention.

Limitations of this study

Diagnostics: Interpatient variation

This variation is due to differences between patients in response and co-morbidity (amebiasis, typhoid fever, etc). With comorbidity overlapping symptoms may confound precise diagnosis. As many data as possible were recorded with the several tests on respective pathologies. Not all patient consented for financial reasons. This limits completeness of data and distinction between symptom patterns. Only for malaria testing was done on all cases.

An exhaustive assessment of co-morbidity symptom disappearance was not possible. The quality of life scores however indicated systemic response after homeopathic treatment. This must be substantiated in a more comprehensive study capable of pre and post-treatment assessment of all co-occurring microbial diseases.

Accuracy

Quantitative measurement of parasite numbers in the peripheral blood as a secondary outcome, was technically impossible so not comparable with the assessment in the hospital clinic.

Microbial tests for other communicable diseases.

The reliability of parasitological and bacterial tests remains a point of debate in tropical diseases, such as the Widal test for salmonella, the only one available.

Drop out

In both studies significant drop out occurred in the cohort attending one of the clinics. In study 2 we had a loss of data of 35% in the Manyanga clinic; logistic reasons were the primary reason, and this affected the Manyanga clinic as this clinic is on the throughway from Mombasa to Uganda where truck drivers attended for a single treatment. Within the nearby region, residence-clinic distance showed not to be a factor (table 11)

However, in the third study, other causes were identified. Rain deficits in the early phase of the wet season prompted many farmers to keep working instead of coming for follow-up. Climate change directly affected our investigation.
Suggestions for further research

1. Through Principal Component Analysis further correlations may be established between remedies and involvement of organs in each patient (figure 1). Comorbidity patterns of affected organs can be identified with larger patient samples. This may assist in linking patterns of affected organs to (combinations of) effective remedies. Their effective prescription, shown by parasitology, is a basis of for this confirmation.

2. The second and third studies suggest effectiveness of this therapy in malaria management. What provides a rationale for larger studies in additional use of homeopathy to artemisin treatment guidelines.

High prevalence, mortality and morbidity of malaria, and microbial resistance also to co-artem, support further research of complementary therapies, in line with WHO concerns regarding drug-resistance [30]. Individualized immune therapy has always been the goal of homeopathic medicine. Increasing scientific evidence supports its application in several types of diseases, including endemic diseases [31].

Accessibility of care makes the use of a pragmatic homeopathic approach relevant, which favor a mix of prescribing techniques, next to conventional single remedy selection in an extended consultation. Which is of importance regarding the debate on whether context effects due to long consultations explain homeopathic effects.

The current studies that all were conducted in the context of short consultations of 15 minutes, due to time and financial constraints, do not support this idea. Homeopathy actually was practiced in ways that limit placebo or context effects [32].

Furthermore, a problem–oriented homeopathic approach seems relevant for endemic and epidemic diseases. Community health workers want to treat their fellow citizens effectively, safely and affordably. This use would be parallel to recent studies which show benefits for the use of traditional medicine in Africa [33]. By using these pragmatic approaches, they will support the WHO mission 'health for all'.

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ETHICS STATEMENT

To the main editor of the International Journal of High Dilution Research

Amsterdam, 03 03 2019

Hereby I state that the third, comparative study as the intervention study from the three studies of our paper has been granted ethical agreement from the Kenyatta University Ethical review Committee, (ERC) head prof N. Gikonyo. Reference number KU/R/Comm/51/396, date February 4, 2015.

The actual trial was not carried out, but a open cohort study instead, due to climate change – drought instead of monsoon, which reduced the number of attending patients - and that made us have to carry out a different non-trial design. We informed the ERC about this change at april, 18, 2015.

With kind regards,

Martien Brands MD PhD,
principal investigator