

Reducing the need for antibiotics

The contribution of
Complementary and
Alternative Medicine

CONFERENCE ON JUNE 6, 2018 IN BRUSSELS



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INTRODUCTION

The purpose of this report is to provide an overview of the aims and results of the JPIAMR (Joint Programming Initiative on AntiMicrobial Resistance) project “Appropriate use of antibiotics: the role of CAM treatment strategies”. An additional aim is to raise some key questions and challenges with respect to the way forward.

On June 6, 2018 the international conference “Reducing the need for antibiotics - The contribution of CAM treatment strategies” was held at the Regione Toscana - Representation of the Tuscany region in Brussels, Belgium. During this conference the results of the JPIAMR 4th call project “Appropriate use of antibiotics: the role of CAM treatment strategies” were presented and discussed with a broad group of invited stakeholders.

The main objectives of the JPIAMR project were:

- To provide an overview of expert and scientific knowledge on CAM / IM (Complementary and Alternative Medicine¹ / Integrative Medicine) treatment of Upper Respiratory Tract Infections (URTIs);

- To develop a CAM / IM guidance document and a first concept expertise- and evidence-based decision-making tool (DMT) for (conventional) doctors at a European level.
- To provide a communication platform on the CAM / IM contribution.

The conference was successful and resulted in clear insights regarding the current status and contribution of CAM, the potential of CAM in reducing the need for antibiotics, and the next steps that should be taken in order to fully realise the potential of CAM.

This report also gives an overview of the conference. It begins with the (slightly adapted) conference paper (Preface until Chapter 7), that the participants were given on the day. The last chapters include summaries of the presentations of the JPIAMR team members (Chapter 7) and the main issues discussed during the conference (Chapter 8).

¹ In this project the CAM modalities anthroposophic medicine, Ayurveda, homeopathy, western herbal medicine, traditional Chinese medicine (TCM) are included.

PREFACE

One of the key objectives of the European One Health action plan against AMR is to boost research, development and innovation by closing current knowledge gaps, providing novel solutions and tools to prevent and treat infectious diseases. The use of effective and safe non-antibiotic treatment of infections is one of the strategies to reduce inappropriate use of antibiotics (ABs). Complementary and Alternative Medicine (CAM) practices prescribe non-antibiotic treatment strategies, aiming to strengthen human' and animal' resilience to infections.

A team of researchers from several European universities has undertaken intensive research with respect to CAM treatments for respiratory infections and suggests some innovative tools which were presented and discussed at the conference. EUROCAM and the research team recommend the testing and further development of these tools, as a pilot case for the potential of CAM in reducing the problem of AMR. This should be given serious consideration and further research should be carried out in this area.

We trust that the informative discussions at the conference will help to improve the proposed way forward, to strengthen existing alliances and to build new alliances in overcoming the remaining challenges with AMR.

The research network project was supported by ZonMw, the Netherlands Organisation for Health Research and Development, under the framework of JPIAMR – Joint Programme Initiative for AntiMicrobial Resistance (4th call).

Topics that were presented and discussed include:

- Mapping of the CAM contribution to reduce antibiotic use
- Antibiotic prescription rates in conventional and CAM general practitioner (GP) practices
- Safety and effectiveness of CAM treatment strategies for respiratory tract infections and other infections
- First concepts of a decision-making tool (DMT), a patient decision aid (PtDA) and information leaflets for health professionals and patients in primary care, enabling the larger community of health professionals to make use of therapeutic options from the field of CAM focusing on URTIs
- An institutional model of structural development of DMTs for doctors, PtDAs for patients and information leaflets on CAM treatment of infections

December 2018

Dr Ton Nicolai, EUROCAM spokesperson
Prof Dr Erik Baars, project leader JPIAMR project

TABLE OF CONTENTS

INTRODUCTION	3
1. EXECUTIVE SUMMARY	8
1.1 Background	8
1.2 Hypothesized value of CAM in bridging the gap between guidelines and practice	8
1.3 Main results	9
1.4 Conclusions: contribution of CAM to reduce AB prescription and use, and to promote appropriate use of ABs	9
1.5 Conclusions: implementation and dissemination of CAM treatment options for URTIs	10
1.6 Short-term and long-term challenges	10
2. PROJECT AT A GLANCE	11
3. BACKGROUND	12
3.1 Antimicrobial resistance (AMR)	12
3.2 Primary care and upper respiratory tract infections (URTIs)	12
3.3 Complementary and Alternative Medicine (CAM)	13
3.4 Existing national guidelines and entry points for integration of CAM treatments	13
4. STUDY RESULTS	14
4.1 The contribution of CAM to reduce antibiotic use (narrative review)	14
4.2 Can CAM treatment strategies reduce antibiotic use or control symptoms of uncomplicated acute RTIs? (systematic review of systematic reviews)	15
4.3 CAM treatments of URTIs - What can we learn from CAM experts? A European survey	15
4.4 Narrative review of prescription rates of CAM treatment of RTIs in daily practice	16
4.5 Retrospective study on antibiotic prescription rates in England over 2016	16
4.6 Systematic review of qualitative studies on patients' and professionals' views on use of CAM for RTIs	16
4.7 Information tools for CAM treatments and fever management	17
5. STRENGTHS AND LIMITATIONS	18
6. SHORT-TERM AND LONG-TERM CHALLENGES	20
7. SUMMARY OF THE PRESENTATIONS BY THE JPIAMR PROJECT TEAM	22
8. SUMMARY OF MAIN ISSUES DISCUSSED DURING THE CONFERENCE	28
8.1 Relevance of a European CAM & AMR research and action network to support the European AMR policy	29
8.2 The context of (the development of) this network	32
8.3 Input for future activities	34
8.4 Key messages from the conference	34
JPIAMR Project Team	35
Acknowledgements	35
Conference program	36
List of speakers	37
References	38

1. EXECUTIVE SUMMARY

1.1 Background

- Resistance to antibiotics (ABs) is a complex and growing international public health problem with important consequences such as increased mortality and economic impact.
- In most global, regional and national policies on antimicrobial resistance (AMR), six main strategies are used to achieve the goal of reducing AB use: infection prevention and control of resistant bacteria, monitoring of both infection prevention and control of resistant bacteria, research on AB resistance and AB use, appropriate use of ABs (e.g. not for viral infections), less AB use (e.g. delayed prescription and alternatives), and development of new ABs.
- In human medicine, CAM treatment strategies, including CAM medicinal products and fever management, are not included in these official AMR policies.
- European AB prescription data show that there are large differences between countries of the European Union, which are not related to geographic or natural conditions and can only be explained by socio-economic factors (policies, values, competencies, ...).
- National guidelines for URTIs demonstrate entry points for delayed prescription and options for CAM treatments as part of delayed prescription strategies.

1.2 Hypothesized value of CAM in bridging the gap between guidelines and practice

- There is a gap between guidelines and current practice in Europe. The guidelines for treatment of uncomplicated URTIs in five European countries (France, Germany, Switzerland, the Netherlands, UK) demonstrate that ABs are only indicated in high risk groups and for complications. However, ABs are often prescribed for these indications, motivated in various ways by patients and health care professionals.
- Primary care is of high relevance for AMR policies.

For example, in the UK 74% of ABs for human use are prescribed in primary care, making it one of the most important contributors to the development of AMR. Reducing the use of ABs in primary care and counteracting the development of AMR are pressing international priorities.

- CAM competence can make a difference: There is a growing amount of evidence that doctors with additional qualification in CAM (CAM doctors) prescribe less ABs overall and for URTIs than conventional doctors. This could be because CAM doctors have additional CAM treatments for infections, and maybe also because patients who do not want to use antibiotics, visit these CAM doctors.

1.3 Main results

- A narrative review, mapping the contributions of CAM, shows that many CAM treatment strategies including CAM medicinal products and fever management, are promising ², but overall there is a lack of high-quality evidence. (See 4.1 (p. 14))
- A systematic review of systematic reviews demonstrates that there are specific, evidence-supported, promising CAM treatments for acute, uncomplicated RTIs and that they are safe. (See 4.2 (p.15))
- A survey among CAM experts with respect to URTIs and a narrative literature review on prescription rates of CAM treatments in daily clinical practice provide the best practices and most prescribed CAM treatments for URTIs respectively. See 4.3 (p. 15) and 4.4 (p. 16)
- A retrospective study within the National Health Service (NHS) England demonstrates that health centres

employing General Practitioners (GPs) additionally trained in IM / CAM have lower AB prescription rates as compared to conventional health centres, both overall and specifically for URTIs. (See 4.5 (p. 16))

- A systematic review of qualitative studies on patients' and health workers' views on the use of CAM for respiratory infections found that patients decide which treatments to use based on their beliefs about the illness (cause and severity) and the treatments (safety and effectiveness). There is a need for reliable, evidence-based advice on which treatments to use. (See 4.6 (p. 16))
- The "FeverApp Register Study", funded by the German ministry of education and research, aims to evaluate and optimise guidelines that help parents deal safely and confidently with acute febrile illnesses by using a Fever App. It is expected that the use of this App will lead to a reduction in AB use by reducing GP consultations and by changing patient behaviour.

1.4 Conclusions: contribution of CAM to reduce AB prescription and use, and to promote appropriate use of ABs

- Based on the results of the studies, we conclude that the contribution of CAM treatment strategies in reducing AB prescription and consumption is promising and is supported by an increasing evidence base. CAM can contribute in two of the strategies for addressing AMR: appropriate use of AB and less AB use. (See narrative review)
- For URTIs especially, CAM treatments can contribute to reduce AB prescription and use, supported by an increasing evidence base. (See systematic review of

2 The term promising is used here for CAM treatments that have positive results in the SRs (SR of SRs), or are judged as best practice by the CAM experts (survey) and/ or are prescribed most often in daily clinical practice by CAM doctors (narrative review of prescription rates of CAM treatment of RTIs in daily practice).

systematic reviews)

- European CAM experts use a wide range of different treatments with medicinal products for delayed AB prescription and / or symptom relief of URTIs. (See expert survey and monitoring of daily practice studies).

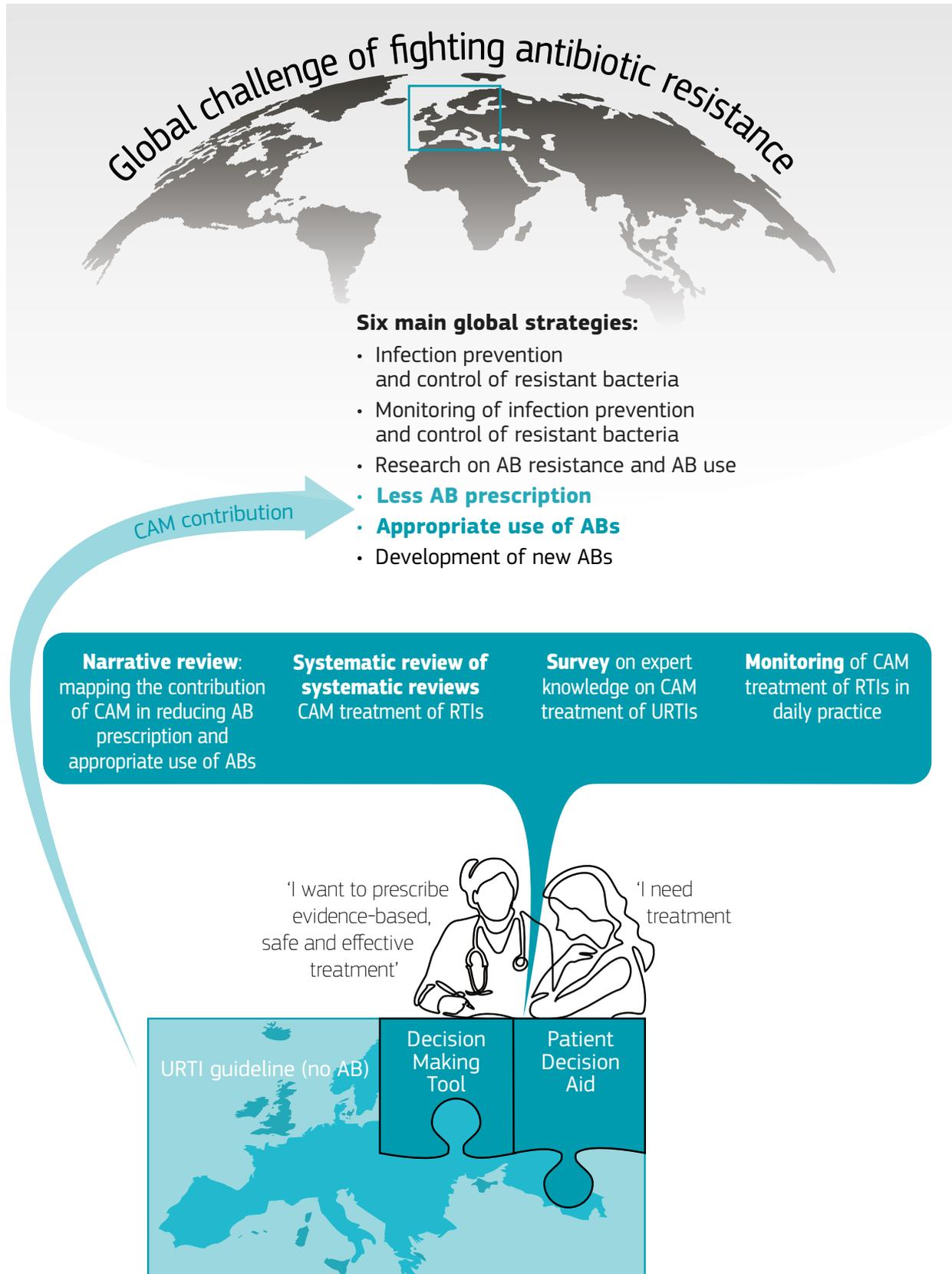
1.5 Conclusions: implementation and dissemination of CAM treatment options for URTIs

- CAM treatments could well fit and could be integrated in delayed AB prescription strategies for treatment of URTIs, both supporting the guidelines to not treat with ABs, and meeting both doctors' and patients' desire for effective symptom relief.
- There is a wide variety of CAM treatments available, but these are often unknown by doctors and patients. Expertise- and evidence-based decision-making tools (DMTs) for doctors, patient decision aids (PtDAs) and information leaflets would provide the trusted advice which they need to support their choice for a specific CAM treatment.
- In this project the first concepts and prototypes of a DMT, a PtDA, and doctors' and patients' information leaflets for acute URTIs were developed, as well as a prototype of a Fever App. The aim here is to demonstrate the CAM contribution, to facilitate the decision-making process in choosing a specific CAM treatment and to make CAM treatments more accessible to stakeholders.

1.6 Short-term and long-term challenges

- Major short-term challenges are:
 - finalisation of the national stakeholder involvement in selected European countries (alpha testing: collecting feedback from doctors and patients on project results and information tools in focus groups)
 - (submission of) publications in peer-reviewed scientific journals
 - execution of next steps in the development and validation of the current doctor and patient information tools in national context (e.g. beta-testing (feasibility studies))
 - further specification of the developed instruments according and / or adjusted to national contexts as a proposal for further European and national communication
 - organisational development of a reliable and legitimate European / international institutional model and organisation of further activities in this field with respect to DMTs for doctors, PtDAs for patients and information leaflets on CAM treatment of infections and FeverApp (research, development, cooperation, implementation, ...) including funding, on a regular basis.
- Major long-term challenges are:
 - high quality studies on testing of safety and effectiveness of 'promising CAM treatments' for URTIs in primary care
 - development of new evidence-based sources of advice on CAM treatment of other infections
 - testing of usability, effectiveness and safety of a fever management app used by parents
 - developing a European knowledge base for CAM treatments for infections
 - executing supporting socio-economic research and activities.

2. PROJECT AT A GLANCE



3. BACKGROUND

3.1 Antimicrobial resistance (AMR)

Resistance to antimicrobials (AMR) is a complex and growing international public health problem. [1, 2] Globally, infections with resistant microorganisms are estimated to kill hundreds of thousands of people every year. An often cited but also criticised scenario suggests that by 2050 that figure could be more than 10 million. The economic cost will also be significant, with the world economy being hit by up to \$100 trillion by 2050 if no action is taken. [1] Formal policies on the global, regional and national level most often use six strategies to reduce antibiotic use: infection prevention and control of resistant bacteria; monitoring of both infection prevention and control of resistant bacteria; research on antibiotic resistance and antibiotic use; appropriate use of antibiotics (e.g. not for viral infections); less antibiotic use (e.g. delayed prescription and alternatives); and development of new antibiotics. [3] However, currently these strategies appear to be insufficient, as for example demonstrated by the unchanged average European consumption rates of antibiotics during the years 2011 – 2014. [4] European statistics also show that there are significant differences between European countries which are not related to geographic or natural conditions and can only be explained by socio-economic factors (policies, values, competencies, ...). [5] For example, in the UK in 2015, for the first time fewer antibiotics were being prescribed by GPs and clinicians across all healthcare settings than in 2014. [6] Nevertheless, the latest “EARS-Net data for 2016 show that antimicrobial resistance remains a serious threat to public health in Europe”. [7]

3.2 Primary care and upper respiratory tract infections (URTIs)

The amount of antibiotic prescribing and consumption varies between European countries. [8-12] Primary care accounts for about 80 to 90% of all antibiotic prescrip-

tions. [13, 14] Seventy-four percent of ABs for humans in the UK are prescribed in primary care, making it one of the most important contributors to the development of AMR. [15] Reducing the use of ABs in primary care and controlling the development of AMR are pressing international priorities. Respiratory tract infections (RTIs) are among the most common infections experienced in the community and are among the most common reasons for AB prescribing internationally (e.g., [16]). Previous studies show that although ABs have small or negligible symptomatic benefits for patients with uncomplicated acute otitis media, pharyngitis, bronchitis, laryngitis and common cold, ABs are still commonly used for these and other viral respiratory infections (e.g., [17, 18]). Delayed prescription strategies in combination with effective and safe non-antibiotic RTI treatment during the delayed prescription period might therefore offer a contribution to reduce AB prescription and use, meeting both doctors' and patients' desire for treating RTIs and symptom relief.

3.3 Complementary and Alternative Medicine (CAM)

Despite widespread public popularity [19], CAM strategies are currently not part of formal policies aiming at reducing antibiotic use. There is also a paucity of research and a lack of investment in studies investigating the potential contribution of CAM to the treatment of infections. However, the proposition from CAM is that it can particularly contribute in two of the strategies for addressing AMR: appropriate use of AB and less AB use.

3.4 Existing national guidelines and entry points for integration of CAM treatments

In all five European countries (France, Germany, Switzerland, the Netherlands, UK) that participated in the JPIAMR project, the national medical guidelines for e.g.

cough and sore throat state that ABs are not indicated. Patient education and symptomatic treatment (e.g. of pain) should be provided. ABs are only indicated for high risk groups and for complications. An effective and safe CAM non-antibiotic RTI treatment (with or without a delayed prescription of antibiotics) could contribute to reducing antibiotic prescriptions and use, meeting both doctors' and patients' desire for symptom relief. In the German medical guidelines several herbal medicines are already indicated for for example cough [20] and rhinosinusitis. [21]

4. STUDY RESULTS

In the JPIAMR project the results of different studies were used to get an overview of expert and scientific knowledge on CAM/ IM treatment of selected infectious diseases (URTIs) and to develop a first CAM/ IM prototype of an expertise- and evidence-based decision-making tool (DMT) for (conventional) doctors at a European level. In addition, patient information tools were developed.

4.1 The contribution of CAM to reduce antibiotic use (narrative review)

Aiming to map the contribution of CAM in reducing AB prescriptions and use and to improve appropriate use of ABs, we conducted a narrative review. The databases PubMed, Embase and the Cochrane Database of Systematic Reviews were searched with a specific, limited set of search terms and input from a group of expert CAM researchers, was collected to answer the question: What is known about the contribution of CAM health (and health promotion) concepts, infection prevention and infection treatment strategies to reduce inappropriate antibiotic use? Twohundred and twelve studies were included in the narrative review.

Key results are: CAM strategies are most often preventive and curative health promotion strategies. There is some evidence that the CAM concepts of health (promotion) agree with current conceptualisation of health and that doctors who practice both CAM and conventional medicine prescribe less antibiotics, although selection bias of the presented studies cannot be ruled out. There is evidence that some CAM prevention and treatment strategies may be effective and safe. In addition, many CAM treatment strategies (e.g., for respiratory and urinary tract infections) are promising, but overall lack high quality evidence. More rigorous research is necessary to provide high quality evidence of safety and (cost-)effectiveness of CAM strategies.

In the JPIAMR project the results of different studies were

used to get an overview of expert and scientific knowledge on CAM/ IM treatment of selected infectious diseases (URTIs) and to develop a first CAM/ IM prototype of an expertise- and evidence-based decision-making tool (DMT) for (conventional) doctors on a European level. In addition, patient information tools were developed.

4.2 Can CAM treatment strategies reduce antibiotic use or control symptoms of uncomplicated acute RTIs? (systematic review of systematic reviews)

Aiming to identify CAM strategies that reduce the use of antibiotics or control symptoms of RTIs, and that are safe, a systematic review (SR) of systematic reviews was conducted. This included observational studies and clinical trials on treatment of acute uncomplicated RTIs with herbal medicine, anthroposophic medicine and homeopathic remedies, from 2008 until April 2018. Primary outcomes were: symptom relief and antibiotic consumption. Secondary outcomes were: antibiotic prescribing, quality of life, RTI symptom duration and re-consultation, and adverse events. SRs including studies comparing CAM with active treatment, placebo controls and no treatment were included. Standard SR methodology was employed for study identification, selection and data extraction. Appropriate quality assessment (AMSTAR-2 checklist) was used to assess SR quality. Thirty studies were included in the review.

Key results: There are several CAM medicinal products for: acute RTIs (e.g. *Pelargonium sidoides*, *Andrographis paniculata*), acute rhinosinusitis, acute tracheobronchitis, acute URTI, bronchiolitis, cough, Influenza A, otitis media and sore throat, that demonstrate positive effects on symptom relief and are safe, according to the conclusions of the systematic reviews. However, several authors describe that the quality of the included studies in the SR is often low or unclear and several systematic reviews themselves have methodological shortcomings.

Nevertheless, given the urgent need for non-antibiotic alternative treatments to reduce inappropriate antibiotic use for RTIs, promising CAM treatments with positive effects and evidence of safety demonstrated in systematic reviews, that are readily available on the European market in a good-quality product, can be used by doctors and patients, for example as part of a delayed prescription strategy to control symptoms of uncomplicated acute RTIs. If so, uncertainty of effectiveness must be transparently communicated.

4.3 CAM treatments of URTIs - What can we learn from CAM experts? A European survey

As an additional source of knowledge and evidence, because most CAM treatments have not been studied in clinical trials yet, a survey was conducted among CAM experts of five CAM types (anthroposophic medicine, Ayurveda, homeopathy, western herbal medicine and traditional Chinese medicine) in five European countries (France, Germany, Switzerland, the Netherlands, UK) to collect and systematise CAM expert knowledge and reach consensus on the best CAM treatments for four indications. CAM experts were approached through the national CAM associations (members of EUROCAM) to complete an online survey to describe the top 3 best CAM treatments, according to their expertise, for the following URTI indications: (1) dry cough, (2) wet cough, (3) sore throat, and (4) sore throat and fever. Lists of 'best CAM treatments' were made based on a ranking of number of times mentioned and following consensus meetings. With 262 respondents in total, the highest response was for anthroposophic medicine (n=99) and homeopathy (n=95). Additional consensus meetings/ feedback loops with experts have been and are currently organised to reach consensus among experts on lists of 'best CAM treatments. Some examples of the outcomes of the survey are:

- Anthroposophic medicine for sore throat: medicinal products (Apis Belladonna, Bolus/ Eukalyptus comp, Apis Belladonna cum Mercurio, Pyrit/ Zinnober, Echinacea Rachenspray, Zinnober comp.), external applications on the neck (Citrus) and tea (Salvia/ Salbei).
- Homeopathy for dry cough: Spongia, Bryonia, Drosera, Aconitum, Phosphorus, Coccus cacti.
- Herbal medicine for wet cough: Thyme, Salbei and Efeu.

4.4 Narrative review of prescription rates of CAM treatment of RTIs in daily practice

Two studies on monitoring prescription of medicinal products in daily practices of homeopathy and anthroposophic medicine demonstrate that there is a variety of CAM treatments used in CAM daily clinical practice. A comparison of the results of the two monitoring studies and the survey among CAM experts (4.3), demonstrates that there is a large overlap between the lists of selected medicinal products based on the survey and the list of most prescribed medicinal products in daily clinical practice. [22, 23]

4.5 Retrospective study on antibiotic prescription rates in England over 2016

A retrospective study was executed to determine differences in antibiotic prescription rates between conventional general practitioners (GP) surgeries and GP surgeries employing general practitioners additionally qualified/certified in CAM/ IM (IM GPs) working within National Health Service (NHS) England. Correlations between IM GPs and antibiotic prescribing rates per STAR-PU (Specific Therapeutic group Age-sex weighting Related Prescribing Unit) and with the number of antibiotic prescriptions (total, and for respiratory and urinary tract infection (RTI/ UTI)) were studied separately.

NHS England GP surgeries employing GPs additionally trained in IM/ CAM have lower antibiotic prescription rates. There were 7283 NHS England General Practices included in the analyses. IM GP surgeries (n=9) were comparable to conventional GP surgeries in terms of list sizes, demographics, deprivation scores and comorbidity prevalence. Despite the very small proportion of IM GP surgeries, the data shows that significantly lower 'total antibiotics' and 'RTI specific antibiotics' per STAR-PU were prescribed at IM GP surgeries compared to conventional GP surgeries within NHS England over 2016. No statistically significant differences were found in median prescription rates of 'UTI specific antibiotics' per STAR-PU in the two kinds of NHS GP surgeries. [24]

4.6 Systematic review of qualitative studies on patients' and professionals' views on use of CAM for RTIs

Six electronic databases were systematically searched. Published papers were included relating to the use of CAM for RTIs, which reported qualitative data collection and analysis.

Ten studies met the inclusion criteria: three were conducted in the UK, focusing on ethnic minorities; one in the USA, and the others in Africa and Asia. Nine focused on parents' treatment of RTIs in their children. In all settings, their decisions on which treatment to use were influenced by beliefs about the illness (cause, severity), beliefs about treatments (efficacy, safety), availability of treatments, and perceived trustworthiness of advice. CAM was widely used and accepted as a viable option for treatment of mild RTIs by ethnic minorities, but very few studies included white Caucasian adults. Many patients felt that they need trustworthy advice on which CAM treatments to use and when.

In conclusion: CAM treatments would be acceptable to patients from many ethnic groups as a possible alterna-

tive to antibiotics for mild RTIs. There is a need for reliable, evidence-based advice on which treatments to use.

4.7 Information tools for CAM treatments and fever management

There is a wide variety of CAM treatments available in Europe, but these are often unknown by doctors and patients and not easily accessible. The comparison of the results of the SR of SRs, the expert survey and the narrative review of prescription rates of CAM treatment of RTIs in daily practice, shows that most of these current best practices or most prescribed CAM treatments in daily practice have not been studied yet in clinical trials or systematic reviews.

Expertise- and evidence-based decision-making tools (DMTs), patient decision aids (PtDAs) and information leaflets for CAM treatment of acute, uncomplicated URTIs for doctors and patients can facilitate delayed prescription strategies in combination with effective and safe non-antibiotic URTI treatment during the delayed prescription period. Meeting both doctors' and patients' desire for treating RTIs and symptom relief, this strategy is expected to contribute to appropriate use of ABs and reducing AB prescription and use.

The discussions within the team and with further European CAM experts as well as "conventional doctors" have shown that this kind of tool requires adjustment according to the specific national context. At the same time the exchange of different national experiences can add great value to the European knowledge base and also help to accelerate the European learning curve. Based on the results of the described studies, additional consensus meetings/ feedback loops with experts and additional information (e.g. regulatory status, availability, estimated costs), first prototypes of an expertise- and evidence-based decision-making tool (DMT) and patient decision aid (PtDA) for CAM treatment of URTIs for doctors

and patients respectively, are currently being developed. These will meet the IPDAS (International Patient Decision Aid Standards) quality and certifying criteria [25] and fit the conventional guidelines of URTI treatment.

In addition, first concepts of doctor information leaflets (DILs) and patient information leaflets (PILs) were developed for one country (UK). The latter were discussed with stakeholder groups of patients, general practitioners and pharmacists, in order to receive feedback from users for further improvements of the leaflets.

A first prototype of an eHealth application for easy use of the DMT/PtDA, DILs and PILs is currently being developed for doctors and patients. This tool may serve as an integrative European tool combining different types of CAM modality specific treatments with additional information about among others evidence of effects and safety, regulatory status, availability, etcetera. Information collected at the European level can be used and adapted for use on the national levels, meeting the national requirements and situation.

A fever management app and registry for parents and healthcare professionals has been developed in cooperation with the German societies of Paediatrics and ambulatory paediatric health care (supported by the German ministry of education and research) and shall be tested with additional partners. It is planned to integrate content of the CAM treatment information tools and the FeverApp step by step.

Depending on the availability of financial resources, it is planned to start testing these tools and the FeverApp in 2019 in Germany, and the Netherlands in cooperation between conventional and CAM/ IM stakeholders (doctors, patients, scientists).

5. STRENGTHS AND LIMITATIONS

The *strengths* of this project are firstly that they include the most important sources of knowledge (systematic reviews, expert knowledge, monitoring of prescription rates in daily clinical practice that show best practices) regarding CAM treatment strategies of URTIs, whereas most CAM treatments have not been studied in RCTs. Secondly, the results cover five CAM types that are most often used by patients and that are available in most European countries. Thirdly, the development of decision-making and information resources, and the use of eHealth applications, shall make a transparent and evidence-supported use of CAM treatments possible for conventional and CAM doctors and patients. Fourthly, the application of CAM treatments fits seamlessly with conventional guidelines, supporting non-antibiotic treatment and delayed prescription strategies including CAM treatment during the delayed period. Fifthly, based on the SR of SRs, the expert survey and expert consultation rounds, expertise- and evidence-supported lists were made of promising non-antibiotic CAM treatments for URTIs, that are safe, that can already be used in clinical practice, meeting doctors' and patients' desire for effective symptom relief, and that can contribute to reducing AB prescription and support appropriate use of ABs.

Limitations of the project are firstly that the systematic reviews and the included studies in the systematic reviews have methodological shortcomings, so that a final scientific judgment on the effectiveness of CAM treatments cannot be given. Secondly there is some bias in the remedies that are included in the SRs as there is always a link between the need for marketing and research. There might be remedies that are very effective, but there is little or no research on the effectiveness of these remedies due to lack of funding. Thirdly, a limitation of the SR is that only SRs were included. Observational studies and RCTs that not have been reviewed in a systematic review were not included. This might have led to an underreporting of the available evidence on CAM treatment of acute uncomplicated RTIs. Time and language limitations might also have resulted in underreporting. Fourthly, with regard to the collecting and systematising of expert knowledge there was an insufficient response for Ayurveda and TCM to make expertise-based lists of CAM best practices for cough and sore throat as part of acute, uncomplicated URTIs. Fifthly, with regard to defining best practices of CAM treatments, many CAM modalities individualize treatment in clinical practice based on a broad assessment of symptoms of the individual patient. There is a limitation with regard to the usability of generic lists of best practices, because best practices should include an individualized choice for a specific CAM treatment.

6. SHORT-TERM AND LONG-TERM CHALLENGES

The main aim is to develop a draft prototype of an expertise- and evidence-based decision-making tool for CAM treatment of infections for doctors on a European level that at the same time is applicable at the national levels, based on the results of the presented projects. More broadly the aim of this project is to demonstrate the CAM contribution to reduce antibiotic use and to develop a way to make CAM treatments of infections acceptable, available and usable for conventional stakeholders (e.g. doctors, patients, medical guideline developers, policy makers).

Against this background the following short-term and long-term challenges are:

Short-term challenges

1. Finalisation of the national stakeholder involvement in selected European countries (alpha testing: collecting feedback from doctors and patients on project results and information tools in focus groups).
2. Submission of publications to peer-reviewed scientific journals.
3. Execution of next steps in the development and validation of the current doctor and patient information tools in national context (e.g. beta-testing (feasibility studies)).
4. Further specification of the developed instruments according and/ or adjusted to national contexts as a proposal for further European and national communication.
5. Organisational development of a reliable and legitimate European/ international institutional model and organisation of further activities in this field with respect to DMTs for doctors, PtDAs for patients and information leaflets on CAM treatment of infections and FeverApp (research, development, cooperation, implementation, ...) including funding, on a regular basis.

Long-term challenges

1. The high-quality testing of safety and effectiveness for 'promising CAM treatments' for URTIs in clinical trials in primary care.
2. The development and testing of new decision-making tools, patient decision aids and information leaflets on CAM treatment of other infections (concepts and prototypes) based on urgency in medicine, best practices and evidence of safe and effective CAM treatments both in primary care and hospital care.
3. The testing of usability, effectiveness and safety of a fever management app (FeverApp) for parents.
4. The integration of content of the doctor and patient information tools and documents regarding CAM treatment options and the FeverApp, and the evaluation of their effectiveness in reducing antipyretic and AB use.
5. The development of algorithms that enable (more) individualised advice on CAM treatments.
6. Socio-economic research and activities supporting the doctor and patient information tools development and implementation and clinical research (e.g., prescription rate studies).
7. Developing a European knowledge base for CAM treatments for infections step by step.
8. The development and communication of an overall CAM research portfolio and strategy for this field.
9. The acquisition of funding for these projects.

7. SUMMARY OF THE PRESENTATIONS BY THE JPIAMR PROJECT TEAM



Professor Erik Baars, Dr Esther van der Werf, Dr Merlin Willcox, Professor David Martin, Dr Ton Nicolai

Presenting JPIAMR project team members

Professor Erik Baars is a senior researcher in Healthcare at the Louis Bolk Institute, a well-known organisation for research and advice for sustainable agriculture, nutrition and health in the Netherlands. In addition, he is a part-time Professor of Anthroposophic Medicine at the University of Applied Sciences in Leiden, the Netherlands. He is the project leader of the JPIAMR project.

Dr Esther van der Werf is a senior lecturer in Epidemiology of Primary Care Infectious Diseases and joined the Bristol Medical School of the University of Bristol (UK) and the Centre of Academic Primary Care (CAPC) in 2015. She is an epidemiologist and trial manager with over 15 years' experience of research, teaching and study management.

Dr Merlin Willcox is an Academic Clinical Lecturer in General Practice at the University of Southampton (UK) and works as a General Practitioner at a health centre in Oxford.

Professor David Martin is Full Professor and holder of the Gerhard Kienle Chair of Medical Theory, Integrative and Anthroposophic Medicine at the University of Witten/Herdecke, Head of the Institute of Integrative Medicine at the Medical Faculty of the University of Witten/Herdecke in Germany.

Professor Roman Huber is a specialist for Internal Medicine and Gastroenterology and heads a centre for CAM at University Medical Centre Freiburg, which is one of the largest University Hospitals in Germany.

Dr Klaus von Ammon is a Senior Officer and Consultant in the homeopathy department of the Institute of Complementary Medicine (IKOM) at the University of Bern, Switzerland. He authored many scientific publications in epidemiology, and clinical and fundamental research.

Results of the CAM-JPIAMR project

The first speaker of the project team, **Prof Erik Baars**, focused on the question of whether CAM can make a contribution in reducing antibiotic use, and if so, how CAM can be made acceptable and accessible for stakeholders.

On behalf of the team he expressed his gratitude for the grant given by ZonMw, the Netherlands Organisation for Health Research and Development, under the frame of JPIAMR - Joint Programme Initiative for AntiMicrobial Resistance. This was a network grant which enabled researchers from universities and research institutes to convene and gather the existing knowledge in cooperation with other stakeholders in the CAM sector.

He quoted economist Lord Jim O'Neill, chairman of the 'Review on Antimicrobial Resistance' who argued that drug-resistant infections already kill hundreds of thousands a year globally and by 2050 that figure could be more than 10 million. The world economy would be hit by up to \$100 trillion by 2050 if we do not take vigorous action

Preliminary studies have shown that there is some evidence that Complementary and Alternative Medicine (CAM) practices and hospitals may have lower antibiotic prescription rates and lower resistance rates as compared to conventional practices and hospitals, based on additional prevention and treatment of infections strategies. In order to offer conventional physicians a safe and effective alternative to antibiotics and to reduce inappropriate use of antibiotics, the research team has started their project to explore and systemise the available practical expertise and scientific knowledge on CAM prevention and treatment strategies.

The deliverables of this research project were to provide:

- An overview of expert and scientific knowledge on CAM / IM treatment of Upper Respiratory Tract Infections (URTIs)

- A first concept expertise- and evidence-based decision-making tool (DMT) for (conventional) doctors and patients at a European level
- A communication platform on the CAM / IM contribution

Professor Erik Baars explained the four projects which the research team had carried out.

1. A narrative review, mapping the contribution of CAM in reducing antibiotic prescription and motivating appropriate use of antibiotics;
2. A systematic review of systematic reviews on CAM treatment of respiratory tract infections (RTIs);
3. A survey on expert knowledge on CAM treatment of specific URTIs symptoms (cough and sore throat);
4. Monitoring of CAM treatments of RTIs in daily practice.

Based on the results of the studies, the team concluded that the contribution of CAM treatment strategies to reducing antibiotics prescription and use is promising and is supported by an increasing evidence base, i.e. from (1) systematic reviews, (2) expertise of CAM experts (survey), and (3) monitored prescription rates in CAM daily clinical practice. CAM can especially contribute in two of the main global strategies for addressing AMR: appropriate use of antibiotics and less antibiotic use. This research work will help to make CAM treatment of RTIs (more) *acceptable*.

When it comes to *accessibility* the team has developed a first prototype of a decision-making tool (DMT) and information leaflets, to help doctors to make rational and appropriate choices when treating patients with RTIs in daily practice by using CAM, and to inform patients about the existence and use of these treatments. Professor Erik Baars explained that, although antibiotics have small or negligible symptomatic benefits for patients with uncomplicated acute otitis media, pharyngitis, bronchitis, laryngitis and common cold, they are still often used for

these and other viral respiratory infections. In addition, he described that decisions on prescribing antibiotics, to a large extent, depend on the attitudes of both doctors and patients. Delayed prescription strategies in combination with effective and safe non-antibiotic RTI treatment during the delayed prescription period might therefore contribute to the reduction of antibiotic prescription and use, meeting both doctors' and patients' demands for treating RTIs. These strategies could be incorporated in currently existing guidelines.

In this way, effective and safe non-antibiotic RTI treatment can be used alone or in the context of a delayed antibiotic prescription strategy. The available knowledge can then be incorporated in DMTs, patient (decision) aids (PtDAs), and Information Leaflets for Doctors and Patients (DILs and PILs).

Antibiotic prescription rates by conventional GPs and GPs trained in CAM

The next speaker, **Dr Esther van der Werf** started her presentation by giving an overview of antibiotic consumption in Europe using an ECDC² graph on outpatient antibiotic consumption over 2017 based on the Defined Daily Dose per 1,000 inhabitants per day. People in the Netherlands and Scandinavia consume less antibiotics than the British, while the British consume less than the French or Italian. A next slide about the antibiotic prescription rate demonstrated the same variations between the individual countries. Variations in the prescription of antibiotics both within and across countries may indicate poor practice, which increases the risk of adverse events for the patient; it could also indicate a waste of health care resources and more importantly this contributes to antibiotic resistance.

Dr van der Werf and colleagues investigated whether there are any differences in antibiotic prescription rates between conventional GPs surgeries and GP surgeries

² European Centre for Disease Prevention and Control

employing GPs additionally trained in Integrative Medicine or CAM within NHS Primary Care in England. Their data demonstrates that significantly fewer 'total antibiotics' and 'RTI specific antibiotics' were prescribed at IM / CAM GP surgeries compared to conventional GP surgeries within NHS England over 2016. The study was published in the British Medical Journal Open and received ample press coverage in the United Kingdom, and worldwide.

She had the following three take-home messages:

- Knowledge and experience of clinicians and patients matter, as do socio-economic, cultural factors: capacity building is needed.
- RTI is an area where a desired reduction in AB prescribing could take place.
- Additional treatment strategies which are safe for common primary care infections used by practices with GPs trained in IM / CAM should be explored to see if they could be used to assist in the fight against antimicrobial resistance and could probably be integrated in patient information leaflets and decision-making tools in primary care.

What do patients, health workers and public think about CAM?

Dr Merlin Willcox, Academic Clinical Lecturer in General Practice at the University of Southampton in the UK, presented two studies, both of which he was the main author. The first was a systematic review of qualitative studies about what do patients, health workers and the public think about the use of CAM for the treatment of acute respiratory infections (ARIs) and what are the barriers and facilitators to the use of CAM for reducing the overuse of antibiotics for ARIs? And what are the barriers and the facilitators to the use of CAM for reducing the overuse of antibiotics for respiratory infections? The conclusions were that if we want to improve appropriate use of CAM and antibiotics we should focus on:

- Providing reliable advice to patients on the severity and cause of their specific ARI.
- Providing trusted advice to patients and health professionals in the UK and to increase awareness of the safety and effectiveness of CAM treatments versus antibiotics for specific ARIs.
- Improving the availability and convenience and lowering the cost of appropriate treatments.

The second study showed the development and piloting of patient information leaflets for the use of CAM in ARIs, which could be given to patients and health professionals.

In a systematic review and meta-analysis of the herb *Andrographis paniculata* for symptomatic relief of acute RTIs in adults and children it was concluded that patients who took *Andrographis* alone compared to usual care got better 3,5 days faster. It seems to be effective in quite a large number of trials and quite a large number of patients with cough and sore throat. Another systematic review demonstrated that the herb *Pelargonium sidoides* may be effective in relieving symptoms of acute bronchitis and sinusitis. It helps patients to get better quicker. However, these results are based on a few trials, so there is a need for more research.

The first question Dr Merlin Willcox and his team discussed was about the choice between a DMT or a PIL. The feedback from GPs in the UK was that a PIL is sufficient because a treatment of acute RTIs is not a complex decision. As far as the contents of the PILs was concerned, some GPs felt that this information would be useful, while others felt that there is not yet enough evidence to recommend any of these products based on the small samples and the studies and the Cochrane review. The patient participation groups were broadly positive about the PILs: they were interested in this information, but they suggested that information on costs of remedies be included.

Additional feedback was that patients should be discouraged from seeing doctors for simple respiratory infections, because the biggest risk for getting antibiotics is seeing a doctor.

There is a need to provide people information on “over-the-counter” treatments and to incorporate this into existing evidence-based information sheets.

Fever management as a strategy to reduce anti-microbial resistance

The next speaker, **Professor David Martin**, presented his project on the correct management of fever while reducing the use of antibiotics and increasing the effectiveness of antibiotics when they are really needed. He argued that fever is a resource, which is increasingly known to most of the people around the world. [26-28] Nevertheless, still many people have a fever-phobia. During his position as intermediary chief of Paediatrics at the Filderlinik, an anthroposophic hospital, fever management used no upper limits for lowering the temperature. After 4 years and over 2,000 patients with fever, there was only one child for whom a temperature threshold was used: a handicapped boy who started to vomit whenever he developed fever, and also some children with heat-sensitive epilepsy. In addition: the hospital's prescription rate for antibiotics was less than half of that of other hospitals in the region.

Professor Martin described the situation and the enormous heterogeneity of views on fever management in a grant application to the German Ministry for Research and Education, proposing to create an App-Based registry to assess and influence real-time and real-life handling of fever. The FeverApp should help to add the Strategy “Fever education” to the other WHO and EC-Action-Plan Strategies. The Registry function will allow us to learn, publish and adapt.

Increasing amount of evidence

As a conclusion of the first presentations, **Profes-**

or Erik Baars argued that the team is on the right track, the research data is promising, and an increasing amount of evidence has been gathered. He summarised the challenges the researchers are facing now:

1. More and higher-quality evidence of CAM treatment for infections is needed, which will increase *acceptability*.
2. Further development and testing of the information tools on safe and effective CAM treatment options for infections and fever management. This should be done in the national contexts and in accordance with national guidelines. This will increase the *accessibility*.
3. The continuation of the work is not only for today or next year, but in the long term as well, so that the researchers are able to organise the scientific and supporting work in the field for infections on a regular basis in Europe which will also increase *sustainability*.

CAM paradox

Professor Roman Huber pointed out that there is a paradox as far as CAM is concerned. On the one hand we know from many surveys that most people, at least in Germany, would like to be treated with natural substances. Surveys conducted among patients in university hospitals show that more than 50% patients at the departments of oncology, gastroenterology and even cardiology are requesting for CAM treatment and wish to be better informed about it. The small department Professor Roman Huber is leading cannot meet the demand in his hospital.

On the other hand, there is only limited funding for CAM treatment studies in Germany, unlike in the US and China which provide substantial budgets to study the efficacy of traditional medicine and herbals. In addition, funding by the industry is limited by the fact that CAM medicinal products are generic and cannot be patented; thus, there are no large profits to be expected from investments in research as for many new biomedical drugs.

There is a gap between the need of the public and the recognition by the politicians and the universities. There is only scattered and isolated activity in the medical faculties in Germany and in other European countries the situation may be even worse.

Professor Huber still believes there are some interesting recent developments. Due to the strong demand from the population for CAM, Baden-Württemberg has funded a university network of CAM researchers. Familiarisation courses about CAM are now included in the medical curriculum for students. They now know more about CAM than the generation before them.

CAMBrella and the Swiss popular vote

Dr Klaus von Ammon spoke about his participation in the CAMbrella project, the first comprehensive CAM research project which was funded by the European Commission under FP7, the previous EU Research Framework Programme. He presented the challenges this project was facing before getting any funding so that we can hopefully learn from the experience of the CAMbrella team. Dr von Ammon emphasised that it had been very important to influence the decision-making process of the Commission on the research programme through the National Contact Points in the various EU countries. The result was that FP7 included a call for research on the situation of CAM in Europe. They succeeded in building a consortium of 16 universities and institutes in 12 European countries. Within approximately one year they were able to submit their research plan which was accepted against nine others. The whole project took three years (2010-2012), resulted in several reports and a roadmap on CAM research until 2020.

One of the conclusions of the CAMbrella report was the need to enable the population to make informed decisions about their wish to use complementary medicine in addition to or as an alternative to conventional medicine. This is in line with the need for involvement of patients to achieve better integration of CAM into the

healthcare system. In Switzerland a great movement “Yes to complementary medicine” resulted in a popular vote in 2009 and a large majority voting in favour. Due to this vote, politicians were forced to include parts of CAM into the healthcare system. In August last year, five CAM methods practised by doctors were included in the compulsory health insurance system, this means fully reimbursed, similar to conventional medicine.

According to Dr Klaus von Ammon not only citizens have an important role to play, but CAM health practitioners can also contribute by collecting their cases and showing the results. In case of antibiotics, it can be demonstrated that doctors with an additional qualification in a CAM modality prescribe substantially fewer antibiotics than non-CAM doctors.

Dr Klaus von Ammon concluded with some comments on the kind of research that is now needed. The CAMbrella research group was in favour of comparative effectiveness research, i.e. comparing CAM treatment with conventional treatment. Insurance companies may fund this kind of research, as they have this data. If they do not only focus on the cost aspect but also look at the health aspect, this will be successful.

8. SUMMARY OF MAIN ISSUES DISCUSSED DURING THE CONFERENCE



Dr Elio G. Rossi, Dr Philippe Hartemann, Ms Rose Gallagher, Dr Dominique Monnet

The three main issues discussed during the conference were:

- Relevance of a European CAM & AMR research and action network to support the European AMR policy
- The context of (the development of) this network
- Input for future activities

Speakers of the panel discussions in addition to team members (see p. 36 for the conference program)

- Ms Rose Gallagher, Lead Nurse, Royal College of Nursing, UK
- Dr Geetha Gopalakrishna, Technical officer of AMR, WHO unit Traditional, Complementary and Integrative Medicine, Switzerland
- Dr Philippe Hartemann, Professor in Public Health at Lorraine University in Nancy, France
- Mr Robert Johnstone, Board Member of European Forum for Good Clinical Practice (EFGHP), Health Quality Improvement Partnership (HQIP) and International Foundation for Integrated Care (IFIC), UK
- Dr Dominique Monnet, Head of the Antimicrobial Resistance & Healthcare-Associated Infections Programme at the European Centre for Disease Prevention and Control (ECDC), Sweden
- Ms Nina Renshaw, Secretary-General, European Public Health Alliance, Belgium
- Dr Elio G. Rossi, Head of the Coordination Centre of Complementary Medicine – Local Health Unit Tuscany North West, Italy

8.1 Relevance of a European CAM & AMR research and action network to support the European AMR policy

A European CAM & AMR network

- Several stakeholders welcomed that within the JPIAMR program a track has been established to build a European network of CAM research organisations, projects and supporting non-scientific networks.
- Important reasons for building a European network of CAM & AMR are:
 - The value of CAM: there are promising contributions of CAM to reducing antibiotic use and stimulating appropriate antibiotic use.
 - The CAM-paradox: CAM treatments are part of daily practice in Europe, increasingly used by patients, but not sufficiently supported by research. Policy makers and universities are most often not interested in studying CAM treatments of infections. As a result, there is a lack of (good) studies that could further underpin the CAM contribution to reduce prescription and demand for antibiotics.
 - The EU position: some speakers observe a growing gap between ambitious strategies for example with respect to supporting evidence of TCM remedies financially supported by China and the reluctance with respect to financing equivalent European CAM treatments (e.g. herbals) by the EU.
- It is therefore seen as relevant that the team involved in the network:
 - expands and deepens the research and action network,
 - develops a research agenda together with relevant stakeholders (e.g. patient organisations, policy makers, pharmacists, nurses and insurance companies),
 - continues to conduct research and develops publicly available information,
 - continues to involve users of information tools (patients, doctors and pharmacists) with respect

- to the further development of these tools,
- raises public awareness,
- connects with broader “One-health” initiatives and by doing this,
- contributes to the further development of the European AMR strategy as part of the JPIAMR program.
- A European research strategy on deepening knowledge about the (potential) contribution of CAM should address the need to:
 - make use of the large amount of professional CAM expertise, data from monitoring of CAM daily practices and / or patient experiences, because most CAM interventions will not be tested in clinical trials in the foreseeable future, due to lack of sufficient financial resources and methodological issues,
 - further determine current (best) practices of CAM expert knowledge with respect to CAM treatments for specific indications,
 - monitor promising treatments which are safe and can possibly help to reduce antibiotic use,
 - evaluate patients’ experiences and preferences with respect to these CAM remedies,
 - generate high-quality evidence regarding some of these most promising treatments (based on already existing positive study results) in order to acquire more scientific acceptance,
 - test developed patient information tools (e.g. in pilot studies, feasibility studies and cost-effectiveness studies) in a larger and more representative group of the population,
 - further develop and test the information tool on fever management, regarding usability and (cost) effectiveness of the tool for reducing antibiotics use / prescription and appropriate use of antibiotics, in the national contexts and in accordance with national guidelines,
 - integrate the content of the doctor and patient information tools and documents regarding CAM treatment options and the FeverApp, and to eval-

- uate their effectiveness in reducing antipyretic and AB use,
- study interactions and side-effects of CAM remedies,
- understand the information needs of patients,
- analyse the relevance of socio-economic factors influencing perception and behaviour of patients, doctors, nurses and pharmacists.

Regional, national and European differences, experiences and initiatives

- Although in some European countries antibiotic prescription rates are decreasing, there is still a lot of work needed to reduce antibiotic use and prescriptions. For example, the evaluation of AMR policy programs in France show that after an initial decrease of antibiotic prescription by general practitioners, prescription rates are now increasing again for unknown reasons.
- Further studies on prescription rates, on socio-economic factors influencing patients’ and doctors’ preferences and behaviour and with respect to the impact of information and training programs as well as other AMR policies may help to understand the differences throughout Europe and the effectiveness of policy interventions.
- Given the large diversity of: national prescription rates for antibiotics, national AMR policies and national prescription policies for antibiotics, the integration of CAM modalities in guidelines, reimbursement for CAM treatments, CAM experience and expertise, acceptance, accessibility and / or availability of CAM remedies etc., a European knowledge base / platform for the exchange of experience could help in sharing knowledge and best practices while also developing benchmarks.
- Regional policies and networks such as in Tuscany or Baden-Württemberg can support the awareness and knowledge with respect to CAM and its contribution to address AMR. An exchange of experience between such regions on a European level may support the



European learning curve.

- The European CAMbrella project has shown that there is a need for the population to make informed decisions about the use of CAM in addition to or as an alternative to conventional medicine and that the population can be mobilised to this end. In Switzerland, the activities of the great movement “Yes to complementary medicine” of the Swiss public, resulted in the inclusion of five CAM modalities practiced by doctors in the compulsory health insurance system, being fully reimbursed like conventional medicine. These projects may inspire the CAM team to mobilise and consult the EU population when developing an EU research agenda.
- The further development of the European AMR action plan may benefit from an increased knowledge base, regional networks, collection of best practice and socio-economic interpretation of the differences between national prescription rates.

The CAM contribution to “One health” policies

- The One Health approach acknowledges the systemic interconnections of human, animal and environmental health. One of the objectives of the European One Health action plan against AMR is “to boost research, development and innovation by closing current knowledge gaps, providing novel solutions and tools to prevent and treat infectious diseases.”
- CAM practices prescribe non-antibiotic treatment strategies. Most importantly this is aimed at the strengthening of human and animal resilience to infections, which is different from the working mechanism of antibiotics. The CAM sector therefore concludes that the CAM approach is in line and may contribute to the European One Health action plan against AMR.

8.2 The context of (the development of) this network

The CAM paradox

- Factors that explain why CAM research is currently not undertaken or is only scarcely undertaken by universities and why it is not supported by public funding were also discussed. Further academic foundation and enhancement of “traditional and old-fashioned” CAM treatments including self-medications that have been used for decades appear less attractive for health and research policy, the pharmaceutical industry and universities. Instead, public and private funding is moving towards “new antibiotics” and other alternatives that are viewed as more innovative. As a result, there is now a gap between the need to study the potential contribution of CAM treatments in reducing antibiotic prescription and consumption and the respective capacity to do so.
- The CAM sector alone does not have the resources to fund the research needed to investigate these possibilities. The CAM industry is small and there are no major financial and /or industrial interests driving research efforts in this field. There are only scattered and isolated scientific activities in some medical faculties in some European countries.
- Nevertheless, based on traditional use and the current scientific evidence as well as growing public awareness with respect to the side-effects of antibiotic use, the relevance of resilience and self-care and last but not least to the urgency of the challenges of AMR, there is another development recognised in which regional and national initiatives and guidelines etc. move towards the integration of CAM competencies.

Inappropriate patients’ demands and empowerment of patients

- Several speakers and participants mentioned the phenomenon of patient demand for antibiotics, this is often based on uninformed or wrong perceptions

of antibiotics and / or as a result of socio-economic factors (e.g. no time to stay at home to look after sick children or to afford the cost of non-antibiotic treatments that are not reimbursed by insurance companies).

- Inappropriate use of antibiotics is also increased as antibiotics can be ordered via the internet. In some member states antibiotics can be purchased over the counter. In the UK and the Netherlands patients can go to the Emergency Department to request antibiotics for which they otherwise may not get from their own general practitioner. The Eurobarometer published again at the end of 2018 or beginning 2019 will describe what the percentage of respondents is in each country that have taken antibiotics without consulting a doctor and from those what was the source.
- With respect to patients’ demand for antibiotics, it is therefore seen as relevant to strengthen capacities and tools for informing and enabling patients especially with respect to maintenance of health, health literacy, nutrition, prevention, self-care and self-medication as well as short-term and long-term side-effects of antibiotics (human microbiome etc.) and interactions with conventional medication.
- Simple patient information leaflets (PILs) adjusted to the national context may support this need. In addition, more complex decision-making tools (DMTs) may support those patients who would like to inform themselves about different options for CAM treatments, their pros and cons, and discuss these options with their doctor. Apart from DMTs/DILs for doctors, similar tools need be developed for pharmacists.
- Currently a first prototype of an eHealth application for RTIs is being developed, where all the information can be found, i.e. the available evidence for this indication, its safety, possible interactions, in accordance with specific national guidelines and further national context information, etc. The usability and (cost)effectiveness of these information tools shall be studied for a few European countries.

- Dr Monnet (ECDC) argued that if some more evidence for the effectiveness of certain CAM medicines can be demonstrated, ECDC may add it to the self-medication list. ECDC is not allowed to recommend something, because ECDC has only a mandate for risk assessment and risk communication, not for risk management, the latter being the responsibility of the Member States. One of the key messages of the European Antibiotic Awareness campaign and Day is about self-medication. “Self-medication without antibiotics may be a good thing.” (see presentation of D. Monnet at <http://cam-amr-conference.eu/videos/>)

Types, levels and quality of evidence

- The studies conducted by the JPIAMR project team as well as their proposals for and prototypes of information tools are based on the use of a broad set of methods and sources to gain evidence including: evidence based on clinical trials (for the reviews undertaken), evidence based on expert knowledge (for the expert survey), doctors’ expertise (prescription rates in daily clinical practice), patients’ and doctors’ preferences (for the design of information tools). For all purposes it is seen as relevant to disclose and explain the methods and sources used and the respective level of evidence for each of the studies.
- Several speaker’s emphasised the gap between the current situation of CAM and the need for high quality evidence of safety and effectiveness of CAM treatments for the indications to become acceptable to several stakeholders (guideline developers, ECDC, etc.). Other speakers’ emphasised that conventional recommendations are also often not based on high quality evidence (e.g. in cardiology guidelines). Most CAM treatments for infections have not been studied at all and will most likely not be studied in the foreseeable future for several reasons. First of all, many CAM interventions are insufficiently tested because they are not in line with the dominant biomedical (mono-substance) models. Secondly, based on an individualised diagnosis, CAM interventions are most often prescribed as part of an individualised, complex intervention with several medicinal products and/ or other non-medicinal therapies, making it difficult to study the specific effect of one medicinal product. Thirdly, the limited financial resources in the CAM sector and the lack of interest from universities and policy makers to finance CAM research capacity are reasons for not studying CAM treatments. As a result, recommendations for CAM treatments in the near future will most often be based on systemised expert knowledge of CAM professionals, data from monitoring of CAM in daily practices and / or patient experiences, types of evidence that are typically seen as “low quality evidence”.
- Team members further explained the “low level or lack of scientific evidence for effectiveness and safety of CAM treatments for RTIs and or CAM treatments in general”. The most relevant reason for this conclusion is not that several studies have proved the absence or low quality of evidence, but the fact that most remedies have not been studied at all. A second reason is that available studies are often of low methodological quality. A third reason is that often no systematic reviews have been conducted. Furthermore, team members explained that for the systematic review of systematic reviews they used a very new, rather strict standard, the AMSTAR 2 checklist (A Measurement Tool to Assess systematic Reviews), because this is the latest and currently best scientific standard for quality assessment of in the review included RCTs. Because all systematic reviews that were studied in the systematic review of systematic reviews, were published before the AMSTAR 2 checklist (September 2017) was published, the authors had not been able to meet the new publication criteria, with a (very) low quality as a result. This resulted even in low and very low-quality scores of Cochrane reviews, which are usually considered as high quality, because often several items were not described in the publication (e.g. funding of the

studies). As a result, it is expected that regarding research on the contribution of CAM for treatment of infections, in the next 5 – 10 years there will only or mainly be input from expertise, which will result in only low-level evidence.

- A relevant bias of systematic reviews was mentioned with respect to scientific evidence based on RCTs. These trials are more often conducted testing new formulations or commercially interesting treatments rather than traditional treatments which have proven their quality in clinical practice.
- Next to the need for good quality RCTs on specific CAM treatments for a specific indication, there is a need to acquire good quality evidence of CAM complex interventions, including natural medicines, non-pharmacological treatments and fever management.

8.3 Input for future activities

- The discussions showed that two approaches are important as part of a future research agenda:
 - To acquire high quality evidence of safety and effectiveness of CAM treatments as preconditions for acceptance of CAM treatments in highly regulated areas of healthcare (e.g., medical and nurse-prescriber' guidelines, ECDC self-medication list).
 - To further test and implement adequate information tools to support patients', doctors' and pharmacists' decision-making in choosing well-informed CAM treatments for infections, based on the best available evidence.
- The discussion proved the need:
 - to implement and study usability and (cost)effectiveness of the first prototype of a CAMEHealth application for RTIs (a DMT for doctors, PtDAs for patients and information leaflets) in accordance with specific national guidelines in selected European countries.
 - to study and better understand factors influencing prescription rates and use of antibiotics in primary care and hospitals.
- It was advised to develop:

- a European research initiative and an institutional model for the development of DMTs for doctors, PtDAs for patients and information leaflets on CAM treatment of infections.
- the European CAM & AMR research agenda by involving not only the research community but also doctors, nurses, pharmacists, hospitals, patients and other stakeholders.
- It was stated that positive developments can be achieved in cooperation with other sciences e.g. economists and social scientists and broader “One-health” stakeholder networks.

8.4 Key messages from the conference

Based on both the presentations and the discussions, the key messages from the conference are:

- There are promising CAM contributions for reducing antibiotic use and for appropriate antibiotic use:
 - Evidence-based and expertise-based knowledge on CAM treatments for infections
 - Information tools for doctors, pharmacists and patients, supporting the decision-making process
- In order for these contributions to achieve their full potential, there is a need for:
 - Better quality evidence on safety and effectiveness of CAM treatments for infections
 - Making use of both CAM expertise, and results of research on CAM complex interventions and specific CAM treatment for specific indications
 - Tested and implemented information tools for doctors, pharmacists and patients
 - Awareness raising about risks of inappropriate use of antibiotics and information with respect to safe alternative strategies, including delayed prescription, with or without CAM treatments, and self-medication.
- To support this development, at a National and EU level there is a need for:
 - More political, public and academic support
 - Cooperation between citizens / patient organisations, researchers, policy makers and other relevant stakeholders in developing, promoting and executing research and action agendas

JPIAMR Project Team

- Prof. Dr. Erik Baars, University of Applied Sciences Leiden, Louis Bolk Institute, Bunnik, the Netherlands (project leader)
- Dr. Klaus von Ammon, University of Bern, CAM centre, Switzerland
- Dr. Thomas Breitzkreuz, Filderlink, Hufelandgesellschaft, Germany
- Prof. Dr. Roman Huber, University of Freiburg, Germany
- Prof. Dr. David Martin, University of Witten / Herdecke, Germany
- Prof. Dr. Harald Matthes, University Charité, Berlin, Head of Havelhöhe Clinic, Berlin, Hufelandgesellschaft, Germany
- Dr. Jan Vagedes, University of Tübingen and Filderlink, Head of ARCIM Institute, Germany
- Prof. Dr. Willem van Leeuwen, University of Applied Sciences Leiden, the Netherlands
- Dr. Esther van der Werf, University of Bristol, UK
- Dr. Merlin Willcox, University of Southampton, UK

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- Dr. Michael McIntyre, Midsummer clinic, UK
- Dr. Ton Nicolai, EUROCAM, Belgium
- Dr. Tido von Schön-Angerer, IVAA, Switzerland
- Dr. H. Szőke, University of Pécs, Hungary
- Dr. Michael Teut, University Charité, Berlin, Germany
- Dr. Madan Thangevelu, European Ayurveda Association e.V., Bell, Germany, University of Cambridge, UK
- Prof. Dr. Ursula Wolf, University of Bern, Head of CAM centre, Switzerland

Conference program

Reducing the need for antibiotics The role of CAM treatment strategies

Venue

Regione Toscana - Representation of the Tuscany region

Rond Point Schuman 14, Bruxelles 1040

<http://www.regione.toscana.it>

AGENDA

- 08:30 **Reception and coffee**
- 09:00 **Welcome**
Mr Enrico Mayrhofer
- 09:03 **Welcome and introduction**
Dr Ton Nicolai
- 09:08 **Welcome key note: The policy of integration of Complementary Medicine in public health of the Tuscany Region**
Dr Elio G. Rossi
- 09:20 **Methodologies and results of the project**
Dr Erik Baars, Dr Esther van der Werf, Dr Merlin Willcox, Dr David Martin
- 10:00 **Questions and Answers understanding the methodologies and results**
- 10:45 **Coffee Break**
- 11:15 **Panel: Immediate next steps to be achieved in the next 12 months**
Dr Klaus von Ammon, Dr Erik Baars, Dr Roman Huber, Dr David Martin, Dr Esther van der Werf, Dr Merlin Willcox
- 12:30 **Lunch break**
- 13:30 **Panel: The way forward - vision for the next 5 years**
Dr Dominique Monnet, Dr Philippe Hartemann, Rose Gallagher, Dr Elio G. Rossi, Dr Erik Baars
- 14:30 **Feedback from public health stakeholders and open discussion**
Dr Dominique Monnet, Dr Philippe Hartemann, Dr Geetha Gopalakrishna, Ms Nina Renshaw, Mr Robert Johnstone
- 15:20 **Wrapping up and conclusion**

List of speakers

Dr Klaus von Ammon
University of Bern, CAM centre, Switzerland

Rose Gallagher
Lead Nurse, Royal College of Nursing, UK

Dr Geetha Gopalakrishna
Technical officer of AMR, WHO unit Traditional, Complementary and Integrative Medicine, Switzerland

Dr Philippe Hartemann
Professor in Public Health at Lorraine University in Nancy, France

Mr Robert Johnstone
Board Member of European Forum for Good Clinical Practice (EFGHP), Health Quality Improvement Partnership (HQIP) and International Foundation for Integrated Care (IFIC), UK

Dr Roman Huber
Professor, University of Freiburg, Head of CAM centre, Germany

Dr David Martin
Professor of Paediatrics at Tübingen University and Witten-Herdecke, Germany

Mr Enrico Mayrhofer
Director of EU liaison office of the Tuscany region, Italy

Dr Dominique Monnet
Head of the Antimicrobial Resistance & Healthcare-Associated Infections Programme at the European Centre for Disease Prevention and Control (ECDC), Sweden

Dr Ton Nicolai
EUROCAM spokesperson, Belgium

Ms Nina Renshaw
Secretary-General, European Public Health Alliance, Belgium

Dr Elio G. Rossi
Head of the Coordination Centre of Complementary Medicine – Local Health Unit Tuscany North West, Italy

Dr Erik Baars
Professor for Anthroposophic Medicine, University of Applied Sciences Leiden, Louis Bolk Institute, the Netherlands

Dr Esther van der Werf
Senior lecturer, University of Bristol, UK

Dr Merlin Willcox
Academic Clinical Lecturer in General Practice, University of Southampton, UK

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