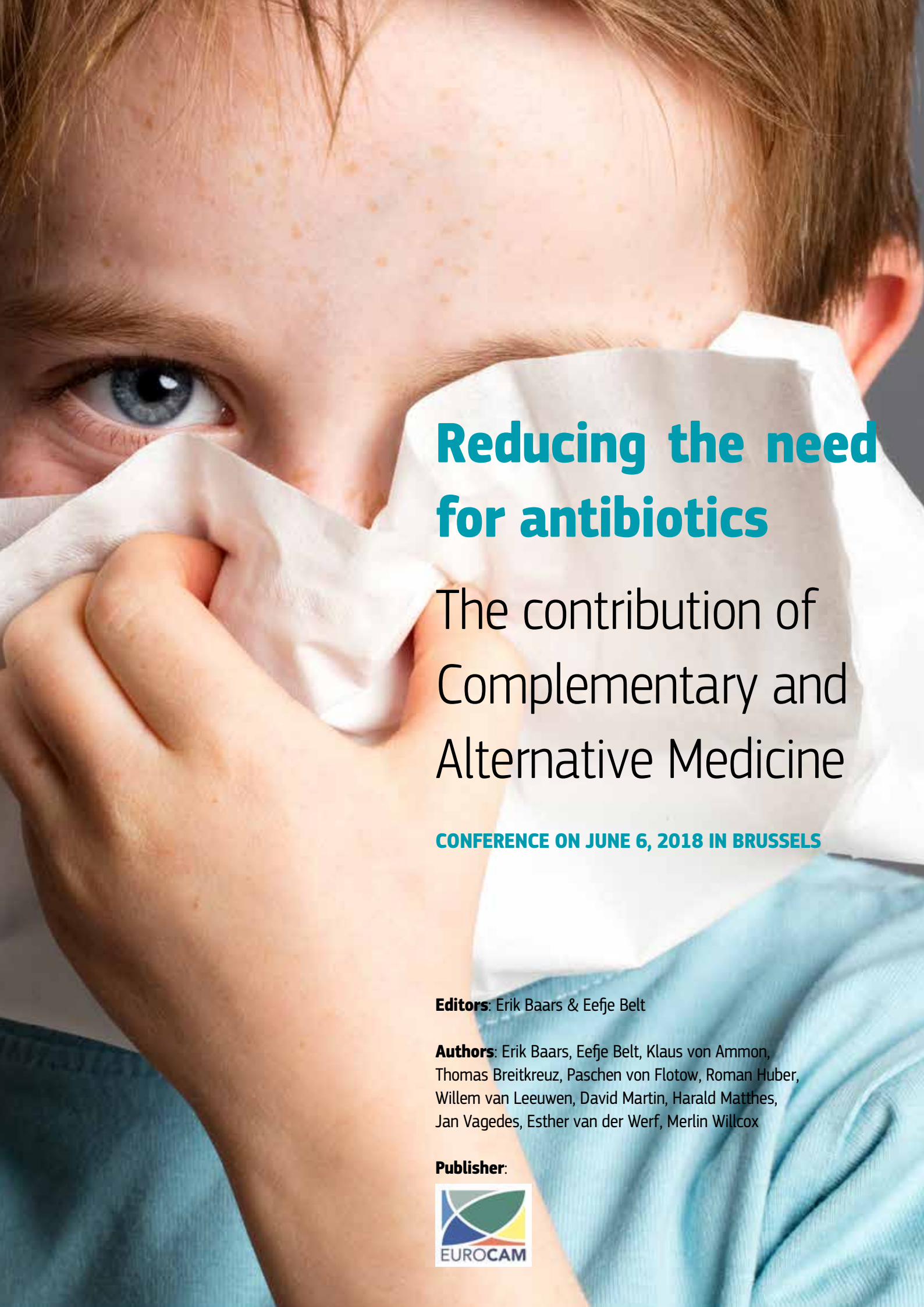

Reducing the need for antibiotics

The contribution of Complementary and Alternative Medicine

CONFERENCE ON JUNE 6, 2018 IN BRUSSELS

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ZonMw

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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 treatments 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 at strengthening humans' and animals' resilience to infections.

EUROCAM is therefore delighted to welcome you at the conference "Reducing the need for antibiotics - The contribution of Complementary and Alternative Medicine". 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 will be presented and discussed at the conference. EUROCAM and the research team recommend that testing and further development of these tools, as a pilot case for the potential of CAM in reducing the problem of AMR, is given serious consideration and that further research is carried out in this area.
We hope that informative discussions during the conference will help to improve the proposed way forward, to strengthen existing alliances and to build new alliances to overcome the remaining challenges.

Topics that will be 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

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

Quotes of the speakers

"Given the urgent need for non-antibiotic alternative treatments to reduce inappropriate antibiotic use, we must invest in studies of safe and promising CAM treatments and their use in delayed prescription strategies".

"Integrative Medicine might be the key to reduce AMR in primary care".

"Multimedia and personalized integrative fever education can contribute towards reducing prescription and use of unnecessary medication, including antibiotics".

"Most patients just want to feel better faster. If we can provide alternative treatments which can help them even more than antibiotics, everyone will be satisfied".

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1. AIM AND SUMMARY

1.1 Aim of the conference paper

The aim of this paper is to provide the participants of the conference 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.

The main objectives of the JPIAMR project are:

- To provide an overview of expert and scientific knowledge on CAM/ IM (Complementary and Alternative Medicine[1] / 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.

1.2 Executive summary

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

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

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.

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.

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, but overall lack high quality evidence. (See 4.1 (p. 12))
- 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.13))
- 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. 13/ 14))
- A retrospective study within National Health Service (NHS) England demonstrates that health centres employing General Practitioners (GPs) additionally trained in IM/ CAM have overall lower AB prescription rates, and lower AB prescription rates for URTIs compared to conventional health centres. (See 4.5 (p. 15))
- 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. 14))
- 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 the App will lead to a reduction of AB use by reducing GP consultations and by changing patient behaviour.

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 to reducing AB prescription and use is promising and is supported by an increasing amount of evidence. CAM can contribute to two of the AMR strategies: 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 amount of evidence. (See systematic review of 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).

Conclusions: implementation and dissemination of CAM treatment options for URTIs

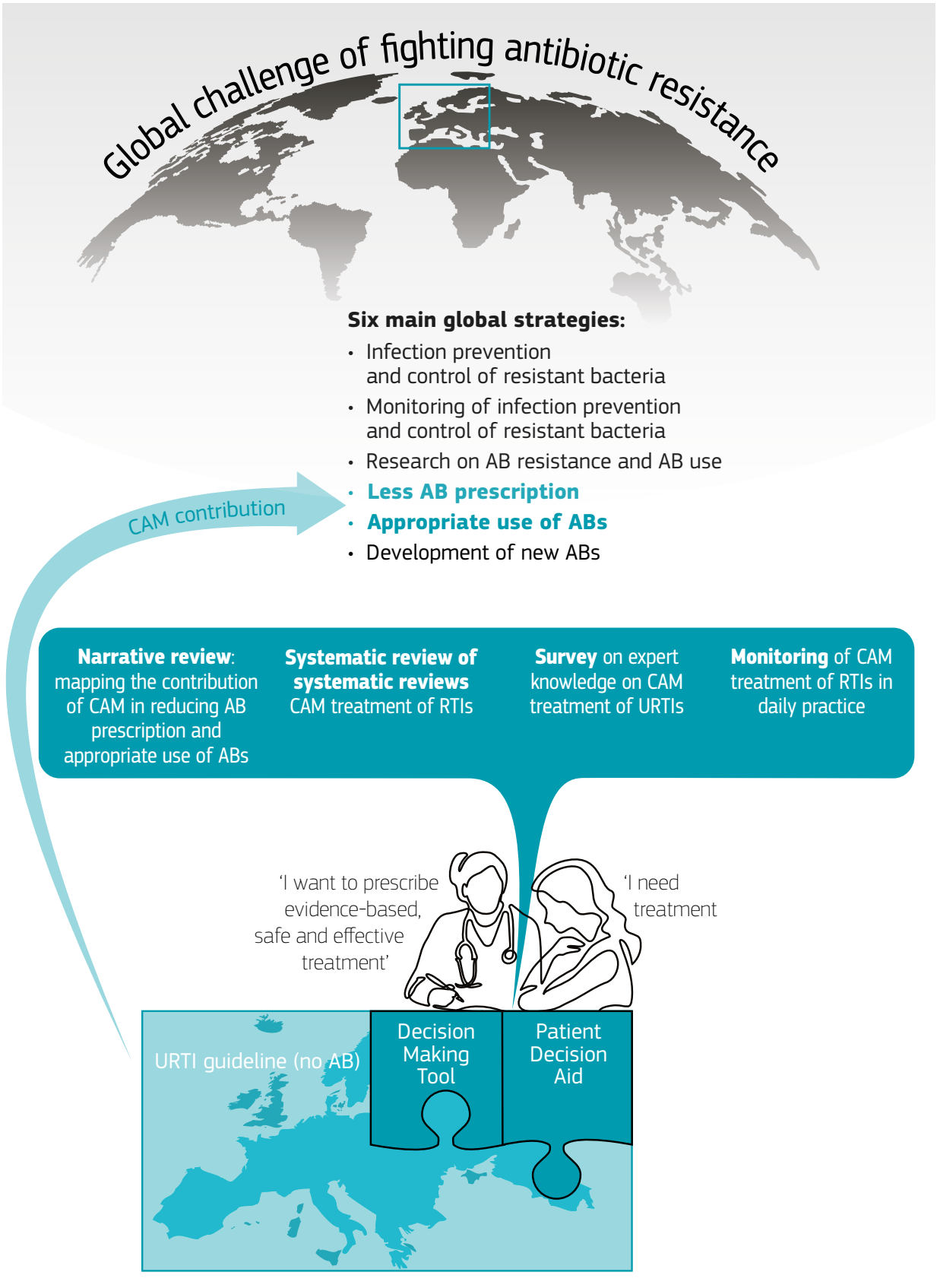
- CAM treatments could well fit and could be integrated in delayed AB prescription strategies for treatment of URTIs, both supporting the guidelines to not treat with ABs, and meeting both doctors' and patients' desire for effective symptom relief.
- There is a wide variety of CAM treatments available, 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 and correspondingly a Fever App were developed, to demonstrate the CAM contribution, to facilitate the decision-making process of choosing a specific CAM treatment and to make CAM treatments more accessible to stakeholders.

Short-term and long-term challenges

- Major short-term challenges (directly after the JPIAMR project) are:
  - finalization of the national stakeholder involvement in the five 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
  - organizational development of a reliable and legitimate European/ international institutional model and organization 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 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. [4, 5] Globally, infections with resistant microorganisms are estimated to kill hundreds of thousands of people every year. An often cited but also criticized 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 we do not take action. [4] 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. [6] 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. [7] 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, ...). [8] 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. [9] Nevertheless, the latest "EARS-Net data for 2016 show that antimicrobial resistance remains a serious threat to public health in Europe". [10]

3.2 Primary care and upper respiratory tract infections (URTIs)

Antibiotic prescribing and consumption varies between European countries. [11-15] Primary care accounts for about 80 to 90% of all antibiotic prescriptions. [16, 17] 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. [18] 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., [19]). 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., [20, 21]). 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 [22], 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 of CAM is that it can especially contribute to two of the AMR strategies: 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. Delayed prescription strategies in combination with an effective and safe CAM non-antibiotic RTI treatment during the delayed prescription period might therefore offer a contribution to reduce antibiotic prescription 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 [23] and rhinosinusitis. [24]

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 on a European level. In addition, patient information tools were developed.

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

Aiming at mapping the contribution of CAM to reduce AB prescription and use, and to improve appropriate use of ABs, we conducted a narrative review. The databases PubMed, Embase and 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? Two-hundred 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 conceptualization 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 some 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.

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. Twenty-six studies were included in the review.

Key results: There are several CAM medicinal products for: acute RTIs (*P. sidoides, A. paniculata, Sanren decoction, Shuanghuanglian*), acute rhinosinusitis (*P. sidoides, Myrtol, Sinupret*), acute trachea-bronchitis (*Tanreqing*), acute URTI (*Ivy leaf*), bronchiolitis (*Shuanghuanglian, Xiao Er Zhi Chuang Tang, Laggera pterodonta*), cough (*P. sidoides, A. paniculata, Ivy/ primrose/ thyme*), Influenza A (*Lianhuaqingwen, Antiwei, Ganmao*), otitis media (T*ongqiao, Tongqiao huoxue, Huanglong tonger, Tsumura tonger, Erzhang decoctions, homeopathy*) and sore throat (*Shuanghuanglian, Qingkailing, A. Paniculata*), 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 to reduce selective AMR pressures, 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 systematize 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 a total response of 262, 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 organized 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 appli-

cations 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 A 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 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. [25, 26]

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) 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 show that significantly fewer '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**.** [27]

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

5. DECISION-MAKING TOOLS, PATIENT DECISION AIDS AND INFORMATION LEAFLETS FOR DOCTORS AND PATIENTS

There are 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 these kind of tools have to be adjusted according to the specific national context. At the same time the exchange of different national experiences can add an enormous value to the European knowledge base and can help accelerating 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 [28] and fit the conventional guidelines of URTI treatment.

In addition first concepts of doctor information leaflets (DILs) and patient information leaflets (PILs) were de-

veloped 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 Pediatrics and ambulatory pediatric 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 sufficient financial resources, it is planned to start testing these tools and the FeverApp in 2019 in Germany, the Netherlands and/ or the UK in cooperation between conventional and CAM/ IM stakeholders (doctors, patients, scientists).

6. STRENGTHS AND LIMITATIONS

The *strengths* of this project are at first 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. At fifth, based on the SR of SRs, the expert survey and expert consultation rounds, expertise- and evidence-supported lists were made of promising[2] 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 effective-

2 The term *promising* is used here for CAM treatments that have positive results in the SRs (SR of SRs), 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).

ness 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 systematizing 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. So 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.

7. SHORT-TERM AND LONG-TERM CHALLENGES

By the end of June 2018, the official timeline of the JPIAMR project (funding) will be ended. The main aim was 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 (France, Germany, Switzerland, the Netherlands, UK), based on the results of the presented projects. More broadly the aims of this project were 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 (directly after the JPIAMR project as a follow-up)

1. Finalization of the national stakeholder involvement in the five European countries (alpha testing: collecting feedback from doctors and patients on project results and information tools in focus groups).
2. Submission of publications in 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. Organizational development of a reliable and legitimate European/ international institutional model and organization 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 on safety and effectiveness of '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) individualized 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.

JPIAMR Project Team

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