Traditional, Complementary and Integrative Healthcare, Infectious diseases and AMR

The GIFTS-AMR global research agenda

TRADITIONAL, COMPLEMENTARY & INTEGRATIVE HEALTHCARE (TCIH)

Strategies & natural medicinal products
to prevent and treat infections
to reduce antimicrobial resistance
with the primary focus on health promotion

jpiamr
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Reading guide

This document starts with an executive summary of the research agenda, the GIFTS-AMR research agenda's contribution to other global antimicrobial resistance (AMR) research agendas, and suggested advocacy actions related to the GIFTS-AMR research agenda.

Chapter 1 provides the background and rationale for developing the research agenda: the burden of AMR, the features and scientific status of TCIH (Traditional, Complementary & Integrative Healthcare), TCIH medicinal products use and prescribing, and introduces the GIFTS-AMR project.

Chapters 2 – 7 are the core of the research agenda. Each chapter is formatted as follows:

- It starts with a short introduction to the main topic.
- Then 2-3 sub-topics relevant to the research agenda are described.
- A summary of the current status is subsequently described for each sub-topic.
- Finally, the research priorities and the prioritized research projects for the next 10 years for the main topic are described.
- In some chapters, suggested advocacy actions related to the GIFTS-AMR research agenda, which were identified during the project, are also described.

Chapter 8 integrates the identified research priorities and prioritized projects of all chapters into an overall list of research themes with research priorities, prioritized projects for the next 10 years, and the overall suggested advocacy actions related to the GIFTS-AMR research agenda.

Chapter 9 describes the connections between the GIFTS-AMR global research agenda and two major global research agendas:

- A One Health priority research agenda for antimicrobial resistance (2023). FAO (UN), UN environment programme, WHO and World Organisation for Animal Health.
- Global research agenda for antimicrobial resistance in human health (2023). WHO.

Executive summary

0.1 About the document

What?

This document describes the global research agenda on Traditional, Complementary & Integrative Healthcare (TCIH) strategies & natural medicinal products[1] to prevent and treat infections and reduce antimicrobial resistance (AMR) primarily focusing on health/resilience promotion. In addition, the connection of this agenda to two global AMR research agendas and suggested advocacy actions are described. Four GIFTS-AMR research themes linked to 14 research priorities, prioritized research projects for the next 10 years and contributions to two global AMR research agendas are presented in a table.

By whom?

The global research agenda was developed by the GIFTS-AMR (Global Initiative for Traditional Solutions to Antimicrobial Resistance) project group, a JPIAMR 10th call funded, globally organized, growing network of TCIH and AMR/infectious diseases research institutes, researchers in both human and veterinary medicine and global/regional policymakers (see also pp. 70 and 71 for the list of contributors).

For whom?

The research agenda provides the strategic basis for the GIFTS-AMR network to collaborate on research proposals and funding applications and provides information on TCIH for policymakers, researchers, healthcare professionals (organizations) and patients (organizations) at national, regional and global level.

1 Other terms often used are: products of natural origin.

0.2 The research agenda

Background

Given the magnitude of the global AMR problem, the insufficient strategies to reduce antibiotic/antimicrobial use and the urgency of AMR of the last decade, there is need for novel strategies. TCIH provides strategies and solutions which contribute to reducing (inappropriate) antibiotic/antimicrobial use, prevention or treatment of infections in both human and veterinary medicine, and, by doing so, may contribute to the promotion of health/resilience of individuals and reduction of AMR.

The scientific status of TCIH for the prevention and treatment of infections

TCIH prevention and treatment of infections strategies in human and veterinary medicine are already based on an increasing number of scientific studies. Some TCIH medicinal products are already integrated into national guidelines for the treatment of infections in human medicine, e.g. in Germany and the UK; are registered in an EU directive (on medicinal products) or EU regulation (on veterinary medicine and organic agriculture) and/or have a European Medicines Agency (EMA) status of Well-established use or Traditional use. Several observational studies support the hypothesis that doctors who practice TCIH, integrating complementary medicine and conventional medicine, compared to their conventional colleagues, have lower antibiotic prescription rates (measured as past use, antibiotics use ever, in the first 12 months of life and after 12 months of life, consumption, prescription rates) and their patient groups have lower antibiotic consumption rates, although in these studies selection bias (e.g. patients who do not want antibiotics may choose a TCIH doctor more often) cannot be ruled out. Reduction in antibiotic use as a result of TCIH infection prevention and treatment strategies has also been described for veterinary medicine. There is an open attitude towards TCIH among large groups of patients, animal owners and farmers for TCIH infection prevention and treatment strategies. At the same time, a complex array of factors influence reluctance to use TCIH, for example the attitudes or lack of knowledge on TCIH of both doctors and patients.

Chapters

Six chapters provide the input for the research agenda and the suggested advocacy actions related to the GIFTS-AMR research agenda:

- The value of TCIH medicinal products (Chapter 2)
- The best TCIH product–market combinations (Chapter 3)
- The most promising TCIH medicinal products for high-quality RCTs (Chapter 4)
- The use of limited evidence and real-world evidence of safety and effectiveness (Chapter 5)
- The transition towards full integration of TCIH in the medical systems (Chapter 6)
- Increasing the accessibility of TCIH medicinal products for infections (information) (Chapter 7)

Each of the chapters presents the introduction to the main topic, the 2-3 sub-topics relevant to the research agenda, the current status for each sub-topic, and, based on this, the research priorities, the prioritized research projects for the next 10 years and, in some chapters, the suggested advocacy actions related to the GIFTS-AMR research agenda.

GIFTS-AMR themes and research priorities

Chapters 2-7 are summarized into 14 research priorities, with prioritized research projects for the

next 10 years across four themes (Table 1).

Table 1. GIFTS-AMR research themes, research priorities, prioritized research projects for the next 10 years and contributions to two global AMR research agendas

Research themes	Research priorities	Prioritized research projects for the next 10 years	Contribution to the WHO global research agenda (2023)*	Contribution to the UN/ WHO/ WOAH global research agenda (2023)**
Patient preferences and stakeholders' needs for non-antibiotic prevention and treatment strategies for infections	1. Assess patients'/ animal owners'/ farmers' preferences, use, satisfaction and acceptability of TCIH MPs in LMICs and developed countries.	• Map out the qualitative and quantitative studies on patients'/animal owners'/ farmers' preferences, use, satisfaction and acceptability of TCIH MPs as alternatives to antimicrobials (scoping review).	New ***	New***

Safety, (cost-) effectiveness, benefits/risks ratios and benefits/ costs ratios of TCIH strategies in human and veterinary medicine	2. Investigate the safety, working mechanisms, and efficacy/ (cost-) effectiveness of the most promising TCIH MPs for indications where antimicrobials are commonly over-used.	• Investigate the (cost-)effectiveness of the most promising TCIH MPs for acute, uncomplicated upper respiratory tract infection (URTI) and recurrent urinary tract infection (rUTI) symptom control and reduction of antibiotics use in primary care and hospital ER departments. a. Investigate the effectiveness of Traditional Chinese Medicine compared to standard conventional treatment and/or placebo, for the prevention of UTIs in patients with a history of rUTIs. • Investigate the (cost-)effectiveness of FeverApp/FeverFriend tools for fever management on symptom control and reduction of antimicrobials use in GP practices and hospital ER departments. • Investigate the (cost-)effectiveness of the most promising TCIH MPs for uncomplicated diarrhea and RTIs in animals. a. Investigate the effectiveness of homeopathy, compared to placebo, for the prevention of ETEC-related post-weaning diarrhea in piglets at risk. • Systematically review the safety and effectiveness of TCIH MPs for gastrointestinal infections in humans and for RTIs and gastrointestinal infections in animals.	• Treatment and care – Antimicrobial stewardship (11-13)	• Interventions - Evaluation
	3. Investigate the feasibility and acceptability of integrating traditional and complementary approaches with conventional primary healthcare (for humans and animals), as a strategy to support delayed use of antibiotics.	• Investigate the feasibility and acceptability of promising TCIH MPs for acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals. • Assess acceptability and effectiveness of updated guidelines on management of self-limiting infections, including recommendations to use TCIH to support delayed use of antibiotics.	New*** • Treatment and care – Antimicrobial stewardship (11-13)	New*** • Interventions - Evaluation
	4. Investigate the types and working mechanisms of health promotion/ resilience and antimicrobial effects of TCIH MPs.	• Investigate the types and working mechanisms of health/resilience promotion and antimicrobial effects of 3-5 TCIH MPs with moderate to high-quality evidence of effectiveness in clinical trials for acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals.	New***	New***

	5. Investigate the benefits/risks ratios and the benefits/costs ratios of TCIH MPs vs antimicrobials, for humans, animals and the environment.	• Investigate the effectiveness and the reduction of adverse effects on animals and environments for TCIH MPs with moderate to high-quality evidence of effectiveness for uncomplicated URTIs and rUTIs in humans and for the prevention of ETEC-related post-weaning diarrhea in piglets at risk.	• Prevention - Water, sanitation and hygiene (WASH) (1-2) • Prevention – Infection prevention and control (3) • Treatment and care – Antimicrobial stewardship (11-13)	• Transmission - Dynamics and drivers • Interventions - Framework conditions
	6. Investigate the effects of whole system approaches (e.g. organic/ biodynamic agriculture and TCIH whole medical system prevention and treatment) on the sustainable reduction of antimicrobial use and consumption.	• Map out the qualitative and quantitative studies on the effects of whole medical systems and whole system approaches in (organic and biodynamic) farming on the reduction of antimicrobial use and consumption (scoping review).	• Treatment and care – Antimicrobial use and consumption (14-16)	• Interventions – Operational research
	7. Develop and evaluate valid score systems which weigh up relevant factors to identify and prioritize the most promising TCIH MPs for urgent indications which can be tested in high-quality RCTs, and which are usable and acceptable for relevant stakeholders.	• Develop valid score systems which weigh up relevant factors to identify and prioritize the most promising TCIH MPs which can be tested in high-quality RCTs, for the treatment of acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals in countries with major over-use of antimicrobials for these indications.	• Treatment and care – Antimicrobial medicine (17-21)	• Interventions - Methodology development
Use of limited evidence and real-world evidence	8. Develop an adapted Evidence-to-recommendation (EtR) system for TCIH MPs for infections using available evidence and additional arguments to weigh up the available information.	• Develop and investigate the feasibility and acceptability of an adapted EtR system for TCIH MPs for the treatment of acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals in countries with major over-use of antimicrobials for these indications.	New***	New***
	9. Investigate the feasibility of using identified additional arguments in an existing EtR framework.		New***	New***
	10. Investigate the acceptability and need for improvements of these EtR procedures for all TCIH modalities in all countries.		New***	New***

Implementation and information tools	11. Investigate the conceptual differences between conventional medicine and TCIH which present a barrier for acceptability and implementation of TCIH prevention and treatment of infections strategies.	• Build a combined expertise- and evidence-based theoretical model of TCIH treatment of acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated gastrointestional tract infections (GTIs) and RTIs in animals to overcome the barrier for acceptability and implementation while preserving the integrity of TCIH prescribing of individualized and non-individualized TCIH treatments, and while considering research on health/resilience promotion (realist review of complex interventions).	New***	New***
	12. Investigate the reasons for current guideline developers to decide on the (non-)inclusion of TCIH MPs in guidelines for the prevention and treatment of infections.	• Investigate the reasons for non-inclusion of TCIH MPs for infections in European countries for those TCIH MPs which already have an EMA status of Traditional use or Well-established use and/or are included in conventional guidelines (e.g. in the UK or Germany): • **EMA status** o *Ivy* for coughs and common cold o *Pelargonium sidoides* for the common cold **German guidelines** o *Pelargonium sidoides* for coughs (DEGAM Leitlinie Nr 11), rhinosinusitis (S2k-Leitlinie) o *Thyme/Primrose* for coughs (DEGAM Leitlinie Nr 11) **UK guidelines** o *Pelargonium sidoides* for coughs (NICE Cough (acute) guideline)	• Treatment and care – Antimicrobial stewardship (11)	• Behavioural insights and change - Dynamics and drivers

	13. Develop and evaluate information tools (websites, eHealth) to provide easily accessible and trustworthy advice for patients on TCIH strategies for self-management of common infections in which antimicrobials are commonly over-used, and trustworthy information for clinicians (including evidence of safety, (cost-)effectiveness, use in clinical practices); and, additionally, on benefits/risks ratios and benefits/costs ratios for research and policy-making.	• Develop and evaluate the usability and acceptability of a TCIH MPs for URTIs prototype app for use in different countries (language and cultural adaptation). • Develop the app further for rUTIs in humans and diarrhea in animals. • Implement and adapt (language and cultural) the FeverApp and FeverFriend app for humans with over-use of antimicrobials related to fever management, in countries other than Germany and The Netherlands. • Develop and evaluate a FeverApp/FeverFriend app for use in veterinary medicine. • Develop and evaluate the quality, usability and acceptability of a TCIH website with science-based information on TCIH strategies for the prevention and treatment of infections, for research, education and use in clinical practices.	• Cross-cutting–Antimicrobial resistance awareness and education (28)	• Interventions - Operational research • Behavioural insights and change - Methodology development
	14. Implement TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs).	• Investigate barriers and promotors of the implementation of TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs). • Investigate implementation methods which will enable TCIH prevention and treatment strategies as part of a One Health approach, including the collaboration between conventional medicine and TCIH in a timely manner, in relevant antimicrobial stewardship programs (ASPs).	• Cross-cutting–Policies and regulations related to antimicrobial resistance (29-33)	• Interventions - Methodology development • Behavioural insights and change - Operational research

* The list refers to the broader research topics and the related research priorities (numbers) for AMR in the WHO agenda: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-npm/who-global-research-agenda-for-amr-in-human-health---policy-brief.pdf?sfvrsn=f86aa073_4&download=true

** The list refers to the priority research (sub)areas in the UN/WHO/WOAH agenda https://www.fao.org/3/cc6213en/cc6213en.pdf

*** This item is new to the content of the existing research agenda

See also p. 46 for the more detailed Table 2.

0.3 The GIFTS-AMR research agenda's contribution to other global AMR research agendas

The GIFTS-AMR research agenda's contributions are described (Table 1) for two global AMR research agendas, published in 2023:

- The WHO 'Global research agenda for antimicrobial resistance in human health':
  - The GIFTS-AMR research agenda contributes to eight of the 13 WHO research areas and four of the five WHO themes; but not to Immunization (Prevention), Diagnosis and Drug-resistant TBC.
- The UN/WHO/WOAH 'A One Health priority research agenda for antimicrobial resistance':
  - The GIFTS-AMR research agenda contributes to 10 of the 17 WHO research areas and four of the five WHO themes; but not to Integrated surveillance.

In addition, the GIFTS-AMR research agenda adds two research themes and two research priorities to the existing two global AMR research agendas:

Research themes

1. Patient preferences and stakeholders' needs for non-antibiotic prevention and treatment strategies for infections.
2. Use of limited evidence and real-world evidence.

Research priorities

1. Investigate types and working mechanisms of health promotion/resilience effects and antimicrobial effects of TCIH MPs.
2. Investigate the conceptual differences between conventional medicine and TCIH which are a barrier for acceptability and implementation of TCIH prevention and treatment of infections.

0.4 Suggested advocacy actions related to the GIFTS-AMR research agenda

Several possible advocacy actions related to the GIFTS-AMR research agenda were identified during the GIFTS-AMR project and are hereby described across three themes, as suggestions for organizations involved with TCIH advocacy.

Research & development

- Continue and broaden the international research network, building on the existing GIFTS-AMR network, consisting of TCIH and conventional researchers with different backgrounds and skills (human medicine, veterinary medicine, human sciences, philosophical, historical, political, etc.) as well as professionals (doctors, veterinarians, pharmacists, biologists, physicists, chemists, pharmacologists, etc.) who are working towards a health-oriented healthcare system. *(GIFTS-AMR project team)*
- Develop a formal trustworthy global scientific 'committee/ working group', recognized by conventional and TCIH stakeholders, which provides valid information on TCIH research, education and information tools for the prevention and treatment of infections, and reduction of AMR. This committee/ working group should be responsible for the development of specific, high-quality databases on TCIH strategies and scientific evidence of TCIH research in this field to ensure patients, animal owners, farmers, healthcare professionals and other stakeholders can access user-friendly evidence-based information/advice on TCIH. *(WHO)*
- Develop and promote databases like CAM on PubMed® and VHL by PAHO and CABSIN among professionals and academic researchers. *(Research field)*
- Develop and use standards for evidence-based education of healthcare professionals (human and veterinary) - undergraduate and postgraduate. *(Universities)*
- Consider a broad range of sources (e.g. context-based/ real-world evidence, users' preferences) in research and guideline development. *(Research field)*
- Promote guideline development considering both quantitative and qualitative research, including results of 'real-world evidence' studies. *(Research field)*
- Expand the role of 'patient choice' in future research, in guideline development, and in education (PPI, public and patient involvement) in those countries where this is not, or insufficiently, organized. *(Research field)*
- Develop information tools (eHealth, website) to provide easily accessible information on evidence. *(Research field)*
- Prioritize research on health/resilience promotion rather than disease control only. *(Ministry of health)*
- Promote One Health research and the collaboration between conventional medicine and TCIH in human, animal, and plant sectors at regional, national, and international levels in a timely manner, while preserving the integrity of prescribing individualized TCIH treatments, and while considering research on health/resilience promotion and disease-specific prevention rather than disease control only. *(Ministry of health)*
- Promote publicly funded research on TCIH treatments, their efficacy/(cost-)effectiveness and safety, and their underlying mechanisms or modes of action. *(Ministry of health)*

Policy

- Connect to (inter)national policymakers
  - to communicate TCIH's contributions in general to many of societies' current questions and strategies regarding health needs.
  - to communicate the value propositions of TCIH MPs/methods/interventions' resilience effects.
  - to foster the One Health approach and the collaboration between conventional medicine and TCIH in human, animal, and plant sectors at regional, national, and international levels to effectively prevent AMR in an environmentally sustainable way, exchange effective techniques and use evidence to support TCIH, for individualized and non-individualized TCIH treatments, preserving the integrity of individualized TCIH prescribing while considering research on health/resilience promotion rather than disease control only.
  - to include TCIH strategies in (inter)national policies to prevent AMR and reduce antimicrobial use.
- Identify relevant developments in the research domain (TCIH and conventional medicine) which can support TCIH research in this field; and use this information to promote TCIH research in this field.
- Emphasize understanding of the One Health concept and emphasize One Health research considering the COHERE guideline.
- Promote the regulation of TCIH training and practices, such as the European Committee for Standardisation (CEN) standard on Services of Medical Doctors with additional qualifications in Homeopathy and the WHO benchmarks for traditional Chinese medicine, Ayurveda, naturopathy, Anthroposophic medicine, osteopathy, acupuncture and others.

Healthcare systems

- Develop a general concept of global regulatory classification of TCIH strategies.
- Connect to national guidelines organizations to include evidence-based TCIH strategies in (inter)national policies (national public health strategies and National Action Plans (NAPs)), guidelines and patient education to prevent AMR and reduce antimicrobial use.
- Improve and communicate the regulation of TCIH training and practices, such as the European Committee for Standardisation (CEN) standard on Services of Medical Doctors with additional qualifications in Homeopathy and the WHO benchmarks for TCIH, such as the one for traditional Chinese medicine, Ayurveda, osteopathy, naturopathy, Anthroposophic medicine, acupuncture and others.
- Promote inclusion of One Health and TCIH-related exposome (physical activity, body weight management, diet, sun exposure, stress, sleep and circadian rhythms, pollution, smoking, and gut microbiome) approaches when developing relevant antimicrobial stewardship programs (ASPs).
- Promote more evidence-based accessibility and TCIH MPs for infections (information). Qualitative outcomes should be shared with healthcare professionals, policymakers, stakeholders, and the public through appropriate tools.

I - Introduction

1.1 The burden of AMR

Resistance to antibiotics/antimicrobials is a complex and growing international public health problem with important consequences, such as increased mortality and economic impact (World Health Organization, 2023a). Back in 2014, a review on antimicrobial resistance (AMR) from the UK already stated that "Drug-resistant infections already kill hundreds of thousands a year globally, and 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." (O'Neill, 2016)

In the last decade, global, regional and national strategies were developed to reduce AMR. The most important strategies are: 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 and the role of artificial intelligence (AI) in this (Rabaan et al., 2022; World Health Organization, 2015).

However, despite all major efforts to reduce antibiotic use and AMR, little progress seems to have been made. Between 2000 and 2015, global antibiotic consumption increased by 65% (21.1–34.8 billion DDDs (defined daily doses)). The increase was driven by low- and middle-income countries (LMICs). In high-income countries (HICs) overall human consumption increased modestly (Klein et al., 2018). In the European Union (EU), there was only a very small decrease of 0.4% in the average total (community and hospital sector combined) consumption of antibacterials for systemic use in humans (European Centre for Disease prevention and Control, 2020). For the EU/EEA population-weighted mean consumption of antimicrobials in food-producing animals, expressed in mg/kg estimated biomass, there was a significant change for the 27 countries included in the analysis. A decline of 32% was observed between 2014 and 2018, while a slight increase was observed in humans (European Centre for Disease Prevention and Control, 2021).

The EARS-Net data on 2018 shows that AMR remains a serious threat to public health in Europe (European Centre for Disease Prevention and Control, 2019) and that current public health actions to tackle the situation remain insufficient. In 2022, Murray et al. demonstrated that AMR is a leading cause of death around the world. The highest burdens are found in low-resource settings. It is estimated that 4.95 million (3.62–6.57) deaths were associated with bacterial AMR in 2019, including 1.27 million (95% UI 0.911–1.71) deaths attributable to bacterial AMR. At regional level, the all-age death rate attributable to resistance was highest in western sub-Saharan Africa, with 27.3 deaths per 100,000 (20.9–35.3), and lowest in Australasia, with 6.5 deaths (4.3–9.4) per 100,000. Globally, the WHO Global AMR Surveillance System (GLASS), reports the increasing prevalence of AMR with serious therapeutic problems (World Health Organization, 2021).

Regarding the costs of AMR, Hofer (2019) estimated that 2.4 million people in Europe, North America and Australia will die from infections with resistant microorganisms in the next 30 years, with Southern European countries hit the hardest. The costs could run up to US$3.5 billion per year. Many LMICs already have high resistance rates. For these countries, the expectation is that these

rates will increase disproportionately. For example, 40–60% of human infections in Brazil, Indonesia and Russia are already caused by resistant microorganisms, and resistance is predicted to rise 4–7 times faster in these countries than in other OECD countries. Poudel et al. (2023) used a systematic review and meta-analysis to demonstrate that the economic burden of antibiotic resistance is still huge.

In 2023 the WHO published the *´Global research agenda for antimicrobial resistance in human health'* and the United Nations (UN), the WHO and the World Organisation for Animal Health (WOAH) the '*A One Health priority research agenda for antimicrobial resistance*'. Both research agendas stated that AMR has been recognized as one of the greatest global threats to the health of humans, animals and ecosystems. LMICs may be disproportionately affected, with higher mortality rates from infections with resistant organisms. And "although antimicrobial resistance is recognized as a global threat requiring urgent action, little progress has been made in improving awareness of antimicrobial resistance, monitoring antimicrobial consumption, implementing infection prevention and control programs and optimizing antimicrobial use in the human sector over the past six years." The One Health approach is regarded to be relevant to all efforts to prevent and control AMR.

Justification of a broad range of possible strategies and solutions

Given the magnitude of the problem, the insufficient strategies to reduce antimicrobial use and the urgency and impact of AMR, there is need for novel strategies. Traditional, Complementary and Integrative Healthcare (TCIH) may provide strategies and solutions which contribute to reducing (inappropriate) antimicrobial use, specifically as part of a delayed prescription strategy or as an alternative and add-on prevention or treatment strategy in both human and veterinary medicine. By doing that, TCIH may contribute to reducing AMR (Baars et al., 2018; Millar et al., 2021; Tierny et al, 2020; Weiermayer et al., 2020).

1.2 About Traditional, Complementary and Integrative Healthcare (TCIH)

The TCIH declaration (TCIH, 2023) states that "The healthcare we envision focuses on the whole person, is participative, respects individual choices, as well as cultural diversity and engages in respectful evidence-informed collaborations between all systems of healthcare." Non-conventional systems of healthcare which are integrated in TCIH (e.g. Anthroposophic medicine, Ayurveda, Homeopathy, traditional Chinese medicine, naturopathy) are so-called whole medical systems. These are complete systems of theory and practice which have independently evolved over time in different cultures and apart from conventional medicine or Western medicine (Baars and Hamre, 2017; Koithan et al., 2012; Schroen et al., 2014). In daily clinical practices, TCIH stimulates a health promotion-oriented lifestyle (prevention) and treats patients to strengthen or support the self-healing or self-regulating ability of the human organism (Van der Bie et al., 2008) to cope with diseases (Baars, 2011; Bhopal, 1986; Goldman et al., 2015; Jagtenberg et al., 2006; Kröz et al., 2016; Leung et al., 2005; Vankova and Kapincheva, 2019; Wang and Tang, 1980). The TCIH approach is also applicable to the field of veterinary medicine.

1.3 The scientific status of TCIH for the prevention and treatment of infections

The use of TCIH prevention and treatment of infections strategies in human and veterinary medicine is already based on an increasing number of scientific studies and evidence. For example, positive results from systematic reviews on TCIH medicinal products for acute, uncomplicated respiratory tract infections (RTIs) were found for *Andrographis paniculata* (Hu et al., 2017), *Pelargonium sidoides* for both general and specific URTI symptoms (e.g. cough and sore throat) (Anheyer et al, 2017a; Kamin et al., 2017; Wagner et al., 2015), *Echinacea* spp. for the common cold (Karsch-Völk et al., 2015; Nahas and Balla, 2011), and a combination of ivy (*Hedera helix* L.), primrose (*Primula veris* L./*Primula elatior* L.), and thyme (*Thymus vulgaris* L./*Thymus zygis* L.) for coughs only (Wagner et al., 2015). A systematic review of mechanisms of action (Veldman et al., 2023) demonstrated that *Andrographis paniculata* acts through immunomodulation and antiviral activity, possibly supplemented by antibacterial and antipyretic effects. *Pelargonium sidoides* acts through antiviral, indirect antibacterial, immunomodulatory and expectorant effects. *Echinacea* species likely act through immunomodulation. The combination of ivy/ primrose/ thyme combines the secretolytic and spasmolytic effects from ivy with the antibacterial effects from thyme.

Several studies examined the effectiveness of homeopathic medicinal products. A recent meta-analyses (MAs) of placebo-controlled randomized efficacy trials of homoeopathy for any indication (Hamre et al., 2023) demonstrated "The quality of evidence for positive effects of homoeopathy beyond placebo (high/moderate/low/very low) was high for I-HOM [red: individualized homeopathy] and moderate for ALL-HOM and NI-HOM [red: non-individualized homoeopathy and all homoeopathy types]. There was no support for the alternative hypothesis of no outcome differences between homoeopathy and placebo. The available MAs of PRETHAIs [red: placebo-controlled randomized efficacy trials of homoeopathy for any indication] reveal significant positive effects of homoeopathy beyond placebo. This is in accordance with laboratory experiments showing partially replicable effects of homeopathically potentized preparations in physico-chemical, in vitro, plant-based and animal-based test systems." Regarding treatment of infections, several studies examined the effectiveness of homeopathic medicinal products either in conjunction with antibiotics in treatment of bacterial infections, or with homeopathy as the sole treatment in humans and animals, demonstrating positive results (Weiermayer, et al., 2020). An economic evaluation of a complex homeopathic MP used showed that, compared with antibacterial treatment, homeopathy had a significantly higher cure rate in the treatment of acute maxillary sinusitis in adults (11% vs 59%; $p < 0.001$) at similar or lower costs (Kneis and Gandjour, 2009).

An example of an outcome study in the field of anthroposophic medicine is an observational study that studied 529 children <18 years from Europe (AT, DE, NL, and UK) or USA, whose caregivers had chosen to consult physicians offering anthroposophic (A-) or conventional (C-) treatment for respiratory tract infection (RTI)/ otitis media (OM). During the 28-day follow-up, antibiotics were prescribed to 5.5% of A-patients and 25.6% of C-patients; unadjusted odds ratio for non-prescription in A- versus C-patients 6.58 (95%-CI 3.45–12.56); after adjustment for demographics and morbidity 6.33 (3.17–12.64). Antibiotic prescription rates in recent observational studies with similar patients in similar settings ranged from 31.0% to 84.1%. Compared to C-patients, A-patients also had much lower use of analgesics, somewhat quicker symptom resolution, and higher caregiver satisfaction. Adverse drug reactions were infrequent (2.3% in both groups) and not serious (Hamre et al., 2005).

Some TCIH medicinal products are already integrated into conventional guidelines, for example in Germany: *Thyme/Primrose* for coughs (DEGAM Leitlinie Nr 11), and *Pelargonium sidoides* for coughs (DEGAM Leitlinie Nr 11, 2021), rhinosinusitis (S2k-Leitlinie); and in the UK: *Pelargonium sidoides* for coughs (NICE Cough (acute) guideline). All these TCIH medicinal products are registered in Germany with the BFarm (BfArM - Besondere Therapierichtungen und traditionelle Arzneimittel) and also have a so-called EMA status of Traditional use or Well-established use (EMA, 2023). In the EU, the registration of homeopathic medicinal products without indication and the authorization of homeopathic medicinal products with an indication are laid down in EU Directive 2001/83 (Directive 2001/83/EC).

For (recurrent) urinary tract infections ((r)UTIs), a systematic review on TCIH medicinal products demonstrates that the latest published meta-analysis, including 28 trials, reports a clear benefit of *Cranberry* products for preventing (r)UTIs in women. Five TCM formulas were found to be equally or more effective than antibiotics in treating UTIs. Furthermore, *Rosa canina* seems to have the potential to prevent UTIs in women undergoing a caesarean section. 'Acidif Plus Tablets' as well as 'Canephron' seem to be promising candidates for treating women with uncomplicated, rUTIs (Van Wietmarschen et al., 2022).

High-quality RCTs supporting the evidence of homeopathy for the treatment of recurrent UTIs are scarce and only available for specific populations (Pannek et al., 2019). However, a survey on use and patients' perceived effectiveness of TCIH and self-care strategies in woman with (recurrent) urinary tract infections in the Netherlands showed the homeopath to be the most popular TCIH health practitioner to be consulted for (r)UTIs and the majority of its users perceived the treatment as effective. These findings warrant further studies into the effectiveness of homeopathy in the prevention and treatment of (r)UTIs (Witteman et al., 2021).

In pigs, promising alternatives for the prevention and treatment of infections are pro- and prebiotics, organic acids such as short- and medium-chain fatty acids, phytogenic substances, bacteriophages, spray-dried plasma, and homeopathy (Camerlink et al., 2010; Castro et al., 2022; Mathie and Clausen, 2015; Weiermayer et al., 2020). In chickens, promising alternatives are Egg Yolk Antibodies (EYA), pro- and prebiotics, antimicrobial peptides such as bacteriocins, ß-defensins, protegrins, insect defensins, and homeopathy (Amalcaburio, 2009; Berchieri et al., 2006; Hadipour et al., 2011; Low et al., 2021; Sandoval et al., 1998; Sato et al., 2012; Velkers et al., 2005). In cows, promising TCIH treatments are phytogenic substances, probiotics, bacteriocins, bacteriophages, stem cells, minerals, trace elements, vitamins, short-chain fatty acids and microbial lipopolysaccharide, and homeopathy (Nair, 2017; Weiermayer et al., 2020; Zeise and Fritz, 2019).

Several, mostly observational, studies support the hypothesis that doctors who practice TCIH (including and integrating both conventional medicine and complementary medicine) have lower antibiotic prescription rates compared to their conventional colleagues (measured as past use, antibiotics use ever, in the first 12 months of life and after 12 months of life, consumption, prescription rates) and their patient groups have lower antibiotic consumption rates, although in these studies selection bias (e.g. patients who do not want antibiotics may choose a TCIH doctor more often) cannot be ruled out (Baars et al., 2019; Van der Werf et al., 2018). Nevertheless, TCIH practices appear to contribute to a reduction of antibiotic use. Reduction in antibiotic use as a result of TCIH prevention and treatment of infections has also been described for veterinary medicine (Maeschli et al 2019, Orjales et al 2016).

Based on a narrative review, we can come to the overall conclusion that there is some evidence that TCIH prevention and some TCIH treatment strategies for infections are effective and safe. Many TCIH treatment strategies for infections are promising, but overall lack high-quality evidence (Baars et al., 2019; Weiermayer et al., 2020).

1.4 Patients', animal owners', farmers' preferences and doctors' (non-) prescription of TCIH medicinal products

Several surveys demonstrate that many people would like to be treated with TCIH in general (De Souza et al., 2014; Witteman et al., 2021). Surveys conducted among patients in university hospitals show that more than 50% of patients in oncology, gastroenterology and even cardiology departments are requesting TCIH treatment and wish to be better informed about it (Gunnarsdottir et al., 2020; Pokladnikova and Selke-Krulichova, 2018; Sharp et al., 2018). The same open attitude towards TCIH can be seen in farmers (Hellec et al., 2021; Maeschli et al., 2019; Orjales et al., 2016).

However, there is a complex array of factors which influence the (non-)prescribing of TCIH. The attitudes of both doctors and patients are shown to be of major significance in prescribing decisions. Many doctors do not (want to) prescribe TCIH antibiotic alternatives, due to patient pressure to prescribe antibiotics, fear of ineffectiveness of TCIH treatments, lack of TCIH knowledge in general, insufficient information on the effectiveness and safety of TCIH treatments, (assumed) insufficient regulation of herbal practitioners, concerns about herbal quality control and potential herb–drug interactions, and due to a lack of communication between doctors and patients about this topic (Baars et al., 2019).

Nevertheless, for example the field of uncomplicated, acute RTIs treatment demonstrates that there is a need and 'market' for TCIH. RTIs are among the most common infections experienced in the community and are among the most common reasons for antibiotic prescribing internationally (e.g. Stanton et al., 2010). Previous studies show that although antibiotics have small or negligible symptomatic benefits for patients with uncomplicated acute otitis media, pharyngitis, bronchitis, laryngitis and the common cold, antibiotics are still commonly used for these and other viral respiratory infections (e.g. Gulliford et al., 2014; Pouwels et al., 2018). The same applies to veterinary medicine, as supported by the published figures from 2018, showing 50% unfounded or improper antibiotic use in veterinary medicine (Manyi-Loh et al., 2018). Effective and safe non-antibiotic TCIH RTI treatment (as an alternative treatment or as part of a delayed prescription strategy) may therefore contribute to reducing antibiotic use and prescription and AMR, meeting both doctors' and patients' desire for treating RTIs and symptom relief. A systematic review of qualitative studies demonstrates that patients are open to TCIH treatment of acute RTIs, but need trusted advice on the safety and effectiveness of TCIH and antibiotics for specific acute RTIs (Willcox et al., 2020). Trusted advice on the effectiveness and safety of TCIH is needed by farmers and respectively the patient's owners too (Hellec et al., 2021; Keller et al., 2019; Sommer, 2009).

1.5 What is GIFTS-AMR?

GIFTS-AMR (Global Initiative for Traditional Solutions to Antimicrobial Resistance) is a JPIAMR 10th call funded, globally organized, growing network of TCIH and AMR/infectious diseases research institutes, researchers in both human and veterinary medicine and global/regional policymakers.

The network aim:

- To develop a global 'Traditional Solutions to Antimicrobial Resistance' network by mapping out and connecting the research fields, research institutes, infrastructures and researchers in human and veterinary medicine involved with TCIH research.
- To develop research agendas starting with at least one to three prioritized indications both in human and veterinary medicine.
- To prepare grant proposals for research projects and the continuation of the network after the JPIAMR project.
- To communicate the existence, activities and output (e.g. research agendas, website) of the Network to relevant stakeholders, both online (report on website, webinars) and during an (online) international conference.

The GIFTS-AMR network further builds on the European network and results of the JPIAMR 4th call funded network project entitled 'Appropriate use of antibiotics: the role of CAM treatment strategies' (Baars and Van der Belt-Zoen (eds.), 2018).

1.6 What is the GIFTS-AMR network's unique position?

Currently, the GIFTS-AMR network involves 17 research institutes and 6 additional organizations worldwide working in the TCIH field on the topic of AMR in both human and/ or veterinary medicine. The various TCIH types are mainly Anthroposophic medicine, Ayurveda, Homeopathy, Phytotherapy and traditional Chinese medicine. A broad range of research types is covered within the network, many working in clinical and pre-clinical research and, for example, on ethnomedicinal surveys, guideline development and public health research. The GIFTS-AMR network can develop a global research agenda on the contribution of TCIH in preventing and treating infections, reducing (inappropriate) antibiotic use and reducing AMR.

1.7 Who is the research agenda intended for?

The research agenda is intended for the GIFTS-AMR network to collaborate on research proposals and funding applications and for policymakers, researchers, healthcare professionals (organizations) and patients (organizations) at national, regional and global level.

1.8 How was the research agenda drawn up?

In the first phase of the GIFTS-AMR project, a survey was disseminated, interviews and kick-off meetings were organized to collect information about the TCIH and AMR status among the network members and to collect input for the research agendas. Based on this collected information, the first objectives were identified, and a first draft of research agenda topics and related research questions per topic was formulated and shared within the network. Members were invited to add and/or change topics. Then for each main topic a working group was formed to work on describing the background, the main topics for the development of the research agenda, the current situation, the research themes and the prioritized research projects for the next 10 years. Consensus on the

research agenda among the GIFTS-AMR group members was reached following several rounds of providing input and comments on concept documents.

1.9 What next?

Research agenda

The research agenda will be presented during the GIFTS-AMR project online conference November 9-10, 2023 and will be disseminated to stakeholders at national, regional and global level. Members of the GIFTS-AMR network will collaborate to develop research proposals and acquire funding for priority projects on the research agenda.

II - The value of TCIH medicinal products

2.1 Background

With the urgent, global antimicrobial resistance (AMR) problem and the insufficient results of global AMR reduction strategies as context, TCIH medicinal products (MPs) appear valuable for both human and veterinary medicine as innovative products for the prevention and treatment of infections, and for reducing AMR. However, several stakeholders have concerns about the efficacy and (cost-) effectiveness of these MPs, their potential adverse reactions, and the insufficient knowledge of the mode of action, contraindications, and interactions with existing orthodox pharmaceuticals and functional foods.

2.2 Main topics for the development of the research agenda

- The specific value proposition of TCIH MPs for each of the stakeholder groups (patients, farmers, doctors, nurses, pharmacists, policymakers).
- The health promotion or resilience effects of TCIH MPs; their value and the way to study these effects.
- The (cost-)effectiveness and safety of TCIH MPs compared to antimicrobials.

2.3 Current situation

2.3.1 The value of TCIH medicinal products

TCIH MPs may serve as an alternative or add-on treatment strategy (instrumental value) for patients and farmers in countries where antimicrobials are over-used, easily accessible over the counter or, in some cases, suffer limited availability. Many people in LMICs already use TCIH MPs, because TCIH MPs for infections fit the patterns of use, are more closely aligned with the own values and beliefs of citizens in these countries (cultural value). And also in many western countries they are commonly used. TCIH MPs appear to promote resilience. Some TCIH MPs appear to improve antibiotics' effects and can therefore be used as add-on MPs. TCIH MPs appear to have less side effects than antimicrobials (see also §2.3.3). Furthermore, the World Health Organization (2013) estimates that 80% of the world's population directly relies upon TCIH MPs for healthcare.

TCIH MPs provide non-antibiotic options for indications where antimicrobials are not indicated and where only symptom reduction with conventional medicine is indicated and/or where antimicrobials are over-used for healthcare professionals (doctors, nurses, pharmacists). In addition, some TCIH MPs appear to improve antibiotics' effects and can therefore be used as add-on MPs, and some have antimicrobial effects (e.g. antibacterial, antiviral or antifungal) themselves (Veldman et al., 2023). For the acceptance of TCIH MPs, it is important that TCIH MPs are increasingly evidence-based (see also §1.3).

The value for researchers is first of all that it fits in with new pharmaceutical approaches. There are clear trends that the mainstream pharmaceutical research is moving away from single molecules or a single target approach, to combination therapies and multiple target approaches. Plant extracts containing several multiple pharmacological compounds have been reported to act on multiple molecular and cellular targets and such an approach is gaining support in the development of drug combinations/extracts to fight diseases. Secondly, TCIH MPs may be important for new drug development (instrumental value). The rising incidence of health-related problems in both developing and developed countries has prompted research in the development of drugs from leads identified from traditional medical uses as a different approach to manage new deadly diseases and those which have become resistant to available drugs.

For policymakers the value of TCIH MPs may be their longstanding use or traditional use. Many TCIH MPs have been used for decades or even hundreds or thousands of years in medicine. Longstanding use and Traditional use are criteria currently used by the EMA to assess herbal MPs and to formulate positive recommendations for use. Secondly, TCIH MPs may be valuable in conventional medicine for new drug development (see paragraph on value for researchers). TCIH MPs may also have less environmental side effects (e.g. less pharmaceutical waste in the environment), may encourage biodiversity, and are in agreement with the One Health approach. TCIH MP treatments are hypothesised to be more cost-effective, also taking the costs of all environmental side effects and healthcare costs into account (see also §2.3.3). The use of TCIH MPs creates major economic value at country and global levels (economic value). In 1997, 71 drugs based on natural MPs were reported to earn more than US$500 million each. 27 drugs based on TCIH MPs earned more than US$1 billion each yearly. Today more than 50% of the drugs on the market are natural MPs or are derivatives of natural MPs. The global market for pharmaceutical products topped US$500 billion in 2004 (Richerzhagen, 2010, 2011). In 2011, the pharmaceutical industry was estimated to earn about US$32 billion a year in profits from products derived from traditional remedies (Richerzhagen, 2010, 2011). This was an increase of 7% compared to 2003 and a 28% percent increase compared to 2001. By 2012, the global industry in traditional Chinese medicine alone was reported to be worth US$83 billion (Kew Royal Botanic Gardens, 2017). Other economic benefits include: employment opportunities (particularly important in regions where TCIH is deeply rooted in the culture), income generation, preservation of traditional knowledge, tourism and cultural exchange, exports, research and development and local industries and entrepreneurships. And lastly, the use of TCIH MPs is supported by WHO policy (WHO (2013). WHO traditional medicine strategy: 2014-2023).

2.3.2 Health or resilience promotion effects of TCIH medicinal products

Health or resilience promotion effects, in general, are effects of interventions which support the organism to overcome the infection by itself by means of strengthening the self-regulating abilities of the organism ('changing the host's capacities'). Specific health/resilience promotion effects are immunomodulatory effects (e.g. regulation of macrophage functioning) and organ physiological function optimizing effects (e.g. expectorant effects and secretolytic effects in the treatment of URTIs) (e.g. Veldman et al., 20123). The value of resilience effects is that they support the self-healing ability of the organism; that they provide additional working mechanisms to the current antimicrobial working mechanisms in the treatment of infections; and that they fit the One Health approach, where promoting resilience is aimed at ecological, animal and human levels.

Resilience effects can and must be studied both empirically and theoretically. Empirical studies should build on the enormous amount of existing traditional expert knowledge on the working

principles of TCIH MPs and on the results of in-vitro studies, both apart from and as part of clinical studies. Theoretical research can build on this research to conceptualize the additional value and working mechanisms of TCIH MPs in comparison to antimicrobials.

2.3.3 (Cost-)effectiveness and safety of TCIH medicinal products compared to antimicrobials

The rising costs of conventional MPs, the overall costs of using antimicrobials in terms of effects on microbiota, future resistance and the impact of the limited availability of effective antimicrobials, as well as the costs associated with (the treatment of) their side effects, may make the use of TCIH MPs cost-effective, particularly for acute, uncomplicated infections. The cost-effectiveness of TCIH MPs compared to antimicrobials is therefore hypothesized, but has hardly been studied.

For example, TCIH appear to generate less side effects compared to antibiotics and appear to be safe. General antibiotics side effects include: antibiotic-associated diarrhea (AAD) (5-39% of patients who are prescribed antibiotics), candidiasis, obesity (associated with childhood use of antibiotics before 2 years), allergies (in 5-10% of all patients and in 10-30% of hospital patients), increase of irritable bowel syndrome (IBS), and irritable bowel disease (IBD) symptoms; in the treatment of acute otitis media, for every 14 children treated with antibiotics, one child experienced an adverse reaction (such as vomiting, diarrhea, or a rash) which would not have occurred if antibiotics had been withheld (Baars et al., 2019).

According to a systematic review of results reported in RCTs with 111 studies of a single herb and 133 of multiple herbs with a total of 15,441 participants, herbal treatment may be considered as safe. However, a few herbal treatments have been associated with severe adverse reactions. Adverse reactions to homeopathic and anthroposophic MPs are infrequent and usually mild to moderate, and anaphylactic reactions can occur, but are very rare (Baars et al., 2019).

2.4 Research priorities

- Assess patients'/animal owners'/farmers' preferences, use, satisfaction and acceptability of TCIH MPs in LMICs and developed countries.
- Investigate the feasibility and acceptability of integrating traditional and complementary approaches with conventional primary healthcare (for humans and animals), as a strategy to support delayed use of antibiotics.
- Investigate the safety, working mechanisms, and efficacy/(cost-)effectiveness of the most promising TCIH MPs for indications where antimicrobials are commonly over-used.
- Investigate the types and working mechanisms of health promotion/resilience and antimicrobial effects of TCIH MPs.
- Investigate the benefits/risks ratio and the benefits/costs ratios of TCIH MPs vs antimicrobials, for humans, animals and the environment.
- Investigate the effects of whole system approaches (e.g. organic/biodynamic agriculture and TCIH whole medical system prevention and treatment) on sustainable reduction of antimicrobial use and consumption.

2.5 Prioritized research projects for the next 10 years

- Map out the qualitative and quantitative studies on patients'/animal owners'/farmers' preferences, use, satisfaction and acceptability of TCIH MPs as alternatives to antimicrobials (scoping review).
- Investigate the feasibility and acceptability of promising TCIH MPs for acute, uncomplicated URTIs and recurrent UTIs in humans and for uncomplicated diarrhea and RTIs in animals.
- Investigate the (cost-)effectiveness of the most promising TCIH MPs for URTI symptom control and reduction of antibiotics use in GP practices and hospital ER departments and for recurrent UTIs symptom control and reduction of antibiotics use in GP practices.
- Assess the acceptability and effectiveness of updated guidelines on management of self-limiting infections, including recommendations to use TCIH to support delayed use of antibiotics.
- Investigate the (cost-)effectiveness of FeverApp/FeverFriend tools for fever management on symptom control and reduction of antimicrobials use in GP practices and hospital ER departments.
- Investigate the types and working mechanisms of health promotion/resilience and antimicrobial effects of 3-5 TCIH MPs with moderate to high-quality evidence of effectiveness in clinical trials for acute, uncomplicated URTIs and recurrent UTIs in humans and for uncomplicated diarrhea and RTIs in animals.
- Investigate the effectiveness and the reduction of adverse effects on animals and environments for TCIH MPs with moderate to high-quality evidence of effectiveness for uncomplicated URTIs and recurrent UTIs in humans and for the prevention of ETEC-related post-weaning diarrhea in piglets at risk.
- Map out the qualitative and quantitative studies on the effects of whole medical systems and whole system approaches in (organic and biodynamic) farming on the reduction of antimicrobial use and consumption (scoping review).

III - The best TCIH product – market combinations

3.1 Background

To guide future research, it is important to determine which indications in both veterinary and human healthcare should be prioritized. Alongside guiding future research, identifying clear product-market combinations can support the acceptability of TCIH products and give clear treatment options which could be integrated in treatment guidelines for specific indications.

Due to the personalized character of many TCIH treatment strategies, making generalizable product-indication combinations is not always possible or representative of the unique qualities of a treatment modality. However, determining the most promising TCIH MPs for indications which urgently require new treatment options – e.g. the best 'product-market combination' - can be considered as a first step in uncovering the potential TCIH treatment modalities hold.

3.2 Main topics for the development of the research agenda

- The most urgent indications for antibiotic alternatives in human and veterinary medicine.
- Promising TCIH medicinal products for specific indications.
- The best TCIH product-market combinations in human and veterinary medicine.

3.3 The current situation

3.3.1 The most urgent indications for antibiotic alternatives

Antibiotic alternatives are urgently needed for different indications for different reasons.

Inappropriate antibiotic prescription in human medicine is most often based on over-prescription in primary care (Pouwels et al., 2018; Tyrstrup, 2017). An increasing number of countries have eliminated antibiotics from their guidelines for mild infections. However, for several reasons antibiotics are still prescribed in clinical practices. Indications and related symptoms with over-prescription are upper respiratory tract infections (URTIs) (McDonagh et al., 2018; Pouwels et al., 2018) and urinary tract infections (UTIs) (Pouwels et al., 2018). Specific symptoms with over-prescription are fever (Hagedoorn et al., 2020; Kumar et al., 2008; McKay et al., 2016) and diarrhea in children and adults in LMICs (Lewnard et al., 2020; Rogawaski et al., 2017). Besides, antibiotics are used without prescription in some indications, which is mostly associated with symptoms of URTIs, diarrhea and UTIs (Batista et al., 2020). Finally, the effectiveness of antibiotics is decreasing in some indications. This is most urgent in bloodstream infections, sexually transmitted diseases, gastrointestinal tract infections and UTIs (World Health Organization, 2022a).

Indications urgently requiring non-antibiotic treatment options in veterinary healthcare

The most urgent indications for antibiotic alternatives for veterinary medicine are for pigs (enteric diseases, respiratory diseases, food borne zoonoses, Maes et al., 2020); for chickens (enteric diseases, respiratory diseases, Low et al., 2021); and for dairy cattle (mastitis, brucellosis, tuberculosis, Johne's disease, leptospirosis, salmonellosis, bovine viral diarrhea, infectious bovine rhinotracheitis, Boireau et al., 2018; Moreira et al., 2019). These animal groups have the largest antimicrobial consumption levels, which accounts for 93.75% of all food animals in total (Tiseo et al., 2020; van Boeckel et al., 2015).

3.3.2 Promising TCIH medicinal products for specific indications

Promising TCIH MPs for specific indications (3.3.1) are based on clinical research with promising results.

Promising TCIH MPs for human medicine for URTIs are *Andrographis paniculata* (Burm. f.) Wall. ex Nees, *Pelargonium sidoides* DC*., Echinacea* Spp., *Hedera helix* L*., Primula veris* L*./Primula elatior* L*. and Thymus vulgaris* L*./Thymus zygis* L., Shuanghuanglian, Lianhuaqingwen, Qingkailing, Sanren Decoction, QiXiangYiQi JieDu, FuFangKang BingDu, JinChaiKang BingDu, Lianhua-qingwen, Maxingshigan decoction, Qingqiao, and Zhi Sou San (Baars et al., unpublished results). For UTIs these are cranberry products (Van Wietmarschen et al., 2022; Luís et al., 2017), the TCM formulas Qing Re Jie Du Tiao Gan Tang, Bai Tou Weng Tang, Er xian Tang, San Jin Wan and Bazheng powder (Flower et al., 2015), Rosa canina, Acidif Plus Tablets containing L-Methionine, *Hibiscus sabdariffa, Boswellia serrata* (L.) Roxb, and Canephron containing *Centaurii* herba, *Levistica* radix, *Rosmarini* folium (Van Wietmarschen et al., 2022). For gastrointestinal infections *Potentilla erecta* and carob bean juice (Anheyer et al., 2017b) are promising, though other MPs need to be reviewed. For bloodstream infections the TCM formula Xuebijing is promising, containing *Carthamus tinctorius*, Paeoniae radix, *Salvia divinorum, Angelica sinensis* and *Lingusticum wallichii* (Mousavi et al., 2016). For both bloodstream infections and sexually transmitted diseases TCIH MPs hold potential as add-on treatments to enhance the effectiveness of antibiotics (Mousavi et al., 2016). This, however, needs to be further reviewed.

In veterinary medicine promising TCIH MPs for enteric diseases in pigs are pro- and prebiotics, organic acids such as short- and medium-chain fatty acids, phytogenic substances (such as bitter citrus extract, thymol and carvacrol (Chang et al., 2022)), bacteriophages, spray-dried plasma (Castro et al., 2022), garlic (*Allium sativum* L.), peppermint (*Mentha x piperita* L.) and sage (*Salvia officinalis* L.) (Ayrle et al., 2016). For respiratory diseases clove oil and minerals such as zinc and copper (Ostma et al., 2015; Wongsawan et al., 2019) and echinacea *(Echinacea purpurea* (L.) Moench), thyme *(Thymus vulgaris* L.) and marshmallow root *(Althea officinalis* L.) (Ayrle et al., 2016) and specific homeopathic medicinal product (such as homeopathic agent Coli 30K (Camerlink et al. 2010)). For mastitis in dairy cattle promising TCIH MPs are ethno-veterinary formulations such as aloe vera, curcuma longa, calcium hydroxide (prevention); pro- and prebiotics (treatment) (Kumar, Deepa & Punnimurthy 2021; Nair & Punniamurthy, 2017). In calves also garlic, peppermint and sage are promising TCIH MPs for enteric diseases and echinacea, thyme and marshmallow root for respiratory diseases (Ayrle et al., 2016).

Since 2007, the EU regulation 834/2007 has been used which states TCIH therapies should be used as a first option in organic livestock. Good results caused this regulation to be updated in the

current European regulation 2018/848, which states that "... phytotherapeutic and homeopathic products shall be used in preference to treatment with chemically synthesized allopathic veterinary medicinal products, including antibiotics, providing their therapeutic effect is effective for the species of animal and for the condition for which the treatment is intended" in organic livestock.

3.4 The best TCIH product-market combinations

The two topics (§3.3.1 "The most urgent indications for antibiotic alternatives" and §3.3.2 "Promising TCIH medicinal products for specific indications") discussed above together form the best TCIH product-market combinations. In other words: the combinations of most urgent indications with the most promising TCIH MPs for these indications.

Infectious diseases could require non-antibiotic treatment strategies due to inappropriate antibiotic use, antibiotic use without prescription or reduced effectivity of antibiotics. TCIH MPs are proposed as promising in situations of non-critical, uncomplicated infections due to their health promotion/ resilience effects. The most promising TCIH MPs are those which have shown to be (most) effective and safe in (high-quality) systematic reviews, or systematic reviews of systematic reviews, as this is considered to be the highest level of evidence. Also, TCIH MPs which have enjoyed good results in clinical studies, expert opinion studies and prescription rate studies can be considered promising for future research.

In human medicine, non-critical, uncomplicated infectious diseases which urgently require non-antibiotic treatment options are URTIs, UTIs and gastrointestinal tract infections. The most promising TCIH MPs reviewed in high-quality systematic reviews are for URTIs *Andrographis paniculata* (Burm. f.) Wall. ex Nees, *Pelargonium sidoides* DC*.,* Echinacea Spp., *Hedera helix* L*., Primula veris* L*./Primula elatior* L*. and Thymus vulgaris* L*./Thymus zygis* L. (Baars et al., unpublished results). For UTIs these are cranberry products (Luís et al., 2017; Van Wietmarschen et al., 2022). For gastrointestinal tract infections *Potentilla erecta* and carob bean juice are promising (Anheyer et al., 2017b), though other TCIH MPs need to be reviewed. Bloodstream infections and sexually transmitted diseases are usually critical and complicated infections, while TCIH MPs are considered more promising in non-critical, uncomplicated indications. These indications are therefore not prioritized for research on TCIH MPs in this document.

In veterinary medicine, pigs, chickens and dairy cattle consume the most antibiotics (Tiseo et al., 2020; van Boeckel et al., 2017). In these species, enteric and respiratory diseases are most urgently in need of other treatment options. Prophylactic treatment and the treatment of (potentially) zoonotic diseases are also prioritized. The most promising TCIH MPs for piglets are phytogenic feed additive of bitter citrus extract, thymol and carvacrol or a specific homeopathic medicinal product: homeopathic agent Coli 30K (Camerlink et al. 2010) in piglets with ETEC related diarrhea (Mathie and Clausen, 2015, Chang et al. 2022). For both piglets and calves, the most promising TCIH MPs in the treatment of enteric diseases are garlic (*Allium sativum L.*), peppermint (*Mentha x piperita L.*) and sage (*Salvia officinalis L.*) (Ayrle et al., 2016). For the treatment of respiratory diseases in piglets and calves this is echinacea (*Echinacea purpurea* (L.) Moench), thyme (*Thymis vulgaris* L.) and marshmallow root (*Althea officinalis* L.) (Ayrle et al., 2016). The most promising TCIH MPs which modulate the immune system and inflammation and which could be used as a prophylaxis for infectious diseases are echinacea (*Echinacea purpurea* (L.) Moench), tea plant (*Camellia sinensis* (L.) Kuntze), licorice root (*Glycyrrhiza glabra* L.) and oregano (*Origanum vulgare* L.) (Ayrle et al.,

2016). Systematic reviews are missing for poultry, but required to determine the most promising TCIH MPs. Hence, in veterinary medicine, uncomplicated infectious diseases which urgently require non-antibiotic treatment options are respiratory tract infections and gastrointestinal tract infections in all species.

3.5 Research priorities

- Investigate the safety, working mechanisms, and efficacy/ (cost-)effectiveness of the most promising TCIH MPs for indications where antimicrobials are commonly over-used.
- Investigate the reasons for current guideline developers to decide on (non-)inclusion of TCIH MPs in guidelines for the prevention and treatment of infections.

3.6 Prioritized research projects for the next 10 years

- Investigate the safety and effectiveness of TCIH MPs for gastrointestinal infections in humans and respiratory and enteric diseases in animals in systematic reviews.
- Map out and investigate the (cost-)effectiveness, safety and working mechanisms of the most promising TCIH MPs for indications where antimicrobials are commonly over-used (i.e. URTIs, UTIs and gastrointestinal infections in human healthcare and enteric and respiratory diseases in pigs, chicken and cattle).
- Investigate the reasons for non-inclusion of TCIH MPs for infections in European countries for those TCIH MPs which already have an EMA status of Traditional use or Well-established use and/or are included in conventional guidelines (e.g. in the UK or Germany):

  EMA status
  - *Ivy* for coughs and the common cold
  - *Pelargonium sidoides* for the common cold

  German guidelines
  - *Pelargonium sidoides* for coughs (DEGAM Leitlinie Nr 11), rhinosinusitis (S2k-Leitlinie)
  - *Thyme/Primrose* for coughs (DEGAM Leitlinie Nr 11)

  UK guidelines
  - *Pelargonium sidoides* for coughs (NICE Cough (acute) guideline)

IV – Identifying and prioritizing the most promising TCIH medicinal products for high-quality RCTs

4.1 Background

In order to have TCIH MPs accepted by conventional stakeholders and implemented in conventional guidelines for the treatment of infections, there is a need for high-quality evidence of the safety and (cost-)effectiveness of these products. However, high-quality, placebo-controlled, randomized clinical trials (RCTs) are very expensive, resources are very limited and research budgets must be optimally spent. Therefore, there is a need for a scientific procedure to select and prioritize the most promising TCIH MPS for specific infections which have not yet been tested in high-quality studies. This identifying and prioritizing procedure will increase the chance of positive results of high-quality, placebo-controlled RCTs to test the safety and (cost-)effectiveness of selected TCIH MPs ('optimal return on investment').

4.2 Main topics for the development of the research agenda

- Knowledge sources which can be used for identifying the most promising TCIH MPs.
- The most efficient research program to identify and prioritize the most promising TCIH MPs for urgent indications for testing in high-quality RCTs.

4.3 The current situation

4.3.1 Knowledge sources which can be used for identifying the most promising TCIH medicinal products

The following sources can be used for determining the most promising TCIH MPs to be tested in a future high-quality RCT: (1) systematic reviews on clinical research (safety, efficacy and effectiveness), (2) systematic reviews on pre-clinical research (safety/mode of action), (3) single RCTs (tolerability/efficacy/effectiveness) and real-world evidence studies, (4) pre-clinical research (safety/mode of action), and (5) clinical experience.

4.3.2 The most efficient research program to identify and prioritize the most promising TCIH medicinal products for urgent indications for testing in high-quality RCTs

A research program to identify and prioritize the most promising TCIH MPs should respect both efficacy/effectiveness and tolerability and further aspects such as availability, costs and environmental impact. A scoring system is hypothesized to be the most appropriate methodology. The following criteria should be included:

- Public health relevance: The indication or medical problem for which the TCIH MP is used should be relevant (e.g. a high prevalence with over-use of antimicrobials or a serious problem with high morbidity without good treatment).
- Clinical experience: The TCIH MP must have been effective according to clinical experience (both professionals and patients experience).
- Evidence from clinical trials: The TCIH MP must have demonstrated safety, (a positive direction of) efficacy or effectiveness in a clinical trial.
- Evidence from basic research: Research on safety and mode of action should complement the evidence from clinical trials.
- Feasibility: Research on the TCIH MP should be feasible. This includes (1) eligible researchers (*who*), (2) eligible infrastructure (*where*) with special respect for the hurdles presented by drug laws for performing clinical trials in different countries too, (3) availability of the product (not like a rare protected plant), and (4) appropriate product costs for broad use.
- One Health Relevance: The TCIH MP and the whole production/ distribution process should be according to the principles of One Health.

A team of experts in the specific TCIH field should develop the score.

4.4 Research priorities

- Develop and evaluate valid score systems which weigh up relevant factors to identify and prioritize the most promising TCIH MPs for urgent indications which can be tested in high-quality RCTs, and which are usable and acceptable for relevant stakeholders.

4.5 Prioritized research projects for the next 10 years

- Develop valid score systems which weigh up relevant factors to identify and prioritize the most promising TCIH MPs which can be tested in high-quality RCTs, for the treatment of acute, uncomplicated URTIs and recurrent UTIs in humans and for uncomplicated diarrhea and RTIs in animals in countries with great over-use of antimicrobials for these indications.

V - The use of limited evidence and real-world evidence of safety and effectiveness

5.1 Background

Most TCIH MPs are not yet being tested in (high-quality) clinical trials and included in systematic reviews and are not likely to be in the foreseeable future (due to a lack of sufficient financial resources, a lack of scientific interest and methodological issues). Many only have a formal or informal status of long traditional use. So questions are therefore: how can we make use of this limited and 'real-world evidence' (e.g. registered use of TCIH MPs by traditional healers)? How can we warrant safety and effectiveness of these products in the absence of high-quality evidence? And, within the context of the urgent, global antimicrobial resistance (AMR) problem, can TCIH MPs with sufficient evidence on safety already be suggested by doctors and used by patients, providing the uncertainties regarding the quality of evidence on safety and efficacy of TCIH MPs and the types of evidence are transparently communicated? We need more scientific information on what type of limited and real-world evidence of safety and effectiveness is acceptable for stakeholders and how to use this information when suggesting TCIH MPs for the treatment of infections.

5.2 Main topics for the development of the research agenda

- Elements of an Evidence to Recommendation (EtR) procedure for TCIH MPs in the absence of high-quality evidence.
- Recommendations on TCIH MPs with sufficient evidence on safety by doctors and use by patients, even if there is only limited evidence of some benefit, providing the uncertainties regarding the quality of evidence on safety and efficacy of TCIH treatment strategies are transparently communicated.
- Knowledge sources and criteria which must be used to assess the safety of TCIH MPs.

5.3 The current situation

5.3.1 The elements of an Evidence to Recommendation (EtR) procedure for TCIH medicinal products in the absence of high-quality evidence

An additional set of methodological and medical arguments, in line with the most used EtRs procedures (e.g. GRADE), can be used when weighing up arguments to decide on the recommendation for a TCIH MP in the absence of high-quality evidence.

Methodological arguments are (1) the existence of a formal status, for example the existence of an EMA (European Medicine Agency) status of Traditional use (TU) or Well-established use (WEU),

or a registration according to the EU Dir 2001/83; (2) the use of EMA criteria used for the TU and WEU assessment: the active ingredient(s) of the MP must have been on the (e.g. European) market for more than 15 years (WEU) or 30 years (TU) and there should be valid and sufficient bibliographic safety and efficacy data; (3) TCIH MPs are registered according to national and/or international directives; and (4) there is mechanistic evidence of a TCIH MP's mode of action (in addition to probabilistic or difference-making evidence of clinical studies).

Medical arguments are (1) TCIH MPs result in significantly less side effects compared to the (severity of the) negative consequences (read: side effects) of antimicrobials for humans/animals and the environment) (weighing up the pros and cons of antimicrobials vs TCIH MPs); (2) TCIH MPs provide alternatives for the prevention and treatment of infections: (a) when antibiotics are not indicated or available (e.g. for URTIs in the GP guidelines in the Netherlands; or in low-income countries with no available antibiotics); and (b) when extra treatment options are useful (e.g. when antibiotics have insufficient effects or are over-used).

Finally, TCIH MPs may be requested in preference of conventional medicine, e.g. in the EU regulation 2018/848 where organic farming requests homeopathy and phytotherapy to be used in preference before conventional medicine under certain circumstances.

5.3.2 Recommendations on TCIH MPs with sufficient evidence on safety by doctors and use by patients, even if there is only limited evidence of some benefit, providing the uncertainties regarding the quality of evidence on safety and efficacy of TCIH treatment strategies are transparently communicated

The following criteria can be used when making recommendations at national level in countries which do not have recommendations for these TCIH MPS for a specific indication:

- A TCIH MP is registered in a specific national registration for TCIH MPs for the indication studied. If there is a national registration for TCIH MPs for the indication studied, and if the selected TCIH MP in a study is already registered at national level, international recommendations can be used at national level by policymakers, doctors and patients.
- A TCIH MP is included in one or more national guidelines of the doctors' association(s) for the indication studied. If so, recommendations at international level can be used at national level by policymakers, doctors and patients.
- A TCIH MP which is not registered at national level and is not included in a national guideline of the doctors' associations, but based on long-term clinical expertise and in-vitro research on the mode of action, is likely to be effective for the indication studied. If so, given the urgent need to reduce inappropriate antibiotic use, TCIH MPs with sufficient evidence on safety (as assessed by a future GIFTS-AMR safety committee) could already be suggested by doctors and used by patients at national level, providing the uncertainties regarding the quality of evidence on safety and efficacy of TCIH MPs and the types of evidence are transparently communicated.

One or more of these arguments can be used to upgrade the level of recommendation in an EtR procedure (see also §5.3.1).

5.3.3 Knowledge sources and criteria which must be used to assess the safety of TCIH medicinal products

Safety data can be collected from the following knowledge sources: (1) the EMA database (if applicable), (2) (systematic) reviews of the MPs of the specific whole medical system overall, (3) from included (systematic) reviews of the selected MPs (if available), (4) pharmacopoeia (WHO, Kommission C, ESCOP, European Pharmacopoeia), (5) pharmacovigilance databases (VigiBase, EudraVigilance, Lareb, EvaMed), (6) literature databases (e.g. PubMed), and (7) national guidelines of doctors/ veterinarians associations (e.g. NHG, NICE, AWMF).

TCIH MPs are deemed to be safe when: (1) they have an EMA Traditional use or Well-established use status, and/or (2) they are registered in a national governmental institute in one of the countries or registered at international level (e.g. in the EU (according to EU Dir 2001/83)), and/or (3) they are included in one or more national guidelines of the doctors' association(s) for the indication studied, or (4) in case of no EMA status and no national or international (e.g. EU) registration, when there is a positive assessment of safety by the future GIFTS-AMR committee on safety.

5.4 Research priorities

- Develop an adapted Evidence-to-recommendation (EtR) system for TCIH MPs for infections using available evidence and additional arguments to weigh up the available information.
- Investigate the feasibility of using identified additional arguments in an existing EtR framework.
- Investigate the acceptability and the need for improvements of these EtR procedures for all TCIH modalities in all countries.

5.5 Prioritized research projects for the next 10 years

- Develop and investigate the feasibility and acceptability of an adapted EtR system for TCIH MPs for the treatment of acute, uncomplicated URTIs and recurrent UTIs in humans and for uncomplicated diarrhea and RTIs in animals in countries with great over-use of antimicrobials for these indications.

VI - Transition towards full integration of TCIH in medical systems

6.1 Background

In the WHO's Traditional Medicine Strategy 2014-2023, the WHO calls for more research into the effects and safety of TCIH. With this strategy, the WHO wants to contribute to Sustainable Development Goal 3 (Ferri and Sedehi, 2018): ensuring healthy living and well-being become accessible to everyone. The WHO sees a major role for TCIH in achieving this goal. To date, 170 of a total of 194 Member States have recognized the role of complementary care (WHO 2019). In 79 Member States there is a national program for TCIH, in 107 Member States there is a national official organization and in 75 Member States there is a national research institute for traditional and complementary care. The most frequently mentioned barriers to implementing TCIH by Member States are a lack of research data (99 Member States) and a lack of funding for research (86 Member States). But except for countries such as Switzerland, India, China, and Israel, full integration of complementary medicine and conventional medicine is still lacking.

A new WHO Traditional Medicine Strategy is currently under development and the First WHO Traditional Medicine Global Summit took place in August 2023, serving as a platform for all stakeholders, including traditional medicine workers, users and communities, national policymakers, international organizations, academics, the private sector and civil society organizations, sharing best practices and game-changing evidence, data and innovation on the contribution of TCIH to health and sustainable development.

Many surveys and other studies demonstrate that many people would like to be treated with TCIH. Surveys conducted among patients in university hospitals show that more than 50% of patients in oncology, gastroenterology and even cardiology departments are requesting TCIH treatment and wish to be better informed about it. A systematic review of qualitative studies has demonstrated that patients are open to TCIH treatment, but need trusted advice on safety and effectiveness of TCIH and antibiotics for specific acute RTIs (Willcox et al., 2020; Witteman et al., 2021).

However, there is a complex array of factors which influence the prescribing of TCIH treatments. Research should focus on the barriers and facilitators of transition processes towards full integration of TCIH in the medical systems. This knowledge can subsequently be used in research and advocacy strategies which promote the transition towards full integration of TCIH in the medical systems.

6.2 Main topics for the development of the research agenda

- Major barriers for stakeholders to recommend, prescribe and/or use TCIH medicinal products in clinical practices and in policy making.
- The necessary information, research projects and research-related activities to promote the transition towards towards full integration of TCIH in the medical systems (patients, doctors, pharmacists, policymakers).

- Implementation strategies which can enable these transitions.

6.3 The current situation

6.3.1 Major barriers for stakeholders to recommend, prescribe and/or use TCIH medicinal products in clinical practices and in policy making

Major barriers are image barriers, knowledge barriers, scientific barriers, regulatory barriers and communication barriers.

Image barriers are many conventional doctors and their respective societies' initial critical view on TCIH due to a lack of information, prejudice, and ignoring patient's preferences and TCIH practitioner's experience, although these are two of the three pillars of evidence-based medicine (Sackett et al., 1996). A second image barrier is the concerns about pharmaceutical quality, quality control and potential drug interactions. Knowledge barriers are (1) the insufficient knowledge of TCIH in general by patients, doctors, pharmacists, researchers, regulators, administrators and other stakeholders and (2) insufficient knowledge on safety and (cost-)effectiveness of TCIH. Scientific barriers are (1) the paucity of high-quality studies on safety and (cost-)effectiveness of non-individualized and individualized TCIH treatments (which preserve the integrity of individualized TCIH prescribing). In individualized TCIH medicinal products are selected for treatment based upon the most relevant symptoms and signs of the individual patient rather than common features of the pathological process as defined by diagnoses; (2) the low number of calls for grant proposals for scientific work in the field of TCIH or which accept proposals on TCIH; and (3) the insufficient number of research centres and expert networks providing expertise in TCIH. Regulatory barriers are the insufficient global regulatory classification of TCIH and TCIH practitioners and the insufficient regulation of TCIH practices and training. Communication barriers are a lack of communication between doctors and patients about the advantages and disadvantages of the use of TCIH (Van der Werf et al., 2018).

6.3.2 The necessary information, research projects and research-related activities to promote the transition towards full integration of TCIH in the medical systems (patients, doctors, pharmacists, policymakers)

Scientific information is needed on (1) the contributions of TCIH to the ongoing transition in medicine from a disease control to a health/resilience promotion approach in general and specifically for the prevention and treatment of infections; (2) safety, (cost-)effectiveness, mode of action of TCIH prevention and treatment for infections; and (3) availability and quality of TCIH strategies which enable patients to make well-informed decisions on the prevention and treatment of infections.

Research projects in human and veterinary TCIH which are needed are: (1) high-quality public health and clinical studies on TCIH prevention and treatment strategies, effects and safety, including context-based research (e.g. pragmatic RCTs), preserving the integrity of individualized TCIH prevention and treatment strategies as suggested for conventional medicine (Skivington et al., 2021), for the whole TCIH field (National Center for Complementary and Integrative Health, 2021) and for separate TCIH modalities (e.g. Gaertner et al., 2023; Kienle et al., 2019; Sun et al., 2021); (2) replication of high-quality studies in those countries where this is necessary for implementation in clinical guidelines; and (3) development of an overall evidence base of TCIH strategies, covering all academic fields (e.g. an easily accessible database).

Major facilitators and solutions are (1) to prioritize research on health/resilience promotion of TCIH treatment and prevention of infections, rather than on disease control only; (2) to emphasize understanding of the One Health concept and research considering the COHERE guideline; (3) to conduct RCTs and real-world evidence studies; (4) to provide context-based research and context-based guideline development considering quantitative and qualitative research, including "real-world evidence" studies; (5) to enable patients and professionals to find easily accessible, user-friendly, evidence-based information/advice on TCIH (eHealth, websites); (6) to expand the existing GIFTS-AMR network with TCIH and conventional researchers with different backgrounds and skills (veterinary/medical, human sciences, philosophical, historical, political, etc.) as well as professionals (doctors, veterinarians, pharmacists, biologists, physicists, chemists, pharmacologists, etc.) who are working towards a health-oriented healthcare system; and (7) to promote science-based education on TCIH prevention and treatment of infections.

Related actions needed concerning research and development are to increase efforts into evaluating non-antibiotic prevention and treatment strategies in clinical and pre-clinical studies of all evidence classes (SRs/MAs, RCTs, RWE studies, quantitative and qualitative research) as alternatives to the already existing and more conservative 'better antibiotics' projects.

6.3.3 Implementation strategies which can enable these transitions

Implementation strategies need to focus on changing the narrative for six different groups of people who need to be informed about the possibilities of, and need for, the introduction of TCIH: patients, pharmacists, doctors/veterinarians, students, researchers, and policymakers/health system managers. Provided information depends on the targeted audience: the specificity of information must comply with the audience and take cultural sensitivities into account.

Patients, as a group, have almost finished the transition towards full integration of TCIH in the medical systems. There is increasing popularity and prevalence of TCIH use among patients, and patients look for different treatment approaches which are more 'natural'. The narrative for this target population needs to consider cultural factors and must be local, direct, and practical. Messages must be positive, linking health and nature, including statements about affordability, recognizing that people are responsible for their health, and ensuring people feel they can participate with health matters.

Pharmacists can be in favor of TCIH because of patients' interests. They are healthcare professionals rating the quality of TCIH medicinal products, and they should meet the needs of their clients. They need high-quality information and training to actively, positively, and intelligently recommend high-quality TCIH MPs.

Some conventional doctors still mistrust TCIH and do not accept it, partly because they are not, or insufficiently, trained in the basics of TCIH. Shifting their focus from what causes illness to what makes patients healthy is expected to change this mentality. Keeping patients healthy is still too often associated with only offering chemical treatments. The introduction of TCIH into the curriculum will help change the way of thinking and working. Specific information should help doctors change their minds: the interest of patients, the interest of the research community, explanatory and pragmatic studies, clinical guidelines, the need for pluralism in medicine, statements by their organizations, quality assurance of training in TCIH like CEN standards, e.g. for homeopathy (CEN, 2016), the WHO benchmarks for TCIH such as the ones for traditional Chinese medicine, Ayurveda, naturopathy,

Anthroposophic medicine, osteopathy, acupuncture and others (World Health Organization, 2010a,b,c, 2020, 2022b, 2023b), specialist degrees recognized by medical/veterinary chambers like in Austria and Switzerland, and changes in the theory of medicine. Within this context, evidence-based education and postgraduate qualifications in TCIH are the strategic pathways forward.

Students are the future. They also need to be provided with support to make the transition from the Western medical model to TCIH. For this target population it is necessary for evidence-based TCIH to be integrated into universities' global medicine, veterinary medicine, and pharmacy curricula.

Researchers need to form collaborating teams of experts in TCIH research, and experts in conventional medicine research, in order to perform high-quality studies, including context-based, pragmatic research according to current scientific standards. They need to be encouraged to use existing research models and develop new models to provide valuable and valid research outcomes for TCIH research. Researchers must be aware of available funds, and positive results should make new funds available. TCIH research results must be widely disseminated (to each stakeholder population) and incorporated into clinical guidelines. Policy statements need to be introduced.

Policymakers require good expert opinions and scientific data to shift their positions from thinking about 'illness' policies (underscored by an industry of illness and therefore more illness- related) to health policies based on making people, animals, as well as the environment healthy. They must be informed that this is a people/patients demand and that this approach will benefit national health provisions.

6.4 Research priorities

- Investigate the conceptual differences between conventional medicine and TCIH which represent a barrier for acceptability and implementation of TCIH prevention and treatment of infections strategies.
- Investigate the safety, working mechanisms, and efficacy/ (cost-)effectiveness (RCTs, RWE studies, SRs (systematic reviews) and MAs (meta-analyses)) of non-individualized and individualized TCIH treatments (which preserve the integrity of individualized TCIH prescribing) for indications where antimicrobials are commonly over-used. Examples are:
    - Investigate the effectiveness of Traditional Chinese Medicine compared to standard conventional treatment and/or placebo, for the prevention of UTIs in patients with a history of recurrent urinary tract infections.
    - Investigate the effectiveness of homeopathy, compared to placebo for the prevention of ETEC-related post-weaning diarrhea in piglets at risk.
- Investigate types and working mechanisms of health promotion/resilience and antimicrobial effects of TCIH MPs.

6.5 Prioritized research projects for the next 10 years

- Build a combined expertise- and evidence-based theoretical model of TCIH treatment of acute, uncomplicated upper respiratory tract infections (URTIs) and recurrent urinary tract infections (UTIs) in humans and for uncomplicated gastrointestional tract infections (GTIs) and RTIs in animals to overcome the barrier for acceptability and implementation, while preserving the

integrity of TCIH prescribing of individualized and non-individualized TCIH treatments, and while considering research on health/resilience promotion (realist review of complex interventions).

- Investigate types and working mechanisms of health promotion/resilience and antimicrobial effects of 3-5 TCIH MPs with moderate to high-quality evidence of effectiveness in clinical trials for acute, uncomplicated URTIs and recurrent UTIs in humans and for uncomplicated GTIs and RTIs in animals.
- Investigate the (cost-)effectiveness of FeverApp/FeverFriend tools for fever management on symptom control and reduction of antimicrobials use in GP practices and hospital ER departments.
- Investigate the (cost-)effectiveness of the natural medicinal products app for URTI symptom control and reduction of antibiotics use in GP practices and hospital ER departments.

6.6 Suggested advocacy actions

Research & development

- Expand the role of 'patient choice' in future research, in guideline development, and in education (PPI, public and patient involvement) in those countries where this is not, or insufficiently, organized.
- Prioritize research on health/resilience promotion rather than disease control only.
- Promote publicly funded research on TCIH treatments, their efficacy/(cost-)effectiveness and safety, and their underlying mechanisms or modes of action.
- Develop information tools (eHealth, website) to provide easily accessible information on evidence.
- Promote guideline development considering both quantitative and qualitative research, including results of 'real-world evidence' studies.

Policy

- Emphasize understanding of the One Health concept and emphasize One Health research considering the COHERE guidelines.
- Promote One Health research and the collaboration between conventional medicine and TCIH in human, animal, and plant sectors at regional, national, and international levels in a timely manner, while preserving the integrity of prescribing individualized TCIH treatments, and while considering research on health/resilience promotion and disease-specific prevention rather than disease control only.
- Promote the regulation of TCIH training and practices, such as the European Committee for Standardisation (CEN) standard on Services of Medical Doctors with additional qualifications in Homeopathy and the WHO benchmarks for traditional Chinese medicine, Ayurveda, naturopathy, Anthroposophic medicine, osteopathy, acupuncture and others.

Healthcare systems

- Develop a general concept of global regulatory TCIH classification.

VII - Increasing the accessibility of TCIH medicinal products for infections (information)

7.1 Background

There is already a great deal of scientific information on TCIH and TCIH MPs. However, this information is often not of high quality and is not always easily accessible (language, format, technical issues) for stakeholders. Accessibility of TCIH MPs for infections (information) might be improved and supported by research and research-related advocacy activities. For example, recognizable global networks and/or societies, databases, eHealth information tools for clinical practices (patient-decision aids (e.g. FeverApp), decision-making tools), and evidence-based education modules may increase the accessibility of TCIH for infections.

7.2 Main topics for the development of the research agenda

- Major barriers for stakeholders to gain access to relevant TCIH MPs for infections information.
- Major facilitators and solutions to increase access to relevant TCIH MPs for infections information and the role of eHealth, websites, and science-based education in this.

7.3 The current situation

7.3.1 Major barriers for stakeholders to gain access to relevant TCIH MPs for infections information?

An initial major barrier is the conceptual differences between conventional medicine and TCIH. It appears that TCIH theories and rationales for prevention and treatment are often not easy to understand for stakeholders in conventional medicine, like the public, doctors and policymakers. Secondly, existing information is not always easily accessible (language issues, target population issues, format, etcetera) for the different groups of stakeholders.

7.3.2 Major facilitators and solutions to increase access to relevant TCIH MPs for infections information and the role of eHealth, websites and science-based education

Major facilitators and solutions are: research and research-related activities, for example, recognisable global networks and/or societies; databases like CAM on PubMed® and VHL by PAHO and CABSIN; eHealth information tools for clinical practices (patient-decision aids, e.g. FeverApp/ FeverFriend app, decision-making tools); evidence-based education of healthcare professionals (human and veterinary) - undergraduate and postgraduate (Vankova, 2023); and the inclusion of One Health and TCIH-related exposome (physical activity, body weight management, diet, sun exposure, stress, sleep and circadian rhythms, pollution, smoking, and gut microbiome) approaches

when developing relevant antimicrobial stewardship programs (ASPs).

7.4 Research priorities

- Investigate the conceptual differences between conventional medicine and TCIH which represent a barrier for acceptability and implementation of TCIH prevention and treatment of infections.
- Develop and evaluate information tools (websites, eHealth) to provide easily accessible and trustworthy advice for patients on TCIH strategies for self-management of common infections in which antimicrobials are commonly over-used, and trustworthy information for clinicians (including evidence of safety, (cost-)effectiveness, use in clinical practices); and, additionally, on benefits/risks ratios and benefits/costs ratios for research and policy-making.
- Implement TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs).

7.5 Prioritized research projects for the next 10 years

- Develop and evaluate the usability and acceptability of a TCIH MPs prototype app for URTIs for use in different countries (language and cultural adaptation).
- Develop the app further for recurrent UTIs in humans and diarrhea in animals.
- Implement and adapt (language and cultural) the FeverApp and FeverFriend app for humans with over-use of antimicrobials related to fever management, in countries other than Germany and The Netherlands.
- Develop and evaluate a FeverApp/FeverFriend app for use in veterinary medicine.
- Develop and evaluate the quality, usability and acceptability of a TCIH website with science-based information on TCIH strategies for the prevention and treatment of infections, for research, education and use in clinical practices.
- Investigate barriers and promoters of the implementation of TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs).
- Investigate implementation methods which will enable TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs).

7.6 Suggested advocacy actions

Research & development

- Develop a formal trustworthy global scientific 'committee/ working group', recognized by conventional and TCIH stakeholders, which provides valid information on TCIH research, education and information tools for the prevention and treatment of infections, and reduction of AMR. This committee/ working group should be responsible for the development of specific, high-quality databases on TCIH strategies and scientific evidence of TCIH research in this field to ensure patients, animal owners, farmers, healthcare professionals and other stakeholders

can access user-friendly evidence-based information/advice on TCIH.

- Develop and promote databases like CAM on PubMed® and VHL by PAHO and CABSIN among professionals and academic researchers.
- Develop and use standards for evidence-based education of healthcare professionals (human and veterinary) - undergraduate and postgraduate.

Healthcare systems

- Promote more evidence-based accessibility and TCIH MPs for infections (information). Qualitative outcomes should be shared with healthcare professionals, policymakers, stakeholders, and the public through appropriate tools.
- Promote inclusion of One Health and TCIH-related exposome (physical activity, body weight management, diet, sun exposure, stress, sleep and circadian rhythms, pollution, smoking, and gut microbiome) approaches when developing relevant antimicrobial stewardship programs (ASPs).

VIII – Overall research agenda, connections and related advocacy actions

The knowledge gaps identified in chapters II-VII and related suggested advocacy actions are summarized here and integrated as an overall research agenda and a list of suggested related advocacy actions. In addition, a description is provided regarding which two major, global antimicrobial resistance (AMR) research agenda items the GIFTS-AMR research agenda items are connected to.

8.1 Overall research agenda

Table 2. GIFTS-AMR research themes, research priorities, prioritized research projects for the next 10 years and contributions to two global AMR research agendas

Research themes	Research priorities	Prioritized research projects for the next 10 years	GIFTS-AMR contributions to the WHO global research agenda (2023)	GIFTS-AMR contributions to the UN/ WHO/ WOAH global research agenda (2023)
Patient preferences and stakeholders' needs for non-antibiotic prevention and treatment strategies for infections	1. Assess patients'/ animal owners'/farmers' preferences, use, satisfaction and acceptability of TCIH MPs in LMICs and developed countries.	• Map out the qualitative and quantitative studies on patients'/animal owners'/farmers' preferences, use, satisfaction and acceptability of TCIH MPs as alternatives to antimicrobials (scoping review).	New***	New***

Safety, (cost-)effectiveness, benefits/risks ratios and benefits/costs ratios of TCIH strategies in human and veterinary medicine	2. Investigate the safety, working mechanisms, and efficacy/(cost-)effectiveness of the most promising TCIH MPs for indications where antimicrobials are commonly over-used.	• Investigate the (cost-)effectiveness of the most promising TCIH MPs for acute, uncomplicated URTI and rUTI symptom control and reduction of antibiotics use in primary care and hospital ER departments. a. Investigate the effectiveness of Traditional Chinese Medicine compared to standard conventional treatment and/or placebo, for the prevention of UTIs in patients with a history of rUTIs. • Investigate the (cost-)effectiveness of FeverApp/FeverFriend tools for fever management on symptom control and reduction of antimicrobials use in GP practices and hospital ER departments. • Investigate the (cost-)effectiveness of the most promising TCIH MPs for uncomplicated diarrhea and RTIs in animals. a. Investigate the effectiveness of homeopathy, compared to placebo for the prevention of ETEC-related post-weaning diarrhea in piglets at risk. • Systematically review the safety and effectiveness of TCIH MPs for gastrointestinal infections in humans and RTIs and gastrointestinal infections in animals.	**Treatment and care – Antimicrobial stewardship** 11. Investigate antimicrobial stewardship interventions (such as implementing the WHO AWaRe antibiotic book,11 guidelines, clinical algorithms, education and training, audit and feedback), alone or in combination, which are context specific, feasible, sustainable, effective and cost-effective to avoid antimicrobial misuse in outpatient and inpatient settings, especially where diagnostic capacity may be limited. 12. Identify feasible, effective and scalable pharmacist antimicrobial medicines dispensing practices in community pharmacies and related regulatory frameworks (such as incentives and disincentives) to improve antimicrobial stewardship in the community, especially in low- and middle-income countries. 13. Investigate criteria and strategies to optimize empirical antimicrobial therapy (such as antimicrobial spectrum, dose, timing of initiation, de-escalation, and stopping), weighting the benefits (e.g. improve outcomes, reduce cost) versus potential harms (e.g. clinical failure, infection relapse, resistance emergence, adverse events), for main community and healthcare-associated infectious syndromes in adults and children, especially in settings where medicine availability, diagnostic capacity and access to healthcare services may be limited.	**Interventions - Evaluation** • What have been the most impactful interventions to prevent, control and mitigate AMR at the One Health interface?

	3. Investigate the feasibility and acceptability of integrating traditional and complementary approaches with conventional primary healthcare (for humans and animals), as a strategy to support delayed use of antibiotics.	• Investigate the feasibility and acceptability of promising TCIH MPs for acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals. • Assess the acceptability and effectiveness of updated guidelines on management of self-limiting infections, including recommendations to use TCIH to support delayed use of antibiotics.	New*** **Treatment and care – Antimicrobial stewardship (11-13)** 11. Investigate antimicrobial stewardship interventions (such as implementing the WHO AWaRe antibiotic book, guidelines, clinical algorithms, education and training, audit and feedback), alone or in combination, which are context specific, feasible, sustainable, effective and cost-effective to avoid antimicrobial misuse in outpatient and inpatient settings, especially where diagnostic capacity may be limited. 12. Identify feasible, effective and scalable pharmacist antimicrobial medicines dispensing practices in community pharmacies and related regulatory frameworks (such as incentives and disincentives) to improve antimicrobial stewardship in the community, especially in low- and middle-income countries. 13. Investigate criteria and strategies to optimize empirical antimicrobial therapy (such as antimicrobial spectrum, dose, timing of initiation, de-escalation, and stopping), weighting the benefits (e.g. improve outcomes, reduce cost) versus potential harms (e.g. clinical failure, infection relapse, resistance emergence, adverse events), for main community and healthcare-associated infectious syndromes in adults and children, especially in settings where medicine availability, diagnostic capacity and access to healthcare services may be limited.	New*** **Interventions – Evaluation** What have been the most impactful interventions to prevent, control and mitigate AMR at the One Health interface?

	• 4. Investigate the types and working mechanisms of health promotion/resilience and antimicrobial effects of TCIH MPs.	• Investigate the types and working mechanisms of health/resilience promotion and antimicrobial effects of 3-5 TCIH MPs with moderate to high-quality evidence of effectiveness in clinical trials for acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals.	New***	New***
	5. Investigate the benefits/risks ratios and the benefits/costs ratios of TCIH MPs vs antimicrobials, for humans, animals and the environment.	• Investigate the effectiveness and the reduction of adverse effects on animals and environments for TCIH MPs with moderate to high-quality evidence of effectiveness for acute, uncomplicated URTIs and rUTIs in humans and for the prevention of ETEC-related post-weaning diarrhea in piglets at risk.	**Prevention - Water, sanitation and hygiene (WASH)** 1. Investigate the impact, contribution, utility, effectiveness and cost–effectiveness of interventions to ensure safely managed water, sanitation and hygiene (including hand hygiene) and waste management practices in the community setting on reducing the burden and drivers of antimicrobial resistance, such as unnecessary antibiotic consumption for diarrheal diseases in low- and middle-income countries. 2. Investigate implementation strategies of WASH-related interventions in healthcare settings (including ensuring access to safely managed water and sanitation, safe hand hygiene, safe management of waste and environmental cleaning), and assess their impact, acceptability, equity and cost–effectiveness on the burden and transmission of resistant healthcare–associated infections and antimicrobial medicine prescribing across socioeconomic settings.	**Transmission - Dynamics and drivers** • To what extent are effluents and solid waste from pharmaceutical and other industrial production sites contributing to the circulation of AMR across One Health in different geographical settings? **Interventions - Framework conditions** • How can we improve early adaptation and innovation for the prevention, control and mitigation of AMR across human health, animal health, plant health and the environment in LMICs?

			Prevention – Infection prevention and control 3. Identify the most effective, cost–effective, acceptable and feasible multimodal infection and prevention control strategies (such as hand hygiene, contact precautions and patient isolation) and the relative effect of their components in reducing different types of healthcare–associated infections caused by multidrug-resistant pathogens across geographical and socioeconomic settings. **Treatment and care – Antimicrobial stewardship** 11. Investigate antimicrobial stewardship interventions (such as implementing the WHO AWaRe antibiotic book, guidelines, clinical algorithms, education and training, audit and feedback), alone or in combination, which are context specific, feasible, sustainable, effective and cost-effective to avoid antimicrobial misuse in outpatient and inpatient settings, especially where diagnostic capacity may be limited. 12. Identify feasible, effective and scalable pharmacist antimicrobial medicines dispensing practices in community pharmacies and related regulatory frameworks (such as incentives and disincentives) to improve antimicrobial stewardship in the community, especially in low- and middle-income countries. 13. Investigate criteria and strategies to optimize empirical antimicrobial therapy (such as antimicrobial spectrum, dose, timing of initiation, de-escalation, and stopping), weighting the benefits (e.g. improve outcomes, reduce cost) versus potential harms (e.g. clinical failure, infection relapse, resistance emergence, adverse events), for main community and healthcare-associated infectious syndromes in adults and children, especially in settings where medicine availability, diagnostic capacity and access to healthcare services may be limited.	

	6. Investigate the effects of whole system approaches (e.g. organic/ biodynamic agriculture and TCIH whole medical system prevention and treatment) on the sustainable reduction of antimicrobial use and consumption.	• Map out the qualitative and quantitative studies on the effects of whole medical systems and whole system approaches in (organic and biodynamic) farming on reduction of antimicrobial use and consumption (scoping review).	**Treatment and care – Antimicrobial use and consumption** 14. Determine optimal (feasible, accurate and cost-effective) methods and metrics to monitor antimicrobial use and consumption in the community and healthcare settings and appropriate targets to monitor progress in reducing inappropriate antimicrobial use and consumption. 15. Determine the levels, patterns, trends and drivers of appropriate and inappropriate prescribing, use and consumption of access, watch and reserve (AWaRe) antibiotics11 across countries and community and healthcare settings, with data disaggregated by sex, age, socioeconomic status and subpopulations, including those experiencing vulnerability and with comorbidities (such as people living with HIV, people with TB and people with malaria). 16. Investigate optimal approaches to effectively use facility- and/ or national-level antimicrobial consumption and antimicrobial resistance surveillance data to inform antimicrobial stewardship programs and treatment guidelines.	New***

	7. Develop and evaluate valid score systems which weigh up relevant factors to identify and prioritize the most promising TCIH MPs for urgent indications which can be tested in high-quality RCTs, and which are usable and acceptable for relevant stakeholders.	• Develop valid score systems which weigh up relevant factors to identify and prioritize the most promising TCIH MPs which can be tested in high-quality RCTs, for treatment of acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals in countries with great over-use of antimicrobials for these indications.	**Treatment and care – Antimicrobial medicine** 17. Investigate efficacious and safe antibiotic treatment regimens based on old and new agents and combinations for infections, especially for extended-spectrum beta-lactamase–producing and/or carbapenem-resistant Enterobacterales, with minimum selection and transmission risk for antimicrobial resistance, especially among children and other subpopulations experiencing vulnerability. 18. Investigate efficacious and safe antibiotic treatment regimens for infections by drug-resistant typhoid and non-typhoidal salmonellae (including for pathogens resistant to cephalosporins and fluoroquinolones) across socioeconomic settings. 19. Investigate efficacious and safe empirical antibiotic treatment (drug choice, drug combination, route, dose and duration) for gram-negative bacteria causing bloodstream infections or sepsis among neonates and young children, especially in settings with high antimicrobial resistance prevalence, limited diagnostic capacity, and antimicrobial medicine availability. 20. Investigate antifungal regimens optimized for efficacy, cost, safety and duration for the treatment of infections caused by WHO fungal priority pathogens with critical importance for antimicrobial resistance (such as Candida auris, Aspergillus fumigatus and Cryptococcus neoformans) in settings with increasing or high prevalence of antifungal resistance. 21. Investigate efficacious and safe regimens based on new or existing antimicrobial medicines for urogenital and extragenital sexually transmitted diseases (such as resistant Neisseria gonorrhoeae and resistant Mycoplasma genitalium) within the context of increasing antimicrobial resistance levels, including in populations experiencing vulnerability (such as people living with HIV, pregnant women and adolescents).	**Interventions - Methodology development** • Which priority tools and frameworks can assist tailoring of One Health interventions for national AMR action plans? • Which criteria should be used to assess interventions aimed at preventing and controlling AMR at the One Health interface?

Use of limited evidence and real-world evidence	8. Develop an adapted Evidence-to-recommendation (EtR) system for TCIH MPs for infections using available evidence and additional arguments to weigh up the available information.	• Develop and investigate the feasibility and acceptability of an adapted EtR system for TCIH MPs for the treatment of acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated diarrhea and RTIs in animals in countries with great over-use of antimicrobials for these indications.	New***	New***
	9. Investigate the feasibility of using identified additional arguments in an existing EtR framework.		New***	New***
	10. Investigate the acceptability and need for improvements of these EtR procedures for all TCIH modalities in all countries.		New***	New***
Implementation and information tools	11. Investigate the conceptual differences between conventional medicine and TCIH which represent a barrier for acceptability and implementation of TCIH prevention and treatment of infections strategies.	• Build a combined expertise- and evidence-based theoretical model of TCIH treatment of acute, uncomplicated URTIs and rUTIs in humans and for uncomplicated gastrointestional tract infections (GTIs) and RTIs in animals to overcome the barrier for acceptability and implementation while preserving the integrity of TCIH prescribing of individualized and non-individualized TCIH treatments, and while considering research on health/resilience promotion (realist review of complex interventions).	New***	New***

	12. Investigate the reasons for current guideline developers to decide on (non)inclusion of TCIH MPs in guidelines for the prevention and treatment of infections.	• Investigate the reasons for non-inclusion of TCIH MPs for infections in European countries for those TCIH MPs which already have an EMA status of Traditional use or Well-established use and/or are included in conventional guidelines (e.g. in the UK or Germany): • **EMA status** o *Ivy* for coughs and the common cold o *Pelargonium sidoides* for the common cold **German guidelines** o *Pelargonium sidoides* for coughs (DEGAM Leitlinie Nr 11), rhinosinusitis (S2k-Leitlinie) o *Thyme/Primrose* for coughs (DEGAM Leitlinie Nr 11) **UK guidelines** o *Pelargonium sidoides* for coughs (NICE Cough (acute) guideline)	**Cross-cutting– Antimicrobial resistance awareness and education** 28. Determine the most (cost-)effective behavioural change interventions to mitigate antimicrobial resistance emergence and spread by targeting and engaging the general public, young people, mass media, healthcare providers and policymakers across socioeconomic settings.	**Behavioural insights and change - Dynamics and drivers** • What role do people's attitudes and understanding of health and well-being (for humans, animals, plants and the environment) play in influencing their attitudes and behaviour with respect to AMU and AMR?

	13. Develop and evaluate information tools (websites, eHealth) to provide easily accessible and trustworthy advice for patients on TCIH strategies for self-management of common infections in which antimicrobials are commonly over-used, and trustworthy information for clinicians (including evidence of safety, (cost-) effectiveness, use in clinical practices); and, additionally, on benefits/risks ratios and benefits/costs ratios for research and policy-making.	• Develop and evaluate the usability and acceptability of a TCIH MPs prototype app for URTIs for use in different countries (language and cultural adaptation). • Develop the app further for rUTIs in humans and diarrhea in animals. • Implement and adapt (language and cultural) the FeverApp and FeverFriend app for humans with over-use of antimicrobials related to fever management, in countries other than Germany and The Netherlands. • Develop and evaluate a FeverApp/ FeverFriend app for use in veterinary medicine. • Develop and evaluate the quality, usability and acceptability of a TCIH website with science-based information on TCIH strategies for the prevention and treatment of infections, for research, education and use in clinical practices.	**Cross-cutting– Antimicrobial resistance awareness and education** 28. Determine the most (cost-)effective behavioural change interventions to mitigate antimicrobial resistance emergence and spread by targeting and engaging the general public, young people, mass media, healthcare providers and policymakers across socioeconomic settings.	**Interventions - Operational research** • How can One Health interventions which have proven impactful for AMR control and mitigation most effectively be translated and scaled up in different contexts or differently resourced settings? **Behavioural insights and change - Methodology development** • What is the role of communication strategies in promoting One Health AMR risk-reductive behaviours, and how can this role be leveraged?

	14. Implement TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs).	• Investigate barriers and promoters of the implementation of TCIH prevention and treatment strategies as part of a One Health approach in relevant antimicrobial stewardship programs (ASPs). • Investigate implementation methods which will enable TCIH prevention and treatment strategies as part of a One Health approach, including the collaboration between conventional medicine and TCIH in a timely manner, in relevant antimicrobial stewardship programs (ASPs).	**Cross-cutting– Policies and regulations related to antimicrobial resistance** 29. Evaluate the implementation of antimicrobial resistance–related policies and regulations at national level and their effectiveness in mitigating antimicrobial resistance and improving health outcomes in the community and healthcare settings across socioeconomic contexts. 30. Investigate strategies for the sustainable and (cost-)effective implementation of national policies, legislation and regulations (including sustainable financing and optimal governance structures) to improve infection prevention and patient care practices and the use of antimicrobial medicines in the community and healthcare settings, across socioeconomic contexts. 31. Identify the most (cost-)effective interventions to mitigate antimicrobial resistance in the human health sector, globally and within countries or regions, and determine the rationale, costs, benefits, feasibility, sustainability and potential returns on investment to achieve the greatest benefit. 32. Investigate strategies to integrate antimicrobial resistance interventions into broader health, health financing, development, welfare structures and national policies, and evaluate their impact on mitigating antimicrobial resistance, enhancing health system efficiency, reducing people's out-of-pocket expenses and improving equitable access to, and use of, diagnostics and antimicrobial medicines.	**Interventions - Methodology development** • Which mix of evidence and evaluation is needed to understand how to implement One Health AMR solutions most effectively in LMICs? • How could implementation research be systematically incorporated into the design of appropriate One Health interventions for AMR in LMICs? **Behavioural insights and change - Operational research** • How can information design sciences (presenting information in an accessible and understandable way) be leveraged to improve effective understanding of the information across different stakeholders in the One Health AMR field?

			33. Investigate how existing regulatory frameworks, marketing incentives (or their absence) and sustainable financing models affect the development and availability of new antimicrobial medicines and identify effective strategies to adapt these approaches to low-income settings to improve availability for adults and children.	

* The list refers to the broader research topics and the related research priorities (numbers) for AMR in the WHO agenda: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-npm/who-global-research-agenda-for-amr-in-human-health---policy-brief.pdf?sfvrsn=f86aa073_4&download=true

** The list refers to the priority research (sub)areas in the UN/WHO/WOAH agenda https://www.fao.org/3/cc6213en/cc6213en.pdf

*** This item is new to the content of the existing research agenda

8.2 Suggested advocacy actions related to the GIFTS-AMR research agenda

Several possible advocacy actions related to the GIFTS-AMR research agenda were identified during the GIFTS-AMR project and are hereby described across three themes, as suggestions for organizations involved with TCIH advocacy.

Research & development

- Continue and broaden the international research network, building on the existing GIFTS-AMR network, consisting of TCIH and conventional researchers with different backgrounds and skills (veterinary/medical, human sciences, philosophical, historical, political, etc.) as well as professionals (doctors, veterinarians, pharmacists, biologists, physicists, chemists, pharmacologists, etc.) who are working towards a health-oriented healthcare system.
- Develop a formal trustworthy global scientific 'committee/ working group', recognized by conventional and TCIH stakeholders, which provides valid information on TCIH research, education and information tools for the prevention and treatment of infections, and reduction of AMR. This committee/ working group should be responsible for the development of specific, high-quality databases on TCIH strategies and scientific evidence of TCIH research in this field to ensure patients, animal owners, farmers, healthcare professionals and other stakeholders can access user-friendly evidence-based information/advice on TCIH.
- Develop and promote databases like CAM on PubMed® and VHL by PAHO and CABSIN among professionals and academic researchers.
- Develop and use standards for evidence-based education of healthcare professionals (human and veterinary) - undergraduate and postgraduate.
- Consider a broad range of sources (e.g. context-based/ real-world evidence, users' preferences) in research and guideline development.
- Promote guideline development considering both quantitative and qualitative research, including results of 'real-world evidence' studies.
- Expand the role of 'patient choice' in future research, in guideline development, and in education (PPI, public and patient involvement) in those countries where this is not, or insufficiently, organized.
- Prioritize research on health/resilience promotion rather than disease control only.
- Develop information tools (eHealth, website) to provide easily accessible information on evidence.
- Promote One Health research and the collaboration between conventional medicine and TCIH in human, animal, and plant sectors at regional, national, and international levels in a timely manner, while preserving the integrity of prescribing individualized TCIH treatments, and while considering research on health/resilience promotion and disease-specific prevention rather than disease control only.
- Promote publicly funded research on TCIH treatments, their efficacy/(cost-)effectiveness and safety, and their underlying mechanisms or modes of action.

Policy

- Connect to (inter)national policymakers
  - to communicate the contributions of TCIH in general to many of societies' current questions and strategies regarding health needs.
  - to communicate the value propositions of resilience effects of TCIH MPs/methods/interventions.
  - to foster the One Health approach and the collaboration between conventional medicine and TCIH in human, animal, and plant sectors at regional, national, and international levels to effectively prevent AMR in an environmentally sustainable way, exchange effective techniques and use evidence to support TCIH, for individualized and non-individualized TCIH treatments, preserving the integrity of individualized TCIH prescribing while considering research on health/resilience promotion rather than disease control only.
  - to include TCIH strategies in (inter)national policies to prevent AMR and reduce antimicrobial use.
- Identify relevant developments in the research domain (TCIH and conventional medicine) which can support TCIH research in this field; and use this information to promote TCIH research in this field.
- Emphasize understanding of the One Health concept and emphasize One Health research considering the COHERE guidelines.
- Promote the regulation of TCIH training and practices, such as the European Committee for Standardisation (CEN) standard on Services of Medical Doctors with additional qualifications in Homeopathy and the WHO benchmarks for traditional Chinese medicine, Ayurveda, naturopathy, Anthroposophic medicine, osteopathy, acupuncture and others.

Healthcare systems

- Develop a general concept of global regulatory classification of TCIH strategies.
- Connect to national guidelines organisations to include evidence-based TCIH strategies in (inter)national policies (national public health strategies and National Action Plans (NAPs)), guidelines and patient education to prevent AMR and reduce antimicrobial use.
- Improve and communicate the regulation of TCIH training and practices, such as the European Committee for Standardisation (CEN) standard on Services of Medical Doctors with additional qualifications in Homeopathy and the WHO benchmarks for TCIH, such as the one for traditional Chinese medicine, Ayurveda, osteopathy, naturopathy, Anthroposophic medicine, acupuncture and others.
- Promote inclusion of One Health and TCIH-related exposome (physical activity, body weight management, diet, sun exposure, stress, sleep and circadian rhythms, pollution, smoking, and gut microbiome) approaches when developing relevant antimicrobial stewardship programs (ASPs).
- Promote more evidence-based accessibility and TCIH MPs for infections (information). Qualitative outcomes should be shared with healthcare professionals, policymakers, stakeholders, and the public through appropriate tools.

8.3 Connection to other global AMR agendas

In 2023, two major global research agendas were published. The first one, "A One Health priority research agenda for antimicrobial resistance (2023). Research agenda by Food and Agriculture Organisation of the United Nations, United Nations environment programme, World Health Organization and World Organisation for Animal Health" states: *"The global threat of AMR spreading among humans, animals, plants and the environment necessitates a "One Health" approach in our evermore connected world. One Health acknowledges the connected and interdependent nature of the health of humans, domesticated and wild animals, plants and the wider environment. Research strategies, interventions and policies based on One Health principles are emerging, but require more evidence to understand what works, in which contexts and for whom."*

The second one, "Global research agenda for antimicrobial resistance in human health (2023) of the WHO states: *"The goal of this research agenda is to identify and give priority to the research topics with the greatest impact on mitigating antimicrobial resistance in the human health sector, in accordance with objective 2 of the Global Action Plan (i.e. on strengthening the knowledge and evidence base through surveillance and research). The research agenda also aims to foster research by 2030 – in accordance with the Sustainable Development Goals timeline – and to catalyse scientific interest and investment among the scientific community and funders on the epidemiology and burden of resistant infections, strategies to prevent infections and the emergence of resistance, how to optimise and best deliver these in low- and middle income countries, and optimised diagnostics and antimicrobial medicines. The current list of priority research topics should be further translated into tangible, concrete research proposals fundable by donors and also implementable in settings with limited resources."*

The GIFTS-AMR research agenda contributes to 10 of the 17 UN/WHO/WOAH research areas and four of the five WHO themes; but not to Integrated surveillance. The GIFTS-AMR research agenda contributes to eight of the 13 WHO research areas and four of the five WHO themes; but not to Immunisation (Prevention), Diagnosis and Drug-resistant TBC. In addition, the GIFTS-AMR research agenda adds two research themes (*Patient preferences and stakeholders' needs for non-antibiotic prevention and treatment strategies for infections* and *Use of limited and real-world evidence*) and two research priorities to both global AMR research agendas (*Investigate the types and working mechanisms of health promotion/resilience effects of TCIH MPs* and *Investigate the conceptual differences between conventional medicine and TCIH which represent a barrier for acceptability and implementation of TCIH prevention and treatment of infections*) (see also Tables 1 and 2).

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