University of Southampton

FACULTY OF MEDICINE

Primary Care, Population Sciences & Medical Education

Andrographis paniculata leaf extract as a symptomatic intervention for acute respiratory tract infections

by

Martin Logue

ORCHID ID: https://orcid.org/0000-0002-7393-0618

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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Acute respiratory tract infections (ARTIs) which include colds, coughs, and sore throats are common in primary care and there are few viable treatments available. Antibiotics are frequently used to treat ARTIs in primary care, however, these medicines are not suitable as most ARTIs are viral and overreliance on these medicines may lead to antimicrobial resistance (AMR). Herbal medicines have been used for centuries to treat respiratory conditions and a herbal medicine called *Andrographis paniculata* has previously shown potential in the treatment of ARTIs. This PhD aimed to examine the role that *Andrographis paniculata* may have in the management of ARTIs and the reduction of AMR.

The first phase of this thesis was a systematic review and meta-analysis which included 33 clinical trials and 7175 participants. The results showed that Andrographis was beneficial and safe for relieving ARTI symptoms and reducing time to symptom resolution however the methodological quality of the reviewed trials was limited. The second phase included a qualitative interview study exploring health professionals' attitudes and beliefs around the use of herbal medicines in the symptomatic treatment of ARTIs. There was cautious acceptance of herbal medicines but most participants were concerned about the safety and evidence around herbal medicines. Questions were asked about health professionals'

experience around clinical trials of herbal medicines and this information was used to inform the design of a subsequent feasibility study. The third phase of this thesis involved a double-blind randomised placebo-controlled feasibility study evaluating the effect of *Andrographis paniculata* in the treatment of adults with ARTIs. The results of the feasibility showed that it was possible to recruit and retain participants to a herbal medicine and that *Andrographis paniculata* may have potential to reduce the number of antibiotics prescribed.

My findings indicate that *Andrographis paniculata* may be a useful herbal medicine in the treatment of ARTIs although more research is required. Data from the feasibility study can be used in the design and implementation of a larger full-scale trial. This PhD thesis adds new knowledge on the use of *Andrographis paniculata* as a potentially useful herbal medicine for the treatment of ARTIs. Firstly, it includes a comprehensive systematic review on *Andrographis paniculata* which identified articles from both English and Chinese language databases. Secondly, It is the first qualitative study within UK primary care that has examined health care providers' views on herbal medicines for ARTIs. Finally, the data from the double-blind randomised controlled feasibility study in the UK on *Andrographis paniculata* can be used to guide the design and implementation of future larger full-scale trials.

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Research Thesis: Declaration of Authorship

Title of thesis: *Andrographis paniculata* leaf extract as a symptomatic intervention for acute respiratory tract infections

I, Martin Logue, declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:-

   Hu X-Y, Wu R-H, Logue M, Blondel C, Lai, LYW, Stuart B, et al. (2017) *Andrographis paniculata (Chuān Xīn Lian) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis*. PLoS ONE 12(8): e0181780.

Signature : Date:

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Definitions and Abbreviations

AR	An adverse reaction is an unwanted or harmful reaction that occurs after administration of a drug or drugs.	Adverse Reaction
AE	An adverse event is any untoward event that occurs during a drug or medical treatment whether or not a causal relationship with the treatment is suspected or proven.	Adverse Event
AMR	This term refers to infectious microbes that have acquired the ability to survive exposures to clinically relevant concentrations of antimicrobial drugs that would kill otherwise sensitive organisms of the same strain.	Antimicrobial Resistance
AP	A herbal medicine used to treat respiratory tract infections in Western, Chinese, and Ayurvedic herbal medicine.	*Andrographis Paniculata*
ARTI	An ARTI is an illness caused by an acute infection, which involves the upper respiratory tract, including the nose, sinuses, pharynx, or larynx. This commonly includes cough, nasal obstruction, sore throat, and the common cold.	Acute Respiratory Tract Infection
CRF	A case report form is a paper or electronic questionnaire specifically used in clinical trial research to collect information from participants.	Case Report Form
CRP	C-reactive protein is a substance produced by the liver in response to	C-Reactive Protein

	inflammation. A high level in the blood may indicate a wide variety of conditions, from infection to cancer.	
CHM	Chinese herbal medicine is one of the complementary set of practices that together make up the system of Traditional Chinese Medicine. Herbal medicines are usually prescribed in complex formulas that are carefully matched to a specific pattern of ill health that underlies the condition being treated.	Chinese Herbal Medicine
CTIMP	A CTIMP is a clinical trial/study that is evaluating the safety or efficacy of a drug Investigational Medicinal Product or obtaining any other information about the drug e.g. how it is absorbed, distributed, metabolised or excreted.	Clinical Trial of an Investigational Medicinal Product
DNA	DNA is the hereditary material in humans and almost all other organisms including bacteria and viruses.	Deoxyribonucleic Acid
EMEA	The EMEA is a European agency for the evaluation of medicinal products.	European Medicines Agency
GCP	GCP is an international quality standard for conducting clinical trials that in some countries is provided by an international body that defines a set of standards, which governments can then convert into regulations for clinical trials involving human subjects.	Good Clinical Practice

NHS	The National Health Service is the publicly funded healthcare system in the UK	National Health Service
NICE	The National Institute for Health and Care Excellence provides national guidance and advice to improve health and social care in the UK.	National Institute of Clinical Excellence
PHE	Public Health England is an executive agency of the Department of Health and Social Care in the United Kingdom government to provide the NHS, government, industry, and public with evidence-based professional, scientific expertise and support.	Public Health England
REC	RECs are independent bodies that review research proposals and give an opinion about whether research is ethical. They also look at issues such as participant involvement in the research.	Research Ethics Committee
RCT	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment, or other intervention.	Randomised Clinical Trial
ROB	The extent to which the design and conduct of a study are likely to have prevented bias or the extent to which the results of a study are correct.	Risk of Bias

SAE	An SAE in human drug trials is defined as any untoward medical occurrence that at any dose might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions, or might result in, or prolong, hospitalisation or morbidity.	Severe Adverse Event
SARS	SARS is an infectious disease with symptoms including fever and cough and in some cases progressing to pneumonia and respiratory failure.	Severe Acute Respiratory Symptoms
TGA	The TGA is Australia's therapeutic goods regulatory authority for prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products.	Therapeutic Goods Administration
TCM	TCM is a traditional medicine system that includes herbal medicine, acupuncture, cupping, qi gong, and dietary therapy.	Traditional Chinese Medicine
WHO	The World Health Organization is a specialised agency of the United Nations responsible for international public health.	World Health Organisation

Chapter 1: Introduction

This thesis examines the role of *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae)*(A.paniculata)* leaf as a symptomatic intervention for acute respiratory tract infections (ARTIs). Acute respiratory tract infections (ARTIs) such as colds, cough, sore throat are common, distressing, and costly both for individuals and the NHS. There is significant pressure to prescribe antibiotics (which have side effects) for ARTIs even though most are viral. This thesis explores the evidence for using *A. paniculata* in the treatment of ARTIs and its potential role in reducing antibiotic prescribing. It includes a systematic review of *A. paniculata* for symptomatic relief of ARTIs (Chapter 5). A qualitative study examining health professionals' views on herbal medicines in primary care is presented (Chapter 7). It also describes the development and implementation of a double-blind, randomised, placebo-controlled clinical trial to test the feasibility of rigorously investigating *A. paniculata* within primary care (Chapter 8).

1.1 Research Rationale

Currently, around 60% of antibiotics prescribed in primary care are for respiratory tract infections (ARTIs) (Gulliford *et al.*, 2014a). ARTIs, including common colds, sore throats, cough, acute bronchitis, otitis media, and sinusitis, are often self-limiting and usually improve without specific treatment. Antibiotics are currently prescribed to treat these conditions due to the difficulty in ascertaining whether these conditions are caused by a bacterial or viral infection, or due to concern by health professionals of missing conditions such as pneumonia and meningitis (Ventola, 2015).

Studies have suggested that antibiotic treatment of ARTIs offers negligible benefit for most patients and is often associated with side effects. NICE (National Institute

for Health and Care Excellence) Guidelines in the United Kingdom recommend that either a 'no antibiotic' prescribing strategy or a 'delayed antibiotic' prescribing strategy should be agreed for most patients with ARTIs (NICE, 2008). However, around 36% of common colds continue to be treated with antibiotics, as do 40% of episodes of sore throat, 70% of otitis media, and 90% of sinusitis (Gulliford *et al.*, 2016).

At present, there is a global issue around the use of conventional antimicrobial medicines to treat infections. There is growing concern that the widespread and sometimes unnecessary use of antibiotics is leading to the development of antimicrobial drug resistance (AMR), and potentially to infections caused by resistant organisms that are difficult to treat (Prestinaci, Pezzotti, and Pantosti, 2015). Many microorganisms, such as bacteria are becoming resistant to the most commonly used antibiotics. Indeed, in some countries, bacteria are showing resistance to the strongest antibiotics available. Resistance to Colistin, one of the antibiotics of last resort has been shown in China where the drug has been used in farm animals.

According to the O 'Neill report (2014), the effects of AMR will lead to massive human and economic cost. Currently 700,000 people die each year from resistant infections, and this will rise to 10 million people if trends continue and there will be a 2-3.5% reduction in world GDP which is equivalent to 100 trillion USD of economic output. The review on antimicrobial resistance suggested investigating alternative therapies, including herbal medicines, to disrupt the rise in AMR (O'Neill, 2014).

Herbal medicines have been used for centuries to treat infections. A recent WHO report on traditional medicines noted that the majority of the world's population depends on traditional medicines for primary healthcare including the treatment of infections (WHO, 2011). Plant secondary metabolites have already demonstrated their potential as antimicrobials when used alone or synergistically, or as

potentiators of other antimicrobial medicines (Abreu, McBain and Simões, 2012). The use of these metabolites and herbal medicines as resistance-modifying agents (RMAs) represents an increasingly active research area (Abreu *et al.*, 2017). Phytomedicines frequently act through different mechanisms than conventional antibiotics and could, therefore be of use in the treatment of resistant bacteria. The therapeutic utility of these products, however, requires further research (Gibbons, 2005). One active area of clinical research is the use of potential herbal medicines for the treatment of respiratory tract infections. Phytomedicines refer to herbal medicines that have scientific research on their therapeutic use. According to the WHO traditional medicine refers to the knowledge, skills, and practices based on theories, beliefs, and experiences indigenous to different cultures used In the maintenance of health as well as prevention, diagnosis, Improvement, or treatment of physical and mental Illness. This involves the use of herbal medicines, minerals, and animal products (Che *et al.*, 2017).

A. paniculata is a herbal medicine used widely to treat respiratory and gastrointestinal infections in Asian and more recently Western herbal medicine. Much of the research on the plant has centred around the activity of the diterpene lactones present in the leaf called the andrographolides (Sheeja, Guruvayoorappan, and Kuttan, 2007). Recent systematic reviews have suggested that *A. paniculata* may be a valid treatment for respiratory tract symptoms and may be a useful alternative or co-medication (N. Poolsup *et al.*, 2004). Due to the evidence base for *A. paniculata,* Pukka herbs (Bristol) decided to support the investigation of this herbal medicine further and fund this PhD.

1.2 Reasons for conducting this PhD

I have worked as an acupuncturist and medical herbalist over the last 20 years. During this time, I have also taught acupuncture and herbal medicine at University.

One of the biggest issues I have encountered within the field of herbal medicine in the UK is the lack of good quality research.

My interest in the use of herbal medicines for respiratory tract infections was stimulated whilst I was on placement in China in 2003. My first rotation was in the Respiratory Department of Xiyuan Hospital in Beijing in the winter season. Over the first week, hundreds of patients visited the department with respiratory disorders and were given herbal medicine prescriptions (There was an outbreak of SARS during the same period). One of the most frequently prescribed herbs was *Andrographis paniculata* (Chuān Xīn Lián). During the course of the next 2 weeks, I observed the doctors in the respiratory department and asked them about the effectiveness of herbal medicines for acute respiratory tract infections. They mentioned that *Andrographis paniculata* was one of the most effective herbs in this area.

Figure 1. Xiyuan Hospital, Beijing, China

When I returned to the UK, I began to research the use of herbal medicines for respiratory tract infections in the Western, Chinese, and Ayurvedic traditions and

noticed that *Andrographis paniculata* featured strongly in all 3 traditions for acute infections of the respiratory and gastrointestinal tracts and there was scientific evidence to support these uses. I was fortunate in 2015 when Pukka Herbs in tandem with the University of Southampton advertised a PhD studentship involving the evaluation of *Andrographis paniculata* for the symptomatic intervention for acute respiratory tract infections. Thankfully, I was offered the position (following interview) which gave me the chance to add to the research base in this area of herbal medicine.

This PhD was sponsored by Pukka herbs and this may be seen as a conflict of interest considering it examined the role of herbal medicines in the treatment of ARTIs. Pukka herbs did not influence the writing or research carried out in this thesis. The work in this thesis was overseen by my supervisors who had no connection with Pukka. As a medical herbalist, I have tried to remain in equipoise throughout the process and reflect on any bias I may have brought to the process through discussion with my supervisors.

1.3 Aims

The overall aim of this PhD was to examine the role of *A. paniculata* leaf extract as a symptomatic intervention for acute respiratory tract infections. This included conducting a systematic review of *A. paniculata*; exploring health professional attitudes and beliefs on the use of herbal medicine in ARTIs through a qualitative study, and investigating the feasibility of carrying out a randomised trial of *A. paniculata*.

1.4 Objectives

The objectives of this thesis were:

- To provide an overview of the existing literature on antimicrobial resistance with a special focus on acute respiratory tract infections in primary care
- To review the current literature on the pharmacology and phytochemistry of *A. paniculata* and its potential (biological plausibility) as a treatment of respiratory tract infections in primary care
- To conduct a systematic review and meta-analysis of clinical trials using *A. paniculata* (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children
- To explore the attitudes and beliefs of primary care health professionals around the use of herbal medicines in the symptomatic treatment of acute respiratory tract infections through a qualitative interview study
- To assess the possibility of evaluating the benefit of *A. paniculata* as a treatment of adults with acute respiratory tract infections through carrying out a double-blind randomised controlled feasibility trial.

1.5 Structure of the thesis

This thesis comprises of nine chapters:

Chapter 1 provides an introduction to my PhD

Chapter 2 provides an overview of AMR in primary care with a special emphasis on the history and use of antibiotics. I explore the use of antibiotics in primary care, how they work, categories, and mechanisms of resistance. I also examine the role that herbal medicines can play in AMR and the treatment of infections.

Chapter 3 looks at acute respiratory tract infections (ARTIs) in primary care. I examine the public and health professional understanding of antibiotic use in ARTIs, consider the strategies to reduce antibiotic prescribing, and look at the clinical use of herbal medicines to treat ARTIs.

Chapter 4 reviews the phytochemical and pharmacological actions of *A. paniculata* whilst also reviewing its potential within the field of antimicrobial resistance.

Chapter 5 is a systematic review and meta-analysis of Chinese and English research on the use of *A. paniculata* for the symptomatic relief of acute respiratory tract infections (ARTIs). It reviews the evidence relating to the safety, effectiveness, and clinical efficacy of *A. paniculata.*

Chapter 6 discusses the mixed methods approach in this thesis. It examines qualitative research in healthcare. I present my philosophical worldview and talk about the pragmatic approach I have followed. The subsequent sections look at semi-structured and telephone interviews and discuss sampling, saturation data collection, analysis, and rigour within qualitative research.

Chapter 7 describes the methods and preliminary findings of a qualitative interview study, exploring the attitudes and beliefs of health professionals around the use of herbal medicines in the symptomatic treatment of acute respiratory tract infections (ARTIs) in primary care. The information gathered in this study aided in the design of the subsequent feasibility study and provided insights into health professionals' attitudes into herbal-based treatments for ARTIs.

Chapter 8 details the final study design, feasibility outcome measurements, and results of a double-blind randomised placebo-controlled feasibility study evaluating the effect of *Andrographis paniculata* leaf in the treatment of adults with acute respiratory tract infections (the GRAPHALO study).

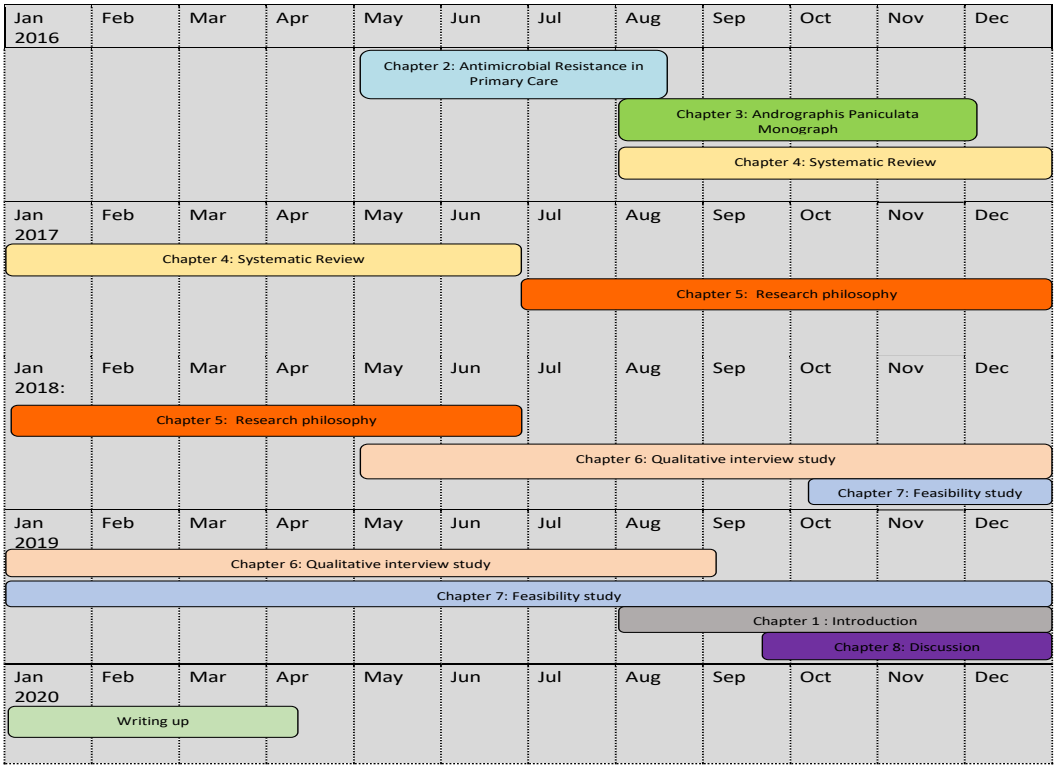
Chapter 9 presents an overview of my PhD journey including the research carried out. The key findings are discussed in relation to current literature and thinking.

The strengths and limitations of my research are highlighted, and I examine the theory and methodology used in this thesis. I finally talk about future directions for my research and areas for further investigation.

1.6 Thesis Timeline

The research in this thesis was conducted and written up between April 2016 and April 2020. The chart below illustrates the work undertaken during this time.

Figure 2. PhD Timeline



Chapter 2: Antimicrobial Resistance (AMR)

2.1 Introduction

Antimicrobial resistance (AMR) is currently one of the biggest public healthcare issues in the world, a situation where microbes that cause infections no longer respond to current usual treatment (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). This results in the associated infection leading to prolonged and possibly more serious illness increased healthcare costs, and the potential risk of death especially in those with immunocompromised conditions (Haque *et al.*, 2018).

Antimicrobial medicines are an integral part of modern healthcare and underpin a wide variety of medical treatments such as cancer treatments, surgery, and organ transplantation. Resistance has the potential to undermine modern healthcare systems (Jasovský *et al.*, 2016).

At the start of the 20th century, there were major advancements in antimicrobial drug discovery and infection control, especially in the field of bacterial infection when Penicillin (one of the first widely used/produced antibiotics) was discovered by Alexander Fleming in 1928. However, this advantage was short-lived when it was discovered almost as soon as antibiotics were used, bacteria responded by developing resistance to these treatments. A situation that Fleming warned about in his Nobel prize speech in 1945. Fleming suggested:

> "*It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body*".

The success of antibiotics might only have been short-lived and it is now expected to be a long-term and perhaps never-ending challenge to find new approaches to combat antibiotic resistance. Antibiotics are becoming an "endangered species" due to the global emergence of AMR (Davies and Davies, 2010a). AMR has become a priority for governments and agencies such as the WHO Global Action plan and the UN around the world (O'Neill, 2014)(World Health Organization., 2012). This scenario is compounded by the lack of discovery and development of new antimicrobial medicines.

According to Huttner et al, bacteria have globalised the planet along with their hosts, while at the same time antibiotic consumption by both humans and animals has increased. The antibiotic gene pool for resistance has never been so accessible, nor its selection pressure so strong (Huttner *et al.*, 2013). These micro-organisms are capable of withstanding continued antibiotic exposure and demonstrate the ability to generate some formidable examples of rapid evolutionary antibiotic-resistant "superbugs."(Davies and Davies, 2010b).

From 2000 to 2010, worldwide human use of antibiotics increased by 36%; the rapidly emerging economies of Brazil, Russia, India, China, and South Africa accounted for three-quarters of this increase (Van Boeckel *et al.*, 2015). Twenty-three percent of this increase was seen in India where antibiotics are available over the counter; hospital use of antibiotics in China accounted for 10.6% of this figure (Zaidi *et al.*, 2011).

One of the main objectives of this PhD was to provide an overview of antimicrobial resistance. Therefore, in this chapter, I looked into the history of antimicrobials and considered their mechanism of action and also examine the topic of resistance. I examined the potential of some herbal medicines in the treatment of antimicrobial infections and explored their role as part of an antimicrobial sparing strategy. Table 1 contains commonly terms used in this chapter/thesis.

Table 1. Commonly used terms in this chapter ('WHO | Antimicrobial resistance', 2018)

Term	Definition
Antimicrobial	In this thesis, the term "antimicrobial" is used to refer to any agent (including an antibiotic) used to kill or inhibit the growth of microorganisms (bacteria, viruses, fungi, or parasites).
Antimicrobial Resistance (AMR)	This refers to infectious microbes that have acquired the ability to survive exposures to clinically relevant concentrations of antimicrobial drugs that would kill otherwise sensitive organisms of the same strain.
Microbiome	The microbiome is the genetic material of all the microbes - bacteria, fungi, protozoa, and viruses - that live on and inside the human body.
Pathogen	An organism capable of causing disease.
Superbug	Bacteria with resistance to several commonly used antibiotics.
Antimicrobial stewardship	Coordinated interventions designed to promote, improve, monitor, and evaluate the judicious use of antimicrobials to preserve their future effectiveness.

2.2 History of Antimicrobials

One of the earliest traces of antimicrobial use leads back to the ancient Sudanese Nubia (350- 1040 CE) who had traces of tetracycline found in their human skeletal remains (Nelson *et al.*, 2010). Tetracycline is an antibiotic used to treat a wide array of illnesses including bacterial infections of the skin, digestive respiratory, and urinary tract. Researchers believe that ancient Nubians were brewing tetracycline-containing grains/plants/herbs into their diets over a long period of time because the compound was found embedded deep in their bones. Interestingly, the population's documented infectious diseases seem to be quite low (Aminov, 2010).

Ancient traditional herbal medicines were used as antimicrobial treatments for a wide array of illnesses. The best-known example is probably Sweet wormwood, *Artemisia annua L. (Qing Hao)* from which the potent antimalarial compound qinghaosu (artemisinin), was extracted in the 1970s. Youyou Tu was awarded the Nobel prize in 2015 for this discovery (Cui and Su, 2009). She was inspired by a Chinese herbalist called Ge Hong (CE 283-343) from the Jin Dynasty who recommended the herb for fever and suggested using cold water extraction. Tu had been previously using hot water extraction techniques before this discovery. She found the cold water extraction technique was better for extracting artemisinin.

At the State Institute for Experimental Therapy in Frankfurt, Paul Ehrlich (1854-1915), a Prussian biochemist, initiated a search for a chemical 'magic bullet' to treat infectious diseases: a chemical that would selectively kill an infectious microbe but not harm the human patient. Ehrlich's idea of a "magic bullet" that selectively targets only disease-causing microbes and not the host was based on an observation that certain synthetic dyes had an affinity for certain types of cell, which could be used to stain specific microbes but not others (Strebhardt and Ullrich, 2008).

Ehrlich was involved in the creation of the first antibiotic called Salvarsan in 1908. Salvarsan was used in the treatment of syphilis but was difficult to administer and had severe side effects (Wright, Seiple and Myers, 2014). Another important step forward in antimicrobial infection therapy began with the discovery of Penicillin by Alexander Fleming in 1928, showing that microbes themselves could produce antibacterial substances, so-called antibiotics. The development of Penicillin for medical use, and its successful application during the Second World War, led to a great interest in searching for other antibiotics, and these findings set up paradigms for future drug discovery research in infectious disease. This resulted in several new antibiotics (Neu and Gootz, 1996).

The 1950's became known as the "golden age" of antibiotic discovery when about half of the antibiotics known today were discovered. Use of the whole-cell antibacterial activity screening platform developed by Waksman focused at a wide variety of fungi and bacteria, led to progress in drug development involved generating synthetic or semisynthetic derivatives of natural antibiotics, with better pharmacokinetic and pharmacodynamics properties, and improved range of activity (Wright, Seiple and Myers, 2014). No new classes of antibiotics were discovered after the 1970's therefore, with the decline of the discovery rate, the mainstream approach for the development of new drugs to combat emerging and re-emerging resistance of microbes to antibiotics has been the modification of existing antibiotics (Wright, 2007). The next section will examine how antibiotics work.

2.3 How do antibiotics work?

Most antibiotic medicines used for the treatment of bacterial infections may be categorised according to their principal mechanism of action. Table 2 below shows types of antibiotics, their mode of action, and features. The following sections looks at categories of resistance and examines the mechanisms that bacteria use to develop resistance to antibiotics.

Table 2. Classes of antibiotics, modes of action, and features.

Antibiotic class	Examples	Mode of action	Features	Reference
β-lactams	penicillins, cephalosporins, carbapenems	Inhibit cell wall biosynthesis	Most widely antibiotics used in NHS	(McManus, 1997)
Glycopeptides	Vancomycin, teicoplanin	Inhibit cell wall biosynthesis	Common "drugs of last resort"	(McManus, 1997)
Aminoglycosides	Streptomycin, neomycin	Inhibits bacteria protein synthesis leading to cell death	Family of over 20 antibiotics	CC, (Drlica and Zhao, 1997)
Chloramphenicol	Chloramphenicol	Inhibits synthesis of proteins preventing growth	Commonly used in low income countries.	CC
Oxazolidinones	Lizezolid,posizolid	Inhibits synthesis of proteins preventing growth	Potent antibiotics commonly	CC

			used “drugs of last resort”	
Fluoroquinolones	Ciprofloxacin, levofloxacin	Interferes with bacterial DNA replication and transcription	Resistance evolves rapidly	CC, (Drlica and Zhao, 1997)
Sulphonamides	Prontosil, sulphonamide	Prevents bacterial growth and multiplication	First commercial antibiotics	CC
Tetracyclines	Tetracycline, doxycycline	Inhibits synthesis of proteins preventing growth	Becoming less popular due to resistance	CC
Macrolides	Erythromycin, clairithromycin	Inhibits synthesis of proteins preventing growth	Second most prescribed antibiotic in the NHS	CC
Ansamycins	Geldanamycin, rifamycin	Inhibit the synthesis of RNA by bacteria leading to cell death	Also has antiviral activity	CC
Streptogramins	Pristnamycin IIA, Pristnamycin IA	Inhibits bacteria protein synthesis leading to cell death	Two groups of antibiotics that act synergistically	CC
Lipopeptides	Daptomycin, surfactin	Disrupts multiple cell membrane	Instances of resistance rare	CC

		functions leading to cell death		

2.4 Categories of Resistance

As mentioned previously resistance occurs when bacteria no longer respond to current usual treatment such as antibiotics. In order to establish resistance, for each bacterium, a panel of antibiotics will be tested to which the bacteria can be susceptible to all, some, or none of the tested drugs. The results are used to guide the treating physician in the choice of antibiotic therapy. A physician may carry out these tests if a patient complains of a responsive or persistent infection such as a recurring sore throat that does not respond to treatment. The term "Susceptible" suggests that the patient is likely to respond well to therapy with this antibiotic, "Intermediate" means that the efficacy is uncertain but that it might work under certain circumstances (e.g. with higher dosing, specific infection sites, or mild disease) and "Resistant" that it is not likely that patient's infection will be cured with this antibiotic (Rodloff *et al.*, 2008).

The Gram stain system provides an important classification system for bacteria structure. Gram-positive bacteria possess a thick (20–80 nm) cell wall as an outer shell of the cell. In contrast, Gram-negative bacteria have a relatively thin (<10 nm) layer of cell wall, but harbour an additional outer membrane with several pores and appendices. These differences in the cell envelope offer different properties to the cell, in particular responses to external stresses, including heat, UV radiation, and antibiotics (Mai-Prochnow *et al.*, 2016).

Many definitions are being used to characterise patterns of resistance in Gram-positive and Gram-negative micro-organisms. Commonly used terms are multidrug-resistant (MDR), extreme drug-resistant (XDR), and pan drug-resistant (PDR):

- MDR – MDR or multidrug resistance means 'resistant to more than one antimicrobial agent'. Many definitions are being used to characterise patterns of multidrug resistance in Gram-positive and Gram-negative organisms. One of

the methods used by various authors and authorities to characterise organisms as MDR is based on *in vitro* antimicrobial susceptibility test results when they test 'resistant to multiple antimicrobial agents, classes or subclasses of antimicrobial agents'. The definition most frequently used for Gram-positive and Gram-negative bacteria is 'resistant to three or more antimicrobial classes' (Falagas, Koletsi, and Bliziotis, 2006). Another method used to characterise bacteria as MDR is when they are 'resistant to one key antimicrobial agent'. These bacterial isolates may have public health importance due to resistance to only one key antimicrobial agent, but they often demonstrate cross or co-resistance to multiple classes of antimicrobials, which makes them MDR (Cleland *et al.*, 2014) (Magiorakos *et al.*, 2012).

- XDR - In the medical literature, XDR has been used as an acronym for several different terms such as 'extreme drug resistance', 'extensive drug resistance', 'extremely drug-resistant' and 'extensively drug-resistant' (Hidron *et al.*, 2008) Initially, the term XDR was created to describe extensively drug-resistant *Mycobacterium tuberculosis* (XDR MTB) and was defined as 'resistance to the first-line agents Isoniazid and Rifampicin, to a fluoroquinolone and to at least one of the three-second-line parenteral drugs (i.e. amikacin, kanamycin or capreomycin)'(Centers for Disease Control and Prevention (CDC), 2006). Subsequently, definitions for strains of non-mycobacterial bacteria that were XDR were constructed according to the principle underlying this definition for XDR MTB (i.e. describing a resistance profile that compromised most standard antimicrobial regimens). Two sets of criteria have mainly been used to characterise bacteria as XDR. The first is based on the number of antimicrobials or classes or subclasses to which a bacterium is resistant, and the second on whether they are 'resistant to one or more key antimicrobial agents'(Cohen *et al.*, 2008).

- PDR – PDR originates from the Greek 'pan', meaning 'all'. Pandrug resistant (PDR) means 'resistant to all antimicrobial agents'. Within the research literature, definitions for PDR vary even though this term is etymologically exact and means that, for a particular species and a bacterial isolate of this species to be characterised as PDR, it must be tested and found to be resistant to all approved and useful agents. Current definitions include: 'resistant to almost all commercially available antimicrobials', 'resistant to all antimicrobials routinely tested' and 'resistant to all antibiotic classes available for empirical treatment', making the definition of PDR subject to inconsistent use and liable to potential misinterpretation of data (Hsueh *et al.*, 2002)(Magiorakos *et al.*, 2012).

2.5 Mechanisms of resistance

As well as being able to categorise resistance, it is important to understand the mechanisms behind AMR to allow insights on how to develop new treatments. Bacteria may manifest resistance to antibacterial drugs through different mechanisms. Two main types of resistance are innate and acquired. Innate resistance occurs when certain species of bacteria are innately resistant to ≥1 class of antimicrobial agents. In such cases, all strains of that bacterial species are likewise resistant to all the members of those antibacterial classes (Tenover *et al.*, 2006).

Acquired resistance is of greater concern, where initially susceptible populations of bacteria become resistant to an antibacterial agent and multiply and spread under the selective pressure of use of that drug. Several mechanisms of antimicrobial resistance are readily spread to a variety of bacterial genera. Common mechanisms are described below (see Figure 3):

- First, bacteria may acquire/activate efflux pumps that expel the antibacterial agent from the cell before it can reach its target site and exert its effect. Efflux pumps allow bacteria to regulate their internal environment by removing toxic substances, including antibiotics, and placing them in the external environment
- Second and third, bacteria may acquire antibiotic modifying and degrading enzymes, that destroy or disable the antibacterial agent before it can have an effect.
- Finally, a common strategy for bacteria to develop antimicrobial resistance is to avoid the effect of the antibiotic by interfering with their target site. To achieve this, bacteria have evolved different strategies, including protection of the target (avoiding the antibiotic to reach its binding site) and modifications of the target site that result in decreased affinity for the antibiotic molecule (Munita and Arias, 2016).

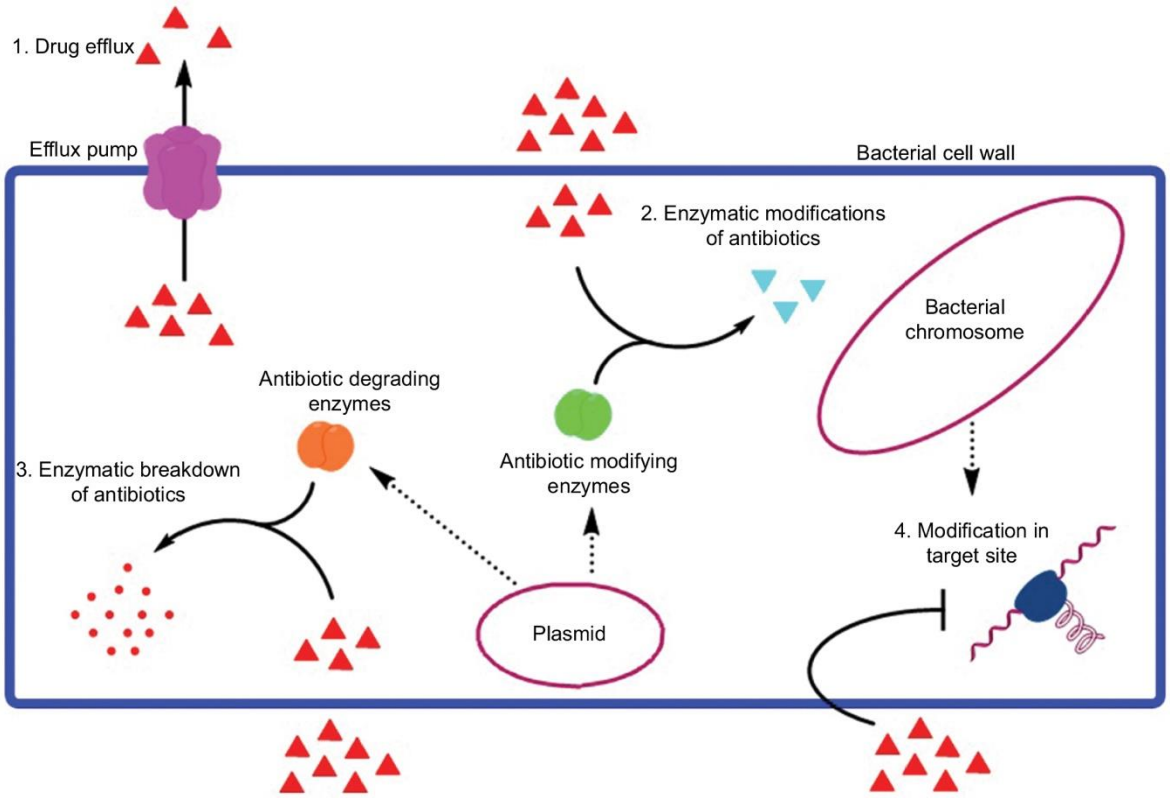


Figure 3. Mechanisms of bacterial resistance (Aslam *et al.*, 2018)

Acquired resistance that develops due to chromosomal transformation and selection is termed *vertical evolution*. Bacteria also develop resistance through the acquirement of new genetic material from other resistant organisms. This is termed *horizontal evolution*, which sometimes occurs between strains of the same species or between different bacterial species or genera. Mechanisms of genetic exchange involve conjugation, transduction, and transformation (see Figure 4). For each of these processes, transposons (A DNA sequence) may facilitate the transfer and incorporation of the acquired resistance genes into the host's genome or plasmids (Holmes *et al.*, 2015). These mechanisms are described more in-depth below:

A. During conjugation, a gram-negative bacterium transfers plasmid-containing resistance genes to a nearby bacterium, often via an elongated proteinaceous structure termed a *pilus*, which joins the 2 organisms. Conjugation among gram-positive bacteria is usually initiated by the production of sex pheromones by the mating pair, which facilitates the clumping of donor and recipient organisms, allowing the exchange of DNA (Grohmann, Muth and Espinosa, 2003).
B. During transduction, resistance genes are transferred from one bacterium to another via bacteriophages.
C. Finally, transformation, i.e., the process whereby bacteria acquire and incorporate DNA segments from other bacteria that have released their DNA complement into the environment after cell lysis, can move resistance genes into previously susceptible strains (Grohmann, Muth and Espinosa, 2003).

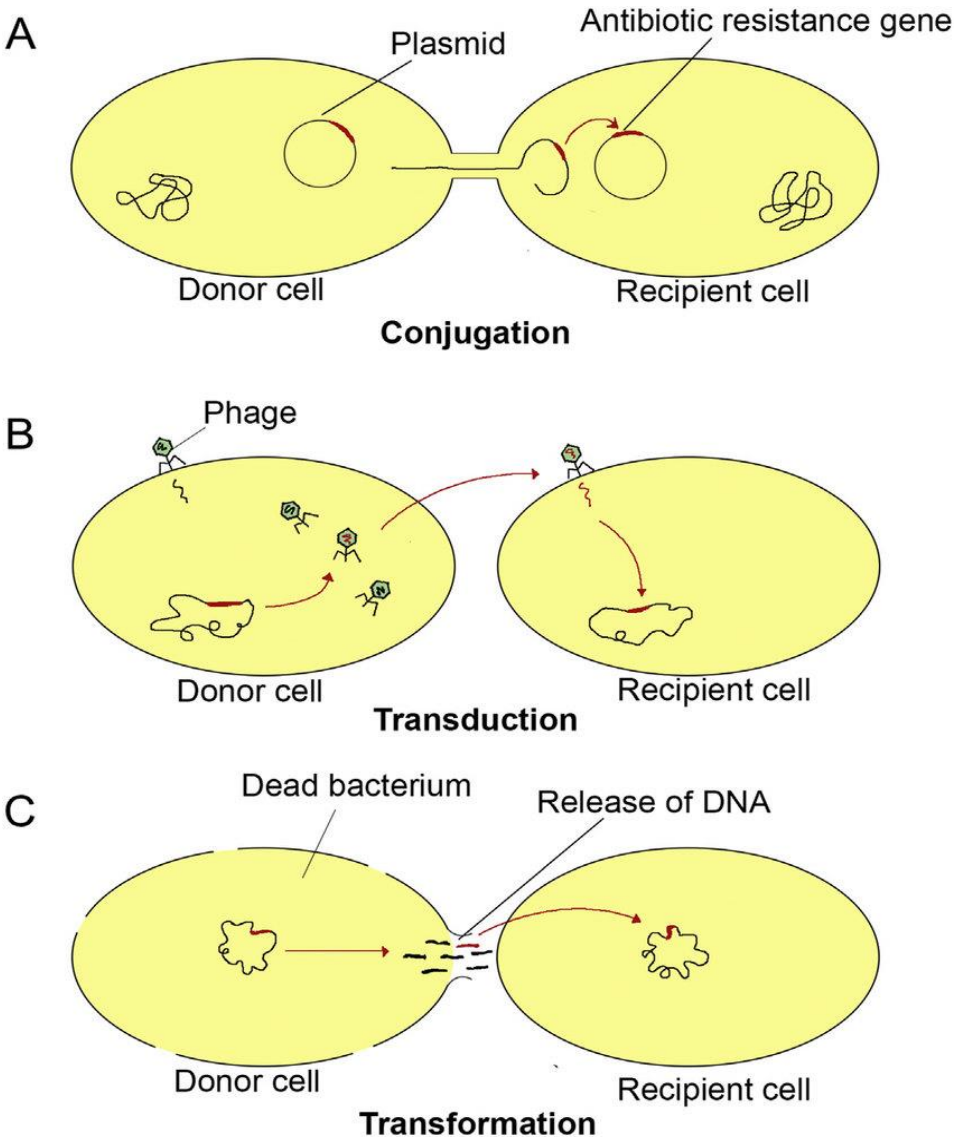


Figure 4. Conjugation, Transduction, and Transformation (Pang *et al.*, 2019)

Mutation and selection, together with the mechanisms of genetic exchange, enable many bacterial species to adapt quickly to the introduction of antibacterial medicines into their environment. Although a single mutation in a key bacterial gene may only slightly reduce the susceptibility of the host bacteria to that antibacterial agent, it may be just enough to allow its initial survival until it acquires additional mutations or additional genetic information resulting in full-fledged resistance to the antibacterial agent. However, in rare cases, a single mutation may

be sufficient to allow high-level, clinically significant resistance upon an organism (e.g., high-level Rifampin resistance in *Staphylococcus aureus* or high-level fluoroquinolone resistance in *Campylobacter jejuni*) (Davies and Davies, 2010b).

Before bacteria develop resistance, they have another way in which to survive antimicrobial treatment; bacteria can survive by entering into a slow or non-multiplying state (Coates *et al.*, 2002). It is thought that about 60% of all clinical infections contain bacteria in this state (Coates, Halls and Hu, 2011). Commensal bacteria, those which naturally live on the skin, in the mouth, nose, and intestines contain large numbers of antibiotic-resistant organisms, and these may be a source of antibiotic-resistance markers for pathogenic bacteria (Gillings *et al.*, 2008).

Andersson points out that antibiotic resistance should not be considered, (particularly in gram-negatives), to be specific to a small number of superbugs. Rather, it is part of a much larger picture, namely the whole of the bacterial kingdom that seems to operate cooperatively, horizontally transferring antibiotic resistance containing DNA between different species (Andersson, 2006). Also, resistant bacteria can survive and persist for a long period of time, even though no antibiotic selective pressure is present (Coates, Halls and Hu, 2011)

A study by Lee et al on novel antibiotic resistance mechanisms in *Escherichia coli* (E coli) suggested the "kin selection" theory, as resistance seems to operate at the population/eco-system level. They suggest that bacterial "charity work" leads to population-wide resistance. Their theory of microbial population dynamics mentions that a small number of antibiotic-resistant bacteria protect the antibiotic sensitive cells, thus ensuring the survival of the whole population under the antibiotic assault (H. H. Lee et al., 2010). Additionally, in complex biofilm, (microbial communities) the protection against antibiotics is offered to all community members, regardless of the kinship, which requires a communication network operating at a system level (H. H. Lee *et al.*, 2010).

From the above text, it appears that bacteria have evolved to survive in hostile environments and have developed the ability to communicate and coordinate collective action to enhance their survival. Perhaps it would be a better strategy to develop a philosophy of living with these complex organisms rather than try and eliminate them. In the next section, I will look at the current state of resistance and predicted outcomes if the situation does not change.

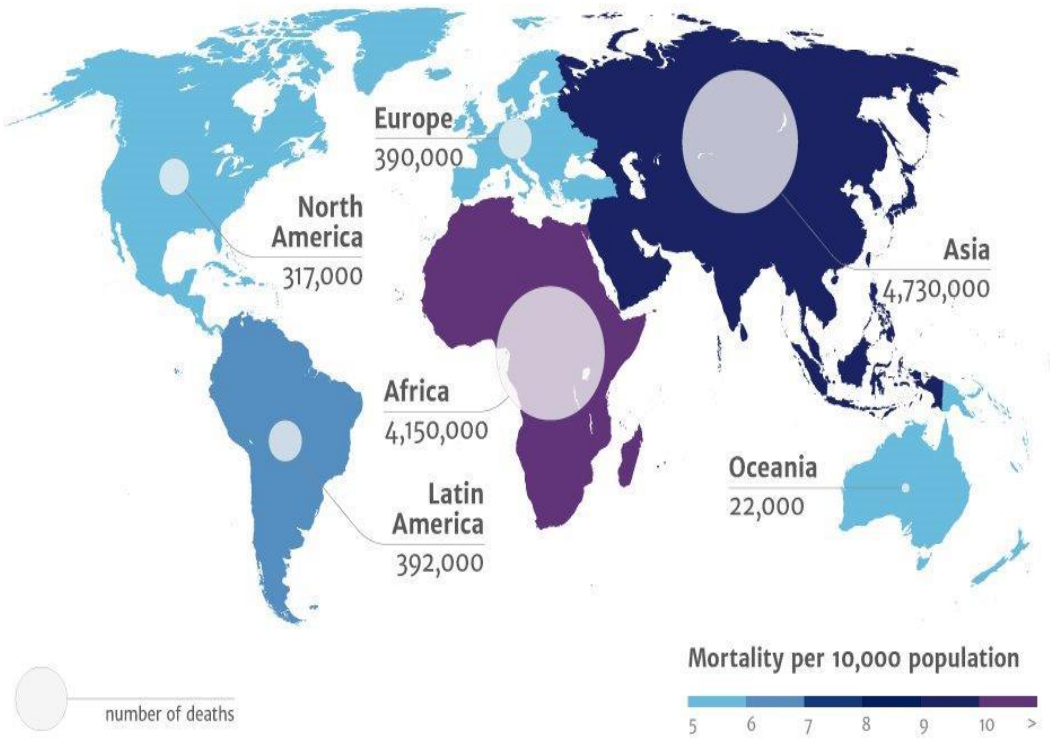
2.6 The current state of resistance and the future

A recent report from Public Health England (PHE) mentioned that although antibiotic consumption is falling, there has been an increase in antibiotic-resistant infections. According to the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report, there was an increase from 55,812 resistant infections in 2017 to 60,788 in 2018, an increase of 9%. Increased resistance was seen in *Escherichia coli* (A common urinary tract infection) to ciprofloxacin and third-generation cephalosporins and with *Klebsiella pneumoniae* (A common intestinal infection) to cephalosporin and quinoline antibiotics. The ESPAUR also found an increase in the detection of the most dangerous antibiotic-resistant pathogens, carbapenemase-producing Enterobacteriaceae (CPE), which rose from 72 isolates in 2009 to 4,028 in 2018. An analysis of 202 CPE infections identified between 2015 and 2019 found a 30-day mortality rate of 23.8%(ESPAUR 2018-19).

Globally, resistance in *Klebsiella pneumoniae* to the last resort treatment (carbapenem antibiotics) has spread to all areas of the world ('WHO | Antimicrobial resistance', 2018). In some countries, because of resistance, carbapenem antibiotics do not work in more than half of people treated for *K. pneumoniae* infections (Peleg and Hooper, 2010).

Resistance in *E. coli* is extensive. Fluoroquinolone antibiotics are one of the most widely used medicines for the treatment of urinary tract infections. Treatment is now ineffective in more than 50% of patients in many parts of the world (Shaikh *et al.*, 2015). Treatment failure to third-generation cephalosporin antibiotics (the last resort of medicine) for gonorrhoea has been confirmed in at least 10 countries (Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden and the United Kingdom of Great Britain and Northern Ireland) ('WHO | Antimicrobial resistance', 2016). *Staphylococcus aureus* resistance is widespread. People infected with MRSA (methicillin-resistant *Staphylococcus aureus*) are estimated to be 64% more likely to die than people with a non-resistant form of the infection. Colistin is the last resort treatment for life-threatening infections caused by Enterobacteriaceae, which are resistant to carbapenems. Resistance to Colistin has recently been detected in several countries and regions, making infections caused by such bacteria untreatable (Ventola, 2015).

Figure 6. Predicted mortality rates from AMR by 2050 (O'Neill, 2014)



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Research commissioned by the UK government has predicted that mortality rates for AMR could reach 150 million people by 2050, with the highest deaths reported in Asia and Africa unless the situation changes (see Figure 6)

To deal with this predicted rise in mortality there is a need for investigation into alternative approaches to dealing with AMR. One area which has promising research potential are herbal medicines. This will be discussed in the next section.

2.7 The role of herbal medicines in antimicrobial resistance

Many of today's most successful modern medicines derive from herbal medicines including aspirin from meadowsweet (*Filipendula ulmaria*) and metformin from goats rue (*Galega Officinalis*). Herbalists in the UK still use meadowsweet and goats rue but use the whole plant rather than a single compound extracted from the herb. Within the UK, there are 3 main traditions of herbal medicine; Western herbal medicine, Chinese herbal medicine, and Ayurvedic herbal medicine (Wachtel-Galor and Benzie, 2011).

Western herbal medicine has its roots in British, European, and North American traditions. Well known herbs in the Western herbal medicine are Echinacea (*Echinacea angustifolia*) and St John's Wort (*Hypericum perforatum*). Both these herbal medicines have antimicrobial effects (Avato *et al.*, 2004)(Hudson, 2012). Western herbalists use a person centred approach where the patient rather than the disease is the focus of the practitioner's attention. Herbalists commonly prescribe tinctures, teas, capsules, and tablets in combinations to address the underlying imbalance within the individual being treated (Bone and Mills, 2013).

Chinese herbal medicine (CHM) has been developed over thousands of years and is used widely throughout the world. The concepts and language in CHM are not based on modern scientific methods. CHM is widely practiced within the tradition of traditional Chinese medicine (TCM) which includes acupuncture, massage, and dietary therapy. TCM has its own diagnostic and treatment system distinct from conventional biomedicine. Terms such as qi, yin, yang, excess, deficiency, and stagnation are used to describe an imbalance (disease/illness) within an organ system in the body. This imbalance needs to be corrected by using a herbal formula to restore harmony within the body. Herbal medicines are chosen according to their "temperature", flavour and direction of movement as well as their actions and indications. The herbs are commonly dispensed as loose herbs (which are decocted in hot water), granules or tablets/capsules (Kaptchuk 2008).

Ayurvedic herbal medicine is part of a system of healthcare that originated in India several thousand years ago called Ayurveda. Ayurveda means the "science of life" which focuses on the principle of health preservation as well as the treatment of disease. Ayurveda pays particular emphasis on a person's constitution which may make them susceptible to certain diseases and influences the choice of herbal medicines used in treatment. Ayurvedic practitioners commonly prescribe herbal powders, capsules, and oils as part of treatment (Lad, Curry , Luna and O' Connor, 2001).

The use of polyherbal formulations to treat each patient is common in many of the traditional systems of herbal medicine. Research has suggested that herbal medicines work through synergy where the combined power of a group of constituents or herbal combinations when working together is greater than the total power achieved by each working separately (Wagner and Ulrich-Merzenich, 2009). This mechanism has been demonstrated in pharmacological research

(Systems biology) (Yang *et al.*, 2014). Synergy occurs at both a pharmacodynamic level (what the drug does to the body) and pharmacokinetic (what the body does to the drug) level (Gertsch, 2011)(Yang *et al.*, 2014). Many herbal medicines used in the treatment of microbial infection seek to strengthen the host's immune response (by stimulating macrophage and phagocytic activity by herbal medicines such as *Echinacea spp*) whilst also treating the infection. (Bone and Mills, 2013)(Manayi, Vazirian and Saeidnia, 2015)(Brush *et al.*, 2006)

Recent research has also suggested that combining herbal medicines and antibiotics may provide solutions to resistance in some cases. Researchers found that antibiotics combined with a Chinese herbal formula were more effective than antibiotics alone in treating drug-resistant enterobacteria (Cai *et al.*, 2017). Berberine, a compound found in many medicinal plants (e.g., *Berberis vulgaris, Coptis chinensis and Phellodendron amurens*) together with antibiotics such as levofloxacin and azithromycin (which had recently been proved ineffective against MRSA), resulted in the reactivation of the efficacy of the antibiotic drugs (Zuo et al. 2012). Synergistic effects between silibinin extracted from *Silybum marianum* and antibiotics have also shown potential to inhibit MRSA (Kang et al. 2011). *Nigella sativa* and omeprazole compared favourably to triple therapy in eradication of Helicobacter pylori in 88 patients with dyspepsia and a positive H. pylori test (Salem et al. 2010). (Further recent research on promising herbal medicines in the area of AMR are included in Table 3 below).

A common question posed by some authors is whether microbes can develop resistance to herbal medicine? (Gupta and Birdi, 2017)(Vadhana, Singh and Bharadwaj, 2015). There is a lack of research in this area, but it is worth investigating. Some authors have suggested microbes can develop resistance to herbal medicines however on examination most of the research is performed on a

constituent of the plant such as the essential oil rather than the whole plant (Vadhana, Singh, and Bharadwaj, 2015).

Simon Gibbons, Professor of Phytochemistry at the University of East Anglia suggested that it is very difficult for microbes to develop resistance to herbal medicines because of the number of constituents in a herbal medicine or herbal formula. He also suggested that herbal medicines usually affect their action through multiple compounds working together to achieve their goal also known as the entourage effect. This combination of compounds produces a stronger influence than any individual one. This is referred to as a synergistic or polyvalent effect (Personal communication 2020). The entourage effect was previously demonstrated in research on the endogenous cannabinoid system (McPartland *et al.*, 2017)(Russo, 2011).

The situation with the compound artemisinin (from *Artemisia annua*) used against the malaria parasite has illustrated the danger of using single compounds in the fight against microbes. Artemisinin resistance is now widespread in Asia (Rasoanaivo *et al.*, 2011). A potential way forward is to use whole plant formulations with conventional antimicrobial medicines to manage AMR.

Table 3. Commonly used herbal medicines with antimicrobial potential

Herbal medicine	Constituents	Mode of action	Microbe	Reference
Artemisia annua	Whole-plant extracts	anti-plasmodial activity 6 to 18-fold greater than artemisinin in an animal model	*P. falciparum**	(Rasoanaivo *et al.*, 2011)
Berberis fremontii Silybum marianum	Berberine synergistically with flavonolignan 5'-methoxyhydnocarpin-D and silybin	Antibacterial action	*S. aureus**	(Frank R. Stermitz *et al.*, 2000).
Rosmarinus officinalis	carnosic acid and carnosol	Potentiators of tetracycline and erythromycin causing an 8-fold reduction in MIC against *S. aureus* strains	*S. aureus**	(Oluwatuyi, Kaatz and Gibbons, 2004)
Thymus vulgaris	Baicalein	Possessing a strong synergistic activity when used in conjunction with tetracycline or the β-lactam antibiotics oxacillin,	MRSA*	(Fujita *et al.*, 2005)

		cefmetazole and ampicillin against		
Commiphora molmol, *Centella asiatica*, *Daucus carota*, *Citrus aurantium,* and *Glycyrrhiza glabra*	Whole-plant extracts	These extracts are of interest as they act on an efflux transporter that is difficult to inhibit due to the greater resistance afforded to the Gram-negative cells due to their structure.	*S. enterica**	(Stavri, Piddock and Gibbons, 2007).
1.Plasmodium falciparum, 2.Staphylococcus aureas, 3.Methicillin-resistant Staphylococcus aureus, 4.Salmonelle enterica,				

2.8 Conclusion

Although the majority of infections were initially successfully controlled with conventional antimicrobial medicines; the use of many of these medicines is no longer viable and new modalities/strategies are required to allow successful treatment of infections.

As outlined in the text above, plant extracts have great potential as antimicrobial compounds against microorganisms especially to address the therapeutic vacuum in managing symptoms or act as antimicrobial medicines themselves. They can be used in the treatment of infectious diseases caused by resistant microbes. The synergistic effect from the association of antibiotics with plant extracts against

resistant bacteria leads to new choices for the treatment of infectious diseases. This effect enables the use of the respective antibiotic when it is no longer effective by itself during therapeutic treatment (Nascimento *et al.*, 2000).

The increase in the prevalence of multiple drug resistance has slowed down the generation of new single compound antimicrobial drugs and has necessitated the search for new antimicrobials from alternative sources. Herbal medicines showing antimicrobial activities have the potential of filling this requirement either used singly or in combination with current conventional antimicrobials. However, this approach is unlikely until more research into herbal medicines in this area is conducted.

In this chapter, I have looked at the topic of antimicrobial resistance especially concerning antibiotics as they are the most widely prescribed/used antimicrobials. The potential of herbal medicines in the future management of AMR has been discussed. The next chapter will focus on acute respiratory infections in primary care, where the majority of antibiotics are prescribed in the UK.

Chapter 3: Acute respiratory tract infections (ARTIs) in primary care

3.1 Introduction

In the UK, around half of the antibiotics by weight consumed (491 tonnes) are for human use, and 80% of these are prescribed in primary care. These medicines are mainly (about 60%) used in acute respiratory tract infections (ARTIs)(One Health HM government, 2019). According to NICE, more than 50% of the general population will experience ARTI symptoms during a 6-month period and one-fifth of them will consult a GP (NICE, 2008).

ARTIs, including common colds, sore throat, cough, acute bronchitis, otitis media, and sinusitis are often self-limiting and are frequently caused by viruses and usually improve without specific treatment. Although criteria such as Centor and FeverPAIN can be used in the identification of bacterial infections, it is sometimes difficult to differentiate viral from bacterial cases in primary care and diagnostic uncertainty often facilitates overprescribing (NICE 2018). However point-of-care diagnostics such as C –reactive protein and procalcitonin platforms are currently being investigated and may become more widely used in primary healthcare (Lubell *et al.*, 2015). The development of rapid point-of-care diagnostic tests is a novel avenue that may assist in curbing the increasing problems created by AMR (Cooke *et al.*, 2015).

In this chapter, I will look at antibiotic use for ARTIs in primary care mainly in the UK (but with some mention of international studies), examine the public and health professionals' understanding of antibiotics and antibiotic use in ARTIs, and consider the strategies/interventions to reduce antibiotic prescribing. I will also look at the use of herbal medicines for ARTIs.

3.2 Antibiotic use for ARTIs in primary care

In primary care, there is a big variation between countries in antibiotic consumption rates. The average consumption of antibiotics for systemic use in the European Union was 18.4 defined daily dose (DDD) per 1000 inhabitants per day (country range: 8.9–32.4) (ECDC, 2018). The defined daily dose (DDD) is a statistical measure of drug consumption, defined by the World Health Organization (WHO). It is used to standardise the comparison of drug usage between different drugs or between different health care environments (ESPAUR, 2016).

During 2009–2018, no statistically significant change was observed for the EU/EEA overall. However, statistically, decreasing trends were observed for 12 countries (Austria, Belgium, Denmark, Finland, Germany, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovenia, Sweden). Statistically significant increasing trends were 0observed for four countries (Bulgaria, Ireland, Latvia, Poland). The average ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromycin), and fluoroquinolones to the consumption of narrow-spectrum penicillins, cephalosporins, and macrolides (i.e. erythromycin) in the community was 2.84 (country range: 0.1–24.0). The average consumption of antimycotics and antifungals for systemic use (ATC groups J02 and D01B) in the community was 1.0 DDD per 1 000 inhabitants per day (country range: 0.39–3.0)(*Summary of the latest data on antibiotic consumption in EU: 2018*).

According to NICE, rates of major complications associated with ARTIs are now low in modern developed countries. Besides, there is no convincing evidence, either from international comparisons or from evidence within countries, that lower rates of prescribing antibiotics are associated with higher rates of complications (NICE, 2008). Therefore, much of the historically high volume of prescribing to prevent complications may be inappropriate. Current guidance in the United Kingdom suggests that either a no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for most patients with ARTIs (NICE, 2008).

Management of ARTIs in the past concentrated on advising prompt antibiotic treatment of presumptive bacterial infections. This advice was considered appropriate, in an era of high rates of serious suppurative and non-suppurative complications, up to and including the immediate post-war period. However, current antibiotic treatment of ARTIs offers minor benefit to affected patients and is often associated with side effects (Del Mar, 2016) (Ahmed, ElMaraghy and Andrawas, 2016). Evidence from Cochrane reviews also shows that antibiotics on average reduce the duration of illness by less than a day (Spinks, Glasziou and Del Mar, 2013).

In a study by Gulliford et al in 2016, data from 610 UK general practices found that 36% of common colds were treated with antibiotics, as were 40% of episodes of sore throat, 70% of otitis media, and 90% of sinusitis. About 50% of all general practice consultations for ARTIs result in an antibiotic prescription, but some general practices issue prescriptions at a rate of more than 80% and others at less than 20%. This compares with practice in the Netherlands, where 22.5% of ARTI episodes in 2010 were treated with antibiotics (Gulliford *et al.*, 2014b) (Gulliford *et al.*, 2009) (Gulliford *et al.*, 2016).

A recent Public Health England report suggests that, although antibiotic prescribing in primary care is high, primary care prescribing of antibiotics in England declined between 2012-2016 from 2.17 to 1.88 (-13.4%) (Defined daily dose) per 1000 people per day (Dolk *et al.*, 2018).

Several factors have been shown to influence antibiotic prescribing including cultural beliefs of the physician and patient, socioeconomic factors, patient demand, and diagnostic uncertainty (Llor and Bjerrum, 2014). Another interesting factor was medico-legal concerns, a systematic review by Krockow et al (2019) found the consequences of antibiotic prescribing decisions are closely linked to patient outcomes. The review found that doctors were concerned about risks

associated with negative patient outcomes including complaints, litigation, and damage to professional reputation (Krockow *et al.*, 2019). The next sections will look at the public and health professional understanding of antibiotics and strategies to reduce prescribing.

3.3 Public and health professional understanding of antibiotic resistance

To reduce AMR it is important to understand the public and health professional understanding of the current situation to help in the management of AMR and reduce antibiotic prescribing. A recent report by PHE found that the public do not understand the effectiveness of antibiotics to treat viral infections or that bacterial infections do not always require antibiotics as many are self-limiting (McNulty *et al.*, 2019). This finding was also echoed in an earlier UK survey which found that 97% of respondents knew that antibiotics should not be taken unnecessarily and 79% were aware that antibiotic resistance was a problem in British hospitals (McNulty *et al.*, 2007). However, 38% thought antibiotics work on most coughs and colds, 54% that antibiotics can kill viruses and 43% did not know that antibiotics can kill the bacteria that normally live on the skin and in the gut (McNulty *et al.*, 2007).

A systematic review of quantitative and qualitative studies carried out in Europe, Asia, and North America demonstrated that the public have an incomplete understanding of and misperceptions about antibiotics and antibiotic resistance (McCullough *et al.*, 2016). Many participants believed they do not contribute to the development of resistance and attributed it to the actions of others, and they are at low risk from antibiotic resistance themselves. They believe the main causes of resistance are using too many antibiotics and not completing a course, and that

strategies to minimise resistance should largely be aimed at clinicians and other patients (McCullough *et al.*, 2016).

A mixed-methods study to examine the "Clinical Iceberg" of ARTIs in primary care was carried out by McNulty et al (2013). A "Clinical Iceberg" is normally used to describe illnesses that go unreported and was used to understand:

- How frequently the public were affected by ARTIs?
- How they managed their ARTI?
- How many patients visited their GP and why?
- What they expected from this visit and their expectations for antibiotics prescribed?
- Whether they had been prescribed immediate or delayed antibiotics and their adherence behaviour. (see Figure 5)

In the study where adults contacted their GP about their most recent ARTI (n=200), 10.3% of patients expected to be prescribed an antibiotic, 7.1% were prescribed an antibiotic and 5.3% finished an antibiotic as prescribed. The study found there was frequent pressure on GPs to prescribe antibiotics, as half of patients who presented to them with an ARTI were expecting antibiotics. Beliefs about the effectiveness of antibiotics for ARTIs were associated with this help-seeking behaviour. Participants who reported expecting their GP to prescribe antibiotics for an RTI were about twice as likely to contact their GP surgery, but concern about side effects of antibiotics was not associated with their expectations for antibiotics. Almost all responders who reported asking for an antibiotic were prescribed one. One-quarter did not finish their recent antibiotic course, and few reported self-medicating with antibiotics for their recent ARTI (McNulty *et al.*, 2013).

According to Coenen et al (2013), there appears to be a dissonance between health professional and patient expectations during consultations of respiratory tract

infections, and that patients were less satisfied with the consultation when they were not prescribed antibiotics (Coenen *et al.*, 2013). A recent survey of UK-based GPs also found that 55% of GPs felt under pressure mainly from patients to prescribe antibiotics even if they were not sure they were necessary and 44% had prescribed antibiotics to get the patient out of the surgery (Cole, 2014).

These studies show the need to support patients managing their symptoms and help physicians in finding alternative ways of responding to consultations for RTIs. The next section discusses alternative ways and strategies to reduce antibiotic prescribing.

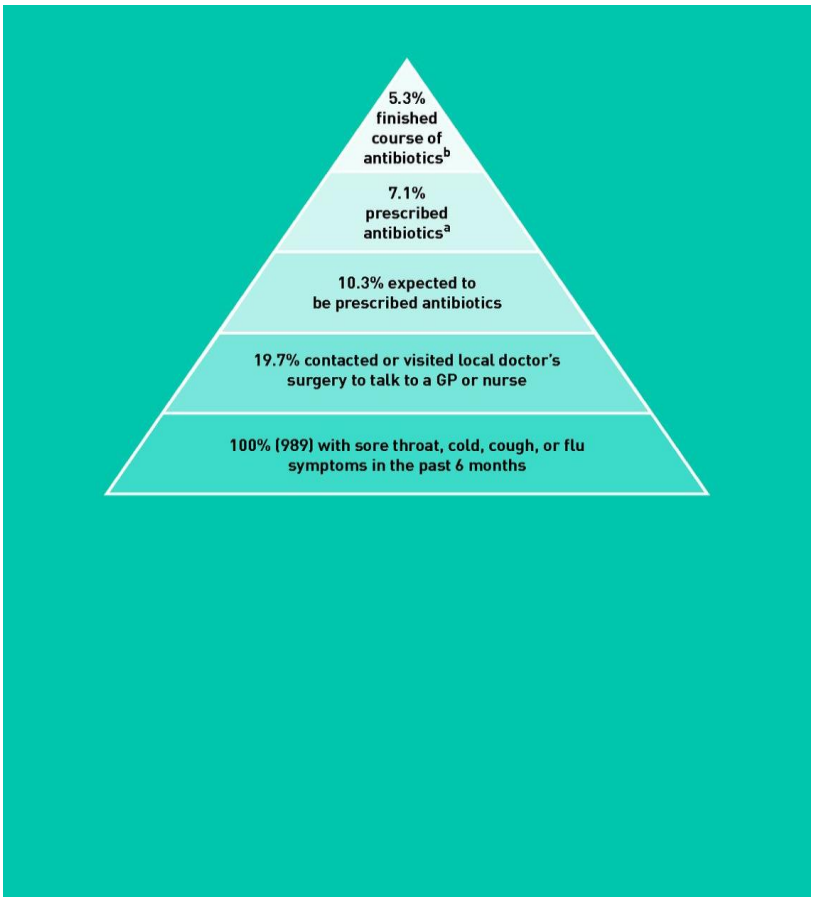


Figure 5. The Clinical Iceberg in ARTIs (McNulty *et al.*, 2013)

3.4 Interventions/strategies to reduce antibiotic prescribing

Currently, a considerable amount of work is being done to develop interventions that might help general practitioners to reduce the rate of antibiotic prescribing for ARTIs. This has been translated into policy guidance, public and stewardship campaigns to control unnecessary use (Anthierens *et al.*, 2015) (Shallcross, 2014). These approaches mainly focus on either reducing diagnostic uncertainty or altering physician and patient behaviour. These include or involve:

- Rapid diagnostic tests that can determine, within hours, whether an antimicrobial treatment should be used or not. Point-of-care testing using C-reactive protein (CRP) can lead to a marked reduction in antibiotic prescribing for acute respiratory tract infection in primary care as it may allow the physician to identify who or who not to treat. This method can also be combined with enhanced communication techniques (Little *et al.*, 2013)(Llor and Bjerrum, 2014).
- Enhanced communication through improved verbal information during consultation, information brochures, and web-based training programmes have all shown to reduce antibiotic prescribing (Little *et al.*, 2013)(Llor and Bjerrum, 2014).
- Delayed prescribing has been shown to reduce antibiotic use by patients in primary care without negatively impacting on patient outcome and has the added benefit that patients become less reliant on antibiotics (Little, Moore, Kelly, Williamson, Leydon, McDermott, Mullee, Stuart, *et al.*, 2014)(Moore, 2013).
- Stewardship programmes that can increase awareness and rationalise prescription practices among health care professionals. A European project entitled Happy Audit was shown to reduce antibiotics through interventions targeting GPs and patients in primary care (Bjerrum *et al.*,

2010). The TARGET antibiotic toolbox aims to improve antimicrobial prescribing in primary care in the UK through guidance, interactive workshops with action planning, patient-facing educational, and audit materials (Jones *et al.*, 2018).

- Mass media campaigns raise public awareness about the dangers associated with inappropriate antimicrobial prescriptions. Other population-level interventions such as school(eBug), and university-based, community-based interventions such as leafets at nurseries and pharmacies have also been investigated (Price *et al.*, 2018)
- NICE self-care guidelines have mentioned using herbal medicines such as *Echinacea purpurea, Pelargonium sidiodes,* and *Andrographis paniculata* to reduce antimicrobial prescribing.

The aforementioned strategies mention the use of herbal medicines to reduce antibiotic prescribing and provide alternative treatments. The next section will provide an overview of commonly used herbal medicines in the treatment of ARTIs.

3.5 Herbal medicines for the treatment of ARTIs

As mentioned in Chapter 2, herbal medicines are widely used for the treatment of infections (including respiratory tract infections) and have been so for centuries.

In 2004 the MHRA introduced a European Directive on Traditional Herbal Medicinal Products for over the counter use. The directive required any new traditional herbal remedy that makes medicinal claims for its use to be either registered as a conventional medicine and obtain a marketing authorisation (i.e. demonstrate quality, safety and efficacy), or to be registered under a new Traditional Herbal Medicines Registration Scheme (THMRS). This directive does not cover herbal medicines prescribed by medical herbalists (MHRA, 2008).

Herbal medicines can exert their effects through many different mechanisms and many have multipurpose actions. Some of these herbal medicines have laboratory-based research supporting their actions (Invitro, cell, and human tissue studies). These include :

- Expectorants - Expectorants aid in the removal of mucus from the airways. They can help to relieve cough by clearing mucus or changing its character so it is easily expelled. Commonly used expectorants include Ginger (*Zingiber officinalis*) and Elecampane (*Inula Helenium*) (Townsend *et al.*, 2013)(Bone and Mills, 2013)
- Respiratory Demulcents – Demulcent herbs contain mucilage which has a soothing and anti-inflammatory action on the respiratory tract. Commonly used demulcents include Marshmallow (*Althaea officinalis*) and Licorice (*Glycyrrhiza glabra*) (Mahboubi, 2019)(Liu *et al.*, 2013)
- Respiratory Spasmolytics – Spasmolytics relax the bronchioles of the lungs and therefore reduce the severity of coughing spasms. Herbs in this

category include Horehound (*Marrubium vulgare*) and Thyme (*Thymus vulgaris*) (Schlemper *et al.*, 1996)(Van Den Broucke and Lemli, 1983)

- Anticatarrhals – Anticatarrhals reduce catarrh or excessive mucus secretions. Common anticatarrhals include Elder (*Sambucus nigra*) and Goldenseal (*Hydrastis canadensis*)(Goldstein, Winter, and Poretz, 1997)(Barrett, 2018)
- Antiallergics – Antiallergic herbs function by reducing allergies. They are useful in conditions such as allergic rhinitis The principal herbal medicines in this area include Baikal skullcap (*Scutellaria baicalensis*) and Goldenrod (*Solidago virgaurea*) (Shin *et al.*, 2014)(Apáti *et al.*, 2003).

3.6 Conclusion

This chapter has examined ARTIs in primary care, antibiotic use in ARTIs, the public understanding of antibiotics and antibiotic resistance, and strategies to reduce antibiotic prescribing in primary care. I have also looked at herbs commonly used in ARTIs that could be considered as alternatives to antibiotics in ARTIs. One of the herbal medicines mentioned for acute cough in section 3.4 was *Andrographis paniculta.* The NICE committee discussion on self-care suggested the clinical significance of benefit was unclear and safety data was not available for *A. paniculata* in acute cough. The next chapter is a monograph of *A. paniculata* which will look at the pharmacology and phytochemistry of this plant. This will be followed by a systematic review of *A. paniculata* examining its clinical efficacy and safety, a chapter on philosophy and methodology, a qualitative interview study with health professionals, and a feasibility study in primary care.

Chapter 4: *Andrographis Paniculata* (Burm.f.) Nees (Acanthaceae) Monograph

4.1 Chapter Overview

In this chapter, I shall present a monograph on *A. paniculata* with an emphasis on the botany, phytochemistry, and pharmacology, traditional and ethnobotanical uses whilst also reviewing its potential within the field of antimicrobial resistance.

A. paniculata is a medicinal herb naturalised and cultivated throughout different regions of China, Southeast Asia, America, West Indies, and Christmas Island (Okhuarobo *et al.*, 2014)(WHO, 2004). The herb has been used for centuries in traditional medicine systems in several Asian countries. It is particularly prominent in Ayurvedic and Traditional Chinese Medicine and has more recently been used in the Western herbal tradition. According to certain authors during the global influenza epidemic in 1919, the medicinal properties of *A. paniculata* were effectively utilised to arrest the spread of the virus in India (Al-Abd *et al.*, 2013). Much of the research on the plant has centred around the diterpene lactones present in the leaf called the andrographolides (Bone and Mills, 2013).

4.2 Botany

The *Andrographis* species originates in southern parts of India and Sri Lanka. The genus *Andrographis* comprises of about 40 species, amongst these *Andrographis paniculata* (*A. paniculata*) is the most popular as a medicinal plant (Solomon Jeeva, 2014). *A. paniculata* grows best in a tropical climate in light black or sandy soil with a PH between 6.6 and 8.5. Andrographolide content

and yield is maximum with July planting and November harvesting (Alok *et al.*, 2013).

4.2.1 Morphology

A. paniculata is an erect, annual herb, growing to a height of 30-110 cm with glabrous leaves and white flowers with rose-purple spots on the petals. The stem is dark green, 30 - 100 cm in height, 2 - 6 mm in diameter, quadrangular with longitudinal furrows and wings on the angles of the younger parts, slightly enlarged at the nodes; leaves glabrous, up to 8.0 cm long and 2.5 cm broad, and lanceolate, pinnate; flowers are small, in lax, spreading axillary and terminal racemes or panicles; seed capsules are linear-oblong, acute at both ends, 1.9 cm x 0.3 cm; seeds are numerous, subquadrate, yellowish-brown (WHO, 2004).

Figure 6. *Andrographis paniculata* flower and stem

4.3 Traditional and Ethnobotanical uses

A. Paniculata is known by various names; it is known as King of Bitters (English), *Mahatikta* (Sanskrit), *Kiryato* (Gujarati), *Mahatita* (Hindi), *Kalmegh* (Bengali), *Fah Talai Jone* (Thai) *Chuan-Xin-Lián* (Chinese) (Okhuarobo *et al.*, 2014).

The aerial parts and roots of *A. Paniculata.* have been widely used in the traditional medicine systems in China, India, Thailand, and other Southeast Asian countries to treat many conditions including respiratory disorders, uncomplicated sinusitis, pharyngotonsillitis, pneumonia, and bronchitis, liver conditions, gut infections, and malaria (see Table 4). In Thailand, farmers are using *A. paniculata* as an alternative to antibiotics in livestock production (Solomon Jeeva, 2014).

A. Paniculata is mentioned in the classical Indian ayurvedic text called the *Charaka Samhita* as a treatment for jaundice and liver pathologies; within Sanskrit *A. Paniculata or* Kalmegh is described as "Sarva roga nivarani," which means a cure for all disease. Currently, *A. Paniculata* is a predominant herb in several Indian indigenous medicine formulations (including Ayurveda, Unani and Siddha) for the treatment of infectious diseases and digestive disorders (Dey *et al.*, 2013). In traditional Chinese medicine, the aerial part of *A. paniculata* is called *Chuan Xin Lian*[1] and is characterised as a heat-clearing and toxin eliminating herbal medicine. It has bitter and cold properties and enters the Lung, Stomach, Large, and Small intestine channels. It is used to treat early-stage febrile disorder and cough due to Lung Heat[2] (Chen, Chen, and Crampton, 2004). (Wen and Seifert, 2000)

[2] Lung heat conditions in TCM include upper respiratory tract infections, bronchitis and pneumonia, lung abscess and sore throats.

Table 4. Ethnobotanical uses of *Andrographis paniculata* (Sanower Hossain et al, 2014)

Country	Parts used	Indications
India	Leaf and root	Fever, liver disease, vitiligo
Japan	Leaf	Fever, common cold
Malaysia	Leaf and root	Diabetes, hypertension
Scandinavia	Leaf	Fever, common cold
Bangladesh	Leaf	Acute diarrhoea, cough, common cold, diabetes, urinary tract infections, lung infections, malaria, mucus, pharyngotonsillitis,
China	Leaf and root	Fever, chickenpox, common cold, cough with thick sputum, herpes zoster, laryngitis, mumps, pneumonia, respiratory infections, snake bites, suppurative otitis media, tonsillitis
Thailand	Leaf	Diabetes, dysentery, enteritis, herpes, skin infections (topical), used as an alternative to antibiotics in livestock
Middle East	Leaf	Gonorrhoea, irregular bowel habits, leprosy, scabies, dyspepsia

4.4 Phytochemistry (Herb and Root)

The chemical content of *A. paniculata* is affected by various factors including geographical region, harvest time, and processing methods (see section 4.2) (Hossain *et al.*, 2014). Phytochemical research has revealed that *A. paniculata* contains diverse and unique primary and secondary plant metabolites including Diterpene lactones, Noriridoids, Flavonoids, Polysaccharides, trace, and macro elements, and other miscellaneous compounds such as phenylpropanoids xanthones (Akbar, 2011). See Table 5 for a summary of the constituents.

4.4.1 Diterpenes

The main active constituents of *A paniculata* are a group of diterpene lactones belonging to the ent-labane class which are present in both free and glycosidic forms and are called andrographolides (Akbar, 2011). These ent-labdane diterpene lactones (ent-LRD'S) are thought to account for a large proportion of the herbs components and therapeutic actions. They are distributed in and have been isolated from the aerial parts and roots. The major andrographolides are known as andrographolide, neoandrographolides, and 14-deoxy-11,12-didehydroandrographolide (Li *et al.*, 2007)(Koteswara Rao *et al.*, 2004).

4.4.2 Noririoids

Five rare noriridoids have been found in the roots of *A. paniculata* named andrographolide A-E, along with curvifloruside (Xu *et al.*, 2012).

4.4.3 Flavonoids

Dua et al (2004) isolated four xanthones from the roots using a combination of thin-layer chromatography and column chromatography; infrared radiation, mass

and NMR spectroscopic were further used to examine these compounds (Md Sanower Hossain, Urbi, Sule, and Hafizur Rahman, 2014).

Table 5. Summary of the main constituents from *Andrographis paniculata ((*Li *et al.*, 2007)(Koteswara Rao *et al.*, 2004; Md Sanower Hossain, Urbi, Sule, and Rahman, 2014)

Class	Constituents	Part
Diterpene lactones	Andrographolides including andrographolide,neoandrographolides and 14-deoxy-11,12-didehydroandrographolide	Root and herb
Noriridoids	Andrographolide A-E, curvifloruside.	Root
Flavonoids	Xanthones	Root
Polysaccharides	Arabinogalactans	Herb
Miscellaneous compounds	Trace elements, potassium, calcium, Caffeic acid, cinnamic acid, furulic acid, chlorogenic acid.	Root and herb

4.4.4 Polysaccharides

Arabinogalactans have been isolated from the dried herb by Prajjal et al in 2007. Studies have shown that the arabinogalactans and andrographolides may exert a synergistic antitussive effect on animal models (Singha, Roy, and Dey, 2003).

4.4.5 Trace Elements

Trace elements (Cr, Mn, Co, Ni, Zn, Cu, Se, Rb, Sr, and Pb) and macro-element (potassium and calcium) were identified and quantified in the roots. Cinnamic acid, caffeic acid, ferulic acid, and chlorogenic acid were also isolated from the whole plant.

4.5 Pharmacology

A. Paniculata has been shown to possess a wide spectrum of pharmacological activities. *In vitro* and bioactivity studies, using the whole plant extracts as well as isolated compounds, suggest that *A. Paniculata* possesses anti-inflammatory, anti-microbial, immunostimulatory, and other health-promoting activities (see Table 6).

Although the in-vitro research suggests that the herb has antimicrobial activity there is a lack of *in-vivo* human studies to confirm these findings. Some authors suggest that *A. paniculata* works mainly by virtue of its immune-enhancing effect. According to Mills and Bone (2000), *A. paniculata* exerts its influence as an immunostimulant through its phagocytic action. They also suggest the herb may possess anti-inflammatory actions through its enhancement of adrenocortical function. Human cell studies examining *A. paniculata* found that the herb increased the proliferation of lymphocyte cells and showed antiviral activity similar to the antiviral medication Lamivudine (Churiyah *et al.*, 2015). The next section will look at the safety profile of *A. paniculata*

Table 6. In vitro antimicrobial actions of *A. paniculata*

Plant part	Extract and method	Active components	AMR activity	Reference
Antibacterial and antifungal activity				
Whole plant	aqueous extracts	Whole plant, andrographolides, arabinogalactans	*Activity against Bacillus subtilis (B. subtilis)*, *Escherichia coli (E. coli)*, *Pseudomonas aeruginosa, Candida albicans*	(Okhuarobo *et al.*, 2014)
Leaf	aqueous extracts; disc diffusion	Whole leaf	*Activity against Bacillus subtilis, Streptococcus aureus, Staphylococcus aureus, Escherichia coli*	(Manjusha, G. V.; Rajathi, K.; Alphonse, J. K. Mini; Meera, 2011), (Chakraborty *et al.*, 2011)
Whole plant	methanolic extracts; cup-plate agar diffusion method	Whole plant, 3-O-β-D-glycosyl-14-deoxyandrographolide, 14-deoxyandrographolide	Broad-spectrum antibacterial activity; more prominent against Gram-positive bacteria (*S.*	(Md Sanower Hossain, Urbi, Sule and Hafizur Rahman, 2014)

			aureus, M. luteus, and S. pyogenes)	
Leaf	ethanolic extract; disc diffusion	Whole plant, andrographolide	*Escherichia coli; Klebsiella pneumonia, Proteus vulgaris, and Streptococcus pneumonia*	(Mishra *et al.*, 2013)
Leaf	ethanolic extract; disc diffusion	Whole plant, andrographolide	*Salmonella typhi*-108, *S. aureous*-2737, *V. alginolyteus*, *Sh. Boydii*-8, *V. cholera*-8103, *E. coli* k-12 row, *B. licheniformis*-10341.	(Banerjee *et al.*, 2017);(Singha, Roy, and Dey, 2003)
Whole plant	dichloromethane, methyl alcohol and aqueous; disc diffusion		*Staphylococcus saprophyticus, Staphylococcus epidermis, Staphylococcus aureus, Streptococcus pyogenes, Bacillus anthracis, Micrococcus*	(Solomon Jeeva, 2014)

			luteus, Enterococcus faecalis) and 5 gram-negative strains; *Proteus mirabilis, Proteus vulgaris, Klebsiella pneumonia, Neisseria meningitis, Pseudomonas aeruginosa*	
Leaf and stem	petroleum ether, acetone, chloroform, and methanol extracts	Whole parts	*Enterococcus faecalis, Streptococcus pyogenes, Klebsiella pneumonia, and Proteus vulgaris.*	(Tandon, Mathur and Sen, 2015)
Whole plant	methanolic and aqueous	Whole plant	*S. typhimurium, E. coli, S. sonnei, S. aureus, P. aeruginosa, S. pneumoniae, S. pyogenes, L.*	Jayakumar *et al* (2013)

			pneumophila or *B. pertussis*	
Antiviral activity				
Leaf	Human bronchial cells	andrographolide	*influenza A virus H1N1*.	(Chen *et al.*, 2009)
Leaf	Ethanolic extract	Whole plant, Andrographolide, neoandrographolide and 14-deoxy-11,12-didehydroandrographolide	herpes simplex virus 1 (HSV-1)	(Chao and Lin, 2010)
Leaf	methanolic	Whole plant	Dengue virus; DENV-1 serotype	(Tang *et al.*, 2012)
leaf	ethanolic	andrographolide	Chikungunya (CHIKV) virus	(Wintachai *et al.*, 2015)
leaf	ethanolic	Whole plant, andrographolide	Epstein–Barr virus (EBV)	(Lin *et al.*, 2008)
Leaf	n-hexane, methanol	andrographolide, bis-andrographolide 14-deoxy-11,12-didehydroandrographolide, andrograpanin, 14-deoxyandrographolide, (±)-5-hydroxy-7,8-dimethoxyflavanone and 5-hydroxy-7,8-	Human immunodeficiency virus (HIV)	(Niranjan Reddy *et al.*, 2005)

		dimethoxyflavone. Andrographolide and 14-deoxy-11,12-didehydroandrographolide		
leaf	ethanolic	andrographolide	Simian Retro Virus	Churiyah et al 2015

4.6 Safety

High oral doses of *A. paniculata* may cause gastric discomfort and vomiting. The Therapeutic Goods Administration (TGV) of Australia and the European Medicines Agency (EMEA), organisations which look at the safety of medicines have noted that the standardised extract with high andrographolide content and products extracted with methanol may cause hypersensitivity reactions in some people (Csupor, Dezső, 2014) (TGA 2015). The TGV report on the whole plant suggests that the herb is safe (data gleaned from clinical trials). There is no data on the safety of using the herb in pregnancy or lactation and is therefore not recommended for use according to WHO (*WHO Monographs on Selected Medicinal Plants - Volume 2: 2004*). Although some side effects are associated with *A. paniculata* these are considered to be acceptable at present for OTC use in the UK.

4.7 Conclusion

A. paniculata is used as a herbal medicine for infectious disease in many cultures. Some authors suggest because of its popularity herbs like *A. paniculata* may have the potential for the placebo effect (Firenzuoli and Gori, 2007). Traditional use in herbal medicine suggests that the herb may be useful as a symptomatic treatment

for ARTIs. Laboratory-based research on *A. paniculata* suggests the whole plant and its constituents work by mediating an immune response against microbial infection and also suggests a direct action against certain pathogens involved in infectious disease. However, in vitro research is limited in its value and is sometimes inconsistent. There is a need for further clinical and pharmacological studies to validate the in vitro evidence. The next chapter is a systematic review of clinical trials outlining the clinical efficacy, effectiveness, and safety of *A. paniculata* for ARTI symptoms.

Chapter 5: *Andrographis paniculata* for symptomatic relief of acute respiratory tract infections (ARTIs): A systematic review and meta-analysis of randomised control trials

5.1 Chapter Overview

The previous chapter examined the phytochemistry and pharmacology of *A. paniculata* and provided an insight into the herbal medicine. As mentioned in Chapter 3 there is a need for investigation into alternatives to antibiotics for ARTIs. The most rigorous way to do this is to conduct a systematic review and meta-analysis of RCTs into herbal medicines with potential in this area. This chapter outlines a systematic review and meta-analysis to review the evidence relating to the clinical efficacy, effectiveness, and safety of *A. paniculata* for symptoms of ARTIs. This was the first systematic review that had no language restrictions and included Chinese RCTs.

A previous systematic review by Coon and Ernst (2004) looked at *Andrographis paniculata* in the treatment of upper respiratory tract infections (systematic review of safety and efficacy). Seven controlled trials (n=896) were included in the efficacy review. Fourteen studies (n=1,235) were included in the review of safety. This systematic review did not mention assessment of heterogeneity in the trials reviewed. Although this systematic review mentioned there were no language restrictions, there was no evidence of Chinese databases being searched. Furthermore, there were no Chinese RCTs included in the review. The authors suggested that *A. paniculata* was a safe and efficacious treatment for upper respiratory tract Infections. In this systematic review, my main roles were to recheck

the search strategy, create a data extraction spreadsheet, data extraction and management, analysis, and writing up.

The authors involved in this review conducted for this PhD were: Xiao-Yang Hu (XYH) Ruo-Han Wu (RHW), Martin Logue (ML), Clara Blondel (CB), Lily Yuen Wan Lai (LYYW), Beth Stuart (BS), Andrew Flower (AF), Yu-Tong Fei (YTF), Michael Moore (MM), Jonathan Shepherd (JS), Jian-Ping Liu (JPL), George Lewith (GL).

The research questions that this systematic review aims to answer are:

1. What is the effectiveness of *A. paniculata* for the treatment of ARTI symptoms?
2. What is the safety and adverse events profile of *A. paniculata* in clinical trial participants?

What clinical data is available regarding forms, dosage, combinations on *A. paniculata* for the treatment of ARTI symptoms. The PICO of the study was as follows (Eriksen and Frandsen, 2018):

- **P**articipant: human participants of all ages, with symptoms of ARTIs
- **I**ntervention: Any form of oral *Andrographis paniculata* (AP) either single or in an herbal mixture
- **C**omparison:

  AP versus placebo or no intervention

  AP (+usual) versus usual care

  AP versus a different herbal intervention

  AP (e.g. tablet) versus AP (e.g. liquid)
- **O**utcome measures

1. Primary

   Improvement in ARTI symptoms

2. Secondary

   Adverse events (AEs)

   Time to resolution

   Reduction in antibiotics usage

This chapter includes data on the methods, outcomes, safety, and adverse events, manufacturing, effect estimates, subgroup analysis, risk of bias, dosage, and variations used in this systematic review. The strength and limitations of the review are also discussed.

5.2 Methods

This systematic review involved collaboration with the Beijing Centre for Evidenced-Based Medicine with whom the department has an existing relationship. My colleague XYH (Mio) worked closely with academics in Beijing to appraise the Chinese language studies. Papers in other languages were translated through a translation service within Southampton University Library. I worked on all the English language studies with CB. This systematic review followed PRISMA reporting guidelines (Liberati *et al.*, 2009) (see Appendix B). The protocol of this review was registered (CDR: CRD42011093101069).

5.2.1 Search strategy and study selection

Only randomised controlled trials (RCTs) were chosen for this review as these were considered the most reliable and rigorous study design. English and Chinese databases including MEDLINE, EMBASE, AMED, Cochrane Library, CINAHL, China National Knowledge Infrastructure (CNKI), Wan Fang, Sino-Med Database, and Chinese Science and Technology Journal Database (VIP) were searched from their

inception to March 2016. These databases were chosen as they were considered the most relevant for this review.

The systematic review was led by XYU who assured adherence to the research protocol was followed. I joined the project in April at the same time I started my PhD. My initial task was to check through the literature search methods.

A range of text words and indexed terms related to "*Andrographis paniculata*" and "respiratory tract infection" were searched (See Appendix A for search terms). The reference lists of studies meeting the inclusion criteria were searched to identify additional relevant studies. There were no exclusions made based on language. Literature searching (XYH, RHW) and study selection (XYH, RHW, ML) were completed independently by at least two authors. Study authors were contacted to obtain relevant missing data if necessary and where resources allowed. A recently updated search (up to March 2020) MEDLINE, EMBASE, AMED, Cochrane Library, CINAHL found no new relevant RCTs.

5.2.2 Data extraction and management

A data extraction spread-sheet was created using Microsoft Excel 2015. The spreadsheet was designed and piloted by XYU and myself with appropriate changes made for this review. The form identified study details, treatment details, trial characteristics, comparison details, quality assessment, characteristics of trial population and conditions, findings (effects and adverse events) details of interventions in all trial arms according to the consolidated standards of reporting trials herbal extension (CONSORT), in terms of features of herbal intervention, details of concomitant interventions, quality assessment, and findings on efficacy, effectiveness and AEs (Gagnier *et al.*, 2006). Two reviewers extracted study data

independently for Chinese (XYH, RHW) and English language (ML, CB) trials, with findings compared and agreed. Where there were differences in how the data should be extracted, XYH was consulted.

5.2.3 Study types

The review included published and unpublished randomised controlled trials (RCTs) (through searching grey literature) (Higgins JPT, 2011). Quasi-RCTs, crossover trials, controlled before and after studies, interrupted time series (ITS) studies, and non-experimental studies were not included due to their potential high risk of bias.

5.2.4 Inclusion and exclusion criteria

Studies included human participants of all ages, with symptoms of ARTIs. A clinical diagnosis of ARTI was the main inclusion criteria. Diagnoses of upper or lower ARTIs included acute common cold, influenza, rhinosinusitis, laryngitis, tonsillitis, pharyngitis, croup, acute otitis media, bronchitis, pneumonia, and acute exacerbations of chronic obstructive pulmonary disease (COPD). Symptoms of ARTIs were defined as having symptoms such as cough, sore throat, fever, runny nose, discoloured sputum, etc., for less than four weeks. Trials were excluded if they evaluated patients with asthma, had active or previous peptic ulceration, were hypersensitive to analgesics, had psychosis, or were severely depressed. Exclusion also applied to trials of patients who required hospital admission (for example, for meningitis, severe pneumonia, epiglottitis, or Kawasaki disease), had a known immune deficiency, or were pregnant or breastfeeding (Little, Moore, Kelly, Williamson, Leydon, McDermott, Mullee and Stuart, 2014).

5.2.5 Types of preparation

The use of *A. paniculata* as part of a formula is common in Western, Ayurvedic, and Chinese herbal medicine, therefore, herbal products included in the review comprised of those solely containing *A. paniculata* and those containing *A. paniculata* in conjunction with other herbs such as with *Scutellaria baicalensis*, or in combination with *Lonicera japonica*, *Forsythia suspense*, and *Aster trinervius*. It was useful to examine if *A. paniculata* worked better on its own or within a combination/formula. No limitation was imposed concerning dosage, methods of dosing, or duration of administration.

5.2.6 Control and co-interventions

Placebo or no intervention; usual care such as analgesics, antivirals, antibiotics, anti-inflammatories, steroids or corticosteroids; or other herbal remedies were included. Studies comparing different preparations of *A. paniculata*, e.g. comparing tablet with granule, were also included in this review.

5.2.7 Outcome measure types

ARTI symptom improvement was the primary outcome measure in this review. This included:

1). Measurement by participant self-report or by clinician/observer assessment. Commonly used measures include:

- Changes in visual analogue scales in key symptoms, including temperature, cough, catarrh, etc.

- Changes in symptoms scored on a Likert-type scale
- Global assessment of symptom improvement by the patient
- Global assessment of symptom improvement by treating clinician

When individual symptoms were reported, data on two key symptoms: cough and sore throat were collected as the target symptoms for this review. If this data was unavailable, information on overall symptom scores (sum of various symptoms such as temperature, cough, catarrh, etc.) were collected and analysed.

Secondary outcome measures included:

1) Adverse events (AEs) included any anaphylactic, allergic reactions, hypersensitivity reactions, or complications of *A. Paniculata*, such as rash, nausea, fatigue, or worsening of RTI symptoms. AEs due to interactions among *A. Paniculata* in combination with other remedies, or potential interactions with medications patients had for their co-morbidities were also collected.
2) Mean time to reported remission or resolution of symptoms. This was measured directly, through patient or clinician/observer report or indirectly as the time to return to normal activities.
3) Reduction in reported antibiotic usage, e.g. number of scripts issued immediately at the time of consultation and update of delayed prescriptions. Trials that did not report either our primary and or secondary outcome measures were excluded from this review.
4) Timing of effect measures: Some studies may have used a repeated-measures approach. Timings of measures for each included trial were documented with commonly reported time points explored if there was sufficient data available.

5) Subgroup analysis: Several subgroup analyses were conducted to compare the effect estimates between studies.

All outcome measures were assessed at baseline and the most appropriate follow-up if data was available. Otherwise, data at the most appropriate follow-up point were assessed.

5.2.8 Risk of bias assessments

The risk of bias of the included RCTs was assessed independently by two reviewers CB and myself using the tool developed by Higgins and Green in the Cochrane Handbook for Systematic Reviews of Interventions (*Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training*, 2011). We assessed bias over the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of researchers conducting outcome assessments), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias. A judgement of 'low risk' of bias, 'high risk' or bias, or 'unclear risk' of bias was provided for each domain. Any disagreements were resolved by discussion or by involving a third reviewer (XYH) until consensus was reached.

5.2.9 Measures of treatment effect

We combined data from individual studies in a meta-analysis only where appropriate. Overall effect sizes were estimated using Review Manager (RevMan) Version [5.3]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 (*Review Manager (RevMan) [Computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*.). Due to the anticipated variability in the populations and interventions of included

trials, a generic inverse variance random-effects model was used to pool the mean difference (MD) with 95% confidence interval (CI) on target continuous outcomes to incorporate heterogeneity. When the units of the outcome measures used across studies were not consistent, the effects as standardised mean differences (SMD) were reported. For dichotomous data, a random-effects method was used to pool the summary risk ratio (RR) with 95% CI. An overall effect size with 0.2-0.5 was regarded as small, 0.5-0.8 as moderate, and more than 0.8 as large. Absolute risk estimates were calculated using the event rates of controlled groups as baseline risks. This data was presented within forest plots.

5.2.10 Missing data

When data were missing or incomplete, we contacted study authors to obtain information where possible. If the means were reported without standard deviations, we attempted to calculate the standard deviation from the information reported such as p-values, f-values, or confidence intervals. Where possible, we performed an intention to treat (ITT) analysis for all outcomes. However, most included trials only reported completed cases.

The primary analysis was carried out on complete case datasets. For each outcome, the number of participants whose data was available at baseline and at follow-up, and the rate of loss to follow-up were recorded. (Akl *et al.*, 2012).

5.2.11 Assessment of statistical heterogeneity

Between study heterogeneity was assessed using the I-squared statistic that describes the percentage of variation across studies that is due to heterogeneity rather than chance. A rule of thumb for interpretation of this statistic suggest that I^2>30% equates to moderate heterogeneity, I^2>50% equates to substantial

heterogeneity, and I-squared >75% equates to considerable heterogeneity. For all I^2 values above 50%, we investigated sources of heterogeneity. Although this threshold is widely used, it is somewhat arbitrary, and therefore if the I^2 value was below 50% but the direction and magnitude of treatment effects suggested important heterogeneity, we investigated the potential sources in a sensitivity analysis and took this into account when interpreting the findings. As high levels of heterogeneity were expected due to complexity in form of *A. Paniculata* (e.g. monotherapy or herbal mixture, capsule, or liquid), it was planned to use a random-effects model to pool the overall effects (Higgins JPT, 2011).

5.2.12 Sensitivity analyses

Sensitivity analyses were conducted for the primary outcomes to determine whether the review conclusions would have differed if eligibility was restricted to trials without a high risk of bias (Higgins JPT, 2011); and if eligibility was restricted to trials that provided any detail on authentication/standardisation of the herb.

5.2.13 Subgroup analyses

If there was sufficient available data, several subgroup analyses were conducted to compare the effect estimates between studies that evaluated:

- Patients with upper ARTI versus lower ARTI;
- Adults versus children (younger than 18);
- *A. paniculata* as monotherapy versus as fixed combinations;
- *A. paniculata* in different preparation, e.g. granule versus tablet or other forms.

5.3 Results

5.3.1 Included studies

The literature search identified 3106 studies; of which a final total of 33 RCTs comprising 7175 patients met the criteria and were included (See Fig 7). Table 1-5 (See Appendix C) shows the characteristics of the included 33 trials. All the trials included had a clinical diagnosis as per the inclusion/exclusion criteria.

The included trials were published between 1991 and 2014, 25 from China (Chang and 常社友, 2012)(Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Zhi Lin, 林志 and 杨芳, 2011; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Li and 李晓卿, 2014)(Dian-Kui Zhang Shou-You Jiang *et al.*, 1994; Deng and 邓燕飞, 1999; Xi and 席管劳, 2006; Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009; Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Li and 李涛, 2010; Tan and 谭朝辉, 2011; Meng Dan, 2012; Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Bao and 包志伟, 2013; 吴芹芹, 2013; Guo and 郭辉, 2013;

Su and 苏国枫, 2014; Xia and 夏君, 2014; Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014) , three from Russia (Kulichenko *et al.*, 2003; Shakhova, Spasov, Ostrovskiĭ, *et al.*, 2003; Spasov *et al.*, 2004), two from Sweden (J. Melchior *et al.*, 2000)(Melchior, Palm and Wikman, 1997) and one each from Thailand (Thamlikitkul *et al.*, 1991), India (R C Saxena *et al.*, 2010a), and Chile (Cáceres *et al.*, 1999).

Two were 3-armed trials (Thamlikitkul *et al.*, 1991; J Melchior *et al.*, 2000) and the remainder were 2-armed parallel RCTs (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Zhi Lin, 林志 and 杨芳, 2011; Chang and 常社友, 2012; Li and 李晓卿, 2014,)(Lin Zhi, 2011)(Liu Jinfeng, Liu Li, Zhong Xiaoli, Ma Xuemei, 2012)(Tan Yongmei, Gao Lan, 2010)(Zhaohui, 2011)(Wang Yinyu, Wang Fang, Feng Changsheng, 2008)(Kulichenko *et al.*, 2003)(Tao, 2010)(Yanfei, 1999)(Zhiwei, 2013)(Sun Junsheng, Zhao Yamei, 2014)(Hui, 2013)(Li Peiguo, Xu Guangfan, Liu Hongwei, 2007)(Dan, 2012)(Tang Yuqi, Yang Chunfu, 2009)(Qinqin, 2013)(Shakhova, Spasov, Ostrovskii, *et al.*, 2003)(Ding Hong, Yang Mingjun, Lu Bin, Dong Yan, Li Xijin, Luo Wenjing et al , 2010)(Guanlao, 2006)(Zhang Diankui, Jiang Xu, 1994)(Zhao Weiguo, Li Yunjing, Yu Yuanlong, Peng Xiabiao, Yang Youye, 2012)(Cáceres *et al.*, 1999)(Melchior, Palm and Wikman, 1997)(R C Saxena *et al.*, 2010b)(J. Melchior *et al.*, 2000)(Chang Jing, Zhang Ruiming, Zhang Ying, Chen Zhibin, Zhang Zongming, Xu Qiang, 2008)(Guofeng, 2014)(Xia and 夏君, 2014).

Six trials on lower ARTIs were all published in China (Li Peiguo, Xu Guangfan, Liu Hongwei, 2007; Sun and Yamei, 2014); Meng Dan, 2012; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009; Wu Qinqin. 2013; Hong Ding et al , 2010) six did not specify upper

or lower (Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Tan and 谭朝辉, 2011;(Kulichenko *et al.*, 2003); Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014; (Spasov *et al.*, 2004); (J Melchior *et al.*, 2000) and twenty two were on upper ARTIs (Li and 李涛, 2010; Li 李晓卿, 2014;) (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Zhi Lin, 林志 and 杨芳, 2011; Yongmei, Gao Lan, 2010; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Tan and 谭朝辉, 2011; (Kulichenko *et al.*, 2003); Bao and 包志伟, 2013;(Shakhova, Spasov, Ostrovskiĭ, *et al.*, 2003); Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Xi and 席管劳, 2006; Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012; Dian-Kui Zhang Shou-You Jiang *et al.*, 1994; Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; (Cáceres *et al.*, 1999)(J Melchior *et al.*, 2000)(R.C. Saxena *et al.*, 2010) Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008; Su and 苏国枫, 2014).

Eleven trials reported the use of guideline-based diagnoses, according to the Chinese medicine clinical research guidelines (CMCRG)(MoHotPsRo., 1997) and the international classification of primary care (ICPC)('WHO | International Classification of Primary Care, Second edition (ICPC-2)', 2012) classification (Tan Yongmei, Gao Lan, 2010; Tan and 谭朝辉, 2011; Wang Yinyu, Wang Fang, Feng Changsheng, Chen Dongyun. 2008; Bao and 包志伟, 2013; Hong Ding Bin Lv, Yan

Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Xi and 席管劳, 2006; Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012; Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008; Su and 苏国枫, 2014; Xia and 夏君, 2014).

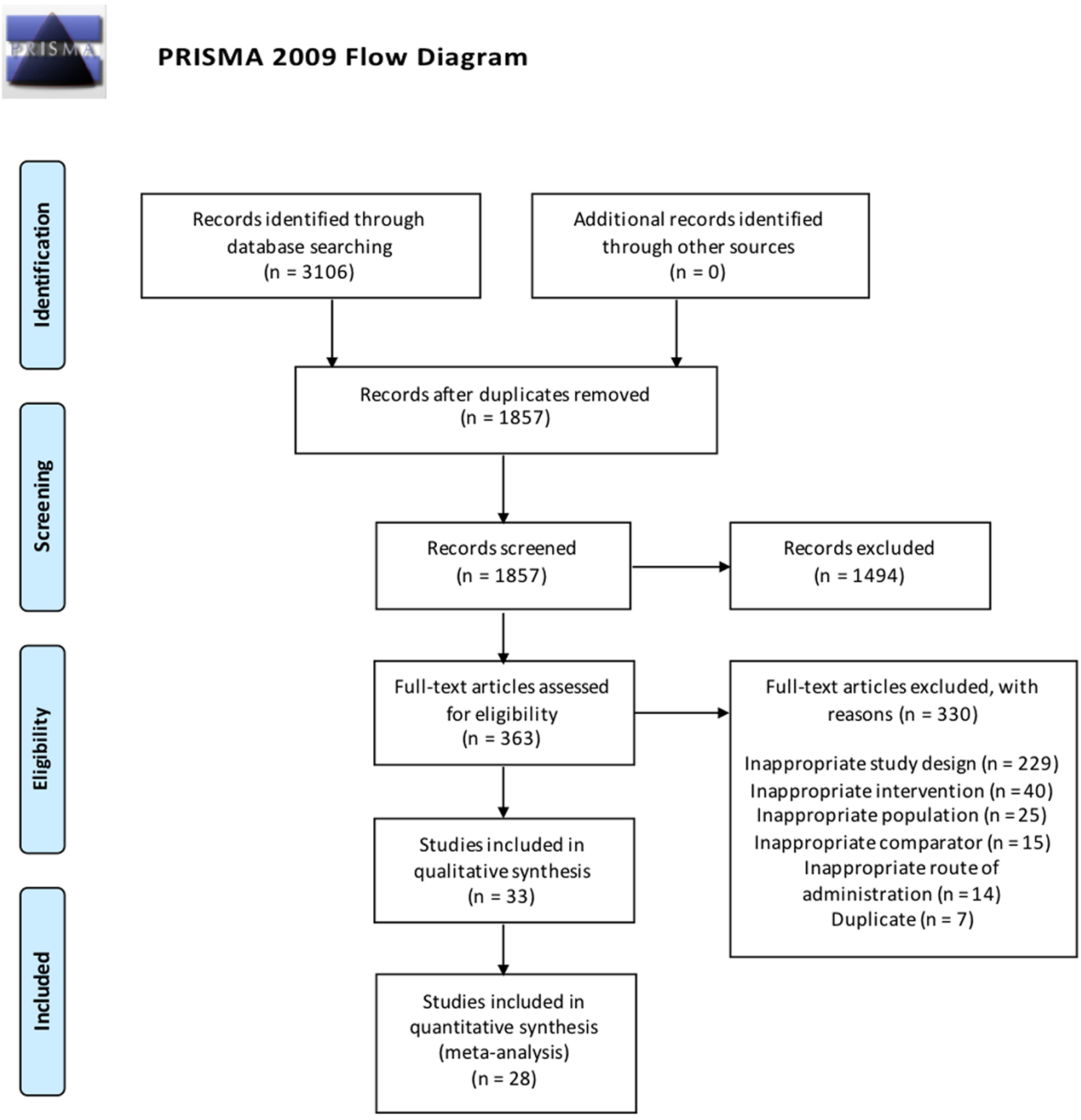


Figure 7. Details of trials included and excluded in the review.

Nearly one-third of the trials did not include patients with co-morbidity or did not report it, but excluded those patients who had other primary diseases, e.g. cardiovascular conditions, liver, kidney or hematopoietic system impairment,

mental health conditions, or rheumatoid arthritis. Two excluded patients who had asthma (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; (Cáceres *et al.*, 1999); two excluded those who had any other infections (Melchior, Palm, and Wikman, 1997; Spasov *et al.*, 2004). Only three trials included patients with co-morbidities: heart failure (Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012; 吴芹芹, 2013), diarrhoea (Deng and 邓燕飞, 1999), and toxic encephalopathy (吴芹芹, 2013); and one trial was formed with children having frequent cold, bronchitis, sinusitis, and pneumonia (Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012).

5.3.2 Interventions

Experimental interventions included *A. Paniculata* as a monotherapy and as an herbal mixture in combination with other herbs. Table 1-5 (see Appendix C) presents the characteristics of *A. Paniculata* reported in the included trials. Seven trials (Li and 李涛, 2010; Tan Yongmei, Gao Lan, 2010; Deng and 邓燕飞, 1999; Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012;Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; Su and 苏国枫, 2014; Xia and 夏君, 2014) did not report the type of product used; one used *A. Paniculata* dried leaves (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009), others reported use of *A. Paniculata* extract, and among these five reported the use of a formulation called SHA-10 (Thamlikitkul *et al.*, 1991; Melchior, Palm, and Wikman, 1997; Spasov *et al.*, 2004; Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008; Bao and 包志伟, 2013).

Trials seldom reported manufacturing or quality control details. Three (Melchior, Palm, and Wikman, 1997; J. Melchior *et al.*, 2000; Spasov *et al.*, 2004) trials reported

methods of measuring andrographolide proportion using HPLC technique but only one reported that the product was produced, analysed and bottled according to good manufacturing practice (GMP) standards (Bao and 包志伟, 2013). Three trials reported added materials (Melchior, Palm, and Wikman, 1997; Spasov *et al.*, 2004; Li and 李涛, 2010) but only one (Melchior, Palm, and Wikman, 1997) provided clear description (200 mg of microcrystalline cellulose). Extract solvents used included ethanol (Melchior, Palm, and Wikman, 1997), polyethylene glycol (Garg *et al.*, 2015), and two used methanol for HPLC extraction (J. Melchior *et al.*, 2000; Spasov *et al.*, 2004). One of the trials provided extract solvent concentration details (Melchior, Palm, and Wikman, 1997).

Comparison interventions included standard care, placebo control, active herbal interventions, and other forms of *A. Paniculata* preparations. Twenty-one trials involved usual care (Chang and 常社友, 2012); Li and 李涛, 2010; Li 李晓卿, 2014) (Kulichenko *et al.*, 2003)(Thamlikitkul *et al.*, 1991)(Shakhova, Spasov, Ostrovskiĭ, *et al.*, 2003)(Spasov *et al.*, 2004) including corticosteroids (Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Li and 李晓卿, 2014), antibiotics/antivirals (Li and 李涛, 2010; Zhi Lin, 林志 and 杨芳, 2011; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Tan and 谭朝辉, 2011; Wang Yinyu, Wang Fang, Feng Changsheng, Chen Dongyun. 2008; Deng and 邓燕飞, 1999; Bao and 包志伟, 2013; Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014; Guo and 郭辉, 2013; Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Meng Dan, 2012; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009) cough suppressant (Bao and 包志伟, 2013; Guo and 郭辉, 2013; Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009) or antipyretics (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Tan Yongmei,

Gao Lan, 2010; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Tan and 谭朝辉, 2011;(Kulichenko *et al.*, 2003); Meng Dan, 2012; Wu Qinqin. 2013;(Shakhova, Spasov, Ostrovskiĭ, *et al.*, 2003); (Spasov *et al.*, 2004).

5.3.3 Outcomes

The most commonly reported primary outcome measure was a global assessment of overall symptoms improvement (Table 1-5 ; Appendix C). Although not clearly reported in every trial, it is anticipated a practitioner measured this outcome. Apart from one trial (Meng Dan, 2012), all Chinese trials reported four categories scores in symptoms of ARTIs, among which 11 (Tan Yongmei, Gao Lan, 2010; Tan and 谭朝辉, 2011; Deng and 邓燕飞, 1999; Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Xi and 席管劳, 2006; Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012; Zhang Diankui, Jiang Xu, Jiang Shouyou,1994; Chang Jing, Zhang Ruiming, Zhang Ying, Chen Zhibin, Zhang Zongming, Xu Qiang, et al, 2008; Su Guofeng, 2014); (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Zhi Lin, 林志 and 杨芳, 2011) reported data based on the Chinese medicine clinical research guidelines (CMCRG). The CMCRG is a four category scoring system to evaluate overall treatment effects based on:

1). Cured: a). no temperature in 3 days, b). no symptom or sign of RTIs, c). accumulated score decrease ≥95%

2) Markedly effective: a). no temperature in 3 days, b). most symptoms and signs

of RTIs disappear, c) accumulated score decrease between 70% to 95%

3). Effective: body temperature decreased in 3 days, b). most of the key symptoms and signs of RTIs disappear, c). accumulated score decrease between 30% to 70%

4). Ineffective or worsening: a). no decrease or increased body temperature, b). no improvement in key symptoms and signs of RTIs or even getting severe, c). accumulated score decrease less than 30%.

The accumulated score was calculated as (baseline score – endpoint score)/baseline score X 100%. Scores were given based on:

1). Symptoms of ARTIs, e.g. symptoms: fever, sore throat, cough, nasal congestion, runny nose, headache, sweating, sneezing, thirst

2). Signs of ARTIs, e.g. aversion to wind, and changes in tongue appearance and pulse

3). Laboratory checks, e.g. chest radiography, circulation, faeces, blood, urine, liver and kidney function, electrocardiogram (ECG). In this review, cure rate and markedly effective (CCME) rates were combined and analysed by the review authors.

Symptom scores on the severity of cough, sore throat, and overall symptoms (commonly a list of 8-12 ARTI symptoms) were reported in seven trials (Shakhova, Spasov, Ostrovskii, *et al.*, 2003; Spasov *et al.*, 2004; Xi and 席管劳, 2006; Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008; Meng Dan, 2012; Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; Bao and 包志伟, 2013).

Secondary outcome measures reported in the included trials included: time to

resolution of cough, sore throat, and overall symptoms; one trial reported a reduction in reported medication usage (Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008).

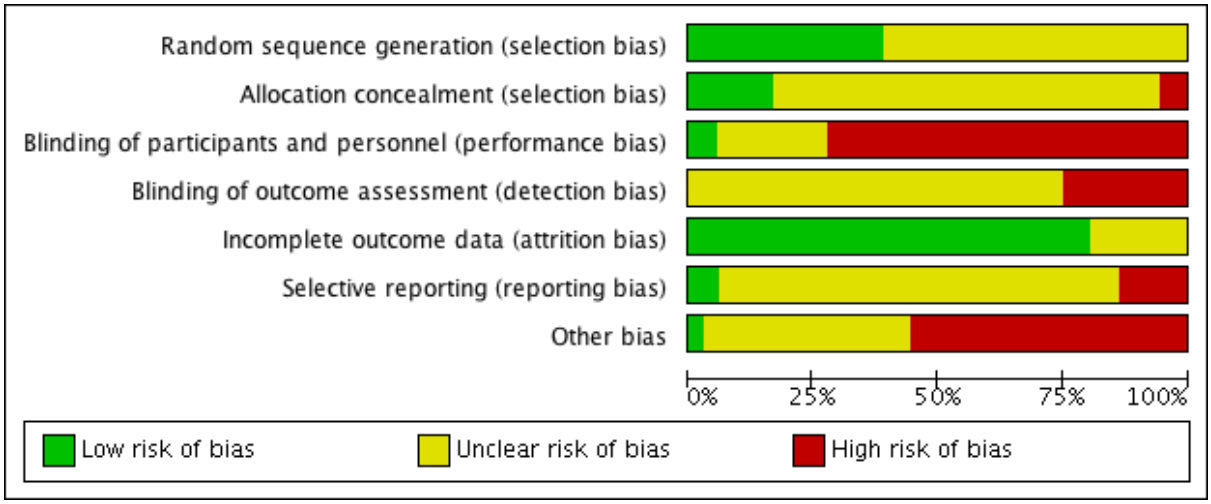
Some trials used a repeated measure approach (Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; R C Saxena *et al.*, 2010b; Chang and 常社友, 2012; Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; Su and 苏国枫, 2014).

Apart from one trial on acute pharyngitis followed-up at 20 days (Li and 李晓卿, 2014), the most common endpoint follow-up reported was 3-7 days and the outcome data of the endpoints closest to 5 days were extracted and assessed (See Appendix C; tables 1-5).

5.3.4 Risk of bias in included studies

Apart from four trials (Melchior, Palm and Wikman, 1997; J Melchior *et al.*, 2000; J. Melchior *et al.*, 2000; Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009) all other trials had some forms of high risk of bias (Fig 8).

Figure 8. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.



All included trials were described as 'randomised', but 20 did not report the method of random sequence generation (Li and 李涛, 2010; (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Zhi Lin, 林志 and 杨芳, 2011; Tan Yongmei, Gao Lan, 2010; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Tan and 谭朝辉, 2011; Wang Yinyu, Wang Fang, Feng Changsheng, Chen Dongyun. 2008;(Kulichenko *et al.*, 2003); Deng and 邓燕飞, 1999; Bao and 包志伟, 2013; Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014; Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009;(Shakhova, Spasov, Ostrovskiĭ, *et al.*, 2003);(Spasov *et al.*, 2004); 71 Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong

Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Xi and 席管劳, 2006; Zhao Weiguo, Li Yunjing, Yu Yuanlong, Peng Xiabiao, Yang Youye, Xiao Ruomei, 2012;(Melchior, Palm, and Wikman, 1997)(J. Melchior *et al.*, 2000); (Su Guofeng, 2014). Among those that did, seven used a random number table (Li and 李涛, 2010; Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014; Guo and 郭辉, 2013; Wu Qinqin. 2013; Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Zhao Weiguo, Li Yunjing, Yu Yuanlong, Peng Xiabiao, Yang Youye, Xiao Ruomei, 2012; Chang Jing, Zhang Ruiming, Zhang Ying, Chen Zhibin, Zhang Zongming, Xu Qiang, et al, 2012 and six used computer-generated random series (Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Meng Dan, 2012; (Kulichenko *et al.*, 2003) (Spasov *et al.*, 2004) (Cáceres *et al.*, 1999) (R.C. Saxena *et al.*, 2010).

Four trials provided information on allocation concealment, among these two were organised by independent third party clinical management personnel (Melchior, Palm, and Wikman, 1997; Pau, Saxena and Welt, 2013), and two used sealed identical jars (J. Melchior *et al.*, 2000)(R C Saxena *et al.*, 2010b).

Most trials (24/33) had a high risk of bias (RoB) in blinding of the participants and personnel as they assessed two interventions that were different in dosage, or form of preparation, or two types of interventions, or compared A+B interventions vs B intervention, without any blinding information given. Two trials that compared *A. Paniculata* with a placebo control had a low risk of bias as both patients and evaluator (J. Melchior *et al.*, 2000), investigator and pharmacist (Thamlikitkul *et al.*,

1991) were blinded to group assignment and could not distinguish between the 2 interventions. The remaining trials provided no information regarding similarities confirmed between two interventions or provided no information to confirm blinding of personnel.

Most included trials failed to provide enough information to decide whether blinding of outcome assessment was achieved. Nine trials (Bao and 包志伟, 2013; Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014; Guo and 郭辉, 2013; Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Meng Dan, 2012; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009; Wu Qinqin. 2013; Hong Ding Bin Lv, Yan Dong, Xi-Jin Li, Wen-Jing Luo, Hong-Yan Ji, Zong-Ming Zhang, Nian-Zhi Zhang, Sheng Wang, Guo-Lin Li, Xue-Ling Li, Da-Yong Zhu, Shuang-Ping Chen, Bing-Hui Lin, Zhi-Bin Chen, Guo-Tong Chen, Su-Qing Fang, Lin-Hui Lian, Lan-Qiong Deng, *et al.*, 2010; Deng and 邓燕飞, 1999) were given a high risk of bias as they assessed subjective outcome measures, and the patients or practitioners knew if they were in a superior group.

Twenty-six trials reported no attrition. Among the 7 trials that had dropout data, three trials reported a 3-8% drop out and conducted ITT by counting those as no effect, and no per-protocol analysis was performed for those three trials (Jin-Feng Liu Xiao-Ling Zhong, Xue-Mei Ma, Ya-Ling Zhang *et al.*, 2012; Wang Yinyu, Wang Fang, Feng Changsheng, Chen Dongyun. 2008; Hong-Lian Yang, 杨红莲 and 刘凤莉, 2012). Two reported 1% ((R.C. Saxena *et al.*, 2010)) and 6% (Li 李晓卿, 2014) dropout rate without ITT analysis. One trial reported a 25% drop out and provided both ITT and PP analysis findings (Cáceres *et al.*, 1999). The author suggested that the dropout rate in two groups was equal and a potential reason for the large dropout might be related to three weeks' winter holiday. One trial did not clarify how they dealt with missing data (Su and 苏国枫, 2014).

Only one trial (main and pilot)(J Melchior *et al.*, 2000) published a protocol with information on outcome measures and follow-up points consistent with the main trial. All the other trials did not have a protocol available. Four trials (Xi and 席管劳, 2006; Wei-Guo Zhao Yuan-Long Yu, Xia-Biao Peng, You-Ye Yang, Ruo-Mei Xiao *et al.*, 2012; Su and 苏国枫, 2014; Xia and 夏君, 2014) reported selected findings that were not fully consistent with the outcome measures set in the methods.

Only one trial had no obvious risk of other bias (Chang J Zhang Y, Chen ZB, Zhang ZM, Xu Q, Yang YP, Long YY, Liu LL, Cai HY, Gao J, Lu N, Mao B, Wang L, Li TQ. *et al.*, 2008) and this was the only trial that declared a conflict of interest. None of the other included trials stated conflicts of interests and three of the included author(s) worked for the pharmaceutical company producing the investigated product (Melchior, Palm, and Wikman, 1997; Kulichenko *et al.*, 2003; Su and 苏国枫, 2014).

The most common reasons for high risk of other bias were:

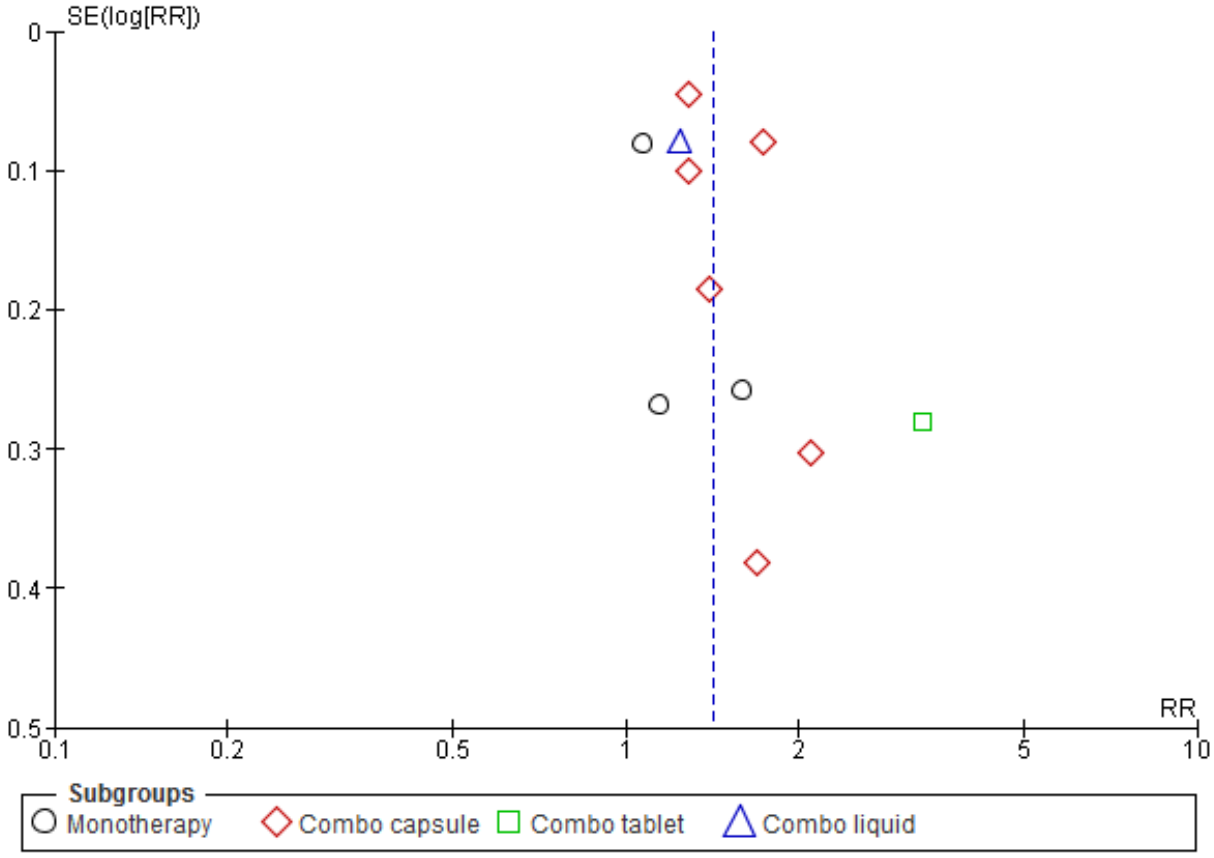
1). In 12 trials diagnostic criteria were not applied at recruitment and there were no inclusion or exclusion criteria specified (Xiao-Yan Hou Di Xin, Qin Qin, Min Gao *et al.*, 2009; Zhi Lin, 林志 and 杨芳, 2011; Wang Yinyu, Wang Fang, Feng Changsheng, Chen Dongyun. 2008; Li Tao, 2010; Deng and 邓燕飞, 1999; Bao and 包志伟, 2013; Pei-Guo Li Hong-Wei Liu, Li-Li Wang *et al.*, 2007; Yu-Qi Tang Wen-Wei Chen *et al.*, 2009; Wu Qinqin. 2013; Zhang Diankui, Jiang Xu, Jiang Shouyou, 1994; Su Guofeng 2014; Xia Jun, 2014).

2). Four trials provided no condition related baseline data, or no sociodemographic characteristic baseline, or neither (Jun-Sheng Sun, 孙俊生 and 赵亚梅, 2014; 75 Zhao Weiguo, Li Yunjing, Yu Yuanlong, Peng Xiabiao, Yang Youye, Xiao Ruomei, 2012; Su Guofeng, 2014; Xia Jun, 2014).

3). Two trials had uneven co-intervention(s) for the intervention and control groups: in one trial, paracetamol was given if body temperature > 39 in the treatment group but 38-38.5 in the control group (Li Tao, 2010); the other trial allowed no additional treatment for the intervention group (Deng and 邓燕飞, 1999).

A Funnel plot for one comparison was performed to investigate potential publication bias (Fig 9). Funnel plots were created to investigate potential reporting bias where this is feasible and there are sufficient studies. Funnel plot tests for asymmetry were separately conducted in STATA, using the metabias command. There was no evidence (p=0.870) of small-study effects.

Figure 9. Funnel plot of comparison: 1 *A. paniculata* vs. Conventional active intervention, outcome: 1.1 Chinese guideline assessment of symptom improvement



5.3.5 Effect estimates

The included trials featured five comparison groups: *A. paniculata* versus placebo (4 trials); *A. paniculata* versus usual care (12 trials); *A. paniculata* plus usual care versus usual care alone (9 trials); *A. paniculata* versus other active herbal interventions (5 trials); and *A. paniculata* pillule (A small pill) versus *A. paniculata* tablet (3 trials). Subgroup analyses were performed only on monotherapy or herbal mixtures, and on different forms of preparation of *A. paniculata*. Subgroup analysis

on upper or lower RTI and adults versus children were not performed due to insufficient data.

A.paniculata vs usual care (n=12)

Data from ten trials showed a statistically significant effect in favour of *A. paniculata* compared to usual care as measured in overall symptoms improvement CCME rate (n = 1347, RR: 1.36, 95%CI: [1.18, 1.57], I^2 = 67%) (See Figure 10). Heterogeneity for the herbal mixture in the capsule subgroup was low when the Wang 2008 trial was removed (p = 0.43, I^2 = 0%). This may be due to: 1). unreported inclusion/exclusion criteria for recruiting participants and lack of clarity on the duration of illness, therefore there was potentially high population heterogeneity; and 2) lack of authentication. Apart from one subgroup (*A. paniculata* as a single herb) failing to show a statistically significant effect, *A. paniculata* as a herbal mixture in capsule and as a herbal mixture in tablet and liquid showed statistically significant effects compared to usual care.

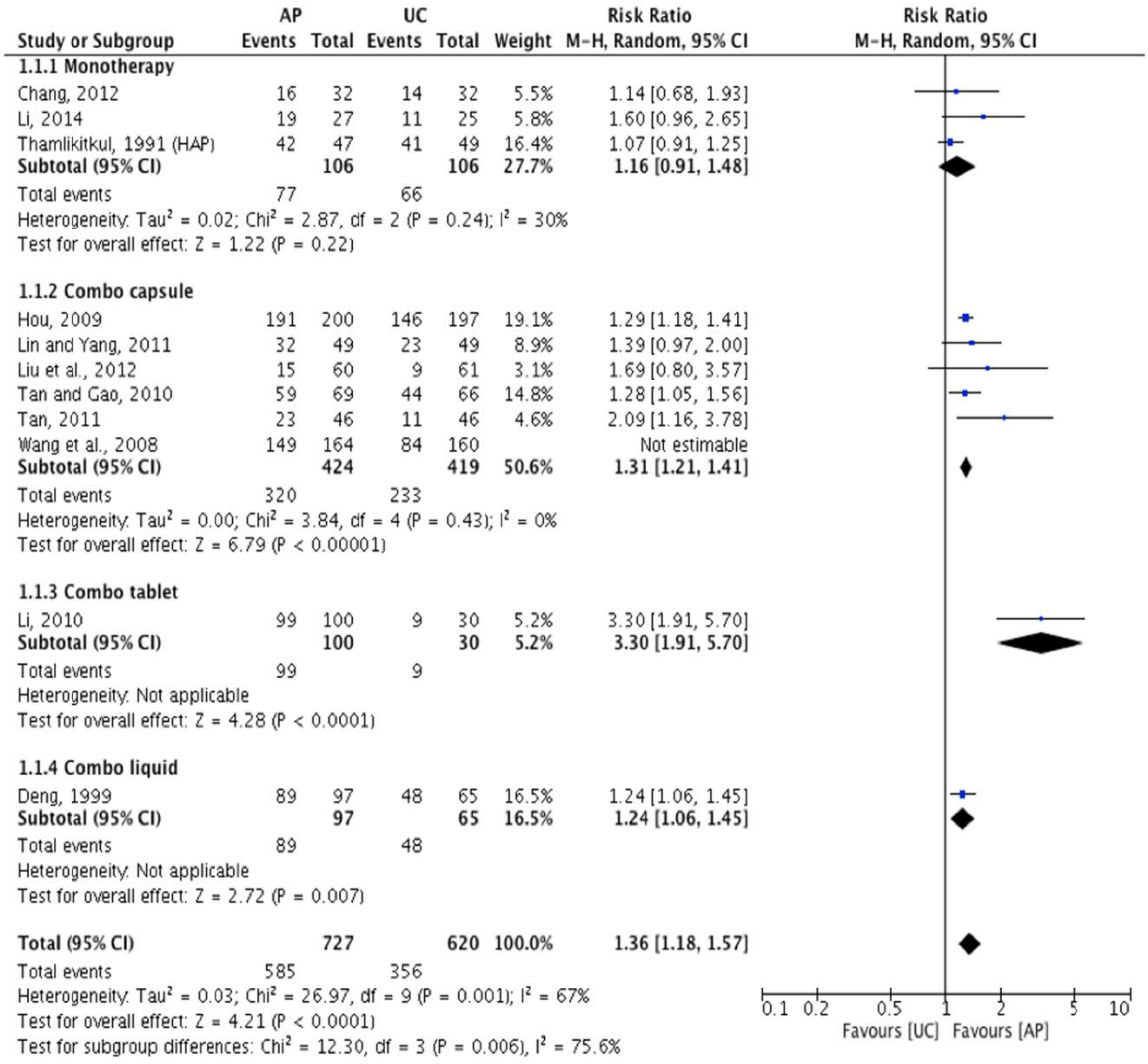


Figure 10. *A. paniculata* versus usual care as measured by global assessment of overall symptoms improvement CCME.

A. paniculata plus usual care vs usual care (n=9)

Six trials showed a statistically significant effect in favour of *A. paniculata* plus standard care compared to standard care alone as measured by assessment of symptom improvement CCME (n=1900, RR: 1.31, 95%CI: [1.16, 1.48], p<0.00001, I^2=81%) (Fig 11). Two trials showed that *A. paniculata* plus standard care shortened the duration of symptoms by approximately 1 day compared to standard care alone (Fig 12). Outcomes of three trials in this comparison group were not pooled and were presented narratively: Sun and Zhao also showed significant improvement in overall symptom as measured by 0-10 VAS (n=78, MD: -0.80, 95%CI: [-1.40, -0.20]). Evidence from two trials showed statistically significant improvements in symptoms and Spasov et al. (2004) suggested reductions in paracetamol intake (55 (mean 1.03) over 95 (mean 2.44), p≤0.0001) and codeine intake (23 (mean 0.43) over 43 (mean: 1.10), p≤0.05) when compared *A. paniculata* plus usual care over usual care alone

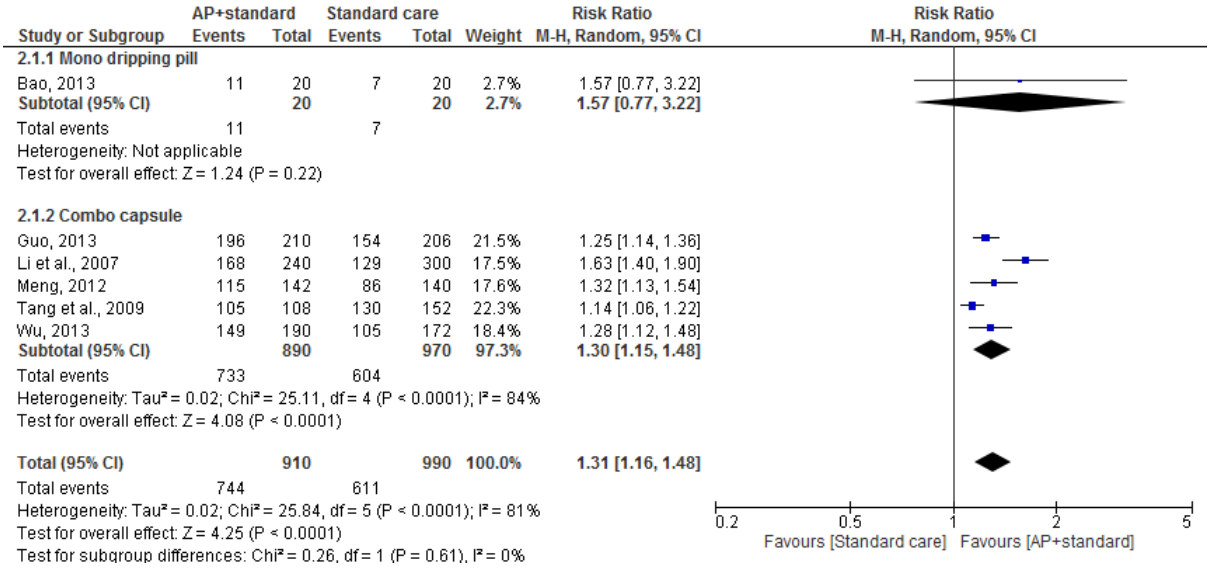


Figure 11. *A. paniculata* plus usual care versus usual care as measured by global assessment of overall symptoms improvement CCME

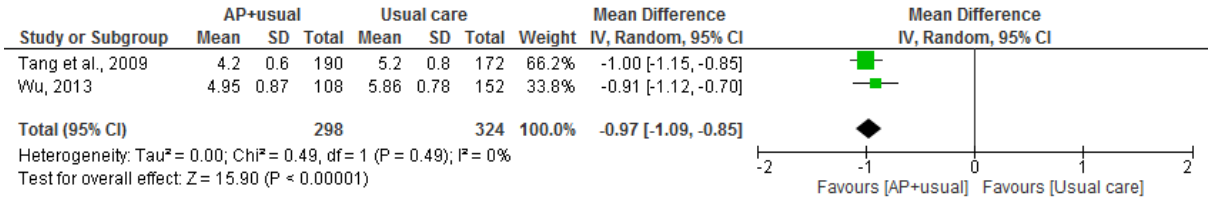


Figure 12. *A. paniculata* plus usual care versus usual care as measured by time to symptom resolution (unit: days)

A.paniculata vs other herbal interventions (n=5)

Five trials showed a statistically significant effect in favour of *A. paniculata* compared to other herbal interventions as measured by improvement rates in overall symptoms (n=827, RR: 1.44, 95%CI: [1.10, 1.89], p<0.00001, I^2=89%). If Zhang 1994 was removed heterogeneity was reduced to I^2=66%. Possible reasons may be down to the fact that this trial targeted children and the product evaluated was not authenticated) (Fig 13).

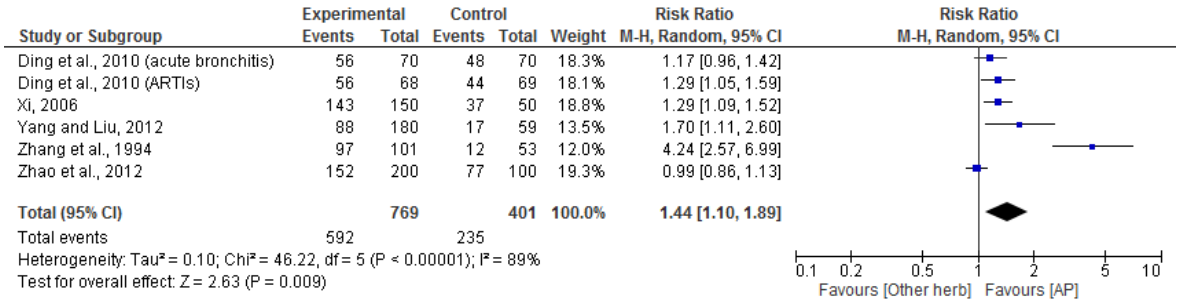


Figure 13. *A. paniculata* versus other herbal interventions as measured by global assessment of overall symptoms improvement

A. paniculata in pillule vs in tablet (n=3)

Three trials failed to show statistically significant differences in *A. paniculata* in pillule (a small pill) when compared to *A. paniculata* in tablet as measured by improvement rate in overall symptoms CCME (n=1076, RR: 1.14, 95%CI: [0.96, 1.79], p=0.0001, I^2=86%) (Fig 14).

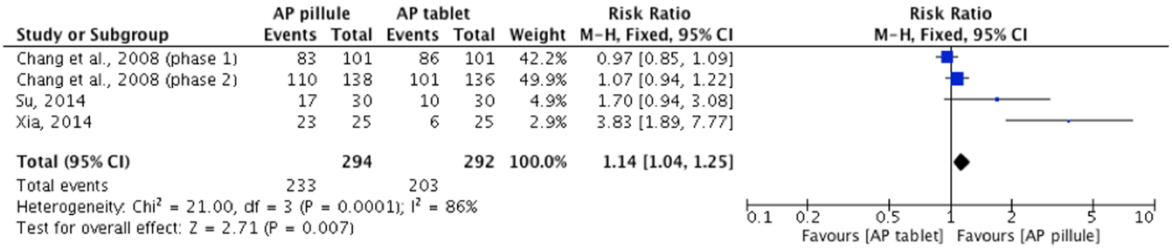


Figure 14. *A paniculata* pillule versus *A. paniculata* tablet as measured by global assessment of overall symptoms

5.3.6 Adverse events

Ten trials did not report on AEs or safety. Among the trials that reported AEs, none reported any acute toxicity and 11 reported no AE in either intervention or control group. AEs in the *A. paniculata* group were reported as one case per trial and included constipation, nausea, vomiting, diarrhoea, unpleasant sensations in the chest, and intensified headache. Four trials did not provide sufficient information to fit into the table are narratively described: Zhang et al (1994) reported some participants had minor AE (vomiting) but did not specify which group or how many participants; Thamlikitkul reported 11 patients in the TG and 9 in CG experienced nausea, vomiting, abdominal discomfort, dizziness, drowsiness, and malaise; and Saxena et al reported 1 vomiting, 1 epistaxis, urticaria, 3 diarrhoea (+ nausea or lethargy), and Melchior et al reported 2 cases of urticaria, without specifying which group.

5.3.7 Summary of evidence

Thirty-three trials involving 7175 patients with ARTIs, comparing *A. paniculata* with conventional interventions, standard care, active herbal interventions, and placebo were included in this review with no language restrictions. Comparison between herbal pillules and tablets was also included. Findings suggest limited but consistent evidence that *A. paniculata* particularly when in combination with other herbs has a statistically significant effect in improving symptoms of RTIs and shortening the duration of symptoms. Reduction in antibiotic usage was seldom reported in the included trials. Although no serious AEs were observed in the included trials, caution is warranted in interpreting safety before comprehensive safety data is available. The quality of included trials was generally lower than desired as many were poorly designed underpowered and inadequately blinded. There was high heterogeneity among trials due to variations in population and outcomes.

5.3.8 Variations in *A. Paniculata*

5.3.8.1 Form of preparation and dosage

The two commonly prescribed preparations in the included trials were capsules and tablets, there were no decoctions. This may due to the extremely bitter nature of the herb described as the "king of bitters". Although single research studies suggested the effects of *A. paniculata* pillules are superior to tablet, our review does not support this finding.

Most *A. paniculata* products have an extraction ratio of 14:1 standardised to contain an average of 35% of andrographolides but solvent extraction ratios were

not reported in most trials. The amount of andrographolide produced from a daily dose of *A. Paniculata* extract containing 15.75mg of andrographolide for URTIs, 225 mg for bronchiectasis, and up to 1200 mg for pharyngotonsillitis. The most common treatment length was 5-7 days, ranging from 3 days for an AURTI to 14 days for bronchiectasis requiring administration three times daily. There is limited dose-finding research available documenting the recommended percentage of the active ingredient, dosage, or ceiling effects so dosage is based on traditional use and herbal textbooks.

5.3.8.2 Common herbal combinations

The most commonly studied co-active ingredients included Scutellaria baicalensis (Huáng Qín [黄芩]), *Isatidis Radix Isatidis* (Ban Lan Gen [板蓝根]), *Flos Lonicera* (Jin Yin Hua [金银花]), Forsythia suspensa (Lian Qiao [连翘]), and Eleuthrococcus senticosus (Ci Wu Jia [刺五加]). Apart from Eleuthrococcus senticosus, the other four herbs and *A. paniculata* are commonly used heat-clearing anti-inflammatory and antimicrobial herbs in Traditional Chinese Medicine, along with *Coptis chinensis* (Huáng Lián [黄连]), *Folium* (Dà Qīn Yè [大青叶]), *Viola yedoensis* (Zǐ Huā Dì Dīn [紫花地丁]), *Pulsatilla Radix* (Bái Tóu Wēng [白头翁]), *Houttuynia cordata* (Yú Xīng Cǎo [鱼腥草]), and *Patrinia Herba* (Bài Jiàng Cǎo [败酱草]). Traditional Chinese Medicine (TCM) prescriptions often involve several herbs with synergistic actives, which are frequently individualised, based on the presenting symptoms and TCM diagnosis. This may result is complex phyto-pharmaceutical interactions and AEs.

5.3.9 Manufacturing

The review identified eight *A. paniculata* products, representing four *A. paniculata* polyherbal preparations (Ke Gan Shuang Qing® capsule and tablet, Fu Fang

Shuang Hua® tablet and liquid, Kan Jang® tablet, Jun Du Qing® capsule) and four *A. Paniculata* monotherapies (Chuan Xin Lian Nei Zhi® pillule and capsule, Chuan Xin Lian® pillule, Kan Jang® tablet, KalmCold® capsule) (see Appendix E).

The active principles of *A. paniculata* have not been fully identified in most trials but it is generally assumed to be the andrographolides. Only three trials provided manufacturing details and chromatographic fingerprints of the herbal preparations to ensure quality and consistency of the products (see Appendix C; Table 1-5). Those studies with inadequate information about the herbal content and manufacturing procedures may not be generalisable to other *A. paniculata* studies as bioequivalence is 'assumed' rather than proven. A CONSORT herbal extension checklist is recommended to guide reporting of herbal trials and to assure herbal quality and bioequivalence (Gagnier *et al.*, 2006).

5.3.10 Safety (AEs and toxicity)

The traditional uses of *A. paniculata* are as a liver tonic to help maintain appetite and digestion; alleviate gastro-intestinal upsets and acute diarrhoea; immune function; to support intestinal function and as treatment of infectious disease (Zhang *et al.*, 2007). This traditional use may reduce adverse reactions (ARs) caused by conventional medicines when they are prescribed in conjunction with *A paniculata*. Minor AEs reported in the included trials were mainly gastrointestinal. This was not consistent with the recent TGA pharmacovigilance analysis, which revealed the most common AEs associated with *A. paniculata* were hypersensitivity or allergic reactions (TGV, 2015). The TGA safety report explored the association between anaphylactic/allergic-type ARs and *A. paniculata*, suggesting that ADRs tend to be related to highly concentrated methanol extracts. Our safety findings are inconclusive as there was an absence of proportionate data on each minor AE in each group thus limiting a comprehensive risk-benefit assessment.

Acute toxicity studies in rats suggested median lethal doses for andrograpolide is more than 40g/kg and 10 mg/kg body weight is when the adverse reactions became apparent. The European Medicines Agency (EMA) reports no acute or genotoxicity data on Andrographis extracts but there is a possibility of very high doses causing reproductive toxicity, with decreases in sperm counts and motility that were linked to disruption of spermatogenesis in rats (Csupor, Dezső, 2014).

5.4 Implications and future direction

This review suggests that *A. paniculata* might act as a safe and effective treatment for uncomplicated RTIs, either alone or in combination with conventional treatment. The findings suggest that *A paniculata* has a statistically significant effect in improving symptoms of ARTIs and shortening the duration of symptoms by 1 day, whether this is a clinically significant finding is something that clinicians and policymakers need to decide on. Manufacturing information may be an important factor that differed among these included trials, and we recommend all further trials are based on a consistently safe and well defined *A. paniculata* product. Pharmacological research exploring correlations between ARs and manufacturing procedures (with methanol, or aqueous solvent, or aqueous-ethanol mixture) is also needed.

Future well-designed trials evaluating effectiveness and safety of oral *A. paniculata* in capsule or tablet form and reported according to the herbal CONSORT checklist are vital and may serve to minimise antibiotic prescription and AMR. Considering the importance of antimicrobial stewardship future trials could explicitly include data on antibiotic use.

5.5 Strengths and limitations

A broad search strategy including both English and Chinese databases was adopted without language restrictions. We attempted to include grey literature by seeking manufacturers' reports and attempted to contact original authors for missing data. We followed Cochrane methodology; data were screened and extracted independently. A substantial patient sample size was identified.

Methodological quality judgements are made based on incomplete reporting of the evidence of effectiveness and may be undervalued (Higgins JPT, 2011). The diagnostic criteria used in included trials were inconsistent and more than one third provided no inclusion/exclusion criteria. Due to the heterogeneous population, diverse settings, variations in the form of *A. paniculata* employed, outcome measures, and different study protocols, data were pooled using a random-effects model. This has restricted the generalisability and the findings, which should, therefore, be interpreted with caution. There was an inadequate number of trials available to allow further subgroup analyses on children or on lower RTIs. This is unfortunate as a high proportion of ARTIs in primary care are among children and this would have been a useful outcome measurement. Some included trials were non-inferiority RCTs as placebo-controlled trials was considered unethical by some researchers. They demonstrated that *A. paniculata* was clinically superior to other herbal interventions but failed to provide evidence on the established effect of the control herb.

One-third of the trials reported obtaining informed consent. Not all trials were performed in countries where the International Council for Harmonisation (ICH) guidelines are legally binding. The included trials rarely clarified whether the

products were GMP certified. It was unclear whether some of the trials were conducted with adequate ethical approval.

5.6 Conclusion

This systematic review suggests that *A. paniculata* appears to be beneficial and safe for relieving ARTI symptoms and reducing time to symptom resolution. The evidence is inconclusive due to the limited methodological quality of included trials and study heterogeneity. Well-designed trials are needed to evaluate effectiveness, efficacy, and safety of *A. paniculata* as a monotherapy or as an herbal mixture for the treatment of ARTIs, as well as exploring its potential to reduce antibiotic prescribing in primary care. The next chapter looks at philosophy and mixed methodology with an emphasis on qualitative research.

Chapter 6: Research philosophy and methodology

6.1 Introduction

The previous systematic review and meta-analysis chapter allowed me to examine the quantitative evidence regarding the effectiveness and safety of *A. paniculata* in treating respiratory tract symptoms (ARTIs). The studies reviewed informed my protocol design for a double-blind randomised placebo-controlled feasibility study which will be presented later in Chapter 8. The review also raised questions about whether such a trial would be acceptable to health professionals in the UK as none of the studies in the systematic review were carried out in the UK.

To explore relatively under-explored questions about people's views and experiences I turned to qualitative research. This chapter will provide the grounding for the next chapter which will examine the attitudes and beliefs of primary care health professionals around the use of herbal medicines in the symptomatic treatment of acute respiratory tract infections through a qualitative interview study.

This chapter discusses the mixed methods approach in this thesis and examines qualitative research in healthcare. I shall consider my philosophical worldview and discuss the pragmatic approach utilised in this thesis. The subsequent sections will look at semi-structured and telephone interviews and discuss sampling, saturation, data collection, analysis, and rigour within qualitative research.

6.2 Mixed methods research used in this thesis

Mixed method research uses both qualitative and quantitative approaches which may provide a better understanding of a healthcare research problem than either of them alone, especially when there is little known about the specific research

topic such as the use of a herbal medicine in ARTIs (O'Cathain *et al.*, 2014). I used a sequential mixed method design in this thesis which involved conducting a systematic review, running a qualitative interview study followed by a feasibility trial. The information from the systematic review provided preliminary data on design and dosage for the upcoming feasibility study but also made me consider why none of the trials in the review were based in the UK. This observation made me question what were health professionals' attitudes and beliefs about, and experiences with, herbal medicines in Southern England. I also wondered whether they would be open to being involved in a subsequent feasibility trial on herbal medicines for ARTIs. I therefore decided to carry out a qualitative study to explore these observations and questions. The next section discusses the importance of qualitative approaches in healthcare.

6.3 Qualitative approaches in healthcare

Qualitative approaches (sometimes alongside quantitative approaches) are necessary in healthcare when researchers want to ask questions about why patients and healthcare professionals behave in a particular way and to focus on participants' feelings, meanings and experiences. For example, quantitative researchers can explore treatment adherence by measuring how much of a given treatment or prescribed medication people actually take. However, this in itself does not help improve treatment adherence, but simply highlights the extent of a problem. Qualitative research aims to explore why it is happening and this may generate ideas to help solve the problem (Greenhalgh, 1997).

According to Braun and Clarke, qualitative research in healthcare offers rich and compelling insights into the real world, experiences, and perspectives of patients and health care professionals in ways that are completely different to, but also sometimes complementary to, the knowledge we can obtain through quantitative methods (Braun and Clarke, 2014). Qualitative research methods are an appropriate means of exploring individuals' perspectives on a complex topic, particularly where relatively little is known already. It provides respondents the platform to reflect and reason on a variety of subjects in a different way and are invaluable for exploring poorly described issues in healthcare and useful for understanding healthcare professionals experiences (such as the use of herbal medicines in primary care) (Yardley *et al.*, 2015)(Khankeh *et al.*, 2015). They can also be used in healthcare to identify obstacles and barriers to practice change by investigating the reasons behind certain behaviours, something to which quantitative research does not lend it itself to (Al-Busaidi, 2008).

Qualitative research can enhance trial design and explore the acceptability and feasibility of an intervention. It provides insights regarding the complexity of interventions and how treatments are provided in practice. Qualitative research can help to optimise interventions and trial procedures, measure the right outcomes in the correct way, and understand more about the health condition under examination, which then feeds back into optimising interventions for that condition. However, researchers cannot undertake qualitative research about all issues for every trial. Researchers may wish to consider problems they think they might face within a particular trial and prioritise the use of qualitative research to

address these issues, while also staying open to emergent issues (O'Cathain *et al.*, 2014).

O' Cathain carried out a systematic review and found 28% (82/296) of articles reported qualitative research undertaken at the pre-trial stage; in a pilot and, feasibility study and in preparation for the main trial. Qualitative research addressed a wide range of aspects of trials focusing on the intervention being trialled (71%); the design, process, and conduct of the trial (15%); the outcomes of the trial (1%); the measures used in the trial (3%); and the target condition for the trial (9%)(O'Cathain *et al.*, 2013). These data provide a quantitative rationale for the importance of using qualitative methods in my research, which explores a relatively poorly understood area of investigation. The next sections in this chapter will focus on qualitative research methods and philosophy and provide the grounding for the next chapter which describes the methods and findings of a qualitative study exploring the attitudes of primary care health professionals in Southern England around the use of herbal medicines in the treatment of ARTIs.

6.4 Qualitative research philosophy

Qualitative research covers a wide range of approaches and methods that are linked to different beliefs about what there is to know about the social world and how to find out about it (Lewis, Jane, Ritchie, 2013). According to Creswell, when researchers undertake a qualitative study, they start with some underlying philosophical or theoretical assumptions, while bringing to the study their worldviews that end up shaping the direction of their research. However, these may not be explicit (Creswell and Creswell, 2013).

Therefore, when conducting this research project it was important for me the researcher to consider my philosophical stance or worldview and how these may shape my research journey. Every researcher has their own view of what constitutes truth and knowledge. These views guide our thinking, our beliefs, and our assumptions about society and ourselves, and they frame how we view the world around us, which social scientists call a paradigm.

A paradigm is a way of describing a world view that is informed by philosophical assumptions about the nature of social reality (ontology -the study of the nature of reality) and ways of knowing (known as epistemology - how do we know what we know?). Ontology is the philosophical study of the nature of being, becoming, existence, or reality. There are many common ontological positions. Two common positions are; realism and idealism. A very basic definition of realism is, "Things exist only in the real world" and, therefore, anything that cannot be observed through the senses is of no consequence. Alternatively, idealism states that "Things exist only within the mind" and, therefore, are open to interpretation. Realism is generally stated as the concept underpinning quantitative research, while idealism is the concept that is said to underpin qualitative research however this categorisation has been challenged by some authors (Creswell, 2012).

Within epistemological thinking, there are two key positions; induction and deduction. Induction is considered a bottom-up approach through which patterns are derived from observation of the world, whereas deduction looks at things from a top-down perspective whereby logically derived propositions or hypothesises are tested against observations. Within induction, researchers begin with specific observations and measures, begin to detect patterns and regularities, formulate some tentative hypotheses that they can explore, and finally end up developing some general conclusions or theories. Within deduction, researchers start with a

theory about a subject. They then narrow it down into more specific *hypotheses* that they can test (Gray, 2014).

Paradigms lead us to ask certain questions and use appropriate approaches to systematic inquiry known as methodology (How should we study the world?). The methodology summarises the research process. It is where the assumptions about the nature, reality and knowledge, values, and theory and practice on a given topic come together. Methods are the means used for gathering data and are an important part of methodology. Certain paradigms may be associated with certain methodologies. Three common paradigms include positivism, constructivism, and pragmatism:

- Positivists believe that there is a single reality. They assume that empirical knowledge based on principles of objectivity, verificationism, and reproducibility is the foundation of all authentic knowledge and are therefore more likely to use quantitative methods to measure this reality (Bryman, 1988). Positivist researchers remain detached from the participants of the research by creating distance, they believe it is important in remaining emotionally neutral to make clear distinctions between reason and feeling. (Carson, D., Gilmore, A., Perry, C., and Gronhaug, 2001).
- Interpretivists/Constructivists believe that there is no single reality or truth and therefore reality needs to be Interpreted. They commonly use qualitative methods to get those multiple realities Interpretivists do not necessarily reject the positivist account of knowledge, but they question the idea that the logic and methods of natural science can be imported into the study of societies. (Lewis, Jane, Ritchie, 2013)(Carson, D., Gilmore, A., Perry, C., and Gronhaug, 2001).

- Pragmatists believe in the idea that there is such a thing as reality but it is ever-changing based on our actions; they do not assume any particular epistemological or ontological position but the researcher will take a practical view when attempting to solve problems and link theory and practice through the research journey (Morgan, 2007). Pragmatism asserts that research approaches are wide-ranging and eclectic and are designed based on the individual researcher's project's circumstances (Glogowska, 2010).

In this PhD, I have taken a pragmatic approach. Pragmatism is both a philosophical stance and methodological approach which allows practical and flexible solutions to the everchanging world of mixed methods research (Morgan, 2007). The use of a pragmatic approach in herbal medicine research (especially in clinical trials) is difficult as in practice herbalists commonly use combinations of herbal medicines to address health issues and it is challenging to gain ethical and regulatory approval in the UK to conduct clinical research this way.

In the qualitative study, I mainly used an inductive approach as health professionals' views and experiences on herbal medicines use is an under-researched area where there is a need to generate new insights without imposing a predefined structure to the area of enquiry. However, for questions relating to the feasibility study design, I adopted a deductive approach as there were preformed questions that I wished to answer. In the next section, I will look at qualitative data collection.

6.5 Qualitative data collection

The main forms of data collection involve interviews, focus groups, observation, documented material collection such as letters and photographs, narrative collections, and open-ended questionnaires (Gill *et al.*, 2008).

Individual interviews are probably the most widely used data collection method in qualitative research. They provide an opportunity to gather an in-depth viewpoint and understanding of peoples' personal perspectives and context on research phenomena. They are generated research methods, which involve reconstruction and retelling of attitudes, beliefs, and behaviours. Generated data gives insight into peoples' perspectives and interpretations of their beliefs and behaviours and crucially an understanding of the meaning associated with them. Different types of interviews include

- Structured interviews
- Semi-structured interviews
- Non-directive interviews
- Focused interviews
- Informal conversational interviews (Edwards, R, and Holland, 2013).

In this study, I chose to use semi-structured telephone interviews which I will discuss in the next two sections.

6.6 Semi-structured Interviews

Semi-structured interviews are in-depth interviews where the respondents are asked pre-defined open-ended questions and thus are widely employed by different healthcare professionals in their research. Semi-structured, in-depth interviews are employed extensively with an individual or within a group setting.

These are single interviews conducted with an individual or with a group and generally last up to an hour. Semi-structured interviews are based on a prepared semi-structured interview or topic guide, which is a schematic presentation of questions or topics and need to be explored by the interviewer (Jamshed, 2014).

To achieve optimum use of interview time, interview guides serve the useful purpose of exploring the views of many respondents more systematically and comprehensively as well as to keep the interview focused on the desired line of action. The questions in the interview guide have a core question and many associated questions related to the central question, which in turn, improves further through pilot testing of the interview guide. The interview guide can be altered to include new topics/areas as data collection progresses and data emerges. To have the interview data captured more effectively, recording of the interviews is considered an appropriate choice but this is always contingent upon consent being obtained from the respondent (Jamshed, 2014).

6.7 Telephone interviews

According to Carr and Worth, the use of the telephone interview as a research method is a reflection of broader social change and technological advances, with increased use and acceptability of telecommunications to support healthcare (Carr and Worth, 2001). Telephone interviewing can be an effective method of data collection when interviewers understand the potential benefits as well as challenges (Carroll, Christ, and Sönksen, 2000).

The potential benefits associated with using telephone interviews as a mechanism of data collection include using economic and human resources efficiently, minimising disadvantages associated with in-person interviewing, developing

positive relationships between researchers and participants, and improving the quality of data collection. The potential limitations to telephone interviewing include maintaining participant involvement and maintaining clear communication, communicating with participants who offer extraneous information (such as nonverbal cues), and encountering participants with health concerns (Musselwhite *et al.*, 2007a).

Some authors have noted that qualitative researchers use telephones infrequently due to concerns about whether telephones are appropriate for the task. They pointed out that interviews typically are assumed to be face-to-face, not via telephone, and that the thought of conducting a clinical research interview via telephone "invites clinical and methodological scepticism" (Sturges and Hanrahan, 2004).

Novick discussed the assumption that face-to-face interviews are superior to telephone interviews. The author suggested that this viewpoint might stem from a legitimate concern that the lack of visual cues may lead to data loss or distortion. If these losses occurred, data analysis and interpretation might be affected, harming the quality of research findings. In her study, she found little evidence that data loss or distortion occurs, or that interpretation or quality of findings is compromised when interview data is collected by telephone. Furthermore, telephone interviews may allow respondents to disclose sensitive information more freely, and telephone conversation has been reported to contain several features that render it particularly suitable for research interviews (Novick, 2008)(Beck, 2005). In this qualitative study, the participants are health care professionals with busy schedules therefore telephone interviews allow flexibility and convenience in collecting data.

6.8 Sampling and saturation in qualitative research

Within qualitative research, sampling can occur at several stages. It can be predetermined, or it can evolve while collecting, interpreting, or reporting data. Sampling while collecting data for qualitative research is not the same as sampling in quantitative research because researchers are not interested in being able to generalise at a statistical level – instead, the key is purposive or strategic sampling (Mason, 2000). In this study, purposeful sampling was used (Al-Busaidi, 2008) (Lewis, Jane, Ritchie, 2013). Purposeful sampling is widely used for the identification and selection of information-rich cases for the most effective use of limited resources. It involves identifying and selecting individuals or groups of individuals that are especially knowledgeable about or experienced within a certain area (Palinkas *et al.*, 2015).

Saturation is said to occur when data from new cases do not contribute to the development of emerging theory, even after the researcher has tried to ensure that new cases are those most likely to extend or challenge their ideas (Mason, 2000). In this qualitative study, I attempted to achieve saturation of the main themes. A recent article by Braun and Clake (2019) questioned the validity of saturation. They suggest that saturation is not a particularly useful term or concept as it is difficult to determine the likely point of data saturation in qualitative research and especially in thematic analysis (which will be discussed below). They suggest using the concept of information power to guide sample size (Braun and Clarke, 2019).

6.9 Qualitative data analysis

Most types of qualitative analysis involve the categorisation of verbal or behavioural data, for the purposes of classification, summarisation, and tabulation. The content can be analysed on two levels. The basic level of analysis is a descriptive account of the data: this is what was said, documented, or observed with nothing read into it and nothing assumed about it. Some texts refer to this as the manifest level of analysis. The higher level of analysis is interpretative: it is concerned with what was meant by the response, what was inferred or implied. It is sometimes called the latent level of analysis. (Hancock B, 2002). In this study, I will focus more on the latent level of analysis for health professionals' views on herbal medicine, and take a more descriptive approach with information relating to the feasibility study.

6.10 Thematic analysis

As mentioned above in the qualitative philosophy section this interview study used an inductive and deductive thematic analysis approach as outlined by Braun and Clarke (2012), which is commonly used in analysing interviews. The inductive approach was used to explore health professionals' experiences with herbal medicine as it is a relatively under-researched area.

A deductive approach was used with data associated with data around clinical trials of herbal medicines as this feedback was used to inform the design of the subsequent feasibility trial. The reason this method was chosen is that a 'rigorous thematic approach can produce an insightful analysis that answers particular research questions' (Braun and Clarke, 2006). Braun and Clarke outline six phases of thematic analysis including, familiarisation with the data, identification of initial

codes searching, reviewing and naming themes, and finally writing up (see Figure 15 below).

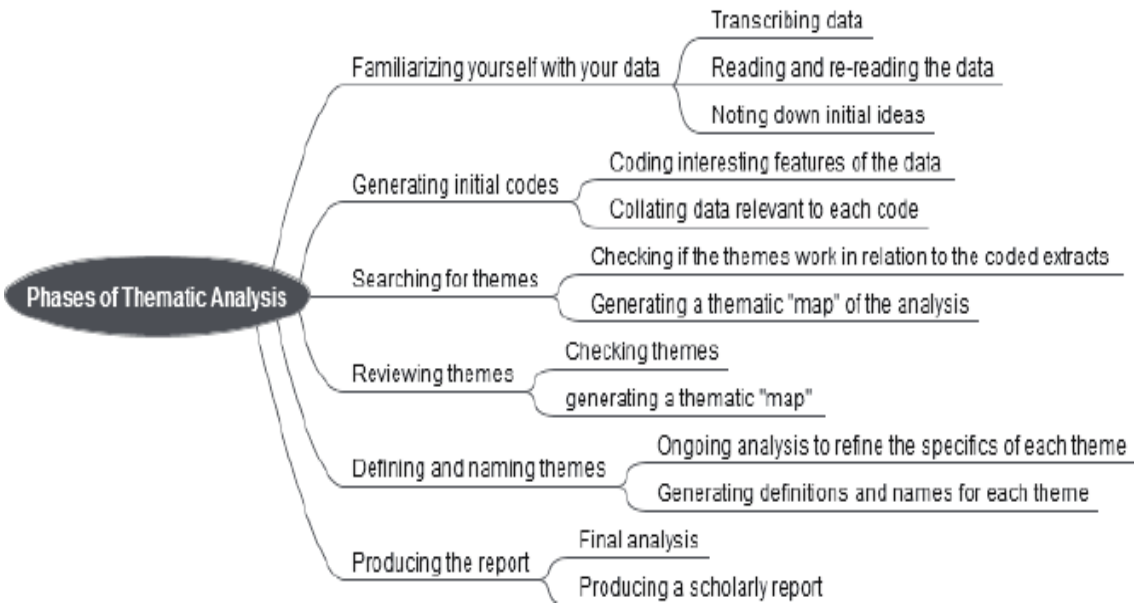


Figure 15. Stages of Thematic Analysis (adapted from Braun and Clarke 2006)

Thematic analysis can provide rich and insightful understandings of complex phenomena, and contribute new ideas to existing theory (Braun and Clarke, 2014) (Joffe, 2012). A theme refers to a specific pattern of meaning found in the data. A key feature of a theme is its relevance to the aims and objectives of a study rather than its recurrence. Another important area relating to themes is whether they are deductive - drawn from a researcher's theoretical idea- or inductive – derived from the raw data itself. The next section discusses rigour in qualitative research.

6.11 Rigour

Researchers conducting quantitative studies use conventional terms such as internal validity, reliability, objectivity, and external validity. In establishing trustworthiness, Lincoln and Guba created stringent criteria in qualitative research, known as credibility, dependability, confirmability, and transferability (Lincoln and Guba, 1985). These criteria are discussed below regarding my study:

- Credibility – Credibility ensures the study measures what is intended and is a true reflection of the social reality of the participants. There are many strategies to address credibility that include "prolonged engagement" and member checks. In this study, I used constant comparison during the analysis which involved comparing and checking the transcripts. During supervision, my supervisors constantly reviewed segments of my data and we discussed the draft coding schedule within the research group. Another way to enhance credibility was to use responder validation, where participants give feedback on the research findings. I was unable to do this due to the time and financial limitations of this PhD
- Dependability - Dependability ensures the process is described in sufficient detail to facilitate another researcher to repeat the work. This requires a

detailed audit trail. I kept a reflective diary noting down thoughts and ideas after each interview and maintained an audit trail of study procedures

- Confirmability - Confirmability is comparable to objectivity in quantitative studies. Here, the goal is to minimise investigator bias by acknowledging researcher predispositions. In this study, I outlined my position as a herbalist and noted down my personal views and thinking in my reflective paragraph (see section 7.9 in the next chapter). After each interview, I listened back to check if my role as a herbalist affected my questioning and responses and amended my responses as necessary. I engaged in reflective practice to maintain transparency and negative case analysis to avoid premature theme formation and incomplete representation of the data
- Transferability -Transferability relates to the ability of the findings to be transferred to other contexts or settings. Because qualitative research is specific to a particular context, it is important a "thick description" of the particular research context is provided allowing the reader to assess whether it is transferable to their situation or not (Maher *et al.*, 2018). In this study, I have documented the methods and findings in-depth so the study could be rerun by another researcher.

6.12 Conclusion

This chapter has looked at research philosophy and methods underpinning this thesis with a special emphasis on qualitative research. In the next chapter, I will document the methods I used in a qualitative study with primary care health professionals in Southern England around the use of herbal medicines to treat

ARTIs. I will also outline the subthemes and themes gleaned from the telephone interview study and examine how these findings informed my feasibility study.

Chapter 7: A qualitative interview study, exploring the attitudes and beliefs of health professionals (HPs) around the use of herbal medicines in the symptomatic treatment of acute respiratory tract infections (ARTIs) in primary care

7.1 Introduction

The previous chapter discussed the philosophy and methodologies underpinning this chapter. This chapter describes the methods and findings of a qualitative study exploring the attitudes of primary care health professionals in Southern England around the use of herbal medicines in the treatment of ARTIs. As mentioned previously qualitative studies allow exploration of the beliefs, experience, and perceptions of health professionals, patients, and the public. This is a particularly useful approach with underexplored topics, such as perspectives on the use of herbal medicines for ARTIs. These insights may then be applied to develop an understanding of the enablers and barriers to providing potentially promising herbal interventions in the real-world clinical setting if shown to be effective (Malterud, Hamberg and Reventlow, 2017).

The information gathered in this study contributed to the design of the subsequent feasibility study (by drawing on health professionals' previous experiences with herbal medicine trials) and provided insight into health professionals' attitudes into herbal-based treatments for ARTIs. Currently, there has been minimal research into the use of herbal medicines in the treatment of respiratory tract infections in primary care; either from the perspective of health professionals, patients, or the public.

Existing qualitative studies in the UK, looking at the role of herbal medicines in the treatment of infection, found that there were concerns about quality control of herbal medicines, fear of litigation if herbal medicines were prescribed or recommended, and a lack of knowledge on the safety of herbal medicines (Flower *et al.*, 2015). The study suggested that more research is needed to explore herbal approaches to current antimicrobial treatment More qualitative studies exploring alternatives to the treatment of acute infections are required due to the emergence of AMR and the lack of new medicines to treat these infections. This chapter will outline the aims and objectives of the study, document the methods used, and includes a section on personal reflection. It will present the findings including the sub-themes and themes including specific information relating to the running of herbal medicine trials. Finally, it will discuss the strengths and limitations of the study.

7.2 Aims and objectives

7.2.1 Aim

The aim of this qualitative interview study was to explore the experiences, views, beliefs, and attitudes of health professionals (HPs) around herbal medicines for the treatment of ARTIs.

7.2.2 Objectives

- To explore the perceptions, beliefs, and attitudes of health professionals regarding the use of herbal medicines to treat ARTIs
- To examine facilitators and barriers to health professionals recommending or prescribing herbal medicines for ARTIs

- To inform a subsequent feasibility study on using herbal medicines in the treatment of acute ARTIs.

7.3 Methods

7.3.1 Design and approach

I decided to carry out qualitative telephone interviews with HPs (doctors and nurses) working in primary care who regularly see patients with ARTIs. HPs were involved in recommending and prescribing herbal medicine to the participants in the subsequent feasibility study, therefore it was important to investigate their opinions and perspectives on the study (including facilitators and barriers), and use the information gathered to aid in the design of the feasibility study protocol. The information gathered underwent both an inductive and deductive thematic analysis to allow themes to be drawn from the data (Braun and Clarke, 2014).

7.3.2 Recruitment

This study required participation from health professionals who regularly see patients with ARTIs to explore their views about safety, acceptability, and efficacy of herbal medicines, as well as the barriers to prescribing or advising herbal medicines for ARTIs in the NHS. The intention was to recruit a purposive sample of health professionals allowing for gender, years of experience, practice location, practice deprivation score, and list size. It was estimated that a sample of 25-30 health professionals would provide sufficient data, although we aimed to continue to recruit until data saturation was reached for main themes (Vasileiou *et al.*, 2018). Following advice from Wessex Clinical Research Network (CRN), it was decided to recruit from Primary Care practices in Wessex, Peninsular, and West of England to

meet the sampling requirements, as this was considered feasible for a single interviewer over the time allocated and the resources available.

7.3.3 Ethics

Research ethics committee approval was sought from the University of Southampton, Faculty of Medicine (27851). Ethical approval was gained with the Health Regulatory Authority via the Integrated Research Application System (IRAS system) (208314). The data was stored on password-protected University computers. Digital recordings were destroyed at the end of the study. Transcripts and consent forms will be stored securely for 10 years in line with University policy.

7.3.4 Data collection

Semi-structured telephone interviews were chosen as a convenient, cost-effective, flexible, and interactive data collection method (Novick, 2008)(Musselwhite *et al.*, 2007b)(Sturges and Hanrahan, 2004). They allowed comprehensive exploration of the range of issues under investigation with coverage of a wide geographical area. The interview guide (see Table 7) was developed from the research aims and objectives and discussions within the supervisory team and was further developed with input from Patient and Public Involvement in Research (PPI). MB, an experienced PPI representative, ensured that all of the participant facing documentation were lay friendly including the topic guide and the participant information sheet (PIS) (See Appendix E). MB provided feedback on the findings and agreed to act as PPI representative on the subsequent feasibility study design and findings. There was on-going feedback and support from the supervisory team on the suitability of the questions.

The guide was piloted with a GP from Aldermoor Health Centre at the University of Southampton, who gave feedback on the arrangement, coherence, and wording of the questions. Results from earlier interviews were used iteratively to inform subsequent data collection and questions were refocused and adopted in response to emerging themes.

The qualitative work remained flexible with respect to participants' agendas but covered the broad topics/questions noted in the interview guide. It is common in qualitative work to iteratively develop topics and questions as new ideas emerge from early data collection. Therefore, new topics were added as the interviews progressed and data collection continued. (Discussion around whether herbal medicine was taken seriously by some health professionals was an example of an added topic) (See Appendix D). However, key topics investigating the perspectives of health professionals' attitudes and beliefs around the use of herbal medicines in ARTIs remained the same.

Data collection continued until no more important novel responses were received and it was considered that saturation of the main themes had been achieved (Saunders *et al.*, 2018). The health professionals involved in the study were reimbursed for their time (£50 per GP; £20 per Practice Nurse) in line with CRN guidance.

Table 7. Interview guide used in this qualitative study

Herbal medicines for acute respiratory tract infections (RTIs): A semi-structured qualitative interview study

1. What are your thoughts about herbal medicines? Do you have any personal experiences with herbal medicines?
    - Personal
    - Family used
    - Patients

2. How do you feel about using herbal medicines for respiratory tract infections?

3. How would you feel about advising patients to use herbal remedies for respiratory tract infections?
    - Prescribing

4. How is it different to administering conventional drugs?

5. Did you have any concerns about herbal medicines?
    - About safety?
    - About efficacy?
    - About compliance?

6. How do you think the herbal treatment differs from conventional care

7. How do you think patients feel about taking herbal medicines?

- In general
- For respiratory tract infections

8. How long have you been in practice?
    - Less then 10 years
    - More than 10 years
    - More than 20 years

9. Is there anything else you would like to tell me?

7.3.5 Data management

The telephone interviews were conducted at Aldermoor Health Centre, Southampton, and ran from August to December 2017. Prior to each interview, the researcher provided the participant with information regarding the study (both written and verbal) (See Appendix D), and also the reasons why the data was important, what it would be used for, and how it would be stored. The interviews lasted on average about 25 minutes for each participant.

The interviews were digitally recorded (Olympus DS-2500), transcribed in full by a professional transcriber, and anonymised using pseudonyms unique to each participant with only the researcher knowing the identity of each participant. The transcripts were compared with the original recorded audio file and any errors were amended. The researcher listened to the recordings to capture not only what was said but also all the features of the talk, including utterances, pauses in speech,

hesitations, and changes in voice tone, which can also convey meaning and context to the data.

7.3.6 Data analysis

The analytic approach in this study was thematic analysis (Braun and Clarke, 2006)(Braun and Clarke, 2014). A hybrid approach (elements of the data relating to herbal medicine trials were explored deductively to aid in the design of a subsequent feasibility study; an inductive approach) was taken with health professionals' views on herbal medicines and ARTIs (Malterud, 2016).

All transcripts were coded on a line-by-line basis by hand while further iterations were made to the coding schedule, in discussion with the supervisory team. Subsequently, the transcripts were coded using NVivo (V.11) Computer Assisted Qualitative Data Analysis Software (CAQDAS). The use of CAQDAS is a tool to assist with data management especially when there are large amounts of data but does not help with interpreting the data corpus. Using NVivo (V.11) allowed a cross-sectional approach where the codes and themes were compared across the whole data set with a focus on emergent themes throughout the process.

The first stage of analysis involved becoming immersed in reading and re-reading the transcripts. Initial thoughts and ideas were noted in a memo. Familiarisation was achieved and patterns that consistently occurred in the data were identified and labelled with codes and sub-codes. Each code label summarised the topic content. A label and full descriptive definition were then provided for each code. Codes and definitions were iteratively refined during a continuous process involving the supervisory team, which involved the codes being grouped, moved, relabelled, added, and removed to produce a set of codes and sub-codes and a coding manual, which adequately fitted and thoroughly explained the data. The

analysis process eventually showed that saturation had been reached as no substantial new information was emerging from the later transcripts.

From the coded data, key preliminary themes were identified, and their relationships with each other and the research questions were mapped into concept 'nodes'. This occurred in conjunction with multiple readings of the transcripts to ensure that participants' responses were not decontextualised nor their original meanings lost. Demographic details were collected including practice location, HP's gender, years' experience as a HP, and number of HPs, including HP registrars where relevant, working in the practice (see Table 8)

Table 8. Participant Characteristics

Health professionals	***N=26***
GPs	22
Practice Nurses	4
Gender	
Male	12
Female	14
Years in Primary Care practice Median (range)	19 (2-37 years)
Demographics	**N=23**[3]
Practice location	
Urban	11
Rural	12
Practice area	
Peninsula	4
Wessex	8
West of England	9
Practice list size	
(Median) range	(11,904) 7325 – 21729

[3] 26 health professionals from 23 Primary Care practices

Practice deprivation scale - Median (range) (1 is most deprived; 10 is least deprived)	5.5 (1-10)

7.3.7 Personal Reflection

After each interview, to reflect on the data collection methods and content of the interviews, I recorded my initial thoughts on a digital recorder. Then, as soon as possible after each interview, I wrote up my reflections, along with the other thoughts that I had about the interview itself, the interaction between myself and the participant, and what, if any, themes were emerging from the data. This process of regular reflection after each interview was a process that I found beneficial as it allowed me to critically examine my thoughts and feelings about how I felt the questions in the interview were asked and how the participants responded.

From both the transcripts and the audio files, I was able to assess which questions worked well in the interviews and which did not. This helped me to further reflect on the interview itself and to document my thoughts and feelings about any given situation encountered during the research process. It also enabled me to adjust my approach and questioning in subsequent interviews. In addition to my reflective notes, I kept a written research diary, which assisted in reflecting on important topics or interesting cases. The research diary also helped me reflect upon issues that arose with the participants that I interviewed. The supervisory team also listened to example audio recordings, read the transcripts, and provided feedback on both the process and the content.

Following the completion of several interviews, I asked interviewees at the end of the interview how they thought the topic guide had worked and whether they thought I should have included any further relevant questions. This helped to

ascertain whether the interview questioning was effective or whether some areas, deemed by the interviewee as important to the research, had been omitted.

As the main researcher in this qualitative study, it was important for me to recognise and reflect on the influence that my training as a Western and Chinese medical herbalist may have had on this study. On one hand, it helped in understanding healthcare professionals' explanations of various medical conditions and treatments. On the other hand, I had to be aware of any preconceptions I had when interviewees spoke negatively about herbal medicine. During the interview process, including when reviewing transcripts, I regularly checked my responses and the framing of my questions to reduce the chance of this happening.

Regarding disclosure of my professional identity, I did not disclose to the participants that I was trained as a medical herbalist or that I was going to be involved in a forthcoming feasibility trial. However, I felt it was important for me to be honest and open with the interviewees, especially if they asked about my background during the interviews. This did happen at the end of one interview where the interviewee disclosed that they practiced homeopathy and asked if I would be working on a herbal medicine trial. I explained that I was trained as a medical herbalist and that I would be working on a herbal medicine trial.

7.4 Main Findings

7.4.1 Themes and sub-themes

Three themes were developed from the analysis with each theme having two or more subthemes (See Table 9). They are subsequently detailed below with quotes from the participants. There was a significant amount of rich data generated in this study analysis therefore, I focus mainly on themes one and two in presenting my findings, as being of particular relevance to my research questions. I also provide a

section on participant feedback which was used to inform the running and design of the subsequent feasibility study.

Table 9. Overview of themes and subthemes

Theme and sub-themes
Theme 1. Making sense of herbal medicine in general practice
• Subtheme 1a: "Old wives tales" and evidence – HP perceptions of the herbal world • Subtheme 1b: Advising, recommending or prescribing – Managing responsibility for herbal medicines • Subtheme 1c: Filling the gap between acceptance and knowledge – Attitudes towards training and expertise in herbal medicine • Subtheme 1d: "Complete opposites" – Patient groups and types • Subtheme 1e: "A whole different kettle of fish" – how and when HPs use herbal medicines
Theme 2. An element of mystique- beliefs, and attitudes towards herbal medicine use by patients
• Subtheme 2a: Powerful medications and ethical dilemmas - herbal medicine and the placebo effect • Subtheme 2b: Faith, belief, and approval – Health professionals views on patient use of herbal medicine • Subtheme 2c: "Natural does not equate to being good" - contrasting beliefs between HPs and patients on herbal medicines

Theme 3: Prejudice and purity- Health professionals' views on herbal governance and production

- Subtheme 3a: Reputation and Reassurance - Manufacturing, quality control and regulation of herbal medicines
- Subtheme 3b: Awareness and familiarity - Safety and interactions of herbal medicines

Theme 1: Making sense of herbal medicines in general practice

This theme explored how health professionals rationalised making decisions around the use of herbal medicines in the context of general practice, including their stance on advising, recommending, and prescribing herbal medicines in general practice; their lack of training or knowledge in this area; and their perceptions of the herbal world. GPs discussed patient groups and types and talked about their own use of herbal medicines. A recurrent talking point throughout this theme was the need for evidence in herbal medicine. Interestingly, some health professionals did not take the title "herbal medicine" seriously.

Subtheme 1a: Old wives tales and evidence – HP perceptions of the herbal world

There was a wide range of opinion in this subtheme. Health professionals talked about their views on the world of herbal medicine. The herbal world includes herbal products, the profession of herbal medicine, and people's beliefs in herbal medicines. It was also viewed as a different belief system by some health professionals or a parallel model. There were three main positions identified; health professionals with positive attitudes to herbal medicines; those who adopted an ambivalent stance and those who were sceptical in their approach to the herbal

world or did not take it seriously. The influence of politics in making herbal medicines less available by removing them from circulation was also discussed.

Although most GPs insisted, they would need to see evidence before considering using herbal medicines; a minority of health professionals said they held a positive stance on herbal medicines and did not mention the need for evidence:

> *"I think we would be – we'd be open to trying Echinacea for instance, for a cold"* (Patrick GP).

Some GPs sat on the fence and described an ambivalent view of non-evidenced based modalities such as herbal medicines. This was related to following an evidenced-based practice philosophy/approach:

> *"But if there is no evidence, I wouldn't encourage or discourage it, obviously if I'd had information about certain problems, then I will highlight it to them, but I'm very much coming from a base of – its got to be evidence-based for me to promote it* "(Nuala, GP).

Several GPs reported a sceptical approach to herbal medicines, citing a lack of understanding and knowledge and the perceived lack of evidence:

> *"My initial reaction is a bit of scepticism and I think that's possibly because of lack of understanding and lack of research. So in terms of the time I spend reading about the options of herbal medicines compared to conventional medicines, its much less, so my understanding isn't there. And probably reflects what we know about them at large, I would have thought. So – yes, so my initial thoughts are scepticism, I think"* (Ciaran, GP).

Interestingly, later in the interview after some hesitancy, the same GP talked about a positive experience with using herbal medicines. It is interesting to note that they initially excluded personal life experiences when they first talked about his approach to herbal medicines:

> *"Not personally. Actually that's not true: that's not true. So – I mean I guess in terms of personal experience, things like [Kalms], particularly going through exams and things like that, the sort of thing with valerian in that you can get over the counter at the supermarkets and things like that; they have been quite helpful. Liquorice … for sort of stomach upsets. I mean I have had some experience personally, yes"* (Ciaran, GP).

Some GPs talked about the perception of the word/title "herbal medicine" and how some doctors may not take them seriously due to their associations with folklore and magic. It was suggested that a name change might make health professionals take the subject more seriously. It was important to distinguish the profession of herbal medicine from the lay use of herbs according to one GP:

> "*I think you're probably going to get some – enhanced resistance from doctors and some patients, calling it a herbal medicine. (I: Mmm) I think that could well be an issue. I think if it was a named chemical compound – then – that might result in less resistance*" (Conor, GP).

> *"Well – I suppose we should make a distinction between – herbal medicine and the use of herbs. Mmm even the word – herbs – has a kind of magic roundabout feeling; you know, really we should be calling them medicinal plants substances, medicinal plant – medicinal plants, really, because, you know, what I'm driving at*

is that herbal medicine is a kind of system with its own kind of canon of beliefs and training colleges and so on and conventional medicine" (Patrick, GP).

The use of herbal medicine was mentioned by some health professionals as "old wives tales" due to the lack of evidence supporting them:

"Obviously, in the meanwhile, until that piece of work is done, which hopefully you'll be doing with this study that you're proposing, it's all just guesswork and it's just old wives tales" (Sarah, GP).

As well as individual attitudes, GPs raised the issue of the collective professionals' attitude of conventional healthcare providers to herbal medicine. There was discussion around the lobby to get herbal medicines banned from the NHS and the reasoning behind this move (Donnelly, 2017). A few GPs mentioned it was not just lack of evidence but a political movement to remove herbal medicines from circulation. Drives to remove herbal medicine from CCG formularies was mentioned by one health professional as a way to remove them from people's consciousness:

"There's a belief they have around – evidence for these sorts of medicines, but it's also, I think, just a kind of wish to – get the whole concept of herbal medicines removed from the zeitgeist, by making them – by marginalising them; it's a kind of paradigm effect, it's just the sort of – it's not necessarily rational. It's more about the kind of – a kind of turf war around ideology" (Patrick, GP).

Subtheme 1b: Advising, recommending or prescribing –Managing responsibility for herbal medicines

This subtheme was characterised by a wide range of opinions and attitudes. To advise, recommended, or prescribe herbal medicines was strongly linked with concerns around evidence, efficacy, and safety, although similar issues around other OTC medications were seldom mentioned.

Many of the health professionals discussed their position regarding prescribing, advising, or recommending herbal medicines to their patients. Others talked about the difference between prescribing and recommending:

> *"I think if you prescribe it, then you are – you're essentially telling them, well you've essentially come to an agreement with them that that is the course of treatment that they should take. I think recommending is, you know, it's optional; it's something you could do if you wanted to, but it's not necessary, not an absolute"* (Bob, GP).

The recommending of herbal medicines to reduce overprescribing of antimicrobials for ARTIs was discussed:

> *" I wouldn't have any kind of issue in either recommending or, you know, prescribing; I guess it's more going to be a recommendation coming out of it to try herbal remedies; absolutely don't have a problem with that at all"* (Molly, PN).

Health professionals were consistently cautious in their decision-making and would recommend/advise/prescribe only if there was scientific evidence. More specifically if there was a trial or study carried out on the herbal medicine:

"So, for example, if there was good, scientific evidence that it works, I would recommend it. At the moment what I find is that I have patients that tell me herbal medicines work for them, which is great, but I don't have any data to back up; do you see what Mmm? So I don't – I don't actively recommend herbal medicines, but, as with any treatment, if there was overwhelming, scientific evidence that it worked the best, then why wouldn't you advise them to use it?" (Marie, GP).

"I might use them if I didn't feel somebody was appropriate to give antibiotics to, who had tried over-the-counter sort of – cough medicines, like honey and lemon or expectorants etc, if they benefit – worth a try, if there was a study being done to prove whether they actually reduce the complications or reduce the length of time people were unwell for. Then if that had been done, if that work had been done, then I would definitely recommend them or prescribe them if they are feasible" (Sarah, GP).

Others questioned the role that evidence played in their decision-making and would use herbal medicine as an alternative if it was "effective". There was a critique by one GP on evidence-based medicine (EBM), which questioned its reliance on constructs such as outcome measures. This GP also questioned whether EBM was flexible or nuanced enough in its approach to herbal medicine:

"How … not that much, to be honest. The reason for it is that it will be usually in a situation where there was no alternative; like if there was something that was really effective that I could take, then I would – I would take it. When I say effective, Mmm

like – whatever evidence-based hoops it's needed to jump through, but the trouble with evidence-based medicine is that it's – for me, it raises almost as many questions as it answers, because you can have evidence, but it depends very much on what sort of outcome measures are looked at" (Patrick, GP).

Several GPs suggested that prescribing medicines rather than recommending had more impact and therapeutic 'power'. Prescribing involves documenting the medicine details in paperwork, which gives the medicine more "authority". A common thread was that recommending was taken less seriously by patients than prescribing and that prescribing herbal medicines would have more impact and 'power':

"Well, I think there's a lot of power in a prescription. If you actually prescribe something and it's one of those GP10 things, in black and green, whatever it is, that is – that's a kind of message that's ... reinforcement is another word for it, but it kind of implies that that's something real and important" (Patrick, GP).

Some talked about the perceived 'strength' of the medicine and the perceptions people would hold if a medicine was not prescribed:

"Some people would probably think that they wouldn't work, so if it's not prescribed, it's not going to work…….. I think there is that sort of – so if it's not prescribed, it's not strong enough – kind of thing." (Juliet, GP)

Rarely, GPs mentioned working with the patient to come to a shared decision on how to proceed with using herbal medicines. In a situation where there is no alternative or choice, this GP would consider recommending herbal medicine:

> *"Mmm – to recommend that is – is quite – is a responsibility and I would be a bit uneasy to – if I couldn't prescribe it but I knew it was effective, then, yes, I would recommend as an alternative. But I would present it as a choice; I think and say, well, these are the choices in this instance. But if I haven't got anything suitable to prescribe to someone, I guess I'd be saying, well, I haven't got much I can do except to suggest that you go and purchase a herbal remedy which, as I said, as long as it is underpinned by evidence, lack of harm and of some benefit, then I'd do that"* (Pat, GP).

Others delegated responsibility to the patients because of their lack of knowledge and expertise:

> *"I don't think I've got enough knowledge myself to advise them in terms of pros and cons or what the problems may be. I say to my patients that I'm an expert in terms of – established medicines and pharmaceuticals, but I know nothing about herbal medication and I'm not aware of any trials, which is what a lot of our current medications that we prescribe are based on. So if they wish to try them out, that's entirely upon their heads, as it were, but it's not something I can give any information or advise on"* (Nuala, GP).

A viewpoint from some health professionals was that herbal medicines are outside their sphere of expertise, therefore, considered it as a "non-treatment":

> *"I think – because probably a lot of other GPs have such a lack of experience with herbal treatments, because of – it's just not involved on any sort of medical school or GP training teaching …, that [I've] experienced and therefore lack of ability to recommend or prescribe it is minimal. So I think probably to a lot of us, it's almost a non-treatment in a way and it's not something that [I've really considered]"* (Michael, GP).

Frequently, health professionals said that they could only advise on herbal medicine use due to lack of evidence and there was a need to mention the "downsides" of the herbal medicines:

> *"I think probably – people are likely to be more happy to advise; the doctors would be more happy to advise until there is a point where there is actually really clear sort of – evidence that there is efficacy there. The downside to advising rather than prescribing, I guess, is that it's sort of less formal; the patient might be less likely to tell, for example, a pharmacist or another doctor, that they're taking it. So, yes, it comes down to sort of just making sure that if you are advising the patient to use a herbal medicine, that you're also making sure that you advise them – about any downsides to taking it or interactions"* (Joanne, GP).

Subtheme 1c: Filling the gap between acceptance and knowledge – health professionals' attitudes towards training and expertise in herbal medicine

This subtheme explored the attitudes of the participants in the study towards training to gain experience and knowledge of herbal medicine and whether they

thought it was necessary for their practice. Some GPs talked about their lack of knowledge and training in herbal medicine and how it affected their decision-making. A number of participants said they felt that it was unnecessary to do such training, as it was the patient's responsibility.

One GP wondered why patients consulted with her about herbal medicine and the responsibility involved and made an analogy with herbal medicine and dentistry:

> *"I've not got the expertise to know, but I think it is a point, isn't it; if you recommend something you have to know that it doesn't do any harm. It's like if you – a patient has got a dental problem and they come to see the doctor and clearly they shouldn't be coming to see the doctor for a dental problem, but we have to be very careful not to give any advice on teeth matters, because if you do, you sort of take clinical responsibility. So I suppose probably us advising – I don't know – that they take that medication, there will be some responsibility on us for that. I don't know, I hadn't thought of that"* (Rosa, GP).

The issue of why patients come to see GPs regarding herbal medicine use (as they don't have the necessary training or expertise) was mentioned. Many described this as a barrier to advising due to lack of training:

> *"Then I sort of wonder why they've come to see me, because it should either be helping or are they just seeking reassurance from me, which might well be the case, in which case I need to be well informed about the herbal medication to – appropriately advise. And I don't have that knowledge base, at the moment"* (Marie, GP).

A minority mentioned that training on safety and interactions of herbal medicines would be useful in practice:

> *"I think that would be helpful – yes – because I mean we do come across it and there's lots of patients that prefer to just take herbal things and I think we certainly need to be – mindful of that and aware, because if we're not aware and something does have potentially – significant interactions or whatever, then we're going to be left in the dark, especially if we don't encourage patients to talk about things. So, yes, I think it probably would be better to have a bit more training and we'd fit it all in, but, yes, I think it probably should be covered somewhere"* (Juliet, GP).

Several GPs mentioned they had trained in other complementary and alternative (CAM) therapies with homeopathy being the most popular. They described this as mainly being in order to gain a greater understanding of the therapy without necessarily leading to use of this modality in their practice:

> *"I did the homeopathy course, because I thought, well, you know, I can learn a little bit more about, you know, what I can tell them, even if I'm not sure if I sort of would do it myself. But – so – you know – it was really just to give me another arm, if you like, so if people asked I was better informed."* (Juliet, GP).

Subtheme 1d: "Complete opposites" – Patient groups and types

GPs discussed their local practice demographic, patient types and distinctive groups as defined by their attitudes and behaviour around herbal medicines and health. Factors such as socioeconomic and educational background were considered influential in a patient's choice of medicine. The tension between personal and professional use of herbal medicines was mentioned. Patients who followed a natural health lifestyle philosophy were a clearly identifiable group:

"So there'll be some of those and then there'll be other people that actually really do believe in sort of healthy lifestyles, eating well, healthy, you know, taking extra vitamins and very much would be into not taking prescription medicines really. So you get completely different types of people, complete opposites" (Juliet, GP).

This GP described the factors that may influence a patient's choice of medicine:

"... it depends on the patient. ... There's a certain group of patients that will be more willing to try something herbal because it's considered more natural, in inverted commas, compared to something – you know - paracetamol for example. Others will go, well, if you think it's okay or if you think it's safe, they'll follow what you say. So it depends on the patient in front of you and their sort of – socio-economic background and all sorts; their general views on health, I suppose" (Marie GP).

Some health professionals talked about different patient groups; those that are keen, and those who are not so interested in herbal medicines and, those in the middle:

"There's two types of patients actually, especially in the sort of area I live in – just – broadly. There's those that wouldn't dream of herbal and there's those that are really keen on herbal" (Rosa, GP).

"I suspect there's probably a [rule of 3] as usual, that a third of them are very – probably keen proponents of it, give it a try, a third are neutral but if I suggest it then they'll take it. And maybe there's a third that say, no, I don't really want to do that, I don't believe in it, what's the evidence? (Pat, GP).

Certain health professionals identified patients who preferred not to have herbal medicines and preferred prescribed medicines because they were considered stronger and more effective than herbal medicines:

> *"There's certainly patient populations that would be more compliant and more likely to use it, versus patient populations that would – think that I was fobbing them off with something, as opposed to treating them, if you see what... Mmm"* (Felicity, GP).

This GP suggested that patients do not want to take any medicines at all especially herbal medicines:

> *"Patients don't really want to take anything if they can get away with it. So – I think you've got that probably even more so in herbal things. I mean you'll get some patients – a patient type that might, you know, stick religiously to the dose as advised on the packet but a lot of people just stop and start things really. So, yes, obviously that's going to play a part with anything"* (Juliet, GP).

According to some health professionals, middle class and educated patients gravitate towards herbal medicines and the 'natural' approach, and prefer not to take antibiotics:

> *"I think it's the demographics of our patients. We've got a lot of middle-class patients, a lot of older patients and I think they probably still challenge us less. But also I do think you probably – it might even be better than traditional medicine"* (Sheila, GP).

"I think quite a few – are quite open to taking them. I don't think it's – I think … particularly – Mmm we are in a fairly rural area and with fairly well educated patients who are very keen not to take antibiotics, for instance, and are keen to try and help themselves before they come and see us, so I think they're used fairly heavily" (Felicity, GP).

Subtheme 1e: "A whole different kettle of fish" – how and when HPs use herbal medicines

This subtheme concerns the personal and familial use of herbal medicines. The use of herbal medicines as part of their upbringing and culture was discussed by some GPs. This frequently included tension between personal versus professional use of herbal medicines.

GPs talked about what situations they and their family would use herbal medicines and whether they act rationally when using them:

"Yes, [my wife] uses herbal medicines for bruises. (I: Arnica, is it Arnica?) Sorry, yes, sorry. She's a very strong advocate for Arnica. All my children and everybody comes , lots of children's parties and when anybody had a bruise, she would be very strong advocate of Arnica. It's quite interesting because she's a highly technical radiologist and [laughter from both]. Anyway, so – yes. So I mean I've certainly, in terms of Echinacea, I've certainly used that a lot and St John's Wort in the past" (Tony, GP).

One GP talked about the difference between taking herbal medicines herself versus prescribing them to a patient and her medico-legal concerns:

"Well, top level really; RCTs and that kind of thing. See, it's interesting. It was me, just me, personally, and you said – oh, you've got a bit of a cold, we think this

works; it's not got any major side-effects that we know of, it's been used for donkeys' years. Being a little bit kind of open to the thing, I might give it a go. But if you said to me, prescribe it to a patient, that's a whole different kettle of fish. (I: Right) I guess you have your medicolegal hat on, you're a bit……" (Marie, GP).

Theme 2: An element of mystique- beliefs and attitudes towards herbal medicine use

In this theme, health professionals discussed their beliefs and attitudes towards readily available herbal medicine products. This included the use of herbal medicines as a placebo. The Oxford English Dictionary defines placebos as a 'drug, medicine, therapy, *etc.*, prescribed more for the psychological benefit to the patient of being given treatment than for any direct physiological effect'.

In this study, the placebo effect was commonly described as eliciting an endogenous self-healing response, although there was a wide range of explanations of what it was and how it worked in a primary care setting.

An interesting corollary expressed by some health professionals was that many conventional medicines such as antibiotics and antidepressants are like herbal medicines in that they are under the guise of being evidenced-based but "everybody knows they aren't."

Patient beliefs were also linked with placebo. There was frequent categorisation of patents into different 'camps': those who follow herbal medicine, those who do not, and those who would follow the health professional's opinion. According to several GPs patients held opposing views when it came to interpretation of the word "natural".

Subtheme 2a: Powerful medications and ethical dilemmas - herbal medicine and the placebo effect

The topic of placebo and herbal medicines was widely discussed. This was a complex area as different practitioners interpreted the placebo effect in different ways. There was discussion around what makes a herb active or placebo and how it could be utilised in practice. In some quotes attitudes towards placebo and herbal medicine were muddled and confused.

Some GPs compared the placebo effect of herbal medicines with that of mainstream drugs such as antibiotics and antidepressants. Health professionals also talked about using herbal medicines as placebos but also mentioned the ethical barriers that arose from such use.

Defining the placebo effect

Several GPs described/defined the self-healing benefits of the placebo effect as mediated through an enhanced feeling for patients of doing something positive about their health. This GP also explains that she approves of using "some of the placebo effects" with patients:

> *"But if people feel they have benefited and it has enhanced their body's ability to get better so they feel they're positively doing something and feeling positive, I think there's every reason to endorse – endorse that kind of action. So the body's ability to – the body's going to heal itself, we hope, and anything you can do to keep people positive about how that's going to work, I think helps and that's how I would see some of the placebo effects perhaps working. Does that make sense?"* (Amanda, GP).

Others felt that this potent "placebo, self-healing response" might be operating in a similar way to conventional medicines such as antidepressants, antibiotics and painkillers, and this was a shared understanding among health professionals:

> *"So it's a kind of – you're using something like a herbal medicine to kind of mediate a placebo, self-healing response, which is a very, very powerful, therapeutic agent and I think – and lots of medicines are used in that way, under the kind of guise of being evidence-based, but everybody knows they aren't. So antibiotics would probably be the best example"* (Patrick, GP).

> *"Mmm if you take antidepressants, 90% of the antidepressant effects for mild to moderate depression is a placebo effect and that's the same in terms of St John's Wort"* (Paul, GP).

Herbs active or placebo

Interestingly, some health professionals suggested that unless the herbal medicine contained identified ingredients that have been recognised as effective through research then they attributed any benefits to the placebo effect:

> *"But the general – my general feeling is that it's a placebo effect that's beneficial, unless it's got specific active ingredients that obviously have been recognised. to be effective"* (Bob, GP).

Some had confusing explanations on how the placebo effect was related to herbal medicines. One GP held the belief that herbal medicine is either a "complete

placebo" (and safe) but people may be still sensitive to them or they contain active constituents and will therefore "work":

> *"it's either going to be a complete placebo, in which case you don't necessarily worry about side-effects, although anybody can get allergic to anything, but if it's actually going to work, if it's really effective, then there's going to be bioactive substances in it"* (Sarah, GP).

Another health professional also suggested that herbal medicines may combine both a potentially powerful specific medicinal effect, which patients are unaware of (and the possibility of side effects), and have the potential to act as a placebo:

> *"So you still get your placebo effect, but you just feel more in control, which is great. I think what sometimes patients don't appreciate is that herbal remedies can carry with them some significant side-effects, because these are potentially quite powerful medications which haven't being regulated"* (Paul, GP).

Role in practice

This participant reported advising patients to use herbal medicines and been able to control or "ramp up" the placebo effect in practise for the benefit of the patient:

> *"But I often do recommend herbal remedies to patients, especially when I'm*

looking to – even if I'm anxious it's got a bit of a placebo effect, if you can ramp up a placebo effect as much as possible, well, you know, then it's worthwhile" (Paul, GP).

Interestingly, one GP appeared conflicted when he talked about how he followed evidenced-based medicine, but also mentioned there were a lot of times where he wished he could use as a placebo (such as a herbal medicine) that was not "clinically effective" to complete a "consultation satisfactorily". However, he was concerned about the ethics of such an approach:

"I think – I'm generally evidence-based therapy, but having said that, there's a lot of times when it will be great to be able to prescribe something which you knew – maybe wasn't clinically effective but it meant that you could complete the consultation satisfactorily...So I think it would just be – a – the ability to prescribe a placebo by the backdoor, really, which I think ethically that's probably not sensible" (Bob, GP).

Other health professionals talked about being able to use herbal medicines as placebos in a consultation but also mentioned the ethical problems associated with this approach including whether to tell the patient:

"I mean I guess there's the whole sort of ethics around them; if you're prescribing something that you know is no better than a placebo, and whether you can actually sort of inform the patient [behind that]" (Ciaran, GP).

One GP described the positive benefits of herbal medicines holding an air of

mystery and intrigue for the user and being something, which they discover themselves. He describes the type of patient who may be susceptible to the placebo effect:

> *"Generally speaking, really positive (I: Okay) and I think that's about them feeling in control and the placebo effect sort of works well when there's this element of mystique around something and that they've discovered something that other people haven't"* (Paul, GP).

Subtheme 2b: Faith, belief, and approval – Health professionals' attitudes on patients' use of herbal medicine

In this subtheme, health professionals frequently talked about people being believers or non-believers and having faith in herbal medicines. This was often closely linked to the placebo effect but is discussed as a feature of the patients themselves rather than of the herbs. The issue of whether some patients decline to disclose the use of herbal medicines with their health professional was discussed.

Patients were described and identified as both 'believers' and 'non-believers' of herbal medicines by some health professionals. This was linked to whether they were effective or not:

> *"..so what people believe in, what might work for them. So people use the Echinaceas and things and swear by them and other people have – have a different response to them or don't feel they work for them"* (Amanda, GP).

One GP talked about how they augment a patient's belief in herbal medicines and described the scenario they go through:

> *"So I will do what I can to enhance something where I think patients have really got faith in its efficacy; but equally there is a sort of moral tightrope that I walk down"* (Paul, GP).

An interesting point discussed in the interviews with health professionals was the feeling that some patients might not disclose the use of herbal medicines because of fear of disapproval and the fact that they hold differing worldviews or come from a different belief system:

> *"I think sometimes maybe people are reluctant to tell us because we might get – we might not be approving that they're taking that because we are sort of the establishment"* (Bob, GP).

> *"….I also get the feeling with herbal medicines that a lot of our patients are using it but don't like to tell us, because they kind of feel that somehow they're going behind our backs or – shows lack of commitment to what we're prescribing"* (Sheila GP).

According to one GP, people from some ethnic minorities may be particularly reluctant to disclose details of their own herbal medicine use:

> *I would say probably – well – you wouldn't necessarily know; they won't perhaps tell you if they're taking them. I live in an area where there is a very – a large*

ethnic minority; so Somali people have a herbal system themselves and I think they do use it, but funnily enough, they never talk about it. They might think we weren't interested, or we might disapprove" (Patrick, GP).

Subtheme 2d. "Natural does not equate to being good" - contrasting beliefs between health professionals and patients on herbal medicines

A common talking point among health professionals was patients and GPs differing views on the significance of something being considered 'natural'. Health professionals mentioned that certain patients view herbal medicines as natural therefore safe compared with conventional medications. This viewpoint was not shared by some GPs who viewed herbal medicines as natural thereby unrefined and potentially toxic. One GP talked about how patients now prefer natural alternatives to antibiotics, which was not the case in the recent past.

Some health professionals mentioned that patients' positive attitudes towards natural things could be viewed as a part of a rejection of the scientific viewpoint:

"I think generally patients love it, because it's perceived as natural and – the fact that many herbs are highly toxic doesn't quite enter into their understanding. But for many of them – I think it's popular and it's a kind of reaction against science and technology, I suppose. But I don't think – I think most patients are very happy with it" (Simon, GP).

One GP thought it's "a cultural thing" when it came to natural versus synthetic. He talked about how some people distrust or are suspicious of the conventional pharmaceutical world and their motives, including putting profits before wellbeing:

"And the general belief, the cultural belief, particularly over the last few years, that

sort of drug companies and Western medicine is corrupt in some way and there's a conspiracy against people, that sort of thing. There's all sorts of reasons why people, rather than take something that's natural and not a synthetic, I think that's a cultural thing" (Bob, GP).

Some GPs believed that patients use natural substances and have better compliance with natural products because they are considered safer, even though these views may be misplaced. One GP suggested that some patients act in an irrational way by choosing something natural:

"There's this misconception that I often see in patients: yes, yes, my diabetics, for example, they'll say yes – a glass of orange juice, that's natural sugar, that's fine. But natural does not mean it's any safer or any more appropriate. Natural sugar does not equate to being good." (Peter, GP).

"If it's natural, not pure, therefore it's more likely to be unsafe and – so I think patients will be happier to be more compliant with it" (Tom, GP).

According to this GP, times are changing, and patients prefer a more natural approach to antibiotics in light of the current situation with AMR. He harked back to a time when there was less awareness of the side effects and limitations of antibiotics and patients demanded antibiotics:

"... Mmm I remember in early 2000 it was always a fight with every patient, but now, now people mainly don't want an antibiotic and therefore if you gave them what they viewed was a safe alternative, and a natural alternative, they would jump at it, I'm sure" (Tom, GP).

Theme 3: Prejudice and purity- Health professionals' views on herbal governance and production

Health professionals talked about regulation, safety and quality control of OTC herbal medicines throughout the interviews. Many GPs expressed anxiety and concern around sourcing, strength, manufacture, composition, and dosage of herbal products. These issues were frequently discussed especially in contrast with conventional medication. Most health professionals were more tolerant of herbal medicines they were familiar with and were less concerned about safety or interactions.

Subtheme 3a: Reputation and Reassurance - Manufacture, quality control and regulation of herbal medicines

The manufacture and quality control of herbal medicines was talked about by many GPs and was a concern. A comparison with how conventional medications were regulated and manufactured was discussed. Some GPs talked about the relationship between modern and herbal medicines and commented on their similarities and differences. Other health professionals suggested that there was a lack of governance regarding herbal medicines and suggested they may be useful if regulated correctly.

One GP talked about how conventional and herbal medicines are produced and manufactured. He expressed concern at the standards and the perceived lack of quality control with herbal medicines:

> *"There's such a clear process for manufacturers' medicines and – and getting the dosage as well we get alerts all the time in a batch when something's been wrong and they have to recall all the drug and I don't know if that would happen at all for herbal – to the manufacturing process, quality assurances"* (Tom, GP).

Another GP suggested that herbal medicines are unrefined and under researched therefore there were questions around their safety and posology:

> *So effectively, most scientific treatments are herbal remedies purified – and standardised so we know what the side effects really are and what the doses should be and everything else"* (Paul, GP).

The different philosophies between how herbal and conventional medicines are thought to work, and how they are produced was explained by one GP. He went on to describe the synergistic effects of herbal medicines, in which different compounds within the plant work together:

> *"And the herbalists believe that the substances in plants actually balance each other, which is – I don't know whether that's true or not, but it's an intriguing thought. So, I don't think – like if you took a whole poppy, would there be some laxative component in that which balances the tendency of opium to cause constipation, for instance? I'm not saying that's the case, but that's the type of argument you'll hear"* (Patrick, GP).

The positive aspect of conventional medicines was also commented on by the same GP. He suggested that the appeal of conventional drugs is related to their high standard of manufacture and quality control, (which herbal medicines cannot match):

> *So conventional drugs are very kind of purified and, to some people, that would be a massive attraction, but there is a kind of counterargument – that argues against that level of purification. I think there are certain issues around quality. I'd like to think that any conventional drug is made in a pretty controlled environment and is very safe from that point of view, whereas herbal medicines ……..but it's just a totally different level of standardisation and quality control"* (*Patrick,* GP).

Some GPs talked about the concern around the lack of governance with herbal medicines and how they are not quite legal which leads to questions over their reputation:

> *"Yes, so – there's - the worry with herbal medicine is that it's under-governed, that the manufacturing process [isn't] legitimate, that someone's creating these things in their basement and [selling] them over the Internet. So, you know, there's no level of quality and guarantee behind it; it isn't the same as – normal pharmaceutical processes. I guess that's where some of the prejudice comes from and I think that because they are outside of most guidelines, I think that probably damages them, the reputation they have, as well"* (Ciaran, GP).

Although this GP expressed concern about the lack of governance around herbal

medicines; If they were properly governed, researched, and regulated they may be useful:

> *"My concern is that the lack of regulation and the fact that these things are creeping in, outside of the MHRA, for example; people are just buying stuff that hasn't really been tested to that extent. But I think, as a concept, if it's probably regulated and investigated, I think there's a lot in it"* (Simon, GP).

Subtheme 3b: Do no harm - Safety and Interactions of herbal medicines

Health professionals talked repeatedly about the safety and interactions associated with herbal medicines. Most GPs mentioned that doing no harm was paramount. The herb St John's Wort was commonly mentioned as a concern over interactions. In contrast to most health professionals, a few GPs suggested that conventional medicine was also dangerous and can cause problems more frequently than herbal medicines. Several participants saw lack of training or knowledge as an obstacle to discussing herbal medicine use with patients.

Most GPs mentioned they are more accepting of the herbal medicines they are familiar with and less so with ones they don't:

> *"As long as – I don't – so the ones that I know, that I can actually find out about and see if there's any evidence, that's okay; the other ones I – feel far more sceptical that they are going to cause side effects or interactions that we are not aware of. And I tell my patients that"* (Andrew, GP).

This GP explained the system she uses to evaluate the safety of things like herbal medicines. She suggested that products that are popular become known and are easier to check up on, and the problems are more with interactions rather than direct toxicity. She was also happy for patients to use herbal medicines if they are safe and not too expensive:

> *'If there is a safety concern, that's the kind of thing that meds management flag up to us. So, for example – we're very aware about St John's Wort and every time I issue a pill prescription, I'm asking a patient about that, just in case they're taking it. So, things that become very popular, problems tend to then become known and then we know what to check for, but it's often interactions rather than actual harm. (I: Okay) And if someone chooses alternative or – complementary treatments that they're finding helpful and can afford and have no harm, then I'm very positive about that"* (Paula, GP).

In contrast to most GPs who were more accepting of herbal medicines they were familiar with; this GP was not worried about his lack of awareness around herbal medicines and was not worried by side effects or interactions:

> *"Well nothing that I'm aware of so far; so, I'm not particularly worried about any – you know – I'm sure there have been things where herbal medicines have contained – things, but, you know, and I'm sure there will be some people that some herbal medicines will interfere with things, but … Yes, I'm just not aware. Obviously, I don't know much about – I only really know about two or three medicines, so I don't have a wide range of knowing about them"* (Tony, GP).

Some GPs compared the harm that conventional medicines cause in comparison with herbal medicines. This GP stressed that although conventional medicines are regulated, they cause issues on a frequent basis whereas this was not the case with herbal medicines. This was very much a minority viewpoint:

> "*Mmm the thing you have to remember is that conventional drugs are just so dangerous; they have – there are quite a few drugs that cause side effects in everyone who takes them. Herbal medicines, you know, like a lot of people like to beat them over the head for being like unregulated and – but – it's relatively rare to hear of somebody harmed by a herb, but it's a daily occurrence that somebody's harmed by a conventional drug"* (Patrick GP).

This GP was also concerned about the safety of conventional medicine but was more reassured of their safety (in comparison to herbal medicines) because they have a licence.

> *"I'm also very concerned about the side-effects of conventional medication. It's not necessarily on principles of just being a herb; possibly more about with conventional medicines, at least there has been some work done before they get their licence to show that they are – reasonably safe. So, again, equally with conventional medicine, you can encounter problems"* (Conor, GP).

7.5 Findings to inform the feasibility study

One of the main aims and objectives of this qualitative study was to glean information from health professionals who had prior involvement with clinical trials or feasibility studies, especially involving herbal medicines. This would help with the subsequent planning and design of a future feasibility study examining the role that herbal medicines may have in the treatment of acute respiratory tract infections and the reduction of antibiotic prescribing.

As I mentioned in Chapter 5, qualitative research is a useful tool to enhance trial design and explore the feasibility of an intervention. In this study, health professionals talked about their previous trial experience including what key information they would require before participating. This included acceptable evidence, safety, trial organisation, and medicine availability.

7.5.1 Acceptable Evidence

Most of the participants suggested that would want some form of evidence before considering taking part in a feasibility study or trial. The majority of participants wanted a clinical trial or RCT before considering participation:

> *"I think you'd want a clinical trial … an RCT" (*Amanda, GP).

A summary of current evidence was enough for some GPs:

> *"What kind of – just a summary of what evidence is there already, I guess, but I mean if you were doing a trial and you were looking for recruitment, you would do that anyway, wouldn't you; summarise what evidence is there"* (Joanne, GP).

Others suggested that if the study had ethical approval that would suffice:

> *"Mmm I would - I suppose one takes comfort from the fact that a research protocol has gone through the Ethics committee and been passed as being suitable and I think myself and my partners would, you know, they do take notice of that really, that it's something that's been…. as being ethically sound, hence basically safe. So, yes*" (Pat, GP).

We decided to send copies of the systematic review to all practices with a summary of the results following the above feedback.

7.5.2 Safety

As well as evidence, safety was frequently mentioned as a prerequisite before health professionals would consider taking participant in a herbal medicine trial:

> *"I think we're talking about – herbal medicines in respiratory tract infections; I'd want good evidence of safety really, so that I wasn't harming by giving something".* (Roger, GP)

> *Well it would be – I suppose – that it was safe; that there might be – perhaps a small – maybe not even significant number but, you know, just some evidence that perhaps some patients had benefited and that it was safe, really.* (Juliet, GP)

We provided safety reports and known side effects of the trial medication before the onset of the trial.

7.5.3 Trial involvement and organisation

Participants who expressed an interest in being involved in a trial talked about the prerequisites they would require. These GPs suggested as long as the trial was "well run" and "regulated" they would participate

> *"But in the concept of a research study where it's properly regulated and understood, that's fine. And as soon as there's a sort of general consensus that this is a valid thing to do then, yes, I'd be up for it; I'd prescribe it before antibiotics"* (Simon, GP).

> *"No problem with a trial. We've been involved with lots of trials that I think, initially think, mmm, that's odd, but actually, no, I think, provided it was a well-designed study, I have no problem with that"* (Tony, GP).

Others talked about the organisation of the trial and were more concerned with the practical aspects of running a trial including having enough staff and ensuring the trial was easy to run:

> *".....our nurses see a lot of the minor respiratory illness and when it does come, it hugely hits the surgery like a steam roller, because – there's a lot of it and so we suddenly get very, very busy. So it's organisational things that would probably – would be more a factor in deciding it"* (Sheila, GP).

> *"But in terms of whether I'd be willing to consider doing a trial, the short answer is – yes, depending on how involved it was, because we have issues with manpower and things like that. Just making it as simple as possible. I mean we've – so we've done a few – or have done lots of different studies here and – and it's just making it as simple as possible to sell it to my non-research colleagues, really"* (Joanne, GP).

This was an important point. I discussed these issues with the trial co-ordinator and considered steps to make the trial as easy to run as possible. We decided that we would visit each practice to answer any questions they may have, and provide them with materials such as crib sheets to provide concise information on the trial medication.

7.5.4 Medicine availability

Some participants were concerned with whether the trial medication would be widely available after the study had elapsed:

> *"There's no point doing a trial and then you say that – that compound that is available for the trial is only specific to the trial; it would have to be something that we could then go on and use in real life if it's going to make any difference to your antibiotic prescribing"* (Conor, GP).

This was an interesting outcome from the qualitative study and I checked to see if the proposed medicine for the clinical trial would be available after the completion of the trial and discovered it was already on general sale.

7.6 Discussion

This study provided a qualitative account of health professionals' attitudes and beliefs relating to various aspects of herbal medicines and the rationales' underpinning these perspectives/views. Key themes included how health professionals made sense of herbal medicine in general practice; beliefs and attitudes towards OTC herbal medicine use; and health professionals' views on herbal medicine governance and production.

There was a wide spectrum of views and stances on how health professionals made decisions about herbal medicine in general practice. Commonly, health professionals cited the lack of a perceived evidence base as a barrier to utilising herbal medicine use in practice. However, health professionals continued to use personal experience as part of their decision-making process and were subject to a wide range of influences, despite the recent emphasis on the use of EBM. Some of the findings provided information on what things health professionals would require before considering taking part in a herbal medicine trial. These findings were used to inform the subsequent feasibility trial.

In this study, when it came to prescribing, recommending, or advising patients on herbal medicine use there were barriers around lack of sufficient knowledge and lack of evidence. Most health professionals mentioned the need for evidence before recommending herbal medicines to their patients. Many also found the situation challenging due to the lack of training, experience, or knowledge. However, some were happy to advise on their use and adopted a shared decision-making approach. I found this situation interesting and wondered why all of the interviewed health professionals did not adopt an EBM approach.

Gabbay and Le May have discussed the tension between evidenced-based and tacit knowledge in primary care in their 2004 BMJ paper. They labelled tacit knowledge in primary care in terms of "mindlines" or guidelines-in-the-head, in which evidence from a wide range of sources has been melded with tacit knowledge through experience and continual learning to become internalised as a clinician's personal guide to practising in varied contexts (Gabbay and May, 2016). Clinicians acquire their "mindlines" over a lifetime, informed by their training, their own and each other's experience, their interactions with colleagues and patients, by their reading, their understanding of local circumstances and systems, their experiences of handling the many conflicting demands, and a host of other influences (Greenhalgh *et al.*, 2016)

Only a few health professionals in this study mentioned extra training they had undergone in CAM therapies, such as herbal medicine, in order to better understand what their patients were taking and/or to be able to talk about how it could impact their wellbeing. Some mentioned it would be useful to have extra training in CAM modalities such as herbal medicine but this was not widely talked about, although a few participants questioned whether or not it was their responsibility. Our finding that lack training and education was seen as a barrier to discussing herbal medicine use with patients, with some GPs viewing it as outside their sphere of expertise, echoes previous research.

A study by Clement et al (2005) found that health professionals generally accepted herbal remedies as a viable option although they lacked sufficient knowledge on the uses and potential risks associated with this modality. This created an interesting scenario where the gap between acceptance and knowledge provides

an ideal opportunity to facilitate the introduction of educational programs and policies that would increase the knowledge base of these healthcare professionals. They suggested that well-informed physicians would be more confident in their interactions with patients and this would improve the quality of healthcare delivery, as more meaningful communication on important issues such as adverse effects and herb-drug interactions would be facilitated.

A widely discussed subject in the interviews was the relationship between herbal medicine and the placebo effect. In common with previous research, health professionals defined the placebo effect in different ways. Some had ambivalent attitudes towards placebos and did not distinguish between pure (no pharmacological effect) and impure placebos (antibiotics for colds and herbal medicines) and were not aware of the impure placebo effect of herbal medicine and antibiotics. Fent et al (2011) identified similar attitudes in their study.

Fent et al reported that herbal medicine has both placebo and pharmaceutical effects (Fent *et al.*, 2011). This topic is also discussed by Howick et al and Bishop et al who looked at placebo use in the UK by primary care practitioners and found that placebos are commonly used but misunderstood in primary care (Howick *et al.*, 2013; Bishop *et al.*, 2014). In this study there appeared no common definition or consensus on what constitutes a placebo effect or how herbal medicines worked as placebos in primary care. A few health professionals described herbal medicines as triggering "a self-healing response"; others talked about how they would use herbal medicines to increase a placebo response whilst others hypothesised that some herbal medicines were placebos and therefore safe whilst others may have active constituents. Generally, there appeared to be a confused or inconsistent understanding of the whole topic of placebo from participants in this study.

Overall there was a cautious acceptance of herbal medicine with concerns around the term herbal medicine and its association with archaic phenomena such as magic. This correlates with Hammond's findings of CAM in general (Hammond, 2014) :

> *"There also seems to be a basic human need to believe in the unbelievable. The success of Harry Potter isn't entirely due to the prose style. Medicine used to be magic and doctors used to be wizards, in touch with other worlds. But conventional medicine is now endlessly demystified in the media. We're like magicians whose tricks have all been explained."*

Interestingly, our findings suggest that health professionals believed that some of their patients used herbal medicines because they believed they were safer than conventional medicine and had fewer side effects. Overall patients were commonly grouped into those who preferred herbal medicines, those who preferred conventional medicines, and those who went with the health professional's recommendation.

We found that many health professionals were more comfortable with recommending herbal medicines that they were familiar with or that were popular because their side effects or interactions were known. This phenomenon is consistent with the Familiarity principle or the Mere Exposure effect where there is a growing preference or affection for something or someone because of familiarity. In his book "Thinking Fast and Slow", Kahneman describes how repetition induces cognitive ease and a comfortable feeling of familiarity and the repeated exposure of a stimulus becomes a safety signal (Kahneman, 2012). For instance, many health

professionals in this study mentioned the use of Echinacea as something they may recommend or were less concerned about because they were familiar with it and had known patients who had taken it in the past without any safety issues. In contrast to this, herbal medicines that were not known or popular were a concern for many health professionals.

In this study, there was an interesting stance on the perception of the word 'natural'. Health professionals suggested that patients view natural as safe and effective compared to synthetic medicines. This view was not shared by GPs who considered many natural products to be impure and therefore potentially toxic. A study by the MHRA looking at the public perception of herbal medicines in 2009 found that users of Chinese herbal medicine were more likely (76%) than any other group of users or non-users to believe that natural means safe (MHRA, 2008).

When talking about patient beliefs in herbal medicines health professionals mentioned that there were some patient types who prefer herbal medicine and those who did not. This psychology of belief was related to many different factors including education, socio-economic status, and demographics.

A Swedish study looked at self-reported beliefs and perceived sensitivity to medicines and their effects in relation to self-reported use of medicines and herbal remedies. Respondents who strongly believed that medicines were harmful and overused and respondents who reported high sensitivity to medicines and their effects were more likely to use herbal remedies. (Andersson Sundell and Jönsson, 2016).

7.7 Strengths and Limitations

This qualitative interview study successfully recruited health professionals across broad sociodemographic regions of Southern England and provided insight into how health professionals view herbal medicines in primary care. The strengths and limitations of this study are mentioned below:

- The use of semi-structured telephone interviews was a useful way to gain detailed and in-depth views and experiences of health professionals. They allowed flexibility and were cost-effective. However face-to-face interviews would have been useful to gauge the reactions and social cues of the respondents as they were being questioned.
- The wide range of views expressed during the study suggested that health professionals were able to speak freely during the interviews. Data collection continued until no new information emerged and data saturation had been reached.
- This sample of health professionals provided useful/rich data as they all were working in primary care practices, which see a high number of RTIs. However, the findings may not be generalisable to the whole UK. This is a small number of health professionals from a relatively localised area, which may not represent the views of the whole country. (Also, mainly white middle-class health professionals are not representative of the country as a whole). The sample included only a few practice nurses and a small number of practitioners from ethnic minorities.
- In this study, I used constant comparison methods, coding supervision, a transparent audit trail, and maintained a reflective journal to record and reflect my own thoughts and ideas on this interview study.

- I am a medical herbalist therefore I may have been biased or hold preconceived ideas in how health professionals viewed herbal medicines. These views may have impacted on my interactions with health professionals during the interviews and the analysis of the results.
- To improve the credibility of the study I could have asked some of the participants to review the findings of the study (respondent validation). However due to time and financial restraints this was not possible.
- Volunteer bias may have restricted health professionals' participation providing either more negative or positive views of herbal medicine. Although some health professionals discussed the capacity or manpower to be involved in a trial. It would have been useful to ask questions on the willingness of health professionals to randomise patients onto a herbal medicine trial.
- Practitioners were identified who were users of herbal medicines and it was useful to see how this shaped their perspectives on herbal medicine use for their patients within their role as a primary care health practitioner.
- It would be interesting to interview health professionals who were not research active or non-academic to see if their views on evidenced-based herbal medicines and herbal medicines would have been the same or different. It would also have been useful to interview pharmacists particularly in the light of the finding that GPs would be more reluctant to prescribe than for patients to seek herbal medicines for themselves.

7.8 Conclusion

This chapter presented the findings of a qualitative study examining health professional views on the use of herbal medicines in primary care. As mentioned previously there was cautious acceptance of herbal medicines in this study sample with most participants concerned about the lack of evidence and safety of herbal medicines. A section of the findings included feedback from health professionals on their experiences with feasibility studies and what things encourage their participation in such a study. The next chapter documents the methods and results of a double-blind placebo-controlled trial using a herbal medicine called *Andrographis paniculata* in the symptomatic treatment of ARTIs.

Chapter 8: GRAPHALO: A double-blind randomised placebo-controlled feasibility study evaluating the effect of Andro*GRAPH*is p*A*nicu*L*ata leaf in the treatment *O*f adults with acute respiratory tract infections (ARTIs)

8.1 Introduction

The preceding chapters in this thesis provided the foundation for the design feasibility study evaluating the role of *A. paniculata* (Andrographis) in the treatment of ARTIs in primary care practices. Chapter 3 provided key information on the research behind the pharmacology and safety of *A. paniculata*. The systematic review on chapter 4 on *A. paniculata* examined previous clinical studies and provided information on outcomes, posology, and study design. Chapter 6 discusses the research philosophy and methodology underpinning this thesis. Chapter 7 was a qualitative interview study that provided information to inform the design of the feasibility study based on their attitudes towards and experience of using herbal medicines.

This current chapter details the final study design, feasibility outcome measurements, and results of the GRAPHALO study. As well as help from my supervisors in advising on trial setup, I worked with the Trial Co-ordinator Jackie Seely (JS) and Trial Statistician, Dr. Beth Stuart (BS). The contributions to the study design, conduct, analysis, and reporting will be discussed in detail at the end of the chapter. The study centre was Aldermoor Health Centre, Southampton. The health professionals working at each of the participating primary care centres are referred to as local investigators. I have followed the CONSORT guidelines on feasibility

studies and herbal interventions in this chapter (Eldridge *et al.*, 2016)(Gagnier *et al.*, 2006).

This feasibility study took the longest time and was the most difficult part of this PhD. It was challenging to set-up, run, and analyse. An agreement was reached with the MHRA in January 2018 that this trial did not constitute a Clinical Trial of an Investigational Medicinal Product (CTIMP) and that I could proceed through the easier regulatory process of a non-CTIMP study as long as only feasibility outcomes are reported, not efficacy and safety.

A summary of the timelines associated with this study are presented in Table 10 below. I shall talk more about the challenges of this study in the discussion section (Section 8.14).

Table 10. Feasibility study set-up timeline

Activity	Date
Agreement with MHRA that trial can be carried out with a THR by GL.	March 2016
Initial meeting with University Sponsor regarding trial. Told feasibility study will be considered a CTIMP.	April 2016
Failure of stability testing of trial medication, therefore, failure of THR application. Trial delayed by at least one year.	September 2016
ML works with/at Pukka on THR application	February to October 2017
GL dies; University sponsor request new notification from MHRA.	March 2017
University ethics application for GRAPHALO study	June 2017 to February 2019
Meeting with MHRA; MHRA agree feasibility can be carried out as long as no claim of efficacy or safety is made.	January 2018
Meeting with NIHR CRN Wessex to discuss promotion of GRAPHALO trial to health professionals	March 2017
CRN mail out and advertising of GRAPHALO trial to health professionals to identify local investigators	June 2017 to October 2018
Expression of interests received from potential local investigators via CRN	October 2018
HRA, REC, and Sponsor (University of Southampton) approval for the trial	November 2018

8.2 Research Aims for the Study

The aim of this double-blind feasibility trial was to conduct a 16-week study of 60 adults with ARTIs aged over 18-years, randomising participants to Andrographis or placebo. The primary outcome of this study was to measure feasibility outcomes while the secondary outcomes were to gather information to inform the numbers needed for a larger more definitive trial. Primary care health professionals provided verum (active treatment) and placebo treatment options; there were 2 arms to this trial:

- Andrographis capsules plus standard care
- Placebo capsules plus standard care

8.3 Study Objectives

The primary study objective was to measure feasibility outcomes to inform the design of a future fully powered trial of *A. paniculata* leaf extract as an alternative to antibiotics for upper respiratory tract infections in UK primary care. The main feasibility outcomes were recruitment, adherence to treatment/placebo, antibiotic use, and completion of outcome measures and retention. Specific feasibility objectives are detailed in the Table 16.

Table 16. Feasibility objectives of the GRAPHALO study

Feasibility Objective	Endpoint used to evaluate
Eligibility: Number of patients included and number excluded (+reasons) from the trial	On-site screening logs
Recruitment: Ability to recruit patients into the intervention from those attending primary care	On-site enrolment records
Randomisation: Willingness to be randomised	Proportion of eligible patients recruited.
Retention: Across the duration of the intervention and return of a fully completed diary	Quantitative data from enrolment Withdrawal rate from study Completion of outcome measures
Intervention compliance	Diary data on adherence to treatment/placebo and returned medication.
Acceptability of the outcome measures, participants' willingness to complete them, and the importance of telephone/text contact.	Quantitative data collection - number of patients returning completed diaries and needing follow-up telephone calls.
Exploration of rates of antibiotic prescription in both groups.	Diary data on day antibiotics commenced

8.4 Trial Methodology

8.4.1 Trial Design

To achieve the aims and objectives of the study, my supervisors and I agreed that a double-blind randomised controlled feasibility study would be carried out in primary care practices in Southern England, as this was the best way of exploring acceptability and the practicality of delivering a herbal medicine intervention within the NHS.

Feasibility studies are useful to determine if a main (larger, definitive) study can be undertaken and also whether an intervention is appropriate (potentially viable) for further investigation. They also enable the developing and testing of outcomes measures, establishing a recruitment strategy, determining response rates, and determining estimates of outcome parameters (Bowen *et al.*, 2009; Tickle-Degnen, 2013).

As mentioned previously I met with the MHRA in January 2018 to establish whether it would be possible to conduct a feasibility study without a CTA (Clinical Trial Authorisation). They agreed we could carry out such a study as long as no claims of efficacy and safety were made following the trial.

8.4.2 Trial setting and participants

The study was set up as a prospective, multi-centred (up to 20 primary care centres), double-blind placebo-controlled randomised feasibility study involving participants recruited opportunistically through primary care. The total recruitment period for the trial was for 16 weeks. Patients who visited their General Practice with ARTI symptoms and agreed to participate in the trial were measured/assessed on the day. Those with suspected ARTIs were invited to participate.

8.4.3 Regulatory Compliance of the Study

The study was reviewed and by the South - Central Hampshire B Research Ethics Committee (REC) and approved on the 20 October 2018 (Appendix E). ML attended the REC committee with Professor Michael Moore to answer any questions that arose. Following minor revisions, REC approval was obtained. The University Governance office and the NIHR Wessex Clinical Research Network (CRN) also reviewed the study. The University of Southampton acted as sponsor. Subsequent research governance approvals were obtained from Peninsula Southwest (PEN SW) CRN.

8.4.4 Study Population

Previous research in the UK on sample sizes in feasibility studies and pilot studies found the median sample size per arm across all the types of study was 30 participants (Billingham, Whitehead and Julious, 2013). The CONSORT extension for reporting feasibility studies states the number of participants in a feasibility study should be based on the feasibility objectives and some rationale should be given (Eldridge *et al.*, 2016). The main concern of this study was the feasibility of recruitment and the estimation was based on this decision.

Following discussion with my supervision team, we decided a sample size of 60 (2 groups of 30) for the feasibility study would be adequate and pragmatic to meet the feasibility objectives. According to Sim (2019) treatment effects calculated from feasibility studies should not be the basis of a sample size calculation for a main trial, as the minimum important difference to be detected should be based primarily on clinical judgement rather than statistics.

8.4.5 Inclusion and exclusion criteria

Patients were eligible for the trial if they were over 18 years of age and presented to their GP with potential ARTI symptoms including an acute cough (≤ 7 days' duration) or sore throat as their main symptom and, with symptoms localising to the upper respiratory tract (e.g. runny nose, facial pain, fever, muscle ache), for which non-infective diagnoses were judged very unlikely. Participants had to be willing and able to give written informed consent.

Participants were excluded from the trial if they were/had:

- Pregnant (or suspected) or breastfeeding; patients who become pregnant during the trial would be asked to discontinue with the trial.
- Women at risk of pregnancy (i.e. not on effective contraception – combined oral contraceptive pill, an intrauterine hormonal device or subcutaneous hormonal trial implant).
- Participants were unable to complete trial documentation, including consent form and symptom diary including those who had difficulty understanding English.
- Already taking Andrographis or other herbal medicine for ARTIs
- Had a known immunodeficiency state or were undertaking chemotherapy treatment
- Allergic/hypersensitive to Andrographis or the capsule material (cellulose)
- Already taking medication for ARTIs (paracetamol and ibuprofen were allowed)

- Severe hepatic or renal diseases (Chronic Kidney Disease Stage 4, GFR <30) as no adequate data are available on the safe use of Andrographis in these conditions
- Suspected pneumonia (i.e., complicated lower-respiratory-tract infection) based on focal chest signs (focal crepitations, bronchial breathing) and systemic features (high fever, hypoxia, tachypnoea,). Serious chronic disorders where antibiotics are needed (e.g. cystic fibrosis, valvular heart disease)
- Signs of severity which may have warranted hospital admission (e.g. SpO_2 <91%, Systolic BP <90mmHg, Heart rate >130)
- Recently/ currently involved in a respiratory trial.

8.4.6 Recruitment

GP practices were identified by JS and ML in Wessex and SW Peninsula with help from the local Clinical Research Networks (CRNs). Three of these practices also took part in the qualitative study. The CRNs were asked to identify practices with a range of socio-demographics in an attempt to achieve a diverse sample for the study.

Recruitment took place in primary care, as this is where the vast majority of participants presenting with acute respiratory tract infections are managed. Eligible patients were informed about the study by the consulting clinician or other staff at their general medical practice, who explained the study and provided them with a patient information leaflet.

Site initiation visits (SIVs) were carried about by JS and ML at each site and recruiting sites were presented with promotional study materials such as posters

and short version participant information leaflets to display and/or hand out, allowing the health professionals an opportunity to find out more about the study and consider participation (see Appendix E). The recruitment period ran from February 2019-June 2019. See Table 11 below for Trial timeline.

Table 11. Trial timeline

Activity	Date
Delivery of trial medication	December 2018
Site initiation visits (SIVs) and medicine delivery	January 2019 – April 2019
Trial recruitment	February 2019 to June 2019
Closure of trial sites	June 2019
Data collection (including participant diaries)	February 2019 to August 2019
Data analysis	June 2019 to October 2019

8.4.7 Consenting Participants

A 3-part procedure for informed consent was required for each eligible participant. The recruiting health professionals gave full verbal and written information (including the participant information sheet) about the trial, questions were then invited, and answers given. When written informed consent had been obtained, the patient became a 'participant' and was formally part of the study. After the participant had entered the trial the clinician remained free to give alternative treatment to that specified in the protocol at any stage if he/she felt it was in the participant's best interest, but the reasons for doing were recorded. In these cases, the participants' remained within the trial for the purposes of follow-up and data

analysis. All participants were free to withdraw at any time from the feasibility study without giving any reason. Upon completion of the informed consent form, the original was stored in the investigator site file (ISF) and a copy was given to the patient, a copy was stored in the patient's medical notes and a copy was sent to JS (see Appendix E).

8.4.8 Ineligible and Non-Recruited Participants

Details of ineligible or non-recruited participants were recorded at each site on a screening log with reasons for non-participation and, who would have no further involvement in the trial (see Appendix E). An anonymised screening log was shared with JS and ML.

8.4.9 Randomisation and Group Allocation

After consent and baseline assessment, participants were randomly allocated to the active or placebo medication. BS, the trial statistician used a computer-generated random numbers table to provide an irregular block allocation sequence prior to the study. Block randomisation to either of the two groups, verum or placebo treatment, was performed with random block sizes of 2, 4 or 6 participants to ensure equal numbers in groups and to prevent the study team from being able to predict a pattern to the randomisation.

The randomisation sequence was used to code the capsules prior to their being sent to GP practices. Capsules were then dispensed according to this sequence and a record of the batch number recorded by the Practice Nurse/Research professional and conveyed to JS. The designated person at Pukka Herbs Ltd (The medicine

supplier) kept a record of the treatment allocation. When the trial was completed the designated person provided necessary details of allocation to JS.

The treatment packs were delivered to the sites in sets of two and each patient received the next available sequentially numbered patient pack at their site. This determined their Patient (Subject) Identifier number. Once a patient had been randomised to the study, the study team was informed through the Notification of Registration form (see Appendix E).

8.4.10 Emergency Unblinding Procedures

A risk assessment was carried out to assess the level of risk. All participants were issued with a GRAPHALO emergency contact card with contact details of relevant personnel in the event of an adverse event.

A standardised procedure for emergency unblinding was carried out by the research team (See Appendix E). The codes were to be broken in case of a major adverse event (such as anaphylaxis or admission to hospital with a life-threatening illness (for example septicaemia, meningitis, severe pneumonia requiring ITU admission or death). The randomisation code was stored electronically on a secure password-protected drive and access was restricted to the Designated Person at Pukka. If unblinding was deemed necessary, the Principal Investigator informed the Designated Person to notify the relevant responsible clinician of the treatment allocation for the relevant participant. The study team were not to be informed which arm of the trial the participant was allocated to. If randomisation of a participant was unblinded during the study then data for that participant, if available, was included in an intention-to-treat analysis.

8.4.11 Withdrawal procedures

The participants were free to withdraw consent from the study at any time without providing a reason. The reason for participant withdrawal was noted if offered, and the reasons were detailed if the participant agreed.

Local Investigators explained to the participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, patients who withdrew from trial treatment remained in follow-up. If participants additionally withdrew consent for this, they reverted to standard clinical care as deemed by the responsible clinician. It was considered useful for the trial team to continue to collect standard follow-up data and unless the participant explicitly stated otherwise, follow-up data were continually collected. Details of trial discontinuation (date, reason if known) were recorded in the CRF (See Appendix E) and medical record.

8.5 Trial Observations and Procedures

8.5.1 Screening procedures

The health professional recruiting the participants conducted a routine clinical examination consulted the patient's medical notes and asked questions to ensure that they met the eligibility criteria. At the initial visit the participant's relevant past medical history, baseline symptoms and vital signs were recorded (see Table 12 below).

Table 12. Baseline symptoms and vital signs

Baseline Symptoms – (the severity of the following symptoms were scored according to the following system 0=no problem, 1=very little problem, 2=slight problem, 3=moderate problem, 4=bad problem, 5=very bad problem, and 6=as bad as it could be)

- cough
- sore throat
- difficulty swallowing
- phlegm
- facial pain (forehead, sinus, and jaw pain)
- blocked or runny nose
- muscle aches
- headaches
- disturbed sleep
- general feeling of being unwell
- fever
- interference with normal activities

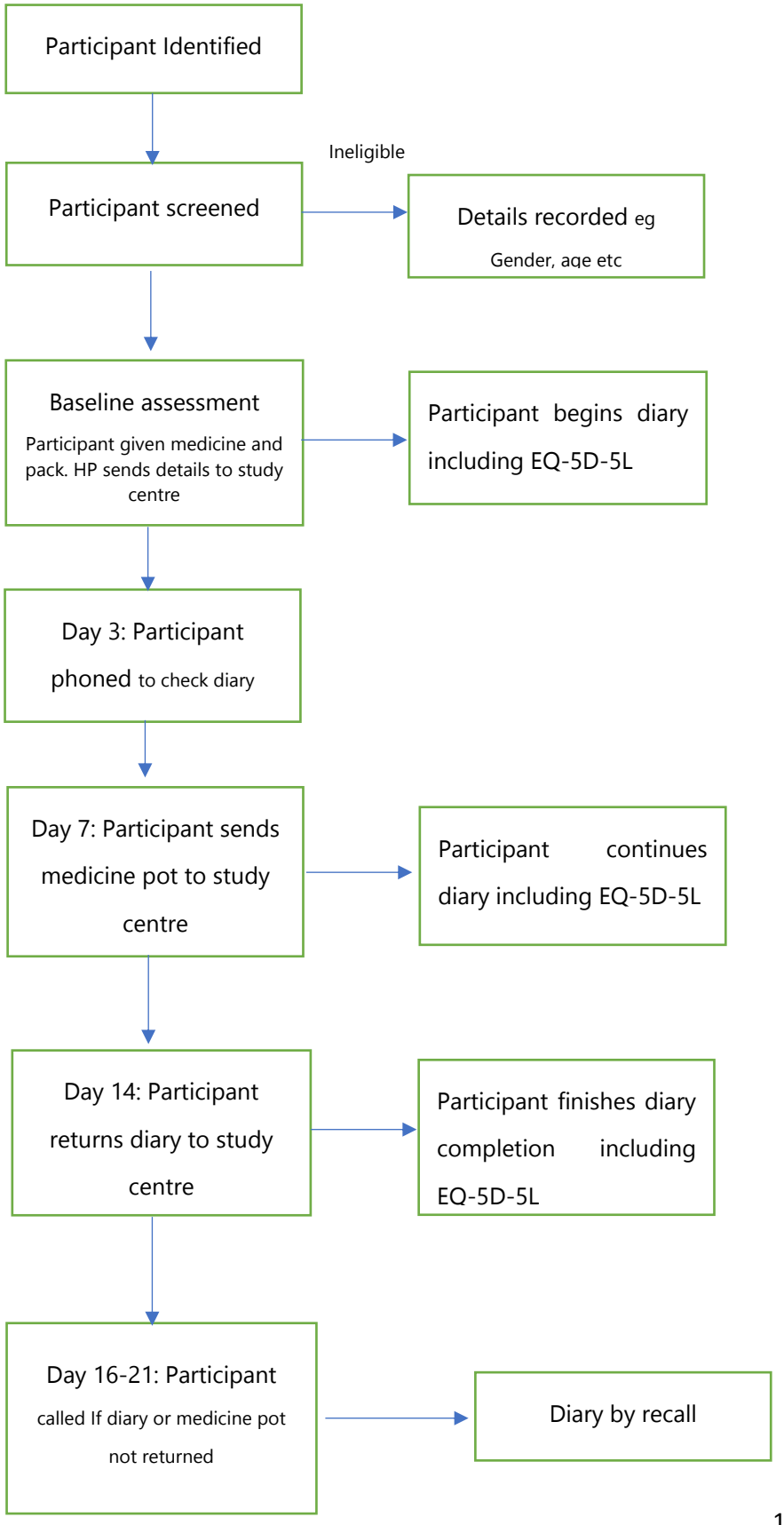
Patient's vital signs

- blood pressure
- heart rate
- temperature

Contact details were collected from all participants to enable follow up telephone calls to be made. The consent form included patient contact details and was sent via an NHS email within 24 hours of randomisation to the study team.

In addition to their trial medication, participants were issued with a diary (after instructions had been given on how to complete it). Participants were asked to return all unused trial medication and packaging to the Southampton research team after 7 days. They were given a pre-paid addressed padded envelope for this purpose (see Figure 17).

Figure 17. Participant trial recruitment procedure flowchart



8.6 Follow up

8.6.1 Participant Symptom Diary

Participants completed a daily diary for up to 14 days after presentation (see Appendix E). They stopped completing the diary after complete resolution of symptoms. The collection of diary scores was not limited to the time whilst study medication was being used to record the total symptom duration. This diary was previously validated in the HATRIC study and was shown to be sensitive to change and internally reliable (Whitehead *et al.*, 2019).

Participants were asked to record:

- The number of times a day trial medication was taken and, if applicable
- When antibiotics or other treatments for their respiratory tract symptoms were taken
- Details about social demographic factors, such as their occupation, employment, and ethnicity
- Present illness and expectations about antibiotic treatment
- Resource use for their upper respiratory tract infection (URTI), including consultations with health care professionals in secondary care; medications purchased, and absences from work.

Participants were asked to complete the EQ-5D-5L questionnaire at the following time points: at baseline (Day 1), day 7, and day 14. This allowed us to assess the acceptability of the frequency in collecting quality of life data.

After recruitment, ML contacted participants after 3 days to check for any problems with diary completion. In the event of diaries not being returned or returned with key information missing, ML phoned participants to collect the key data (which

would be needed for primary feasibility outcome analysis) after 14 days. Completed diaries were returned to the Study Centre in a Freepost envelope.

8.6.2 Deviations and Serious Breaches

Any study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites were to be reported to the Study Centre immediately. The Study Centre then advised of and/or undertook any corrective and preventative actions as required. All serious protocol deviations/violations and serious breaches of Good Clinical Practice and /or the study protocol were immediately reported to the Sponsor.

8.6.3 Trial Discontinuation

Patients who consented to the study agreed to the study intervention, follow-up, and data collection. Patients were to be discontinued from the study procedures at any time in the event of:

- A clinical decision, as judged by the Principal Investigator
- The development of toxicity, regardless of causality, which in the Investigator's opinion, precludes further treatment under this protocol
- The patient withdrew consent
- The recruiting physician's judgement due to medical reason e.g. concurrent illness, pregnancy
- Non-compliance with the protocol.

Full details of the reason for trial discontinuation were recorded in the CRF and medical record.

8.7 Treatments

In primary care sites, participants were randomised to either active or placebo groups who took the capsules for 7 days:

1. *Andrographis paniculata* leaf extract – three 250mg capsules 4x daily, to be taken 30 minutes before meals plus standard care
2. Placebo - three 250mg capsules 4x daily, to be taken 30 minutes before meals plus standard care

The capsules including matching placebo were provided by Pukka Herbs/ Ginsana, Bristol, (England) who currently manufacture and market the product in the UK.

Trial medication was to be taken daily until 2 -3 days after symptoms had resolved but treatment duration was not to exceed one week. If a dose was missed, the participant was instructed not to take twice the dose but continue to take their usual dose at the usual time.

Both groups continued to receive standard care (This included paracetamol, ibuprofen, or a prescription for antibiotics) from their usual healthcare provider for their ARTI. This included reconsulting as required and the use of concomitant medications if necessary. Health professionals were encouraged to use a delayed antibiotic prescription strategy as part of standard care and offered one of three following antibiotic strategies in addition to the randomised intervention:

1) Immediate antibiotics
2) Delayed antibiotics
3) No antibiotics

Participants offered a delayed prescription were asked to wait 7-10 days before collecting this unless their symptoms showed substantial deterioration.

8.8 Accountability

The GRAPHALO trial capsules were stored at the study centre and distributed to primary care sites by JS and ML during the SIVs. Drug accountability logs were maintained by the local Investigator and at individual sites. JS and ML provided sites with logs (See Appendix E). Accurate records were kept at the Study Centre and at sites of the amounts and dates of trial medication received and dispensed during the study, and for unused trial medication returned for destruction. Site drug accountability logs were made available for inspection by the Study Centre at any time.

Participants were asked to record trial medication usage in their patient diary and to return all unused trial medication and packaging to the Southampton research team at the Study Centre. A record was kept by JS of all returns made by patients.

8.9 AEs and SAEs reporting

All AEs (Adverse events) and SAEs (Severe adverse events) were recorded from the time the participant consented to join the study until diary completion (Day 14). The local Investigator and designated study personnel monitored each subject for Adverse Events during the study. All Adverse Events reported between consent and diary completion were recorded in the Case Report Form (CRF) (See Appendix E).

Participants were to be asked if they had been admitted to hospital, had any accidents, used any new medicines, or changed concomitant medication regimens. If there was any doubt as to whether a clinical observation was an AE, the event was recorded.

8.10 Study Medications

Two interventions were compared in this study – a 250mg active capsule with *Andrographis paniculata (Burm.f.; Acanthaceae)* leaf and an identical 250mg opaque placebo capsule containing a green powder consisting of mannitol, silicon dioxide, and magnesium stearate. The capsules were made of cellulose. Both capsules were produced according to EU required Good Manufacturing Practice (GMP) standards by Ginsana SA (trading as SFI Switzerland) for Pukka Herbs Ltd, Bristol. UK. Please see Table 13 below for active medicine characteristics.

Table 13. Active trial medicine characteristics

Duration of use	For oral short term use only, up to 7 days. Start at the first sign of symptoms. Do not use for more than 7 days.
Dosage information/instructions	Adults: Take 3 capsules 4 times a day (3g per day). Try to take capsules at the same time each day. Swallow the capsule whole with water or other liquid. Do not chew the capsules. You can take the capsules with or without food.
Contraindications	Hypersensitivity to the ingredient or capsule (cellulose) or other members of the *Acanthaceae* family.
Special warnings and precautions for use	Do not exceed stated dose. If symptoms worsen during use of the medicinal product or persist for more than 10 days, a member of the study team should be consulted.
Interactions	There was a lack of data on interactions with other medications. It is suggested that Andrographis is taken an hour before any other medication due to its bitter effects.
Pregnancy and lactation	There is no adequate data for the use of Andrographis during pregnancy and lactation. As a general precaution use of Andrographis is not recommended during pregnancy or lactation.

Undesirable effects	Adverse effects are mild and do not occur frequently. Andrographis at the recommended dose is safe and well-tolerated. Systematic reviews have reported that Andrographis is well tolerated, with occasional gastric disturbances and skin irritations, which resolve when the product is discontinued.
Overdose	No case of overdose has been reported. As Andrographis is a bitter, it may cause gastric disturbance, loss of appetite, and vomiting if taken over the recommended dose.
Storage precautions	Store below 30 *C. Store in original package
Nature and contents of container	Amber glass bottle with cap. 84 capsules per pot

8.11 Statistics and data analyses

The key feasibility outcomes, including the recruitment, adherence to treatment, completion of outcome measures,, and retention, were explored descriptively and graphically. We explored the variability of the key feasibility outcome measures. No formal quantitative testing of active and placebo groups took place as the feasibility study was not powered for this. Data were analysed using SPSS v17. Testing acceptability and frequency in collecting EQ5D5L and key resource usage associated with the intervention and potential influence on service usage was performed.

8.12 Funding

Pukka Herbs, Bristol UK funded MLs time, the research costs, and the trial medication. NIHR CRN funded the service support costs to practices and NHS Solent and Pukka Herbs funded JS time. The participants in the study received a £10 High Street shopping voucher on entering the trial.

8.13 Results

8.13.1 Practice Recruitment overview

Recruitment commenced in February 2019 and finished in June 2019. Twenty practices in Wessex and Peninsula South West (PENSW) initially agreed to take part in the study however 4 declined before recruitment commenced; 3 practices said they had no capacity and 1 said they only wanted to their paramedics recruit. Therefore 16 practices (8 in Wessex and 8 in PEN SW) took part in the study. The GP practice demographics are presented in the table below.

Table 14. GP practice demographics

Practice Demographics	**N=16**
Practice area	Peninsula 8 Wessex 8
Practice list size *Mean (range)*	15,710 (4,241 – 43,165)
Practice deprivation scale *Median (range)* (1 is most deprived; 10 is least deprived)	6 (4-10)

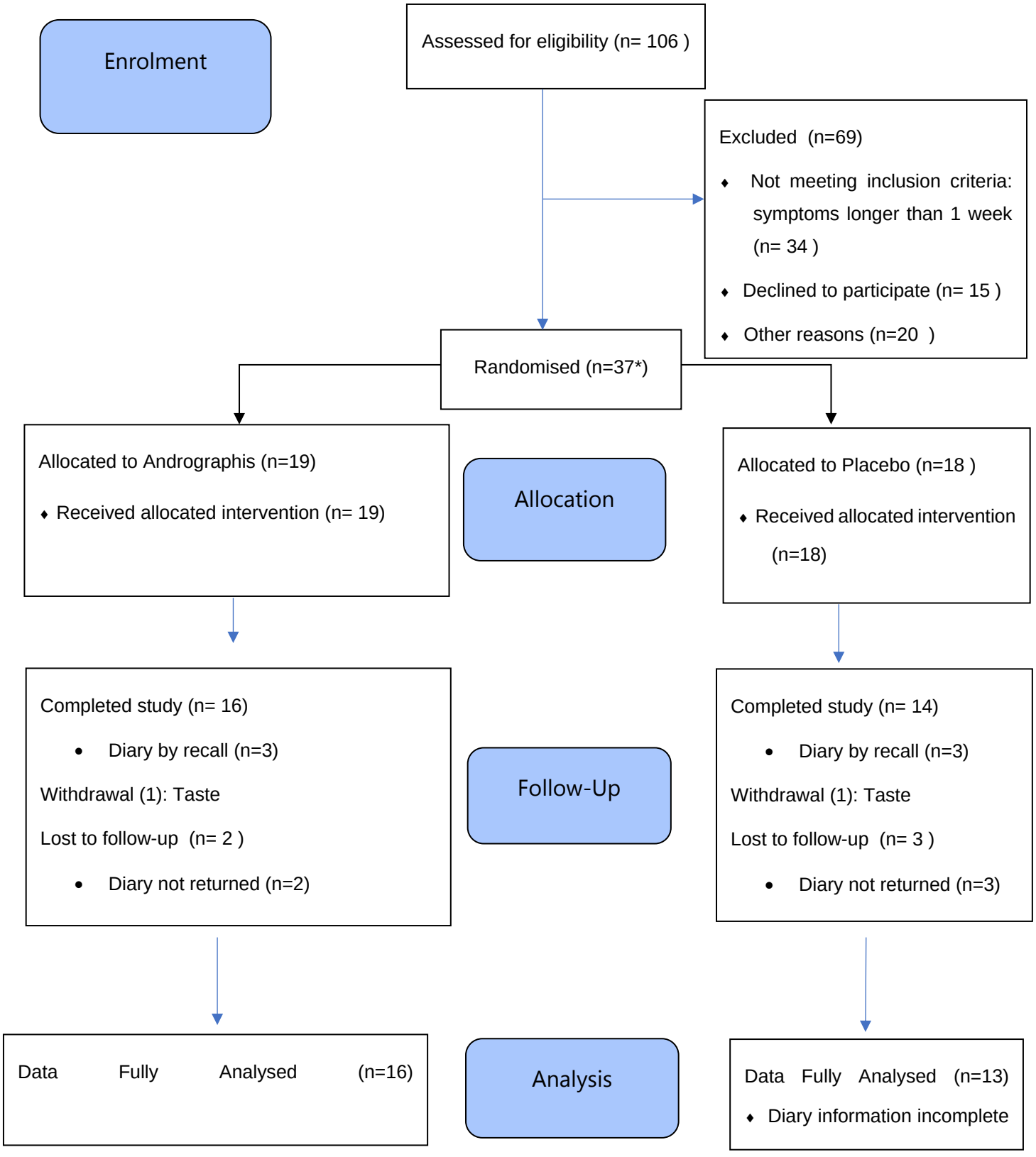
8.13.2 Participant recruitment

106 participants were screened and 38 (35.8 %) participants were initially recruited but one was subsequently withdrawn as ineligible*(see CONSORT diagram, figure 18). Most of the people screened were not eligible as their symptom duration was over 1 week. The recruitment period ran from February to June 2019 rather than September 2018 to January 2019 as originally planned which may have affected the recruitment rates. Table 15 documents the number of participants from each practice and each recruitment area.

Table 15. GRAPHALO Recruitment Overview

Wessex CRN			
Site	SIV Date	Activation date	Recruitment
Liphook and Liss (1 & 3)	23/01/19	Opened 11/2/2019	6
Swanage Medical Practice (06)	13/02/19	Opened 6/3/2019	8
Denmead Practice (10)	05/03/19	Opened 20/3/2019	2
Wareham Surgery (02)	28/01/19	Opened 27/3/2019	0
Three Chequers (05)	12/02/19	Opened 26/3/2019	2
Park & St Francis (04)	06/02/19	Opened 20/3/2019	1
Chawton Park Surgery	25/04/19	Opened 7/5/2019	1
TOTAL			20
PEN SW			
Site	SIV Date	Comment	Recruitment
Teignmouth Medical Group	07/03/19	21/5/2019	0
Teign Estuary Medical Group (12)	07/03/19	9/4/2019	1
Middleway surgery	26/02/19	Opened 2/5/2019	2
Brunel Medical Practice (08)	26/02/19	Opened 21/3/2019	8
Bovey Tracey & Chudleigh (15 & 16)	04/04/19	Opened 23/4/2019	4
Beacon Medical Group	07/03/19	Opened 21/3/2019	1
Oak Tree Surgery (07)	25/02/19	Opened 2/4/2019	2
TOTAL			18

Figure 18. Consort diagram detailing flow of participants through the study



8.13.3 Study population

37 participants were randomised and 30 participants remained after 2 withdrew and 5 did not return their diary (see Figure 17). One participant in the placebo group returned a diary with incomplete data and was therefore not included in the baseline characteristics table*.

The baseline characteristics of the participants are set out in Table 16 below. Due to the size of the feasibility study, we would not necessarily expect the randomisation to produce perfectly balanced groups. The population was primarily white with an average age of around 50 years old. The majority of participants were female.

Table 16 Baseline characteristics

	Active (n=16)	**Placebo (n=13)**
Female	10 (62.5%)	8 (61.5%)
Age*	51.49 (18.59)	47.95 (15.99)
Ethnicity (Self-reported)		
White	15 (93.8%)	13 (100%)
Asian/Asian-British	1 (6.2%)	0 (0.0%)
Employment		
Full/part time	11 (68.8%)	11 (84.6%)
Unable to work	1 (6.3%)	0
Retired	3 (18.8%)	2 (15.4%)
Unemployed	1 (6.3%)	0

*Mean and standard deviation

8.13.4 Baseline Consultation

Table 17 sets out the data from the baseline consultation. The active treatment group consulted on average somewhat later than the placebo group (5 days compared to 3 days) and they were slightly more unwell (baseline symptom severity 3.01 compared to 2.51). Symptoms were measured on a scale from 0-8 (0=normal/not affected; 8= as bad as it could be).

In both groups, most participants had tried an over the counter medication prior to consultation. Most people came for the reason "other " from those listed on the diary. There were 5 participants prescribed antibiotics in the baseline CRF (see Table 18).

Table 17. Baseline consultation information

Baseline consultation information	**Active (n=16)**	**Placebo (n=14)**
Baseline symptom severity	3.01 (1.03)	2.51 (0.86)
Median duration of illness prior to consultation (LQ, UQ)	5 (3,7)	3 (2,5)
Treated with OTC medication prior to consultation	12 (80.0%)	12 (92.3%)
Main reason for visit		
You are worried about a more serious condition	4 (25.0%)	2 (15.4%)
To get other treatment for this illness	2 (12.5%)	3 (23.1%)
A friend or family member made you go	3 (18.8%)	1 (7.8%)
To get a sick note/certificate	0	1 (7.8%)
To get antibiotic treatment for this illness	2 (12.5%)	1 (7.7%)
Other	5 (31.3%)	5 (38.5%)

8.13.5 Symptom resolution and severity

There are several definitions of symptom resolution detailed in Table 18 below. This data is based on diary data but if diary data is missing, it includes information captured using the diary by recall where this is available. The symptom severity was slightly lower in the placebo group (see Table 17).

Table 18. Symptom duration and medication use (In days from diary)

	Active (n=16)	Placebo (n=14)
Last day of all moderately bad symptoms	7 (4.5, 14)*	5 (3,6)
First day of no moderately bad symptoms	8 (5,9)	5 (3,7)
Last day of any symptoms	10.5 (7.5, 14)	7 (4, 9)
First day of no symptoms	10 (5.5, 11)	7 (5, 8)
Moderately bad symptoms resolved day 7	9 (56.3%)	11 (84.6%)
Moderately bad symptoms resolved day 14	16 (100%)	13 (100%)
All symptoms resolved day 7	4 (25.0%)	7 (53.9%)
All symptoms resolved day 14	16 (100%)	13 (100%)
Antibiotics started	2/8 (25.0%)	3/9 (33.3%)

*Median and range

Table 19. Symptom severity (from diary)

	Active (n=16)	Placebo (n=14)
Symptom severity days 2-4 all symptoms	2.25 (0.90)	1.98 (1.12)

8.13.6 Euro QOL

At day 1 29/30 participants completed the EQ5D and at 7 days 28/30 participants completed it. It is, therefore, feasible to collect this data to facilitate cost-effectiveness analysis in a future trial.

8.13.7 Adherence to treatment

Participants in both groups took an average of 20 doses of active treatment or placebo. In the active group, the median was 20 (14,24) and in the placebo group it was 20 (8,24). Assuming 4 doses per day, this would be around 5 days worth of the medication. We know that 6 people in each group were still taking the full 4 doses of the medication on day 7. Only 1 participant (active) took 28 doses of medication (4x per day for 7 days).

The graph below shows the adherence to medication on each day. For those people who did not complete the diary data on medication, we have assumed that they did not take the dose. It appears that most people either took the full dose or did not take the dose. The protocol advised patients to stop taking the study medication 2-3 days after their symptoms resolved

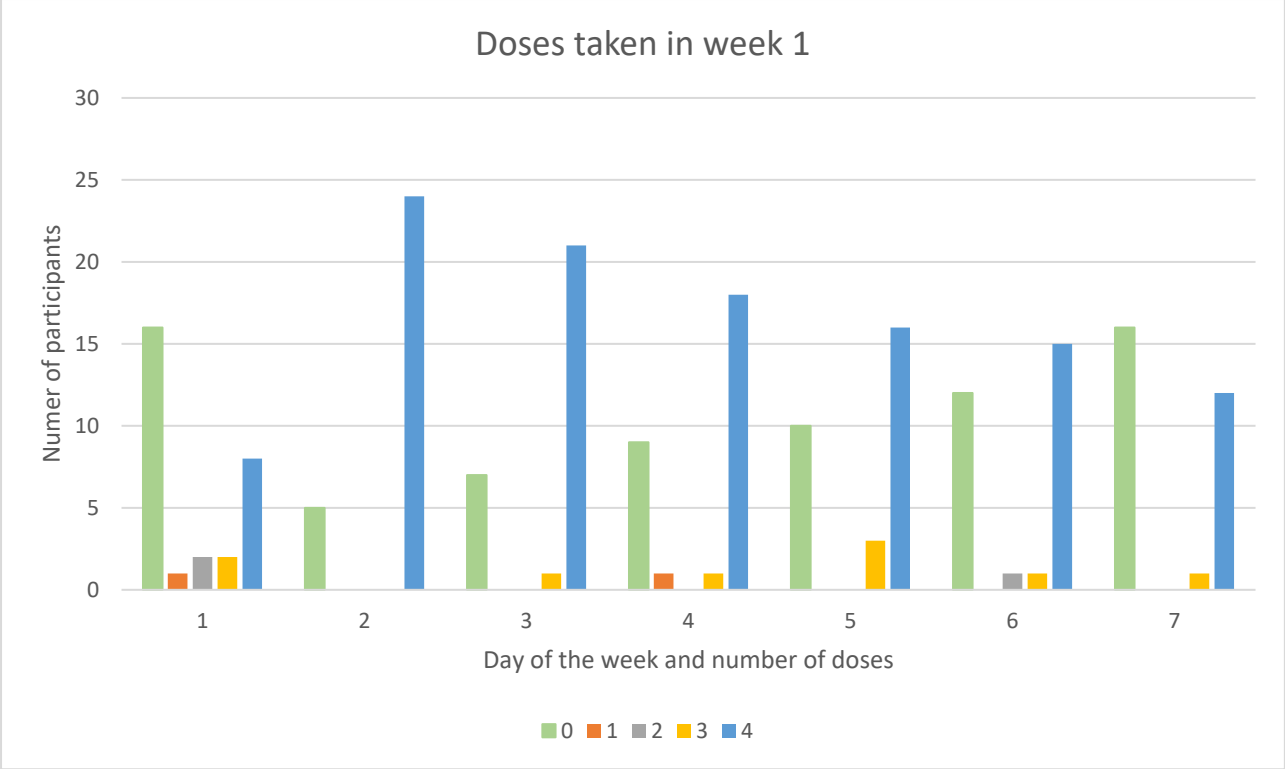


Figure 19. Medication adherence on each day including number of doses taken each day.

8.13.8 Antibiotic use

2/16 people in the active group (12.5%) and 3/13 people in the placebo group (23.1%) reported taking an antibiotic in week 1. Three of these were delayed prescriptions; 1 was for Acne and 1 was ongoing for UTI prophylaxis. One further person in the placebo group reported taking an antibiotic in week 2.

8.13.9 Medicine return

14 of 38 participants did not return their medication. The returned medication was checked by JS and checked against the diary data. The number of capsules returned

was consistent with diary information suggesting that self-reported adherence was a useful process

8.13.10 Side Effects, SAEs and Hospitalisations

One patient in the placebo group attended an outpatient's appointment for a skin related issue. Under reasons for stopping medication, 2 people reported headaches (one in each group), 1 reported indigestion (active) and 2 reported nausea (placebo). There were also comments about the taste and volume of capsules.

8.13.11 Protocol breach and deviations

Most of the practices involved in the study followed the GRAPHALO protocol guidelines, however, one practice recruited a participant that was ineligible for the study. This was discovered when the baseline characteristics form was sent through to the study team. Once this was discovered I contacted the participant and asked her to discontinue with the study medication. I also rang the practice but was unable to contact the local investigator. I subsequently sent an email to the study investigator explaining the situation and asked them to cease recruitment until retraining was undertaken. I also contacted the sponsor and explained the situation and they asked me to document my findings. The following day the practice recruited another participant. I, therefore, sent another email to the practice explaining they were being removed from the study because they did not follow the study instructions. I asked the local CRN to visit the practice and remove the medication and close down the study at the practice. The next section mentions some of the issues with the setting up and running of the trial and discusses the feasibility outcomes.

8.14 Discussion

There were many issues in setting up and running this feasibility study including getting approvals from the sponsor (University of Southampton), the health regulatory authority (HRA) and the medicines and healthcare regulatory authority (MHRA). My supervisor, George Lewith had obtained permission to carry out a feasibility study in 2016. However, this agreement was not accepted by the sponsor after George passed away in 2017. The sponsor requested that I obtain new permission from the MHRA before they would act as sponsor for the study. We met with the MHRA in January 2018 and they agreed that the study could continue as long as no claims were made of efficacy and safety from the trial. This was an important breakthrough as this trial was considered a non – CTIMP. CTIMP trial applications take years to complete and can take a significant amount of time and money. Subsequent approvals from the Sponsor, REC, and HRA were obtained in Autumn 2018. There was also difficulty in receiving secure participant facing information due to the phasing out of fax machines in primary care practices. I was lucky enough to have previously acquired an NHS.net email account, otherwise, there would have been issues with the receiving of participant trial information such as the consent forms. I needed to submit an amendment to the HRA and Sponsor to be allowed collect this information.

In terms of preparation of the medicines, there were issues with stability of the product and the THR application (which was originally required to run the feasibility study), which delayed the project by one year. There were also issues with milling of the product (Andrographis powdered herb) to the correct micron, which would allow the powder to fit inside the capsule. The original plan was to dispense 6 capsules per day, fitting 500mg of powdered herb into each capsule however this was not possible due to problems getting the powder to settle in the capsule,

therefore we had to place 250mg in the capsule which doubled the amount of capsules per day to 12. This capsule burden may have affected adherence to treatment and some participants commented on this within the diary. There is a paucity of feasibility studies on single herbal medicines to treat ARTIs. A feasibility study by Flower et al (2019) exploring the role of Chinese herbal medicine for the treatment of urinary tract infections found it was feasible but challenging to conduct a trial on Chinese herbal medicine in primary care. The authors concluded that although recruitment was slow and there were issues with the retention rate; the study showed some promising data in symptom improvement and a reduction in antibiotic use.

The main feasibility outcomes of this study were based around recruitment, adherence to treatment/placebo, antibiotic use and completion of outcome measures and retention:

- Recruitment - Recruitment onto the study was successful with 16 primary care practices and 35.8% of the total participants screened recruited onto the study. Recruitment was supposed to run from September 2018 to January 2019 to include the cold and flu season however due to late delivery of the medicine and the need to submit an amendment to the application, recruitment did not begin till February 2019. This may have adversely affected the recruitment numbers. Restrictions on concomitant medication (participants were only allowed paracetamol, Ibruprofen, and antibiotics) stated in the eligibility criteria also have affected the recruitment numbers. In a larger trial, it may be worth allowing participants to use all other usual care medication Including OTC products (apart from antibiotics) as this may increase participant recruitment.
- Randomisation and retention - All of the participants recruited in the study were happy to be randomised. In terms of retention of participants, 81% of

participants remained in the study. One area where there was a lack of information was willingness to randomise among clinicians. Some of the practices did not recruit any participants but were not asked about this in the trial. This is an important issue and may have affected the recruitment numbers in the trial

- Outcome measurements - In terms of suitability of the diary, most people came for a reason other than those listed on the diary, which suggests that from a feasibility standpoint we may need to alter these questions in a larger trial. However, of the 12 who gave a reason, 7 were worried about what illness they had or that it wasn't improving. So perhaps these fit under "you were worried about a more serious condition" if by that we mean that they are seeking reassurance from the GP/nurse. The diary proved useful in collecting quality of life data and showed its feasible to collect this data to facilitate cost-effectiveness in a future trial.
- Adherence to treatment - Some of the participants complained about the number and taste of capsules and this may have affected adherence to the medication. In a larger trial adherence may improve if there are fewer capsules for the participants to take. Data from the diary looking at adherence to treatment indicated that most people either took the full dose or did not take the dose at all. Measures of symptom resolution are problematic as we have several definitions of symptoms resolution (none of which may be the patient's own definition) and we do not know whether they decided to stop at day 2, day 3, or somewhere in between. So a feasibility outcome might be that clearer instructions and clearer reporting systems are needed if we want to measure adherence in a larger trial.
- Symptom resolution – The active group consulted on average later than the placebo group (5 days compared to 3). Symptoms appeared to settle more

quickly in the placebo group, with moderately bad symptoms lasting a median of 5 days in the placebo group compared with 7 days in the active treatment group. This trend was apparent regardless of the definition used but this does not control for the slightly lower symptom severity at baseline severity in the placebo group.

- **Antibiotic use** – Antibiotic use was low in both groups with a sightly larger intake by the placebo group. The data collected showed it is possible to collect antibiotic usage in this feasibility trial.
- **Safety and Adverse events –** Overall the feasibility trial showed that the trial medication was safe to take as there were few adverse events or side effects. Some of the participants commented they did not like the number of capsules they had to consume and others complained about the taste of the capsules. In a larger trial, it may be worth reducing the number of capsules that participants need to consume and improving the taste of the capsules.

8.15 Reflection

Overall, this feasibility study took the most effort compared to the rest of the other projects in this PhD due to governance, manufacture, and production of the study medication. At many stages, I thought the project would not go ahead and I, therefore, discussed other options with my supervisory team including an observational study. I found the governance and ethics processes extremely lengthy and frustrating. One of the governance team suggested that carrying out research on herbal medicines was not recommended, as herbal medicines are not regulated, unlike conventional medications. Despite this methodical approach,

which at times felt frustrating, I am grateful to the University of Southampton for sponsoring this study.

I found the CRNs at Wessex and Peninsula South-west very helpful throughout the study. Most of the health professionals I encountered and communicated with were friendly and open to researching herbal medicines. Many of them asked useful questions, which helped me to focus on problems, they may have encountered with the study. One of the most common questions was about the use of concomitant medicines that participants were taking.

8.16 Contributions

I think one area that is overlooked in many clinical trials is the teamwork that goes on behind the scenes. Most clinical trials or feasibility studies involve a lot of collaboration and experience to run smoothly. Although I led all aspects of the feasibility study, I needed support and input throughout this feasibility study. At the onset of this journey, I was fortunate enough to have an experienced team of supervisors including Dr. Miriam Santer, Dr. Andrew Flower, Professor Michael Moore, and Professor George Lewith, who helped early on with getting the necessary approvals to set up the study.

The team at Pukka which included Barry Moore and Nadia Thornhill worked tirelessly to get the necessary manufacturing approvals ratified. Jackie Seely was invaluable as a Trial coordinator. She worked tirelessly to create and oversee much of the administration of the study. I had no idea the amount of paperwork and administration that was involved in running a trial. The input from experienced trial managers such as Wendy O' Brien, Julie Hooper, Jane Vennik, and Jo Kelly was extremely helpful especially when we ran up against trial-related issues. Dr. Beth

Stuart advised on the statistical analysis of the study and talked through the most important feasibility outcome measurements.

8.17 Strengths and Limitations

As this was a feasibility study, the analysis was mainly descriptive, and I did not conduct inferential statistical or hypothesis testing as stipulated by the MHRA. The sample size was pragmatic and designed to meet the feasibility objectives. We recruited 38 practices in primary care in Southern England with diverse sizes and locations. There was potential for selection bias to occur as practices that were research active and had an interest in alternative treatments for ARTIs were more likely to become involved in the study. We were successful in recruiting 37 participants over the recruitment period which ran from February to March. We may have recruited a larger number of participants had the recruitment period ran over the Winter months, but this was not possible due to the late delivery of the trial products and the need to submit a study amendment. The study showed that the trial medication was safe to take with few side effects and adverse events however this was a feasibility study and further safety research would be useful to inform larger studies of *A. paniculata.*

8.18 Conclusion

The primary study objective of this study was to measure feasibility outcomes to inform the design of a future fully powered trial of *A. paniculata* leaf extract as an alternative to antibiotics for upper respiratory tract infections in UK primary care. Overall, the study showed it was possible to collect and measure feasibility

outcomes from GP practices into a study for ARTIs to inform the design of a fully powered trial. Specific feasibility outcomes included recruitment, adherence to treatment/placebo, antibiotic use, and completion of outcome measures and retention were all successfully gathered and analysed. These findings suggest that a larger trial would be feasible to conduct however there are a number of issues that would need to be addressed. Table 20 shows the processes that worked well and those that did not in the study.

Table 20. Feasibility study objective evaluation information

Feasibility Objective	Endpoint used to evaluate	Outcome
Eligibility: Number of patients included and number excluded (+reasons) from the trial	On-site screening logs	This information was successfully collected.
Recruitment: Ability to recruit patients into the intervention from those attending primary care	On-site enrolment records	We were able to collect this information.
Randomisation: Willingness of participants to be randomised	Proportion of eligible patients recruited.	Most participants were happy to be randomised.
Randomisation: Willingness of health professionals to randomise participants	Number of participants recruited at each practice	No information was collected on health professionals willingness to randomise participants. This information would be useful to collect in a large scale trial.
Retention: Across the duration of the intervention and return of a fully completed diary and medicines	Quantitative data from enrolment Withdrawal rate from study Completion of outcome measures	Retention was good however some of the medicine pots were not returned. The study information may need to

		clarified in a larger trial
Intervention compliance	Diary data on adherence to treatment/placebo and returned medication.	The diary was successful in collecting data but some of the questions may need to be rephrased.
Acceptability of the outcome measures, participants' willingness to complete them and the importance of telephone/text contact.	Quantitative data collection - number of patients returning completed diaries and needing follow-up telephone calls.	Most participants returned the diary however it may be useful to emphasise to participants to return the diary in a larger trial.
Exploration of rates of antibiotic prescription in both groups.	Diary data on day antibiotics commenced	This data was collected. More information on why antibiotics were prescribed would be useful to collect.

I discussed the issues and hurdles associated with the management of this trial and the benefit of working in an academic environment with lots of experience in running clinical trials. The most important lesson, I have learned through the setup and running of this trial it is important to have an experienced team of people to guide you through the ups and downs of trial management and never give up even when it seems that everything is going badly

Chapter 9: Discussion

9.1 Introduction

The aim of this PhD was to examine the role of *A. paniculata* leaf extract as a symptomatic intervention for ARTIs. The main body of this thesis comprises of three phases of original research described within nine chapters. The first phase was a systematic review and meta-analysis of RCTs conducted with a research group in China. The second was a qualitative study of health professionals' views on using herbal medicines for respiratory tract infections, and the final phase was a clinical trial to explore the feasibility of investigating the effects of *A. paniculata* in the symptomatic treatment for ARTIs within primary care.

This final chapter presents an overview of my PhD including a summary of the previous chapters, a discussion of the key findings concerning the current literature, the strengths and limitations of my research, and proposed future recommendations. I shall discuss the use of the systematic review, qualitative study, and feasibility study in underpinning my research and informing the selection of appropriate methodology and research methods to answer my research aims. Finally, I shall discuss the role of other researchers and research groups and their contribution to the chapters in this PhD as well as reflecting on my own personal journey.

9.2 Thesis summary

In Chapter 2, I examined the existing work on antimicrobial resistance (AMR) and looked at the potential of herbal medicines to contribute to this field. Reducing the inappropriate use of antibiotics, as well as ensuring that they can be used when

needed, represent important components of a strategy to control infectious diseases. The third chapter looked at acute respiratory tract infections (ARTIs) in primary care. I examined the public and health professional understanding of antibiotic use in ARTIs, considered the strategies to reduce antibiotic prescribing, and looked at the clinical use of herbal medicines to treat ARTIs. Both these chapters indicate that herbal medicines have a valuable role to play in the management of ARTIs and the reduction of AMR.

In the fourth chapter, I reviewed the current literature on the pharmacology and phytochemistry of *A. paniculata* and examined its potential as a treatment of respiratory tract infections. The in-vitro evidence reviewed suggested that *A. paniculata* is a valuable tool in the armoury against AMR. Laboratory-based research on *A. paniculata* suggests the whole plant and its constituents operate via biologically plausible pathways by mediating an immune response against microbial infection and also having direct antiviral, antibacterial, and antifungal actions. However, there are limitations to invitro research in herbal medicines and these require further research and validation through other research methods such as clinical trials.

The systematic review and meta-analysis in chapter 4 included Chinese and English language research on the use of *A. paniculata* for the symptomatic relief of acute respiratory tract infections (ARTIs)(Hu *et al.*, 2017). This review was a joint project between researchers in the UK and China. The review included thirty-three trials involving 7175 patients with ARTIs, comparing *A. paniculata* with conventional interventions, standard care, active herbal interventions, and placebo with no

language restrictions. The findings suggest limited but consistent evidence that *A. paniculata* has a statistically significant effect in improving symptoms of ARTIs and shortening the duration of symptoms. Reduction in antibiotic usage was seldom reported in the included trials which is a shame considering the current situation with AMR. *A paniculata* appeared to be relatively safe as no serious AEs were observed in the included trials. There was high heterogeneity among the trials due to variations in dosage, population, and outcomes and the methodological quality of the trials reviewed was generally poor. Overall, this review does provide some preliminary evidence to suggest that *A paniculata* is likely to be safe and is a promising candidate in the treatment of ARTIs. This is the first published systematic review of *A paniculata* which looks at English and Chinese research papers and is the largest to date (Hu *et al.*, 2017).

Chapter 6 discussed the mixed methods approach in this thesis. It examined the role of qualitative research in healthcare. I presented my philosophical worldview and talked about the pragmatic approach I have followed. The subsequent sections look at semi-structured and telephone interviews and discussed sampling, saturation data collection, analysis, and rigour within qualitative research.

Chapter 7 of this project was a qualitative telephone interview study with health professionals asking them about their views and perspectives in using herbal medicines for ARTIs. The information gathered from health professionals in this study aided in the subsequent design of the feasibility study (by using their feedback on how they would like a trial to run into the design) and provided insight into health professionals' attitudes into herbal-based by using feedback treatments for ARTIs and the rationales underpinning these perspectives and views. Key

themes included how health professionals made sense of herbal medicine in general practice; beliefs and attitudes towards OTC herbal medicine use; and health professionals' views on herbal medicine governance and production. In terms of how health professionals made decisions about herbal medicine in general practice, there was a wide spectrum of views and stances. Commonly, health professionals cited the lack of a perceived evidence base as a barrier to considering herbal medicine use in their practices.

When it came to prescribing, recommending, or advising patients on herbal medicine use, most health professionals again mentioned the need for evidence or training before talking about herbal medicine with patients. However, some respondents were happy to advise on the use of herbal medicines and adopted a shared decision-making approach and talked with the patient about the choices available. The finding that lack of training and education was seen as a barrier to discussing herbal medicine use with patients, with some GPs viewing it as outside their sphere of expertise. A widely discussed subject in the interviews was the relationship between herbal medicine and the placebo effect. The placebo effect was defined in different ways by health professionals.

There was discussion around patient types by many health professionals. They mentioned that there were patients who preferred herbal medicine and those who didn't. This belief was related to many different factors including education, socio-economic status, and demographics. We found that many health professionals were more comfortable with recommending herbal medicines that they were familiar with or that were popular because their side effects or interactions were known (such as St John's Wort or Echinacea). Some health professionals suggested that patients view "natural" as safe and effective compared to synthetic medicines.

This view was not shared by other GPs who considered many natural products to be impure and therefore potentially toxic.

Chapter 8 of the PhD details the study design, outcomes, and results of a double-blind placebo-controlled feasibility study in primary care comparing 2 treatment arms; *A. paniculata* versus placebo. We successfully recruited 37 participants to the study from 20 practices in Wessex and PEN SW areas. For a larger trial, it will be important to recruit at the optimum time of the year (Autumn/ Winter) to reach the required number of participants. Both active and placebo capsules appeared to be safe and there were few side effects. The use of the diary to collect participant data was successful but will require some adjustments in a possible future trial; some of the participants did not return the diary or the remaining medication. Subsequent use of the diary will need adjustments to improve these outcomes. The collection of the quality of life measurements was successful. Participants in both groups took an average of 20 doses of trial medication and it appears that participants either took the full dose or did not take the dose at all. There was also a low uptake of antibiotics in both arms which was an important finding in terms of planning future research.

It is clearly beyond the framework of this research to suggest that *A. paniculata* was effective or ineffective in treating ARTIs and reducing antibiotic prescribing, as the feasibility trial was not powered for this. My findings suggest it is feasible to conduct a fully powered trial with *A. paniculata.*

9.3 Key Findings in relation to current literature

Since I began this PhD in 2016 there have been changes in the use of antibiotics. In January 2019, the UK government published a 5-year plan to tackle antimicrobial resistance across human and animal health. The report suggested that the Defined Daily Dose per 1000 people per day has dropped from 23.4 in 2014 to 21.7 in 2017, a drop of 7.3% due to stewardship programmes. However, the UK still prescribes at least twice as many antibiotics as The Netherlands or Sweden, with 20% of these prescriptions considered inappropriate. The report mentions the need to develop alternatives for people and animals and build an academic base for antimicrobial resistance research (PHE infectious diseases strategy - *GOV.UK*, 2018).

The findings in our systematic review are similar to previous systematic reviews, although ours is more comprehensive. A systematic review by Coon and Ernst (2004) looked at seven double-blind clinical trials (n=896) for efficacy and fourteen studies (n=1,235) for safety. The authors suggested that *A. paniculata* may have a role in the alleviation of ARTI symptoms and is relatively safe however they did mention that due to the low number of trials, the review may be prone to error or bias (Coon and Ernst, 2004). A further review by Poolsup et al (2004) found that *A. paniculata* alone or in combination with other herbs may be more effective than placebo for uncomplicated ARTIs (Poolsup *et al.*, 2004). Our systematic review included 7175 patients and included 33 RCTs with 25 of these in Chinese. The review found that *A. paniculata* was beneficial and safe for ARTI symptoms and reduced time to symptom resolution although there were issues with the methodological quality of some of the trials.

No qualitative interview studies were found examining health professionals' attitudes towards herbal medicine for ARTIs. Some studies explored the views of health professionals on herbal medicines and CAM generally. A study by Bhamra et al (2019) to explore UK based health professionals' opinions and experiences via an online questionnaire found that those who personally used herbal medicines had a positive impression of herbal medicines and were more likely to recommend them to patients. Health professionals identified their lack of knowledge and training in herbal medicines as a barrier to advising patients on the use of herbal medicines (Bhamra *et al.*, 2019). The qualitative study in this thesis also found that training and lack of education acted as a barrier to health professionals recommending herbal medicines. Although some participants who used herbal medicines would recommend them to patients' others were more cautious in their approach because of medico-legal concerns

A study based in Switzerland looking at 1,247 health professionals' sources of knowledge in CAM showed that physicians tended to rely more on scientific evidence and literature while nurses and midwives relied more on personal and clinical experience. The study also reported that 85% of participants lacked knowledge about CAM and noted most discussions were started by patients (Aveni *et al.*, 2017). It is difficult to compare this finding with my qualitative study as only 2 practice nurses participated in the qualitative study however many health professionals in our study cited lack of evidence and experience as a barrier to considering herbal medicines in primary care. This finding was echoed by Maha and Shaw (2007) looking at academic doctors' perspectives on CAM and its role within the NHS. They found that most participants were sceptical about the use of

CAM in this setting. The authors suggested that the lack of scientific evidence remains a significant barrier to greater integration of CAM within the NHS (Maha and Shaw, 2007). Perhaps further research needs to be conducted to get health professionals to accept CAM or make CAM more evidenced-based.

An Australian study found that herbal medicines were the primary mode of CAM advocated for the prevention or treatment of infections. The study suggested that more knowledge about the limitations and benefits of CAM such as herbal medicines is needed by health professionals (Wilkinson 2005). Some participants in our qualitative study also suggested that herbal medicines were more useful in maintaining health rather than treating illness.

The feasibility study was the first of its kind in the UK comparing *Andrographis paniculata* with placebo in primary care for ARTIs. This may partly explain why there were difficulties in getting the necessary approvals to run the feasibility study. It was also a new venture for Pukka Herbs who funded the study and I think this was also a learning experience for them.

The work in this PhD would not have been possible without collaboration with other researchers in the UK and China. The systematic review was led by Dr. Xiaoyang Hu and she collaborated extensively with the Centre for Evidenced Based Chinese Medicine at Beijing University for Chinese Medicine. My main role was to screen and extract data from the clinical trials in English and assist in the analysis, writing up, and editing of the review data. During the set-up and running of the GRAPHALO feasibility study, I worked closely with the Trial Co-ordinator, Jackie

Seely. I led the design, governance processes, and study set-up and we both worked together in delivering the site initiation visits. Jackie dealt with the correspondence between the practice sites and the Study Centre at Southampton and was instrumental in the creation of the study documents and the overall administration of the trial.

9.4 Reflection – what I have learned

I have been a herbalist and acupuncturist for over 20 years and I have seen in my practice how herbal medicines such as *A paniculata* have benefited patients but also become aware of their limitations and the need for further research into these remedies. My decision to pursue research was to increase the knowledge base and evidence of herbal medicines especially in the area of infection control but also understand the application of research within CAM. One of the main attractions was also to work with Professor George Lewith, a towering figure in CAM research who has sadly passed away during this PhD. This PhD has helped me to develop a wide range of skills, techniques, and a better understanding of research methods. I have been lucky to have completed training in a wide range of research skills including clinical trials, qualitative research, systematic reviews, statistics, health economics, and scientific writing.

The process of carrying out this PhD has also taught me that undergoing research in primary care is difficult and that undertaking research in herbal medicine is even more so! I had no idea how many hurdles there were to get over especially within herbal research. I realise now that many of these hurdles are necessary to deliver rigorous research. Currently, in the UK, herbal medicine as a profession is not

regulated and the world of over the counter (OTC) herbal products is viewed with suspicion from many quarters.

However, I do not think that means that herbal medicine research should be abandoned. I think it means the opposite. I have realised through doing this PhD there is a dearth of good quality research in herbal medicine (both qualitatively and quantitatively). In order to tackle public health issues such as AMR, more high-quality research is needed in herbal medicine.

I feel lucky to have had the chance to work with Pukka Herbs Ltd (The PhD funder) throughout my PhD. Whilst I was waiting for the stability testing to be completed on the trial products I spent time working as part of the herbal team. Working with Pukka helped me understand the challenges that herbal companies face when trying to undergo research into their products. Most research on herbal medicine is funded by herbal companies such as Pukka and this could be seen as a conflict of interest in some quarters. Throughout the PhD I have worked independently from Pukka and conducted research under the guidance and direction of my supervisors who had no connection with Pukka.

Whilst doing the PhD I have continued working as a practitioner and I think this has helped in developing my role both as a practitioner and as a researcher. I feel I now have a wider appreciation of the research world and the stakeholders involved – patients, doctors, nurses, researchers, sponsors and ethics committees, funders, commissioners, regulatory authorities, and manufacturers. As a practitioner, I feel I have become much more sceptical when it comes to evidence

and I have now more questions than answers, which I do not think is a bad thing. I have been lucky to work with some of the best academics and thinkers in primary care and CAM and have seen how they view the world and the contributions they have made. I feel privileged to have worked with these people.

Throughout the PhD, I have struggled with the discrepancy with how I practice (and think) as a herbalist on day to day basis with how clinical research on herbal medicine is carried out. For instance, as a herbalist, I rarely use *A. paniculata* on its own. This is common in Western and Chinese herbal medicine traditions. I normally prescribe it with other herbal medicines depending on the symptom picture of the patient I am treating. This approach is based on traditional use. For instance, Andrographis is commonly prescribed with Echinacea and Elderberry to treat ARTIs. I also vary the dose from patient to patient. Within most clinical research a recognised standard dose is required and each participant receives the same dose. This is not representative of the real world of herbal medicine practice. This situation is described by some researchers as model validity (Tilburt and Kaptchuk, 2008). According to Khorsan and Crawford (2014), when there is a failure to measure external validity and model validity, practitioners are often unable to determine if a given study's findings apply to their local setting, population staffing, or resources. This lack of information on external validity and model validity can contribute to the failure to translate research into public health practice. Therefore, policy and administrative decision-makers are unable to determine the generalisability or breadth of applicability of research findings (Khorsan and Crawford, 2014). Future research into herbal medicines should be mindful of model validity if they want to overcome these shortcomings. This PhD contributes to new knowledge through the information provided by the systematic review, the

qualitative study, and the feasibility study. The systematic review provided new information on *Andrographis paniculata* by including Chinese language studies. The qualitative study provided fresh insights into health professionals' views of herbal medicines in the treatment of ARTIs and the feasibility study was the first of its kind on the trial of *Andrographis paniculata* to treat ARTIs.

9.5 Strengths and Limitations

My research set out to examine the potential of *A. paniculata* as a treatment for ARTIs in primary care. The use of a mixed-methods approach allowed me to choose appropriate and pragmatic methods to achieve my research objectives. Although mixed methods approaches are complex and time-consuming they help to understand the contradictions in research, allow a flexibility methodological approach whilst also allowing participants a voice in the research. The combination of quantitative and qualitative methods in this study allowed me to examine the quantitative elements of this PhD such as the systematic review and feasibility study and compare these with the findings of the qualitative study.

The systematic review in chapter 4 was the first systematic review on *Andrographis paniculata* published which included both Chinese and English language research. The review examined the clinical studies already ready carried out on *A. paniculata* in the treatment of ARTIs and provided information on dosage, participant types, and trial design. It also provided information on whether it was worthwhile pursuing further research on *A. paniculata*. Although the findings suggest that *A. paniculata* were promising there were issues with heterogeneity and with the methodological quality of the trials included. Also, the reduction in antibiotic use was not reported in many of the trials in the systematic review which is one of the

main reasons to conduct a trial in this area of research. This is not uncommon in herbal medicine trials as most herbal medicines are not internationally standardisation to the same constituents and dosages are not consistent in the different countries that conduct RCTs. There is need for a new equivalent method of assessing these trials which allows flexibility and an understanding of the nuances of herbal medicines.

I conducted a qualitative study interviewing health professionals and examining the barriers and facilitators to using herbal medicines for ARTIs in primary care. Although the findings from the qualitative study are not generalisable they provided a useful insight into how some health professionals view the world of herbal medicine and provided insight into the potential barriers to the wider use of herbal medicines. The study also provided information (from health professionals suggestions) that helped in the design and implementation of a feasibility study using a herbal medicine in the treatment of ARTIs in primary care. It would have been useful to explore the public/patient view of using herbal medicines in ARTIs to provide a broader appreciation of the issues concerned with administering herbal medicine via primary care however there was not enough time to carry this out.

Although this feasibility study was not powered for efficacy, it provided useful data for the design for a fully powered study of Andrographis in primary care. I managed to recruit 37 participants to the study during the off-peak season for ARTIs. This was a positive outcome considering the participants knew that some of them would receive a placebo medicine. It is difficult to comment on the differences between the two groups in the study as the baseline severity scores were very different and

the active group consulted on average later than the placebo group for their symptoms. The study population was mainly white, employed and over 50 therefore the results are not generalisable to the wider population. Although adherence to the trial medication was good, participants complained about the taste and number of capsules they had to consume. Data from the diary suggested that participants either took the full dose or no dose at all. The measures of symptom resolution were difficult as there were several definitions; none of these were the patients own definition. This suggests that more coherent instructions would be needed in a larger trial. The trial medication was generally safe with few adverse events of side effects reported.

Throughout my PhD, I included Patient and Public involvement in reviewing and providing feedback on both my qualitative and quantitative research materials, particularly for public-facing documents such as the participant information sheets. Margaret Bell who acted as PPI representative on both the qualitative and feasibility study provided suggestions to make the text in the patient-facing documents more lay friendly. At the time I commenced the research projects in my PhD I had little awareness of the amount that PPI Involvement could have facilitated and strengthened my research. For instance, I could have gone a step further and included the PPI representative in the interpretation of the research findings. I have subsequently worked on a research study where I have seen the enormous value of including a public contributor from the onset through to the completion of the research.

9.6 Recommendations for future research

Although in some ways this thesis thoroughly examined the role of herbal medicines such as *A. paniculata* in ARTIs. It would be useful to run a fully powered trial on the use of *A. paniculata* to build on the feasibility study and examine its role as a potential medicine in the treatment of ARTIs and reduce the need for antimicrobials in these conditions.

This feasibility study showed it was possible to recruit participants through primary care for ARTIs. Key learning points from the feasibility study for a full-scale trial include the following:

- To recruit for a larger trial it will be necessary to increase the recruitment period to reach the required target number
- To ensure optimum recruitment it will be important that the trial medication is ready during peak season
- To recruit a more diverse population it may be necessary to target more urban locations as most of the participants in this were white and around 50 years of age.
- Following analysis of the diary, it will be necessary to alter the questions in several ways, especially concerning symptom resolution. Adherence to treatment was satisfactory considering this was a feasibility study however 14 of 38 participants did not return their medication therefore it is difficult to ascertain if all the data on the diary was reliable.
- Although 60% of patients who visit their primary care practice leave with antibiotics this was not the case in this study. This may be due to the use of *A. paniculata* but may also be due to the fact that most participating practices were research active in reducing antibiotic prescribing. Interestingly, one of the participating practices that was new to research had

problems with the study and had to be shut down due to the recruitment of an ineligible patient. These experiences demonstrate the importance of careful selection of sites in a full-scale trial.

- Many of the participants in the study who were screened were ineligible because their symptoms lasted longer than 7 days. This poses the question as to whether primary care is the best place to recruit patients for a herbal trial to treat ARTIs? Would it be better to run such a study in a pharmacy where patients would visit their pharmacist for preventative advice and herbal medicines? Although carrying out research in this setting may be problematic due to the workload on pharmacists.

On a final note as I write this text the world is in lockdown due to COVID-19 which is a respiratory tract infection caused by a virus (SARS – CoV-2). Currently, there are no effective treatments for this infection and many people are in self-isolation due to the extremely contagious nature of this micro-organism. In China, many doctors have used herbal medicines in the management of COVID-19 and this approach appears to have helped both patients and healthcare professionals. (Yang *et al.*, 2020)(Xu *et al.*, 2020). It may be the case that herbal medicine could play an important role in helping to manage this and future pandemics, and we may be able to learn from the famous Persian physician Avicenna who suggested

" There are no incurable diseases - only lack of will. There are no worthless herbs - only lack of knowledge".

I hope that this PhD has made a small contribution of knowledge to this important field of study and provides inspiration to those people who continue to carry out herbal research!

APPENDICES

Appendix A: Systematic review searches

MEDLINE (Ovid): From 1946 to March 2016

1. exp Respiratory Tract Infections/

2. (respiratory tract infection* or (respiratory adj3 infection*) or RTI* or (chest adj3 infection*) or upper respiratory tract infection* or upper respiratory infection* or lower respiratory tract infection* or lower respiratory infection*).mp.

3. exp Rhinitis/

4. exp Sinusitis/

5. exp Pharyngitis/

6. Nasopharyngitis/

7. exp Laryngitis/

8. (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or

rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*).mp.

9. exp Bronchitis/

10. exp Supraglottitis/

11. Tracheitis/

12. exp Pneumonia/

13. (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*).mp.

14. (cough* or cold* or catarrh or flu or influenza or (sore adj3 throat) or (throat adj3 pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* adj3 nose) or (short* adj3 breath*) or rhinorrh?ea or congest* or discharge*).mp.

15. or/1-14

16. Andrographis/

17. (andrograph* or paniculata or andrographis paniculata or king of bitter*

or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin).mp.

18. 16 or 17

19. 15 and 18

Limit 19 to human(s)

*=truncation, exp=explode, adj3=adjacent within 3 words of each other in either direction, ?=substitute for one or no characters

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

AMED (Ovid): From 1985 to March 2016

1. exp Respiratory Tract Infections/

2. (respiratory tract infection* or (respiratory adj3 infection*) or RTI* or (chest adj3 infection*) or upper respiratory tract infection* or upper respiratory infection* or lower respiratory tract infection* or lower respiratory infection*).mp.

3. exp Rhinitis/

4. exp Sinusitis/

5. exp Pharyngitis/

6. Nasopharyngitis/

7. (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or

rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*).mp.

8. exp Bronchitis/

9. exp Supraglottitis/

10. Tracheitis/

11. exp Pneumonia/

12. (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*).mp.

13. (cough* or cold* or catarrh or flu or influenza or (sore adj3 throat) or (throat adj3 pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* adj3 nose) or (short* adj3 breath*) or rhinorrh?ea or congest* or discharge*).mp.

14. or/1-13

15. (andrograph* or paniculata or andrographis paniculata or king of bitter*

or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin).mp.

16. 14 and 15

*=truncation, exp=explode, adj3=adjacent within 3 words of each other in either direction, ?=substitute for one or no characters

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Embase (Ovid): From 1947 to March 2016

1. exp Respiratory Tract Infections/

2. (respiratory tract infection* or (respiratory adj3 infection*) or RTI or (chest adj3 infection*) or upper respiratory tract infection* or upper respiratory infection* or lower respiratory tract infection* or lower respiratory infection*).mp.

3. exp Rhinitis/

4. exp Sinusitis/

5. exp Pharyngitis/

6. Nasopharyngitis/

7. exp Laryngitis/

8. (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or

rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*).mp.

9. exp Bronchitis/

10. exp Supraglottitis/

11. Tracheitis/

12. exp Pneumonia/

13. (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*).mp.

14. (cough* or cold* or catarrh or flu or influenza or (sore adj3 throat) or (throat adj3 pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* adj3 nose) or (short* adj3 breath*) or rhinorrh?ea or congest* or discharge*).mp.

15. or/1-14

16. Andrographis/

17. (andrograph* or paniculata or andrographis paniculata or king of bitter*

or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin).mp.

18. 16 or 17

19. 15 and 18

Limit 19 to human(s)

*=truncation, exp=explode, adj3=adjacent within 3 words of each other in either direction, ?=substitute for one or no characters

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

CINAHL Plus with Full Text (EBSCO): From 1937 to March 2016

1. (MH "Respiratory Tract Infections+")

2. TI respiratory tract infection* or AB respiratory tract infection* or SU respiratory tract infection* or TI (respiratory N3 infection*) or AB (respiratory N3 infection*) or SU (respiratory N3 infection*) or TI RTI* or AB RTI* or SU RTI* or TI (chest N3 infection*) or AB (chest N3 infection*) or SU (chest N3 infection*)

3. TI (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*) or AB (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*) or SU (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*)

4. TI (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*) or AB (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*) or SU (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*)

5. TI (cough* or cold* or catarrh or flu or influenza or (sore adj3 throat) or (throat adj3 pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* adj3 nose) or (short* adj3 breath*) or rhinorrh?ea or congest* or discharge*) or AB (cough* or cold* or catarrh or flu or influenza or (sore adj3 throat) or (throat adj3 pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* adj3 nose) or (short* adj3 breath*) or rhinorrh?ea or congest* or discharge*) or SU (cough* or cold* or catarrh or flu or influenza or (sore adj3 throat) or (throat adj3 pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* adj3 nose) or (short* adj3 breath*) or rhinorrh?ea or congest* or discharge*)

6. TI ((cough* or cold* or catarrh or flu or influenza or (sore N3 throat) or (throat N3 pain) or (blocked N3 nose) or (runn* N3 nose) or (stuff* N3 nose) or (short* N3 breath*) or rhinorrh?ea or congest* or discharge*)) or AB ((cough* or cold* or catarrh or flu or influenza or (sore N3 throat) or (throat N3 pain) or (blocked N3 nose) or (runn* N3 nose) or (stuff* N3 nose) or (short* N3 breath*) or rhinorrh?ea or congest* or discharge*)) or SU ((cough* or cold* or catarrh or flu or influenza or (sore N3 throat) or (throat N3 pain) or (blocked N3 nose) or (runn* N3 nose) or (stuff* N3 nose) or (short* N3 breath*) or rhinorrh?ea or congest* or discharge*))

7. or/1-6

8. TI (andrograph* or paniculata or andrographis paniculata or king of bitter* or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or

kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin) or AB (andrograph* or paniculata or andrographis paniculata or king of bitter* or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin) or SU (andrograph* or paniculata or andrographis paniculata or king of bitter* or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin)

9. 7 and 8

*=truncation, N3=finds the words if they are within five words of one another, regardless of the order in which they appear, ?= replaces that number of character(s)

MH=MeSH, TI=title, AB=abstract, SU=subject,

Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library: From inception to March 2016

1. MeSH descriptor: [Respiratory Tract Infections] explode all trees

2. (respiratory tract infection* or (respiratory near infection*) or RTI or (chest near infection*) or upper respiratory tract infection* or upper respiratory infection* or lower respiratory tract infection* or lower respiratory infection*)

3. (rhinit* or sinusit* or pharyngit* or laryngit* or rhinosinusit* or rhinopharyngit* or rhinolaryngit* or nasosinusit* or nasopharyngit* or nasolaryngit* or sinonasal* or

rhino-sinusit* or rhino-pharyngit* or rhino-laryngit* or naso-sinusit* or naso-pharyngit* or sino-nasal*)

4. (bronchit* or supraglottit* or epiglott* or peumon* or pulmon* or tracheit* or brochopneumon* or pleuropneumon* or respirat*)

5. (cough* or cold* or catarrh or flu or influenza or (sore near throat) or (throat near pain) or (blocked adj3 nose) or (runn* adj3 nose) or (stuff* near nose) or (short* near breath*) or rhinorrh?ea or congest* or discharge*)

6. #1 or #2 or #3 or #4 or #5

7. MeSH descriptor: [Andrographis] explode all trees

8. (andrograph* or paniculata or andrographis paniculata or king of bitter*

or kalmegh* or kalamegh* or nilavembu or nila-vembu or kanjang or kan-jang or kiryat or chiretta or fa-ta-lai-jone or fa-talai-jone or chuanxinlian or chuan-xin-lian or yijianxi or yi-jian-xi or lanhelian or lan-he-lian or Indian-echinacea or immunoguard or livfit or livo-plus or didehydroandrographolide or didehydro-

andrographolide or dehydroandrographolide or dehydro-andrographolide or neoandrographolide or neo-andrographolide or andrograpanin)

9. #7 or #8

10. #6 and #9

19. #15 AND #18

*=truncation, exp=explode, adj3=adjacent within 3 words of each other in either direction, ?=substitute for one or no characters

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

China Network Knowledge Infrastructure (CNKI): From inception to March 2016

SU=('呼吸道感染'+'鼻炎'+'鼻窦炎'+'咽炎'+'喉炎'+'鼻咽炎'+'扁桃体炎'+'支气管炎'+'气管炎'+'肺炎'+'咳嗽'+'感冒'+'外感'+'流感'+'喉咙痛'+'咽痛'+'咽喉痛'+'咽痒'+'鼻塞'+'流涕'+'咳'+'嗽'+'喘'+'肺'+'鼻'+'咽'+'喉') AND SU=('穿心莲'+'圆锥药须草'+'榄核莲'+'一见喜'+'斩舌剑'+'苦草'+'苦胆草'+'四方草'+'斩蛇剑'+'日行千里感'+'四方莲'+'金香草'+'金耳钩'+'春莲夏柳'+'印度草'+'万病仙草'+'四支邦'+'斩龙剑'+'春莲秋柳'+'清感双舒'+'复方双花'+'感咳双清'+'新雪丹'+'喉康散'+'感冒清')

SU= subject heading

Chinese Scientific Journals Database (VIP): From inception to March 2016

M=(呼吸道感染+鼻炎+鼻窦炎+咽炎+喉炎+鼻咽炎+扁桃体炎+支气管炎+气管炎+肺炎+咳嗽+感冒+外感+流感+喉咙痛+咽痛+咽喉痛+咽痒+鼻塞+流涕+咳+嗽+喘+肺+鼻+咽+喉) * M=(穿心莲+圆锥药须草+榄核莲+一见喜+斩舌剑+苦草+苦胆草

+四方草+斩蛇剑+日行千里感+四方莲+金香草+金耳钩+春莲夏柳+印度草+万病仙草+四支邦+斩龙剑+春莲秋柳+清感双舒+复方双花+感咳双清+新雪丹+喉康散+感冒清)

M= title and abstract

Wan Fang database: From inception to March 2016

主题:('呼吸道感染'+'鼻炎'+'鼻窦炎'+'咽炎'+'喉炎'+'鼻咽炎'+'扁桃体炎'+'支气管炎'+'气管炎'+'肺炎'+'咳嗽'+'感冒'+'外感'+'流感'+'喉咙痛'+'咽痛'+'咽喉痛'+'咽痒'+'鼻塞'+'流涕'+'咳'+'嗽'+'喘'+'肺'+'鼻'+'咽'+'喉') * 主题:('穿心莲'+'圆锥药须草'+'槛核莲'+'一见喜'+'斩舌剑'+'苦草'+'苦胆草'+'四方草'+'斩蛇剑'+'日行千里感'+'四方莲'+'金香草'+'金耳钩'+'春莲夏柳'+'印度草'+'万病仙草'+'四支邦'+'斩龙剑'+'春莲秋柳'+'清感双舒'+'复方双花'+'感咳双清'+'新雪丹'+'喉康散'+'感冒清')

主题= subject heading

Sino-Med Database: From inception to March 2016

1. (((((("呼吸道感染"[中文标题:智能]) OR "呼吸道感染"[摘要:智能]) OR "鼻炎"[中文标题:智能]) OR "鼻炎"[摘要:智能]) OR "鼻窦炎"[中文标题:智能]) OR "鼻窦炎"[摘要:智能]) OR "咽炎"[中文标题:智能]) OR "咽炎"[摘要:智能]

2. (((((("喉炎"[中文标题:智能]) OR "喉炎"[摘要:智能]) OR "鼻咽炎"[中文标题:智能]) OR "鼻咽炎"[摘要:智能]) OR "扁桃体炎"[中文标题:智能]) OR "扁桃体炎"[摘要:智能]) OR "支气管炎"[中文标题:智能]) OR "支气管炎"[摘要:智能]

3. (((((("气管炎"[中文标题:智能]) OR "气管炎"[摘要:智能]) OR "肺炎"[中文标题:智能]) OR "肺炎"[摘要:智能]) OR "咳嗽"[中文标题:智能]) OR "咳嗽"[摘要:智能]) OR "感冒"[中文标题:智能]) OR "感冒"[摘要:智能]

4. (((((("外感"[中文标题:智能]) OR "外感"[摘要:智能]) OR "流感"[中文标题:智能]) OR "流感"[摘要:智能]) OR "喉咙痛"[中文标题:智能]) OR "喉咙痛"[摘要:智能]) OR "咽痛"[中文标题:智能]) OR "咽痛"[摘要:智能]

5. (((((("咽喉痛"[中文标题:智能]) OR "咽喉痛"[摘要:智能]) OR "咽痒"[中文标题:智能]) OR "咽痒"[摘要:智能]) OR "鼻塞"[中文标题:智能]) OR "鼻塞"[摘要:智能]) OR "流涕"[中文标题:智能]) OR "流涕"[摘要:智能]

6. ((((((((((("咳"[中文标题:智能]) OR "咳"[摘要:智能]) OR "嗽"[中文标题:智能]) OR "嗽"[摘要:智能]) OR "喘"[中文标题:智能]) OR "喘"[摘要:智能]) OR "肺"[中文标题:智能]) OR "肺"[摘要:智能]) OR "鼻"[中文标题:智能]) OR "鼻"[摘要:智能]) OR "咽"[中文标题:智能]) OR "咽"[摘要:智能]) OR "喉"[中文标题:智能]) OR "喉"[摘要:智能]

7. 1+2+3+4+5+6

8. (((((((("穿心莲"[中文标题:智能]) OR "穿心莲"[摘要:智能]) OR "圆锥药须草"[中文标题:智能]) OR "圆锥药须草"[摘要:智能]) OR "槛核莲"[中文标题:智能]) OR "槛核莲"[摘要:智能]) OR "一见喜"[中文标题:智能]) OR "一见喜"[摘要:智能]) OR "斩舌剑"[中文标题:智能]) OR "斩舌剑"[摘要:智能]

9. (((((((("苦草"[中文标题:智能]) OR "苦草"[摘要:智能]) OR "苦胆草"[中文标题:智能]) OR "苦胆草"[摘要:智能]) OR "四方草"[中文标题:智能]) OR "四方草"[摘要:智能]) OR "斩蛇剑"[中文标题:智能]) OR "斩蛇剑"[摘要:智能]) OR "日行千里感"[中文标题:智能]) OR "日行千里感"[摘要:智能]

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智能]) OR "春莲秋柳"[中文标题:智能]) OR "春莲秋柳"[摘要:智能]) OR "清感双舒"[中文标题:智能]) OR "清感双舒"[摘要:智能]

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10. 8+9

11. 7*10

Appendix B: Prisma Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix C: Systematic review tables

C: 1- 5 Trial characteristics tables

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & co-intervention if available	Details of CG	Outcome measures	End point
Caceres et al., 1999 [76] Chile	Common cold	NR	NR; 25–50 as inclusion criteria	TG: 53.9%; CG: 45.2%	158/208	AP mono (tablet)	Placebo tablet, 4 tablets, tid, 5d	[ITT] Improvement in cough intensity and frequency (VAS, 10cm)	0–4
Melchior et al., 1997 [77] Sweden	Common cold	Within 3d	NR	NR	50/50	AP mono (tablet)	Placebo tablet, 400mg, tid, 5d	CCME (patient reported); Symptom relief (VAS)	5
Saxena et al., 2010 [78] India	Uncomplicated URTIs	Within 3d	TG: 34.36 ±0.97; CG: 32.42±1.1	TG: 67%; CG: 62%	220/223	AP mono (capsule)	Placebo capsules, 300mg, bid, 5d	[PP data] Severity of overall severity of 8 symptoms (VAS, 0–100); Severity of cough (VAS, 0–100); Severity of sore throat (VAS, 0–100)	5
Melchior et al., 2000 [79] Russia	Uncomplicated URTIs	Within 36h	Range: 18–55 (inclusion criteria)	NR	178/179	AP mixture (tablet)	Placebo tablet, 400mg, tid, 3d	Severity of symptom sum score	3
Melchior et al. 2000 Pilot [79] Sweden	Uncomplicated URTIs	Within 36h	TG: 39, range: 30–48; CG: 42.8, range: 32–52	TG: 35%; CG: 39%	45/46	AP mixture (tablet)	Placebo tablet, 400mg, tid, 3d	Severity of symptom sum score; Cough (frequency/dry/ productive); Sore throat improvement score	4–6

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A. Paniculata*, URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections, Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based)

https://doi.org/10.1371/journal.pone.0181780.t001

Table 1. Trial characteristics: *A. Paniculata* versus Placebo (n = 4).

C:2

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & co-intervention if available	Details of CG	Outcome measures	End point
Chang 2012 [50] China	AURTIs	1.5d, range: 0.5–3d	38.5 (15–65)	44%	64/64	AP mono (granule)	Ribavirin, iv, 10mg/kg in 250ml 5% Glucose solution, qd; penicillin, cefazolin; for 3–7d)	CCME	3–7
Li 2014 [51] China	Acute pharyngitis (Hou Bi)	NR	TG: 30.5 ±1.7; CG: 29.8±1.8	TG: 68%; CG: 60%	52/52	AP mono (pillule)	Cefixime capsule, 400mg, qd, 7d/ session, 2 sessions	CCME	20
						One off treatment: inhalation of small amount Glucocorticoids (dosage N/A), healthy diet, no alcohol or cigarettes			
Thamlikitkul et al 1991 [52] Thailand	Pharyngotonsillitis	NR; "recent fever" (inclusion criteria)	TG1: 29.3 ±8.1; TG2: 29.4±6.4; CG: 28.2 ±7.4	TG1: 51%; TG2: 48%; CG: 53%	142/152	AP mono (capsule); TG1: HAP; TG2: LAP	Paracetamol capsule, 325mg, qid, 7d	CCME (sore throat)	3
						Antibiotic, antihistamine or/and decongestant, antitussive			
Hou et al 2009 [53] China	AURTIs:	Within 3d (inclusion criteria)	*TG: 21.87 ±19.92; CG: 21.33 ±14.05 (m)	TG: 59%; CG: 61%	397/397	AP mixture (capsule)	Ribavirin; 6d	CCME	NR, probably 6
Lin and Yang 2011 [54] China	Herpes Anginosus	NR; participants all had sudden fever	*Range: 6m–7y	51%	98/98	AP mixture (capsule)	Ribavirin	**CCME	7
						Antipyretic or physically cooling down; antibiotics (If WBC > 10x10(9)/L-); IV fluid infusion (if participants couldn't eat)			
Liu et al 2012 [55] China	AURTIs	NR	TG: 41.56, range: 20–63; CG: 41.87, range: 20–65	TG: 48.33%; CG: 50.82%	121/121	AP mixture (capsule)	Ribavirin granule, 0.3g, tid, 7d	CMCRG-CCME; Time to resolution (cough and sore throat)	7
						Anti-infection, anti-cough, and antipyretic			
Tan and Gao 2010 [56] China	ARTIs (wind heat)	TG: 1.71 ±0.46; CG: 1.67±0.48	TG: 40.3 ±11.43; CG: 38.45 ±12.36	TG: 55%; CG: 56%	124/144	AP mixture (capsule)	Ribavirin, 0.3g, tid, 3d	[FAS data] CCME; Symptom improvement (cough and sore throat); Time to resolution (cough)	3, 7
						Drink plenty of water, saline gargle, bid; Phenol caplets, po, 2 tablets, tid; Fu Fang Gan Cao He Ji (if cough), po, 10ml, tid; Physical cooling down (if >38˚C); Benorilate, po, 1g (if >39˚C)			
Tan 2011 [57] China	URTIs—group B coxsackieviruses (wind heat)	TG range: 7–14d; CG range: 8–14d	TG median: 27; CG median: 28	TG: 47.83%; CG: 41.3%	92/92	AP mixture (capsule)	Ribavirin tablet; 0.3g, tid, 7d	CMCRG-CCME	7
						Drink plenty of water, rest; physically cooling down (if > 38˚C)			
Wang et al 2008 [58] China	ARTIs	NR	TG: 42.38 ±1.12; CG: 42.56 ±1.44	TG: 52.22%; CG: 49.44%	324/347	AP mixture (capsule)	Ribavirin granule	**CMCRG-CCME; Time to resolution (overall symptoms)	6
						Dry suspension of cefaclor (if bacterial infection)			
Kulichenko et al., 2003 [59] Russia	Diagnosed Influenza viral infection	NR	Range: 19–63	NR	66/66	AP mixture (tablet) + paracetamol (if >39˚C)	Amantadine "according to prescription", regimen not clearly stated but possibly same as in the pilot study listed below	Cough and sore throat (Patient's self-evaluation (scale 0–3); Sore throat (Patient's self-evaluation (scale 0–3); Time to resolution (cough and sore throat)	5
Pilot [59] Russia	Diagnosed Influenza viral infection	NR	Range: 19–63	NR	540/540	AP mixture (tablet) + paracetamol (if >39˚C)	Antiviral (Amandine with ascorbic acid as an adjuvant). 1st day: 2*0.05g tablet, tid; 2nd & 3rd day: 2*0.05g tablet, bid; 4th day: 2*0.05g tablet, qd. Paracetamol (if > 38˚C), 1*0.05 g tablets, tid, 2–3d	CCME (cough and sore throat); Days of sick leave; Time to resolution (cough and sore throat)	4–5
Li 2010 [60] China	ARTIs (Feng Wen Re Du)	TG: 7d; CG: 8d	*TG: 9 ±1.5; CG: 8±1.7	TG: 69%; CG: 70%	130/130	AP mixture (tablet)	Aciclovir tablets, po, 0.8g, 5 times a day; Vitamin C, po, 0.2g, tid	**CCME	NR; probably 7
						Ru Yi Huang Jin San (external use, Cu Tiao) and health advice (avoid sun and wind; no spicy or strong flavour food)			
Deng 1999 [61] China	Acute tonsillitis	2h-7d	*TG: 5–62; CG: 5–62	TG: 52.58%; CG: NR	162/162	AP mixture (liquid)	Erythromycin ethylsuccinate; 250–500mg, tid-qid (children: 30–50ml/kg, tid-qid), 7d	CCME; Time to resolution (overall symptoms)	7

*Trials on or involved children;

**Practitioner evaluated

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A. Paniculata*, HAP: high dose *A. Paniculata*, LAP: low dose *A. Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based). CMCRG-CCME: cure rate and markedly effective rate based on the Chinese medicine clinical research guidelines

https://doi.org/10.1371/journal.pone.0181780.t002

Table 2. Trial characteristics: A. Paniculata versus Usual care (n = 12).

C:3

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & co-intervention if available	Details of CG	Outcome measures	End point
Bao 2013 [62] China	Acute pharyngitis	NR	TG: 23.6±1.2; CG: 22.4±1.9	TG: 60%; CG: 57.5%	40/40	AP mono (pillule)+ usual care	Usual care: Corticosteroids combined with antibiotics (Gentamicin and dexamethasone), 1 ml for 15 mins/d, 5d; Cydiodine Buccal tablets, 1.5mg, tid, 5d	CMCRG-CCME	5
Sun and Zhao 2014 [63] China	Bronchiectasis (Fei Yong)	NR; "Acute exacerbation"	TG: median: 49.2, range: 21–80; CG: median: 50.1, range: 22–78	TG: 46%; CG: 51%	78/78	AP mono (capsule) + usual care	Usual care: Cefixime, po, 150mg, bid; Levofloxacin, po, 0.2g, bid; Dextromethorphan hydrobromide and guaifenesin syrup, po, 20ml, tid; all for 14d	Severity of cough (VAS, 0–10)	11
Guo 2013 [64] China	ARTIs (External wind heat)	Within 3d	*TG: 5.25 ±1.42; CG: 5.43±1.39	TG: 61%; CG: 58%	416/416	AP mixture (capsule) + Ribavirin	Ribavirin	**CCME	NR, probably 7
Li et al 2007 [65] China	Pneumonia	10.5 (range: 7–14)	*Range: 1m–5y	TG: 58.33%; CG: 60%	540/540	AP mixture (capsule) + usual care	Usual care: Antibiotics and antivirals; Aminophylline; Vitamin K; Sedation, diuretic, cardiac, oxygen (if heart failure); Dehydrating agent and brain cell activator (if toxic encephalopathy)	**CCME	NR, probably 7
Meng 2012 [66] China	Acute tracheitis and bronchitis	Within 5d (as inclusion criteria)	NR	NR	282/282	AP mixture (capsule) + usual care	Usual care: Drink more water, rest, gargle bid; If there were symptoms of URTIs such as nasal congestion, runny nose, or sneezing, Paracetamol Triprolidine Hydrochloride and Pseudoephedrine Hydrochloride tablets were given, po, 2 tablets, tid; If cough with no or little sputum, Pentoxyverine Citrate Tablets was given, 250mg, po, tid; If cough with sputum, Bisolvon Tablets was given, po, 160mg, tid; If fever, physical cooling; If there was clear evidence of bacterial infection, antibiotics such as macrolides, penicillins, cephalosporins, or quinolones were used	**CCME; Severity of cough	7
Tang et al 2009 [67] China	Bronchitis	Range: 1–2d	*7.5m, range: 3–12m	56%	260/260	AP mixture (capsule) + usual care	Usual care: Anti-infection, sedation, ultrasonic atomization, sputum suction, shoot back	**CCME; Time to resolution (cough)	7
Wu 2013 [68] China	Acute bronchitis	5.4 ±3.6, range: 1–13	9–73, 34.2 ± 11.2	53%	362/362	AP mixture (capsule) + usual care	Usual care: Paracetamol Triprolidine Hydrochloride and Pseudoephedrine Hydrochloride tablets, po, 2 tablets, tid; Pentoxyverine Citrate tablets, po, 250mg, tid; Bromhexine, po, 160mg, tid	**CCME	7
Shakhova et al 2003 [69] Russia	URTIs	Within 24h	*NR; children	NR	93/93	AP mixture (tablet) + usual care	Usual care: drink plenty of warm water; milk and vegetable diet with food containing vitamins; deep throat rinse with Alkaline and mouth washing; 1–2% solution of protargola (silver proteinate); paracetmal	Severity of symptom sum score	3–5 and 7–9
Spasov et al., 2004 [70] Russia	URTIs	Within 24h (inclusion criteria)	*TG: 7.17 ±0.32; CG1: 6.78±0.34; CG2: 6.47 ±0.29	TG: 49%; CG1: 49%; CG2: 56%	133/133	AP mixture (tablet) + usual care	CG1: Immual (Echinacea purperea) drop + usual care; CG2: Usual care (lavish warm drinks, throat gargles, antiseptic nose drops, and paracetamol, 500mg, tid (if fever or severe headache)	Severity of symptom sum score (patient and practitioner evaluated), reduce in medications	5

*Trials on or involved children;

**Practitioner evaluated

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A. Paniculata*, HAP: high dose *A. Paniculata*, LAP: low dose *A. Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based). CMCRG-CCME: cure rate and markedly effective rate based on the Chinese medicine clinical research guidelines

https://doi.org/10.1371/journal.pone.0181780.t003

Table 3. Trial characteristics: *A. Paniculata* plus usual care versus Usual care (n = 9).

C:4

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & co-intervention if available)	Details of CG	Outcome measures	End point
Ding et al 2010 [71] China	Acute bronchitis (wind heat)	TG: 2.76 ±1.03d; CG: 2.80±1.18d	TG: 37.68 ±13.25; CG: 34.96 ±13.32	TG: 53%; CG: 38%	136/137	AP mixture (capsule) + CG placebo	Qing Gan Chuan Xin Lian tablet (Chuan Xin Lian + Mai Ma Teng), 0.25g, tid + TG placebo	**CMCRG-CCME	0, 2, 3, 4, 8
	ARTIs (wind heat)	TG: 18.91 ±9.85h; CG: 18.63±12.24h	TG: 35.97 ±13.12; CG: 33.27 ±12.57	TG: 43%; CG: 40%	138/140	Same as above			
Xi 2006 [72] China	Cold (Shu Shi)	Within 3d (inclusion criteria)	TG: 36 ±2.26; CG: 35±2.12	TG: 56%; CG1: 56%; CG2: 50%	250/250	AP mixture (tablet)	CG1: Huo Xiang Zheng Qi pill, 6–8 pills, tid, 3d; CG2: Su Xiao Shang Feng capsule, 2 capsules, tid, 3d	CMCRG-CCME	3
Yang and Liu 2012 [73] China	URTIs (wind heat)	Within 48h (within 24h: n = 160)	TG: 35.47; CG: 34.56 (SD NR)	TG: 43%; CG: NR	233/239	AP mixture (tablet)	Fu Fang Yu Xing Cao tablet; 4 tablets, tid, 3d	CMCRG-CCME	3
Zhang et al 1994 [74] China	Acute tonsillitis (criteria given)	Within 3d	*TG: <10: n = 47, >10: n = 54; CG: <10: n = 21; >10: n = 32	TG: 60%, CG: 53%	154/154	AP mixture (liquid)	Yin Huang liquid: Jin Yin Hua extract 12g + Huang Qin extract 24g, 10ml, tid, 7 days (children half dose)	CCME	7
Zhao et al., 2012 [75] China	Common cold (wind heat)	Within 48h (inclusion criteria)	TG: 30.7; CG: 31.1 (SD NR)	TG: 50%; CG: 50%	300/300	AP mixture (granule)	Gan Mao Ling granule; one pack, tid, 5d	CMCRG-CCME; Severity of symptom score (cough and sore throat)	5

*Trials on or involved children;

**Practitioner evaluated

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A. Paniculata*, HAP: high dose *A. Paniculata*, LAP: low dose *A. Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based). CMCRG-CCME: cure rate and markedly effective rate based on the Chinese medicine clinical research guidelines

https://doi.org/10.1371/journal.pone.0181780.t004

Table 4. Trial characteristics: *A. Paniculata* versus Herbal active intervention (n = 5).

C: 5

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & co-intervention if available	Details of CG	Outcome measures	End point
Chang et al 2008 (phase 1) [80] China	ARTIs (External wind heat)	TG: 22.44 ±12.22h; CG: 20.7±8.46h	TG: 36.31 ±11.63; CG: 37.55±12.69	TG: 57%; CG: 62%	200/202	AP mono (pillule)	Chuan Xin Lian tablet, 0.15g; tid; 3d	[FAS data] CMCRG-CCME	0, 2, 4
(phase 2) [80] China	ARTIs	NR	TG: 37.18 ±13.64; CG: 36.09±14.43	TG: 48.55%; CG: 46.32%	271/274/276	AP mono (pillule)	Chuan Xin Lian tablet, 0.15g; tid; 3d	[FAS data] CMCRG-CCME	0, 2, 4
Su 2014 [81] China	Acute pharyngitis	NR	26.5 (range: 20–40)	53%	60/60	AP mono (pillule)	Chuan Xin Lian tablet; 1g, tid, 5d	CMCRG-CCME	5
						Inhalation of Gentamicin 80,000 ∪, dexamethasone 5mg; 15 mins, bid, 5d			
Xia 2014 [82] China	Acute pharyngitis	NR	TG: 35.6, range: 16–68; CG: 36.4, range: 17–63	TG: 55%, CG: 52%	125/125	AP mono (pillule)	Chuan Xin Lian tablet, 0.3g, tid, 3–7d	CMCRG-CCME	3–7

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A. Paniculata*, HAP: high dose *A. Paniculata*, LAP: low dose *A. Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based)

https://doi.org/10.1371/journal.pone.0181780.t005

Table 5. Trial characteristics: *A. Paniculata* (pillule) versus *A. Paniculata* (tablet) (n = 3).

Appendix D: Qualitative study documentation

D 1: Herbal medicines for acute respiratory tract infections (RTIs): A semi-structured qualitative interview study: added questions (in italics)

Interview guide

10. What are your thoughts about herbal medicines? Do you have any personal experiences with herbal medicines?
    - Personal
    - Family used
    - Patients

11. How do you feel about using herbal medicines for respiratory tract infections?
    - *Have you ever recommended any herbal medicines in your practice?*
    - *How do you think that the herbal treatment differs from conventional medication?*

12. How would you feel about advising patients to use herbal remedies for respiratory tract infections?
    - Prescribing
    - *What level of evidence would you require to take herbal medicine yourself?*
    - *What level of evidence would you require to recommend herbal medicines to your patients?*

- *What sort of evidence would you require to be involved in a trial using herbal medicines in respiratory tract infections?*

13. How is it different to administering conventional drugs?

14. Did you have any concerns about herbal medicines?
    - About safety?
    - About efficacy?
    - About compliance?
    - *How would you like to be informed about herbal medicine – about research on herbal medicine?*
    - *What are your thoughts around herbal training within medicine?*
    - *You mentioned you are sceptical about herbal medicines; can you tell me more about that?*

15. How do you think the herbal treatment differs from conventional care
    - *Tell me do you think there's any issues with the name herbal medicine?*
    - *Can you tell me more about the placebo effect with herbal medicines?*

16. How do you think patients feel about taking herbal medicines?
    - In general
    - For respiratory tract infections
    - *Tell me do many of your patients take herbal medicines?*

17. How long have you been in practice?
    - Less then 10 years
    - More than 10 years
    - More than 20 years

18. Is there anything else you would like to tell me?

D 2: Participant information sheet

Participant Information Sheet

A qualitative study exploring the attitudes and beliefs of health professionals around the use of herbal medicines in the treatment of symptoms of acute respiratory tract infections

Principal Investigator:

Associate Investigator: **Ethical approval number: 24550**

This is an invitation to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve.

Who is running this study?

We are a group of researchers based at the Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, undertaking research in complementary and integrative medicine.

Why have I been approached?

You have been chosen because we are interested to explore views of health practitioners regarding the use of herbal medicines to treat respiratory tract infections.

Do I have to take part?

Participation in the project is entirely voluntary. If you decide to take part, you will be asked to sign a consent form that is enclosed with this letter. If you decide to take part you are still free to withdraw from the study at any time during the study, without giving a reason.

Why is this study being done?

Acute respiratory tract infections (RTIs) are the most common acute problem dealt with in general practice. Around 50-70% of patients consulting with RTIs receive antibiotics and reducing the use of antibiotics is one of the key factors of the Department of Health antimicrobial resistance strategy. This study is being carried out to explore health professionals' views of using herbal medicines as an alternative treatment for acute respiratory symptoms as well as the enablers and barriers to recommending these. This will inform a feasibility study of using *Andrographis paniculata* capsules for acute RTIs.

What should I expect if I take part in this study?

If you are interested in participating please post to, email or phone Martin Logue directly using details provided below If you are suitable for the study you will be asked to sign the consent form.

What are the possible disadvantages of participating?

Questions in the telephone interview will not cover sensitive topics. You may refuse to answer any question during the discussion and you may withdraw from the study at any time. The interviews will take place at a time convenient to you.

What are the possible benefits of participating?

You will be offered a payment of £20.00 (voucher) to recompense for your time following completion of the interviews. We will post the voucher to an address of your choice. At the end of the study, you will be provided with a copy of the findings. The information we get from this will inform the design of a subsequent feasibility study to evaluate the clinical effects and safety of using andrographis as a treatment for RTIs.

Will my participation be confidential?

All information that you provide will be strictly confidential, held by the University of Southampton in accordance with the Data Protection Act 1998. You will be identified by an ID number and the information you provide will be stored on a password-protected computer. All audio records will be destroyed as soon as they are transcribed. You will not be identifiable from any information you provide that is disseminated and will remain anonymous from other participants throughout this research study.

What will happen to the results of the research study?

The anonymised results of the research will be presented at medical conferences and through scientific publications in medical journals, and used for teaching and research purposes and in the media. When the study is completed, we will provide copies of the published results directly to you.

Who is organising and funding the research?

The research is funded by the National Institute for Health Research, a Department of Health organisation that funds research relevant to the NHS. It is being organised by a study team within the University of Southampton, Faculty of Medicine, department of Primary Care and Population Sciences.

Who has approved this study?

This study has received ethical approval from the Faculty of Medicine Ethics Committee at the University of Southampton [**24550**]. The ethics committee ensures that the study is conducted according to internationally recognised ethical principles as described in the Declaration of Helsinki.

Thank you for reading this information and for considering participation in this study.

Reply slip

A qualitative study exploring the attitudes and beliefs of health professionals around the use of herbal medicines in the treatment of symptoms of acute respiratory tract infections

Name:	
My preferred telephone number to call for interview is: Additional telephone number:	
My email address is:	
The best day(s) and time(s) to contact me is: Please indicate if you would prefer email or telephone contact.	
I am **willing** to take part in a telephone interview. Please tick	
I am **unwilling/unable** to take part in this study	If you wish, you can provide us with a reason for why you are unable or do not wish to take part – this can help us in the design of future studies: Reason for not taking part……

ONCE COMPLETED PLEASE SEND THIS FORM BACK IN THE FREEPOST ENVELOPE TO:

D 3 :Consent form

Consent Form

Title of Project: A qualitative study exploring the attitudes and beliefs of health professionals around the use of herbal medicines in the treatment of symptoms of acute respiratory tract infections

Principal Investigator: **Ethical approval number:** 24550

Please write your **initials** on the lines beside each statement:

Your initial	Statement
_____	I confirm that I have read and understand the participant information sheet (version xx, dated xx). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
_____	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons.

_____ I agree to take part in the telephone interview and, I agree that my interview will be audio taped and transcribed. I understand that the audio recording will be destroyed following verification of transcriptions.

_____ I understand that interview data will be stored anonymously; direct quotations may be used but will be anonymised.

_____ I agree to take part in the above study.

Please keep one copy for your own records and, return one completed consent form to Martin Logue:

Appendix E: Feasibility study documentation

E 1: PIS sheet

Participant Information Sheet

Study Title: *A double blind, randomised, placebo controlled, feasibility trial evaluating the possibility of delivering Andrographis paniculata (Immunographis) as a treatment of adults with Acute Respiratory Tract Infections (ARTIs)*

Researcher: **Ethics number**: 208314 **ERGO number:** 27851

You are being invited to take part in the above research study. To help you decide whether you would like to take part or not, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully and ask questions if anything is not clear or you would like more information before you decide to take part in this research. You may like to discuss it with others but it is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

This trial will investigate the use of a herbal medicine (*Andrographis paniculata*) in the treatment of sore throats, coughs and colds (acute respiratory tract infections (ARTIs)). Herbal medicine is not currently available on the NHS. Our research will explore whether Andrographis paniculata can help to treat sore throats, coughs and colds; if it can improve quality of life and if there are any side effects. We will also investigate how people with sore throats, coughs and colds feel about taking herbal medicine and whether it is a treatment that could be prescribed by GP's in the future.

The trial is sponsored by the University of Southampton. It is a PhD student project and it is being funded by Pukka Herbs, (Bristol).

Why have I been asked to participate?

You have been invited to take part because you are aged 18 or over and you have visited your GP surgery with a sore throat, cough or cold. We aim to recruit 60 participants into this trial.

Do I have to take part?

No, it is entirely up to you if you would like to take part in this research. The study team will discuss the treatment options available to you. If you chose not to take part, then it will not affect the treatment you currently receive from your GP.

What will happen to me if I take part?

A GP/Nurse prescriber will check that you are eligible to take part in this trial. If you take part in the trial you will be asked to read and sign a consent form confirming that you understand what the trial involves and that you are willing to take part. All participants in the trial will be asked to take either a placebo herbal remedy or a herbal remedy called Andrographis paniculata. The placebo looks and tastes very similar to the remedy being tested (Andrographis paniculata) but it does not have an active ingredient. We will recruit 30 people into the placebo remedy group and 30 people into the Andrographis paniculata remedy group. You will be randomly allocated into one of these two groups. This means that you will not be able to choose which remedy you take and you will not know which remedy you have been given. Your GP or nurse will not know which remedy you have been given either.

Random allocation helps ensure we are comparing two very similar groups of patients, so if one group does better than the other, it is very likely to be because the treatments being compared have different effects, and not because of differences between the people in the groups.

The herbal remedy consists of 250mg cellulose capsules in sealed, plastic containers. You will be asked to take 3 capsules 4 times a day over 7 days. The capsules should be taken half an hour before food and on an empty stomach with warm water. During the trial, if you are concerned about your symptoms, you are free to return to your GP and, if necessary, use conventional medicines such as antibiotics for any acute infections.

The GP or nurse will also give you a trial diary to take home with you. We would like you to complete the diary each day for 14 days or until your symptoms resolve. The diary asks questions

about your symptoms and should only take 5-10 minutes each day to complete. After 1-2 days we will telephone you to check if you have any problems with completing the diary. You will be given a pre-paid envelope to return the diary once you have completed it. If we have not received your diary or if there is key information missing, we will telephone you again to collect this information.

Are there any benefits in my taking part?

You may find the treatment reduces the severity of your symptoms. However these benefits have not been proven and the aim of this research is to explore whether Andrographis paniculata can help. If the results suggest that Andrographis paniculata may be a useful treatment then it will support the need for a larger future trial that should be able to investigate this further. You will be offered a £10 voucher to say thank you for taking part in the trial and for completion of the trial symptom diaries.

Are there any risks involved?

Andrographis paniculata can cause nausea (feeling like you might be sick) and/or diarrhoea for 2 or 3 days in some people. If you experience these symptoms half the dose of the capsules (take 2 capsules three times daily) and take after meals.

It is also possible that there could be side effects from taking Andrographis paniculata which we are not already aware of. If your symptoms are getting worse or if you think you are experiencing side effects you can return to your GP for further advice.

If you have any concerns about the herbal remedy you can telephone the Chief Investigator

We do not know if it is safe for herbal remedies to be taken during pregnancy and therefore we ask all participants to take contraception whilst on the trial. If you are already pregnant you will not be able to participate in the trial.

What data will be collected?

If you decide to participate in this trial the research team will collect certain personal information from you, this information will be kept confidential and will only be used for the purpose of this research trial.

Firstly, the GP or nurse will ask you to complete a consent form, which will include your name address and contact telephone number. The GP or nurse will also complete a trial report form which asks information about your general health and your cold, cough or sore throat symptoms. This trial form will not have your name on it. Instead, it will have a participant code which is unique to you and which you will be given when you join the trial. Finally the GP or nurse will give you a diary to take home. The diary asks questions about your symptoms and how you are feeling each day until you are feeling better.

Will my participation be kept confidential?

Your participation and the information we collect about you during the course of the research will be kept strictly confidential. For further information please read Data Protection Section on page 5.

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form to show you have agreed to take part.

What happens if I change my mind?

You have the right to change your mind and withdraw at any time without giving a reason and without your participant rights *(or routine care if a patient)* being affected. If you wish to withdraw from the study please contact the study team by

We may ask you the reasons why you have decided to withdraw from the trial, and if we can use your data in the trial analysis. This information will help us with designing future trials.

What will happen to the results of the research?

Your personal details will remain strictly confidential. Research findings made available in any reports or publications will not include information that can directly identify you without your specific consent. The results will be written up and included in Martin Logue's PhD thesis. We would also aim to have results of the study published in a reputable journal. You will not receive a copy of the results unless you specifically request them. We will provide your GP surgery with a synopsis of the study results.

Where can I get more information?

If you have any questions or concerns and you would like to speak to a member of the research team you can contact the Chief Investigator

What happens if there is a problem?

If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions.

To contact the research team:

Alternatively, if you wish to make a complaint through the NHS complaints procedure you can contact the Patient Advice and Liason Service (PALS). The contact details for your nearest PALS office are:

XXXXXXXXXXX Insert local PALS office for each participating GP site.

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly funded organisation, the University has to ensure that it is in the public interest when we use personally identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

The GP surgery will store a copy of both your consent form and your trial report form. These forms will be kept in separate folders so that the information on your trial report form can not be linked to your name. The folders will be stored in a lockable storage unit at the GP surgery and access will be limited to authorised personnel who are involved in the trial.

The GP surgery will also post a copy of your consent form and your trial report form to the study team based at the University of Southampton. The forms will be posted in separate envelopes. Once you have completed your trial symptom diary you will also be asked to post this to the study team at the University of Southampton. Once received at the University of Southampton the information from the consent form, the trial report form and the diary will be transferred by an authorised member of the trial research team to a database which will be encrypted and password protected and held on the secure University server. The paper copy of the forms will be held in separate files in a locked cabinet at the University of Southampton with access limited to authorised study personnel only. Information will be coded and real names will be deleted to preserve confidentiality. Any emails sent by research participants will have their content coded and preserved within a password protected Word document. A paper copy of the email will be printed out and filed in a locked cupboard accessible only to authorized personnel. Contact details and original emails will be deleted.

Once we have finished analysing all the data we will keep all study information for a further 10 years. The information will be archived at a secure location approved by the University of Southampton with limited access to authorised personnel only. At the end of the 10 years the information will be destroyed. The GP surgery will also keep a copy of your consent form and trial report form in a secure approved archiving location with limited access to authorised personnel for 10 years at which point the information will be destroyed.

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed.

For studies involving other recruitment sites the following information must be included:

[NHS/ other site] will keep identifiable information about you from this study [for 10 years after the study has finished/ until 2028]

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such

information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer.

Thank you

We would like to say thank you for taking the time to read the information sheet and considering taking part in our research trial.

E 4: Consent form

Centre ID:

Study Number:

Participant Trial ID:

Ethics Number:

GRAPHALO

A double blind, randomised, placebo controlled, feasibility trial evaluating the possibility of delivering Andrographis paniculata (Immunographis) as a treatment of adults with Acute Respiratory Tract Infections (ARTIs)

CONSENT FORM

Name of Researcher:

If you agree please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Southampton, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me may be used to support other research in the future organised by The University of Southampton, and may be shared anonymously with other researchers. ☐

5. I agree to my contact details being shared with the study team so they can contact me regarding completion of the study diary. ☐

6. I am happy for my GP/Healthcare professional to be informed about my involvement in this study.

7. I agree to take part in the above study. ☐

OPTIONAL

8. I agree that if I decide to withdraw from the study my data can be collected and used in the trial analysis ☐

Data Protection

I understand that information collected about me during my participation in this study will be stored on a password-protected computer. All files containing any personal data will be made anonymous.

_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____

Name of Participant Date Signature

Address:

Contact Number:

E 5: GRAPHALO poster

Herbal Medicines for Acute Respiratory Tract Infections

- Antibiotic resistance is increasing.
- Treatment of acute respiratory tract infections (ARTIs) do not always require antibiotics
- Symptoms such as cough and sore throat are unpleasant and alternative ways are needed to treat these issues.

This practice is currently involved in a trial looking to see if the herbal medicine "Andrographis" can provide relief for symptoms of ARTIs.

We want to know if this herbal medicine can reduce symptoms and reduce the need for antibiotic use.

If you would like more information about joining this trial, please speak to your GP/Nurse Practitioner/ Health Practitioner.

For more information on the study please contact

E 6: GP Letter

The GRAPHALO trial

Date

Dear Dr.

I am conducting a feasibility study exploring the role of a herbal medicine *(Andrographis paniculta*) in the treatment of acute respiratory tract infections (ARTIS) and the feasibility of administering this approach within primary care.

The trial will involve 60 adults randomised into active and placebo groups. Participants will be assessed by an experienced health professional and will be asked to take either an active or placebo herbal capsule over a 1-week period. Assessments will involve a patient diary reporting the duration, severity and incidence of ARTI symptoms.

Please find enclosed a Participant Information Sheet, which explains how the GRAPAHLO trial will operate.

If you would like any more information, then don't hesitate to contact me.

Yours sincerely

Martin Logue
(Chief Investigator of the GRAPHALO trial)

E 7: GRAPHALO unblinding risk assessment

Category	**Hazard**	**Vulnerability/concern** • *For each vulnerability/concern providing details of how it will be identified*	**Assessment of the risk/hazard** *(refer to CTU/FLOW/5015)*				**Mitigation strategies / Action to minimise the risk/hazard** • *Address each vulnerability/concern identified* • *Describe how actions will be reviewed if it is not covered under column 'monitoring requirements' and documented in the Trial Monitoring Plan(TMP)*
			Likelihood *H/M/L*	*Impact* *H/M/L*	*Detection* *H/M/L*	*Risk category* *H/M/L*	
9 to 5 unblinding service to be provided - not 24 hour unblinding service.	Inability to unblind treatment group for participants presenting with adverse events/effects between 5pm and 9am, Monday to Friday or during weekends and bank holidays.	Side effect of trial medication	L	H	H	L	Undesirable effects of the capsule study medication are possible, it is extremely unlikely that minor side effects will generate a call out of working hours. In very rare cases where a serious hypersensitivity

							reaction or Hepatoxicity occurs these would be treated accordingly and no immediate unblinding would be required. All participants will carry a Trial Information Card which will detail the dosing regimen for each group so that treating clinicians will be aware of the maximum/minimum treatment the patient may be receiving
9 to 5 unblinding service to be provided - not 24 hour unblinding service.	Inability to unblind treatment group for participants presenting with adverse events/effects between 5pm and 9am, Monday to Friday or during weekends and bank holidays.	Patient exceeds the stated dose of capsule	L	H	M	M	There is no data on cases of overdose and the effects are unknown. The SPC states overdose is likely to increase side effects, thus treatment should be symptomatic and as clinically indicated. All participants will carry a Trial Information Card which will detail the dosing regimen for each group so that treating clinicians will be aware of the maximum/minimum treatment the patient may

							be receiving. Patients will be directed at point of dispensing on dosage.
9 to 5 unblinding service to be provided - not 24 hour unblinding service.	Inability to unblind treatment group for participants presenting with adverse events/effects between 5pm and 9am, Monday to Friday or during weekends and bank holidays.	Unexpected deterioration and progression of infection - e.g. lower respiratory infections or pneumonia	L	H	H	L	In the event of an unexpected deterioration and progression of the infection, treatment could be commenced immediately and unblinding would not be necessary at the point of care. The Patient Information Sheet instructs the patient on what action to take should their symptoms worsen. The patient carries a trial treatment card with emergency contact numbers.
9 to 5 unblinding service to be provided - not 24 hour unblinding service.	Inability to unblind treatment group for participants presenting with adverse events/effects between 5pm and 9am, Monday to Friday or during weekends and bank holidays.	SmPC provides data stating that a Child under the age of 12 should not consume the tablet formulation or under the age of 6 consume the liquid formulation. Risk is that children under these ages consume the medication.	L	H	M	M	The Trial Medications will be labelled to advise the Patient to keep the product out of the reach of children. There is no data on cases of overdose and the effects are unknown for these ages (<12 tablet, <6 liquid). The SPC states overdose is likely to increase side effects, thus

							treatment should be symptomatic and as clinically indicated. Inclusion criteria is over 18 yrs.
9 to 5 unblinding service to be provided - not 24 hour unblinding service.	Inability to unblind treatment group for participants presenting with adverse events/effects between 5pm and 9am, Monday to Friday or during weekends and bank holidays.	Risk when ALDERMOOR CENTRE is not staffed during hours 9-5	M	H	H	M	Out of hours answerphone has message saying the hours of Centre opening. GPs aware when planned unmanned periods will be. Unblinding will not materially alter treatment of participant therefore this poses no extra risk.

Overall assessment

Identified risks although potentially serious are of low probability and high detection level. Risks cannot be mitigated or better managed by provision of a 24 hour unblinding service.

All participants will carry a Trial Information Card, which will detail the dosing regimen for each group so that treating clinicians will be aware of the maximum/minimum treatment the patient may be receiving.

Therefore it is deemed appropriate by the CI and Aldermoor to manage this trial with 9-5 unblinding service.

E 8: REC approval letter

Study title:	A double blind, randomised, placebo controlled, feasibility trial evaluating the possibility of delivering Andrographis paniculata (Immunographis) as a treatment of adults with Acute Respiratory Tract Infections (ARTIs)
IRAS project ID:	208314
REC reference:	18/SC/0447
Sponsor	University of Southampton

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the

basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales? You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here

Please do not hesitate to contact me for assistance with this application. My

contact details are below. Your IRAS project ID is **208314**. Please quote this

on all correspondence.

Yours sincerely

GRAPHALO

A double blind randomised placebo controlled feasibility study of *Andrographis paniculata* (Immunographis) in the treatment of adults with acute respiratory tract infections (ARTIs).

ELIGIBILITY ASSESSMENT, RANDOMISATION & BASELINE CASE REPORT FORM

CRF	0	1

Participant Trial ID							

Complete Participant Trial ID after patient has been randomised

Participant Initials			

(If no middle initial insert '-')

Participant Month and Year of	M	M	Y	Y	Y	Y

Date of Visit	D	D	M	M	Y	Y	Y	Y

Section A: Centre

GP Practice	
Name of GP	

Section B: Eligibility

Inclusion Criteria			
*If the answer to any of the following is **NO** then the patient is **NOT** eligible for the Trial*		**Yes**	**No**
1.	Is the patient over 18		
2.	Is the patient able to provide written informed consent?		
3.	Has the patient presented with an acute cough ((≤ 7 days' duration) or sore throat as their main symptom?		
4.	Does the patient have symptoms localising to the upper respiratory tract including runny nose, fever, muscle ache and facial pain		

Exclusion Criteria			
*If the answer to any of the following is **YES** then the patient is **NOT** eligible for the Trial*		Yes	No
1.	Is the patient pregnant or breast-feeding?		
2.	Is the patient currently/recently involved in a respiratory trial?		
3.	Is the patient known to have an immunodeficiency or to be on long-term corticosteroid therapy or receiving chemotherapy?		
4.	Does the patient have suspected pneumonia or a serious chronic disease where antibiotics are needed?		
5.	Does the patient have any of the following known contra-indications or cautions to Andrographis and any as listed in the current SmPC ?		
	A. Known hepatic or renal disease		
	B. Allergic to Andrographis or capsule material (cellulose)		
6.	Does the patient have psychosis, dementia or terminal illness that may prevent completion of symptom diaries?		

7.	Has the patient commenced a new treatment (conventional or CAM) for ARTIs in the previous 2 weeks? This includes: • OTC medications (paracetamol and Ibuprofen are allowed) • Supplements such vitamin C or Zinc Prophylactic antibiotics either taken continuously or after intercourse Commonly used herbs for acute respiratory tract infections including: Goldenseal(*Hydrastiscanadensis*) Marshmallow root (*Althea officinalis*) Echinacea (Echinacea spp) Elderberry(Sambucusnigra) Horsetail (*Equisetum arvense)* Probiotics such as acidophillous, bifidus Other _____		

Is the patient eligible for the trial?	Yes		No	

If NO, the patient is not eligible, please cross through the remaining sections and sign on page 6. Please give the patient the invitation letter and PIS *Please enter patient details onto screening log.*

If YES, please complete the sections C to I.

Section C: Consent

Please consent the participant.

	Date Informed Consent signed	DD	MM	YYYY

Section D: Randomisation

Randomise your patient by selecting the next available sequentially numbered Patient Pack.

Participant Trial ID Number (*enter your site ID in the first two boxes followed by the five digit Patient Pack number*)							

Please now enter this number on the consent form, the Notification of Registration Form and on any documentation given to the participant.

Section E: Baseline Procedures

1. Please confirm that a physical examination has been performed (including vital signs **Yes** ☐

Blood pressure: Temperature: Heart rate:

2. Have patient contact details been collected? **Yes** ☐ **No** ☐

If no, please record the reason here. ☐

Section F: Relevant Medical History

1. Does the patient suffer from asthma? Yes/ No

2. Does the patient suffer from diabetes? Yes/ No

3. Does the patient suffer from respiratory problems, such as COPD/Chronic Lung Disease? Yes/ No

4. Does the patient suffer from cardiovascular disease? Yes/ No

5. Does the patient suffer from hypertension? Yes/ No

Section G: Current Symptoms

1. Please rate the patient's current symptoms using the scoring system below:

0 = Normal/not affected

1 = Very little problem

2 = Slight problem

3 = Moderately bad

4 = Bad

5 = Very bad

6 = As bad as it could be

Please enter a number for each symptom/problem

SYMPTOM/PROBLEM	SCORE
Cough	
Sore throat	
Difficulty swallowing	
Phlegm	
Blocked or runny nose	

Muscle aches	
Headaches	
Disturbed sleep	
Fever	
General feeling of being unwell	
Interference with normal activities	

2. How long has the patient had ARTI symptoms?

☐

Section H: Treatment

1. Please record any **antibiotics** that the patient is currently taking.

Name	**Dose/unit**	**Times/day**	**Duration (days)**

2. Please record any **other medication** that the patient is currently taking.

Name	**Dose/unit**	**Times/day**	**Duration (days)**

Section I: Checklist

Please confirm that the patient has been provided with the following:		Please tick box
1.	Pack of study medication	
2.	Diary	
3.	Emergency contact card	
4.	Patient information sheet	
5.	Copy of consent form	
6.		Or enter N/A
7.		Or enter N/A

Signed		**Date of completion**	DD/MM/YYYY
Print name			

Authorised person - only those entered on Delegation Log

.

1	Patient Declined *(please state reason)*	**2**	Pregnant, risk of becoming pregnant, breast feeding
3	Unable to complete trial documentation including consent	**4**	Already taking Andrographis
5	Already taking another herbal medicine	**6**	Known immunodeficiency or undertaking chemotherapy
7	Allergic to Andrographis or capsules	**8**	Severe hepatic or renal disease
9	Suspected pneumonia	**10**	Other (explain)

E 10 : Screening log

PARTICIPANT SCREENING LOG

Strictly Confidential

REC reference: 18/SC/0447 Trial Site ID and Name:

IRAS number: 208314 Principal Investigator Name:

Date	Patient	DOB	Enrolled?		Participant Trial ID	Screened by
			Y/N	If No: State reason for exclusion		

E 11: GRAPHALO Notification of Registration Form

Trial acronym: GRAPHALO Principle Investigator:

Trial Site:

Patient Pack Number:							

Site ID:							

****Patient ID:**							

Patient initials			

Patient Month and Year of birth	M	M	Y	Y	Y	Y	Y

Date of Visit	D	D	M	M	M	Y	Y	Y	Y

PLEASE FILE completed Form in Section (XXXXX) of your Investigator Site File

** Patient ID = Site ID followed by Patient Pack Number

E 12: Drug accountabillity logs

GRAPHALO Herbal Product Accountability Log

Short Title	GRAPHALO
REC number:	18/SC/0447
Sponsor	University of Southampton
Name of GP Practice	
Site ID	

Received by Site			**Issued to Participants**				**Returned**		
Date Received	Patient Pack Number	Received by (initials)	Date of issue	Participant Trial ID Number	Participant Initials	Issued by (initials)	Date Returned	Returned to	Returned by (initials)

Once completed please fax or email a scanned copy to the Study team on XXXXXXX or to……. Please file the original completed form in the Investigator Site File section 10.5.

E 13: PARTICIPANT DIARY

Date of Registration	D	D	M	M	Y	Y	Y	Y
Participant Trial ID								
Participant Initials								

Participant

Diary

Thank you for agreeing to take part in this trial. Please start to complete this diary today,on the day you saw your GP or nurse.Further instructions on how to complete the diary are given overleafand at the beginning of each section.

Once you have completed this diary, please return to the address below using the pre-paid addressed envelope provided.

The diary is divided into three sections:

Section 1: About you

This section contains questions about you; your health; your expectations when you visited your GP or nurse and your quality of life. ***Please complete this section on the day you saw your GP or nurse.***

Section 2: Diary of your respiratory* symptoms/problems/treatments

This section is for you to record your symptoms and any treatments you have taken for your symptoms on a daily basis for 14 days. ***Please start completing this section on the day you saw your GP or nurse. This is Day 1.*** Once your symptoms have gone you can stop filling in section 2 and proceed to section 3.

This Section also includes Quality of Life questionnaires, which we would like you to complete on days 1, 7 and 14.

Section 3: After your symptoms have gone

This section contains questions about any visits you may have made to a hospital(s), in the 14 days after you joined the trial, for a respiratory infection. ***Please complete this section on the day you stop completing Section 2.***

**Respiratory symptoms include cough, sore throat, blocked or runny nose.*

SECTION 1

Please complete this section on the day you saw your doctor.

ABOUT YOU

1. Please enter your month and year of birth

M	M	Y	Y	Y	Y

2. **<u>Occupation And Employment</u>**

a) Which of the following best describes you? (*please tick one box only*)		
Employed (full or part time, including self-employed)		Unemployed
Unable to work due to long-term illness/disability		In full time education
Retired from paid work		Not working for other reasons
b) Please describe your current or most recent paid employment. If you have more than one job, tell us about your main job. If you have never been in paid work; please go to the next question.		

3. Ethnicity

Please describe your ethnic group *(please tick one box only)*

White	☐	Asian or Asian British	☐
Black or Black British	☐	Chinese or other Ethnic Group	☐
Mixed	☐	Prefer not to answer	☐

4. Your respiratory symptoms

How many days were you unwell before you saw your GP or nurse for this illness? ☐

1.1.1.1

a) **Did you treat this illness with any over the counter* medications before going to your GP?** ☐ **Yes** **No** ☐

If yes, please give details of what you took in the table below

Name of Over the Counter Medicine	Number of days you took the medicine

**Over the counter medication refers to any medicine which you bought at the chemist or the supermarket which you did not need a prescription for*

5. Reasons for visiting your GP or nurse

What was the *main* reason for your GP or nurse visit today? *(please tick one box only)*			
You are worried about a more serious condition		To get other treatment for this illness	
A friend or family member made you go		To get a sick note/certificate	
To get antibiotic treatment for this illness		Other	
If other please specify			

6. Antibiotic Treatment

Do you agree or disagree with the following statements?	Agree	Disagree	Neither
When I came to see the doctor/nurse I was expecting antibiotic treatment			
I would prefer to consider alternatives to antibiotics to treat my symptoms.			
If my illness did not need an antibiotic I would be happy to accept no treatment			

Quality of Life: ***Please complete on the day you saw your GP or Nurse (Day 1)***

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

SECTION 2:

DIARY OF RESPIRATORY SYMPTOMS/PROBLEMS/TREATMENTS

- Please fill in the diary on the next few pages to record your symptoms and any treatments you have used for your respiratory symptoms.
- Please start **THIS EVENING** (Day 1 - the evening of the day on which you saw your doctor or nurse) and continue to fill this in each evening for 2 weeks or until you have been symptom free ***and*** no treatments are being taken. Once your symptoms have gone you can proceed to section 3.
- For each week the diary is split into two sections – please could you record your symptoms in the first section and all treatments taken in the second section.
- In addition, during Week 1 and 2, please could you complete the Quality of Life questionnaires on Days 7 and 14.

WEEK 1: RESPIRATORY SYMPTOMS

For your symptoms relating to your respiratory infection, the answer you give should reflect how you have felt over the last 24 hours. If you have no symptoms or problems, please enter 0 (to indicate normal/not affected). Equally, if a symptom or problem ends during the period of the diary, enter 0 until the end of the diary.

For each symptom/problem, rate how bad it has been using the following scale.

0 = Normal/not affected

1=Very little problem

2=Slight problem

3=Moderately bad

4 =Bad

5 = Very bad

6 = As bad as it could be

Symptom/Problem	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cough							
Sore throat							
Difficulty swallowing							
Phlegm or sputum							
Facial pain (forehead, cheek or jaw pain)							
Blocked or runny nose							
Muscle aches							
Headaches							
Disturbed sleep							
General feeling of being unwell							
Fever or feeling feverish							
Interference with normal activities							

WEEK 1 TREATMENTS

For trial medication: *Please TICK in each box to indicate whether or not you have taken the study medication at each time point on each day.*

For antibiotics: *Please record the name of the antibiotic and tick the relevant box to indicate that you have taken antibiotics on that day.*

For other treatments: *Please record details of the treatment taken for your chest infection and tick the relevant box to indicate that you have taken the treatment on that day.*

TRIAL MEDICATION ***Do not take trial medication for more than 7 days***		***Tick box to indicate you have taken the treatment on that day***						
		DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**
Time of Day	**Morning**							
	Midday							
	Afternoon							
	Evening							
ANTIBIOTICS		***Tick box to indicate you have taken antibiotics on that day***						
Name of Antibiotic		**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**
OTHER TREATMENTS TAKEN FOR YOUR RESPIRATORY INFECTION e.g. paracetamol or decongestant		***Tick box to indicate you have taken the treatment on that day***						
Name of Other Medication or Product	**Strength (if applicable) or number of tablets**	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**

Have you stopped taking your study medication?

If yes, Please record the date here

Yes. No

☐ ☐

If yes please explain why?

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Quality of Life: *Please complete on Day 7*

WEEK 2: RESPIRATORY SYMPTOMS

For your symptoms relating to your respiratory infection, the answer you give should reflect how you have felt over the last 24 hours. If you have no symptoms or problems, please enter 0 (to indicate normal/not affected). Equally, if a symptom or problem ends during the period of the diary, enter 0 until the end of the diary.

For each symptom/problem, rate how bad it has been using the following scale.

0 = Normal/not affected

1=Very little problem

2=Slight problem

3=Moderately bad

4 =Bad

5 = Very bad

6 = As bad as it could be

Symptom/Problem	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cough							
Sore throat							
Difficulty swallowing							
Phlegm or sputum							
Facial pain (forehead, cheek or jaw pain)							
Blocked or runny nose							
Muscle aches							
Headaches							
Disturbed sleep							
General feeling of being unwell							
Fever or feeling feverish							
Interference with normal activities							

Section 3:

These questions are to be filled in when you have not experienced any symptoms for 2 days in a row or after 14 days

WEEK 1 TREATMENTS

For trial medication: *Please TICK in each box to indicate whether or not you have taken the study medication at each time point on each day.*

For antibiotics: *Please record the name of the antibiotic and tick the relevant box to indicate that you have taken antibiotics on that day.*

For other treatments: *Please record details of the treatment taken for your chest infection and tick the relevant box to indicate that you have taken the treatment on that day.*

TRIAL MEDICATION *Do not take trial medication for more than 7 days*		***Tick box to indicate you have taken the treatment on that day***						
		DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**
Time of Day	**Morning**							
	Midday							
	Afternoon							
	Evening							

ANTIBIOTICS	***Tick box to indicate you have taken antibiotics on that day***						
Name of Antibiotic	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**

OTHER TREATMENTS TAKEN FOR YOUR RESPIRATORY INFECTION e.g. paracetamol or decongestant		***Tick box to indicate you have taken the treatment on that day***						
Name of Other Medication or Product	**Strength (if applicable) or number of tablets**	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**

Since you saw your doctor or nurse on Day 1:

1. **Have you consulted with a health professional** about your symptoms?

Yes ☐ No ☐

If yes, then who did you see and how many times?

GP ☐

Nurse ☐

Other ☐

Since joining this study have you attended

An outpatients appointment Yes ☐ No ☐

A and E Yes ☐ No ☐

Day Care Yes No

Did you stay overnight in hospital? Yes ☐ No ☐

If yes, how many nights did you spend in hospital ☐

4. Have you bought any medication for your symptoms? (Not including the study medication or the antibiotics) **Yes** ☐ No ☐

Thank you for taking the time to answer our questions.

The information you have provided will remain confidential and the pooled data will help us to improve our management and treatment of patients with respiratory illness.

Please return your completed study diary using the freepost envelope supplied.

Please remember to return any unused trial medication in the freepost envelope supplied.

If you have any problems or queries about the diary, please contact:

THANK YOU!

You have made a valuable contribution to this medical research.

E 14 : PUBLISHED SYSTEMATIC REVIEW OF *A. Paniculata*

Andrographis paniculata (Chuān Xīn Lia´n) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis

Xiao-Yang Hu[1]*, Ruo-Han Wu[2], Martin Logue[1], Clara Blondel[3], Lily Yuen Wan Lai[1],

Beth Stuart[1], Andrew Flower[1], Yu-Tong Fei[2], Michael Moore[1], Jonathan Shepherd[4], JianPing Liu[2], George Lewith[1†]

1 Primary Care and Population Sciences, Aldermoor Health Centre, Southampton, United Kingdom,
2 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China,
3 AgroParisTech, Paris Institute of Technology for Life, Food and Environmental Sciences, Paris, France,
4 Southampton Health Technology Assessments Centre (SHTAC), Faculty of Medicine, University of

Southampton, Southampton, United Kingdom

† Deceased.

* X.Hu@soton.ac.uk

Abstract

Introduction

Antimicrobial resistance (AMR) is a substantial threat to public health. Safe and effective alternatives are required to reduce unnecessary antibiotic prescribing. *Andrographis Paniculata* (*A*. *Paniculata*, Chuān Xīn Lia´n) has traditionally been used in Indian and Chinese herbal medicine for cough, cold and influenza, suggesting a role in respiratory tract infections (RTIs). This systematic review aimed to evaluate the clinical effectiveness and safety of *A*. *Paniculata* for symptoms of acute RTIs (ARTIs).

Materials and methods

English and Chinese databases were searched from their inception to March 2016 for randomised controlled trials (RCTs) evaluating oral *A*. *Paniculata* without language barriers (Protocol ID: CRD42016035679). The primary outcomes were improvement in ARTI symptoms and adverse events (AEs). A random effects model was used to pool the mean differences and risk ratio with 95% CI reported. Methodological quality was evaluated using the Cochrane risk of bias tool; two reviewers independently screened eligibility and extracted data.

Results

Thirty-three RCTs (7175 patients) were included. Most trials evaluated *A*. *Paniculata* (as a monotherapy and as a herbal mixture) provided commercially but seldom reported manufacturing or quality control details. *A*. *Paniculata* improved cough (n = 596, standardised mean difference SMD: -0.39, 95% confidence interval CI [-0.67, -0.10]) and sore throat

author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Competing interests: The authors have declared that no competing interests exist.

(n = 314, SMD: -1.13, 95% CI [-1.37, -0.89]) when compared with placebo. *A*. *Paniculata* (alone or plus usual care) has a statistically significant effect in improving overall symptoms of ARTIs when compared to placebo, usual care, and other herbal therapies. Evidence also suggested that *A*. *Paniculata* (alone or plus usual care) shortened the duration of cough, sore throat and sick leave/time to resolution when compared versus usual care. No major AEs were reported and minor AEs were mainly gastrointestinal. The methodological quality of included trials was overall poor.

Conclusions

A. *Paniculata* appears beneficial and safe for relieving ARTI symptoms and shortening time to symptom resolution. However, these findings should be interpreted cautiously owing to poor study quality and heterogeneity. Well-

designed trials evaluating the effectiveness and potential to reduce antibiotic use of *A*. *Paniculata* are warranted.

Introduction

Respiratory tract infections (RTIs) are one of the most common reason for primary care consultations in the UK [1]. Treatments for RTIs are mainly symptomatic [2], and often include analgesics, antipyretics [3], mucolytics, expectorants, decongestants [4], and educational interventions [5], although evidence supporting currently used symptomatic treatment is still limited [6]. Antibiotics are frequently prescribed in primary care settings in Europe [7] with 60% of all antibiotic prescribing in the UK occurring in primary care [1]. Research has suggested RTIs are predominantly of viral aetiology [8], and that antibiotics are of very limited benefit in the majority of uncomplicated infections [9, 10]. Systematic reviews to date have failed to provide evidence for the effectiveness of antibiotics for RTIs [11]. Antibiotics showed no benefit in symptom improvement for acute RTIs (ARTIs) such as colds [12], persisting acute purulent rhinitis [12], or acute laryngitis [13]; and suggested little absolute benefits for reducing symptom duration or complications in sore throat [14], bronchitis [15, 16], sinusitis [17] and acute otitis media [18].

Antimicrobial resistance (AMR) is an evolving major global threat to public health [19]. A recent Public Health England report showed a 6% increase in total antibiotic use in England between 2010 and 2013 and it remains an important government priority to reduce antibiotic prescribing [20, 21]. The marginal benefit of antibiotics for ARTIs are outweighed by increasing AMR and common adverse reactions [3] leading to unnecessary increases in healthcare costs [22–24].

Research is urgently needed to explore other treatments that may be offered for symptomatic relief to reduce unnecessary antibiotic prescribing. In order to facilitate rapid translation of research into clinical practice, there has been much

interest in researching options currently available to the general public. This has involved over the counter (OTC) pharmacological treatments such as paracetamol as well as herbal alternatives. Evidence from previous systematic reviews suggested promising but limited evidence for Chinese herbs in influenza [25], common colds [26], upper RTI [27], and cough [28].

A. Paniculata (Burm.f.) Wall ex Nees (Acanthaceae family), also known as nemone chinensi, Chuān Xīn Lia´n, has traditionally been used in Indian and Chinese herbal medicine. It is traditionally used as an antipyretic for relieving and reducing the severity and duration of

symptoms of common colds and alleviating fever, cough and sore throats, or as a tonic to aid convalescence after uncomplicated RTIs [29][30]. There is encouraging evidence to demonstrate the potential mechanistic for effects of *A*. *Paniculata* for RTIs. The active constituents of *A*. *Paniculata* include the diterpene, lactones commonly known as the andrographolides which have shown anti-inflammatory, antiviral, anti-allergic, and immune-stimulatory activities [31]. They inhibit platelet-activating factor mediated inflammatory response [32], reduces expression of pro-inflammatory proteins such as cyclooxygenase-2 [33, 34], and demonstrates analgesic effects as well as antipyretic effects comparable to paracetamol [35]. *A*. *Paniculata* has also been shown, in vitro, to be effective against avian influenza A (H9N2 and H5N1) and human influenza A H1N1 viruses, possibly through blocking the binding of viral hemagglutinin to cells [36], or by inhibiting H1N1 virus-induced cell death [37].

Two previous systematic reviews showed that *A*. *Paniculata* alone or in combination with *A*. *senticosus* is superior to placebo for reducing symptom severity in upper RTIs [38, 39]. However, the clinical evidence for *A*. *Paniculata* for symptoms of lower RTI has not yet been systematically evaluated and would be important to review prior to conducting further research in this area. Furthermore, previous systematic reviews have been limited to Englishlanguages searches and given that *A*. *Paniculata* is used in Indian and Chinese herbal medicine, an up-to-date systematic review without language restrictions is warranted.This systematic review therefore evaluated the clinical efficacy, effectiveness and safety of *A*.*Paniculata* for of the treatment of ARTIs.

Materials and methods

This systematic review followed PRISMA reporting guidelines (S1 Table). A protocol of this review has been registered (CDR: CRD42016035679, S1 File). Ethics statement: N/A.

Search strategy and study selection

MEDLINE, EMBASE, AMED, Cochrane Library, CINAHL, China National Knowledge Infrastructure (CNKI), Wan Fang, Sino-Med Database, and Chinese Science and Technology Journal Database (VIP) were searched from their inception to March 2016. A range of freetext words and indexed terms related to

"*Andrographis Paniculata*" and "respiratory tract infection" were searched. The reference lists of studies meeting the inclusion criteria were searched to identify additional relevant studies. A detailed search strategy and search term alternatives for each database are available as supporting information; see S2 File. There were no exclusions made based on language. Literature searching (XYH, RHW) was followed by independently screening with at least two authors (XYH, RHW, ML). Study authors were contacted to obtain relevant missing data if necessary and where resources allowed.

Data extraction and management

A data extraction spreadsheet was designed and piloted with appropriate changes made for this review. The form identified trial characteristics, characteristics of trial population and conditions, details of interventions in all trial arms according to the consolidated standards of reporting trials (CONSORT) herbal extension in terms of features of herbal intervention [40], details of concomitant interventions, quality assessment, and findings on efficacy, effectiveness and AEs. Two reviewers extracted study data independently for Chinese-language (XYH, RHW, LL) and English-language (ML, CB) trials, with findings compared and agreed.

Eligibility criteria

This review included published and unpublished randomised controlled trials (RCTs). QuasiRCTs, crossover trials, controlled before and after studies, interrupted time series (ITS) studies, and non-experimental studies were not included due to their potential high risk of bias.

Studies of human participants of all ages, with symptoms of ARTIs. A clinical diagnosis of ARTI was the main inclusion criteria. Diagnoses of upper or lower ARTIs include acute common cold, influenza, rhinosinusitis, laryngitis, tonsillitis, pharyngitis, croup, acute otitis media, bronchitis, pneumonia, and acute exacerbations of chronic obstructive pulmonary disease (COPD). Symptoms of ARTIs are defined as having symptoms such as cough, sore throat, fever, runny nose and discoloured sputum for a duration of less than four weeks. Trials were excluded if they recruited participants with asthma, had active or previous peptic ulceration, were hypersensitive to analgesics, had psychosis, or were severely depressed. Exclusion also applied to trials that included patients who required hospital admission (for

example, for meningitis, severe pneumonia, epiglottitis, or Kawasaki disease), had a known immune deficiency, or were pregnant or breastfeeding [41].

Examples of herbal mixture include: products containing *A*. *Paniculata* in combination with Scutellaria baicalensis, or in combination with Lonicera japonica, Forsythia suspense, and Aster trinervius. No limitation was imposed concerning dosage, methods of dosing or duration of administration.

We included comparisons such as placebo or no intervention; usual care such as analgesics, antivirals, antibiotics, anti-inflammatories, steroids or corticosteroids; or other herbal remedies. Studies comparing different preparations of *A*. *paniculata*, e.g. comparing tablet with granule, were also included in this review.

Outcome measures

The following primary outcome measures were included in this review:

1. Participant self-reported or clinician/observer assessment on overall ARTI symptoms; or two target symptoms cough and sore throat. Commonly used measures included:

Changes on visual analogue scales (VAS)

Changes in symptoms scored on a Likert-type scale

Global assessment of symptom improvement by the patient

Global assessment of symptom improvement by treating clinician

2. AEs: This included any anaphylactic, allergic reactions, hypersensitivity reactions, or complications of *A*. *Paniculata*, such as rash, nausea, fatigue, or worsening of ARTIs symptoms. We also collected information regarding AEs due to interactions among *A*. *Paniculata* in combination with other remedies, or potential interactions with medications patients had for their co-morbidities.

We defined serious AEs according to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines as any event that leads to death, is life-threatening, requires hospitalisation or leads to persistent or significant disability;

biochemistry results such as electrolytes, liver and kidney function tests (alanine aminotransferase and creatinine) [42]. Secondary outcome measures included:

Mean time to reported remission or resolution of symptoms. This may be measured directly, through patient or clinician/observer report or indirectly as the time to return to normal activities.

Reduction in reported antibiotic usage, e.g. number of scripts issued immediately at the time of consultation and uptake of delayed prescriptions. Although the Chinese government launched a special campaign to promote the rational use of antimicrobials in healthcare settings in the 2011 healthcare reform, this has yet to be implemented in many places in China [43]. Antibiotics are prescribed on patients' initial visit if there were suspicions of bacteria inflammation, therefore scripts immediately issued at the time of consultation was recorded.

Trials that did not report either our primary and or secondary outcome measures were excluded from this review.

Timing of effect measures: Some studies may have used a repeated measures approach. Timings of measures for each included trial were documented with commonly reported time points explored if there was sufficient data available. All outcome measures were assessed at baseline and data for all time points were extracted with the aim to pooling those trials that collected data at similar time points. Otherwise, data at the most appropriate follow-up point were assessed.

Assessment of risk of bias in included studies

The risk of bias of the included RCTs was assessed independently by two reviewers using the tool developed by Higgins and Green in the Cochrane Handbook for Systematic Reviews of Interventions [44]. We assessed bias over the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of researchers conducting outcome assessments), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias. A judgement of 'low risk' of bias, 'high risk' or bias, or 'unclear risk' of bias was provided for each domain. Any disagreements were resolved by discussion or by involving a third reviewer until consensus was reached.

Measures of treatment effect

Data from individual studies were combined in a meta-analysis when interventions were performed in a homogeneous clinical environment, with similar population, settings, intervention and comparison, and outcome measures. Overall effect sizes were estimated using Review Manager (RevMan) Version [5.3] [45]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Because of the anticipated variability in the populations and interventions of included trials, a generic inverse variance random effects model was used to pool the mean difference (MD) with 95% confidence interval (CI) on target continuous outcomes to incorporate heterogeneity [46, 47]. When the units of the outcome measures used across studies were not consistent, the effects as standardised mean differences (SMD) were reported. An overall effect size of 0.2–0.5 was regarded as small, 0.5–0.8 as moderate and more than 0.8 as large [48]. For dichotomous data, a random effects method was used to pool the summary risk ratio (RR) with 95% CI. Absolute risk estimates were calculated using the event rates of control groups as baseline risks.

Dealing with missing data

Where data was missing or incomplete, we contacted study authors to obtain this where possible. If the means were reported without standard deviations, we calculated the standard deviation from the information reported such as p-values, F-values or confidence intervals. As far as possible, we utilised intention to treat (ITT) analysis data for all outcomes. However, most included trials reported complete cases only; and complete case data were the primary analysis dataset. For each outcome, the number of participants whose data was available at baseline and at follow up, and the rate of loss to follow-up were recorded.

Assessment of heterogeneity

Between-study heterogeneity was assessed using the I^2- statistic which describes the percentage of variation across studies that is due to heterogeneity rather than chance. Rules of thumb for interpretation of this statistic suggest that I^2>30% equates to moderate heterogeneity, I^2>50% equates to substantial heterogeneity and I^2>75% equates to considerable heterogeneity [46]. For all I^2 values

above 50%, we investigated potential sources of heterogeneity. Although this threshold is widely used, it is somewhat arbitrary and therefore if the I^2 value was below 50% but the direction and magnitude of treatment effects suggest important heterogeneity, we investigated the potential sources in a sensitivity analysis and took this into account when interpreting the findings. As high levels of heterogeneity were expected due to complexity in the form of *A. Paniculata* (e.g. monotherapy or herbal mixture, capsule or liquid), it was planned to use a random effects model to pool the overall effects [46].

Assessment of reporting biases

Funnel plots were created to investigate potential reporting bias where this was feasible and there were sufficient studies [49]. Funnel plot tests for asymmetry were conducted separately in STATA software version 14 using the metabias command.

Sensitivity analysis

Sensitivity analyses were conducted for the primary outcomes to determine whether the review conclusions would have differed if eligibility was restricted to trials without high or unclear risk of bias for either in sequence generation or allocation concealment domains) [46]; and if eligibility was restricted to trials that provided any detail on authentication or standardisation of the herb.

Subgroup analysis

If there was sufficient available data, several subgroup analyses were planned *a priori* to compare the effect estimate between studies that evaluated:

Patients with upper ARTIs versus lower ARTIs;

Adults versus children (younger than 18);

A. Paniculata as monotherapy versus as fixed combinations;

A. Paniculata in different preparation, e.g. granule versus tablet or other forms

Results

Description of included trials

The literature search identified 3106 studies, of which a final total of 33 RCTs [50–82], comprising 7175 patients, met the criteria to be included (Fig 1). Authors of two trials [52, 69] were contacted for further information but received no response. Tables 1–5 shows the characteristics of the 33 included trials. The included trials were published between 1991 and 2014, with 25 from China [50, 51, 53–58, 60–68, 71–75, 80–82], three from Russia [59, 70, 79], two from Sweden [77, 79], and one each from Thailand [52], India [78], and Chile [76]. Two were

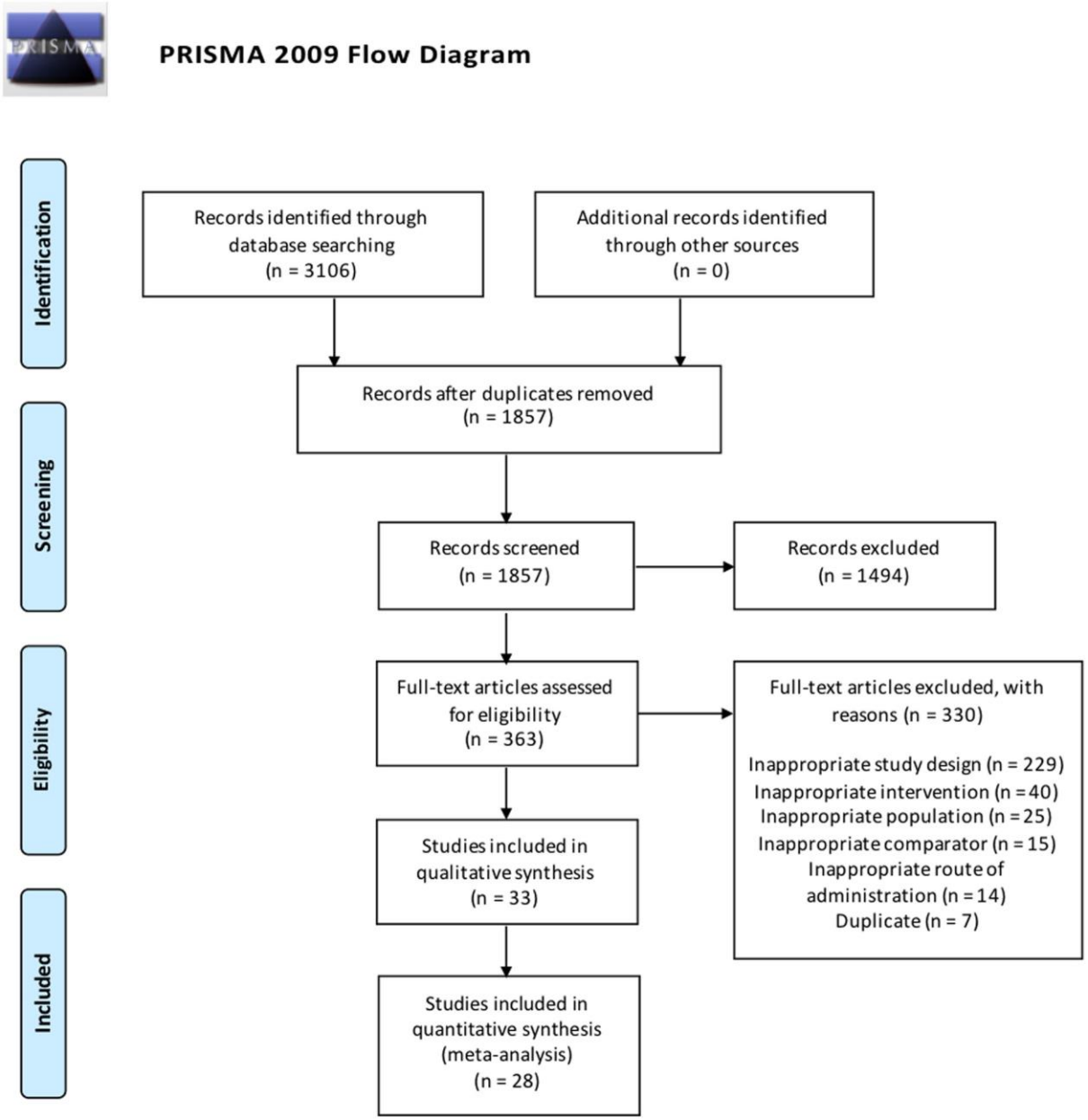

Fig 1. Flow and identification of trials to include in review.

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Table 1. Trial characteristics: *A*. *Paniculata* versus Placebo (n = 4).

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & cointervention if available	Details of CG	Outcome measures	End point
Caceres et al., 1999 [76] Chile	Common cold	NR	NR; 25–50 as inclusion criteria	TG: 53.9%; CG: 45.2%	158/208	AP mono (tablet)	Placebo tablet, 4 tablets, tid, 5d	[ITT] Improvement in cough intensity and frequency (VAS, 10cm)	0–4
Melchior et al., 1997 [77] Sweden	Common cold	Within 3d	NR	NR	50/50	AP mono (tablet)	Placebo tablet, 400mg, tid, 5d	CCME (patient reported); Symptom relief (VAS)	5
Saxena et al., 2010 [78] India	Uncomplicated URTIs	Within 3d	TG: 34.36 ±0.97; CG: 32.42±1.1	TG: 67%; CG: 62%	220/223	AP mono (capsule)	Placebo capsules, 300mg, bid, 5d	[PP data] Severity of overall severity of 8 symptoms (VAS, 0–100); Severity of cough (VAS, 0–100); Severity of sore throat (VAS, 0–100)	5
Melchior et al., 2000 [79] Russia	Uncomplicated URTIs	Within 36h	Range: 18–55 (inclusion criteria)	NR	178/179	AP mixture (tablet)	Placebo tablet, 400mg, tid, 3d	Severity of symptom sum score	3
Melchior et al. 2000 Pilot [79] Sweden	Uncomplicated URTIs	Within 36h	TG: 39, range: 30–48; CG: 42.8, range: 32–52	TG: 35%; CG: 39%	45/46	AP mixture (tablet)	Placebo tablet, 400mg, tid, 3d	Severity of symptom sum score; Cough (frequency/dry/ productive); Sore throat improvement score	4–6

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A*. *Paniculata*, URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections, Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based)

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three-armed trials [52, 70], and the remaining were two-armed parallel RCTs [50, 51, 53–69, 71–82].

Twenty-two trials [50–55, 57, 59, 61, 62, 69, 70, 72–79, 81, 82] were on upper ARTIs; while six trials on lower ARTIs were published in China [63, 65–68, 71]; and six did not specify upper or lower [56, 58, 60, 64, 71, 80]. Eleven trials [55, 57, 58, 62, 71–73, 75, 80–82] reported the use of guideline based diagnosis, according to the Chinese medicine clinical research guidelines (CMCRG) [中药新药临床研究指导原则] [83]; the international classification of

primary care (ICPC) classification [84]; the criteria of diagnosis and therapeutic effect of diseases and syndromes in traditional Chinese medicine [中医病证诊断疗效标准] [85]; and the common clinical diseases and diagnosis criteria [常见疾病诊断依据与疗效判断标准]

[86].

Nearly one third of the trials did not include patients with a co-morbidity or did not report existence of a co-morbidity, but they excluded patients who had other primary diseases [50, 52, 53, 56, 59, 71, 77–80], e.g. cardiovascular conditions, liver, kidney or hematopoietic system impairment, mental health conditions, or rheumatoid arthritis. Two trials excluded patients who had asthma [52, 77]; two excluded those who had any other infections [76, 78]. Only three trials included patients with co-morbidities: heart failure [65, 67], diarrhoea [58], and toxic encephalopathy [65]; and one trial recruited children with frequent cold, bronchitis, sinusitis and pneumonia [69].

Interventions

Experimental interventions included *A. Paniculata* as a monotherapy and as an herbal mixture in combination with other herbs. Table 6 presents the characteristics of *A. Paniculata* reported

Table 2. Trial characteristics: *A. Paniculata* versus Usual care (n = 12).

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & cointervention if available	Details of CG	Outcome measures	End point

Chang 2012 [50] China	AURTIs	1.5d, range: 0.5–3d	38.5 (15–65)	44%	64/64	AP mono (granule)	Ribavirin, iv, 10mg/kg in 250ml 5% Glucose solution, qd; penicillin, cefazolin; for 3–7d)	CCME	3–7
Li 2014 [51] China	Acute pharyngitis (Hou Bi)	NR	TG: 30.5 ±1.7; CG: 29.8±1.8	TG: 68%; CG: 60%	52/52	AP mono (pillule)	Cefixime capsule, 400mg, qd, 7d/ session, 2 sessions	CCME	20
						One off treatment: inhalation of small amount Glucocorticoids (dosage N/A), healthy diet, no alcohol or cigarettes			
Thamlikitkul et al 1991 [52] Thailand	Pharyngotonsillitis	NR; "recent fever" (inclusion criteria)	TG1: 29.3 ±8.1; TG2: 29.4±6.4; CG: 28.2 ±7.4	TG1: 51%; TG2: 48%; CG: 53%	142/152	AP mono (capsule); TG1: HAP; TG2: LAP	Paracetamol capsule, 325mg, qid, 7d	CCME (sore throat)	3
						Antibiotic, antihistamine or/and decongestant, antitussive			
Hou et al 2009 [53] China	AURTIs:	Within 3d (inclusion criteria)	*TG: 21.87 ±19.92; CG: 21.33 ±14.05 (m)	TG: 59%; CG: 61%	397/397	AP mixture (capsule)	Ribavirin; 6d	CCME	NR, probably 6
Lin and Yang 2011 [54] China	Herpes Anginosus	NR; participants all had sudden fever	*Range: 6m–7y	51%	98/98	AP mixture (capsule)	Ribavirin	**CCME	7
						Antipyretic or physically cooling down; antibiotics (If WBC > 10x10(9)/L-); IV fluid infusion (if participants couldn't eat)			
Liu et al 2012 [55] China	AURTIs	NR	TG: 41.56, range: 20–63; CG: 41.87, range: 20–65	TG: 48.33%; CG: 50.82%	121/121	AP mixture (capsule)	Ribavirin granule, 0.3g, tid, 7d	CMCRG-CCME; Time to resolution (cough and sore throat)	7
						Anti-infection, anti-cough, and antipyretic			
Tan and Gao 2010 [56]	ARTIs (wind heat)	TG: 1.71 ±0.46; CG:	TG: 40.3 ±11.43;	TG: 55%; CG: 56%	124/144	AP mixture (capsule)	Ribavirin, 0.3g, tid, 3d	[FAS data] CCME; Symptom improvement	3, 7

China		1.67±0.48	CG: 38.45 ±12.36			Drink plenty of water, saline gargle, bid; Phenol caplets, po, 2 tablets, tid; Fu Fang Gan Cao He Ji (if cough), po, 10ml, tid; Physical cooling down (if >38˚C); Benorilate, po, 1g (if >39˚C)		(cough and sore throat); Time to resolution (cough)	
Tan 2011 [57] China	URTIs—group B coxsackieviruses (wind heat)	TG range: 7–14d; CG range: 8–14d	TG median: 27; CG median: 28	TG: 47.83%; CG: 41.3%	92/92	AP mixture (capsule)	Ribavirin tablet; 0.3g, tid, 7d	CMCRG-CCME	7
						Drink plenty of water, rest; physically cooling down (if > 38˚C)			
Wang et al 2008 [58] China	ARTIs	NR	TG: 42.38 ±1.12; CG: 42.56 ±1.44	TG: 52.22%; CG: 49.44%	324/347	AP mixture (capsule)	Ribavirin granule	**CMCRG-CCME; Time to resolution (overall symptoms)	6
						Dry suspension of cefaclor (if bacterial infection)			
Kulichenko et al., 2003 [59] Russia	Diagnosed Influenza viral infection	NR	Range: 19–63	NR	66/66	AP mixture (tablet) + paracetamol (if >39˚C)	Amantadine "according to prescription", regimen not clearly stated but possibly same as in the pilot study listed below	Cough and sore throat (Patient's self-evaluation (scale 0–3); Sore throat (Patient's self-evaluation (scale 0–3); Time to resolution (cough and sore throat)	5
Pilot [59] Russia	Diagnosed Influenza viral infection	NR	Range: 19–63	NR	540/540	AP mixture (tablet) + paracetamol (if >39˚C)	Antiviral (Amandine with ascorbic acid as an adjuvant). 1st day: 2*0.05g tablet, tid; 2nd & 3rd day: 2*0.05g tablet, bid; 4th day: 2*0.05g tablet, qd. Paracetamol (if > 38˚C), 1*0.05 g tablets, tid, 2–3d	CCME (cough and sore throat); Days of sick leave; Time to resolution (cough and sore throat)	4–5

(*Continued*)

Table 2. (*Continued*)

STUDY ID	Diagnosis (syndrome	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product &	Details of CG	Outcome measures	End point

	differentiation)					**cointervention if available**			
Li 2010 [60] China	ARTIs (Feng Wen Re Du)	TG: 7d; CG: 8d	*TG: 9 ±1.5; CG: 8±1.7	TG: 69%; CG: 70%	130/130	AP mixture (tablet)	Aciclovir tablets, po, 0.8g, 5 times a day; Vitamin C, po, 0.2g, tid	**CCME	NR; probably 7
						Ru Yi Huang Jin San (external use, Cu Tiao) and health advice (avoid sun and wind; no spicy or strong flavour food)			
Deng 1999 [61] China	Acute tonsillitis	2h-7d	*TG: 5–62; CG: 5–62	TG: 52.58%; CG: NR	162/162	AP mixture (liquid)	Erythromycin ethylsuccinate; 250–500mg, tid-qid (children: 30–50ml/kg, tid-qid), 7d	CCME; Time to resolution (overall symptoms)	7

*Trials on or involved children;

**Practitioner evaluated

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A*. *Paniculata*, HAP: high dose *A*.

Paniculata, LAP: low dose *A*. *Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based). CMCRG-CCME: cure rate and markedly effective rate based on the Chinese medicine clinical research guidelines

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in the included trials. Out of the 33 trials, seven did not report the type of product used [50, 54, 61, 73, 75, 81, 82] whilst one used dried leaves of *A*. *Paniculata* [52]. The remaining 25 trials [51, 53, 55–72, 76–80] reported using *A*. *Paniculata* extract and among these five reported the use of an extract by the name of SHA-10 [59, 70, 76, 78, 79].

Included trials seldom reported manufacturing or quality control details. Three reported method of measuring andrographolide proportion using HPLC technique [76–78]; and only one reported that the product was produced, analysed and bottled according to good manufacturing practice (GMP) standard [59]. Three trials reported added materials [57, 76, 78] but only one [78] provided clear description (200 mg of micro crystalline cellulose). Extract solvents used included methanol [78], polyethylene glycol

[80], and two used methanol for HPLC extraction [76, 77]. Only one trial provided extract solvent concentration details [78].

Comparison interventions included usual care, placebo control, and active herbal interventions. All the 21 trials involving usual care [50–70] included some form of active intervention such as corticosteroids [51, 62], antibiotics or antivirals [50, 53, 55, 57–59, 61–67], cough suppressant [55, 56, 63, 65, 66, 68], or antipyretics [52, 54–56, 60, 66, 68–70].

Outcome measurements

The most commonly reported primary outcome measure was global assessment on overall symptoms improvement (Tables 1–5). Although not clearly reported in every trial, it is assumed this outcome was measured by the practitioner. Apart from one study [63], all Chinese-language trials reported four-category scores in symptoms of ARTIs, among which 11 [55, 57, 58, 62, 71–73, 75, 80–82] reported data based on the CMCRG [中药新药临床研究指导原则]. The CMCRG is a four-category scoring system to evaluate overall treatment effects based on: 1). Cured: a). no temperature in 3 days, b). no symptom or sign of RTIs, c). accumulated score decreases 95%; 2) Markedly effective: a). no temperature in 3 days, b). most symptoms and signs of RTIs disappear, c) accumulated score decrease between 70% to 95%; 3). Effective: body temperature decreased in 3 days, b). most of key symptoms and signs of

3. Trial characteristics: *A. Paniculata* plus usual care versus Usual care (n = 9).

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & cointervention if available	Details of CG	Outcome measures	End point
Bao 2013 [62] China	Acute pharyngitis	NR	TG: 23.6±1.2; CG: 22.4±1.9	TG: 60%; CG: 57.5%	40/40	AP mono (pillule)+ usual care	Usual care: Corticosteroids combined with antibiotics (Gentamicin and dexamethasone), 1 ml for 15 mins/d, 5d; Cydiodine Buccal tablets, 1.5mg, tid, 5d	CMCRG-CCME	5
Sun and Zhao 2014 [63] China	Bronchiectasis (Fei Yong)	NR; "Acute exacerbation"	TG: median: 49.2, range: 21–80; CG: median: 50.1, range: 22–78	TG: 46%; CG: 51%	78/78	AP mono (capsule) + usual care	Usual care: Cefixime, po, 150mg, bid; Levofloxacin, po, 0.2g, bid; Dextromethorphan hydrobromide and guaifenesin syrup, po, 20ml, tid; all for 14d	Severity of cough (VAS, 0–10)	11
Guo 2013 [64] China	ARTIs (External wind heat)	Within 3d	*TG: 5.25 ±1.42; CG: 5.43±1.39	TG: 61%; CG: 58%	416/416	AP mixture (capsule) + Ribavirin	Ribavirin	**CCME	NR, probably 7
Li et al 2007 [65] China	Pneumonia	10.5 (range: 7–14)	*Range: 1m–5y	TG: 58.33%; CG: 60%	540/540	AP mixture (capsule) + usual care	Usual care: Antibiotics and antivirals; Aminophylline; Vitamin K; Sedation, diuretic, cardiac, oxygen (if heart failure); Dehydrating agent and brain cell activator (if toxic encephalopathy)	**CCME	NR, probably 7

Meng 2012 [66] China	Acute tracheitis and bronchitis	Within 5d (as inclusion criteria)	NR	NR	282/282	AP mixture (capsule) + usual care	Usual care: Drink more water, rest, gargle bid; If there were symptoms of URTIs such as nasal congestion, runny nose, or sneezing, Paracetamol Triprolidine Hydrochloride and Pseudoephedrine Hydrochloride tablets were given, po, 2 tablets, tid; If cough with no or little sputum, Pentoxyverine Citrate Tablets was given, 250mg, po, tid; If cough with sputum, Bisolvon Tablets was given, po, 160mg, tid; If fever, physical cooling; If there was clear evidence of bacterial infection, antibiotics such as macrolides, penicillins, cephalosporins, or quinolones were used	**CCME; Severity of cough	7
Tang et al 2009 [67] China	Bronchitis	Range: 1–2d	*7.5m, range: 3–12m	56%	260/260	AP mixture (capsule) + usual care	Usual care: Anti-infection, sedation, ultrasonic atomization, sputum suction, shoot back	**CCME; Time to resolution (cough)	7
Wu 2013 [68] China	Acute bronchitis	5.4 ±3.6, range: 1–13	9–73, 34.2 ± 11.2	53%	362/362	AP mixture (capsule) + usual care	Usual care: Paracetamol Triprolidine Hydrochloride and Pseudoephedrine Hydrochloride tablets, po, 2 tablets, tid; Pentoxyverine Citrate tablets, po, 250mg, tid; Bromhexine, po, 160mg, tid	**CCME	7

(*Continued*)

3. (*Continued*)

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & cointervention if available	Details of CG	Outcome measures	End point
Shakhova et al 2003 [69] Russia	URTIs	Within 24h	*NR; children	NR	93/93	AP mixture (tablet) + usual care	Usual care: drink plenty of warm water; milk and vegetable diet with food containing vitamins; deep	Severity of symptom sum score	3–5 and 7–9

							throat rinse with Alkaline and mouth washing; 1–2% solution of protargola (silver proteinate); paracetmal		
Spasov et al., 2004 [70] Russia	URTIs	Within 24h (inclusion criteria)	*TG: 7.17 ±0.32; CG1: 6.78±0.34; CG2: 6.47 ±0.29	TG: 49%; CG1: 49%; CG2: 56%	133/133	AP mixture (tablet) + usual care	CG1: Immual (Echinacea purperea) drop + usual care; CG2: Usual care (lavish warm drinks, throat gargles, antiseptic nose drops, and paracetamol, 500mg, tid (if fever or severe headache)	Severity of symptom sum score (patient and practitioner evaluated), reduce in medications	5

*Trials on or involved children;

**Practitioner evaluated

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A*. *Paniculata*, HAP: high dose *A*.

Paniculata, LAP: low dose *A*. *Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based). CMCRG-CCME: cure rate and markedly effective rate based on the Chinese medicine clinical research guidelines

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RTIs disappear, c). accumulated score decrease between 30% to 70%; 4). Ineffective or worsening: a). no decrease or increased body temperature, b). no improvement in key symptoms and signs of RTIs or even getting severe, c). accumulated score decreases less than 30%. Accumulated score was calculated as: (baseline score—endpoint score)/baseline score X100%. Scores were given based on: 1). Symptoms of ARTIs, e.g. symptoms: fever, sore throat, cough, nasal congestion, runny nose, headache, sweating, sneezing, thirst, 2). Signs of ARTIs, e.g. aversion to wind, and changes in tongue appearance and pulse; and 3). Laboratory checks, e.g. chest radiography, circulation, faeces, blood, urine, liver and kidney function, electrocardiogram (ECG). In this review, the combined cure and markedly effective (CCME) rate was considered as improved by the review authors. Symptom score on severity of cough [59, 63, 66, 75, 76], sore throat [59, 75], and overall symptoms (commonly a list of 8–12 ARTI symptoms) [69, 70] were reported in seven trials.

Secondary outcome measures reported in the included trials were: time to resolution of cough [55, 56, 59, 67], of sore throat [55, 56, 59], and of overall symptoms [58, 61]; only one trial reported reduction in reported antibiotic usage [70].

A few trials used a repeated measures approach [50, 56, 69, 71, 80]. Apart from one trial on acute pharyngitis which followed-up at 20 days [51], the most common end point follow-up that was reported ranged from 3 to 7 days and the outcome data for the end points closest to an average of 5 days were extracted and assessed (Tables 1–5).

Risk of bias of included trials

Apart from four trials [52, 76, 78] (and pilot of [79]), all other trials were judged at high risk of bias on at least one domain (Fig 2). Each risk of bias item for each included trial are provided in supplement information; see S1 Fig.

4. Trial characteristics: *A. Paniculata* versus Herbal active intervention (n = 5).

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & cointervention if available)	Details of CG	Outcome measures	End point
Ding et al 2010 [71] China	Acute bronchitis (wind heat)	TG: 2.76 ±1.03d; CG: 2.80±1.18d	TG: 37.68 ±13.25; CG: 34.96 ±13.32	TG: 53%; CG: 38%	136/137	AP mixture (capsule) + CG placebo	Qing Gan Chuan Xin Lian tablet (Chuan Xin Lian + Mai Ma Teng), 0.25g, tid + TG placebo	**CMCRG-CCME	0, 2, 3, 4, 8
	ARTIs (wind heat)	TG: 18.91 ±9.85h; CG: 18.63±12.24h	TG: 35.97 ±13.12; CG: 33.27 ±12.57	TG: 43%; CG: 40%	138/140	Same as above			

Xi 2006 [72] China	Cold (Shu Shi)	Within 3d (inclusion criteria)	TG: 36 ±2.26; CG: 35±2.12	TG: 56%; CG1: 56%; CG2: 50%	250/250	AP mixture (tablet)	CG1: Huo Xiang Zheng Qi pill, 6–8 pills, tid, 3d; CG2: Su Xiao Shang Feng capsule, 2 capsules, tid, 3d	CMCRG-CCME	3
Yang and Liu 2012 [73] China	URTIs (wind heat)	Within 48h (within 24h: n = 160)	TG: 35.47; CG: 34.56 (SD NR)	TG: 43%; CG: NR	233/239	AP mixture (tablet)	Fu Fang Yu Xing Cao tablet; 4 tablets, tid, 3d	CMCRG-CCME	3
Zhang et al 1994 [74] China	Acute tonsillitis (criteria given)	Within 3d	*TG: <10: n = 47, >10: n = 54; CG: <10: n = 21; >10: n = 32	TG: 60%, CG: 53%	154/154	AP mixture (liquid)	Yin Huang liquid: Jin Yin Hua extract 12g + Huang Qin extract 24g, 10ml, tid, 7 days (children half dose)	CCME	7
Zhao et al., 2012 [75] China	Common cold (wind heat)	Within 48h (inclusion criteria)	TG: 30.7; CG: 31.1 (SD NR)	TG: 50%; CG: 50%	300/300	AP mixture (granule)	Gan Mao Ling granule; one pack, tid, 5d	CMCRG-CCME; Severity of symptom score (cough and sore throat)	5

*Trials on or involved children;

**Practitioner evaluated

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A*. *Paniculata*, HAP: high dose *A*.

Paniculata, LAP: low dose *A*. *Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based). CMCRG-CCME: cure rate and markedly effective rate based on the Chinese medicine clinical research guidelines

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All included trials were described as 'randomised', but 20 did not report the method of random sequence generation [50, 52–55, 57, 58, 60–62, 65, 67, 69, 72–74, 77, 79, 81, 82]. Among those that did, seven used random number table [51, 63, 64, 68, 71, 75, 80] and six used computer-generated random series [56, 59, 66, 70, 76, 78]. Only four trials provided information on allocation concealment, among these two were organised by independent third party clinical management personnel [78, 80], and two used sealed identical jars [76, 79].

Most trials (24 of 33) had a high risk of bias in blinding of the participants and personnel as they assessed two interventions that were different in dosage, or form of preparation, or two

5. Trial characteristics: *A. Paniculata* (pillule) versus *A. Paniculata* (tablet) (n = 3).

STUDY ID	Diagnosis (syndrome differentiation)	Course of symptoms: mean±SD	Age: Mean ±SD (y)	Gender (% of male)	N (analysed/ recruited)	Name of the TG product & cointervention if available	Details of CG	Outcome measures	End point
Chang et al 2008 (phase 1) [80] China	ARTIs (External wind heat)	TG: 22.44 ±12.22h; CG: 20.7±8.46h	TG: 36.31 ±11.63; CG: 37.55±12.69	TG: 57%; CG: 62%	200/202	AP mono (pillule)	Chuan Xin Lian tablet, 0.15g; tid; 3d	[FAS data] CMCRG-CCME	0, 2, 4
(phase 2) [80] China	ARTIs	NR	TG: 37.18 ±13.64; CG: 36.09±14.43	TG: 48.55%; CG: 46.32%	271/274/276	AP mono (pillule)	Chuan Xin Lian tablet, 0.15g; tid; 3d	[FAS data] CMCRG-CCME	0, 2, 4
Su 2014 [81] China	Acute pharyngitis	NR	26.5 (range: 20–40)	53%	60/60	AP mono (pillule)	Chuan Xin Lian tablet; 1g, tid, 5d	CMCRG-CCME	5
						Inhalation of Gentamicin 80,000 [, dexamethasone 5mg; 15 mins, bid, 5d			

Xia 2014 [82] China	Acute pharyngitis	NR	TG: 35.6, range: 16–68; CG: 36.4, range: 17–63	TG: 55%, CG: 52%	125/125	AP mono (pillule)	Chuan Xin Lian tablet, 0.3g, tid, 3–7d	CMCRG-CCME	3–7

NR: not reported, TG: treatment group, CG: control group, SD: standard deviation, Y: year, m: month, d: day, h: hour. AP: *A*. *Paniculata*, HAP: high dose *A*.

Paniculata, LAP: low dose *A*. *Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral. FAS: full analysis set, PP: per-protocol, ITT: intention-to-treat. CCME: cure and markedly effective rate (not reported as guideline based)

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types of interventions, or compared *A*. *Paniculata* plus usual care versus usual care, without any blinding information given. Two trials comparing *A*. *Paniculata* with placebo control had low risk of bias as both patients and evaluator [76] or investigator and pharmacist [78] were blinded to group assignment and could not distinguish between the two interventions. The remaining trials [52, 55, 59, 71, 74, 77, 79] provided no information regarding similarities between interventions, or provided no information to confirm whether or not blinding of personnel was conducted.

Most included trials failed to provide enough information to determine whether blinding of outcome assessment was achieved. Nine trials were judged to be at high risk of bias as they assessed subjective outcome measures and the patients or practitioners knew that which intervention they had been assigned to (i.e. *A*. *Paniculata* plus usual care versus usual care) [62–70].

Twenty-six included trials reported no attrition. Among the 7 trials that had dropouts, three trials reported 3–8% dropout and conducted ITT by assuming no effect for dropouts. No per protocol analysis was performed for those three trials [56, 58, 73]. Two trials reported dropouts (1% [78] and 6% [52]) without ITT analysis. Another trial reported 25% dropout and provided both ITT and per protocol analysis findings [76]. The author suggested that the dropout rate in two groups were equal and that

the potential reason for large dropout may have been related to three weeks' winter holiday. One trial did not clarify how missing data was dealt with [70].

One trial [79] published a protocol containing information on outcome measures and follow-up points that were consistent with the main trial report. All remaining trials did not have a protocol available. Four trials [65, 71, 75, 82] reported selected findings that were not fully consistent with the outcome measures set in the methods.

6. Characteristics of *A. Paniculata* used in the included trials.

Name	Ingredient	Form	Manufacturer	ID	Active content and dose strength (s)	Treated condition (syndrome differentiation if available)	Regimen
Ke Gan Shuang Qing	Huang Qin Gan, Chuan Xin Lian Nei Zhi	Capsule	Chengdu Kanghong Pharmaceuticals Group Co., Ltd	[71]*	Baicalin: Andrographolide ratio 4:1 (100mg and 25mg)	Acute bronchitis (Wind heat) & ARTIs	125mg, 3 capsules, tid, 4d
				[56]*	Baicalin: Andrographolide ratio 4:1 (150mg:37.5mg)	AURTIs	375mg, tid, 3d
				[57]*		URTIs—group B coxsackieviruses (Wind heat)	2 capsules, tid, 7d
				[55]	Baicalin and Andrographolide 4:1	AURTIs	2 capsules, tid, 7d
				[68]*	NR	Acute bronchitis	2 capsule, tid, 7d
				[66]*		Acute tracheitis and bronchitis	2 capsule, tid, 7d
			NR	[67]	Baicalin: Andrographolide ratio 4:1 (150mg:37.5mg)	Bronchiolitis	2 capsules, tid, 7d
				[64]	Baicalin and Andrographolide 4:1	Acute RTIs (External wind heat)	1 capsule, tid, 7d
				[58]	NR	ARTIs	2 capsules, tid, 6d

				[53]		AURTIs	1 capsule, tid, 6d
				[54]		Herpes Anginosus	1 capsule, tid, 5–7d
				[65]		Pneumonia	Tid, “till discharge"
		Granule	NAP	[50]	10g Chuan Xin Lian + 10g Huang Qin	ARUTIs	Qid, 3–7d
Fu Fang Shuang Hua	Chuan Xin Lian, Yin Hua, Lian Qiao, Ban Lan Gen	Tablet	Shanxi Kanghui Pharmaceutical Co., Ltd	[73]*	NR	URTIs (Wind heat)	4 tablets, qid, 3d
				[72]*	NR	Cold (Shu Shi)	4 tablets, tid, 3d
				[60]	NR	ARTIs (Feng Wen Re Du)	4 tablets, tid, course of treatment NR
		Liquid	Beijing Haierfu Pharmaceutical Co., Ltd	[61]	NR	Acute tonsillitis	5–7 yrs: 10ml, qid; children above 7 yrs: 20ml, tid; adult: 20ml, qid; 7d
			NR	[74]	NR	Acute tonsillitis	For children (<3yrs: 10ml, tid; 3–7yrs: 10ml, qid; >7yrs: 20ml, tid); For adult (20ml, qid); 7d
Kan Jang	Elethrococcus senticosus, *A. paniculata*	Tablet	The Swedish Herbal Institute, Goteborg, Sweden	[69]	Elethrococcus senticosus and AP	URTIs	2 tablets, tid, 5–7d
				[79]*	AP extract (EX20101) 85mg, SHA containing 5.25mg Andrographolide and deoxyandrographolide per tabet; Acanthopanax senticosus EX20095 9.7mg containing total Eleuthroside B and Eleuthroside E 2%	Uncomplicated URTIs	Main: 4 tablets (400mg), tid, 3d; pilot: 4 tablets (400mg), tid, 4–6d
				[59]*	88.8mg AP; Eleuthrococcus senticosus 10.0mg	Influenza viral infection	300mg, tid, 5d

				[70]*	85mg of AP containing 5.25mg andrographolide and deoxyandrographolide and extract of Eleuthrococcus senticosus EX20095, 9.7mg	URTI	200mg, tid, 5d
Jun Du Qing	Ban Lan Gen, Xuan Shen, Qian Cao, Dan Shen, Jin Yin Hua	Granule	Sun Yat-sen university affiliated hospital	[75]*	NR	Common cold (Wind heat)	2 packs, tid, 5d

(*Continued*)

6. (*Continued*)

Name	**Ingredient**	**Form**	**Manufacturer**	**ID**	**Active content and dose strength (s)**	**Treated condition (syndrome differentiation if available)**	**Regimen**
Chuan Xin Lian Nei Zhi	*A. Paniculata* monotherapy	Pillule	Tianjin Tasly Pharmaceutical Co., Ltd	[80]*	NR	ARTIs (External wind heat)	0.15g, tid, 3d
				[51]*	NR	Acute pharyngitis (Hou Bi)	0.15g, tid, 7d
				[62]*	NR	Acute pharyngitis	0.15g, tid, 5d
		Capsule	Jiuhui Pharmaceutical Co., Ltd	[63]*	75mg Andrographolide/capsule	Bronchiectasis (Fei Yong)	0.33g, tid, 14d
Chuan Xin Lian		Pillule	Sichuan Herun Pharmacy Co., Ltd	[82]*	NR	Acute pharyngitis	630mg (42mg/pillule X15 pillule), tid, 3–7d
				[81]	NR	Acute pharyngitis	630mg, tid, 5d
Kang Jang		Tablet	The Swedish Herbal	[77]*	Each tablet contained 85mg of AP	Common cold	400mg, tid, 5d

			Institute	[76]*	100mg each of AP herb dried extract; Standardised to a minimum of 5mg of total andrographolide and deoxyandrographolide	Common cold	4 tablets, tid, 5d (1200 mg/day of A *paniculata* dried extract)
KalmCold™		Capsule	M/s Natural Remedies Pvt. Ltd. Bangalore, India	[78]*	200 mg of KalmCold dissolved in 100 ml of Methanol	Uncomplicated URTI	one capsule (100 mg active component), bid after breakfast and dinner, for 5d
LAP/HAP		Capsule	The Department of Medical Science, Ministry of Public health	[52]	HAP: 500 mg AP per capsule (casule of 500 mg); LAP: 250 mg AP per capsule (capsule of 250 mg)	Pharyngotonsillitis	HAP: 3 capsules 4 times a day during 7d: 6g of Andrographis a day, LAP: 3 capsules 4 times a day during 7d: 3g of Andrographis a day

*Products with authentication information provided

NAP: not a product. NR: not reported, TG: treatment group, CG: control group, d: day, yrs: years. AP: *A*. *Paniculata*, HAP: high dose *A*. *Paniculata*, LAP: low dose *A*. *Paniculata*. URTIs: upper respiratory tract infections, AURTIs: acute upper respiratory tract infections. Qd: once daily, bid: twice daily, tid: three times daily, qid: four times daily, po: oral

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Only one trial had no obvious risk of other bias [80] and this was the only trial that stated that there was no conflict of interests. None of the other included trials stated whether or not a conflict of interest existed and three trials included one or more author who worked for the pharmaceutical company of the product being evaluated as an intervention [59, 71, 77]. The most common reasons for high risk of other bias were: 1). In 12 trials, diagnostic criteria were not applied at recruitment and there were no inclusion or exclusion criteria specified [53, 54, 58, 60–62, 65, 67, 68, 74, 81, 82]; 2). Four trials provided either no condition-related baseline data [63, 75, 81, 82], or no sociodemographic characteristic baseline [59, 79], or neither [69]; and 3). Two trials reported discrepancies between permitted co-intervention(s) for the intervention and control groups: in one trial, paracetamol was given if body temperature > 39 in the treatment group but 38–38.5 in the control group [59]; the other trial allowed no additional treatment for the intervention group only [61]. One third of the trials reported informed consent [55, 56, 59, 64, 66, 69–71, 78–80].

Funnel plot for one comparison was performed to investigate potential publication bias (Fig 3). There was no evidence ($p = 0.870$) of small-study effects.

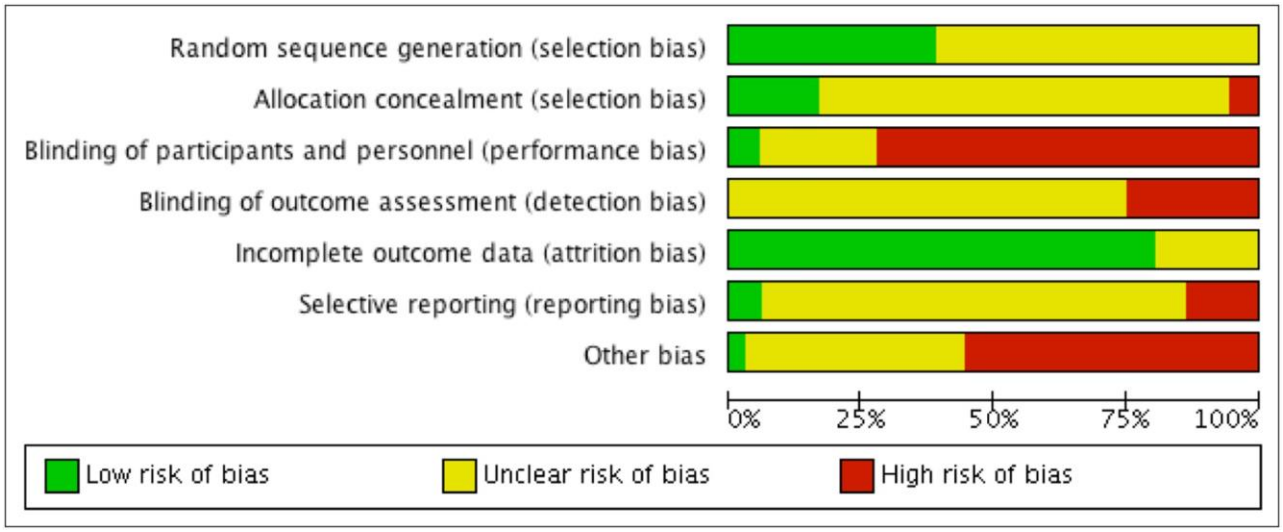

Fig 2. Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included trials.

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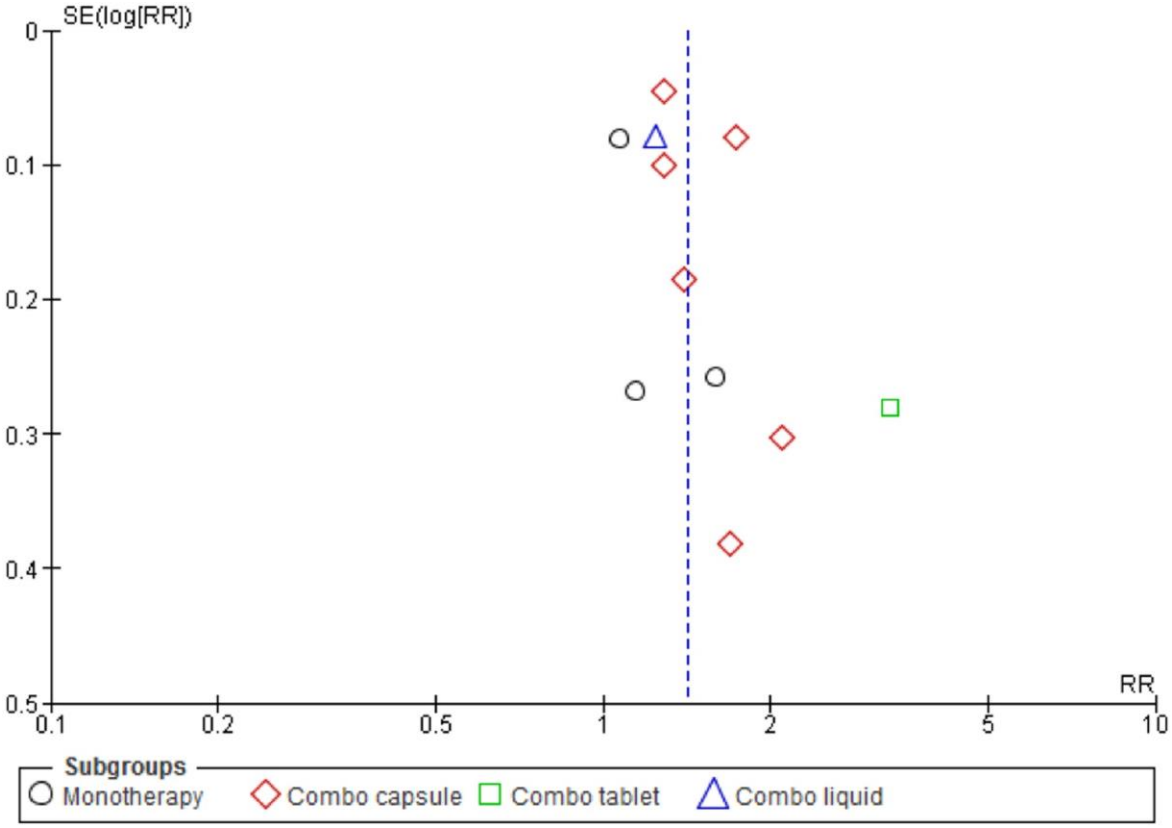

Fig 3. Funnel plot of comparison: 1 *A. Paniculata* vs. Conventional active intervention, outcome: 1.1 Chinese guideline assessment of symptom improvement.

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Effect estimates

The included trials featured five comparison groups: *A*. *Paniculata* versus placebo (4 trials); *A*. *Paniculata* versus usual care (12 trials); *A*. *Paniculata* plus usual care versus usual care alone (9 trials); *A*. *Paniculata* versus other active herbal interventions (5 trials); and *A*. *Paniculata* pillule versus *A*. *Paniculata* tablet (3 trials).

Subgroup analyses were performed for two of the planned subgroups: monotherapy or herbal mixture and different forms of preparation of *A*. *Paniculata*. These were conducted for primary outcome measures in *A*. *Paniculata* versus usual care and *A*. *Paniculata* plus usual care versus usual care. Subgroup analysis in other comparison groups and subgroup analysis on upper or lower ARTIs, and adults versus children were not performed due to insufficient data.

***A*. *Paniculata* vs placebo (n = 4).** Evidence from four trials (three had low or medium RoB [76, 78, 79] showed a statistically significant effect in favour of *A*. *Paniculata* compared to placebo in overall symptom improvement (n = 445, SMD: -0.69, 95%CI [-1.26, -0.12], I^2 = 86%), cough (n = 596, SMD: -0.39, 95%CI [-0.67, -0.10], I^2 = 63%), and sore throat (n = 314, SMD: -1.13, 95% CI [-1.37, -0.89], I^2 = 0%) (Fig 4) [76–79]. One trial showed a statistically significant effect in favour of *A*. *Paniculata* as a single herb in tablet compared to placebo as measured by patient reported rate of improvement in overall symptoms (n = 50, RR: 2.80, 95%CI [1.19, 6.30]) [77]. No data was available under this comparison for time to symptom resolution or antibiotic medication usage.

***A*. *Paniculata* vs usual care (n = 12).** Evidence from ten trials showed a statistically significant effect in favour of *A*. *Paniculata* compared to usual care as measured in overall symptoms improvement CCME rate (n = 1347, RR: 1.36, 95%CI: [1.18, 1.57], I^2 = 67%) (Fig 5). Heterogeneity for the herbal mixture in capsule subgroup was low when the Wang 2008 trial was removed (p = 0.43, I^2 = 0%). This may be due to: 1). not reporting inclusion/exclusion criteria for recruiting participants and the duration of illness were not clear, therefore there was

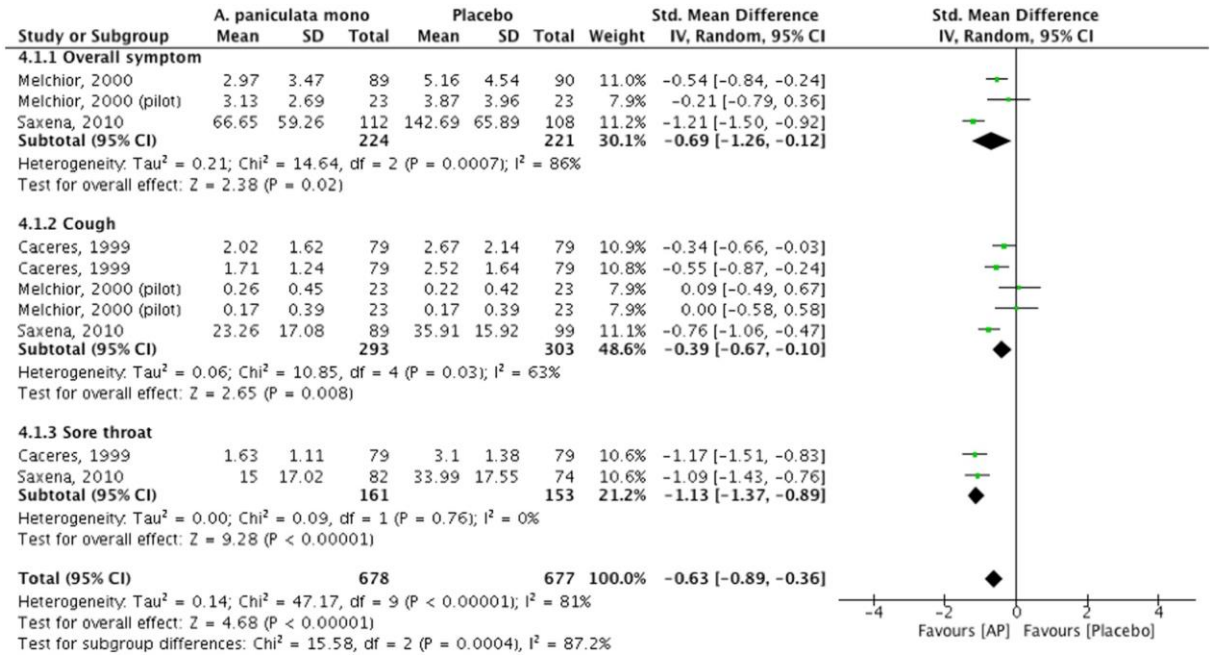

Fig 4. *A. Paniculata* versus placebo as measured by symptom improvement score.

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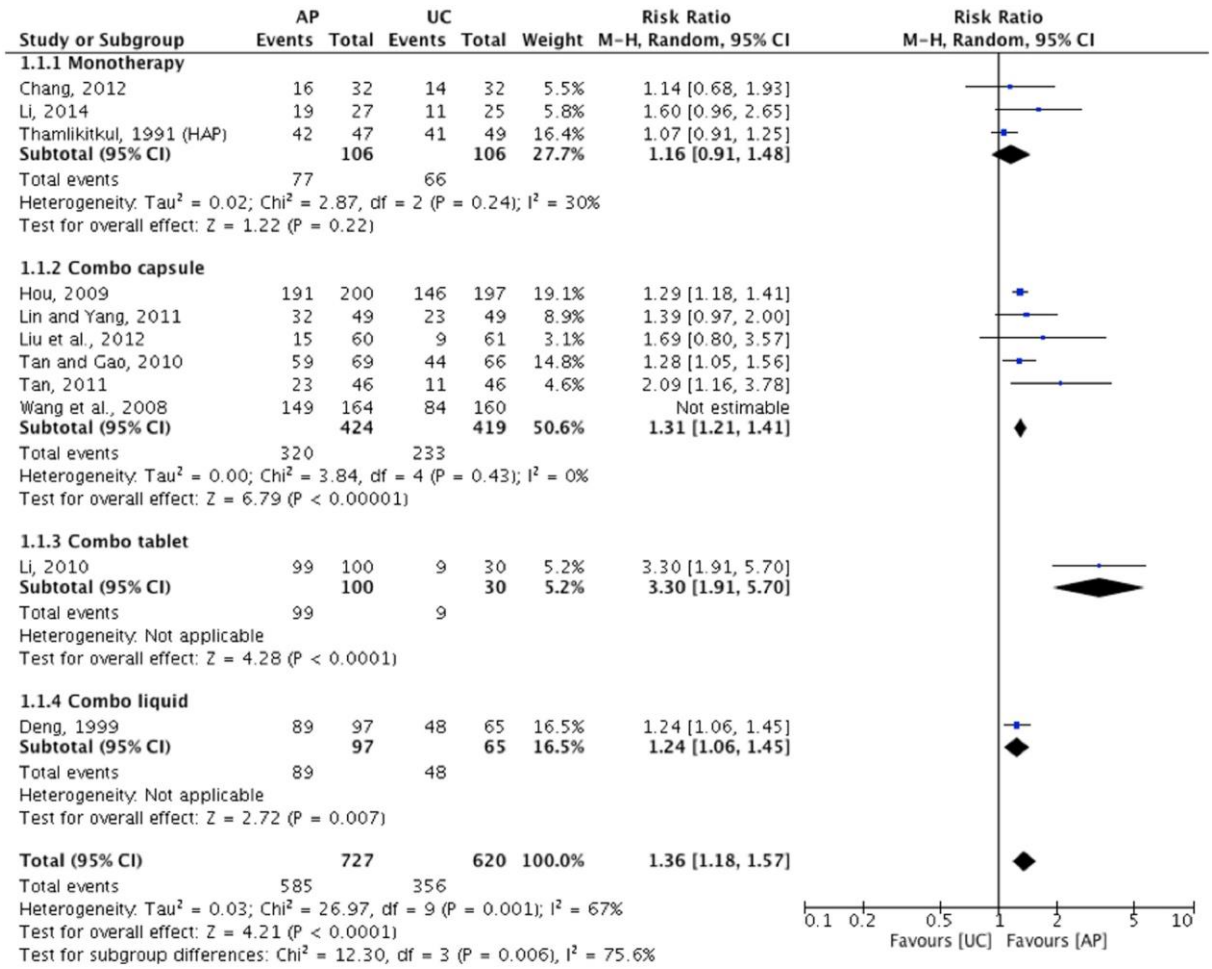

Fig 5. *A. Paniculata* versus usual care as measured by global assessment of overall symptoms improvement CCME.

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potentially high population heterogeneity; and 2) lack of authentication. Apart from one subgroup (*A. Paniculata* as a single herb) failing to show a statistically significant effect [50, 51], *A. Paniculata* as herbal mixture in capsule [53–58] and as herbal mixture in tablet [60] and liquid [61] showed statistically significant effects compared to usual care.

When compared with usual care, *A. Paniculata* showed a statistically significant reduction in the duration of sore throat: (n = 187, SMD: -3.92 [-6.76, -1.07], I^2 = 96%) and sick leave:

(n = 540, SMD: -4.81 [-5.19, -4.42]), but not in cough: (n = 187, SMD: -2.55 [-6.42, 1.33], I^2 =

98%) (Fig 6) [55, 59]. No data were available on medication usage for this comparison group.

***A. Paniculata* plus usual care vs usual care (n = 9).** Evidence from six trials [62, 64–68] showed a statistically significant effect in favour of *A. Paniculata* plus usual care compared to usual care alone as measured by assessment of symptom improvement CCME (n = 1900, RR:

1.31, 95%CI: [1.16, 1.48], I^2 = 81%) (Fig 7).

Evidence from two trials [67, 68] showed that *A. Paniculata* plus usual care shortened the duration of symptoms by approximately 1 day compared to usual care alone: (n = 622, SMD:

-1.27, [-1.58, -0.97], I^2 = 67% (Fig 8).

Outcomes of three trials in this comparison group were not pooled and were presented narratively: Sun and Zhao also showed significant improvement in overall symptom as measured

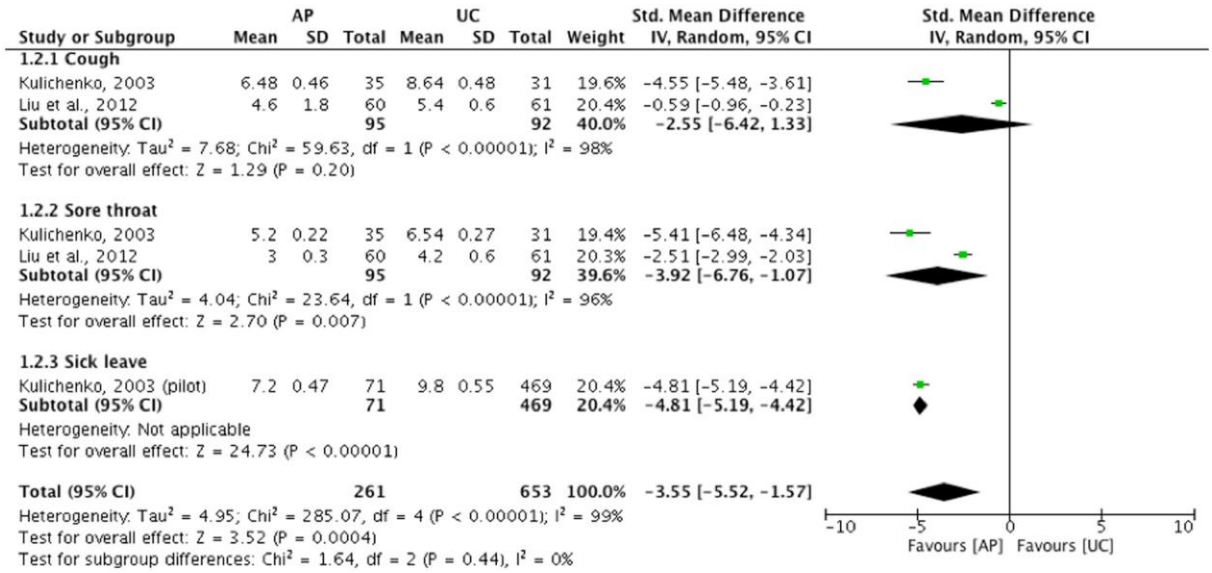

Fig 6. *A. Paniculata* versus usual care as measured by time to symptom resolution (Unit: Day).

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by 0–10 VAS (n = 78, MD: -0.80, 95%CI: [-1.40, -0.20]) [63]; Evidence from two trials showed statistically significant improvements in symptoms [69, 70] and Spasov et al. (2004) suggested reductions in paracetamol intake (55 (mean 1.03) over 95 (mean 2.44), p0.0001) and codeineintake (23 (mean 0.43) over 43 (mean: 1.10), p0.05) when compared *A. Paniculata* plus usual care over usual care alone [70].

***A. Paniculata* vs other herbal interventions (n = 5).** Evidence from five trials showed a statistically significant effect in favour of *A. Paniculata* compared to other herbal interventions

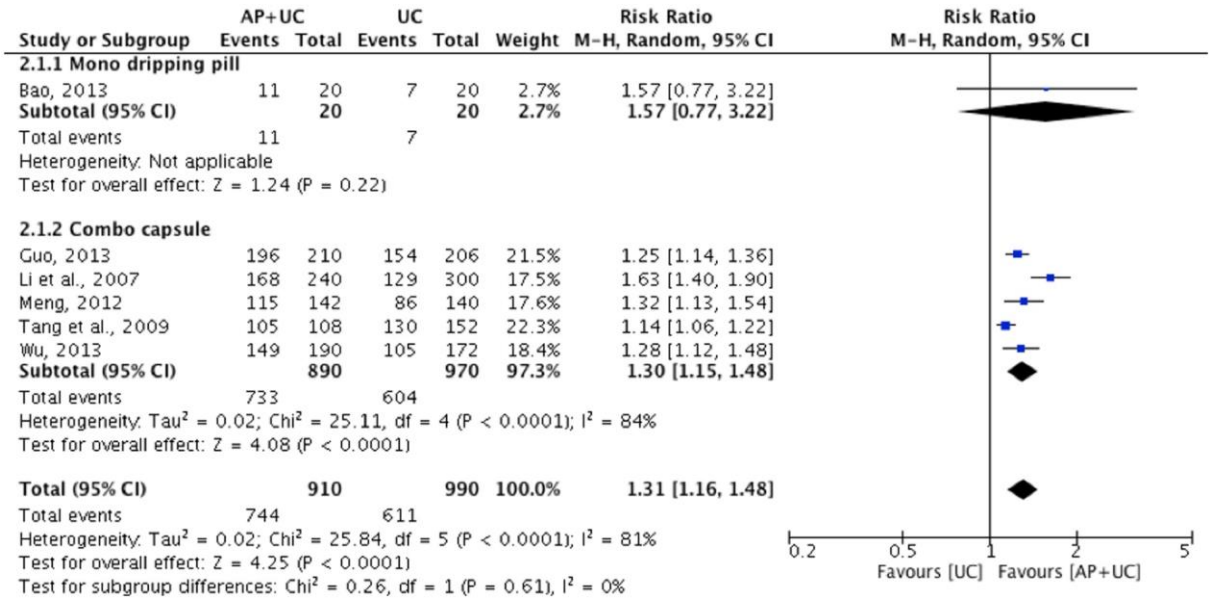

Fig 7. *A. Paniculata* plus usual care versus usual care as measured by global assessment of overall symptoms improvement CCME.

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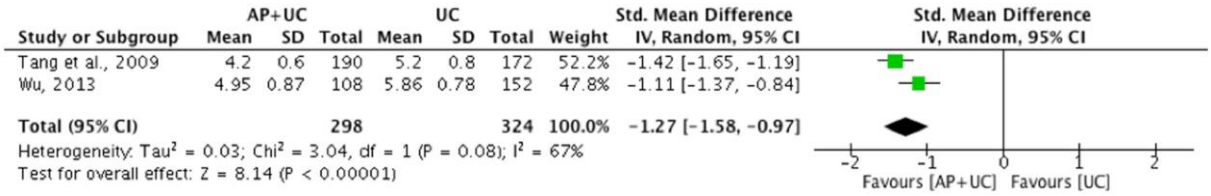

Fig 8. *A. Paniculata* plus standard care versus standard care as measured by time to symptom resolution (unit: days).

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as measured by improvement rate in overall symptoms (n = 827, RR: 1.44, 95%CI: [1.10, 1.89], I^2 = 89%). Upon removing Zhang 1994 from the analysis, heterogeneity was reduced (I^2 = 66%), while did not greatly change the summary estimates. Possible reasons for this may be that this trial targeted children and that the product evaluated was not authenticated (Fig 9). No data were available for time to resolution or antibiotic medication usage for this comparison group.

***A. Paniculata* in pillule vs in tablet (n = 3).** Evidence from three trials [80–82] showed a statistically significant effect in *A. Paniculata* in pillule compared to *A.*

Paniculata in tablet as measured by improvement rate in overall symptoms CCME (n = 586, RR: 1.14, 95%CI: [1.04, 1.25], I^2 = 86%) (Fig 10). No data was available under this comparison for time to symptom resolution or antibiotic medication usage.

Sensitivity analysis

Sensitivity analyses were conducted by restricting inclusion in the meta-analysis to trials with low risk of bias in both sequence generation and allocation concealment domains [50, 76, 78].

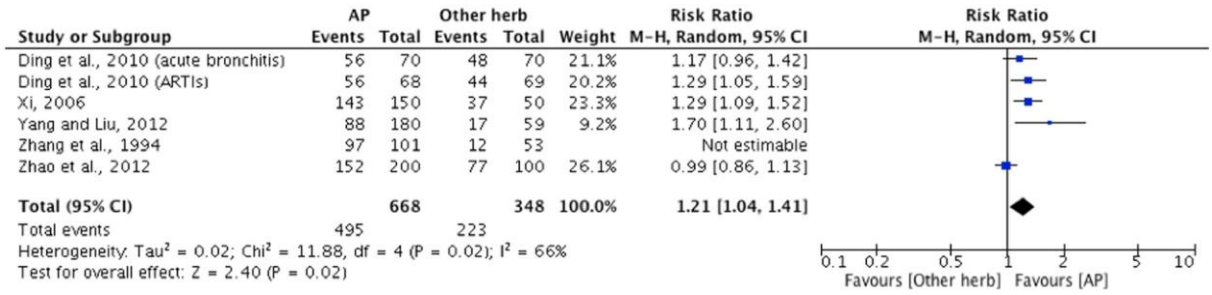

Fig 9. *A. Paniculata* versus other herbal interventions as measured by global assessment of overall symptoms improvement.

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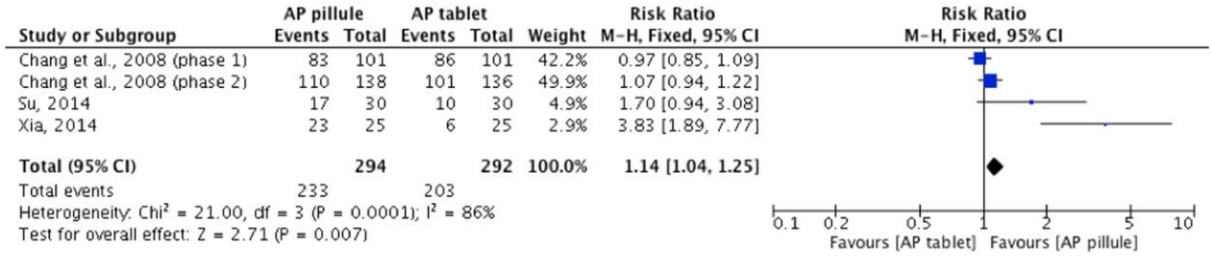

Fig 10. *A. Panicualta* pillule versus *A. Paniculata* tablet as measured by global assessment of overall symptoms improvement CCME.

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The effect of *A. Paniculata* over placebo was enhanced in overall symptoms (n = 219, SMD: -1.21 [-1.50, -0.92]) and in cough (n = 504, SMD: -0.56 [-0.80, -0.31], I^2 = 46%); while the effect for overall symptoms of using *A. Paniculata* in pollule over *A. Paniculata* tablet remained similar. Removal of trials that did not provide

authentication or standardisation information [50– 55, 57, 60, 61, 63–65, 69, 71, 79, 81] did not greatly change the summary estimates. Data from two trials [58, 74] were removed from the meta-analysis with reasons given above.

Adverse events

All but10 trials [53, 55, 57, 59, 60, 63, 64, 67, 69, 75] reported AE or safety. Among those that reported AEs, none reported any acute toxicity and 11 reported no AE in either intervention or control group [50, 54, 55, 62, 67, 68, 72, 73, 76, 81, 82]. For each of the following AEs associated with the *A. Paniculata* group, one case was reported for each trial: constipation [66, 71], nausea [80], vomiting [64], diarrhoea [80], unpleasant sensations in the chest [79], and intensified headache [79] (supplement information; see S2 Table). Four trials did not provide sufficient information to fit into the table are narratively described: Zhang et al. reported some participants had minor AE (vomiting) but did not specify which group or how many participants [74]; Thamlikitkul reported 11 patients in the TG and 9 in CG experienced nausea, vomiting, abdominal discomfort, dizziness, drowsiness and malaise [52]; and Saxena et al reported 1 vomiting, 1 epistaxis, 1 urticarial, 3 diarrhoea (+ nausea or lethargy) [78], and Melchior et al reported 2 cases of urticarial [77], without specifying which group. Saxena et al (2010) stated that the adverse effect between groups were found to be the same ($p>0.05$) [78].

Discussion

Summary of evidence

Thirty-three trials involving 7175 patients with ARTIs were included in this review with no language restrictions. Findings suggest limited but consistent evidence that *A. Paniculata* improved cough and sore throat when compared with placebo. *A. Paniculata* (alone or plus usual care) has a statistically significant effect in improving overall symptoms of ARTIs when compared to placebo, usual care, and other herbal therapies. *A. Paniculata* in pillule tended to be more effective in improving overall symptoms over *A. Paniculata* in tablet. Evidence also suggested that *A. Paniculata*

(alone or plus usual care) has shortened the duration of cough, sore throat and sick leave/time to resolution when compared versus usual care. Reduction in antibiotic usage was seldom evaluated in the included trials.

Although no serious AE was observed and minor AEs were mainly gastrointestinal in the included trials, caution is warranted in interpreting safety before comprehensive safety data is available. The quality of included trials was generally lower than desired as many were poorly designed, underpowered and inadequately blinded. There was high heterogeneity among trials due to variations in population and outcomes.

Variations in *A. Paniculata*

Form of preparation and dosage. The two commonly prescribed preparations in the included trials were capsules and tablets; there were no decoctions. This may due to the extremely bitter nature of the herb described as the "king of bitters". Findings of this review showed *A. Paniculata* pillules are superior to tablets in reliving overall symptoms [80–82], suggesting a place for pillule preparations.

Most *A. Paniculata* products have an extraction ratio of 14:1 standardised to contain an average of 35% of andrographolides [27] but solvent extraction ratios were not reported in most included trials. The amount of andrographolide produced from a daily dose of *A. Paniculata* extract varied from 15.75mg of andrographolide for URTIs [70], 225 mg for bronchiectasis [63], and up to 1200 mg for pharyngo-tonsillitis [52]. The most common treatment length was 5–7 days, ranging from 3 days for an AURTI [56] to 14 days for bronchiectasis [63] requiring administration three times daily. There is limited dose-finding research available documenting recommended percentage of active ingredient, dosage or ceiling effects so dosage is based in traditional use and herbal textbooks.

Common herbal combinations. The most commonly studied co-active ingredients included *Scutellaria baicalensis* (Hua´ng Qı´n [黄芩]) [50, 53–56, 58, 64–

68, 71], *Isatidis Radix Isatidis* (Baˇn La´n Ge¯n [板蓝根]) [60, 61, 72–75], *Flos Lonicera* (Jīn Yı´n Huā [金银花]) [60, 61,

72–75], *Forsythia suspense* (Lia´n Qiào [连翘]) [60, 61, 72–74], and *Eleuthrococcus senticosus* (Cı` W¯ı Jiā [刺五加]) [59, 69, 70, 79]. Apart from *Eleuthrococcus senticosus*, the other four herbs and *A. Paniculata* are commonly used heat-clearing anti-inflammatory and antimicrobial herbs in Traditional Chinese Medicine, along with *Coptis chinensis* (Hua´ng Lia´n [黄连]), *Folium* (Dà Qīng Yè [大青叶]), *Viola yedoensis* (Zıˆ Huā Dı` Dīng [紫花地丁]), *Pulsatilla Radix*

(Ba´i To´u We¯ng [白头翁]), *Houttuynia cordata* (Yu´ Xīng Caˇo [鱼腥草]), and *Patrinia Herba* (Bài Jiàng Caˇo [败酱草]) [87]. Traditional Chinese Medicine (TCM) prescriptions often involve several herbs with synergistic actives which are frequently individualised based on the presenting symptoms and TCM diagnosis. This may result in complex phyto-pharmaceutical interactions and AEs.

Manufacturing.

The review identified eight *A. Paniculata* products, representing four *A. Paniculata* polyherbal preparations (Ke Gan Shuang Qing[1] capsule and tablet, Fu Fang Shuang Hua[1] tablet and liquid, Kan Jang[1] tablet, Jun Du Qing[1] capsule) and four *A. Paniculata* monotherapies (Chuan Xin Lian Nei Zhi[1] pillule and capsule, Chuan Xin Lian[1] pillule, Kan Jang[1] tablet, KalmCold[1] capsule) (Table 6).

The active ingredients of *A. Paniculata* has not been fully identified in most trials but it is generally assumed to be the andrographolides. Only three trials [76–78] provided manufacturing details and chromatographic fingerprints of the herbal preparations to ensure quality and consistency of the products (Table 6). Those studies with inadequate information about the herbal content and manufacturing procedures may not be generalisable to other *A. Paniculata* studies as bioequivalence is 'assumed' rather than proven. A CONSORT herbal extension checklist is recommended to guide reporting of herbal trials and to assure herbal quality and bioequivalence.

Safety (adverse events and toxicity)

The traditional uses of *A. Paniculata* are as a liver tonic to help maintain appetite and digestion; alleviate gastro-intestinal upsets and acute diarrhoea; immune function and to support intestinal function [27]. This traditional use may reduce adverse reactions caused by conventional medicines when they are prescribed in conjunction with *A Paniculata*. Findings of this review showed five cases of minor AEs in *A. Paniculata* group [71, 79, 81] (two cases were *A. Paniculata* plus usual care [64, 66]) and 48 cases [51, 58, 61, 64] were reported in control groups in the included trials. Minor AEs were mainly gastrointestinal, while there were two cases of dry mouth (Ribavirin [61]) and six cases of skin reaction (Cefixime [51] and *Echinacea purperea* [70]) reported. This was not consistent with the recent therapeutic goods administration (TGA) pharmacovigilance analysis, which revealed most common AEs associated with *A. Paniculata* were hypersensitivity or allergic reactions [29]. The TGA safety report explored association between anaphylactic/allergic type ADRs and *A. Paniculata*, suggesting that ADRs tend to be related to highly concentrated methanol extracts [29]. Our safety findings are inconclusive as there was an absence of proportionate data on each minor AE in each group thus limiting a comprehensive risk-benefit assessment.

Acute toxicity studies in rats suggested median lethal doses for andrograpolide is more than 40g/kg and 10 mg/kg body weight is when the ADRs became apparent [88]. The European Medicines Agency (EMA) reports no acute or genotoxicity data on Andrographis extracts but there is a possibilty of high doses causing reproductive toxicity, with decreases in sperm counts and motility that were linked to disruption of spermatogenesis in rats [89]. Animal research showed andrographolide-induced induction of CYP1A2, indicating an interaction with theophylline [90]. And Baicalin tends to interact with Omeprazole Chlorzoxazone Losartan [91], Rosuvastatin [92] and Acetaaminophen [93]. Mechanism of actions

among herbal mixtures included in this review were not properly documented to support their use.

Implications and future direction

This review suggests that *A. Paniculata* might act as a safe and effective treatment for ARTIs, either alone or in combination with usual care, as monotherapy or as a herbal mixture. Manufacturing information may be an important factor that differed among these included trials, and we recommend all further trials are based on a consistent, safe and well-defined *A. Paniculata* product. Pharmacological research exploring correlations between ADRs and manufacturing procedures (with methanol, or aqueous solvent, or aqueous-ethanol mixture) are also needed. Sensitivity analysis showed that higher quality trials suggested an enhanced improvement in overall symptoms and cough. Future well designed trials evaluating effectiveness and safety of oral *A. Paniculata* in capsule or tablet form and reported according to the herbal CONSORT checklist are vital and may serve to minise antibiotic prescription and AMR. The potential for antibiotic sparing should be studied in future trials.

Strengths and limitations

Cochrane methodology was followed with a protocol of this systematic review registered and published online. A broad search strategy including both English and Chinese databases was adopted without language restrictions. Papers identified were screened and eligible trials extracted independently by two reviewers. We attempted to include grey literature by seeking manufacturers' reports and attempted to contact original authors for missing data. A number of studies including a substantial patient sample were identified; characteristics of the herb were documented following the criteria of CONSORT herbal extension.

Methodological quality of included trials was restricted as randomisation was not well documented; 73% of the trials included were not blinded; where ITT analysis were performed, loss to follow-up data were counted as no effect [56, 58, 73]; and

most trials were published without a protocol available. The diagnostic criteria used in included trials were inconsistent and more than one third provided no inclusion/exclusion criteria. Not all trials were performed in countries where the International Council for Harmonisation (ICH) guidelines were legally binding. The included trials rarely clarified whether the products were GMP certified. However, methodological quality judgements were made on the basis of incomplete reporting the evidence of effectiveness may be undervalued [44]. Chinese-language randomised trials present a prominent excess of significant results that requires cautious interpretation [94]. It was not clear whether some of the trials were conducted with adequate ethical review; whether the products evaluated were not authenticated, or whether these details were poorly reported.

There were heterogeneities among trials included due to the heterogeneity population, clinical setting, variations in the form of *A*. *Paniculata* and controlled intervention employed, outcome measures, and different study protocols. Inadequate number of trials were available to allow further subgroup analyses on children or on lower ARTIs. Some included trials were non-inferiority RCTs as placebo control was considered unethical by some researchers. They demonstrated that *A*. *Paniculata* was clinically superior to other herbal interventions but failed to provide evidence on the established effect.

Conclusions

A. *Paniculata* appears to be beneficial and safe for relieving ARTI symptoms and reducing time to symptom resolution. The evidence is inconclusive due to limited methodological quality of included trials and study heterogeneity. Well-designed trials evaluating effectiveness, efficacy and safety of *A*. *Paniculata* as a monotherapy, or as an herbal mixture, as well as exploring its potential to reduce antibiotic prescribing in primary care, are warranteD

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Author Contributions

Conceptualization: LL MM GL.

Formal analysis: XYH BS.

Funding acquisition: LL MM GL.

Investigation: XYH RHW ML CB LL.

Methodology: XYH LL BS AF YTF MM JS JPL GL.

Supervision: GL MM JPL.

Writing – original draft: XYH.

Writing – review & editing: XYH RHW ML CB LL BS AF YTF MM JS JPL GL.

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