Antimicrobial resistance: what role for herbal medicines?

Dr Merlin Willcox, Academic Clinical Lecturer

Professor George Lewith
Professor Mike Moore
Professor Paul Little
Dr Andrew Flower
Dr Xiao-Yang Hu
Dedication

Professor George Lewith
1950-2017
Department of Primary Care and Population Sciences

- 3rd best UK outputs for Primary Care Research

- Within the NIHR School for Primary Care Research (SPCR), which also includes: Bristol, Cambridge, Keele, Manchester, Newcastle, Nottingham, Oxford, University College London.

- Collaborative work between departments, universities and countries!
Integrative Medicine Group

• A team of clinicians, pharmacologists, herbalists and other CAM practitioners, statisticians and health economists

• PhDs and post-docs

• Commercial sponsors

• Chinese colleagues and many other international links

• MHRA relationship
Outline

- The problem of antibiotic resistance
- Which patients really need antibiotics?
- Strategies to reduce antibiotic prescribing
- Herbal medicines as alternatives to antibiotics?
  Ongoing trials:
  - ATAFUTI
  - GRAPHALO
  - RUTI
  - HATRIC
- How to prioritise which herbs to research in future clinical trials?
What was the world like before antibiotics?

- My great-grandfather was a doctor in 1908 – 1941
- My grandfather was a doctor in 1936 – 1979
- Before introduction of antibiotics (1940s), it was “normal” for patients in the UK to die from sepsis, endocarditis
- How was it in China?
Antibiotics are life-saving

Professor Sir Howard Florey, BMJ, 1944:

Bacteria Sensitive to Penicillin

Gram-positive.—Streptococcus pyogenes, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus viridans, Bacillus anthracis, Corynebacterium diphtheriae, Actinomyces bovis, Clostridium tetani, Cl. welchii, Cl. septique, Cl. oedematiens.

Gram-negative.—Neisseria gonorrhoeae, N. meningitidis.
Which patients most benefitted from the introduction of antibiotics?

• Severe infections:
  – Sepsis
  – Endocarditis
  – Meningitis
  – Infected wounds
  – Gonorrhoea

• NOT patients with mild, self-limiting infections (otitis, bronchitis, sinusitis, etc...)
Antibiotics are a precious and limited resource

• Very few new antibiotics have been developed in the last 20 years

• There is very little incentive for drug companies to develop new antibiotics

• We must not waste them by using them for patients who do not need them

• Otherwise we face the prospect of returning to the world of our grandparents, where many people died of serious infectious diseases
Deaths attributable to AMR every year

- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Measles: 130,000
- Diarrhoeal disease: 1.4 million
- Cholera: 100,000–120,000
- Cancer: 8.2 million
- AMR now: 700,000 (low estimate)
- AMR in 2050: 10 million
Global Growth in antibiotic use 2000-2010

35 % increase in 10 years

Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data  
Van Boeckel  
*Lancet Infect Dis* 2014; 14: 742–50
Agricultural use

- In the UK, 50% of antibiotics used in agricultural practice
- Use is predicted to increase by 67% from 2010 to 2030:
Increase in Antibiotics

Change 2000-2010

76% of the growth in consumption was in Brazil, Russia, India, China, and South Africa

Van Boeckel Lancet ID 2014
Antibiotic consumption per person (2010)

Top 3 consumers:
- India: 12.9 billion units
- China: 10.0 billion units
- USA: 6.8 billion units

Van Boeckel, Lancet ID 2014
What are we using antibiotics for?

• In England, 74% of human antibiotics are prescribed in general practice (ESPAUR report, 2016)

• The majority are prescribed for self limiting conditions
  • Sore throats 60%
  • Acute bronchitis 60%
  • Urinary tract infection 93%
Do antibiotics help symptoms? (evidence from RCTs and systematic reviews)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Average duration before seeing a doctor</th>
<th>Average duration after seeing a doctor</th>
<th>Total duration if untreated</th>
<th>Benefit from antibiotic (hours)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis media</td>
<td>1-2 days</td>
<td>3-5 days</td>
<td>4 days</td>
<td>8-12 hours</td>
<td>18</td>
</tr>
<tr>
<td>Sore throat</td>
<td>3 days</td>
<td>5 days</td>
<td>8 days</td>
<td>12-18 hours</td>
<td>10-20</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 days</td>
<td>7-10 days</td>
<td>12-15 days</td>
<td>24 hours</td>
<td>13</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>10 days</td>
<td>10-12 days</td>
<td>20-22 days</td>
<td>24 hours</td>
<td>10-20</td>
</tr>
</tbody>
</table>
High use = High resistance

Penicillin Use correlates with prevalence of penicillin-resistant *Streptococcus pneumoniae*

Antibiotic prescribing in primary care: resistance a meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio risk for resistance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antibiotic &lt;2 m</td>
</tr>
<tr>
<td>UTI (5 studies, 14,348)</td>
<td>2.5 (2.1-2.9)</td>
</tr>
<tr>
<td>RTI (7 studies, 2,605)</td>
<td>2.4 (1.4-3.9)</td>
</tr>
</tbody>
</table>

Longer duration and multiple courses were associated with higher resistance rates

Costelloe et al, *BMJ* 2010;340:c2096
Which patients really need antibiotics?

- Patients with SEVERE infections
- Coughs / chest infections: only patients with signs of pneumonia (focal crepitations, bronchial breathing, high fever)
- Green sputum?

Kaplan-Meier survival estimates for time to symptom resolution - green phlegm subgroup
Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial

Paul Little, Beth Stuart, Michael Moore, Samuel Coenen, Christopher C Butler, Maciek Godycki-Cwirko, Artur Mierzcke, Slawomir Chlabicz, Antoni Torres, Jordi Almirall, Mel Davies, Tom Schaberg, Sigvard Mølstad, Francesco Blasi, An De Sutter, Janka Kersnik, Helena Hupkova, Pia Touboul, Kerenza Hood, Mark Mullee, Gilly O’Reilly, Curt Brugman, Herman Goossens, Theo Verheij, on behalf of the GRACE consortium

Summary

Background Lower-respiratory-tract infection is one of the most common acute illnesses managed in primary care. Few placebo-controlled studies of antibiotics have been done, and overall effectiveness (particularly in subgroups such as older people) is debated. We aimed to compare the benefits and harms of amoxicillin for acute lower-respiratory-tract infection with those of placebo both overall and in patients aged 60 years or older.

Methods Patients older than 18 years with acute lower-respiratory-tract infections (cough of 128 days’ duration) in whom pneumonia was not suspected were randomly assigned (1:1) to either amoxicillin (1 g three times daily for 7 days) or placebo by computer-generated random numbers. Our primary outcome was duration of symptoms rated “moderately bad” or worse. Secondary outcomes were symptom severity in days 2–4 and new or worsening symptoms. Investigators and patients were masked to treatment allocation. This trial is registered with EudraCT (2007-001586-15), UKCRN Portfolio (ID 4175), ISRCTN (52261229), and FWO (G.0274.08N).

Findings 1038 patients were assigned to the amoxicillin group and 1023 to the placebo group. Neither duration of symptoms rated “moderately bad” or worse (hazard ratio 1.06, 95% CI 0.96–1.18; p=0.229) nor mean symptom severity (1.69 with placebo vs 1.62 with amoxicillin; difference –0.07 [95% CI –0.15 to –0.007]; p=0.074) differed significantly between groups. New or worsening symptoms were significantly less common in the amoxicillin group than in the placebo group (162 [15.9%] of 1021 patients vs 194 [19.3%] of 1006; p=0.043; number needed to treat 30). Cases of nausea, rash, or diarrhoea were significantly more common in the amoxicillin group than in the placebo group (number needed to harm 21, 95% CI 11–174; p=0.025), and one case of anaphylaxis was noted with amoxicillin. Two patients in the placebo group and one in the amoxicillin group needed to be admitted to hospital; no study-related deaths were noted. We noted no evidence of selective benefit in patients aged 60 years or older (n=595).

Interpretation When pneumonia is not suspected clinically, amoxicillin provides little benefit for acute lower-respiratory-tract infection in primary care both overall and in patients aged 60 years or more, and causes slight harms.
Strategies to reduce antibiotic use

• Prevent infections (hand-washing etc)
• Delayed prescribing
• Symptom relief
• Herbal medicines?
Prevention of infections

• PRIMIT study: digital intervention to promote hand-washing in the UK

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RTI at 4 months</td>
<td>51%</td>
<td>59%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any RTI (in household)</td>
<td>44%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Lancet* 2015; 386: 1631–39

An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial

Prof Paul Little, FMedSci, Beth Stuart, PhD, Prof F D R Hobbs, FMedSci, Prof Mike Moore, FRCP, Jane Barnett, BA, Deborah Popoola, MSc, Karen Middleton, Joanne Kelly, MSc, Mark Mullee, MSc, Prof James Raftery, PhD, Guiqing Yao, PhD, Prof William Carman, PhD, Douglas Fleming, PhD, Helen Stokes-Lampard, PhD, Ian Williamson, MRCP, Judith Joseph, PhD, Sascha Miller, PhD, Prof Lucy Yardley, PhD

Published: 06 August 2015
Delayed prescribing

• Its easy, but needs to be done properly

• 6 Rs: (mostly simply good practice!):
  – Reassurance
  – Reasons (not to use antibiotics - side effects/allergy/AMR)
  – Relief: support paracetamol
  – Realistic natural history (total: 1/2 week (OM), 1 wk (throat), 2 wks (sinus) 3 wks (chest); or average duration after the consultation: 3, 5, 7, 10 days)
  – Reinforce key message:
    » **ONLY use if getting worse or not even STARTING to settle in the expected average time**
  – Rescue (Safety netting)
Delayed antibiotics for respiratory infections

Geoffrey KP Spurling, Chris B Del Mar, Liz Dooley, Ruth Foxlee, Rebecca Farley

First published: 30 April 2013

Editorial Group: Cochrane Acute Respiratory Infections Group

DOI: 10.1002/14651858.CD004417.pub4

10 studies:

<table>
<thead>
<tr>
<th>Antibiotic use</th>
<th>Patient Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate antibiotics</td>
<td>93%</td>
</tr>
<tr>
<td>Delayed prescription</td>
<td>32%</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>13%</td>
</tr>
</tbody>
</table>
Symptom relief: PIPS study

- In RTIs, Ibuprofen did not help when added to paracetamol except in children and in patients with chest infections
- Ibuprofen increased reconsultations
- Steam did not help

Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial

BMJ 2013; 347 doi: https://doi.org/10.1136/bmj.f6041

Paul Little general practitioner and professor of primary care research, Michael Moore general practitioner and reader in primary care, Joanne Kelly senior trial manager, Ian Williamson general practitioner and senior lecturer in primary care, Geraldine Leydon social scientist, principal research fellow, Lisa McDermott research fellow, Mark Mullee statistician, director research design service, Beth Stuart research fellow, on behalf of the PIPS investigators

University of Southampton, Alderwood Health Centre, Southampton SO16 5ST, UK
Could herbal medicines help to reduce antibiotic use?

- **Respiratory tract infections:**
  - *Andrographis paniculata*: systematic review, qualitative study, pilot trial
  - *Pelargonium sidoides*: HATRIC trial

- **Urine infections:**
  - *Arctostaphylos uva-ursi*: ATAFUTI trial
  - TCM: RUTI trial
Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis

Xiao-Yang Hu¹ *, Ruo-Han Wu², Martin Logue¹, Clara Blondel³, Lily Yuen Wan Lai¹, Beth Stuart¹, Andrew Flower¹, Yu-Tong Fei², Michael Moore¹, Jonathan Shepherd⁴, Jian-Ping Liu², George Lewith†

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
**Andrographis paniculata** for symptomatic relief of acute respiratory tract infections

- 33 trials, comprising 7175 patients
- 5 comparison groups:
  - *A. paniculata* vs usual care (n=12)
  - *A. paniculata* plus usual care vs usual care (n=9)
  - *A. paniculata* vs other herbal interventions (n=5)
  - *A. paniculata* vs placebo (n=4)
  - *A. paniculata* in pillule vs in tablet (n=3)
### Andrographis vs Placebo

#### Symptom severity improvement

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>A. paniculata mono</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>4.1.1 Overall symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melchior, 2000</td>
<td>2.97</td>
<td>3.47</td>
<td>89</td>
</tr>
<tr>
<td>Melchior, 2000 (pilot)</td>
<td>3.13</td>
<td>2.69</td>
<td>23</td>
</tr>
<tr>
<td>Saxena, 2010</td>
<td>66.65</td>
<td>59.26</td>
<td>112</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>224</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.21; Chi² = 14.64; df = 2 (P = 0.0007); I² = 86%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.38 (P = 0.02)</td>
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</tr>
</tbody>
</table>

| 4.1.2 Cough                |                    |         |                      |                    |         |       |        | IV, Random, 95% CI                     |
| Caceres, 1999              | 2.02               | 1.62    | 79                   | 2.67               | 2.14    | 79    | 10.9%  | -0.34 [-0.66, -0.03]                  |
| Caceres, 1999              | 1.71               | 1.24    | 79                   | 2.52               | 1.64    | 79    | 10.8%  | -0.55 [-0.87, -0.24]                  |
| Melchior, 2000 (pilot)     | 0.26               | 0.45    | 23                   | 0.22               | 0.42    | 23    | 7.9%   | 0.09 [-0.49, 0.67]                    |
| Melchior, 2000 (pilot)     | 0.17               | 0.39    | 23                   | 0.17               | 0.39    | 23    | 7.9%   | 0.00 [-0.58, 0.58]                    |
| Saxena, 2010               | 23.26              | 17.08   | 89                   | 35.91              | 15.92   | 99    | 11.1%  | -0.76 [-1.06, -0.47]                  |
| Subtotal (95% CI)          | 293                |         |                      | 303                |         |       | 48.6%  | -0.39 [-0.67, -0.10]                  |
| Heterogeneity: Tau² = 0.06; Chi² = 10.85; df = 4 (P = 0.03); I² = 63% |        |         |                      |                   |         |       |        | IV, Random, 95% CI                     |
| Test for overall effect: Z = 2.65 (P = 0.008) |        |         |                      |                   |         |       |        | IV, Random, 95% CI                     |

| 4.1.3 Sore throat          |                    |         |                      |                    |         |       |        | IV, Random, 95% CI                     |
| Caceres, 1999              | 1.63               | 1.11    | 79                   | 3.1                | 1.38    | 79    | 10.6%  | -1.17 [-1.51, -0.83]                  |
| Saxena, 2010               | 15                 | 17.02   | 82                   | 33.99              | 17.55   | 74    | 10.6%  | -1.09 [-1.43, -0.76]                  |
| Subtotal (95% CI)          | 161                |         |                      | 153                |         |       | 21.2%  | -1.13 [-1.37, -0.89]                  |
| Heterogeneity: Tau² = 0.00; Chi² = 0.09; df = 1 (P = 0.76); I² = 0% |        |         |                      |                   |         |       |        | IV, Random, 95% CI                     |
| Test for overall effect: Z = 9.28 (P < 0.000001) |        |         |                      |                   |         |       |        | IV, Random, 95% CI                     |

Total (95% CI) Total (95% CI) 678 677 100.0%  -0.63 [-0.89, -0.36]

Heterogeneity: Tau² = 0.14; Chi² = 47.17; df = 9 (P < 0.00001); I² = 81%
Test for overall effect: Z = 4.68 (P < 0.000001)
Test for subgroup differences: Chi² = 15.58, df = 2 (P = 0.00004), I² = 87.2%
Conclusions

• *A. paniculata* appears beneficial and safe for relieving RTI symptoms and shortening time to symptom resolution

• This evidence is inconclusive

• Limited methodological quality

• Heterogeneous population, setting, interventions

• Lack of consistent standard diagnostic criteria

• Poor reporting, e.g. Informed consent; Manufacturing or quality control details or whether the products were GMP certified
GRAPHALO study

- *Andro*GRAPH*His pAnicuLata* in the treatment Of adults with Acute Respiratory Tract Infections (ARTIs): a double blind randomised placebo controlled feasibility study
  - 2 groups of 30 patients
  - Capsule andrographis (whole plant), 300 mg, 3 capsules 4 times daily versus matching placebo
  - Outcomes: recruitment feasibility; primary outcome: proportion of symptom improvement, side effects, antibiotic prescription, symptom diary for 14d; EQ-5D

- Interviews with GPs regarding their views on herbal medicine for acute RTI in primary care
Pelargonium sidoides

• Cochrane review:
  – 3 trials of efficacy for acute bronchitis in adults
  – Liquid preparation was effective, tablets were not

Pelargonium sidoides extract for treating acute respiratory tract infections

Antje Timmer, Judith Günther, Edith Motschall, Gerta Rücker, Gerd Antes, Winfried V Kern
First published: 22 October 2013
Editorial Group: Cochrane Acute Respiratory Infections Group
DOI: 10.1002/14651858.CD006323.pub3
HATRIC trial

- **Herbal Alternative Treatment for lower Respiratory tract Infections with Cough in adults**
- Mixed methods feasibility study: double blind, randomised placebo controlled trial
- 4 groups of 40 patients:
  - Liquid *Pelargonium sidoides* root extract, 30 drops 3x daily versus matching placebo
  - Tablets of *Pelargonium sidoides* root extract, 20mg 3x daily, versus placebo
- Outcomes: recruitment feasibility; primary outcome (antibiotic prescription, symptom diary for 28d); EQ-5D
- Interviews with participants and GPs regarding their views on herbal medicine for RTI in primary care
HATRIC trial

- Participants will be identified in primary care when presenting with acute cough illness.
- We will encourage no antibiotics or a delayed antibiotic prescription.
- GPs will be allowed to offer an immediate antibiotic prescription, if they feel it is really needed, to maximise recruitment and generalisability.
- Funding: NIHR, Industrial sponsorship.
Urinary Tract Infections (UTIs)

- UTIs are common: 40-50% of women experience a UTI
- 20-30% will have a second infection
  - 25% of these will have recurrent infections (≥3 episodes in 12 months)
- The symptoms associated with UTIs are distressing.
  - usually settle without complications within 3 - 4 days
  - but antibiotics shorten the duration of symptoms
- A delayed prescription strategy may help, but is unlikely to be accepted without better symptom relief
- Prophylactic antibiotics are given for recurrent UTIs, but resistance is increasing
Alternative Treatments for Adult Female Urinary Tract Infection: a randomised controlled trial

PI: Dr Mike Moore, University of Southampton

Prof Paul Little, Prof George Lewith, Prof Alastair Hay, Prof Simon Gibbons, Jeanne Trill, Dr Merlin Willcox
Arctostaphylos uva-ursi (Bearberry)

- First documented in *The Physicians of Myddfai*, a 13th century Welsh herbal
- Commonly prescribed by herbalists in UK for UTIs
- Available over the counter in pharmacies in the UK and Germany
Research question

- P: In adult women with suspected UTI
- I: does Uva-Ursi, or ibuprofen, or a combination of both
- C: compared to placebo
- O: provide relief from urinary symptoms?
Trial design: a factorial RCT

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uva-ursi</td>
<td>Group 1</td>
<td>Group 3</td>
</tr>
<tr>
<td>Placebo</td>
<td>Group 2</td>
<td>Group 4</td>
</tr>
</tbody>
</table>

- Patients were advised to take the study medicines for 5 days:
  - Ibuprofen 400mg tds
  - Uva Ursi, 3 caps 3x daily (as a 20% arbutin extract, prepared to GMP and IMP standards)
- A matching placebo (brown rice flour and some brown malt colouring + 30 mg Spirulina to produce a herbal flavour)
- Quality control: extraction of materials from each batch and fingerprinting by NMR spectroscopy and mass spectrometry
Trial population

- Adult women (18-70) presenting to primary care with suspected lower urinary tract infection
- Study sites: 60 primary health care centres in the UK
- Recruitment: GPs or experienced nurses invited suitable patients to take part in the trial
- Women prepared to accept a delayed antibiotic prescription for their symptoms were consented for randomisation to one of the four treatment groups.
“Rescue” treatment

• NHS prescription was issued for an antibiotic (clinician’s choice, according to local guidelines)

• If symptoms failed to settle or worsened, participants were instructed to collect and commence their delayed antibiotic prescription after 3-5 days.
Outcome assessment

- **Primary outcome:**
  - Symptom severity at day 2-4 recorded in a validated self report symptom diary

- **Secondary outcomes:**
  - Use of antibiotics to treat UTI
  - Re-consultation in one month with UTI
Challenges

• Finding a manufacturer who can produce herb to GMP standards

• Start was delayed by >12 months, cost increased by £50000

• Ibuprofen manufacturer lost its license
Challenges to recruitment

• Many patients felt they had waited long enough for antibiotics and didn’t want to wait longer

• GPs short of time – difficult to recruit patients during a “duty doctor” session in 5-min appointments
The RUTI trial

A double blinded, randomised, placebo controlled feasibility study exploring the possible role of Chinese herbal medicine in the treatment of Recurrent Urinary Tract Infections.

Dr Andrew Flower
Prof George Lewith
Dr Kim Harman
Objectives

Primary objectives:

- Feasibility of delivering CHM in UK primary care
- Safety of CHM
- Exploratory estimates of effect size on reducing the frequency and severity of infection
- Impact on antibiotic use
RUTI Trial

• Groups
  – Standardised active herbs vs standardised placebo, delivered by GP
  – Individualised active herbs vs individualised placebo, administered by practitioners of Chinese herbal medicine

• Aims to explore:
  – Differences between active and placebo herbs (specific effect)
  – Differences between standardised and individualised herbs
  – A comparison between contextual effects of CHM via a GP clinic consultation versus a CAM clinic consultation
Recruitment

- 62 women recruited (31 in each arm)
- Slow recruitment via primary care network due to using medical record search based on symptoms and signs
- Individualised arm - self referral
- 14/31 (45%) of women in Individualised arm taking continuous antibiotics for RUTIs vs 4/31 (13%) of standardised arm.
- In Individualised group 9/31 (29%) withdrew or were lost to follow up compared to 16/31(52%) in the standardised group.
- Placebo control in individualised arm failed due to misunderstanding of herbal pharmacy...who added active herbs to the placebo mix!
**Formulae**

**Standardised formulae**

**Acute formula:**
- Bai Hua She She Cao
- Huang Bai
- Jin Qian Cao
- 4 x 0.4g capsules q.d.

**Preventative formula:**
- Huang Qi
- Ku Shen
- Wu Yao
- 4 x 0.4g capsules b.d.

**Individualised formula - example**
- Bai Hua She She Cao 20
- Ban Zhi Lian 15
- Bai Jiang Cao 15
- Pu Gong Ying 15
- Ku Shen 9
- Huang Qin 12
- Shi Wei 15
- Jin Qian Cao 15
- Qu Mai 15
- Bian Xu 12
- Wu Yao 9
- Yi Mu Cao 15
- Gan Cao 6

Formula provided as herbal granules and made into a decoction.
Initial feasibility findings

- It is possible to do a CTIMP trial on CHM in the UK
- Recruitment to CHM trials via primary care is challenging
- Descriptive statistics suggest positive reduction in symptoms and decrease in antibiotic use
How to prioritise herbal remedies and TCM for future clinical trials?

- There are thousands of herbal medicines
- There is little money for conducting trials
- Many trials produce a “negative” outcome

-> How to maximise chances of picking the best remedy for a trial?
  - Plant(s) and plant part(s)
  - Preparation
  - Dosage
Do ethnobotanical and laboratory data predict clinical safety and efficacy of anti-malarial plants?

Merlin Willcox¹,²*, Françoise Benoit-Vical¹,³,⁴, Dennis Fowler¹, Geneviève Bourdy⁵,⁶, Gemma Burford¹,⁷, Sergio Giani⁸, Rocky Grazioso⁹, Peter Houghton¹⁰, Milijaona Randrianarivelojosia¹¹, Philippe Rasoanaivo¹²

Abstract

Background: Over 1200 plant species are reported in ethnobotanical studies for the treatment of malaria and fevers, so it is important to prioritize plants for further development of anti-malarials.

Methods: The “RITAM score” was designed to combine information from systematic literature searches of published ethnobotanical studies and laboratory pharmacological studies of efficacy and safety, in order to prioritize plants for further research. It was evaluated by correlating it with the results of clinical trials.

Results and discussion: The laboratory efficacy score correlated with clinical parasite clearance ($r_s=0.7$). The ethnobotanical component correlated weakly with clinical symptom clearance but not with parasite clearance. The safety component was difficult to validate as all plants entering clinical trials were generally considered safe, so there was no clinical data on toxic plants.

Conclusion: The RITAM score (especially the efficacy and safety components) can be used as part of the selection process for prioritising plants for further research as anti-malarial drug candidates. The validation in this study was limited by the very small number of available clinical studies, and the heterogeneity of patients included.
The “RITAM” score

• Components:
  – 1: Frequency of citation in ethnobotanical studies (weighted according to quality of study)
  – 2: Efficacy *in vitro* and *in vivo*
  – 3: Safety

• detailed scoring system was drafted and revised by a multidisciplinary working group
Does the score correlate with clinical effectiveness?

<table>
<thead>
<tr>
<th>Remedy</th>
<th>RITAM score</th>
<th>Clinical results</th>
<th>Study characteristics</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnobotanical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parasite clearance d7 (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever clearance d7 (%)</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Side effects (%)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>ACR d14 (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean age (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Geometric mean parasitaemia d0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Artemisia annua L. (Asteraceae)</strong></td>
<td>19.9</td>
<td>74%</td>
<td>86%</td>
<td>72</td>
</tr>
<tr>
<td>aerial parts infusion</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vernonia amygdalina Delile (Asteraceae)</strong> leaf decoction</td>
<td>17.0</td>
<td>32%</td>
<td>67%</td>
<td>33</td>
</tr>
<tr>
<td><strong>Argemone mexicana L. (Papaveraceae)</strong></td>
<td>14.9</td>
<td>21%</td>
<td>74%</td>
<td>231</td>
</tr>
<tr>
<td>leaf decoction</td>
<td>1.9</td>
<td></td>
<td>7%</td>
<td>10</td>
</tr>
<tr>
<td><strong>Cochlospermum planchonii Hook. f. ex Planch. (Bixaceae)</strong> root decoction</td>
<td>6.0</td>
<td>52%</td>
<td>62%</td>
<td>46</td>
</tr>
<tr>
<td><strong>Combretum micranthum G. Don (Combretaceae)</strong> mixtures</td>
<td>0.5</td>
<td>14%</td>
<td>79%</td>
<td>78</td>
</tr>
<tr>
<td><strong>Data from these two studies were pooled for the analysis.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Correlations are absent / weak

- Ethnobotanical score
  - did not correlate with parasite clearance \( (r_s = 0) \)
  - slight correlation with symptom clearance \( (r_s = 0.5) \).

- Efficacy score
  - Correlated with parasite clearance \( (r_s = 0.6) \)

- Safety score
  - Unable to assess
Discussion

• It may be possible to improve the scoring system...
• This scoring system could be adapted for other diseases
• But is there any point?
• We need better methods to predict clinical effectiveness!
The RTO
(Retrospective treatment-outcome study)

Ask patients – or relatives – about treatment recently used, and health outcome of this treatment.

⇒ which treatment is followed by the best or the worst outcomes?

= “Epidemiological ethnopharmacology”
The RTO is novel because:

• Patients, not healers, are interviewed
• Information is collected on outcomes
• Statistical methods are used to explore correlations between treatments and outcomes
Are the most commonly used plants also the most effective?

Population survey

Recorded treatments

Recorded outcomes

Disease

1

2

3

Statistical analysis
(full tables included 66 plants and 166 recipes for 952 cases).

<table>
<thead>
<tr>
<th>Plant</th>
<th>Number who used</th>
<th>Number Improved</th>
<th>Number Failed</th>
<th>% Improved (95% CI)</th>
<th>P (Fisher exact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argemone mexicana</td>
<td>30</td>
<td>30</td>
<td>0</td>
<td>100% (88-100)</td>
<td>reference</td>
</tr>
<tr>
<td>Carica papaya</td>
<td>33</td>
<td>28</td>
<td>5</td>
<td>85% (68-95)</td>
<td>0.05</td>
</tr>
<tr>
<td>Anogeissus leiocarpus</td>
<td>33</td>
<td>27</td>
<td>6</td>
<td>82% (64-93)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Reverse Pharmacology

- Took 6 years to develop an “improved traditional phytomedicine” in Mali
- Cost about 0.4m Euros
- End product is easily affordable and available
Could the RTO be modified for TCM?

- We could ask patients which formulae they used or which practitioners they consulted.

- The practitioners associated with the best outcomes could discuss then be invited to take part in a consensus process on the best remedies (e.g. Delphi, Nominal group technique).
Acknowledgements

- Funders: NIHR SPCR, Pukka herbs, Schwabe
- Southampton Clinical Trials Unit
- Thank you for your kind invitation!