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**Article:**

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Title: Cost-effectiveness of antibiotic treatment of uncomplicated urinary tract infection in women

Authors: Susi Sadler¹,², Michael Holmes¹, Shijie Ren¹, Stephen Holden³, Swati Jha⁴, Praveen Thokala¹

1: School of Health and Related Research, University of Sheffield, Regent Court, Regent Road, Sheffield. S1 4DA

2: University of Exeter Medical School, University of Exeter, St Luke’s Campus, UK

3: Department of Medical Microbiology, Nottingham University Hospitals NHS Trust, QMC Campus, Derby Road, Nottingham NG7 2UH

4: Sheffield Teaching Hospitals NHS Foundation Trust, Northern General Hospital, Herries Road, Sheffield, South Yorkshire, S5 7AT

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Abstract:

**Background:** Urinary tract infections (UTIs) are one of the most common reasons for women to attend primary care. There are four different antibiotics currently recommended in England for treatment of uncomplicated UTI but little evidence on their comparative cost-effectiveness.

**Aim:** To assess the relative cost-effectiveness of the four antibiotics currently recommended in England for treatment of uncomplicated UTI in adult women.

**Design and Setting:** Adult women with signs and symptoms of uncomplicated UTI in primary care in England treated with fosfomycin, nitrofurantoin, pivmecillinam or trimethoprim.

**Method:** A decision tree economic model of the treatment pathway encompassed up to two rounds of treatment, accounting for different resistance levels. End points included recovery, persistence, pyelonephritis and/or hospitalisation. Prescription, primary and secondary care treatment and diagnostic testing costs were aggregated. Cost-effectiveness was assessed as cost per UTI resolved.

**Results:** Trimethoprim 200mg twice daily (for 3 or 7 days) was estimated to be the most cost-effective (£70 per UTI resolved) treatment where resistance was lower than 30%. However, if resistance to trimethoprim reached or exceeded 30%, fosfomycin 3g once became more cost-effective, and at greater than 35% resistance levels for trimethoprim, both fosfomycin 3g once and nitrofurantoin 100mg twice daily for 7 days appeared to be more cost-effective.

**Conclusion:** Knowing local resistance levels is key to effective and cost-effective empirical prescribing. Recent estimates of trimethoprim resistance rates are close to 50%, in which case a single 3g dose of fosfomycin is likely to be the most cost-effective treatment option.
How this fits in

Four different antibiotics are currently recommended for treatment of uncomplicated urinary tract infection in adult women. It is usual practice to treat empirically at first presentation, but no studies to date have compared the relative cost-effectiveness of these treatments, so there is little to guide clinicians in their prescribing choice. Our results suggest that if trimethoprim resistance is relatively low, trimethoprim 200mg twice daily is likely to be the most cost-effective first-line treatment (three days is currently recommended). However, more recent estimates of trimethoprim resistance rates are close to 50%, and at any level at or above 30% resistance a single 3g dose of fosfomycin is likely to be the most cost-effective option for empirical treatment.
Introduction

Urinary tract infections (UTIs) are one of the most common reasons for women to attend primary care, and are likely to affect at least half of all women in their lifetimes (1). In England in 2011, 14% of antibiotic prescriptions for community-acquired infections were for UTI (2). Nitrofurantoin, a recommended first-line UTI treatment in England with no other recommended use, was prescribed over 2.3m times in 2015 (3).

For women with suspected uncomplicated UTI, Public Health England (PHE) recommends first-line treatment with nitrofurantoin, trimethoprim or pivmecillinam. Fosfomycin or pivmecillinam are indicated where resistance risk is higher (4). In most cases, empirical treatment without urine culture is recommended so the causative organism and its antimicrobial susceptibility are unknown. In practice, trimethoprim prescribing is still very common, despite some evidence of high levels of resistance. Whilst nitrofurantoin prescribing is still growing (5), actual prescribing practice varies considerably between local areas (6).

Antibiotic resistance is a key public health threat, and good prescribing practice is essential to reducing the spread of resistance (6). The aims of antibiotic prescribing should be to ensure treatment is effective, whilst minimising cost and reducing “collateral damage” such as the emergence of multi-drug resistant pathogens. Therefore, a good understanding of the effectiveness and cost-effectiveness of the drug as well as national and local resistance levels are necessary to aid decision-making in primary care.

For clinical decision-making where several relevant treatments options are recommended, it is important to understand the comparative efficacy and cost-effectiveness of all options. Whilst clinical trials to date have made direct head-to-head comparisons between treatments, network meta-analyses (allowing direct and indirect treatment comparisons) are needed in order to understand how the different treatments compare against each other. There are two previous meta-analyses of treatments in uncomplicated UTI (7, 8) but neither include clinical outcomes for all the treatments currently recommended by PHE for the treatment of uncomplicated UTI in the England, and neither extend their findings to cost-effectiveness analysis. The aim of this study is to compare these treatments for the first time and to explore the effect of changing resistance levels for trimethoprim.
Methods

Model Structure

The perspective was the UK NHS in England. Our model was based on a decision tree model developed by McKinnell et al (9) (see Figure 1), updated to include UK-specific costs. The pathway was checked by specialist clinicians (SJ and SH).

In the model, patients were prescribed an antibiotic treatment regimen at first GP appointment. Infection responded or failed to respond to treatment, depending on whether bacteria were resistant or susceptible to the antibiotic. Persistence of symptoms resulted in a repeat GP visit and second prescription. A potential consequence of persistent infection was pyelonephritis, treated either in hospital or primary care, in line with UK practice. We assumed all patients treated in hospital had a follow-up outpatient visit. We assumed all patients treated for a second time in primary care for either persistent UTI or pyelonephritis switched to a different antibiotic for the second course, in line with PHE guidance (4).

Model timings were 9 days for the initial treatment round (the weighted average of follow-up periods in the trials used for effectiveness data) followed by 7 days for second-round treatment if in primary care or 5 days if in hospital (based on a recent UK study (10)) plus two days of outpatient treatment for pyelonephritis, giving a total of 16 days. After two treatment courses all patients were assumed to have achieved cure.

Clinical Effectiveness

Clinical cure rates were informed by a systematic review and network meta-analysis (NMA) of studies in adult women with signs and symptoms of uncomplicated UTI (see Appendix for full details). The systematic review identified 11 studies which formed a connected evidence network used in the NMA (figure 2) (11-21). The studies covered eight treatment regimens:

- Nitrofurantoin, 50mg four times a day for 7 days
- Nitrofurantoin modified release (MR), 100mg twice daily for 7 days
- Nitrofurantoin, 100mg four times a day for 3 days
- Pivmecillinam, 200mg three times a day for 7 days
- Pivmecillinam, 400mg twice daily for 3 days
- Pivmecillinam, 200mg twice daily for 7 days
- Trimethoprim, 200 mg twice daily for 7 days
- Trimethoprim, 200mg once
- Fosfomycin 3g once

[INSERT FIGURE 2]
A random (treatment) effects model with a logit link function was used to allow for heterogeneity in treatment effects between studies. The model assumed a fixed (i.e. unconstrained) baseline effect in each study so that treatment effects were estimated within study and combined across studies. The network meta-analysis model fitted the data well, with a total residual deviance of 20.47 being close to the number of data points included in the analysis, 21. The between study standard deviation was estimated to be 0.21 (95% CrI: 0.01, 0.68), implying mild heterogeneity in treatment effects between studies. Clinical cure rates for each of these regimens derived from the NMA are reported in Table 1.

[INSERT TABLE 1]

The ratio of resistant to sensitive cure rate (0.63) was applied to overall cure rates from the NMA to estimate sensitive and resistant cure rates for each regimen (see Table 3). This ratio was taken from a UK prospective cohort study which found significant differences in clinical cure rates between those infected with trimethoprim-resistant or susceptible organisms (22) and assumed to be consistent across all treatments. Resistance rates to each drug were taken from the ECO-SENS II study (23) which provided UK-specific resistance rates for *E. coli* only. Table 2 summarises the cure rates and resistance rates used in the base case.

**Other model parameters**

GP appointment cost was taken from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2014 (24). Dipstick test cost was taken from a Health Technology Assessment by Little et al (25). The Healthcare Resource Groups National Schedule of Reference Costs (26) was used for the cost of pyelonephritis hospitalisation, pyelonephritis outpatient visits and urine analysis tests. The cost of nitrofurantoin, trimethoprim and pivmecillinam were taken from the British National Formulary (27). The cost of fosfomycin was provided by the manufacturer.

As in McKinnell *et al* (9), we assumed that 4% of those not achieving clinical cure at first treatment develop pyelonephritis, and 20% of those with pyelonephritis require hospitalisation. Model parameters are summarised in Table 2.

[INSERT TABLE 2]

**Analysis**

The outcome was cost per UTI resolved. No incremental analysis was carried out as all treatments assessed are currently recommended for use in the NHS in England.

**Sensitivity Analysis**

To account for uncertainty, probabilistic sensitivity analysis (PSA) was carried out using 2,000 sets of model results. Parameters were sampled from the following distributions: beta (resistance rates), gamma (health service costs) and the posterior distribution of the NMA (clinical cure rates). Resistance
to nitrofurantoin (0%) and prescription costs were fixed. PSA results were illustrated on a cost-effectiveness plane.

Deterministic Analyses were carried out to test the sensitivity of model outcomes to

a) **Incorporation of resistance rates to bacteria other than *E. Coli***:
Because nitrofurantoin, despite having 0% resistance rate for *E. Coli* is non-effective against some strains of Klebsiella and Enterobacter and most strains of Proteus. Resistance rates were estimated using the distribution of bacterial isolates in uncomplicated UTI for the UK and Ireland taken from an earlier ECO-SENS report (28) combined with (non-UK-specific) resistance rates to each of these pathogens from the original ECO-SENS results (29) and for *E. Coli* from the ECO-SENS-II results (23).

b) **updated estimates of *E. coli* resistance**
Recently published by Kahlmeter *et al.* (30) (trimethoprim-46.0%, nitrofurantoin-5.6% and pivmecillinam-4.8%). Results are from a single centre but suggest increasing trimethoprim resistance.

c) **estimated cure rates for 3-day regimens for trimethoprim and nitrofurantoin**
Since 3-day courses of trimethoprim and nitrofurantoin are recommended by PHE, whereas 7-day regimens are reported in the RCTs. Using the relative risk of treatment failure from Goettsch *et al.* (52) between 3- and 7-day trimethoprim (0.87) and nitrofurantoin (0.64) regimens. Prescription costs were reduced accordingly.

In addition a threshold analysis was carried out varying the level of trimethoprim resistance between 15% and 50% in 5% increments to determine whether the choice of most cost-effective treatment regimen is affected by increasing trimethoprim resistance.
Results

Probabilistic economic model results

Central estimates from the PSA in terms of costs, health outcomes and cost per UTI resolved are reported in Table 3. Trimethoprim 200mg twice daily for 7 days was estimated to be the most cost-effective treatment regimen at £70 per UTI resolved, followed by fosfomycin 3g once at £78 per UTI resolved. Trimethoprim 200mg twice daily for 7 days also had the highest probability of being the most cost effective treatment (59% of PSA runs).

Figure 3 (top left panel) shows the probabilistic average total cost and number of UTIs resolved per 1,000 patients for each treatment regimen. A group of three treatments (trimethoprim 200mg twice daily for 7 days, fosfomycin 3g once and nitrofurantoin 100mg twice daily for 7 days) stand out as being most effective for resolution (approximately 850 resolved per 1,000) and amongst the lowest total cost (£60,000-£70,000). The other panels of figure 3 illustrate the uncertainty around the central estimates of cost-effectiveness, showing the results of each of the 2,000 probabilistic model runs for each treatment regimen.

Deterministic Sensitivity Analysis

Results are summarised in Table 3. Scenario a) had the expected effect of reducing the apparent cost-effectiveness of nitrofurantoin relative to the other treatments. Scenario b) reduced the cost-effectiveness for all treatments with increased resistance, as expected. In particular, the cost-effectiveness of trimethoprim reduced significantly (from a deterministic value of £69 to £91 per UTI resolved for trimethoprim 200mg twice daily 7 days), making trimethoprim 200mg twice daily no longer the most cost-effective treatment. Scenario c) reduced the cost-effectiveness of both treatments, however, trimethoprim 200mg twice daily was still considered the most cost-effective treatment (up from £69 to £73 per UTI resolved).

The threshold analysis on trimethoprim resistance showed that up to 25% resistance, trimethoprim 200mg twice daily for 7 days remained the most cost-effective option. However, at 30% resistance fosfomycin 3g once became more cost-effective, and at greater than 35% resistance levels both fosfomycin 3g once and nitrofurantoin 100mg twice daily for 7 days appeared to be more cost-effective than trimethoprim 200mg twice daily.

[INSERT TABLE 3]

[INSERT FIGURE 3]
Discussion

Summary

The highest clinical cure rate was estimated to be with trimethoprim 200mg twice daily. In general, higher cure rates were seen with 7-day regimens compared with 3-day regimens, however, treatment effects were not significantly different.

Trimethoprim 200mg twice daily for 7 days was estimated to be the most cost-effective treatment regimen, followed by fosfomycin 3g once. In line with best practice for antimicrobial stewardship, 7-day trimethoprim prescriptions are now falling, with almost 50% of prescriptions being for the recommended 3-day courses (31). Due to lack of trial evidence, we estimated the impact of reducing the course length of both trimethoprim and nitrofurantoin from 7 to 3 days. This did not alter the fact that trimethoprim 200mg twice daily was the most cost-effective treatment but nitrofurantoin (MR) 100mg twice daily became less cost-effective than both pivmecillinam 200mg twice daily for 7 days and nitrofurantoin 50mg four times a day for 7 days.

The base case model results account only for resistance in E. coli. However, other species are known to have higher levels of resistance to all the antibiotics we assessed. In particular, nitrofurantoin is non-effective against a number of Klebsiella, Enterobacter and Proteus strains. When we accounted for resistance in other species, the cost-effectiveness was reduced (especially for nitrofurantoin) but the ranking of treatments was unaffected.

Recent work points to considerable increases in the resistance of common uropathogens. Kahlmeter et al. observed increased rates of resistance of E. coli in uncomplicated UTI in the UK to nitrofurantoin, pivmecillinam and trimethoprim (30). At this higher level of resistance, and even at resistance levels as low as 30%, trimethoprim 200mg twice daily was no longer the most cost-effective treatment. Assuming fosfomycin resistance is unchanged (it has been rarely prescribed in the UK to date and there is some evidence that resistance rates, at least to E. coli remain stable, even in countries with systematic fosfomycin use (32)), fosfomycin 3g once would be the most cost-effective option for empirical treatment, followed by nitrofurantoin (MR) 100mg twice daily for 7 days.

Strengths and limitations

We acknowledge several limitations in this analysis. There was the lack of evidence available to inform differential cure rates with resistant versus sensitive bacteria strains. Due to a lack of RCT evidence, we estimated the differential rates from the ratio of sensitive to resistant cure in a UK cohort study which investigated trimethoprim only (11), based on expert clinical opinion. The results of the study conformed to prior expectations: i.e. that cure rates would be lower in matched patients infected with organisms resistant to the treatment antibiotic. The derivation also reflects the fact that clinical resolution occurs in a proportion of untreated patients (previous studies showed rates from 25 to 42%) (12) (13) (14) and that when patients are treated with an antimicrobial agent to which the infecting uropathogen is resistant on laboratory testing, it is generally expected that cure rates will be higher than with placebo.
The study design also had a number of important strengths: The context was the UK health service; laboratory testing and clinical management was in accordance with established practice and national recommendations that remain broadly the same at the present time; patients with host factors that could bias the data were excluded, such as structural abnormalities of the renal tract, pregnancy and recurrent UTIs.

Comparison with existing literature

Le and Miller (33) carried out a similar analysis in a US setting, comparing trimethoprim-sulfamethoxazole (TMP-SMX - the recommended first line treatment) with fluoroquinolones (recommended above a 10-20% resistance threshold) and subsequently, McKinnel et al. compared nitrofurantoin to these two treatments, also in a US setting. Increasing TMP-SMX resistance was shown to increase mean costs of UTI treatment such that when resistance to TMP-SMX exceeded 22%, fluoroquinolones were the less costly option (33) and that when fluoroquinolone resistance exceeded 12%, nitrofurantoin was the least costly option (9). Similarly, our study showed trimethoprim to be the most cost-effective option compared with the other treatments recommended in the England, as long as resistance was below 30%. Above this threshold fosfomycin became more cost-effective, and above 35% nitrofurantoin was also preferred.

Implications for research and/or practice

Several pieces of additional evidence would enhance our model estimates, were they available. Very few studies analysed both in vitro susceptibility and clinical response, meaning differential cure rates for sensitive and resistant strains had to be estimated. Similarly, recent, multi-centre antimicrobial resistance surveillance data from all patients with uncomplicated UTI, including those ordinarily treated empirically without sampling would be very valuable.

Whilst this analysis confirmed that all four currently recommended treatments for uncomplicated UTI in England are effective in treating the condition, in terms of relative cost-effectiveness, trimethoprim 200mg twice daily for either 3 or 7 days appeared to be the preferable treatment. However, evidence of rapid increases in trimethoprim resistance in the UK, coupled with the potential for local level variation, casts doubt on its cost-effectiveness in empirical treatment of uncomplicated UTI. Assuming resistance to fosfomycin has not increased since 2008, fosfomycin 3g once appears to be the most cost-effective option for empirical treatment given potentially high levels of trimethoprim resistance.

The four drugs examined all have a relatively low propensity to cause *Clostridium difficile* infection and it is likely that acquired resistance to nitrofurantoin, pivmecillinam and fosfomycin, despite widespread global use for many years, has not readily emerged due to their rapid absorption and minimal impact on the human gastrointestinal tract flora. These properties make them ideal treatments for uncomplicated UTI.

Our modelling estimates suggest that fosfomycin 3g once is likely to be the most cost-effective choice for first-time empirical treatment of uncomplicated UTI in adult women, unless trimethoprim resistance
is believed to be below 30% and that where resistance exceeds 35% nitrofurantoin (MR) 100mg twice daily would also be a cost-effective choice.

**Additional information**
This work was funded by Profile Pharma Ltd, a subsidiary of Zambon SpA. We would like to acknowledge Gina Craig and Alex Black of Profile Pharma Ltd for input into the project, including providing the price of fosfomycin.
Tables and figures

FIGURE 1 Illustrating the model pathway from first presentation in primary care, until up to two rounds of treatment have been given (after which it is assumed that all patients achieve cure).
FIGURE 2 Diagram illustrating the network of trials identified in the systematic review and included in the network meta-analysis to estimate relative effectiveness of different treatment regimens.
FIGURE 3: Cost effectiveness plane comparing all treatment regimens: Probabilistic average cost versus number of UTIs resolved per 1,000 patients for each treatment regimen and individual results of 2000 probabilistic model runs for each treatment regimen, illustrating the range of uncertainty around cost-effectiveness of each treatment.

a = nitrofurantoin 100mg 4 times a day x3, b = trimethoprim 200mg once, c = pivmecillinam 400mg twice daily x3, d = pivmecillinam 200mg three times a day x7, e = nitrofurantoin 50mg four times a day
x 7, f = pivmecillinam 200mg twice daily x 7, g = nitrofurantoin 100mg twice daily x 7, h = fosfomycin 3g once, i = trimethoprim 200mg twice daily x 7
TABLE 1: NMA results; odds ratios for clinical cure and posterior mean values for clinical cure rates used in the cost-effectiveness model along with derived values for sensitive and resistant cure rates and resistance rates. None of the treatment effects were statistically significantly different at a conventional 5% level and pairwise comparisons indicated that no one treatment was significantly more effective than any other.

<table>
<thead>
<tr>
<th>Medication Description</th>
<th>Odds ratio</th>
<th>95% credible interval</th>
<th>Posterior mean cure rate</th>
<th>Resistant cure rate</th>
<th>Sensitive cure rate</th>
<th>Resistance rate from ECOSENS II (23)</th>
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</thead>
<tbody>
<tr>
<td>Fosfomycin, 3g once</td>
<td>1</td>
<td>-</td>
<td>84.2%</td>
<td>53.1%</td>
<td>84.3%</td>
<td>0.5%</td>
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<td>Nitrofurantoin, 50mg 4 times a day for 7 days</td>
<td>0.82</td>
<td>0.30-2.18</td>
<td>79.9%</td>
<td>50.3%</td>
<td>79.9%</td>
<td>0.0%</td>
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<td>Nitrofurantoin (MR), 100mg twice daily for 7 days</td>
<td>1.15</td>
<td>0.55-2.56</td>
<td>85.0%</td>
<td>53.6%</td>
<td>85.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Nitrofurantoin, 100mg 4 times a day for 3 days</td>
<td>0.34</td>
<td>0.06-2.05</td>
<td>62.4%</td>
<td>39.3%</td>
<td>62.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pivmecillinam, 200mg 3 times a day for 7 days</td>
<td>0.63</td>
<td>0.16-2.57</td>
<td>75.0%</td>
<td>47.4%</td>
<td>75.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Pivmecillinam, 400mg twice daily for 3 days</td>
<td>0.47</td>
<td>0.14-1.57</td>
<td>69.8%</td>
<td>44.2%</td>
<td>70.1%</td>
<td>1.0%</td>
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<td>Pivmecillinam, 200mg twice daily for 7 days</td>
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<td>0.17-2.78</td>
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<td>48.2%</td>
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<td>Trimethoprim, 200 mg twice daily for 7 days</td>
<td>1.29</td>
<td>0.43-4.02</td>
<td>85.9%</td>
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<td>90.8%</td>
<td>14.9%</td>
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<tr>
<td>Trimethoprim, 200 mg once</td>
<td>0.31</td>
<td>0.06-1.38</td>
<td>61.1%</td>
<td>40.8%</td>
<td>64.7%</td>
<td>14.9%</td>
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TABLE 2: Model parameters including costs and treatment pathways used in the model and their sources

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<th>Parameter</th>
<th>Type</th>
<th>Mean</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td><strong>Costs</strong></td>
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<td></td>
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<tr>
<td>Fosfomycin, 3g once</td>
<td>Prescription</td>
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<td>Profile Pharma*</td>
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<td>Trimethoprim, 200 mg once</td>
<td>Prescription</td>
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<td>Pyelonephritis</td>
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<td>£3,992</td>
<td>National Schedule of Reference Costs (26)</td>
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<td>Pyelonephritis</td>
<td>Outpatient visit</td>
<td>£94</td>
<td>PSSRU (24)</td>
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<td>Urine analysis</td>
<td>Test</td>
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<td></td>
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<td>Little et al (25) Error! Book mark not defined.</td>
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<td><strong>Pathway</strong></td>
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<tr>
<td>Risk of pyelonephritis if clinical cure not achieved</td>
<td>4%</td>
<td>McKinnel et al. (9)</td>
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<tr>
<td>Risk of hospitalisation if pyelonephritis</td>
<td>20%</td>
<td></td>
<td></td>
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</table>

*This price was provided by Profile Pharma who are the approved UK distributor of Monuril (fosfomycin trometamol) on behalf of the MA holder Zambon. Monuril was launched onto the UK market at this price in August 2016.
TABLE 3: Probabilistic costs (£), health outcomes and cost per UTI resolved (£) for each treatment regimen modelled. Baseline analysis compared with the two deterministic scenarios tested: a) including resistance rates from pathogens other than E.Coli and b) including updated resistance measures for trimethoprim, nitrofurantoin and pivmecillinam, and c) using estimated effectiveness for 3-day dosing, which is in line with the current PHE guidance for use of these treatments.

Note: treatments ordered by lowest cost per UTI resolved.

<table>
<thead>
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<th>Treatment</th>
<th>Total cost</th>
<th>UTIs resolved</th>
<th>Cost per UTI resolved</th>
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</thead>
<tbody>
<tr>
<td>Trimethoprim 200mg twice daily x7</td>
<td>60</td>
<td>857</td>
<td>70</td>
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<tr>
<td>Fosfomycin 3g once</td>
<td>65</td>
<td>842</td>
<td>78</td>
</tr>
<tr>
<td>Nitrofurantoin (MR) 100 mg twice daily x7</td>
<td>69</td>
<td>849</td>
<td>82</td>
</tr>
<tr>
<td>Pivmecillinam 200 mg twice daily x7</td>
<td>67</td>
<td>766</td>
<td>88</td>
</tr>
<tr>
<td>Nitrofurantoin 50 mg 4 times a day x7</td>
<td>78</td>
<td>799</td>
<td>98</td>
</tr>
<tr>
<td>Pivmecillinam 200 mg 3 times a day x7</td>
<td>78</td>
<td>753</td>
<td>103</td>
</tr>
<tr>
<td>Pivmecillinam 400 mg twice daily x3</td>
<td>78</td>
<td>704</td>
<td>111</td>
</tr>
<tr>
<td>Trimethoprim 200 mg once</td>
<td>81</td>
<td>609</td>
<td>133</td>
</tr>
<tr>
<td>Nitrofurantoin 100 mg 4 times a day x3</td>
<td>87</td>
<td>631</td>
<td>138</td>
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</tbody>
</table>
APPENDIX

Systematic review inclusion/exclusion criteria

- Population - women 18+ with signs and symptoms of uncomplicated UTI
- Interventions - fosfomycin, trimethoprim, nitrofurantoin, pivmecillinam (those recommended for treatment of uncomplicated UTI by PHE (4)).
- Outcomes - UTI resolution, persistence, pyelonephritis development and health-related quality of life (HRQoL)
- Exclusion criteria were: no clinical response measure, not in English, studies specifically of the elderly (no specific age cut-off), pregnant or catheterised patients.

Search Strategy

RCT and systematic review study search strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>

Search Strategy:
Population Terms (1-6)
1. exp Urinary Tract Infections/
2. urinary tract infection$.ab,ti.
3. uti.ab,ti.
4. acute cystitis.ab,ti.
5. Cystitis/
6. 1 or 2 or 3 or 4 or 5

Intervention Terms (7-14)
7. Fosfomycin/
8. fosfomycin.ab,ti.
9. phosphonomycin.ab,ti.
10. phosphomycin.ab,ti.
11. monuril.ab,ti.
12. monurol.ab,ti.
13. 2N81MY12TE.rn.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13

Population and Intervention Terms combined (15)
15. 6 and 14

Comparator Terms (16-47)
16. Nitrofurantoin/
17. nitrofurantoin.ab,ti.
18. furadoine.ab,ti.
19. furantoin.ab,ti.
20. macrodantin.ab,ti.
21. furadonine.ab,ti.
22. furadantine.ab,ti.
23. furadantin.ab,ti.
24. macrobid.ab,ti.
25. 927AH8112L.rn.
26. Trimethoprim/
27. trimethoprim.ab,ti.
28. proloprim.ab,ti.
29. trimpex.ab,ti.
30. monotrim.ab,ti.
31. triprim.ab,ti.
32. tmi.ab,ti.
33. tmp.ab,ti.
34. AN164J8Y0X.rn.
35. Amdinocillin Pivoxil/
36. pivmecillinam.ab,ti.
37. amdinocillin.ab,ti.
38. selexid.ab,ti.
39. pivamdinocillin.ab,ti.
40. fl 1039.ab,ti.
41. fl-1039.ab,ti.
42. fl1039.ab,ti.
43. mecillinam.ab,ti.
44. penomax.ab,ti.
45. coactabs.ab,ti.
46. 1WAM1OQ30B.rn.
47. or/16-46
Population and Comparator Terms combined (48)
48. 6 and 47
Population and Intervention OR Population and Comparator (49)
49. 15 or 48
Excluded Comparator (50-54)
50. Trimethoprim-Sulfamethoxazole Combination/
51. Sulfamethoxazole.ab,ti.
52. sulphamethoxazole.ab,ti.
53. 50 or 51 or 52
54. 49 not 53
Search Filter to identify RCTs (92-106)
92. randomized controlled trial.pt.
93. controlled clinical trial.pt.
94. randomized controlled trials/
95. random allocation/
96. double blind method/
97. single blind method/
98. clinical trial.pt.
99. exp Clinical Trial/
100. (clin$ adj25 trial$).ti,ab.
101. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
102. placebos/
103. placebos.ti,ab.
104. random.ti,ab.
105. research design/
106. or/92-105
(Population and Intervention OR Population and Comparator) AND RCT Filter (107)
107. 54 and 106
Search results

The searches identified 978 citations, of which 958 were excluded by title or abstract and 20 full papers were reviewed. 7 were excluded due to having no clinical outcome measure. Of the remaining 13 RCTs, 11 formed a connected network of evidence and were used in the NMA (Figure 2). A total of 3,983 participants were randomised across the trials with mean age across the trials ranging from 21 to 48 years.

Evidence Synthesis

Evidence on clinical cure rates for the different regimens was synthesised by NMA using a random (treatment) effects model with a logit link function to allow for heterogeneity in treatment effects between studies. All analyses were implemented in WinBUGS (34). Results of the NMA are reported in terms of the odds ratios and 95% credible intervals (CrI) relative to fosfomycin 3g which was used as the reference intervention. Absolute estimates of clinical cure rates were estimated for each intervention by projecting the estimates of treatment effect (log odds ratio) from the NMA onto the fosfomycin 3g clinical cure rates.
References

6. NICE. Antibiotic prescribing – especially broad spectrum antibiotics. 2015.


