Recurrent Urinary Tract Infections Among Adult Women: Comparative Effectiveness of Five Prevention and Management Strategies Using A Markov Chain Monte Carlo Model

Samantha J. Eells, M.P.H.[1], Kirin Bharadwa, M.D.[1], James A. McKinnell, M.D[1], Loren G. Miller, M.D., M.P.H.[1,2,3],

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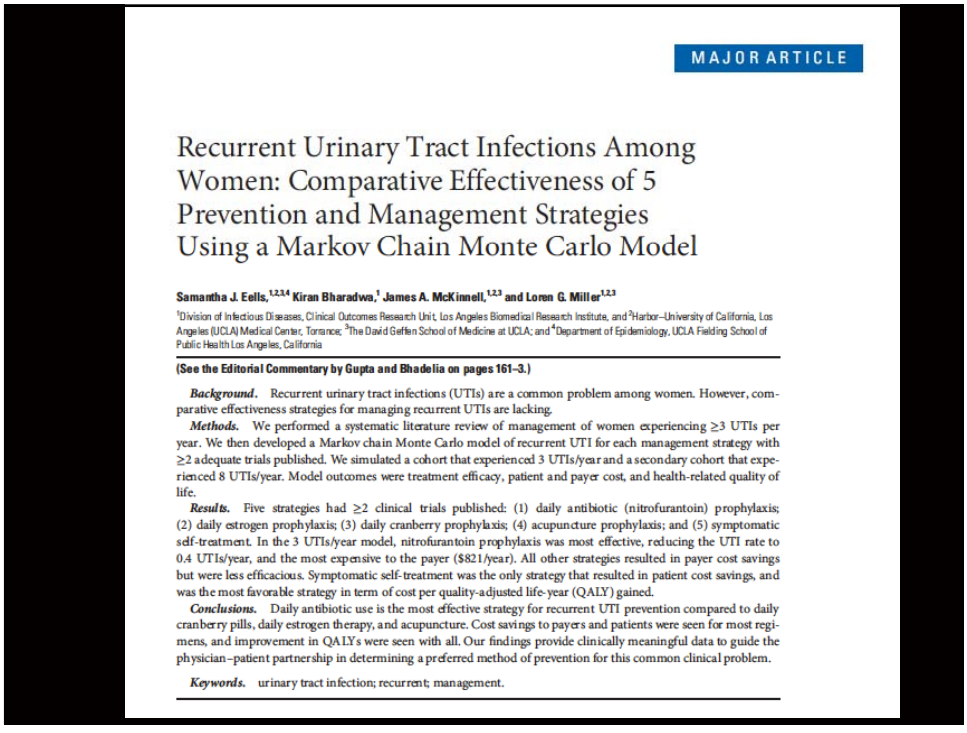

MAJOR ARTICLE

Recurrent Urinary Tract Infections Among Women: Comparative Effectiveness of 5 Prevention and Management Strategies Using a Markov Chain Monte Carlo Model

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(See the Editorial Commentary by Gupta and Bhadelia on pages 161–3.)

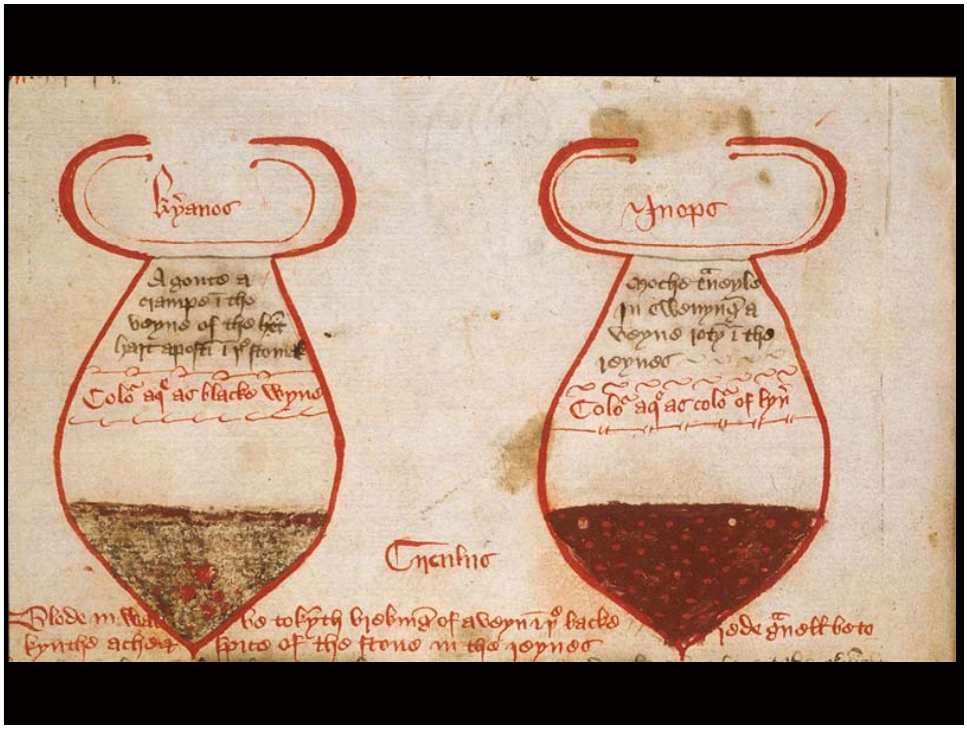
Background. Recurrent urinary tract infections (UTIs) are a common problem among women. However, comparative effectiveness strategies for managing recurrent UTIs are lacking.

Methods. We performed a systematic literature review of management of women experiencing ≥3 UTIs per year. We then developed a Markov chain Monte Carlo model of recurrent UTI for each management strategy with ≥2 adequate trials published. We simulated a cohort that experienced 3 UTIs/year and a secondary cohort that experienced 8 UTIs/year. Model outcomes were treatment efficacy, patient and payer cost, and health-related quality of life.

Results. Five strategies had ≥2 clinical trials published: (1) daily antibiotic (nitrofurantoin) prophylaxis; (2) daily estrogen prophylaxis; (3) daily cranberry prophylaxis; (4) acupuncture prophylaxis; and (5) symptomatic self-treatment. In the 3 UTIs/year model, nitrofurantoin prophylaxis was most effective, reducing the UTI rate to 0.4 UTIs/year, and the most expensive to the payer ($821/year). All other strategies resulted in payer cost savings but were less efficacious. Symptomatic self-treatment was the only strategy that resulted in patient cost savings, and was the most favorable strategy in term of cost per quality-adjusted life-year (QALY) gained.

Conclusions. Daily antibiotic use is the most effective strategy for recurrent UTI prevention compared to daily cranberry pills, daily estrogen therapy, and acupuncture. Cost savings to payers and patients were seen for most regimens, and improvement in QALYs were seen with all. Our findings provide clinically meaningful data to guide the physician–patient partnership in determining a preferred method of prevention for this common clinical problem.

Keywords. urinary tract infection; recurrent; management.



Background: Urinary Tract Infection (UTIs)

- Common infection in adult women
  - 10-13% experience a UTI annually
  - Lifetime risk > 50%
  - Annually in U.S.
    - >6 million outpatient visits
    - 479,000 hospitalizations

Foxman B et al. *Ann Epidemiol.* 2000;10:509-515
Griebling TL. *J Urol.* Apr 2005;173:1281-1287

Background: Urinary Tract Infection (UTIs)

- UTIs cause
  - Pain
  - Restriction of work and school
  - Bed rest
  - $2.4 billion in U.S. annually

Griebling TL. *J Urol.* Apr 2005;173:1281-1287
Foxman B et al. *Am J Public Health* 1985;75:1308-1313

Background: Recurrent UTIs

- Common problem in clinical practice
- Among women w/ UTI in next 6 months
  - 20-30% Have a second UTI
  - 3% will experience a third UTI
- Defined by experts as ≥ 3 UTIs during a one-year time span

Foxman B. *Am J Public Health*1990;80:331-333
Nicolle LE et al. *Infect Dis Clin North Am* 1987;1:793-806
Pfau A et al. *J Urol* 1983;129(6):1153-1157

Background: Recurrent UTIs

- Represent challenge for treating physicians
- No clear ideal prevention strategy
- No comparative trials of strategy

Background: Recurrent UTIs

- Treatment Prevention Strategies
  - Antibiotic prophylaxis
  - Estrogens
  - Cranberry juice/supplement
  - Self-diagnosis/self-treatment
  - Acupuncture
  - *Lactobacillus*
  - Vaccine

Hypothesis

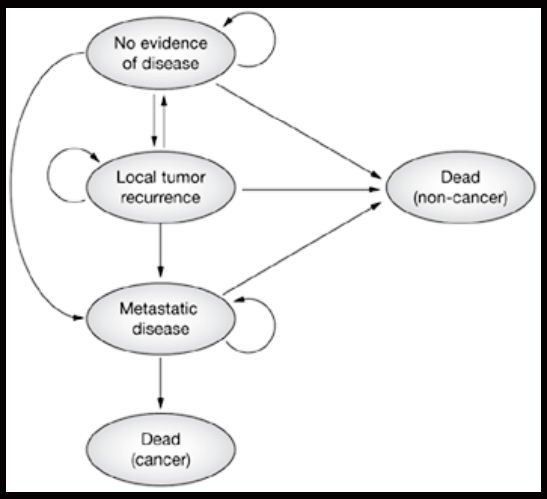
- We hypothesized that preffered treatment strategies to prevent recurrent UTIs would differ depending on the outcome of preference

Investigation Aim

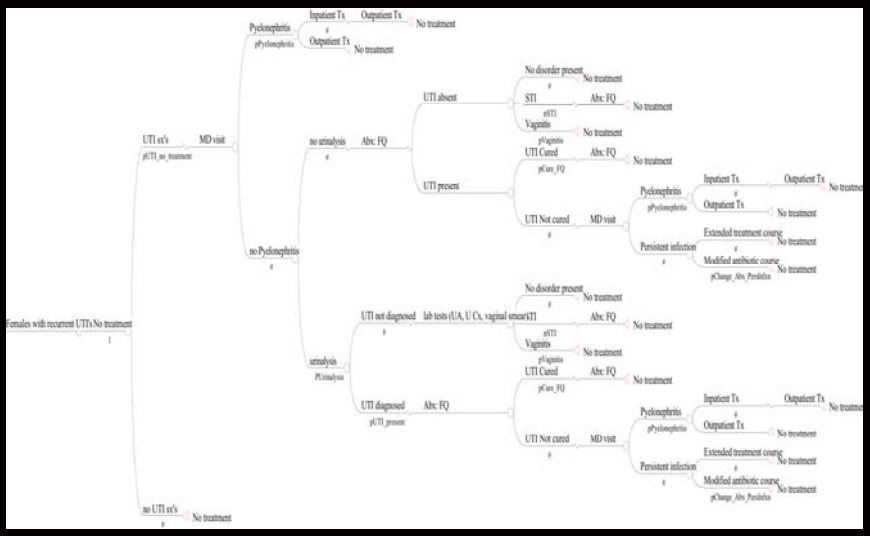
- Quantify outcomes of recurrent UTI strategies
  - Effectiveness
  - Cost
  - HRQOL

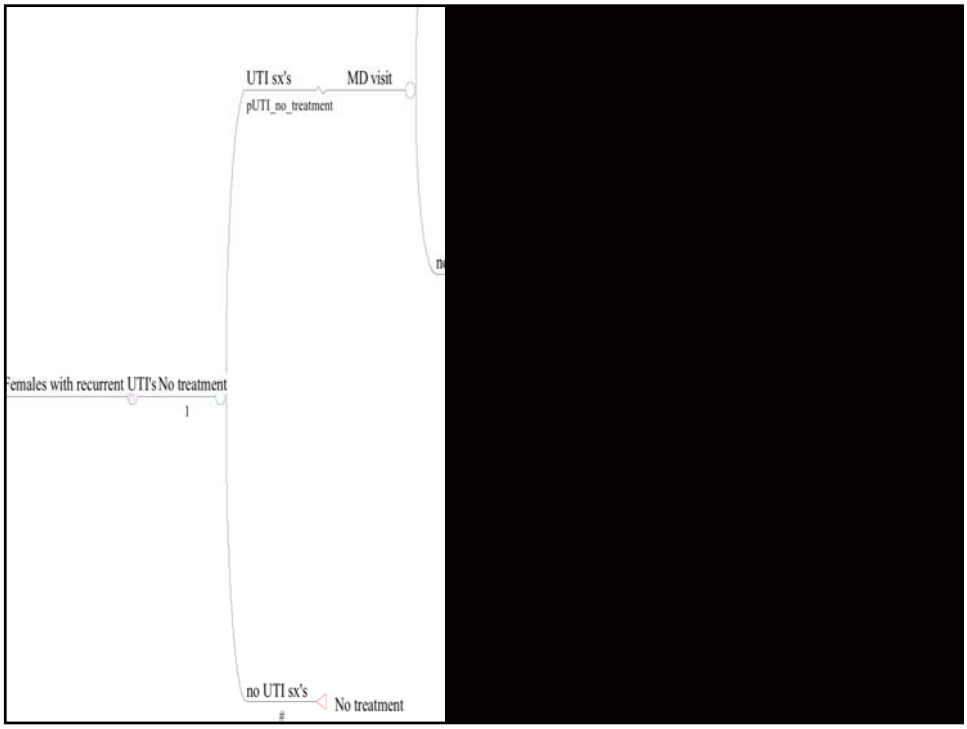
Methods

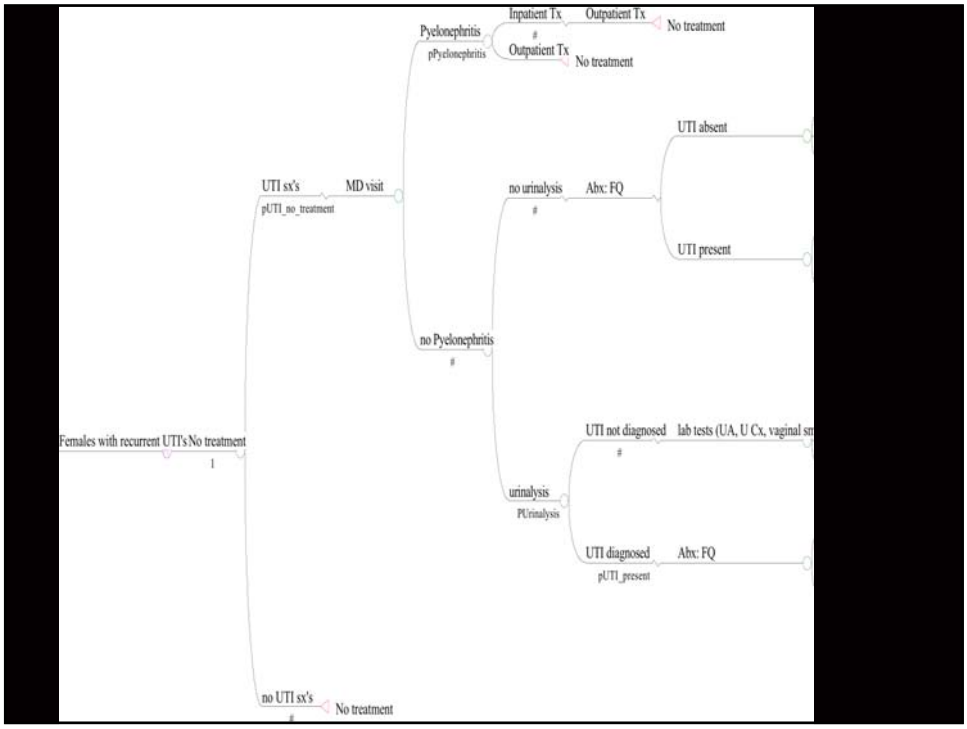
- Markov decision analysis
- Monte Carlo simulation
  - Cohort of patients undergoing each strategy
  - Cohort of “control” patients with no intervention
- Systematic review of literature of efficacy

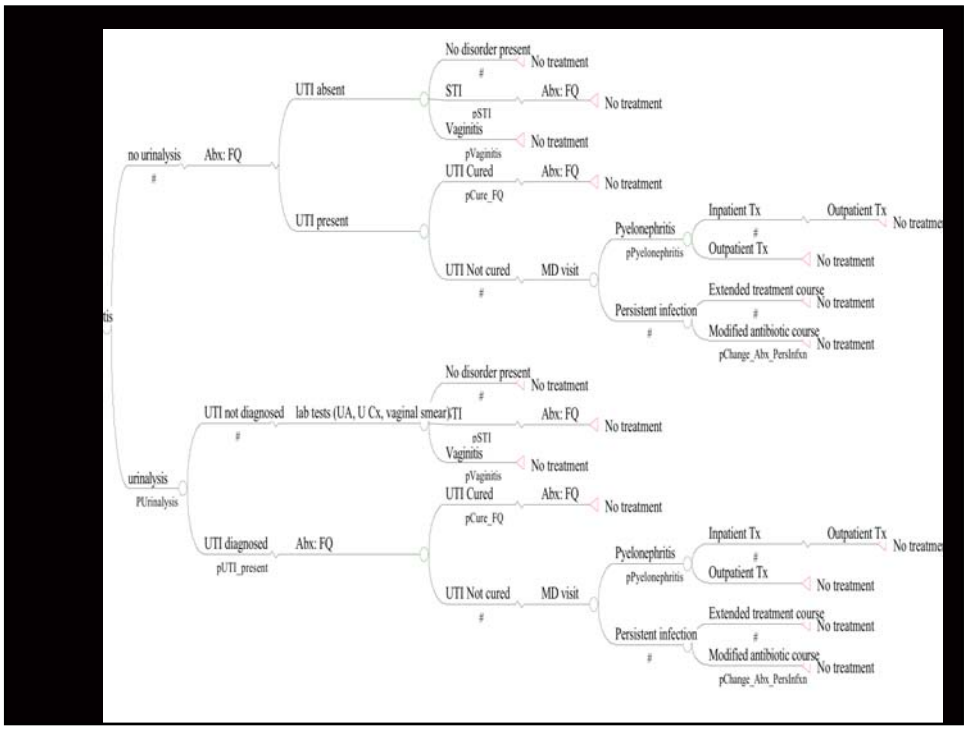


Markov Model






Females with recurrent UTI's
No treatment
1
UTI sx's
pUTI_no_treatment
MD visit
no UTI sx's
#
No treatment
Pyelonephritis
pPyelonephritis
Inpatient Tx
Outpatient Tx
No treatment
#
Outpatient Tx
No treatment
no Pyelonephritis
#
no urinalysis
#
Abx: FQ
UTI absent
UTI present
urinalysis
PUrinalysis
UTI not diagnosed
lab tests (UA, U Cx, vaginal sm
#
UTI diagnosed
pUTI_present
Abx: FQ


tis
no urinalysis
#
Abx: FQ
UTI absent
UTI present
urinalysis
PUrinalysis
UTI not diagnosed
#
lab tests (UA, U Cx, vaginal smear)
UTI diagnosed
pUTI_present
Abx: FQ
No disorder present
#
No treatment
STI
pSTI
Abx: FQ
No treatment
Vaginitis
pVaginitis
No treatment
UTI Cured
pCure_FQ
Abx: FQ
No treatment
UTI Not cured
#
MD visit
Pyelonephritis
pPyelonephritis
Inpatient Tx
Outpatient Tx
No treatment
#
Outpatient Tx
No treatment
Persistent infection
#
Extended treatment course
No treatment
#
Modified antibiotic course
No treatment
pChange_Abx_PersInfxn

Methods

- Outcomes measured:
  - Number of UTIs/year
  - Annual cost from the payer's (i.e., health plan's) perspective
  - Annual cost from the patients' perspective
  - Quality-adjusted life-days (QALD).
    - As opposed to QALY (QALD=QALY/365)

Methods

- Software program
  - DATA (version 4.0, TreeAge Software, Williamstown, MA)

Methods

- Systematic literature review
  - MEDLINE, Embase, and Cochrane Library databases
  - Searched for articles from 1966 to Jan. 2012
  - Keywords:
    - recurrent [recur*]
    - urine or urinary [urin*] AND
    - infectious or infection(s) [infectious, infection*].

Methods

- Two reviewers assessed each abstract
  - If both believed abstract might contain:
    - Data on management strategy for recurrent UTIs or
    - Review article that may reference such data
  - Then article was pulled for review
  - If the reviewers differed, 3rd reviewer tie-broke
  - Reference lists of retrieved articles also reviewed for additional (missed) studies

Methods

- Inclusion criteria for study popoulation
  - Adult (>18 years of age) non-pregnant females
  - Study population with ≥ 3 UTIs per year
  - Comparative clinical trial:
    - Using either an untreated/placebo control group or
    - Quantified patients' pre-intervention and post-intervention UTI incidence
  - English abstract and/or text

Methods

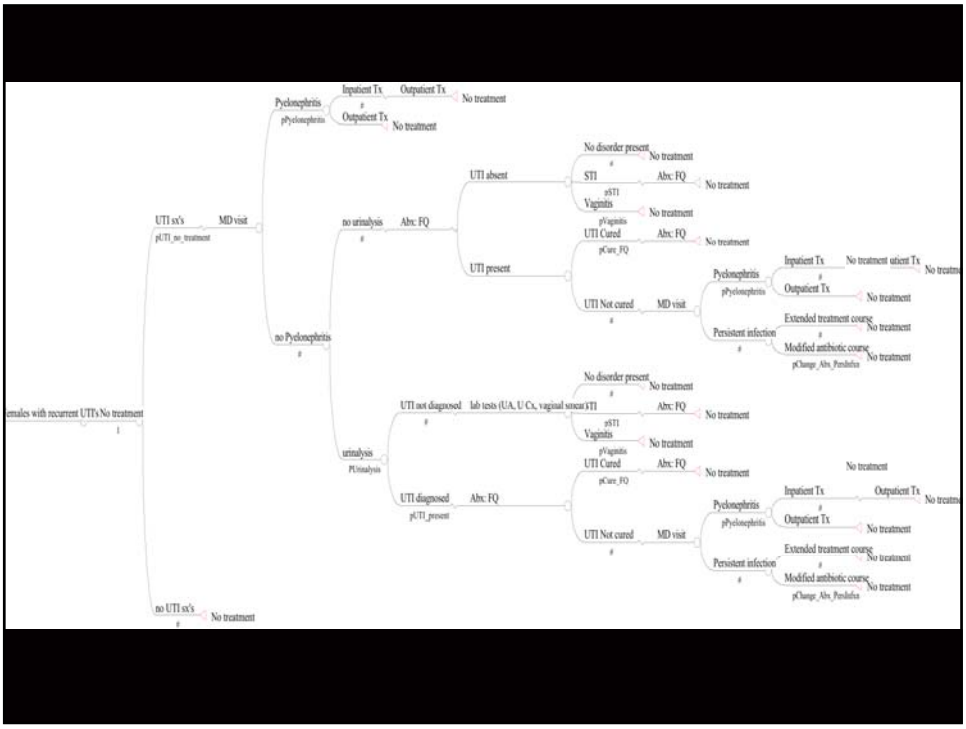
- Probability of UTI prevention
  - Obtained from articles presenting original data
  - Risk reduction calculated by comparing Tx strategy to control or pre-intervention group
- Pooled mean risk reduction weighted by study sample size
- Only modeled interventions with ≥2 published investigations

Methods

- Monte Carlo simulation
  - 10,000 subject simulations
  - One day Markov cycle
  - Untreated group has mean 3 UTIs/year
  - Second set of models with 8 UTIs/year
  - Probabilities from literature search
    - Risk reduction decreased UTI risk by x%

Methods

- Monte Carlo simulation
  - Patients present with Sx's of UTI
    - Most with cystitis, small probability of STI, vaginitis
  - UTIs
    - Required visit to MD
    - Treated with systemic antibiotics
    - Most present with cystitis, some w/ pyelo
    - Small proportion require hospitalization



Costs

- Costs:
  - Program (payer) perspective
  - Patient perspective

Methods

- Costs:
  - Hospitalization: American Hospital Association
    - 10% cost burden on patient
  - MD visits: CMS
  - Pharmaceutical costs: Red Book
    - Patient co-pay
  - Cranberry: pill costs from 3 national commercial pharmacies (mean costs)
  - Acupuncture: survey of 30 clinics (mean cost)
  - Lab costs: survey of 2 major commercial labs

Methods

- HRQOL:
  - Taken from generic health states from the literature

Kaplan RM et al. *J Chronic Dis* 1984;37:85-95

Methods

- Taken from generic health states from the literature
- HRQOL states examples
  - Perfect health 1.0
  - UTI (“Painful, burning, or frequent urination”) 0.9673
  - Pyelonephritis (“fever or chills with aching all over and vomiting or diarrhea”) 0.9288

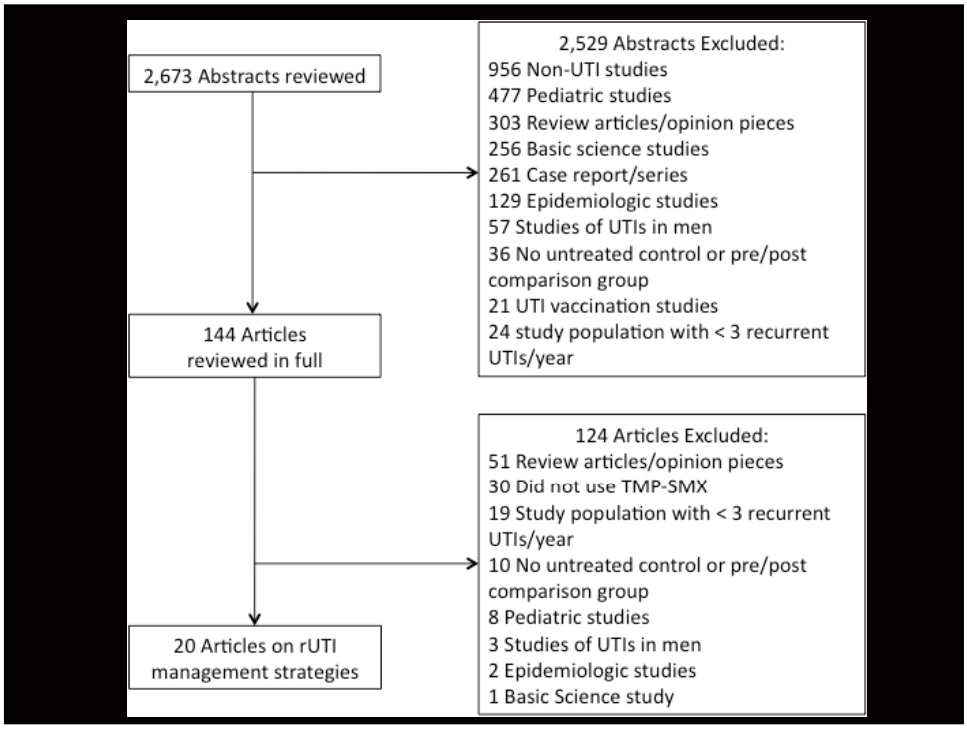
Kaplan RM et al. Health status: types of validity and the index of well-being. *Health Serv Res*. 1976; 11(4): 478–507.

Methods

- One-way sensitivity analyses:
  - Performed for each
    - Probability
    - Cost
    - QALD value
  - Each value ranged over the minimal & maximal values determined from the literature or cost survey

Kaplan RM et al. *J Chronic Dis* 1984;37:85-95

RESULTS


2,673 Abstracts reviewed
2,529 Abstracts Excluded:
956 Non-UTI studies
477 Pediatric studies
303 Review articles/opinion pieces
256 Basic science studies
261 Case report/series
129 Epidemiologic studies
57 Studies of UTIs in men
36 No untreated control or pre/post comparison group
21 UTI vaccination studies
24 study population with < 3 recurrent UTIs/year
144 Articles reviewed in full
124 Articles Excluded:
51 Review articles/opinion pieces
30 Did not use TMP-SMX
19 Study population with < 3 recurrent UTIs/year
10 No untreated control or pre/post comparison group
8 Pediatric studies
3 Studies of UTIs in men
2 Epidemiologic studies
1 Basic Science study
20 Articles on rUTI management strategies

Results

- The systematic literature review yielded 2,791 articles
- We found 20 articles that were clinical trials of UTI prophylaxis for UTIs that met our criteria
  - Antibiotic prophyalxis (n=6)
  - Estrogen prophylaxis (n=5)
  - Acupuncture prophylaxis (n=2)
  - Cranberry prophylaxis (n=4)
  - Self-treatment (n=3)

Results

Table 1. Probability values for variables in model

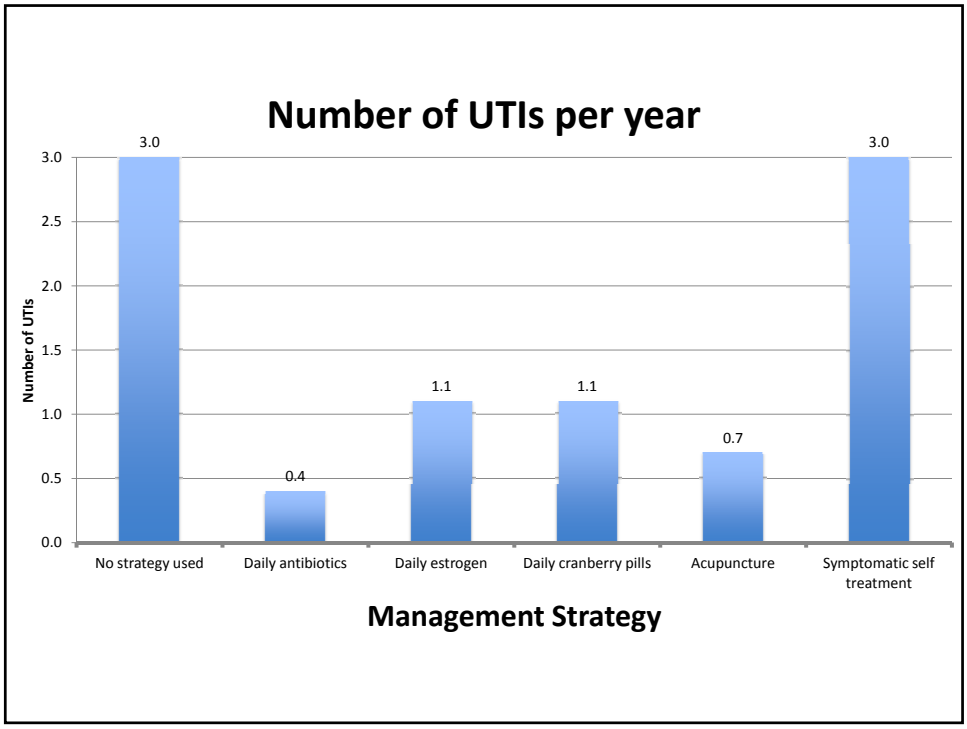
Description	Probability	Range of probabilities tested	References
Acupuncture risk reduction	0.68	0.6-0.7	24,25
Cranberry risk reduction	0.50	0.4-0.8	9,10,16,17
Daily antibiotics/Nitrofurantoin, 100 mg bid risk reduction	0.86	0.6-1.0	11,19-23
Estrogen use risk reduction	0.65	0.3-1.0	12-15,18

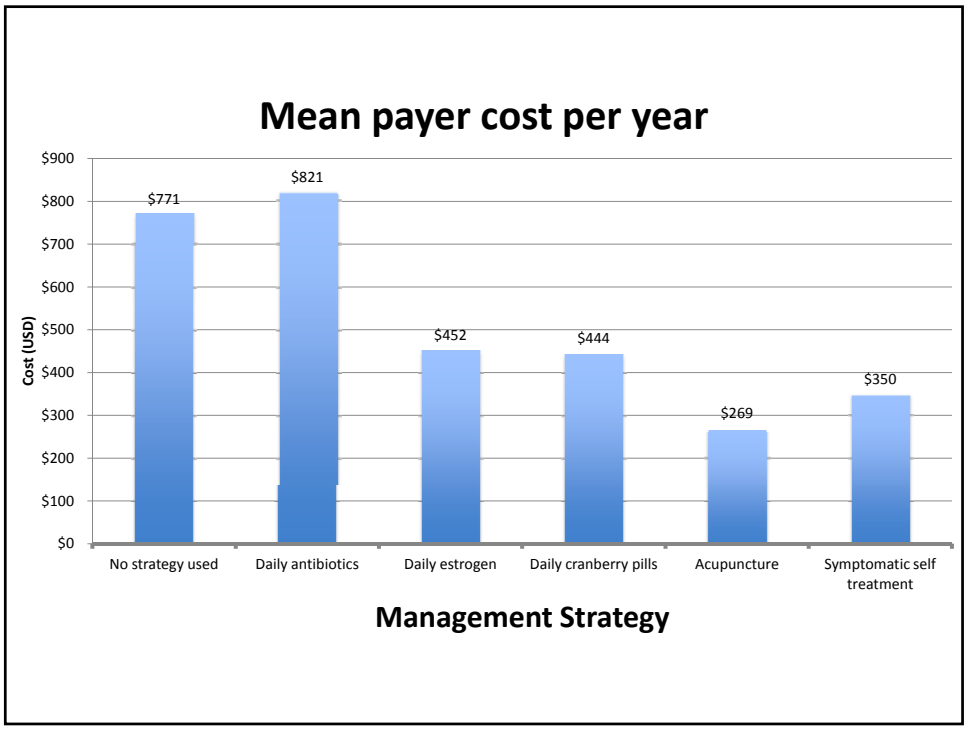
Clinical cure of fluoroquinolone-sensitive infection treated with fluoroquinolone	0.94	0.9-1.0	45,64-66
Vaginal yeast infection after ≤3 days of therapy	0.05	0-0.2	33,66,67
Vaginal yeast infection after >3 days of therapy	0.07	0-0.2	45,68,69
Medical visit for vaginal yeast infection	0.25	0-0.5	53
Change of therapy due to lack of clinical response (versus extending treatment)	0.75	0-1	32,33
Physician orders urine analysis	0.769	0.25 - 1	39
UTI when symptoms are present	0.8481	0.6 - 1	26-28
Pyelonephritis	0.04	0.00 - 0.08	32,33,37,38
Outpatient treatment for pyelonephritis	0.80	0.5 - 1	32,33
STI present	0.157	0 - 0.5	40
Vaginitis present	0.133	0 - 0.5	40,41
No disorder present	0.709	0.5 - 1	41

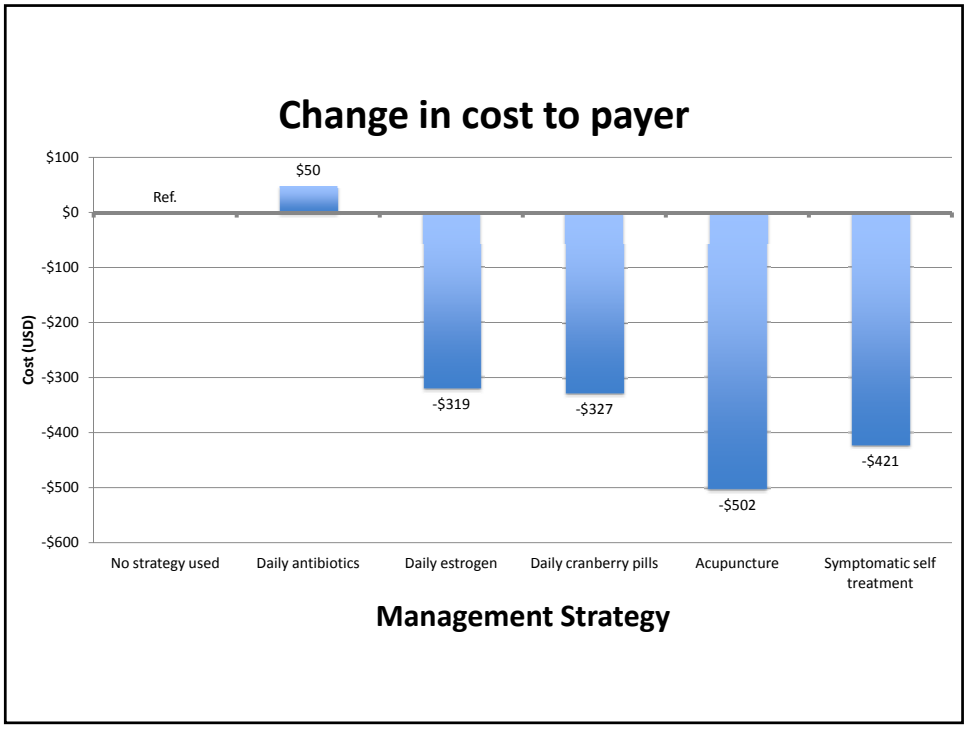
Results

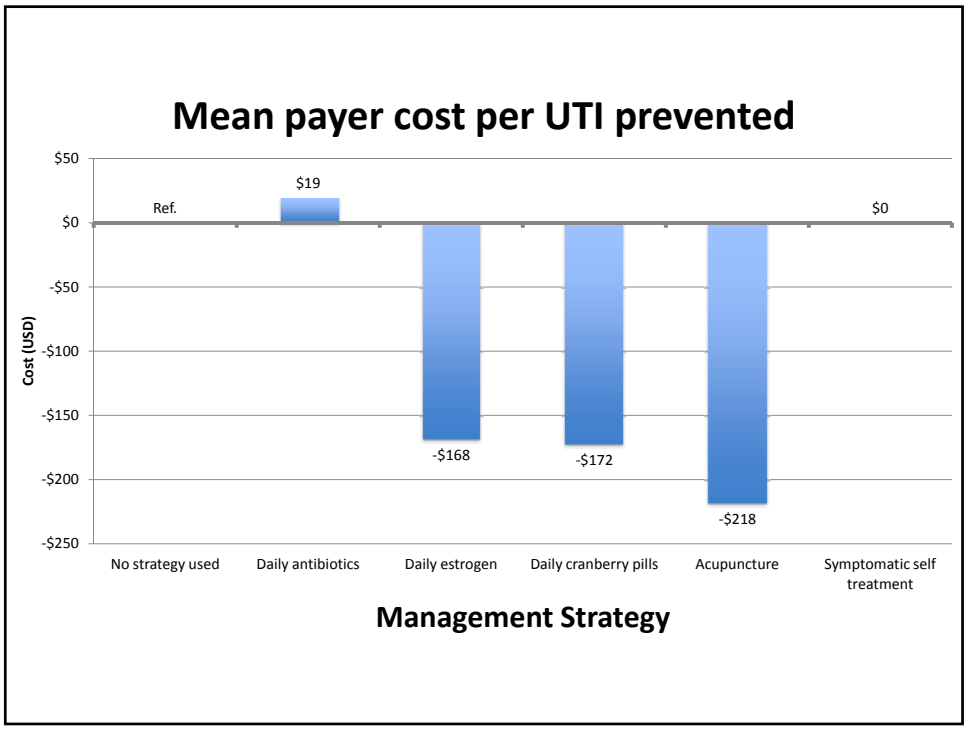
Table 2. Cost of interventions to prevent or treat recurrent urinary tract infections and duration of clinical events

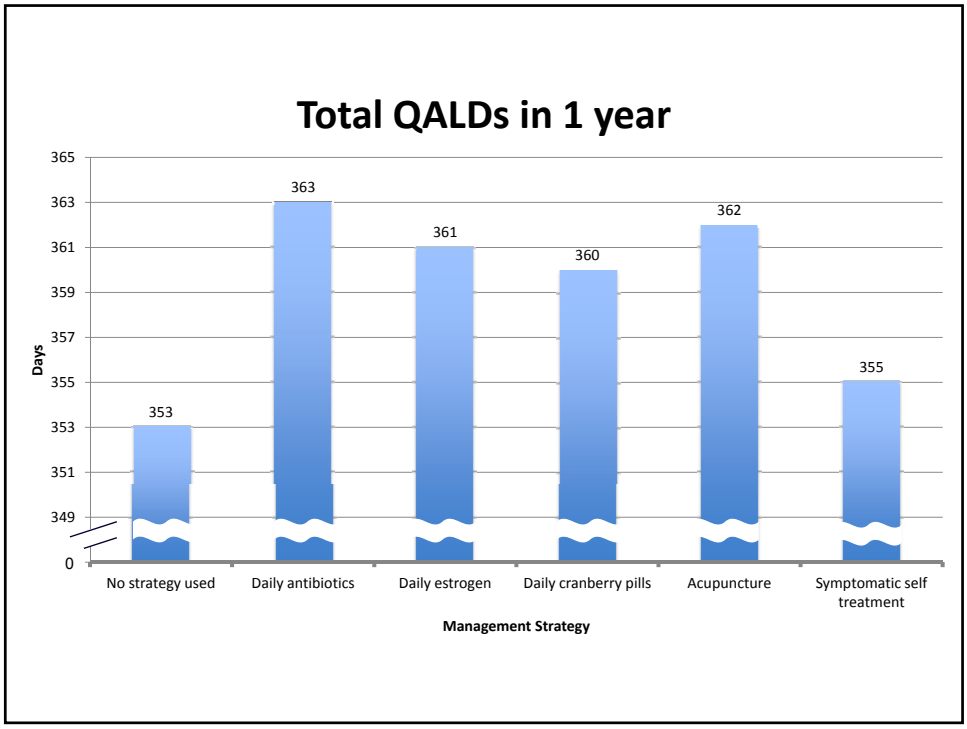
Description	Mean cost per unit time or per item (US dollars)	Range tested (US dollars)	References
Acupuncture, initial session fee plus each monthly session	2.51/day	1.37-4.60	See text
Cranberry pill	0.75/day	0.13-2.25	See text
Estrogen	0.50/day	0.14-31.63	48
Daily antibiotics/Nitrofurantoin, 100 mg bid (AWP)	1.95/day	1-4	48
Ciprofloxacin, 250 mg bid (AWP)	4.44/day	2-10	48
Ciprofloxacin, 500 mg bid (AWP)	5.38/day	2-11	48
Self-treatment for yeast infection	16.14	8-32	See text
Hospitalization for pyelonephritis	1782.28/day	850-3600	49
Outpatient treatment for infection unresponsive to fluoroquinolones or pyelonephritis	29.77/day	15-60	48
Follow-up physician visit	97.77	65-132	50-53
Initial urinalysis	20.78	10-42	See text
Follow-up urinalysis	20.78	10-42	See text
Urine culture	46.42	23-93	See text
Vaginal smear	13.50	10.65-16.25	See text
STI test	67.60	20-155	See text
Description	**Duration (days)**	**Range (days)**	**References**
Hospitalization for pyelonephritis	3	1-5	36,37
Outpatient treatment for infection unresponsive to fluoroquinolones	5	3-10	37
Outpatient treatment for pyelonephritis	7	5-14	64,70

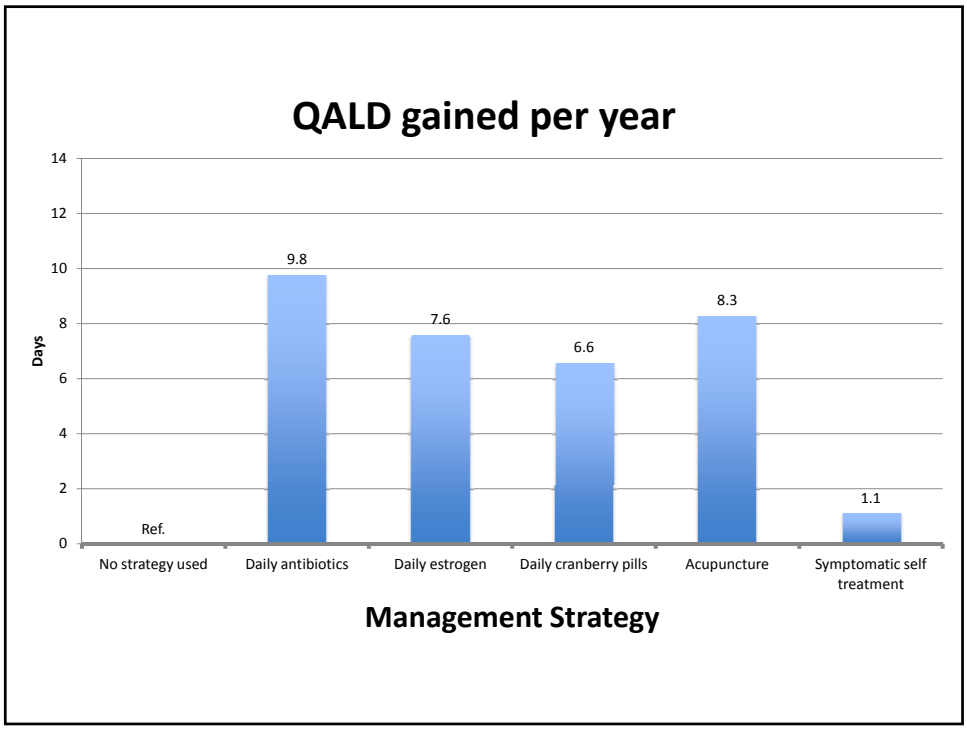

Number of UTIs per year
Number of UTIs
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3.0
0.4
1.1
1.1
0.7
3.0
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

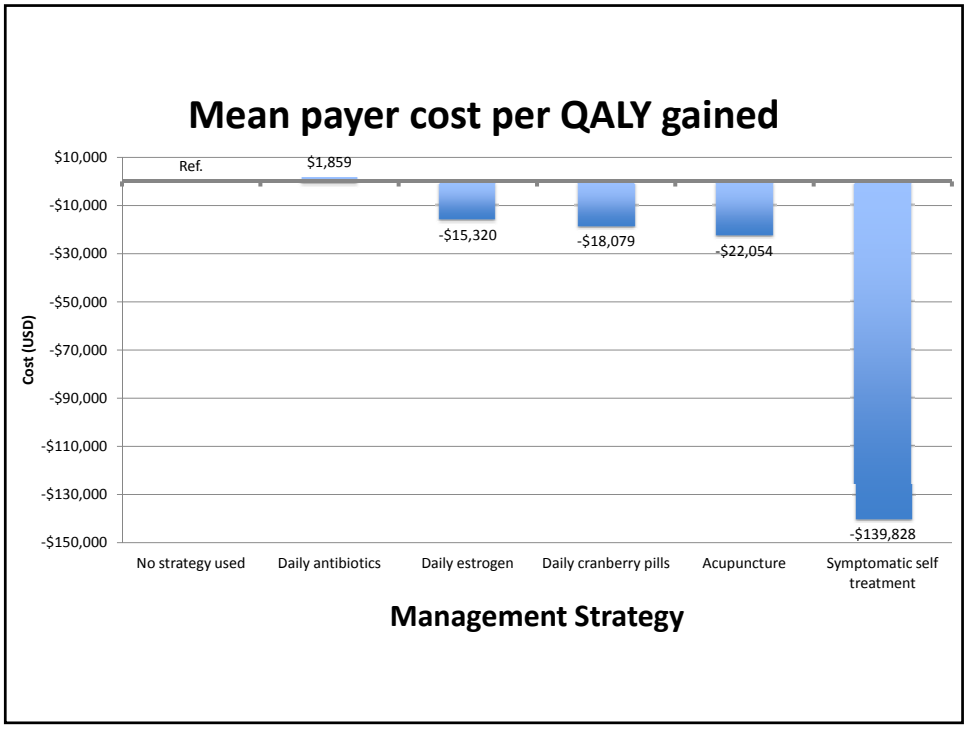

Mean payer cost per year
Cost (USD)
$900
$800
$700
$600
$500
$400
$300
$200
$100
$0
$771
$821
$452
$444
$269
$350
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

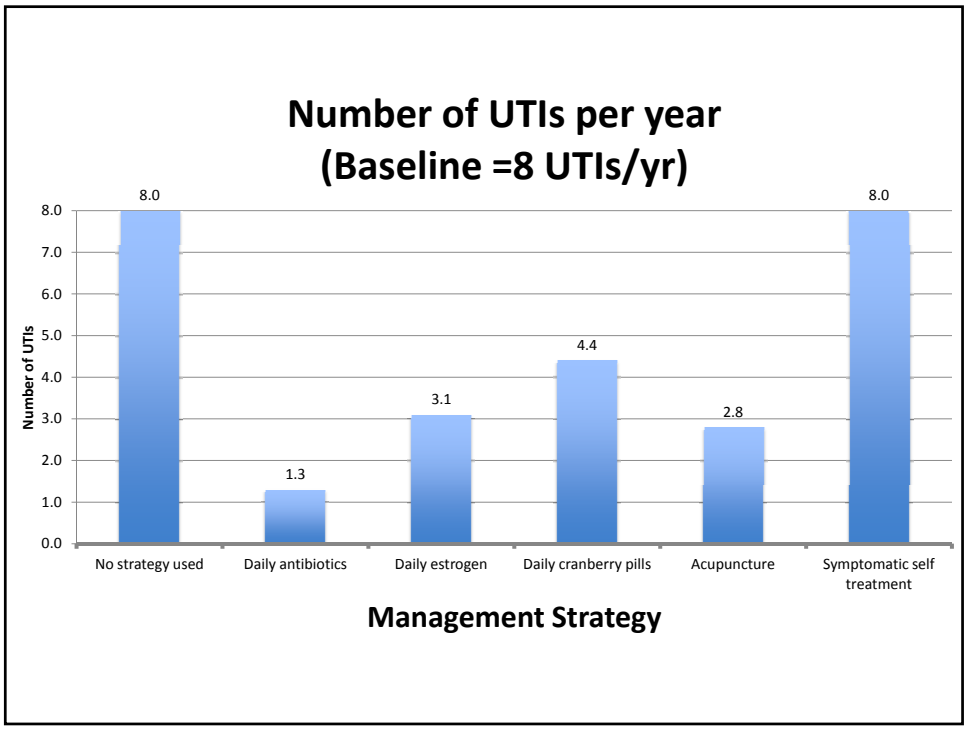

Change in cost to payer
$100
$0
-$100
-$200
-$300
-$400
-$500
-$600
Cost (USD)
Ref.
$50
-$319
-$327
-$502
-$421
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

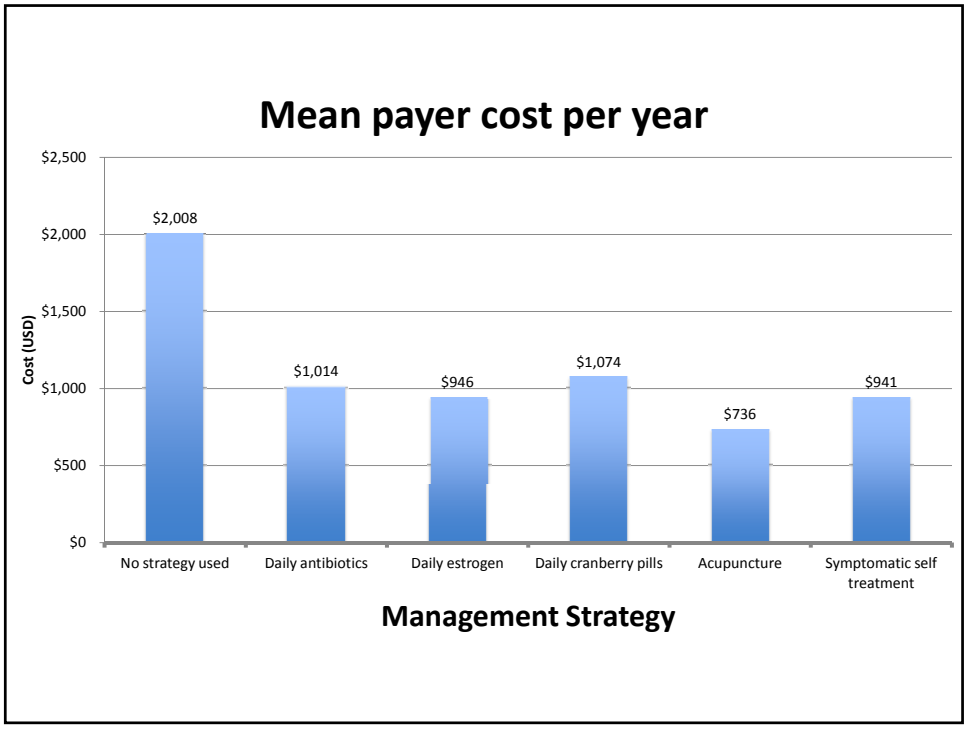

Mean payer cost per UTI prevented
$50
$0
-$50
-$100
-$150
-$200
-$250
Cost (USD)
Ref.
$19
$0
-$168
-$172
-$218
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

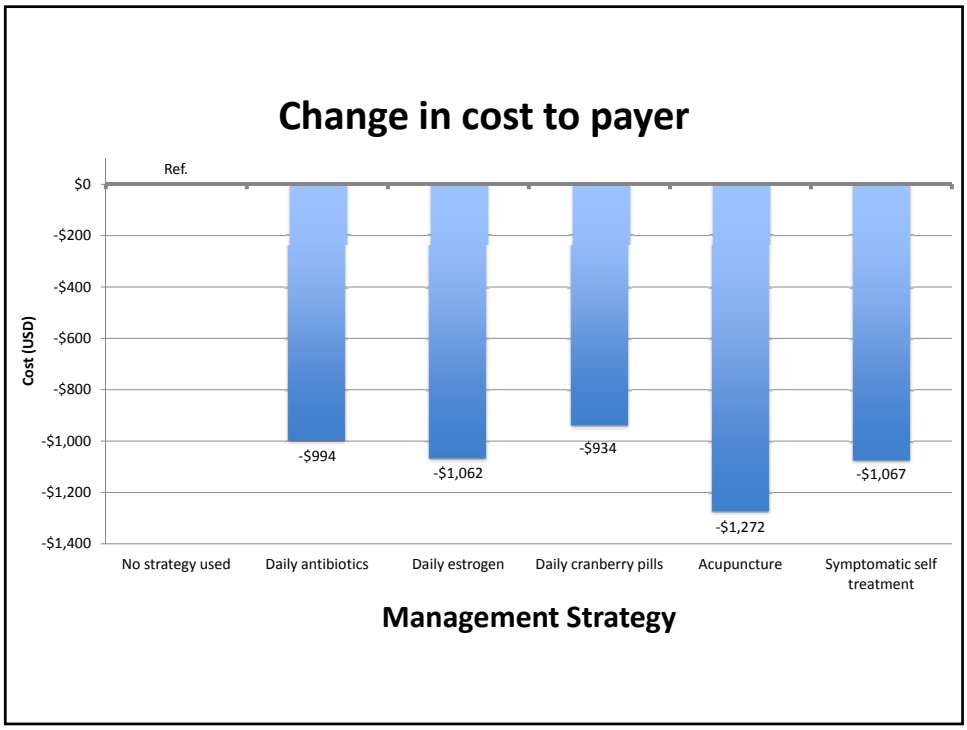

Total QALDs in 1 year
Days
365
363
361
359
357
355
353
351
349
0
353
363
361
360
362
355
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

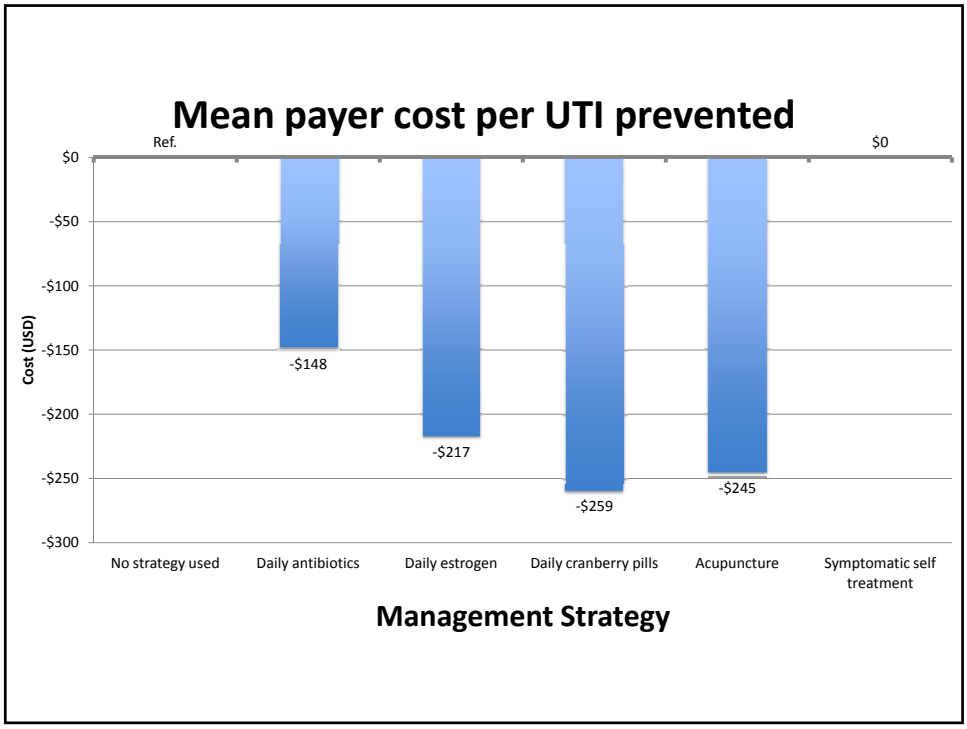

QALD gained per year
Days
14
12
10
8
6
4
2
0
Ref.
9.8
7.6
6.6
8.3
1.1
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

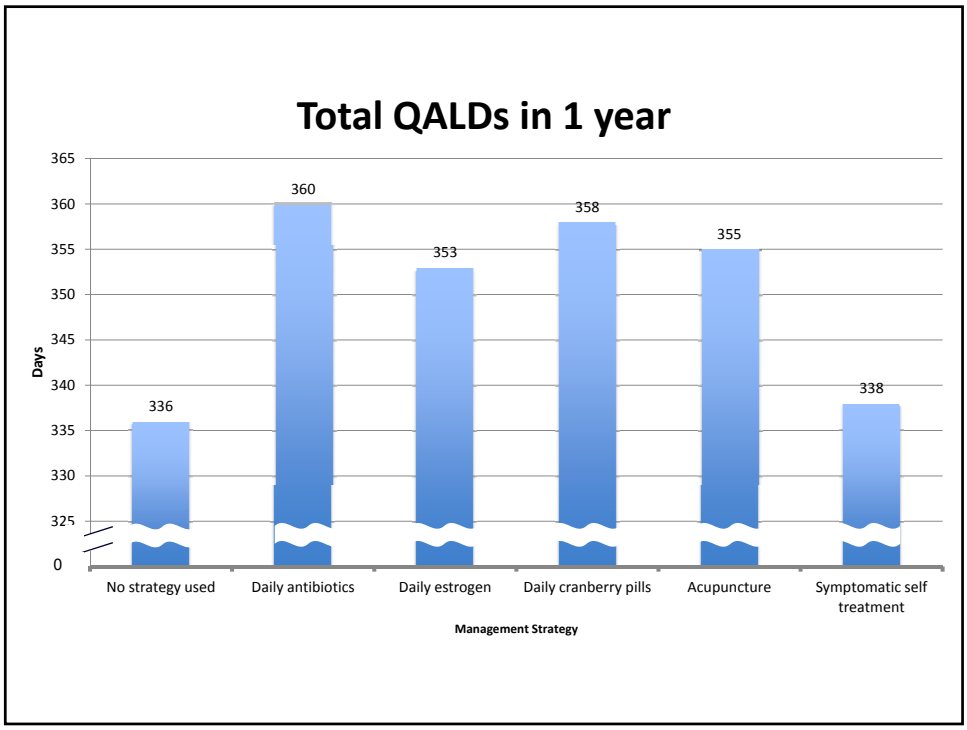

Mean payer cost per QALY gained
$10,000
-$10,000
-$30,000
-$50,000
-$70,000
-$90,000
-$110,000
-$130,000
-$150,000
Cost (USD)
Ref.
$1,859
-$15,320
-$18,079
-$22,054
-$139,828
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

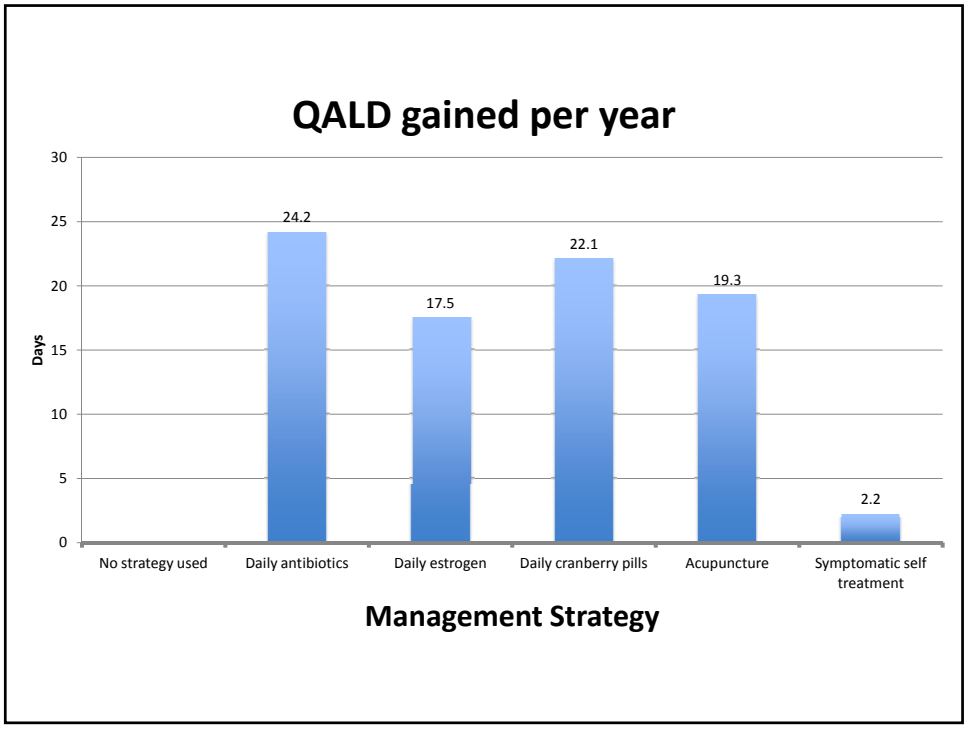

Number of UTIs per year
(Baseline =8 UTIs/yr)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Number of UTIs
8.0
1.3
3.1
4.4
2.8
8.0
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

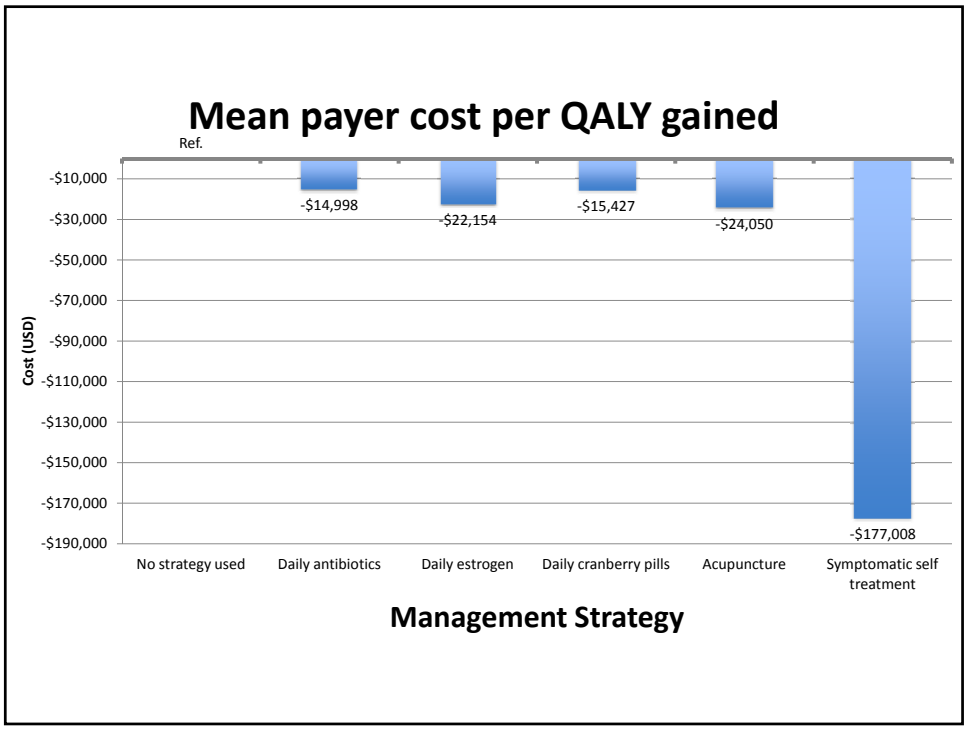

Mean payer cost per year
$2,500
$2,000
$1,500
$1,000
$500
$0
Cost (USD)
$2,008
$1,014
$946
$1,074
$736
$941
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy


Change in cost to payer
Ref.
$0
-$200
-$400
-$600
-$800
-$1,000
-$1,200
-$1,400
Cost (USD)
-$994
-$1,062
-$934
-$1,272
-$1,067
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy


Mean payer cost per UTI prevented
Ref.
$0
$0
-$50
-$100
-$150
-$200
-$250
-$300
Cost (USD)
-$148
-$217
-$259
-$245
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy


Total QALDs in 1 year
365
360
355
350
345
340
335
330
325
0
Days
336
360
353
358
355
338
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy


QALD gained per year
30
25
20
15
10
5
0
Days
24.2
17.5
22.1
19.3
2.2
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy


Mean payer cost per QALY gained
Ref.
-$10,000
-$30,000
-$50,000
-$70,000
-$90,000
-$110,000
-$130,000
-$150,000
-$170,000
-$190,000
Cost (USD)
-$14,998
-$22,154
-$15,427
-$24,050
-$177,008
No strategy used
Daily antibiotics
Daily estrogen
Daily cranberry pills
Acupuncture
Symptomatic self treatment
Management Strategy

Results from Payer's Perspective (3 UTIs/Year)

Strategy	Number of UTI/year	Mean payer cost/year	Change in cost to payer	Mean payer cost/UTI prevented	Total QALDs in 1 year	QALD gained/year	Mean payer cost/QALY gained
No strategy used	3.0	$771	REF	REF	353	REF	REF
Daily antibiotics	0.4	$821	$50	$19	363	9.8	$1,859
Daily estrogen	1.1	$452	-$319	-$168	361	7.6	-$15,320
Daily cranberry pills	1.1	$444	-$327	-$172	360	6.6	-$18,079
Acupuncture	0.7	$269	-$502	-$218	362	8.3	-$22,054
Symptomatic self treatment	3.0	$350	-$421	N/A	355	1.1	-$139,828

Results from Payer's Perspective (8 UTIs/Year)

Strategy	Number of UTI/year	Mean payer cost/year	Change in cost to payer	Mean payer cost/UTI prevented	Total QALDs in 1 year	QALD gained/year	Mean payer cost/QALY gained
No strategy used	8.0	$2,008	REF	REF	336	REF	REF
Daily antibiotics	1.3	$1,014	-$994	-$148	360	24.2	-$14,998
Daily estrogen	3.1	$946	-$1062	-$217	353	17.5	-$22,154
Daily cranberry pills	4.4	$1,074	-$934	-$259	358	22.1	-$15,427
Acupuncture	2.8	$736	-$1272	-$245	355	19.3	-$24,050
Symptomatic self treatment	8.0	$941	-$1067	N/A	338	2.2	-$177,008

Results from Patient's Perspective (3 UTIs/Year)

Strategy	Mean patient cost/year	Change in cost to patient	Mean patient cost/UTI prevented	Mean patient cost/QALY gained
No strategy used	$139	REF	REF	REF
Daily antibiotics	$140	$1	$0	$19
Daily estrogen	$169	$30	$15	$1,412
Daily cranberry pills	$341	$202	$106	$11,121
Acupuncture	$946	$807	$351	$35,467
Symptomatic self treatment	$69	-$70	N/A	-$23,260

Results from Patient's Perspective (8 UTIs/Year)

Strategy	Mean patient cost/year	Change in cost to patient	Mean patient cost/UTI prevented	Mean patient cost/QALY gained
No strategy used	$365	REF	REF	REF
Daily antibiotics	$178	-$187	-$28	-$2,822
Daily estrogen	$261	-$104	-$21	-$2,167
Daily cranberry pills	$458	$93	$26	$1,541
Acupuncture	$998	$633	$122	$11,971
Symptomatic self treatment	$181	-$184	N/A	-$30,444

Results: Sensitivity Analysis

- Payer costs sensitive to:
  - Estrogen costs ($0.50/day)
    - 30% reduction if estrogen cost was $0.14/day or a 2400% increase if the cost was $32/day
  - Antibiotic prophylaxis
    - 43% cost reduction to 89% cost increase
- Other costs had lesser effects

Results: Sensitivity Analysis

- Patient costs sensitive to:
  - Cranberry pills
    - 64% cost reduction to 155% cost increase
  - Acupuncture
    - 43% cost reduction to 79% cost increase
- Other costs had lesser effects

Results: Sensitivity Analysis

- Probabilities with influence on results
  - Antibiotic prophylaxis
    - 0.0 to 1.2 UTIs/year
  - Pyelopephritis probability
    - 23% decrease to 346% increase in payer costs
  - QALD affected by FQ treatment cure %
    - 348-361 QALD (baseline 353)

Summary

- Daily antibiotics
  - Least expensive for patient
  - Cost for payer
    - Cost savings for 8 UTI/year model
    - Modest cost ($50 year) for 3 UTI/year model

Summary

- Acupuncture
  - Least expensive for payer
  - Very expensive for patient
  - Of note
    - Access to treatment poorly understood
    - Efficiency of intervention poorly understood
    - Ideal regimen unclear
      - In studies, Rx administered 2x/week x 4 weeks & women then followed x 6 months

Summary

- Daily estrogens, cranberry
  - Similar reductions in UTIs
    - 1.1 UTIs/year for 3 UTI/year model
  - Similar payer costs, QALY gained
  - But cranberry very expensive to patient

Summary

- Daily estrogens
  - Optimal method unclear
    - Oral, transdermal, vaginal
  - May not be tolerated by some women

Summary

- Symptomatic self-treatment
  - No reduction in UTIs
  - Minimal improvement in QALY
  - Very cost effective to patient, provider
  - May be very attractive to some persons, very unattractive to other

Limitations

- Model had many many assumptions
- Only based on published data
  - Publication bias
- Quality of some clinical trials relatively poor
  - Double blind placebo controlled RCTs ideal but rare
- Cost of medications not as clear as expected

Limitations

- Long term tolerability, efficacy not modeled
  - But rare events have minimal effects on cost in prior studies
- CAM interventions not well standardized
- No disease specific HRQOL measures
- Models not stratified by patient related factors, e.g., age
  - Model assumed patients in perfect health
- Didn't perform credibility ranges

Strengths

- Multiple complementary outcomes
- Multiple perspectives
- Systematic review of the literature
- Summary, comparative outcomes

Implications

- Interventions to prevent UTIs
  - Generally efficacious
  - Cost-effective
- Data will help patients/provider partnership individualize treatment strategy