Empiric Prescription for Uncomplicated UTI: Are the Costs of Collateral Damage too High?

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Abstract

Background: Urinary tract infections (UTIs) are common in the United States resulting in significant costs. Increasingly, UTIs caused by antibiotic resistant *Escherichia coli* do not respond to commonly prescribed antibiotics resulting in additional treatment cost and lost productivity. Empiric prescription is recommended as a cost-effective strategy over lab-based diagnostic tests, but antimicrobial resistance challenges this modality. Collateral damage (e.g., selection for multidrug resistance) is associated with antibiotic use but has only recently been considered in Infectious Disease Society of America treatment recommendations. Despite these new concerns of multidrug resistance associated with increased cost of treatment, empiric prescription has not been adequately re-tested for cost-effectiveness in patients with uUTI.

Methods: PubMed/MEDLINE, Scopus, JSTOR, and Web of Science were searched in January and September of 2015 using search terms related to UTI, empiric prescription, antibiotic resistance, and cost-analyses to answer the question "In adults, does antibiotic resistant status of an *E. coli* uUTI affect success and cost of treatment?" Additional analysis was done to compare categories of expenses included for analysis such as direct, indirect, social (e.g., lost productivity), or societal (i.e., collateral damage). The strength of the evidence was determined based on the quality of the evidence and risk of bias from each study using a method adapted from the Navigation Guide systematic review methodology.

Results: Sixteen studies met inclusion criteria and were included in the review. The risk of treatment failure was found to be greater in community-acquired UTI patients with resistant strains of *E. coli* versus susceptible ones*;* and it is associated with delay of identifying appropriate treatment, increased length-of-stay, additional outpatient medical care, and increased overall costs of care. Cost is measured relatively consistently across the medical literature but is limited to direct costs such as hospital expenditures or antibiotic cost. No cost-effective analysis for community-acquired UTI reviewed in this paper incorporates social (e.g., lost productivity) or societal costs (e.g., the risk of increasing resistance over time).

Conclusions: Empiric prescription is the commonly recommended course of action because it is considered cost-effective, but in populations with high rates of resistance to commonly prescribed antibiotics, it can result in delayed treatment and increased medical costs. Furthermore, receiving unnecessary antibiotics due to empiric prescription without bacterial infection is associated with collateral damage. As resistance to commonly prescribed antibiotics continues to grow, there is a need for health economists, public health professionals, and physicians to develop new risk-benefit models for empiric antibiotic therapy to inform international treatment guidelines for community-acquired uUTI.

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Background

Urinary tract infections (UTIs) are common in the United States and it is estimated that by the age of 24, one-third of women will have been seen by a physician, and treated with antibiotics for a UTI (Foxman 2000). The costs of UTIs are significant, totaling 1.6 billion US Dollars annually from direct and indirect costs. Direct costs include clinical charges such as antibiotic acquisition, lab fees, or doctor visits. Indirect costs traditionally include lost productivity such as days unable to work, but can also include downstream effects considered externalities or collateral damage (e.g., reduction in local effectiveness of a class of antibiotics) (Coast 1996). Infections that are community-acquired are often treated in outpatient clinics and routinely receive antibiotic prescriptions empirically (i.e., without specific knowledge of pathogen or susceptibilities) based on treatment guidelines and patient symptoms alone.

The predominant causative pathogen for uncomplicated UTI (uUTI; i.e., UTIs among healthy, non-pregnant adult women, including postmenopausal women, with no functional or anatomical abnormalities) is *Escherichia coli* (*E. coli*), accounting for approximately 80% of cases (Sahm 2001). Historically, the predictable nature of causative agents among patients eliminated the need of costly urinalyses promoting the use of empiric treatment for uUTI over directive treatment (i.e., using culture or molecular-based diagnosis and susceptibility testing) (Schultz 1984).

However, in the last decades antibiotic-resistant community-acquired UTIs have increased in incidence in the US (Sanchez 2012), and resistance to commonly used antibiotics such as Trimethoprim/sulfamethoxazole (TMP-SMX), Ciprofloxacin, and Nitrofurantoin has risen respectively from 17.9% to 22.9%, 3% to 16%, and 0.8% to 3% from 2000 to 2008. Resistant infections are associated with worse treatment outcomes, higher treatment costs, and mortality

(French 2005, McNulty 2006, Melzer 2007, Wu 2014); and could result in additional, societal costs (e.g., research and development for new antibiotics) (Coast 1996, Pitout 2010). Collateral damage refers to ecological adverse effects resulting from antibiotic use, such as the selection of drug-resistant organisms or the colonization of multidrug-resistant organisms (e.g., E. coli producing extended-spectrum beta-lactamase (ESBL) enzymes), and has been associated with certain classes of antibiotics including fluoroquinolones (FQs) (e.g., Ciprofloxacin) (Gupta 2011).

National and international guidelines have been developed to guide outpatient practitioners for empiric treatment of community-acquired uUTI (Warren 1999, Bruyere 2008, Guay 2008, Gupta 2011), although adherence to guidelines has consistently been demonstrated to be imperfect (Kahan 2004, Grover 2007, Denes 2012). In 1999, the guidelines from the Infectious Disease Society of America (IDSA) recommended the standard therapy for acute UTIs be three days of TMP-SMX empirically (Warren 1999). If local resistance rates to TMP-SMX surpassed ten to twenty percent, more costly FQs were considered to have similar effectiveness. Following the release of the IDSA guidelines, health economists modeled cost-effectiveness of TMP-SMX versus FQs, determining when FQs were recommended over TMP-SMX based on local resistance rates (Le 2001, Perfetto 2004). Following these recommendations, FQ prescriptions increased, thus selecting for FQ-resistant uropathogens (Kahlmeter 2003, Johnson 2008). .

Due to the rapid loss of effectiveness of FQs and TMP-SMX in the last two decades, the ISDA updated their recommendations in 2010 to use TMP-SMX only when local resistance rates were below twenty percent and the patient had not been recently treated for a UTI with it in the last three months (Gupta 2011). The updated guidelines recommended Nitrofurantoin, Fosfomycin, or Pivmecillinam over TMP-SMX; and, FQs were demoted to a last resort if other

treatments were inappropriate (e.g., due to allergies). Clinical cost-analyses have inconsistently been utilized for decision-making regarding antibiotic resistance and uUTI treatment strategies (Fenwick 2000, Le 2001, Noskin 2001, Perfetto 2004, Alam 2009). Most frequently they have included direct costs (e.g., pharmaceutical costs, outpatient treatment, and/or hospitalizations) occasionally including secondary infections (e.g., vaginal yeast or kidney infections). It is unclear whether current studies have gone beyond direct costs and additionally compared the social (e.g., lost productivity) or external (e.g., decreased effectiveness of a drug) costs of resistant infections when identifying optimal treatment for uUTI.

Despite the increased awareness of the rising costs of antibiotic resistance, the association between local antibiotic prescription and resistance as well as the recent emergence of rapid diagnostic tests, empiric prescription is still favored and considered the recommended choice for cost-effectiveness and cost-benefits (i.e., patient outcomes) (Gupta 2011). The rationale for empiric prescription has not been re-tested since resistance rates have escalated (Schultz 1984), and collateral damage has not been included in cost-effective models. Health economists should continue to test the assumption that empiric prescription is the most cost-effective treatment strategy using relative resistance scenarios; and the complete costs of resistance should be included in the calculations (e.g., indirect costs such as those incurred in the future or secondary infections).

Goal/Specific Aims

Given the rising prevalence and costs associated with multidrug-resistance across the globe, the IDSA must continually review the literature for UTIs to identify which treatment strategies are optimal in the sense of effectiveness, the chance for reoccurrence, and adverse effects. Factoring in collateral damage has only recently been incorporated into the medical decision-

making (Gupta 2011); however, it is unclear whether the current body of literature is adequately calculating these issues from a holistic, public-health perspective.

This systematic review seeks to identify the epidemiological landscape of current uUTI treatment decision-making in adult outpatients through two aims:

1. Review the rates of treatment failure, recurrence, and progression (i.e., a kidney or blood infection) associated with treating resistant uUTIs using empiric and/or directive treatment strategies.
2. Compare total costs to treat resistant *vs.* susceptible uUTI given variations in accounting within study designs performing cost-analyses across treatments.

Methods

This systematic review of published reports of experimental, observational, and simulation studies for management of uUTI in the wake of antibiotic resistance was conducted based on established protocols for public health reviews, namely those established by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement (Liberati 2009) and the Navigation Guide Systematic Review Methodology (Johnson 2014, Woodruff 2014).

Specifying the Study Question

The purpose of this review is to describe the landscape of community-acquired uUTI treatment in regard to costs-effective treatment strategies and antibiotic resistance in adults in order to answer the question in Aim 1: "In adults, does the antibiotic-resistance status of an *E. coli* uUTI affect success and cost of treatment?" A PECO (participants, exposure, comparator, and outcomes) statement was formulated to develop the question:

Participants: human females aged 16 or older seeking treatment for a community-acquired urinary tract related infection (e.g., uUTI, kidney or blood infection) caused by *E. coli*.

Exposure: empirically prescribed antibiotic

Comparators: humans with an antibiotic resistant infection versus an all-antibiotic sensitive one (i.e., a dichotomous comparison of resistant *vs.* susceptible patients).

Outcomes: rates and risk (e.g., odds ratio, hazard rate ratio) of treatment failure (i.e., clinical or bacteriological) as well as total costs associated with treating the infection (e.g., antibiotic acquisition, outpatient care, lost productivity, collateral damage).

The same PECO statement was used for addressing Aim 2 in order to answer the question: "Are cost-analyses adequately including all classifications of expenses (e.g., direct, indirect, social, and societal) incurred among different populations of adult patients with uUTI when comparing treatment strategies?"

Selecting the Evidence

Search Methods

Relevant studies for this review began with an initial search in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) utilizing the MeSH subject headings *"cost and cost analysis," "drug resistance, multiple, bacterial," "drug resistance, bacterial," "urinary tract infections," "community-acquired infections," "cystitis,"* and *"drug prescriptions"* in combinations with the keywords *"cost*," "economic," "urinary," "uncomplicated cystitis," "urinary tract infection," "empiric," "resistance," "collateral damage," "multidrug resist*," "antibiotic resist*,"* and *"outpatient"*. Additional filters within the Boolean search included the exclusion of results with the terms *"hospital-acquired"* or *"nosocomial."* We conducted searches January 23, 2015, and again September 27, 2015. In most cases, the search was not

limited by language or publication date in order to capture the changing landscape and clinical opinions regarding treatment strategies and resistance patterns; however, in some cases it was warranted to keep the number of search results manageable. The health-related databases PubMed, MEDLINE, and Scopus (http://www.scopus.com/) were searched as well as JSTOR (http://www.jstor.org/) and Web of Science (apps.webofknowledge.com) to expand the search beyond strictly medical databases. The resulting reference lists of search results were then screened and the relevant publications reviewed. Figure 1 describes the process by which studies were screened and included in the review. To minimize the introduction of bias, abstracts were screened twice, two months apart to check for consistent inclusion of relevant studies.

Study Selection Criteria

Studies in which antibiotic susceptibility profiles were conducted for patients seeking treatment for urinary tract infections in outpatient and/or inpatient settings were selected for this review. Populations including adolescents (i.e., aged 0 months to 15 years), geriatric, patients with complicated UTI (cUTI) (i.e., patients who are pregnant or have anatomical abnormalities) as they typically have additional complications associated with UTIs. Additionally, since uncomplicated infections are typically caused by *E. coli* and treated in outpatient settings, papers specific to hospital-acquired infections or organisms other than *E. coli* were excluded.

Data Extraction

A single researcher extracted the data into a standardized form for the following data points: the rate of treatment failure by antibiotic or resistance status, the observational association between resistant infections and treatment failure, the origin of infection and infection type, study location, study design, the number of study participants, and site of enrollment. For cost-effectiveness studies, data was extracted regarding study location, economic model

characteristics, sources of data, categories of included costs, and sources of funding. Tables 2 and 3 contain information on all studies included in the review. No additional data was obtained from the authors of reviewed manuscripts.

Rating the Quality and Strength of the Evidence

A single researcher rated the quality and strength of the evidence for all included studies by a) screening for risk of bias that may have introduced systematic error in the direction or magnitude of the results; b) rating the quality of the evidence across studies; and c) rating the strength of the evidence across studies.

Assessing Risk of Bias

A single researcher assessed the risk of bias for each study using a standardized form adapted from the Navigation Guide instructions for making risk determinations (Johnson 2014) including recruitment and selection bias, exposure assessment, complete outcome assessment, adequate controlling for confounders, additional sources of bias, and funding sources. Additional notes on selective reporting and publication bias were recorded. We assigned each bias domain as "high risk," "probably high risk," "low risk," and "probably low risk" based on instructions for each category in order to maximize consistency across included studies and recorded rationale for each designation (Appendix).

Rating the quality and strength of evidence across all studies

A single researcher rated the quality of evidence using the methodology outlined in the Navigation Guide originally adapted from the Grading of Recommendations Assessment Development and Evaluation (GRADE) method. The final rating was determined after downgrading or upgrading the quality from a pre-specified initial quality (i.e., moderate) for the following factors: risk of bias, indirectness (i.e., not directly comparable to the PECO set forth in

this review), inconsistency (i.e., variability in results), imprecision (e.g., small sample size), publication bias, large magnitude of effect, and whether confounding minimizes the effect (i.e., whether residual confounders or biases would underestimate the effect). Possible ratings included 0 (no change), -1 (one level downgrade), -2 (two level downgrade), +1 (one level upgrade) and +2 (two level upgrade).

One researcher rated the overall strength of the body of evidence based on the a) quality of evidence; b) direction of the effect estimate; c) likelihood that additional evidence would impact effect estimates; and d) additional elements that would influence certainty. Based on these results, the possible strength of evidence ratings was "sufficient evidence," "limited evidence," "inadequate evidence," and "lack of evidence" based on definitions provided in Johnson *et al* (2014) in Table 1.

Results

Search results

The search returned 768 total documents; including 420 from PubMed, 70 from Medline, 100 from Scopus, 89 from Web of Science, and 4 identified from other sources. Titles and abstracts were uploaded into Refworks to remove duplicates (N=166). Non-duplicated titles were screened for abstract review based on their relevance to the topic of antibiotic resistance and UTI. Abstracts were reviewed (N=351) to identify papers including treatment costs or comparing resistant versus susceptible community-acquired UTIs due to *E. coli*. Articles chosen for full-text screening (N=93) were reviewed for PECO inclusion criteria. Eleven articles met the PECO criteria for aim 1 (i.e., comparing treatment failure across antibiotic resistance status) and five compared expenses incurred for treatment of resistant *vs.* susceptible infections.

Treatment failure for resistant versus susceptible infections

Eleven documents reported clinical outcomes in resistant versus sensitive UTI-related infections in patients enrolled in outpatient clinics (N=8), hospital admissions (N=2), and health trusts (N=1) across six distinct geographical areas (Table 2). The majority of the studies parsed results apart by acquisition of infection (i.e., community-acquired or hospital-acquired), pathogen-specific (i.e., *E. coli* infection), and uncomplicated versus complicated or recurring infections (rUTI), although two studies did not break down the risk of mortality by community-acquired or hospital-acquired infection (Melzer 2007, Anunnatsiri 2012).

As shown in Table 2 and Figure 2, community-acquired antibiotic-resistant UTI-related infections were significantly associated with a longer duration of symptoms and greater risk of treatment failure and follow-up visits. Studies using follow-up culture results to determine treatment failure found short-term treatment failure occurred in nearly half of patients with TMP-SMX-resistant infections compared to one-fifth among patients with TMP-SMX-sensitive infections (Raz 2002, McNulty 2006), and FQ-resistant isolates were independently associated with an 85% increase in rates of treatment failure among women with uUTI (Gagliotti 2008). Clinical treatment failure (e.g., continuation of symptoms) was significantly associated with an infection resistant to the antibiotic empirically prescribed (Butler 2006, Johnson 2011, MacVane 2014) as well as infections with the ST131 *E. coli* clone (Can 2015) and TMP-SMX resistant infections (Talan 2000, Noskin 2001, Raz 2002, McNulty 2006). Two studies also found that TMP-SMX resistant infections exhibited treatment failure even if initially treated appropriately (i.e., infection sensitive to antibiotic prescribed) compared to patients with infections sensitive to all antibiotics (Noskin 2001, Butler 2006). In patients with multidrug-resistant bacterial

infections caused by organisms producing ESBL enzymes, the risk of mortality was significantly higher among inpatients infected with ESBL-producing *E. coli* compared to those infected by non-ESBL-producing *E. coli* largely due to delay in appropriate treatment (Melzer 2007, Anunnatsiri 2012).

While empiric versus directive treatment strategies were not directly compared, follow up and/or re-consultation was included in two designs (McNulty 2006, Johnson 2011). For those with TMP-SMX-resistant isolates, McNulty et al. (2006) found re-consultation significantly decreased the hazard rate ratio compared to those who did not re-consult, although the authors did not specify whether culture results informed the antibiotic choice. Johnson et al. (2011) found that patients with infections resistant to the antibiotic prescribed were more likely to initiate follow up, but acknowledges that culture results were not available by the time most patients followed up.

Cost-based outcomes

Five documents examined the costs to treat patients with resistant and sensitive community-acquired UTIs within clinical settings (Table 3). Two observational studies found that resistant infections cost nearly twice as much to treat than susceptible *E. coli* UTI infections (Alam 2009, MacVane 2014). Three simulation studies utilized similar decision-tree models to calculate the cost breakeven points for treating infections among different susceptibility pattern scenarios with TMP-SMX, Ciprofloxacin, and Nitrofurantoin (Le 2001, Perfetto 2004, McKinnel 2011). Cost categories ranged from antibiotic acquisition and additional outpatient services (Alam 2009) to direct outpatient and inpatient costs (including pharmaceutical lab costs) (Le 2001, Perfetto 2004, McKinnel 2011), and direct plus indirect costs (i.e., as determined by the hospital accounting department) (MacVane 2014). No document comparing the monetary costs from

treating resistant to sensitive UTIs included social costs (e.g., productivity lost) or societal costs (i.e., the decreased local effectiveness of prescribed antibiotics).

When comparing the costs of resistant versus susceptible community-acquired uUTI among ESBL-positive inpatients, inappropriate initial antibiotic prescription resulted in a delay for appropriate treatment, prolonged length of stay, and an additional cost of care ($10,741 versus $7,083, p=0.02) (MacVane 2014). For patients with UTI-associated bacteremia, cases (i.e., ESBL-positive patients) and controls (i.e, ESBL-negative patients) had a median delay to appropriate therapy of 56 versus 2 hours, respectively (p=0.003). Infections resistant to TMP-SMX cost nearly double the amount to treat than TMP-SMX-sensitive infections and were virtually unchanged when controlling for age, gender, previous bladder operation, co-morbidity, and previous catheterization (Alam 2009). The authors conclude that if their population were generalizable across Wales, patients with a uUTI resistant to one antibiotic would result in an extra £5.8 million annually (confidence interval (CI): £1.5-9.8 million) due to re-consultations and additional prescriptions alone.

Consistently, simulation studies demonstrated that increased resistance and treatment failure rates resulted in greater costs to treat resistant infections, primarily due to follow-up appointments and secondary infections (i.e., kidney or vaginal yeast infection) (Le 2001, Perfetto 2004, McKinnel 2011). Costs of treatment ranged from $57.50 to $159 across plausible susceptibility patterns among the population (e.g., 0-40% resistant to TMP-SMX, 0-12% resistant to FQ, or 1.2% resistant to Nitrofurantoin). Simulation studies consistently included costs due to the antibiotic acquisition, outpatient care, and subsequent hospitalizations or treatment for secondary infections (i.e., kidney or vaginal yeast infections). Using a telephone-based empirical prescription protocol, Perfetto et al (2004) estimated treatment cost at $4.19 per

patient when resistance rates to TMP-SMX and Ciprofloxacin were low (i.e., 4.3% and 1%, respectively). In the same study, "treatment failure including an ER visit" was over $300 while "failure without ER" ranged from $174 to $222 and "treatment success" ranged from $0.21 (empiric telephone scenario) to $48.23 (outpatient care). Consistently, authors of simulation studies conclude that prescribing a more expensive per dose antibiotic (i.e., Ciprofloxacin over TMP-SMX) will not increase costs and may lower the cost of care (Le 2001, Perfetto 2004, McKinnel 2011).

Quality and Strength of Evidence

Risk of Bias

Eleven studies from Aim 1 were reviewed for risk of bias according to instructions predetermined by the author (Appendix) as high risk, probably high risk, probably low risk, and low risk (Figure 3). Incomplete outcome assessment had the leading count of studies outside of the "low risk" classification, with two studies considered "high risk", two as "probably high risk" among studies that determined treatment failure within one month of treatment (Noskin 2001, Butler 2006, Johnson 2011, Can 2015) and probably low risk among studies with uncertain lost to follow-up (N=4) (Talan 2000, Melzer 2007, Gagliotti 2008, MacVane 2014). Important confounders (i.e., history of hospitalization, surgery, or catheters, abnormal urinary anatomy or other factors related to complicated UTI, history of recent or recurring UTI, recent antibiotic prescription) were controlled for in various combinations across studies. Probably low risk (N=6) distinctions for confounding had unclear descriptions as to what medical records were extracted (Noskin 2001, Butler 2006, Melzer 2007), did not include factors related to rUTI or cUTI (Gagliotti 2008, Can 2015), or did not distinguish between community-acquired and hospital-acquired infections (Anunnatsiri 2012). One study had probably high risk as it did not control for

factors related to previous hospitalization, surgery, or catheter (Raz 2002). Selection bias was considered low risk across the majority of included studies (N=9) with one study classified as high risk because there was a differential amount of cases transferred from another hospital than controls (MacVane 2014). Exposure assessment was predominately low risk with the exception of four studies that provided minimal information relative to the quality control of laboratory procedures (Raz 2002, Butler 2006, Melzer 2007, MacVane 2014).

Two retrospective studies had a risk of bias due to enrollment based on existing urine cultures (Gagliotti 2008, Anunnatsiri 2012), and two prospective ones had a risk of bias due to subjects enrolled solely from a single hospital. Both scenarios had the risk that participants had UTIs with greater severity or risk factors than typical outpatient uUTIs, which prompted the need for hospital admission and/or culture tests. Lastly, three publications were supported directly by pharmaceutical companies (Talan 2000, Noskin 2001, MacVane 2014) while the remaining declared no competing interests (N=4), supplied no details on possible conflicts (N=2), or disclosed non-industry sources of funding (N=2).

Quality & Strength of Evidence

The evidence was upgraded (+2) and downgraded (-2) resulting in an overall quality rating of "moderate" for human evidence (Table 4). Five studies were considered indirect because they did not differentiate between hospital-acquired and community-acquired infections (Melzer 2007, Anunnatsiri 2012) or between *E. coli* infections and other organisms (Raz 2002, Johnson 2011, MacVane 2014). Although the search was comprehensive with consistent findings across studies of variable size and funding sources, the quality was downgraded for publication bias because only two studies reported no effect or insignificant findings (i.e., $p>0.05$) for primary outcomes (Johnson 2011, MacVane 2014). Effect sizes ranged from 1.85 to 7.76 and, therefore,

were considered to have a large magnitude of an effect. Lastly, it was theorized that residual confounding potentially from previous UTI and prescription history, facility catchment populations, or prescription duration could have minimized the effect size.

The strength of evidence considerations was determined to be sufficient based on four factors. The quality of the body of the evidence was moderate as discussed previously. The direction of the effect estimate consistently was positive with treatment failure was more frequent in resistant infections than susceptible ones. The confidence in effect estimate was considered unlikely that a new study would have an effect estimate decreasing these overall trends should a meta-analysis be conducted. Based on the interpretation of the included studies, a positive relationship between susceptibility status of uUTI and treatment failure where chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes results from one or more well-designed, well-conducted studies; and, the conclusion is unlikely to be strongly affected by the results of future studies.

Discussion

The risk of treatment failure was greater in community-acquired UTI patients with resistant strains of *E. coli* versus susceptible ones*;* and it is associated with a delay until appropriate treatment, increased length-of-stay, additional outpatient medical care, and increased cost of care. The costs were measured relatively consistently across the medical literature but limited to direct costs such as hospital expenditures or antibiotic cost. No cost-effective analysis for community-acquired UTI reviewed in this paper incorporated social (e.g., lost productivity) or societal costs (e.g., the risk of increasing resistance over time); however, Butler et al (2006) did include lost productivity in nonmonetary terms and concluded that patients with UTIs resistant to

TMP-SMX or their antibiotic prescribed had a significantly higher risk of feeling "out of action" for over five days.

Basis for prior IDSA recommendations

Empiric treatment is recommended by the IDSA based on previous analyses concluding it is cost-effective and reduces symptom days and delays in appropriate treatment for those with susceptible uUTIs (Schultz 1984, Fenwick 2000, Gupta 2011), but due to its imperfect nature, it has also been concluded to be the least effective treatment strategy when compared to more directive approaches (Rothberg 2004). Among hospitalized patients, receiving inappropriate treatment (i.e., a prescription for an infection that has *in vitro* resistance to that drug) within 72 hours using empiric prescription was associated with septicemia; and, patients subsequently receiving directive treatment (i.e., based on lab results) had a 0.5 days median time decrease to appropriate treatment compared to empiric prescription among ESBL-producing and non-ESBL-producing infections (Anunnatsiri 2012). Additionally, empiric prescription led to unnecessary exposure to antibiotics in patients with negative culture results resulting in collateral damage (e.g., subsequent antibiotic-resistant infections) (Noskin 2001, Costelloe 2010). Of the 156 patients empirically treated in Noskin et al. (2001), 42 patients were unnecessarily exposed to antibiotics as outpatients and one developed bacteremia necessitating two weeks of hospitalization and $25,000 in charges. Shultz et al (1984) first published that empiric prescription was more cost-effective than laboratory testing for pathogens; however, within their sample, there were no antibiotic-resistant uropathogens. Resistance rates to commonly prescribed antibiotics increased rapidly over the two last decades and the results of this review call into question the current policy of empiric prescription as a cost-effectiveness treatment strategy. Furthermore, as seen in Table 3, most cost-effectiveness measures do not include the risk of

increasing resistance over time (i.e., considering resistance as dynamic rather than static) resulting in potentially shortsighted recommendations not generalizable to future population resistance scenarios.

Factors in increased cost of care

The increase in the cost of care for resistant infections is overwhelmingly not due to antibiotic acquisition or laboratory costs (e.g., urinalysis and culture tests) which have the potential for reducing delay until appropriate treatment (Noskin 2001, MacVane 2014). Opponents for performing routing cultures cite expensive laboratory costs as the rationale against cost- effectiveness; however, four hospitalizations totaling $35,000 in Noskin et al (2001) due to UTI progression and collateral damage were far greater than the lab costs ($4,700) to perform susceptibility profiles on all 156 participants in this study. In relation to treatment failure, McNulty et al (2006) calculated that for every 23 UTI patients receiving urinalysis and culture tests only one had a resistant infection with treatment failure concluding that laboratory testing was ineffective compared to empiric treatment. In contrast, patients enrolled into their study using nitrite dipstick tests compared to those enrolled by symptoms alone were more likely to have a positive culture (83% *vs.* 71%, p=0.004) thereby decreasing collateral damage among patients without bacterial infections receiving unnecessary antibiotics. Despite the advantages of directive treatment and the rapid emergence of community-acquire UTI resistance among multiple commonly prescribed antibiotics, the most recent ISDA guidelines do not recommend routine testing as standard care but instead recommend empiric prescription based on local surveillance data (Gupta 2011).

The results of this review suggest the medical literature lags behind in considering the true costs of treating community-acquired UTI (Table 3). Economic models of cost-effectiveness

including antibiotic resistance have been present for decades (Coast 1996, Rubin 1996, Laxminarayan 2010) and include assumptions related to the complexities of antibiotic resistance (e.g., annual increases to rates of resistance); yet, these were not utilized in any publications reviewed in this review. Given that laboratory testing is not a major contributor to the overall costs of treating a resistant infection (Butler 2006, MacVane 2014), is it time to reconsider the value of diagnostic testing in routine treatment of community-acquired uUTI?

Point-of-care tests (POCT) allow for informed antibiotic prescribing (e.g., using a dipstick to guide antibiotic prescribing), but range in sensitivity and specificity and do not address antibiotic resistance specifically (Chalmers 2015). Combinations of POCT with susceptibility tests conducted within 24 hours assessed against overall treatment failure are currently being tested by a research team in Denmark and may be able to reduce the number of unnecessary antibiotics prescribed (Holm 2015). Ultimately, because delaying treatment is painful and, therefore, undesired, a rapid diagnostic test and/or POCT must be quick enough to encourage use among patients who have been conditioned to expect an empiric prescription for uUTI. Including new diagnostic tests in future cost-analyses comparing uUTI management strategies will be of paramount importance to identifying optimal treatment strategies in populations with significant antibiotic resistance to commonly prescribed antibiotics.

Strengths and limitations of this review

Previous systematic reviews primarily served as meta-analyses to identify treatments with the greatest clinical success of treatment (i.e., rates of cure and improvement) with the fewest side effects often ignoring complicating factors such as resistance. In contrast, this literature review is the first to compare the methods and results from observational studies used in clinical decision-making for UTIs with respect to antibiotic resistance and cost. Additionally, this is the first

review to take a public health perspective on the empiric treatment of uUTIs with consideration to the economic externalities as well as utilizing a tool for assessing the strength of the evidence in the field of environmental epidemiology. The author has no funding declarations or competing interests to report.

This review was conducted by a single researcher allowing for bias to enter at article selection, data extraction, assigning risk, and rating study quality and strength of evidence. This could influence the results either through the inclusion of inappropriate studies or the exclusion of relevant studies as well as imposing a personal bias when assigning risk, rating quality, and determining the strength of evidence. Additional limitations also include exclusion of relevant publications that are applicable to cost-effective decision-making within other types of resistant infections (e.g., hospital-acquired UTI). However this review is meant to be generalizable to outpatient practitioners utilizing empiric treatment of community-acquired UTI, and the inclusion of hospital-acquired infections could bias the results. Lastly, due to the small number of publications meeting inclusion criteria, the risk of treatment failure was compared generally despite wide variability in definitions of clinical success, thereby limiting opportunities for directly comparing results.

Conclusions

Patients with resistant uUTIs had a greater chance of treatment failure and cost more to treat, but this review finds that the body of evidence comparing economic outcomes for patients with resistant versus susceptible community-acquired UTIs is not adequate to determine true cost-effectiveness across treatment strategies. Empiric prescription should be reevaluated incorporating external costs against new diagnostic and point of care technology using current and expected antibiotic resistance rates. There is a need for health economists, public health

professionals, and physicians to utilize new and existing models that include social and societal costs in order to inform international treatment guidelines for community-acquired uUTI.

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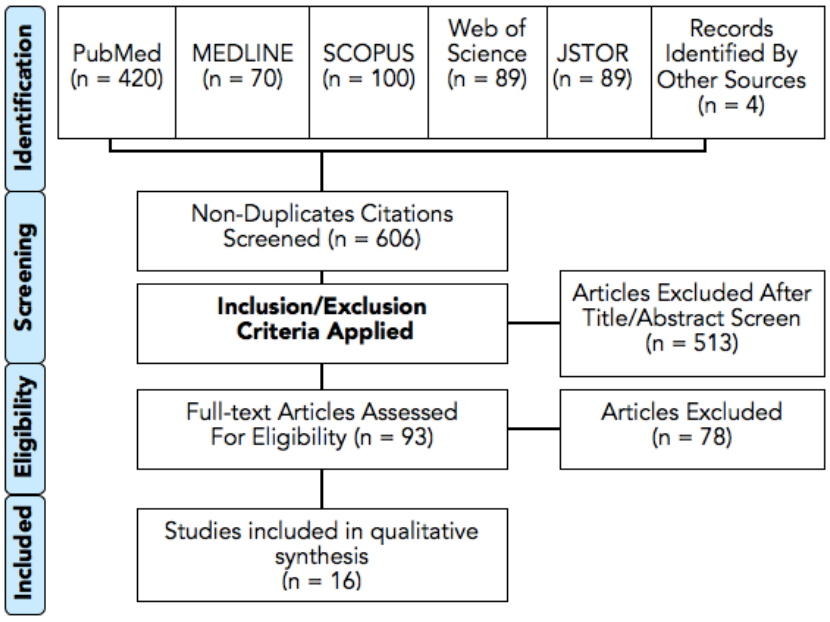

Figure 1. Flow diagram of inclusion/exclusion process using the PRISMA 2009 Flow Diagram

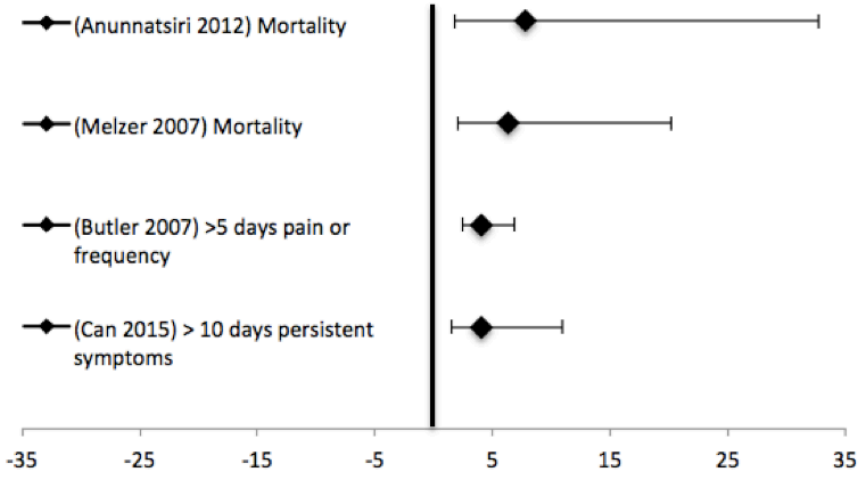

Figure 2. Forest plot across observational studies displaying odds ratio of treatment failure with 95% confidence intervals.

Strength Rating	Definition (Johnson 2014)
Sufficient Evidence	A positive relationship is observed between exposure and outcome, where chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes results from one or more well designed, well-conducted studies, and the conclusion is "unlikely to be strongly affected by the results of future studies."
Limited Evidence	A positive relationship is observed between exposure and outcome, where chance, bias, and confounding cannot be ruled out with reasonable confidence. Confidence in the relationship is constrained by factors such as "the number, size, or quality of individual studies" or "inconsistency of findings across individual studies." As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion
Inadequate Evidence	"The available evidence is insufficient to assess effects" of the exposure. The evidence is insufficient because of "the limited number or size of studies," low quality of individual studies, or "inconsistency of findings across individual studies." More information may allow an assessment of effects.
Lack of Evidence	No relationship is observed between exposure and outcome; and chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes consistent results from more than one well-designed, well-conducted study at the full range of exposure levels that humans are known to encounter, and the conclusion is unlikely to be strongly affected by the results of future studies. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

Table 1. Strength of evidence classification definitions.

Outcome	Resistance Profile	OR or Point Estimate[f]	% Treatment Failure or Primary Outcome[a]		Infection	N=	Reference
			Resistant	Sensitive			
Mortality	ESBL-producing *E. coli*	7.76 (1.84-32.72)	24.1	5.7	Septicemia	134	(Anunnatsiri 2012)
Mortality	ESBL-producing *E. coli*	6.32 (1.99-20.09)[b]	-	-	UTI-caused bacteremia	239	(Melzer 2007)
>5 days pain or frequency	TMP-SMX	4.0 (2.4-6.9)[c]				835	
>5 days out of action	TMP-SMX	3.6 (2.0-6.4)					
Follow up visit < 30 days	TMP-SMX	2.48 (1.70-3.59)	-	-	UTI		(Butler 2006)
>5 days pain or frequency	Antibiotic Prescribed	3.4 (2.1-5.5)[c]				797	
>5 days out of action	Antibiotic Prescribed	3.4 (2.0-5.8)					
>10 days persistent symptoms	ST131 Clone	4.0 (1.51-10.93)[d]	-	-	UTI	294	(Can 2015)
Short-term relapse[e]	Ciprofloxacin	1.85 (1.32-2.60)[f]	-	-	uUTI	772	(Gagliotti 2008)
Follow up visit < 2 weeks	Antibiotic prescribed	-	52[a]	5[a]	uUTI	783	(Johnson 2011)
Positive follow up culture[g]	TMP-SMX	-	58 (54-70)	18 (8-19)	uUTI	484	(Raz 2002)
Persistence of symptoms > 6 days	TMP-SMX	-	48	17	uUTI	317	(McNulty 2006)
Positive follow up culture	TMP-SMX		42	20			
Antibiotic failure[h]	ESBL-EK	-	61.8	5.5	UTI	110	(MacVane 2014)
Required additional antibiotics[i]	Any antibiotic	-	39	11	uUTI	89	(Noskin 2001)
	TMP-SMX		45	17			
Persistence of symptoms >3 days[i]	TMP-SMX	-	65	8	Kidney infection[j]	100	(Talan 2000)

Table 2. Point estimations and percent treatment failure among included studies for aim 1. b: adjusted for age, sex, site of infection, hospital-acquired or community-acquired, presence of intensive care, hypotension at the time of bacteremia, malignancy, and neutropenia; c: all values adjusted for age, sex, comorbidity, previous bladder operation, and previous catheterization; d: adjusted for age, recent antibiotic use, hospitalization, or surgery, chronic heart disease, diabetes, chronic renal failure, ST131 clone, quinolone resistance, ESBL production, and multidrug resistance; e: a second isolation of *E. coli* from urine between 4 and 30 days after the first one; f: rate ratio; g: converted from dichotomous category of bacteriologic cure 5-9 days after cessation of therapy; h: switch to alternative prescription or infection-related mortality while on index antibiotic; i: converted from dichotomous category of clinical cure; j: acute uncomplicated pyelonephritis.

Study Type	Cost to Treat Resistant	Cost to Treat Sensitive	Susceptibility Profile	Cost Classifications	Infection	Reference
Observational	£4.68 £17.35 £22.04	£1.65 £9.18 £10.82	TMP-SMX	Pharmaceutical costs Follow up costs Total Costs	UTI; N=865	(Alam 2009)
Observational	(+)3,658 $27,671	- $5,898	ESBL-EK ESBL-EK Bacteremia	Pharmaceutical costs Direct hospital costs Indirect hospital costs	UTI; N=110	(MacVane 2014)
	Susceptibility Breakeven Point	**Cost**	**% Resistance**	**Cost Classifications**	**Infection**	**Reference**
Simulation	10% - FQ 26% TMP-SMX	$92 $106 $120	0% TMP-SMX 20% TMP SMX 40% TMP-SMX	Pharmaceutical costs Hospitalizations Outpatient care Secondary infections Urinalysis and cultures	uUTI	(Le 2001)
Simulation	1.2% - Nitro 12% - FQ 17% TMP-SMX	$151 $159	0% FQ 12% FQ	Pharmaceutical costs Hospitalization Outpatient care Secondary infections Urinalysis and cultures	uUTI	(McKinnel 2011)
Simulation	10% - FQ 13% TMP-SMX	$57.50	10% FQ 13.3% TMP-SMX	Pharmaceutical costs Outpatient treatment Secondary infections Ambulatory care Urinalysis and cultures Lab fees	uUTI	(Perfetto 2004)

Table 3. Cost to treat patients with resistant and sensitive *E. coli* UTIs including categories of expenses and resistance rate tipping points where it becomes cost-effective to use the more expensive antibiotic. ESBL-EK: extended-spectrum beta -lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species.

Quality Factors	Rating	Basis
		Downgrade
Risk of Bias Across Studies	0	There was no indication of substantial risk of bias.
Indirectness	-1	Two studies included hospital-acquired infections within their analysis (Melzer 2007, Anunnatsiri 2012) and three included organisms other than *E. coli* (Raz 2002, Johnson 2011, MacVane 2014).
Inconsistency	0	Results across studies were similar in direction and magnitude.
Imprecision	0	With the exception of two studies (Melzer 2007, Anunnatsiri 2012) confidence intervals were sufficiently narrow.
Publication Bias	-1	Only two of the eleven studies reported negative or insignificant findings.
		Upgrade
Large Magnitude of Effect	1	Effect sizes ranged from 1.85 to 7.76.
Confounding Minimizes Effect	1	Two studies had evidence that residual confounding would reduce effect estimate (Melzer 2007, MacVane 2014), and all but one study (Gagliotti 2008) ended the data collection within one month of treatment.
Overall Quality of Evidence (Initial Rating is "Moderate")	Moderate	Moderate + (0) = Moderate.
		Strength Considerations
Quality of Body of Evidence	N/A	Moderate.
Direction of Effect Estimate	N/A	Treatment failure was more frequent in resistant infections than susceptible ones.
Confidence in Effect Estimate	N/A	It is unlikely a new study would have an effect estimate that would decrease the overall trends.
Other Compelling Attributes of the Data that may Influence Certainty	N/A	None.
Overall Strength of Evidence	Sufficient	Based on our interpretation of the included studies, a positive relationship between susceptibility status of UTI and treatment failure where chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes results from one or more well-designed, well-conducted studies; and, the conclusion is unlikely to be strongly affected by the results of future studies.

Table 4. Ratings for the quality and strength of evidence regarding rates and risk of treatment failure among uUTI in patients with resistant *vs.* susceptible organisms

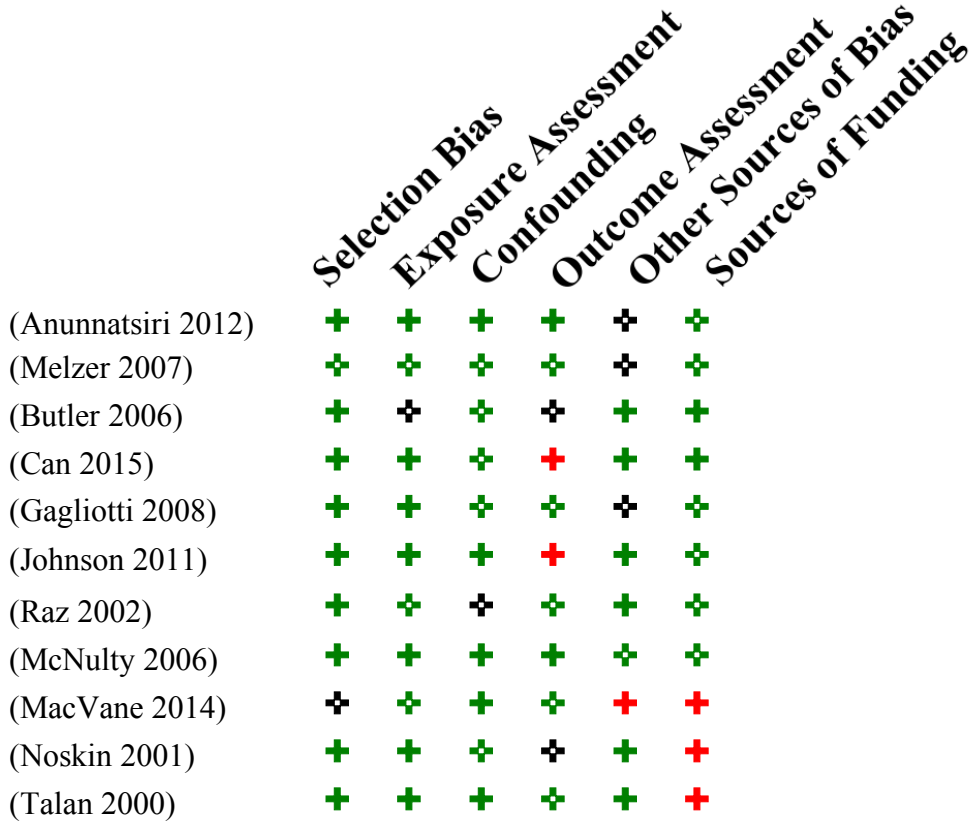

Figure 3. Risk of bias summary of included studies.

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Appendix: Criteria for making risk of bias determinations

1. Was the strategy for recruiting participants consistent across study groups?	
Low	Protocols for recruitment and inclusion/exclusion criteria were applied similarly across study groups, and any one of the following: • Study participants were recruited from the same population at the same time frame
Probably Low	There is insufficient information about participant selection to permit a judgment of 'YES', but there is indirect evidence that suggests that participant recruitment and inclusion/exclusion criteria was consistent, as described by the criteria for a judgment of 'YES'.
High	Any one of the following: • Protocols for recruitment or inclusion/exclusion criteria were applied differently across study groups; or • Study participants were recruited at different time frames; or • Study participants were recruited from different populations and proportions of participants from each population in each study group are not uniform
Probably High	There is insufficient information about participant selection to permit a judgment of 'NO', but there is indirect evidence that suggests that participant recruitment or inclusion/exclusion criteria were inconsistent, as described by the criteria for a judgment of 'NO'.
2. Were exposure assessment methods robust?	
Low	The reviewer judged that there is low risk of exposure misclassification and any one of the following: • There is high confidence in the accuracy of the exposure assessment methods to determine UTI susceptibility and culture results AND if applicable, appropriate QA/QC for methods are described and are satisfactory
Probably Low	There is insufficient information about the exposure assessment methods to permit a judgment of 'YES', but there is indirect evidence that suggests that methods were robust, as described by the criteria for a judgment of 'YES'.
High	The reviewer judged that there is high risk of exposure misclassification and any one of the following: • There is low confidence in the accuracy of the exposure assessment methods to determine UTI susceptibility profiles; or • less-established or less direct exposure measurements are not validated and are suspected to introduce bias that impacts the outcome assessment (example: participants are asked to report exposure status retrospectively, subject to recall bias) • Uncertain how exposure information was obtained
Probably High	There is insufficient information about participant selection to permit a judgment of 'NO', but there is indirect evidence that suggests that participant recruitment or inclusion/exclusion criteria was inconsistent, as described by the criteria for a judgment of 'NO'.
3. Was confounding adequately addressed?	
Low	The study accounted for (i.e., matched, stratified, multivariate analysis or otherwise statistically controlled for) important potential confounders such as history of recurrent UTI and complicated UTI, hospitalization, surgery, or urinary catheter; or • reported that potential confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may be informed by the data, including the studies included in the review.
Probably Low	The study accounted for most but not all of the important potential confounders AND this lack of accounting is not expected to introduce substantial bias.
High	The study did not account for or evaluate important potential confounders.
Probably High	The study accounted for some but not all of the important potential confounders AND this lack of accounting may have introduced substantial bias.

4. Were incomplete outcome data adequately addressed?	
Low	Participants were followed long enough to obtain outcome measurements relative to reinfection (>1 months for UTI) and any one of the following: • No missing outcome data; or • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); or • Missing outcome data balanced in numbers across exposure groups, with similar reasons for missing data across groups.
Probably Low	There is insufficient information about incomplete outcome data to permit a judgment of 'YES', but there is indirect evidence that suggests incomplete outcome data was adequately addressed, as described by the criteria for a judgment of 'YES'.
High	Participants were not followed long enough to obtain outcome measurements relative to reinfection (<1 months for UTI) OR any reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across exposure groups.
Probably High	There is insufficient information about incomplete outcome data to permit a judgment of 'NO', but there is indirect evidence that suggests incomplete outcome data was not adequately addressed.
5. Was the study apparently free of other problems that could put it at a risk of bias?	
Low	The study appears to be free of other sources of bias.
Probably Low	There is insufficient information to permit a judgment of 'YES', but there is indirect evidence that suggests the study was free of other threats to validity.
High	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used or population recruited; or • Had extreme imbalance of characteristics among exposure groups; or • Selective reporting of subgroups; or • Had some other problem.
Probably High	There is insufficient information to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of other threats to validity.
6. Was the study free of support from a company, study author, or other entity having a financial interest in any of the exposures studied?	
Low	The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples include the following: • Funding source is limited to government, non-profit organizations, or academic grants funded by government, foundations and/or non-profit organizations; • Chemicals or other treatment used in study were purchased from a supplier; • Company affiliated staff are not mentioned in the acknowledgements section; • Authors were not employees of a company with a financial interest in the outcome of the study; or • Company with a financial interest in the outcome of the study was not involved in the design, conduct, analysis, or reporting of the study and authors had complete access to the data; • Study authors make a claim denying conflicts of interest; • Study authors are unaffiliated with companies with financial interest, and there is no reason to believe a conflict of interest exists; • All study authors are affiliated with a government agency (are prohibited from involvement in projects for which there is a conflict of interest or an appearance of conflict of interest).
Probably Low	There is insufficient information to permit a judgment of 'YES', but there is indirect evidence that suggests the study was free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of 'YES'.
High	The study received support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples of support include: • Research funds; • Chemicals provided at no cost; • Writing services; • Author/staff from study was employee or otherwise affiliated with company with financial interest; • Company limited author access to the data; • Company was involved in the design, conduct, analysis, or reporting of the study; • Study authors claim a conflict of interest.
Probably High	There is insufficient information to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study.