

# US-Focused Conceptual Health Care Decision-Analytic Models Examining the Value of Pivmecillinam Relative to Current Standard-of-Care Agents Among Adult Patients With Uncomplicated Urinary Tract Infections due to Enterobacterales

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**Background.** Pivmecillinam is approved for the treatment of adults with uncomplicated urinary tract infection (uUTI) in Canada and Europe and is pending United States (US) Food and Drug Administration submission for consideration for approval. US-focused health care decision-analytics were developed to define the value of an agent like pivmecillinam relative to current standard-of-care (SOC) agents among adult patients with Enterobacterales uUTIs based on its improved microbiologic activity against common Enterobacterales.

**Methods.** The model population was 100 theoretical adult outpatients with Enterobacterales uUTIs under 4 different uUTI first-line empiric treatment scenarios (ie, pivmecillinam, nitrofurantoin, trimethoprim-sulfamethoxazole [SXT], or fluoroquinolones). The total mean uUTI-related 30-day costs, including inappropriate treatment costs, were calculated for each regimen. The range of pivmecillinam regimen costs that conferred cost savings relative to the current SOC agents based on its potentially improved microbiologic activity against common Enterobacterales was determined.

**Results.** The 30-day uUTI-related costs associated with nitrofurantoin, SXT, and fluoroquinolones were \$655.61, \$687.57, and \$659.69, respectively. The pivmecillinam neutral regimen cost thresholds that resulted in the same uUTI-related 30-day per-patient costs for nitrofurantoin, SXT, and fluoroquinolones were \$83.50, \$115.45, and \$87.58, respectively. The overall antimicrobial susceptibility improvement required with pivmecillinam fixed at \$200/regimen, for it to be cost savings relative to SOC agents, was 28%.

**Conclusions.** The analyses suggests that an agent like pivmecillinam, if approved in the US, has the potential to reduce the economic burden associated with inappropriate treatment of adult outpatients with uUTIs, especially in patients at high risk for an Enterobacterales uUTI that is resistant to SOC agents.

**Keywords.** modeling; outcomes; pivmecillinam; treatment; UTI.

Uncomplicated infections of the urinary tract are commonplace and among the most frequently encountered infections in the outpatient setting. It is estimated that there are >30 million uncomplicated urinary tract infections (uUTI) treated with short-course antibiotics each year, typically occurring in adult females who are otherwise healthy [1, 2]. Most patients

with uUTIs in the outpatient setting receive treatment with either nitrofurantoin, trimethoprim-sulfamethoxazole (SXT), or fluoroquinolones [3, 4]. Despite their longstanding use, the United States (US) Food and Drug Administration (FDA) recommends that fluoroquinolones only be prescribed for patients with uUTIs when there are no treatment alternatives given increased reports of rare but serious side effects [5]. Furthermore, resistance to both fluoroquinolones and SXT among *Escherichia coli*, the predominant cause of uUTIs, exceeds 20% in most US regions [6–8]. Although nitrofurantoin remains highly active against *E coli*, including extended-spectrum  $\beta$ -lactamase (ESBL)-producing strains, it is less active against other uropathogenic Enterobacterales. This is concerning because non-*E coli* Enterobacterales represent >20% of uUTIs in the outpatient setting [6, 9, 10]. Due to the high prevalence of resistance, approximately 1 in 5 adult outpatients with a uUTI

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will receive empiric treatment with an antibiotic for which the offending uropathogen is resistant [11, 12]. The rate of inappropriate therapy among adult uUTI outpatients with current standard-of-care (SOC) agents is highly concerning because empiric treatment with a microbiologic inactive agent has been directly linked to the progression of the infection in many patients, resulting in a substantial number of treatment failure-related physician office, emergency department (ED), and hospital visits [10–16].

Pivmecillinam, an oral prodrug of mecillinam, is approved for the treatment of uUTI in Europe and Canada and is expected to be submitted for consideration for approval in the US for the treatment of adults with uUTIs. It is highly active against *E coli* and other Enterobacterales, including ESBL-producing strains [17–19]. It is frequently used as a first-line uUTI agent in Europe [18] and is recommended as a first-line therapy for uUTI in the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases guidelines [20, 21]. Despite its frequent and continued use, resistance among common gram-negative Enterobacterales uropathogens has only been reported to be 1%–4% across most European countries [18]. Consistent with other  $\beta$ -lactam antibiotics, pivmecillinam has a well-established safety profile [22]. Despite nearly 30 years of clinical use, only 437 individual cases of adverse events have been registered in EudraVigilance between 1994 and October 2019 [23].

Given the critical need for additional empiric uUTI agents with robust in vitro microbiological activity against common Enterobacterales uropathogens, the intent of this study was to develop a US-focused conceptual health care decision-analytic model to define the potential value of an agent like pivmecillinam relative to current SOC agents among adult patients with uUTIs due to Enterobacterales. The primary objectives were (1) to define the total uUTI-related 30-day health care resource costs, factoring in the costs due with empiric receipt of an antibiotic for which the offending uropathogen is resistant (ie, inappropriate empiric treatment), associated with the use of nitrofurantoin, SXT, and fluoroquinolones for patients with uUTIs due to Enterobacterales; (2) to quantify the range of total regimen costs for pivmecillinam that conferred cost-savings (ie, cost-neutral threshold) relative to current SOC agents based on its potentially greater microbiologic activity against common Enterobacterales relative to current first-line treatments; and (3) to quantify the net improvement in susceptibility with pivmecillinam relative to current SOC agents to support a cost-neutral threshold of \$200 per regimen.

## METHODS

### Model Description

A deterministic framework from the US payer perspective was used to develop the conceptual health care decision-analytic

model that compared an agent like pivmecillinam to current SOC agents for the first-line empiric treatment of adult outpatients with uUTIs due to Enterobacterales. Despite lacking current US approval for treatment of adult patients with uUTIs, the US perspective was selected to demonstrate the potential cost savings or value associated with a new uUTI agent like pivmecillinam that could be anticipated at market entry given the observed rates of treatment failure and resistance among Enterobacterales with current SOC agents. For the purposes of this analysis, SOC agents included nitrofurantoin, SXT, and fluoroquinolones, as these are the most prescribed first-line agents in the US among adult outpatients with uUTIs due to Enterobacterales [3, 4]. We used a deterministic vs probabilistic model because the temporal associations between events have been well established. A deterministic model was also better suited for addressing the primary study objective (ie, define the total regimen cost for an agent like pivmecillinam that that conferred cost-savings relative to current SOC agents). Furthermore, we did not have data on patients' future health status that would affect their subsequent health care resource utilization beyond 30 days and on patient-centric outcomes like quality of life and ability to resume normal daily activities.

One of the major underlying model assumptions was that pivmecillinam, nitrofurantoin, SXT, and fluoroquinolones had similar effectiveness and safety profiles. This assumption was based on the similar outcomes observed between pivmecillinam, nitrofurantoin, SXT, and fluoroquinolones in a systematic network meta-analysis of randomized controlled uUTIs trials [24] and 2 real-world comparative effectiveness studies [13, 25]. Although effectiveness and safety were deemed to be equivalent in the model, another major underlying assumption was that treatment failure rates for each treatment varied as a function of the appropriateness of the initial empiric agent received (ie, in vitro microbiologic activity of the empiric agent received against the Enterobacterales identified on urine culture) and that similar outcomes were observed among patients who received appropriate vs inappropriate empiric therapy, regardless of initial agent received. Numerous studies, including both randomized clinical trials [15, 16, 26] and real-world evidence studies [10–14], have demonstrated that receipt of a microbiologic inactive empiric agent (ie, inappropriate empiric treatment) independently increases the risk of treatment failure.

### Model Structure and Population

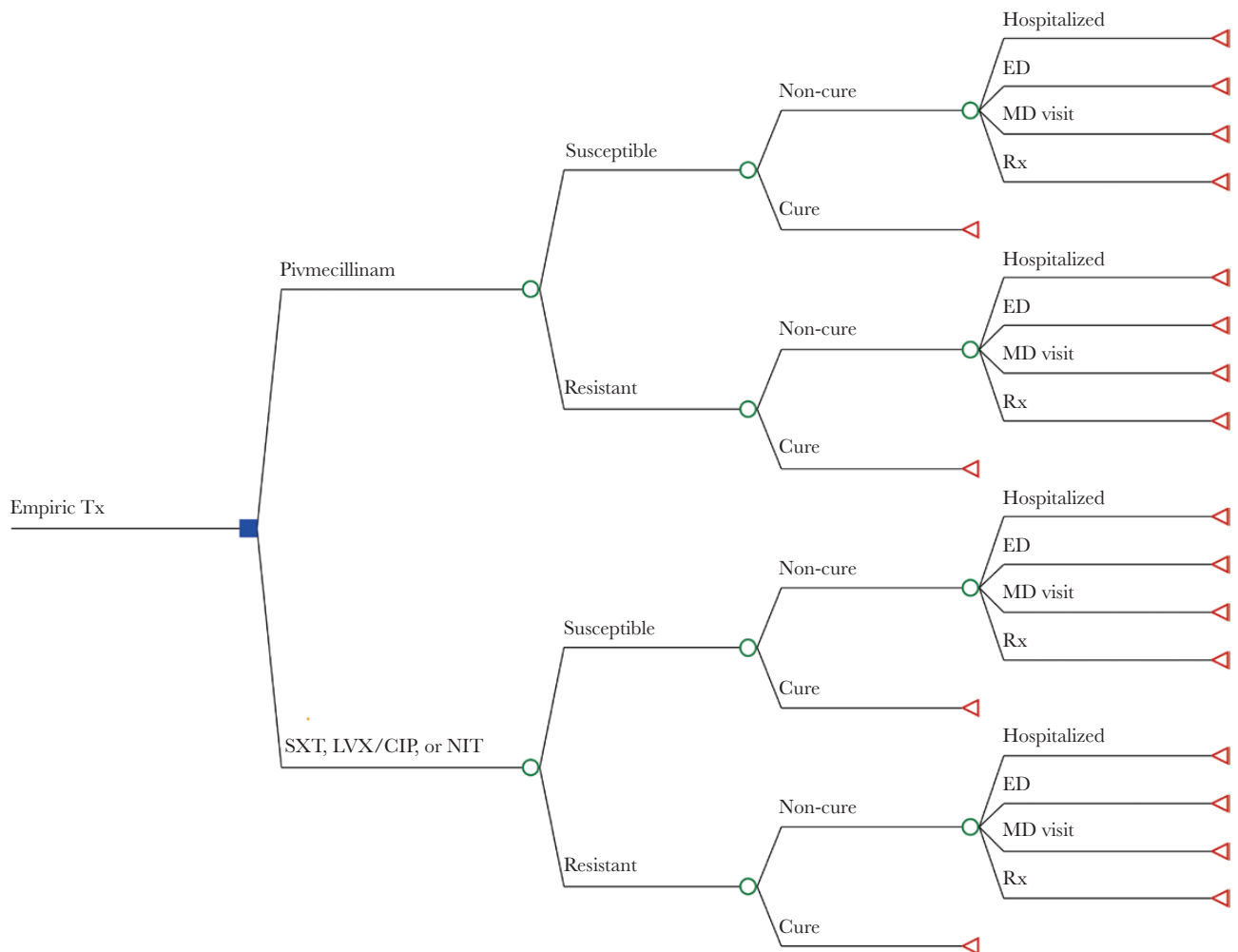
Two model populations were evaluated. The first model population was 100 theoretical adult outpatients with uUTIs due to Enterobacterales under 4 different uUTI first-line empiric treatment scenarios (ie, treatment with either pivmecillinam, fluoroquinolones, SXT, or nitrofurantoin) (Figure 1). The second model population was restricted analysis that only included women. For all treatment scenarios in both sets of models, the population was first stratified by uUTI pathogen

(*E coli* vs other non-*E coli* Enterobacterales) and further bifurcated based on whether the first-line empiric agent received was appropriate (ie, susceptible) or inappropriate (ie, resistant) to the identified Enterobacterales on the initial urine culture. Within each appropriateness of empiric agent received arm, outcomes were classified as a 30-day cure or failure. The occurrence of a cure was a terminal node while 30-day failure resulted in 4 mutually exclusive events (outpatient retreatment with a different antibiotic, urinary tract infection (UTI)-related physician office visit, UTI-related ED visit, and UTI-related hospitalization). No subsequent events were considered in the 4 failure nodes and all patients were assumed to be cured after the second round of retreatment.

### Model Inputs and Assumptions

The full list of inputs included in the model shown is in Tables 1-3. For both models, pivmecillinam in vitro microbiologic activity against Enterobacterales uropathogens (*E coli* vs other Enterobacterales), based on current Clinical and Laboratory

Standards Institute susceptibility breakpoints, were obtained from a recent surveillance study of 1090 Enterobacterales isolates, enriched for ESBL-producing *E coli* and *Klebsiella pneumoniae*, from patients with urinary tract infections in the US during 2018 [27]. Distribution of outpatient uUTI Enterobacterales (*E coli* vs other Enterobacterales) and their respective weighted susceptibilities to nitrofurantoin, SXT, and fluoroquinolones for both models were obtained from a study of outpatient antimicrobial susceptibility trends observed in urinary pathogens in New York State (Table 1) [6]. This study was used as the basis for antimicrobial susceptibility because it was the most comprehensive recent assessment of outpatient drug resistance among urinary tract isolates in the published literature. In this study, the probabilities of *E coli* vs non-*E coli* Enterobacterales among all adult outpatients with a reported Enterobacterales on urine culture were 78.5% vs 21.5%, respectively. Among all adult outpatients, the overall weighted susceptibilities for nitrofurantoin, SXT, and fluoroquinolones were 83.6%, 76.6%, and 81.5%, respectively. The susceptibilities for *E*



**Figure 1.** Conceptual health care decision-analytic model. Abbreviations: ED, emergency department; LVX/CIP, levofloxacin/ciprofloxacin; MD, physician; NIT, nitrofurantoin; Rx, prescription; SXT, trimethoprim-sulfamethoxazole; Tx, treatment.

**Table 1. Model Assumptions for Pathogen Distribution and Antimicrobial Susceptibility for Enterobacterales for All Patients and Women Only**

Item	All Patients	Women Only
Probability of <i>E coli</i> vs non- <i>E coli</i> Enterobacterales [6]	78.5% vs 21.5%	79.8% vs 20.2%
Pivmecillinam susceptibility [27]	Overall: 96.4% <i>E coli</i> : 97.7% Non- <i>E coli</i> : 91.4%	Overall: 96.4% <i>E coli</i> : 97.7% Non- <i>E coli</i> : 91.4%
Nitrofurantoin susceptibility [6]	Overall: 83.6% <i>E coli</i> : 97.0% Non- <i>E coli</i> : 34.6%	Overall: 83.5% <i>E coli</i> : 97.4% Non- <i>E coli</i> : 28.7%
SXT susceptibility [6]	Overall: 76.6% <i>E coli</i> : 73.0% Non- <i>E coli</i> : 90.0%	Overall: 73.5% <i>E coli</i> : 73.8% Non- <i>E coli</i> : 72.7%
Quinolone susceptibility [6]	Overall: 81.5% <i>E coli</i> : 78.0% Non- <i>E coli</i> : 94.3%	Overall: 78.7% <i>E coli</i> : 78.7% Non- <i>E coli</i> : 79.0%

Abbreviations: *E coli*, *Escherichia coli*; SXT, trimethoprim-sulfamethoxazole.

*coli* to nitrofurantoin, SXT, and fluoroquinolones were 97.0%, 73.0%, and 78.0%, respectively, while the weighted susceptibilities for non-*E coli* Enterobacterales to nitrofurantoin, SXT, and fluoroquinolones were 34.6%, 90.0%, and 94.3%, respectively. For nitrofurantoin, susceptibilities among *Proteus mirabilis*, *Providencia rettgeri*, and *Serratia marcescens* were not reported in the study by Rank and colleagues [6] and were assumed to be 100% resistant to nitrofurantoin based on other studies that has indicated that nitrofurantoin has no in vitro activity against these pathogens [9]. Similarly, susceptibility was not reported for SXT against *P rettgeri* and resistance was assumed to be 100% based on previous reports, indicating that SXT has very limited in vitro activity against this pathogen [28].

In the model restricted to women, the proportions with *E coli* vs non-*E coli* Enterobacterales were 79.8% and 20.2%, respectively. Within the model restricted to women, the corresponding weighted susceptibilities for nitrofurantoin, SXT, and fluoroquinolones were 83.5%, 73.5%, and 78.7%, respectively. The same methodology as described above was applied to the model restricted to women to determine susceptibility of each agent and pathogens not reported by Rank et al were again assumed to have 0% susceptibility.

For both models, cure and failure rates for receipt of an appropriate or inappropriate first-line empiric agent were obtained from a multicenter real-world evidence analysis by Puttagunta et al that assessed the impact of the appropriateness of initial empiric therapy on the outcomes of adult outpatients with uUTIs due to Enterobacterales [12]. This study was selected to serve as the input for treatment failure rates and subsequent outcomes based on appropriateness of the first-line empiric treatment since its design most closely aligns with the health care conceptual model employed in this study. In this study, 30-day failure was defined as receipt of a new antibiotic prescription or UTI-related hospitalization. Among outpatients who received an appropriate (ie, susceptible) first-line empiric

agent, 19.1% received a new antibiotic and 5.2% had an UTI-related hospitalization. In contrast, 34% of outpatients who received an inappropriate (ie, resistant) first-line empiric agent in this study had a new UTI-related antibiotic prescription and 12.2% had a UTI-related hospitalization. The number of individuals who had both a 30-day UTI-related re-prescription and UTI-related hospitalization was not reported nor was the number of individuals with UTI-related physician office visits and UTI-related ED visits. Given these data gaps, we conservatively assumed that the 30-day overall treatment failure rates in the appropriate and inappropriate first-line empiric agent arms were the 30-day UTI-related re-prescription rates (19.1% and 34.0%, respectively) reported by Puttagunta and colleagues [12] (Table 2). In the failure arms by appropriateness of therapy (ie, susceptible vs resistant), the UTI-related hospitalization rates observed in the study by Puttagunta et al were inputted for the UTI-related hospitalization rate in each respective terminal node. The remainder of the total 30-day failure rates observed in the study by Dunne et al [11], after subtraction of the UTI-related hospitalization rates observed in each respective group, was then evenly apportioned in each failure arm between outpatient retreatment with a different antibiotic, UTI-related physician office visit, and UTI-related ED visit. The basis for this derived from several studies that demonstrate that patients who have a nonresponding uUTI frequently seek additional care at a physician's office or ED [10, 29–33].

We focused on UTI-related rather than total costs for both models since many costs (initial physician office visit, non-UTI-related hospitalization, etc) would be the same regardless of choice of antimicrobial (Table 3). Wholesale acquisitions costs (RedBook) were used as the inputted costs for fluoroquinolones, SXT, and nitrofurantoin [34]. Duration of therapy was 3 days for fluoroquinolones and SXT and 5 days for nitrofurantoin [4, 20]. Since the total cost of a pivmecillinam regimen has not been established as the drug is not approved in the US, it was fixed at

**Table 2. Model Assumptions for Probability of Treatment Outcomes for Both Models (All Patients and Women Only)**

Event	Probabilities	Final Model Input
Probability of treatment failure [12]	Antibiotic re-prescription rate: Susceptible (19.1%) Nonsusceptible (34.0%)	Susceptible: 19.1% Resistant: 34.0%
Components of treatment failure		
Probability of UTI-related hospitalization [12]	Hospitalization, UTI-related Susceptible (5.6%) Nonsusceptible (12.2%)	Susceptible: 5.6% Resistant: 12.2%
Probability of UTI-related physician's visit [10, 29–33]	Nonhospital probability divided by 3	Susceptible: 4.5% Resistant: 7.3%
Probability of UTI-related ED visit [10, 29–33]	Nonhospital probability divided by 3	Susceptible: 4.5% Resistant: 7.3%
Probability of UTI-related Rx only [10, 12, 29–33]	Nonhospital probability divided by 3	Susceptible: 4.5% Resistant: 7.3%

Abbreviations: ED, emergency department; Rx, prescription; UTI, urinary tract infection.

zero dollars in the base-case analyses to facilitate comparisons with the SOC agents. It also enabled a clear delineation of the cost-neutral threshold associated with pivmecillinam relative to each SOC agent. The cost of a UTI-related re-prescription was assumed to be \$10 based on the price of nitrofurantoin [34]. The cost of a UTI-related hospitalization was assumed to be \$8000 (4 days at \$2000/day) [1, 35]. The cost of a UTI-related ED visit was assumed to be \$2000 [36, 37]. The cost of a physician office visit, including the urinalysis, was assumed to be \$336.74 [36, 38]. All of the costs in this article are in US dollars and any inputs derived from publications that preceded 2020 were scaled to 2020 dollars using the US Consumer Price Index [39].

### Model Output and Analyses

The overall mean weighted average 30-day costs per 100 theoretical patients were calculated for each agent for both models. The overall incremental mean weighted 30-day costs per patient associated with pivmecillinam relative to each SOC agent were also determined. The mean weighted average 30-day costs per 100 theoretical patients were also calculated for each agent for *E coli* and non-*E coli* Enterobacterales separately.

Two sets of 1-way sensitivity analyses were performed for each model. In the first set, the pivmecillinam neutral regimen cost thresholds that resulted in the same average per-patient costs as each SOC agent were calculated. In the second, the overall improvement in antimicrobial susceptibility required with pivmecillinam, fixed at a theoretical cost of \$200/regimen, relative to SOC agents for it to be dominant (cost savings) was determined. This was done by subtracting the overall pivmecillinam susceptibility (Table 1, 96.4% for overall model and women-only model) by the susceptibility threshold identified.

### Parameter Sample Sensitivity Analyses

Second order, probabilistic, parameter sample sensitivity analyses were performed to assess the effect of simultaneously varying multiple input variables on cost outputs (Table 4) for both sets of models. The specific inputs that were varied were cost of hospitalization and probability of treatment failure. These variables were selected because they were the most influential variables within the structural model. The original parameters for these variables were transformed into distributions.

**Table 3. Cost Inputs for Both Models (All Patients and Women Only)**

Model Cost Inputs
Drug costs
SXT was assumed to be \$0.30/tablet [34] × twice-daily administration × 3 days [4, 20] = \$2
Nitrofurantoin was assumed to be \$0.55–\$1.60/tablet [34] × twice-daily administration × 5 days [4, 20] = \$10
Ciprofloxacin was assumed to be \$0.30/tablet [34] × twice-daily administration × 3 days [4, 20] = \$2
Cost of pivmecillinam varied in models; fixed at \$100/regimen and \$200/regimen for overall susceptibility threshold
Costs for all treatment regimens
Each hospital day was assumed to cost \$2000/day × 4 days [1, 35] (median excess LOS observed) = \$8000
The cost of emergency department/observation room visit (inflated to 2020 dollars) [36, 37] was assumed to be \$2000
The cost of a physician office visit without urinalysis (inflated to 2020 dollars) [36] was assumed to be \$336.74
The cost of repeat urinalysis (CPT code 810005) and urine culture [38] was assumed to be \$20
The cost of re-prescription was assumed to be \$10 based on the price of nitrofurantoin [34]

Abbreviations: CPT, Current Procedural Terminology; LOS, length of stay, SXT, trimethoprim-sulfamethoxazole.



**Table 4. Results of the 5000-Sample Monte Carlo Simulation Analyses for the Pivmecillinam Cost-Saving Thresholds in the Overall and Women-Only Uncomplicated Urinary Tract Infection Models**

Population	Fluoroquinolones	Nitrofurantoin	SXT
Overall population			
Mean	87.79	83.85	115.97
SD	9.67	8.34	12.77
Minimum	59.92	61.51	75.52
Maximum	120.84	110.49	156.16
25th percentile	80.85	77.88	106.66
Median	87.35	83.60	115.56
75th percentile	94.40	89.59	124.80
Women-only population			
Mean	104.63	84.90	134.15
SD	11.45	8.31	15.07
Minimum	73.46	59.99	94.50
Maximum	142.48	109.74	181.31
25th percentile	96.43	78.91	123.26
Median	104.38	84.62	133.64
75th percentile	112.49	90.38	144.42

Abbreviations: SD, standard deviation; SXT, trimethoprim-sulfamethoxazole.

A triangular distribution was applied for each of these variables as variance surrounding these variables is not well described in the literature. The minimum and maximum values for cost of hospitalization were set at \$6000 and \$10 000, respectively. For probability of treatment failure, 2 sets of 95% confidence intervals (CIs) were calculated (1 for susceptible and the other for resistant infections) using the original data from Puttagunta et al [12] where the lower and upper bounds of the 95% CI were used as minimum/maximum values in the distribution. A Monte Carlo simulation was performed with 5000 samples to estimate mean (standard deviation), median (interquartile range), and minimum/maximum cost of pivmecillinam associated with cost savings relative to SOC agents. To ensure stability and consistency of the values, the process was repeated multiple times. All data analyses and calculations were performed in TreeAge Pro Healthcare software (TreeAge, Williamstown, Massachusetts).

## RESULTS

For the overall analysis, the overall mean weighted 30-day per-patient costs for each regimen are shown in Figure 2. Assuming a pivmecillinam regimen cost of zero US dollars, the overall (Figure 2A) mean weighted 30-day per-patient costs for pivmecillinam was \$572.12. The overall mean weighted uUTI-related 30-day per-patient costs for nitrofurantoin, SXT, and fluoroquinolones were \$655.61, \$687.57, and \$659.69, respectively. The mean weighted 30-day per-patient costs when examining *E coli* or non-*E coli* Enterobacterales separately are shown in Figure 2B and 2C. For the SOC agents, the lowest mean weighted 30-day per-patient costs for *E coli* were observed for nitrofurantoin, fluoroquinolones, and SXT. In contrast,

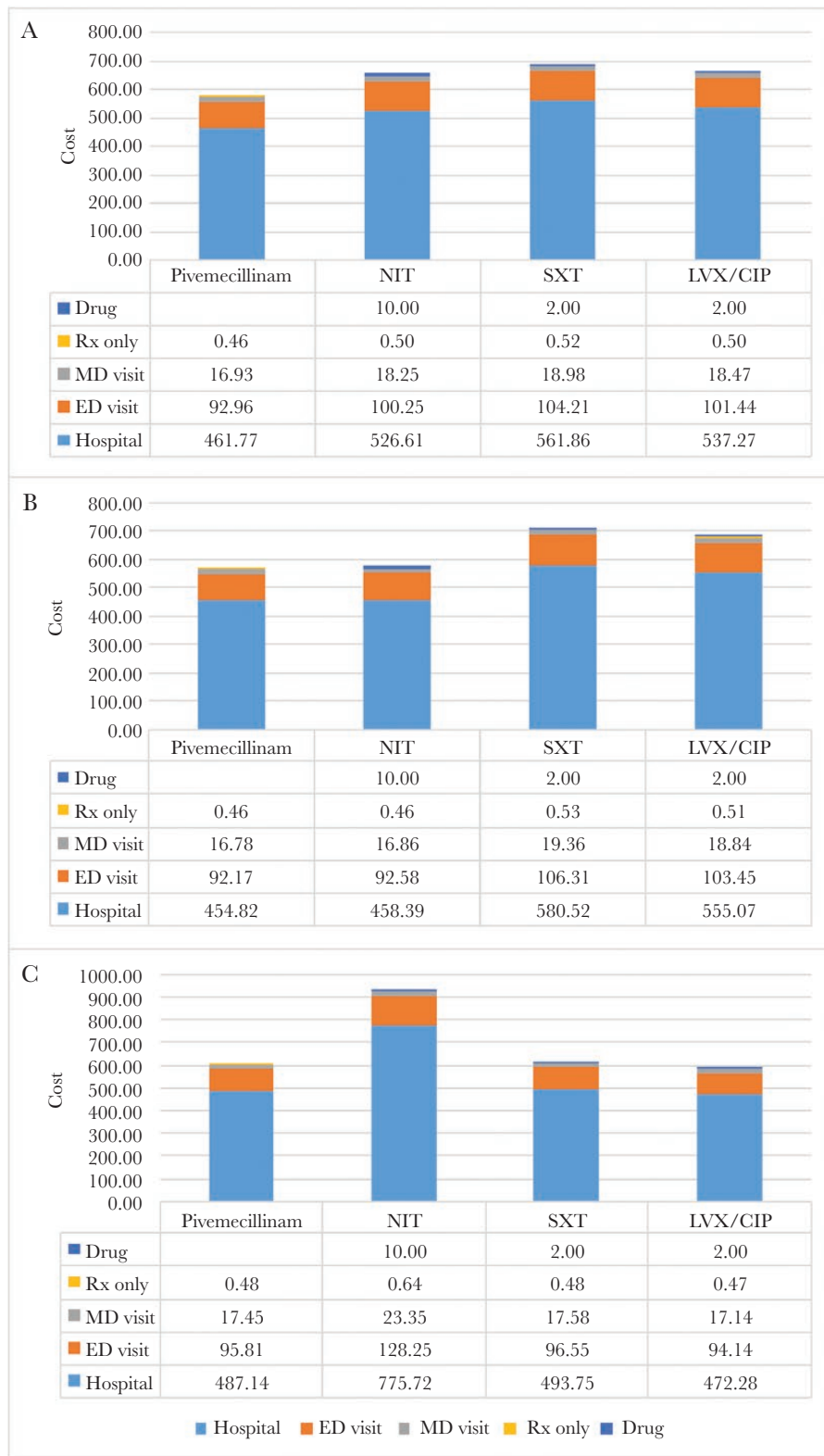
the lowest mean weighted 30-day per-patient costs among SOC agents for non-*E coli* Enterobacterales were observed for fluoroquinolones, SXT, and nitrofurantoin. Similar to the overall mean weighted 30-day per-patient cost findings, UTI-related hospitalization costs accounted for majority of the mean weighted 30-day per-patient costs in the analyses stratified by pathogen. In the model restricted to women, nearly identical overall and *E coli*-specific mean weighted 30-day per-patient costs were observed between pivmecillinam and SOC agents given the similar pathogen and susceptibility profiles in the overall relative to the women-restricted group (Supplementary Figure 1).

In the overall model, the pivmecillinam neutral regimen cost thresholds that resulted in the same overall average per-patient costs as each SOC agent are shown in Figure 3. For nitrofurantoin, the pivmecillinam neutral regimen cost threshold was \$83.50 (Figure 3A). The pivmecillinam neutral regimen cost threshold for SXT was \$115.45 (Figure 3B) and that for fluoroquinolones was \$87.58 (Figure 3C). The overall antimicrobial susceptibility improvement required with pivmecillinam, fixed at a theoretical cost of \$200/regimen, relative to SOC agents for it to be dominant (cost savings) was found to be 28% (Figure 4). In the model restricted to women, the pivmecillinam neutral regimen cost thresholds against nitrofurantoin, SXT, and fluoroquinolones were \$84.38, \$113.74, and \$104.19 (Supplementary Figure 2). Similar to overall analysis, a 28% antimicrobial susceptibility improvement was required with pivmecillinam, fixed at a \$200/regimen, relative to SOC agents for it to be dominant (cost savings).

The 5000-sample Monte Carlo simulation analyses (Table 4), where the cost of hospitalizations and probability of treatment failure were varied, demonstrated cost savings relative to fluoroquinolones, nitrofurantoin, and SXT when the pivmecillinam regimen cost was a median of \$87.35, \$83.60, and \$115.56, respectively, in the overall population. Similar findings were observed in the analyses restricted to women only where the median pivmecillinam regimen cost associated with savings was highest against SXT (\$133.64) and lowest for nitrofurantoin (\$84.62).

## DISCUSSION

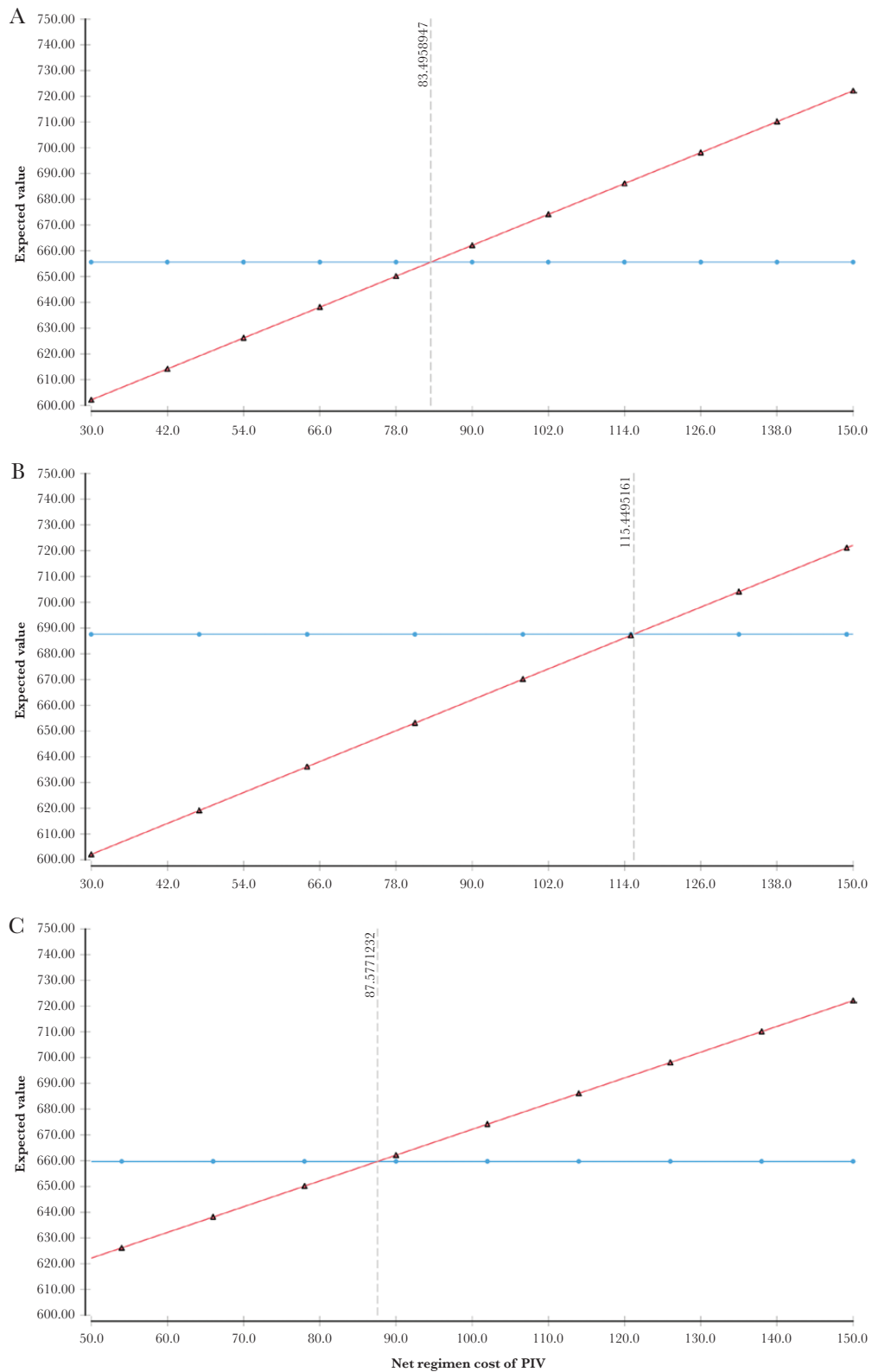
Cognizant of the (1) growing resistance concerns with current first-line uUTI, (2) clinical and economic consequences associated with empiric receipt of an inappropriate agent, and (3) highly favorable in vitro microbiologic activity of pivmecillinam against the most common Enterobacterales uropathogens, we developed conceptual health care decision models to determine the range of total regimen costs for pivmecillinam in which it would be prudent to consider it over current first-line SOC agents in adults outpatients with uUTIs due to Enterobacterales. Although uUTI due to Enterobacterales



**Figure 2.** Mean weighted 30-day per-patient costs by antimicrobial treatment for all patients: overall (A), *Escherichia coli* only (B), and non-*E. coli* Enterobacteriales only (C). Abbreviations: ED, emergency department; LVX/CIP, levofloxacin/ciprofloxacin; MD, physician; NIT, nitrofurantoin; Rx, prescription; SXT, trimethoprim-sulfamethoxazole.

uropathogens are perceived to be associated with low overall costs due to the drug acquisition costs of currently used agents, overall mean weighted uUTI-related 30-day per-patient costs

for nitrofurantoin, SXT, and fluoroquinolones were \$655.61, \$687.57, and \$659.69, respectively. The uUTI-related costs were driven in large part by the rates of inappropriate empiric

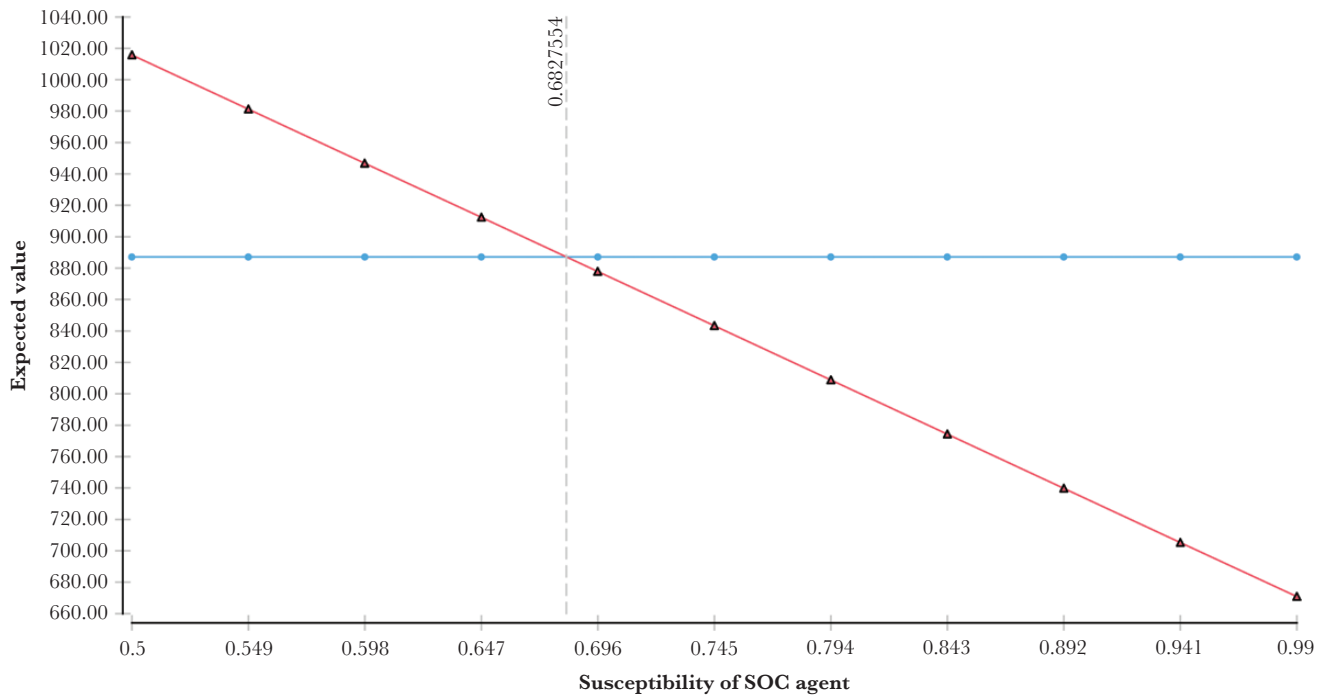


**Figure 3.** Cost-neutral net regimen cost threshold for pivmecillinam (PIV) for all patients relative to nitrofurantoin (A), trimethoprim-sulfamethoxazole (B), and fluoroquinolones (C). Diagonal line indicates pivmecillinam; horizontal line indicates standard-of-care agent.

treatment (ie, empiric receipt of microbiologically inactive treatment based on prevailing Enterobacteriales resistance rates [6]) associated with each SOC agent. Based on the

potential higher rates of susceptibility and likelihood of appropriate empiric therapy with pivmecillinam relative to current SOC uUTI agents, the neutral regimen cost threshold of





**Figure 4.** Overall susceptibility improvement threshold in which pivmecillinam at \$200/regimen is dominant (cost savings) relative to current standard-of-care (SOC) agents was 28%. Overall pivmecillinam susceptibility was fixed at 96.4% [27] for this analysis.

pivmecillinam appears to be between approximately \$85 and \$115/treatment course. These findings were identical to model using the pathogen distribution and rates of resistance observed only in women [6]. Regardless of comparator agent, the overall weighted susceptibility improvement required with pivmecillinam to justify a theoretical cost of \$200 per regimen was found to be 28%. Although the price of pivmecillinam has not been established as it has not been considered for FDA approval in the US, the 28% overall weighted susceptibility improvement suggests that pivmecillinam would be of greatest value in patients at higher risk for resistance to SOC agents. Patient populations at greatest risk for resistant uUTIs are well described in the literature and include male sex, advanced age, previous history of uUTIs, prior receipt of antibiotics, presence of diabetes, and recent residence in acute and long-term health care facilities [40].

Several items should be noted when interpreting the findings. The models centered on the outcomes associated with empiric receipt of an appropriate vs inappropriate agent. For our model, the outcomes associated with appropriateness of empiric therapy were based on a real-world multicenter study by Puttagunta and colleagues of adult outpatients with uUTIs due to Enterobacteriales [12]. Other studies could have been used for this input, but we believed the study by Puttagunta et al was the most conservative and aligned best with our proposed US health care conceptual model. In the study by Puttagunta et al.[33], there was a 15% difference in treatment failure rates

between patients who received appropriate vs inappropriate therapy, and the absolute difference in UTI-related hospitalizations between appropriateness groups was 6.6%. In contrast, a retrospective database analysis of insured beneficiaries who were 18–64 years of age and treated for a UTI due to an Enterobacteriales reported that the difference in failure, defined as a retreatment with a new or different antibiotic or UTI-related observation or inpatient stay, was 29% [11]. Similarly, 30-day clinical treatment failure rates, defined as receipt of a new UTI prescription for a UTI or UTI-related hospital admission, among adult outpatients with a uUTI due to *E coli* was found to be >25% higher among patients who received an inappropriate empiric agent relative to an appropriate agent, regardless of empiric agent received [13]. Jorgensen and colleagues also reported that adult outpatients with uUTIs who presented to the ED for their care and received an inappropriate empiric agent had considerable higher rates of early ED revisits relative to those who received an appropriate agent (47.1% vs 28.1%, respectively) [10]. In an open-label clinical trial comparing nitrofurantoin vs SXT for the treatment of adult women with uUTIs, 30-day clinical failure rates, defined as persistence or recurrence, were 40% higher in SXT receipt who had a SXT-resistant UTI relative to those with a SXT susceptible uUTI (84% vs 41%, respectively) [15]. Similarly, an open-label study that examined the outcomes of adult women with uUTIs treated with SXT reported a 34% difference in clinical cures 5–9 days after cessation of therapy between those infected with a SXT resistant

vs susceptible pathogen (88% vs 54%, respectively) [16]. Based on the collective literature, we believe the inputs we used to define the outcomes and costs associated with appropriateness of empiric therapy accurately reflect the potential value of an agent like pivmecillinam that has improved activity against Enterobacterales uropathogens relative to other first-line SOC uUTI agents.

There are also other aspects of this analysis that suggest the reported pivmecillinam regimen cost-neutral thresholds were highly conservative. The model was limited to 30-day outcomes based on available literature. However, data suggest that the consequences of failing to receive an appropriate empiric agent may extend beyond 30 days [13–16, 30–32]. We did not capture the costs associated with patient-centered outcomes like patient satisfaction, quality of life, ability to return to normal daily activities, and prescription co-payments. We also did not consider the costs associated with the disabling and potentially permanent serious side effects associated with fluoroquinolone use, which led to the FDA's recommendation to limit their use in uUTI when there are no alternative treatment options [5]. Finally, the cost savings presented here should be viewed as an initial estimate; the potential value of pivmecillinam relative to SOC agents could be greater when purchasing discounts or when other cost-saving measures are incorporated.

The biggest driver of the excess costs associated with receipt of inappropriate empiric treatment was cost of hospitalization. For the primary analyses, we assumed that the cost of a hospitalization for a UTI was \$8000 (\$2000/day for 4 days) [1, 35]. As costs associated with a UTI-related hospitalization vary across hospitals and payers [37], the pivmecillinam cost-neutral regimen thresholds presented in this study should be considered as an initial estimate of the potential value of pivmecillinam relative to other SOC uUTI agents. We attempted to address this by performing a 5000-sample Monte Carlo simulation to vary the costs from the most plausible values of \$6000 (\$1500/day) to \$10000 (\$2500/day). Health care systems should consider their local costs, especially UTI-related hospitalization costs, when determining if replacement of current uUTI SOC with an agent like pivmecillinam can improve the quality and efficiency of health care delivery within their system. Health care systems should also consider their own outpatient Enterobacterales resistance rates when evaluating these findings as our model used published outpatient susceptibility data from New York State by Rank et al [6]. Although the findings from Rank et al are consistent with other outpatient US surveillance studies [7, 8], there are limited published data at this time on outpatient resistance among common uUTI pathogens, and further study is needed to determine if the resistance rates observed in New York State are consistent with other regions in the US. Furthermore, mecillinam susceptibility was not available in the study by Rank et al, and susceptibility data from a recent surveillance study of 1090 Enterobacterales isolates, enriched for ESBL-producing

*E coli* and *K pneumoniae*, from patients with UTIs in the US during 2018 were used as the input for pivmecillinam susceptibility against Enterobacterales in the analyses [27]. Given this surveillance study was enriched for ESBL producers, it is likely a conservative estimate of the in vitro microbiologic activity of pivmecillinam against uUTI Enterobacterales encountered in the outpatient setting. Last, our findings are not unique to pivmecillinam and could be applied to any antibiotic that has greater microbiologic activity against common Enterobacterales uropathogens relative to the current uUTI SOC agents.

In summary, the analyses indicate that an agent like pivmecillinam that is highly active against the most common Enterobacterales uropathogens in the US [27] would be a welcome addition to the antimicrobial armamentarium for the treatment of adult outpatients with uUTI. A critical consideration in the treatment of adult outpatients with uUTIs due to Enterobacterales is the appropriateness of empiric therapy, as failure to treat patients empirically with a microbiologically active agent increases 30-day uUTI-related health care resource utilization and costs. Findings from the model presented here illustrate the potential economic impact associated with ensuring that adult outpatients with uUTIs due to Enterobacterales have a higher likelihood of receiving an appropriate agent empirically. Based on the model's assumptions and inputs, this analysis suggests that an agent like pivmecillinam has the potential to reduce the economic burden associated with inappropriate treatment of adult outpatients with uUTIs, especially in patients at high risk for resistance [40]. Health care systems aspiring to minimize the consequences associated with delivery of inappropriate uUTI therapy, improve patient outcomes, and contain costs by reducing UTI-related health care visits and hospitalizations should examine their outpatient resistance rates among common Enterobacterales uropathogens and determine whether the replacement of current SOC agent(s) with an agent like pivmecillinam is warranted. This type of assessment will be particularly useful in health care systems that manage many adult outpatients with uUTIs and have weighted Enterobacterales resistance rates of >20% to current uUTI SOC agents. Like all studies of this nature, the findings require validation in real-world settings.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

**Author contributions.** All authors participated in the study design, implementation of the study protocol, analysis and interpretation of the data, drafting of the report, and critical review. The approval of the manuscript and decision to submit the manuscript for publication were the responsibility of the coauthors, led by T. P. L.

**Patient consent statement.** As this was a conceptual health care decision-analytic modeling study that used published data for its inputs,

requirements of patient consent and institutional review board approval were not applicable.

**Data availability.** Data are not publicly available.

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**Potential conflicts of interest.** A. S. H. and T. H. are current employees of UTILITY therapeutics. T. P. L. has served as a consultant and scientific advisor for, and received grants from, UTILITY Therapeutics. N. P. reports no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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