The Columbia University JOURNAL of GLOBAL HEALTH

A COMMON PROBLEM INCREASINGLY WITHOUT A SOLUTION: The Rise of Antibiotic-Resistant Urinary Tract Infections

Emma Kaufman[1]

[1]Barnard College, Columbia University, NY, USA

ABSTRACT Urinary tract infections (UTIs) are one of the most common infections globally for both inpatients and outpatients. The bacteria causing these infections, primarily *E.coli*, have demonstrated increasing levels of resistance to traditionally prescribed antibiotics. Contributors to this rise in resistance include the over-prescription of antibiotics, poor patient adherence and a lack of knowledge about antibiotic use, all of which are affected by cultural attitudes and access to healthcare. In the U.S. and around the world, incidence of antibiotic resistance is higher in areas of lower socioeconomic status (SES) often due to a lack of trained medical professionals and non-prescription antibiotic use. Low and middle-income countries may also lack adequate infrastructure for sanitation and water distribution, increasing exposure to resistant bacteria. To combat the spread of resistance, many health departments and physicians begin to practice antibiotic stewardship, avoiding the prescription of antibiotics if not absolutely necessary. There has also been a movement towards prophylactic non-antibiotic remedies including cranberry juice and probiotics which, combined with antibiotic stewardship, can reduce bacterial exposure to antibiotics and thus reduce the development of resistance.

KEYWORDS: antibiotics, antibiotic resistance, urinary tract infection, microbiology

INTRODUCTION

The development of resistance to antibiotics by bacteria is not a new occurrence, however; current practices surrounding antibiotic use have allowed antimicrobial resistance (AMR) to flourish. Antibiotics act as a selective pressure, killing or inhibiting the growth of bacteria, leaving only the microbes able to reject them to repopulate the body's microbiome[1]. The more exposure bacteria have to an antibiotic, the more opportunities they have to develop resistance and the less effective that antibiotic becomes. For common infections like urinary tract infections (UTIs), this means that once easily treatable infections may not respond to tried-and-true drugs.

UTIs are incredibly common, with 400 million infections diagnosed globally in 2019. While the 60% increase in diagnoses between 1990 and 2009 could be due to an increase in diagnosed infections rather than an increase in actual infection occurrence, it does indicate an increase in individuals with UTIs receiving medical treatment, most likely antibiotics[2]. Infection occurs when bacteria enter the body through the urethra and spread to the

Send correspondence to: ekk2131@alum.barnard.edu

bladder. The risk of UTIs is higher in women, especially women with a history of past UTIs, frequent sexual activity and changes in bacterial flora. Men are at a higher risk of UTIs if they have an enlarged prostate or other urinary tract problems. General risk factors include immunosuppression and catheter use. UTIs are characterized by a strong urge to urinate (even after just having gone), burning during urination, frequent urination, urine that is cloudy or has a strong smell or pelvic pain[3]. While minor infections are easily treated with a round of antibiotics, untreated UTIs can spread to the kidneys and then travel through the bloodstream to cause sepsis. When infections reach this point, they can become fatal. UTIs are a significant cause of death in women of all ages, as well as infant boys and older men[4]. Infections are either considered uncomplicated—occurring in a healthy, non-pregnant female—or complicated, occurring in an individual who is immunocompromised, male, pregnant or otherwise unhealthy[5]. During pregnancy, the chance of a UTI is higher due to pressure on the bladder and ureter[6]. Complicated infections are less well-studied and require different considerations when prescribing treatment.

WOMEN AT A HIGHER RISK

Female anatomy is more susceptible to UTIs both because of the short female urethra and the comparatively short distance between the anus and urethral opening[7]. There is a greater chance of gut-fecal bacteria exposure to the urethra, and it is easier for that bacteria to enter the bladder and cause infection. Because of this, women experience UTIs at up to 30 times the frequency of men[8]. Between 25% and 30% of women experience a second UTI within six months of their first and some experience recurrent infections, a condition defined as three or more UTIs in a year[4,9]. These recurring infections can be detrimental to the mental health and quality of life of the women who suffer with them, in addition to their physical health.

Social stigma surrounding UTIs can leave the women who suffer from recurrent infections feeling shame, embarrassment and restriction in their daily life[10,11]. On average, a single UTI episode can result in 6.1 days of symptoms, 2.4 days of restricted activity, 1.2 days where women are unable to go to class or work, and 0.4 days in bed[12]. This is a significant disruption, especially when it occurs at least three times a year. Chronic pain has been widely accepted to affect quality of life, yet the burden of chronic pain as a result of recurring UTIs is less accepted. UTI-related pain has been shown to affect all areas of the Working Model of Adjustment to Chronic Illness, a model used to assess the impact of certain factors associated with chronic pain on quality of life[13]. By using an accepted method of measuring the impact of pain on daily life, Maxwell et al. legitimize the impact of chronic UTI pain for many women. Recurrent UTIs are also associated with anxiety and depression, especially at the onset of a new infection. The feeling of loss of quality of life and pain associated with a UTI can, justifiably, lead to symptoms of depression[14].

DIAGNOSIS

Characteristics of Studies

Diseases that primarily affect women have historically been under-researched, and UTIs are no exception[15]. Diagnosis is dependent on a combination of reported symptoms, urine cultures and dipstick tests. Dipstick testing is a general urinalysis tool used to measure pH, concentration, protein levels, sugars, ketones, bilirubin and white-blood cell products[16]. The test can be done within a few minutes and is approximately 75% accurate at detecting signs of a UTI[17]. Dipstick testing is inexpensive and only takes a few minutes to perform, meaning patients can get relief quickly. Dipstick testing can only identify the presence of bacteria, but it cannot identify whether the bacteria are causing an infection, the species of bacteria, or to which drugs they might be susceptible. For a more specific diagnosis of infection, physicians turn to urine cultures. UTIs can be caused by gram-positive and gram-negative bacteria as well as some fungi, including yeasts. The most common bacterial cause is *Escherichia coli*, which has been known to cause up to 80% of uncomplicated infections[18]. In addition to *E.coli*, UTIs can be caused by *Proteus, Klebsiella, Serratia, Pseudomonas, Enterobacter, Candida* and many other bacteria[14]. For many women with genitourinary symptoms, finding a diagnosis can be difficult, if not impossible. In Berg et al., a diagnosis was only made 34% of the time in symptomatic patients using the standard urine culture protocol, rising to 66% when non-standard testing was performed[19]. Urine culture technique has been optimized to identify *E.coli*-caused UTIs, detecting approximately 90% of infections caused by *E.coli*[20]. This standard protocol requires a concentration of at least 10^5 CFU/mL of the known pathogen, so, while it is effective at identifying the presence of *E.coli,* this protocol is not effective at detecting the other UTI-causing bacteria that make up 20% of infections[20]. An enhanced quantitative urine culture protocol, or EQUC, proposed by Price et al. includes the culture of urine samples at three different volumes and with seven combinations of agars and environments, expanding the standard protocol of a single volume on two agars in the same environment. This variety increases the potential for identifying microorganisms that would have been categorized as "no growth" with the standard protocol. The enhanced protocol also proposes individualized, sometimes lower, thresholds for different microbes rather than holding all microbes identified to the same concentration. Compared with the standard protocol, the EQUC was significantly more effective at detecting uropathogens. There is no completely effective method of detection, so diagnosis also relies on patient identification of signs and symptoms, where interpretation is up to the individual healthcare provider.

While not yet refined for common use, multiplex PCR offers a possible alternative to urine culture. One study found multiplex PCR to be comparable to urine culture as far as accuracy in identifying bacteria; however, this technique is significantly faster, which removes the need for empiric therapy while waiting for culture results[21].

TREATMENT

Once a diagnosis has been made, antibiotics are the standard treatment for UTIs. Urine cultures are not required or recommended in all cases, and many patients receive a prescription for broad-spectrum antibiotic treatment without one ever being performed. Patients who do require a urine culture may be prescribed broad-spectrum antibiotics to alleviate discomfort while waiting for results and are then prescribed a more specific antibiotic. The combination drug trimethoprim-sulfamethoxazole is broadly active against most uropathogens and is considered the standard for antibiotic UTI treatment. It has little impact on anaerobic vaginal and fecal flora and is well tolerated, making it less disruptive[22]. Fluoroquinolones including Levofloxacin and Ciprofloxacin have historically been commonly prescribed as a broad-spectrum treatment for UTIs; however, in 2016 the FDA issued a "black box" warning for their safety due to potential adverse side effects[23][24]. Other antibiotic therapies include nitrofurantoin and fosfomycin, which can be used in the case of resistance to other antibiotics. Nitrofurantoin is commonly prescribed specifically for uncomplicated UTIs due to the difficulty of maintaining therapeutic levels in blood and inability to penetrate certain tissues[25]. β-lactams have historically been used to treat UTIs, but increasing resistance to drugs like ampicillin and amoxicillin make them less effective first-line therapies. Patients also experience a higher rate of recurrence while using them[22]. Urine cultures are used to identify causal bacteria and to perform susceptibility testing to identify whether certain antibiotics will be effective.

Length of treatment can vary from a single dose to fourteen days, with the standard being three days. Fosfomycin is the only antibiotic approved by the FDA for single-dose therapy to treat uncomplicated UTIs as it maintains therapeutic concentrations for up to four days[26]. Trimethoprim-sulfamethoxazole, fluoroquinolones, and trimethoprim three-day regimens have been found to be as effective as longer-duration regimens with fewer side effects[22]. Those with complicated UTIs may require longer courses of therapy.

As a last resort for patients with recurrent UTIs, antibiotics may be prescribed prophylactically. These antibiotics can be used intermittently at a low dose or after sexual intercourse if that is a known cause of recurrent infections[27]. Use of the antibiotics trimethoprim-sulfamethoxazole, fluoroquinolones, and nitrofurantoin within two hours after sexual activity have also been shown to reduce the rate of UTI occurrence[28].

ASYMPTOMATIC BACTERIURIA

Prophylactic antibiotics have been a contentious topic, especially in the case of asymptomatic bacteriuria. This is a condition where an individual has the concentration of UTI-causing bacteria in their urine required for a diagnosis but does not experience any UTI-associated symptoms[29]. Having asymptomatic bacteriuria does not guarantee a UTI will develop, and most individuals don't have any negative health effects. In pregnant women, there is a 25% chance of a UTI after asymptomatic bacteriuria is detected, which would justify the use of prophylactic antibiotics [30]. For the diagnosis of asymptomatic bacteriuria, dipstick tests are considered reliable and make the diagnostic process inexpensive and accessible[31]. Prophylactic antibiotic treatment in pregnant women decreases the risk of pyelonephritis, a complication of a UTI that results in kidney inflammation, as well as lowers the chance of preterm delivery and low-birthweight children[29]. Nitrofurantoin and trimethoprim-sulfamethoxazole are common choices for prophylactic use in pregnant women[32]. Outside of pregnant women, patients with asymptomatic bacteriuria do not benefit from prophylactic antibiotic treatment and exposure to unnecessary antibiotics can encourage the development of antibiotic-resistant bacteria.

DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

Many methods of empiric antibiotic therapy have fallen out of favor due to an increase in antimicrobial resistance, or AMR. When antibiotics are prescribed, it is important that the patient takes the medication at the same time each day for the full regimen. Bacteria are constantly evolving to better survive in their environment and part of that survival is the development of AMR. Failing to take the full dose prevents full eradication of infection-causing organisms, giving them an opportunity to develop resistance. Like seeing the answer key before a test, the bacteria will then be more prepared should the patient take the same antibiotic again. AMR is a growing issue for the international community and was associated with an estimated 4.95 million deaths in 2019[33]. This death count includes a myriad of infections caused by many different types of bacteria, but the impact of resistance on UTI therapy illustrates how even the most by-the-book infections are complicated by the global problem of resistance. Antibiotics that have been used for decades, like β-lactams, are no longer effective methods of treatment, forcing physicians to turn to other antibiotics and other types of therapy.

Research about the efficacy of antibiotics must now consider the speed at which bacteria develop resistance as a criterion for use. Although Warren et al. found trimethoprim-sulfamethoxazole to be the most effective option for therapy in 1999, the development of resistance against the drug has increased to the point where Jancel and Dudas recommended it not be used in communities where resistance is greater than 10% to 20%[34].

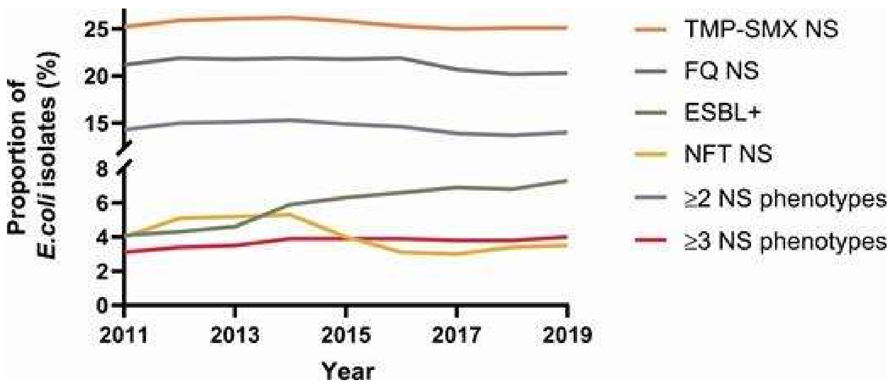

FIGURE 1: THIS GRAPH, FIGURE 4 FROM KAYE ET AL., 2021, SHOWS THE TREND IN RESISTANCE OF E.COLI ISOLATES TO COMMON ANTIBIOTICS OVER TIME. RESISTANCE TO TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMX), FLUOROQUINOLONE (FQ), EXTENDED-SPECTRUM Β -LACTAMASE-PRODUCING (ESBL+), AND NITROFURANTOIN (NFT) WERE MEASURED. NS INDICATES NO SUSCEPTIBLE.

The above figure shows the varying levels of resistance to commonly prescribed antibiotics for UTIs over time[35]. Resistance to trimethoprim-sulfamethoxazole and resistance to fluoroquinolones have both been over 20% for all years, the upper boundary of Jancel and Dudas' recommendation. This would suggest that resistance to these drugs is consistently high enough that other options should be considered before prescribing them.

Even in the mid-1990s, resistance to trimethoprim-sulfamethoxazole was growing. A Seattle study found that, between 1992 and 1996, *E.coli* resistance to trimethoprim-sulfamethoxazole increased from 9% to >18%, respectively, which would put them above the threshold for use described in Jancel and Dudas in only four years[36]. A 2019 study found that, in Saudi Arabia, 50% of UTI-causing bacteria assessed were resistant to trimethoprim-sulfamethoxazole, a significant increase compared to studies from twenty years prior. The same study found that 92% of UTI-causing bacteria are resistant to at least one common antibiotic and that 80% are resistant to at least two[37]. For women with recurrent UTIs, the dramatic increase in resistance means fewer treatment options and therefore a lower chance of relief. This could exacerbate the mental and physical impacts of recurrent UTIs and result in higher levels of kidney damage, sepsis and death.

ALTERNATIVE ANTIBIOTIC TREATMENTS

With many first-line drugs no longer a sure-thing, physicians turn to other antibiotics that seem to generate less resistance. In the table below, from Gupta et al., the increasing trend in overall antibiotic resistance is clear. However, not all antibiotics experience the same rate of resistance. N nitrofurantoin experienced a much lower increase in resistance, never hitting above 9%, compared with trimethoprim-sulfamethoxazole resistance which increased from 9% to 18%.

Table 1. Percentages of Urinary Isolates From Women With Acute Uncomplicated Cystitis Resistant to Selected Antimicrobial Agents*

	1992		1993		1994		1995		1996	
	E coli (n = 567)	All (n = 653)	*E coli* (n = 931)	All (n = 1081)	*E coli* (n = 967)	All (n = 1127)	*E coli* (n = 691)	All (n = 807)	*E coli* (n = 580)	All (n = 674)
Ampicillin†	26	29	29	32	31	33	32	34	34	38
Cephalothin†	20	20	25	24	38	37	32	32	28	28
Ciprofloxacin hydrochloride	0.2	0.3	0	0.2	0.1	1	0	0.3	0.2	0.3
Gentamicin	2	2	1	1	1	1	0.4	0.4	1	1
Nitrofurantoin	1	7	1	6	2	9	1	7	0.2	6
Sulfamethoxazole	22	21	25	24	26	24	25	22	27	26
Trimethoprim-sulfamethoxazole†	9	8	10	9	9	9	12	12	18	16
Trimethoprim†	9	9	10	9	10	9	12	12	18	16

*Percentages reflect the number of isolates tested with each antimicrobial agent; this may be less than the total number for each column. *E coli* indicates *Escherichia coli*.
†There was a significant increasing linear trend in resistance from 1992 to 1996 for *E coli* and all isolates: ampicillin (*P*<.002), cephalothin (*P*<.001), trimethoprim (*P*<.001), and trimethoprim-sulfamethoxazole (*P*<.001), using the χ^2 test for linear trend.

TABLE 1. FROM GUPTA ET AL. DEMONSTRATES THE TREND OF INCREASING RESISTANCE IN E.COLI AND OTHER UTI-CAUSING BACTERIA OVER FOUR YEARS IN WOMEN AGED 18-50 IN SEATTLE, WASHINGTON. THIS TABLE MAKES CLEAR THAT RESISTANCE AGAINST CERTAIN ANTIBIOTICS IS LESS COMMON THAN OTHERS, PROVIDING A POSSIBLE ALTERNATIVE TREATMENT.

A 1999 study comparing trimethoprim-sulfamethoxazole, nitrofurantoin, and ciprofloxacin found that the drugs had comparatively high eradication rates, while ciprofloxacin had a significantly higher eradication rate after 4-6 weeks[38]. Since then, increased resistance to trimethoprim-sulfamethoxazole has rendered it a less effective treatment, but resistance towards the other two drugs has remained relatively low. These drugs have the potential to offer a similar broad-spectrum effect as trimethoprim-sulfamethoxazole in a more resistant environment.

Understanding how bacteria specifically develop resistance to antibiotics is useful for understanding how to combine existing medications to go around mechanisms of resistance. One example of this type of treatment is the combination of cefepime and enmetazobactam to treat resistant complicated UTIs caused by gram-negative pathogens. Many gram-negative UTI-causing pathogens have developed a resistance to cefepime, a cephalosporin, and can release enzymes that break down the drug. By combining cefepime with enmetazobactam, the drug is protected long enough that the enzymes are no longer effective. The therapy was 79.1% successful at eradicating the infection[39]. Using existing medications in novel ways can hold off the full impact of AMR, but it is not a solution. In order to truly address the threat of AMR, it is necessary to explore the reasons it has been able to develop so quickly.

CONTRIBUTING FACTORS

Over-treatment

The rise of AMR is the result of many factors, but antibiotic over-treatment is a key culprit. Over-treatment includes incorrect drug selection, improper dosing, unnecessary prescriptions and excessive durations. A review of antibiotic appropriateness found that only 56% of patients who received the correct antibiotic had an appropriate dose and duration[40]. If the incorrect drug is prescribed or the dose is too low, the drug can act as a selective pressure for bacteria without killing the entire population, making the population more effective at resisting the antibiotic in the future. The use of antibiotics for a longer duration than necessary can also contribute to resistance by allowing bacteria more time to develop resistance[41]. While antibiotics have been a lifesaving innovation on a major scale, there are many cultural misconceptions about when and how to use them appropriately. Pressure from misinformed patients can impact physician decisions, especially when they rely on patient satisfaction as a metric of success. Patients who receive antibiotic prescriptions have been shown to review their physicians more positively[42]. This is possibly because patients feel that the prescription of antibiotics indicates that their symptoms are being taken seriously and review the physician positively because they feel they are being heard.

In addition to patient pressure, Pew identified time constraints, decision fatigue and uncertain diagnosis as other causes of antibiotic over-prescription[43]. Doctors often don't have much time with each patient, and it can be difficult to both diagnose and decide on treatment quickly. Many doctors, rather than explaining why the drugs aren't necessary to patients, opt to go for the safe rather than sorry route and prescribe antibiotics for issues they normally wouldn't. There is a misguided notion that antibiotics aren't harmful if they are taken unnecessarily and that the worst thing that can happen is that patients have to come back. Even when physicians acknowledge that there is an issue of over-prescription, there is still a lack of personal accountability. A Pew survey found that while 91% of physicians acknowledged the issue that inappropriate antibiotic use poses, only 37% agreed it was an issue in their own practice[44].

Antibiotic Misuse

Misuse of antibiotics also contributes to the development of AMR. In the U.S., healthcare costs can make proper diagnosis and treatment inaccessible. Nonprescription antibiotic use is not well-researched, but a review of existing literature found that it to be a prevalent issue. The review incorporated studies on various groups with widely varied results, but between 14% and 48% of all groups reported storing antibiotics for future use[45]. A driver of this practice is the idea that leftover antibiotics could be used for future infections in either the original patient or someone else. With the prevalence of misconceptions about what antibiotics can treat and how long they need to be taken, it is unlikely that a patient with no medical background could give someone the correct antibiotic, possibly harming them in the process. Saving part of a regimen for later use neglects to consider that different antibiotics are used for different infections, and there is no guarantee that a future infection would be responsive to a previously prescribed antibiotic. If a regimen is incomplete, organisms that have been exposed to the antibiotic but not eradicated have experienced selection for resistance and are free to multiply, potentially making that individual resistant to that drug in the future. In the context of UTIs, failing to complete a full regimen of antibiotics can increase the risk of recurrence and makes future infections more difficult to treat.

THE ROLE OF SOCIOECONOMIC STATUS

The role of unaffordable healthcare in incentivizing misuse hints at the larger impact of economic conditions on the rise of AMR. In the U.S., socioeconomic status (SES) has been identified as a risk factor for multidrug-resistant (MDR) UTIs[46]. This effect also exists outside of the U.S., with one study in Bangladesh showing the high prevalence of UTIs in female garment factory workers[47]. A community cohort study also in Bangladesh identified a number of indicators of lower socioeconomic status as risk factors for UTIs, including low household wealth and less paternal education[48]. In southeastern Nigeria, prevalence of asymptomatic bacteriuria, or the presence of UTI-causing bacteria without symptoms, was inversely correlated with level of education, with the least educated women having the highest rate of asymptomatic bacteriuria[49]. Women of lower SES are less likely to have access to clean facilities and healthcare and may face stigma for what is seen as a sex-related infection, which could discourage seeking medical help. These are the women that will suffer most as resistant UTIs become more common.

Although AMR is a global issue, the World Health Organization identifies low- and middle-income countries as the most affected due to the role of poverty and inequality as contributors to AMR[50]. Consumption of antibiotics has grown exponentially in these countries, driven by increased availability that comes with rapid economic growth. Misuse of antibiotics on the part of both underqualified medical providers and the general population has contributed to an ever-increasing population of resistant bacteria.

Lack of Resources and Education

Inadequate education about antibiotic use is not unique to low- and middle-income countries. A survey conducted by the WHO found that, in a sample of over 10,000 people from 12 countries, 64% thought that antibiotics could be used to treat colds and the flu[51]. This misconception is also prevalent in some healthcare workers: one study of nurse trainees in Sri Lanka found that approximately 40% thought that antibiotics could be used to treat colds[52].

The additional challenge in low- and middle-income countries is a lack of sufficient skilled healthcare workers. Many clinic and community health workers don't have the time or resources to specifically diagnose and provide the correct antibiotic for an infection, and treatment is often determined by which antibiotics they have available[53]. This can contribute to resistance because treating bacteria with the incorrect antibiotic can be ineffective at eradicating the infection-causing bacteria. Incorrect diagnosis of a UTI can lead to the prescription of a medication that won't solve the infection, allowing it to spread to the kidneys and possibly the blood. Women can also face stigma if the UTI is incorrectly diagnosed as a sexually transmitted infection, which are also commonly treated with antibiotics. Even if medical professionals do have the proper training, there is often insufficient time to explain the importance of taking a full regimen. Poor patient adherence, such as saving drugs at the end of a regimen for later, means that even correct prescription and dosage is not enough.

Options for diagnoses are limited in low-resource settings, forcing medical professionals to rely on cheap and accessible diagnostic tools. Rather than urine culture, most clinics rely on symptom reporting and dipstick testing for diagnosis, a general test that does not identify the type of bacteria or whether it is causing infection[54]. Even as AMR is increasing in these countries, most healthcare facilities do not have the capacity to set up a microbiology laboratory capable of performing urine cultures that could provide a more specific diagnosis. Improving accessibility to urine culture analysis would require more funding and a concerted effort to make the practice widespread in order to reduce the use of empiric treatment.

Non-prescription Use

Misuse by the general population is amplified by the accessibility of nonprescription antibiotics in low- and middle-income countries. Many low-resource settings allow antibiotics to be sold over the counter, allowing anyone to purchase antibiotics without information about treatment regimens or dosage. One study of pharmacies in rural Bangladesh found that 48% of antibiotic purchases were less than the dose for a single day and that purchases of complete regimens were rare[55]. Incomplete treatments can lead to recurrence and incorrect dosage can encourage resistance. Pharmacists and vendors are often not trained medical professionals and profit from the sale of these drugs, creating an economic incentive to recommend their use even when unnecessary[53]. For women with recurrent UTIs, the stigma of infection can lead women to avoid doctors entirely, choosing instead to self-medicate with an antibiotic regimen that is not informed by any medical knowledge.

ENVIRONMENTAL IMPACT

The effect of the environment on the development of AMR cannot be understated. Low- and middle-income countries are less likely to have adequate water infrastructure including sewage management, continuous clean water distribution and flood drainage. Without proper sewage infrastructure, the resistant bacteria in waste from a population overusing antibiotics are not completely separated from areas of daily activity[56]. Gut bacteria are shed in waste, and exposure to antibiotics leaves only bacteria. In areas where sewage is not properly contained, these resistant bacteria can seep into the ground and anyone coming into contact with that soil can be exposed, especially children playing outdoors. For communities where regular disinfection of surfaces, tools and food is not customary, individuals can be colonized by resistant bacteria by working or eating[57].

The unreliability of running water in urban settlements can cause people to look for other sources of drinking water. Multidrug-resistant *E.coli* have been identified in rural groundwater supplies used for drinking, which could expose anyone who drinks the water to resistant bacteria without them ever having to take an antibiotic themselves[58]. A review done by Graham et al. proposes that waterborne UTIs (WUTIs) could occur due to the colonization of the gut by uropathogenic *E.coli* in drinking water that spreads to the bladder and urethra[59]. If groundwater is contaminated by MDR *E.coli*, then it is possible for MDR UTIs to affect an entire community through environmental exposure.

Improper drainage after flooding further amplifies the problems caused by poor sewage management, providing an incubator for the spread of resistance genes among bacteria. While resistance can be acquired through random mutation and then spread due to selective pressure from antibiotics, genes conferring resistance can also be spread between bacteria through horizontal gene transfer. Antibiotic residues from raw sewage can act as a selective pressure, encouraging the transfer of resistance genes. As Nadimpalli et al. points out, this suggests that not only are informal urban settlements the recipients of antibiotic resistant bacteria, the conditions in these settlements can also propagate new types of resistance[57]. Flooding can also mobilize resistant bacteria in soil and sewage, dispersing these bacteria into other communities that did not have the same pattern of resistance.

Pharmaceutical effluent also contributes to the spread of resistance when released into the environment. The production of antibiotics produces wastes that contain high levels of the drug[60]. Effluent released from production plants puts low concentrations of antibiotics into the environment, pressuring bacteria there to develop resistance. This mix of drugs and resistant bacteria then flow into bodies of water and groundwater where they spread their resistance genes. When comparing a lake in India subject to industrial pollution with one in Sweden, resistance genes were 7,000 times more abundant[61]. While there is currently not much of a focus on pharmaceutical effluent, future steps could include the neutralization of residues before they are released or enforcing a limit on the concentration of drug in effluent.

ANTIBIOTIC STEWARDSHIP

The realization of over-prescription as a contributor to AMR has led to a push for a decrease in use of antibiotics, for antibiotic stewardship and for more education about the contributors to AMR. The World Health Organization released a practical toolkit for antimicrobial stewardship in healthcare facilities in low- and middle-income countries in 2019. This toolkit lays out steps for healthcare facilities to implement an antimicrobial stewardship program, including various structures for programs, performance metrics, ways to provide feedback to healthcare workers and future steps after a stewardship program has been implemented[68]. These programs require funding and perceived legitimacy to be effective, but they can help slow the spread of resistance until other measures can be implemented. Similarly, an information campaign focused on correct antibiotic usage in countries where a prescription isn't required could reduce the speed of resistance spread. For UTIs, providing information about risk factors, preventative measures and symptoms could help improve diagnostic accuracy and reduce stigma in lower-income settings. Improved diagnostic accuracy could reduce the use of empiric therapies and, therefore, selective pressure for resistance.

While the long-term impact of antibiotic stewardship programs on the development of resistance is yet to be seen, programs have had success in reducing the number of antibiotic prescriptions. One study of Urgent Care clinics found that the program resulted in a 14.5% reduction in antibiotic prescription overall and a 22% reduction in the first month[69]. This is consistent with CDC findings that in the period after the implementation of an early stewardship program there was a 24% decrease in antibiotic prescribing at office visits[70].

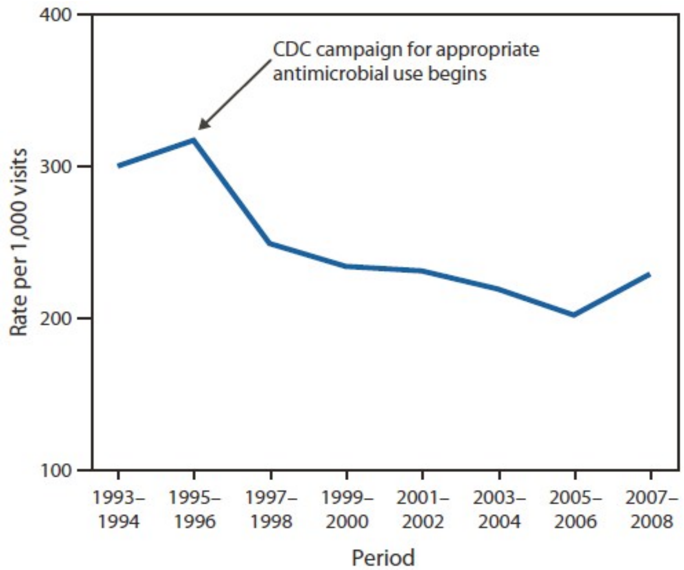

FIGURE 2. CDC DATA BETWEEN 1993 AND 2008 SHOWS THAT THE IMPLEMENTATION OF A STEWARDSHIP PROGRAM RESULTED IN A 24% DECREASE IN PRESCRIBING RATES.

ANTIBIOTIC USE IN AGRICULTURE

Antibiotic stewardship extends outside the realm of human medical treatment and encompasses agriculture-based antibiotic use as well. Direct consumption of antibiotics is only one piece of the puzzle; industrialized agriculture utilizes antibiotics to optimize animal production. In food animal production, antibiotics are used to prevent infection in crowded living conditions as well as to promote growth[62]. Residues of the drugs used in these animals can be found in the meat they produce, possibly causing health problems in unknowing consumers. At a high enough concentration, residues can select for resistant bacteria so their presence in food is cause for alarm. As a measure to address this issue, the FDA has implemented regulations limiting the use of antimicrobials for a period of time before slaughter[63].

Food animals act as reservoirs for antibiotic-resistant microbes which can transfer to consumers. If improperly cooked, resistant bacteria, such as *E.coli,* in meat can colonize the intestines of consumers and potentially cause drug-resistant UTIs[64]. The more frequently meat is consumed, the more opportunities there are to acquire drug-resistant *E.coli* and the more likely a UTI is to occur. Different animals can have different types of resistant bacteria. Women with UTIs caused by MDR *E.coli* have been found to consume chicken more frequently compared to women with susceptible UTIs, while women with ampicillin or cephalosporin-resistant *E.coli*-caused UTIs consume pork at a higher frequency. This suggests that both pork and chicken can act as reservoirs for resistant UTI-causing bacteria but that susceptibility varies based on the animal consumed[65]. The role of foodborne zoonotic *E.coli,* or FZEC, as a cause of UTIs has been discussed for decades. A recent study of human extraintestinal *E.coli* isolates (mostly from UTIs) found that 8% originated in food. Based on this number, researchers estimated that 640,000 UTIs are caused by FZEC each year[66]. With this many infections related to meat consumption, the impact of drug resistance in FZEC would impact a significant portion of the population.

While it is impossible to prevent animals from acting as bacterial reservoirs, the decision of which antibiotics can be used by farmers makes a difference in the types of resistance that bacteria can develop. As of June 2023, the FDA requires a prescription to use medically-important antibiotics in animals, pivoting away from over-the-counter access[67]. By restricting the use of medically important antibiotics, bacteria in animals have fewer opportunities to develop resistance, and there is less of a chance of resistant FZEC infection.

NON-ANTIBIOTIC ALTERNATIVES

AMR as an issue is constantly evolving and will be a battle for the foreseeable future. In the meantime, actions can be taken to help women facing recurrent UTIs that are increasingly resistant to treatment. Emphasis has turned from treatment of infections to prophylactic measures and prevention, although many of these measures have limited supporting evidence. An old home remedy, cranberry juice, has been shown to reduce the risk of UTIs in women with recurrent infections. Proanthocyanidins in the juice prevent E.coli from binding to cells in the lining of the bladder, making colonization more difficult[71]. Hydration has long been recommended to dilute and flush infection-causing bacteria from the urinary system. A clinical trial identified that an increase of 1.5 L of water per day decreased the occurrence of infection in women with recurrent UTIs[72]. Probiotics have also been posited as a preventative measure, with researchers arguing that the disruption to gut flora caused by antibiotics contributes to recurrence. Patients with a history of recurrent UTIs experienced fewer infections when their gut microbiome was more diverse[73]. Probiotics repopulate the gut, competing with UTI-causing bacteria for resources and reducing the chance of a population large enough to cause infection. The use of the antiseptic methenamine hippurate prophylactically has been proposed as an alternative to prophylactic antibiotic use. Methenamine is converted to formaldehyde in acidic urine, killing potentially infection-causing bacteria[74]. These measures turn away from antibiotics altogether, leaving them as a treatment only when infection does occur. While the measures listed here are widely regarded as safe, results are often inconsistent and less pronounced than with antibiotic treatment.

NEXT STEPS

New recommendations set by the UK National Institute for Health and Care Excellence share a similar sentiment. Rather than prescribing an antibiotic for uncomplicated UTIs, physicians are encouraged to advise patients on symptom-management, prescribing a back-up antibiotic for use only if symptoms don't improve after 48 hours. Physicians are also recommended to prescribe D-mannose, a compound that inhibits bacterial binding similarly to cranberry juice as a prophylactic measure for recurrent UTIs before antibiotics. Prophylactic vaginal estrogen is recommended for postmenopausal women to encourage diversity in the vaginal microbiome similarly to probiotics[75].

Mitigating the impact of AMR requires cooperation between physicians and patients. Public health communication must target both parties in order to prevent the over-prescription and misuse that are fueling the development of drug-resistant bacteria. In response to rising rates of Bactrim-resistant *E.coli*, the New York City Department of Health introduced a mobile app that provides prescribers with a list of UTI-causing bacterial strains and the antibiotics to which they are resistant[76]. This type of access to information should be combined with public health campaigns informing patients about best antibiotic practices.

CONCLUSION

Misuse of antibiotics has led to growing resistance that threatens their efficacy as treatment. For the millions of people that contract urinary tract infections, the loss of antibiotic effectiveness means identification of a treatment is growing more challenging. A once easily treated infection can prove to be complex and even fatal if treatment fails and infection reaches the blood. There are methods of discouraging infection, but there are not yet any real alternatives to existing antibiotics. It is crucial that countries treat the development of AMR as a priority and invest further into existing antibiotic stewardship programs with an emphasis on expanding public awareness. Because the issue of AMR is not contained within each individual country, the work of connecting researchers globally is crucial and is one of the goals of organizations like CARB-X and ReAct. Bacteria are constantly evolving, a strategy that the scientific community must also adopt in order to keep up.

REFERENCES

1. Kolář, M., Urbánek, K., & Látal, T. (2001). Antibiotic selective pressure and development of bacterial resistance. *International Journal of Antimicrobial Agents*, *17*(5), 357–363. https://doi.org/10.1016/S0924-8579(01)00317-X
2. Yang, X., Chen, H., Zheng, Y., Qu, S., Wang, H., & Yi, F. (2022). Disease burden and long-term trends of urinary tract infections: A worldwide report. *Frontiers in Public Health*, *10*, 888205. https://doi.org/10.3389/fpubh.2022.888205
3. *Urinary tract infection (UTI)—Symptoms and causes*. (n.d.). Mayo Clinic. Retrieved October 24, 2023, from https://www.mayoclinic.org/diseases-conditions/urinary-tract-infection/symptoms-causes/syc-20353447
4. Flores-Mireles, A. L., Walker, J. N., Caparon, M., & Hultgren, S. J. (2015). Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*, *13*(5), 269–284. https://doi.org/10.1038/nrmicro3432
5. Sabih, A., & Leslie, S. W. (2024). Complicated Urinary Tract Infections. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK436013/
6. Habak, P. J., & Griggs, J. (2023). Urinary Tract Infection in Pregnancy. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK537047/
7. Czajkowski, K., Broś-Konopielko, M., & Teliga-Czajkowska, J. (2021). Urinary tract infection in women. *Menopausal Review*, *20*(1), 40–47. https://doi.org/10.5114/pm.2021.105382
8. Foxman, B. (2002). Epidemiology of urinary tract infections: Incidence, morbidity, and economic costs. *The American Journal of Medicine*, *113 Suppl 1A*, 5S-13S. https://doi.org/10.1016/s0002-9343(02)01054-9
9. *When urinary tract infections keep coming back*. (2015, August 5). Harvard Health. https://www.health.harvard.edu/bladder-and-bowel/when-urinary-tract-infections-keep-coming-back
10. Eriksson, I., Olofsson, B., Gustafson, Y., & Fagerström, L. (2014). Older women's experiences of suffering from urinary tract infections. *Journal of Clinical Nursing*, *23*(9–10), 1385–1394. https://doi.org/10.1111/jocn.12422
11. Thomas-White, K., Navarro, P., Wever, F., King, L., Dillard, L. R., & Krapf, J. (2023). Psychosocial impact of recurrent urogenital infections: A review. *Women's Health*, *19*, 17455057231216537. https://doi.org/10.1177/17455057231216537
12. Foxman, B. (2010). The epidemiology of urinary tract infection. *Nature Reviews Urology*, *7*(12), Article 12. https://doi.org/10.1038/nrurol.2010.190
13. Maxwell, K., Roberts, L., Kramer, M., & Finlay, K. (2021). Using the Working Model of Adjustment to Chronic Illness to explain the burden of recurrent urinary tract infection: A survey-based study. *International Journal of Pharmacy Practice*, *29*(Supplement_1), i5–i6. https://doi.org/10.1093/ijpp/riab016.006
14. Medina, M., & Castillo-Pino, E. (2019). An introduction to the epidemiology and burden of urinary tract infections. *Therapeutic Advances in Urology*, *11*, 1756287219832172. https://doi.org/10.1177/1756287219832172
15. Mirin, A. A. (2021). Gender Disparity in the Funding of Diseases by the U.S. National Institutes of Health. *Journal of Women's Health (2002)*, *30*(7), 956–963. https://doi.org/10.1089/jwh.2020.8682
16. *Urinalysis—Mayo Clinic*. (n.d.). Retrieved October 24, 2023, from https://www.mayoclinic.org/tests-procedures/urinalysis/about/pac-20384907
17. Mambatta, A. K., Jayarajan, J., Rashme, V. L., Harini, S., Menon, S., & Kuppusamy, J. (2015). Reliability of dipstick assay in predicting urinary tract infection. *Journal of Family Medicine and Primary Care*, *4*(2), 265–268. https://doi.org/10.4103/2249-4863.154672
18. Lee, D. S., Lee, S.-J., & Choe, H.-S. (2018). Community-Acquired Urinary Tract Infection by Escherichia coli in the Era of Antibiotic Resistance. *BioMed Research International*, *2018*, 7656752. https://doi.org/10.1155/2018/7656752
19. Berg, A. O., Heidrich, F. E., Fihn, S. D., Bergman, J. J., Wood, R. W., Stamm, W. E., & Holmes, K. K. (1984). Establishing the Cause of Genitourinary Symptoms in Women in a Family Practice: Comparison of Clinical Examination and Comprehensive Microbiology. *JAMA*, *251*(5), 620–625. https://doi.org/10.1001/jama.1984.03340290034016
20. Price, T. K., Dune, T., Hilt, E. E., Thomas-White, K. J., Kliethermes, S., Brincat, C., Brubaker, L., Wolfe, A. J., Mueller, E. R., & Schreckenberger, P. C. (2016). The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. *Journal of Clinical Microbiology*, *54*(5), 1216–1222. https://doi.org/10.1128/JCM.00044-16
21. Robledo, X. G., Arcila, K. V. O., Riascos, S. H. M., & García-Perdomo, H. A. (2022). Accuracy of molecular diagnostic techniques in patients with a confirmed urine culture: A systematic review and meta-analysis. *Canadian Urological Association Journal*, *16*(9), E484. https://doi.org/10.5489/cuaj.7677
22. Jancel, T., & Dudas, V. (2002). Management of uncomplicated urinary tract infections. *Western Journal of Medicine*, *176*(1), 51–55.
23. Bader, M. S., Loeb, M., & Brooks, A. A. (2017). An update on the management of urinary tract infections in the era of antimicrobial resistance. *Postgraduate Medicine*, *129*(2), 242–258. https://doi.org/10.1080/00325481.2017.1246055
24. Commissioner, O. of the. (2020, March 24). *FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions*. FDA; FDA. https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics-risks-mental-health-and-low-blood-sugar-adverse
25. Munoz-Davila, M. J. (2014). Role of Old Antibiotics in the Era of Antibiotic Resistance. Highlighted Nitrofurantoin for the Treatment of Lower Urinary Tract Infections. *Antibiotics*, *3*(1), 39–48. https://doi.org/10.3390/antibiotics3010039
26. Stein, G. E. (1998). Single-Dose Treatment of Acute Cystitis with Fosfomycin Tromethamine. *Annals of Pharmacotherapy*, *32*(2), 215–219. https://doi.org/10.1345/aph.17227
27. Hooton, T. M., & Stamm, W. E. (1997). DIAGNOSIS AND TREATMENT OF UNCOMPLICATED URINARY TRACT INFECTION. *Infectious Disease Clinics of North America*, *11*(3), 551–581. https://doi.org/10.1016/S0891-5520(05)70373-1
28. Melekos, M. D., Asbach, H. W., Gerharz, E., Zarakovitis, I. E., Weingaertner, K., & Naber, K. G. (1997). Post-intercourse versus daily ciprofloxacin prophylaxis for recurrent urinary tract infections in premenopausal women. *The Journal of Urology*, *157*(3), 935–939.
29. Givler, D. N., & Givler, A. (2023). Asymptomatic Bacteriuria. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK441848/
30. Gilstrap, L. C., & Ramin, S. M. (2001). Urinary tract infections during pregnancy. *Obstetrics and Gynecology Clinics of North America*, *28*(3), 581–591. https://doi.org/10.1016/s0889-8545(05)70219-9

31. Mignini, L., Carroli, G., Abalos, E., Widmer, M., Amigot, S., Nardin, J. M., Giordano, D., Merialdi, M., Arciero, G., Del Carmen Hourquescos, M., & World Health Organization Asymptomatic Bacteriuria Trial Group. (2009). Accuracy of diagnostic tests to detect asymptomatic bacteriuria during pregnancy. *Obstetrics and Gynecology*, *113*(2 Pt 1), 346–352. https://doi.org/10.1097/AOG.0b013e318194f109
32. Ailes, E. C. (2018). Antibiotics Dispensed to Privately Insured Pregnant Women with Urinary Tract Infections—United States, 2014. *MMWR. Morbidity and Mortality Weekly Report*, *67*. https://doi.org/10.15585/mmwr.mm6701a4
33. Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S., Haines-Woodhouse, G., Kashef Hamadani, B. H., Kumaran, E. A. P., McManigal, B., … Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet*, *399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
34. Warren, J. W., Abrutyn, E., Hebel, J. R., Johnson, J. R., Schaeffer, A. J., & Stamm, W. E. (1999). Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *29*(4), 745–758. https://doi.org/10.1086/520427
35. Kaye, K. S., Gupta, V., Mulgirigama, A., Joshi, A. V., Scangarella-Oman, N. E., Yu, K., Ye, G., & Mitrani-Gold, F. S. (2021). Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management. *Clinical Infectious Diseases*, *73*(11), 1992–1999. https://doi.org/10.1093/cid/ciab560
36. Gupta, K., Scholes, D., & Stamm, W. E. (1999). Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA*, *281*(8), 736–738. https://doi.org/10.1001/jama.281.8.736
37. Ahmed, S. S., Shariq, A., Alsalloom, A. A., Babikir, I. H., & Alhomoud, B. N. (2019). Uropathogens and their antimicrobial resistance patterns: Relationship with urinary tract infections. *International Journal of Health Sciences*, *13*(2), 48–55.
38. Iravani, A., Klimberg, I., Briefer, C., Munera, C., Kowalsky, S. F., & Echols, R. M. (1999). A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *The Journal of Antimicrobial Chemotherapy*, *43 Suppl A*, 67–75.
39. Kaye, K. S., Belley, A., Barth, P., Lahlou, O., Knechtle, P., Motta, P., & Velicitat, P. (2022). Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA*, *328*(13), 1304–1314. https://doi.org/10.1001/jama.2022.17034
40. Chardavoyne, P. C., & Kasmire, K. E. (2020). Appropriateness of Antibiotic Prescriptions for Urinary Tract Infections. *Western Journal of Emergency Medicine*, *21*(3), 633. https://doi.org/10.5811/westjem.2020.1.45944
41. Spellberg, B. (2016). The New Antibiotic Mantra—"Shorter Is Better." *JAMA Internal Medicine*, *176*(9), 1254. https://doi.org/10.1001/jamainternmed.2016.3646
42. Martinez, K. A., Rood, M., Jhangiani, N., Kou, L., Boissy, A., & Rothberg, M. B. (2018). Association Between Antibiotic Prescribing for Respiratory Tract Infections and Patient Satisfaction in Direct-to-Consumer Telemedicine. *JAMA Internal Medicine*, *178*(11), 1558. https://doi.org/10.1001/jamainternmed.2018.4318
43. *What Drives Inappropriate Antibiotic Use in Outpatient Care?* (2017, June 28). http://pew.org/2tS7kC2
44. Zetts, R. M., Garcia, A. M., Doctor, J. N., Gerber, J. S., Linder, J. A., & Hyun, D. Y. (2020). Primary Care Physicians' Attitudes and Perceptions Towards Antibiotic Resistance and Antibiotic Stewardship: A National Survey. *Open Forum Infectious Diseases*, *7*(7), ofaa244. https://doi.org/10.1093/ofid/ofaa244
45. Grigoryan, L., Germanos, G., Zoorob, R., Juneja, S., Raphael, J. L., Paasche-Orlow, M. K., & Trautner, B. W. (2019). Use of Antibiotics Without a Prescription in the U.S. Population: A Scoping Review. *Annals of Internal Medicine*, *171*(4), 257–263. https://doi.org/10.7326/M19-0505
46. Casey, J. A., Rudolph, K. E., Robinson, S. C., Bruxvoort, K., Raphael, E., Hong, V., Pressman, A., Morello-Frosch, R., Wei, R. X., & Tartof, S. Y. (2021). Sociodemographic Inequalities in Urinary Tract Infection in 2 Large California Health Systems. *Open Forum Infectious Diseases*, *8*(6), ofab276. https://doi.org/10.1093/ofid/ofab276
47. Moran, J., Fitch, T. J., Villanueva, G., Quadir, M. M., Chien, L.-C., & Alamgir, H. (2020). Urinary symptoms and infections among female garment factory workers in Bangladesh. *Work (Reading, Mass.)*, *65*(4), 847–856. https://doi.org/10.3233/WOR-203136
48. Lee, A. C., Mullany, L. C., Koffi, A. K., Rafiqullah, I., Khanam, R., Folger, L. V., Rahman, M., Mitra, D. K., Labrique, A., Christian, P., Uddin, J., Ahmed, P., Ahmed, S., Mahmud, A., DasGupta, S. K., Begum, N., Quaiyum, M. A., Saha, S. K., & Baqui, A. H. (2019). Urinary tract infections in pregnancy in a rural population of Bangladesh: Population-based prevalence, risk factors, etiology, and antibiotic resistance. *BMC Pregnancy and Childbirth*, *20*, 1. https://doi.org/10.1186/s12884-019-2665-0
49. Oli, A. N., Okafor, C. I., Ibezim, E. C., Akujiobi, C. N., & Onwunzo, M. C. (2010). The prevalence and bacteriology of asymptomatic bacteriuria among antenatal patients in Nnamdi Azikiwe University Teaching Hospital Nnewi; South Eastern Nigeria. *Nigerian Journal of Clinical Practice*, *13*(4), 409–412.
50. *Antimicrobial resistance*. (n.d.). Retrieved December 19, 2023, from https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
51. *WHO multi-country survey reveals widespread public misunderstanding about antibiotic resistance*. (n.d.). Retrieved November 16, 2024, from https://www.who.int/news/item/16-11-2015-who-multi-country-survey-reveals-widespread-public-misunderstanding-about-antibiotic-resistance
52. Gunasekera, Y. D., Kinnison, T., Kottawatta, S. A., Silva-Fletcher, A., & Kalupahana, R. S. (2022). Misconceptions of Antibiotics as a Potential Explanation for Their Misuse. A Survey of the General Public in a Rural and Urban Community in Sri Lanka. *Antibiotics*, *11*(4), 454. https://doi.org/10.3390/antibiotics11040454
53. Okeke, I. N., Lamikanra, A., & Edelman, R. (1999). Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerging Infectious Diseases*, *5*(1), 18–27.
54. Maina, J., Mwaniki, J., Mwiti, F., Kiiru, S., Katana, J., Wanja, F., Mukaya, J., Khasabuli, O., Asiimwe, B., Gillespie, S., Stelling, J., Mshana, S., Holden, M., Sabiiti, W., Kiiru, J., & Consortium, H. (2023). Evaluation of the diagnostic performance of the urine dipstick test for the detection of urinary tract infections in patients treated in Kenyan hospitals. *Access Microbiology*, *5*(6), acmi000483.v3. https://doi.org/10.1099/acmi.0.000483.v3

55. Hossain, M. M., Glass, R. I., & Khan, M. R. (1982). Antibiotic use in a rural community in Bangladesh. *International Journal of Epidemiology*, *11*(4), 402–405. https://doi.org/10.1093/ije/11.4.402
56. Okeke, I. N., Laxminarayan, R., Bhutta, Z. A., Duse, A. G., Jenkins, P., O'Brien, T. F., Pablos-Mendez, A., & Klugman, K. P. (2005). Antimicrobial resistance in developing countries. Part I: Recent trends and current status. *The Lancet Infectious Diseases*, *5*(8), 481–493. https://doi.org/10.1016/S1473-3099(05)70189-4
57. Nadimpalli, M. L., Marks, S. J., Montealegre, M. C., Gilman, R. H., Pajuelo, M. J., Saito, M., Tsukayama, P., Njenga, S. M., Kiiru, J., Swarthout, J., Islam, M. A., Julian, T. R., & Pickering, A. J. (2020). Urban informal settlements as hotspots of antimicrobial resistance and the need to curb environmental transmission. *Nature Microbiology*, *5*(6), Article 6. https://doi.org/10.1038/s41564-020-0722-0
58. McKeon, D. M., Calabrese, J. P., & Bissonnette, G. K. (1995). Antibiotic resistant gram-negative bacteria in rural groundwater supplies. *Water Research*, *29*(8), 1902–1908. https://doi.org/10.1016/0043-1354(95)00013-B
59. Graham, J. P., Amato, H. K., Mendizabal-Cabrera, R., Alvarez, D., & Ramay, B. M. (2021). Waterborne Urinary Tract Infections: Have We Overlooked an Important Source of Exposure? *The American Journal of Tropical Medicine and Hygiene*, *105*(1), 12–17. https://doi.org/10.4269/ajtmh.20-1271
60. Larsson, D. G. J., de Pedro, C., & Paxeus, N. (2007). Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *Journal of Hazardous Materials*, *148*(3), 751–755. https://doi.org/10.1016/j.jhazmat.2007.07.008
61. Bengtsson-Palme, J., Boulund, F., Fick, J., Kristiansson, E., & Larsson, D. G. J. (2014). Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India. *Frontiers in Microbiology*, *5*. https://doi.org/10.3389/fmicb.2014.00648
62. Isaacson, R. E., & Torrence, M. E. (2002). *The Role of Antibiotics in Agriculture: This report is based on a colloquium sponsored by the American Academy of Microbiology held November 2–4, 2001, in Santa Fe, New Mexico*. American Society for Microbiology. http://www.ncbi.nlm.nih.gov/books/NBK559438/
63. *USDA ERS - Restrictions on Antibiotic Use for Production Purposes in U.S. Livestock Industries Likely To Have Small Effects on Prices and Quantities*. (n.d.). Retrieved December 19, 2023, from https://www.ers.usda.gov/amber-waves/2015/november/restrictions-on-antibiotic-use-for-production-purposes-in-u-s-livestock-industries-likely-to-have-small-effects-on-prices-and-quantities/
64. Seaton, J. (n.d.). *Antibiotic-Resistant UTIs Are Common, and Other Infections May Soon Be Resistant, Too*. Scientific American. Retrieved December 19, 2023, from https://www.scientificamerican.com/article/antibiotic-resistant-utis-are-common-and-other-infections-may-soon-be-resistant-too/
65. Manges, A. R., Smith, S. P., Lau, B. J., Nuval, C. J., Eisenberg, J. N. S., Dietrich, P. S., & Riley, L. W. (2007). Retail Meat Consumption and the Acquisition of Antimicrobial Resistant *Escherichia coli* Causing Urinary Tract Infections: A Case–Control Study. *Foodborne Pathogens and Disease*, *4*(4), 419–431. https://doi.org/10.1089/fpd.2007.0026
66. Liu, C. M., Aziz, M., Park, D. E., Wu, Z., Stegger, M., Li, M., Wang, Y., Schmidlin, K., Johnson, T. J., Koch, B. J., Hungate, B. A., Nordstrom, L., Gauld, L., Weaver, B., Rolland, D., Statham, S., Hall, B., Sariya, S., Davis, G. S., … Price, L. B. (2023). Using source-associated mobile genetic elements to identify zoonotic extraintestinal E. coli infections. *One Health*, *16*, 100518. https://doi.org/10.1016/j.onehlt.2023.100518
67. FDA Center for Veterinary Medicine. (2023, June 12). *FDA Announces Transition of Over-the-Counter Medically Important Antimicrobials for Animals to Prescription Status*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-transition-over-counter-medically-important-antimicrobials-animals-prescription-status
68. *Antimicrobial stewardship programmes in health-care facilities in low—And middle -income countries*. (n.d.). Retrieved December 19, 2023, from https://www.who.int/publications-detail-redirect/9789241515481
69. Stenehjem, E., Wallin, A., Willis, P., Kumar, N., Seibert, A. M., Buckel, W. R., Stanfield, V., Brunisholz, K. D., Fino, N., Samore, M. H., Srivastava, R., Hicks, L. A., & Hersh, A. L. (2023). Implementation of an Antibiotic Stewardship Initiative in a Large Urgent Care Network. *JAMA Network Open*, *6*(5), e2313011. https://doi.org/10.1001/jamanetworkopen.2023.13011
70. *Office-Related Antibiotic Prescribing for Persons Aged ≤14 Years—United States, 1993—1994 to 2007—2008*. (n.d.). Retrieved November 17, 2024, from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6034a1.htm
71. Williams, G., Hahn, D., Stephens, J. H., Craig, J. C., & Hodson, E. M. (2023). Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews*, *4*. https://doi.org/10.1002/14651858.CD001321.pub6
72. Hooton, T. M., Vecchio, M., Iroz, A., Tack, I., Dornic, Q., Seksek, I., & Lotan, Y. (2018). Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomized Clinical Trial. *JAMA Internal Medicine*, *178*(11), 1509–1515. https://doi.org/10.1001/jamainternmed.2018.4204
73. Worby, C. J., Schreiber, H. L., Straub, T. J., van Dijk, L. R., Bronson, R. A., Olson, B. S., Pinkner, J. S., Obernuefemann, C. L. P., Muñoz, V. L., Paharik, A. E., Azimzadeh, P. N., Walker, B. J., Desjardins, C. A., Chou, W.-C., Bergeron, K., Chapman, S. B., Klim, A., Manson, A. L., Hannan, T. J., … Earl, A. M. (2022). Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. *Nature Microbiology*, *7*(5), Article 5. https://doi.org/10.1038/s41564-022-01107-x
74. Lee, B. S. B., Bhuta, T., Simpson, J. M., & Craig, J. C. (2012). Methenamine hippurate for preventing urinary tract infections. *The Cochrane Database of Systematic Reviews*, *2012*(10), CD003265. https://doi.org/10.1002/14651858.CD003265.pub3
75. Lancet, T. (2018). Balancing treatment with resistance in UTIs. *The Lancet*, *391*(10134), 1966. https://doi.org/10.1016/S0140-6736(18)31077-8
76. Richtel, M. (2019, July 13). Urinary Tract Infections Affect Millions. The Cures Are Faltering. *The New York Times*. https://www.nytimes.com/2019/07/13/health/urinary-infections-drug-resistant.html