

**ANTIBIOTIC-RESISTANT GONORRHEA: THE CURRENT THREAT AND FUTURE  
PUBLIC HEALTH IMPLICATIONS**

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**ABSTRACT**

Gonorrhea is a sexually transmitted bacterial infection with a high incidence rate in the United States and abroad. Untreated gonorrhea infections can lead to Pelvic Inflammatory Disease (PID), infertility in both men and women and blindness in babies infected by their mothers. The morbidity associated with gonorrhea, however, has been inhibited by the use of antibiotics, especially in the developed world. Since antibiotics were first used to cure gonorrhea in 1937, a variety of antibiotics have been used and subsequently discarded as first line drugs to treat the disease due to the gonorrhea bacterium's adept ability to develop antibiotic resistance. Currently, the first line drug to treat gonorrhea is ceftriaxone, an injectable drug in the cephalosporin class of antibiotics. However, recent treatment failures after a standard dose of ceftriaxone, which have occurred in Japan, Australia and throughout Europe, have prompted experts' concern about the future of gonorrhea treatment. While a variety of other antibiotics have been suggested as possible replacements for ceftriaxone, no known drug is a particularly good or immediate substitute, either because of insufficient research, a proven lack of efficacy or already-existing resistance within prevalent gonorrhea strains. In the absence of another antibiotic to take ceftriaxone's place, the focus of public health professionals and clinicians must be on prevention. The Centers for Disease Control and Prevention (CDC), World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) should

adjust their antibiotic-resistant gonorrhea working plans to prioritize prevention, rather than surveillance, in order to stem the tide of what could be a pandemic of an untreatable bacterial infection, the likes of which have not been experienced in the modern antibiotic era. The public health consequences of such an epidemic would be severe with global increases in morbidity, costs and Disability Adjusted Life Years (DALYs) lost due to gonorrhea infection.

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## **PREFACE**

I would like to thank Dr. John Marx, Dr. Mary Hawk and Dr. Jeanette Trauth for their time, support and assistance in writing this thesis.

## **1.0 INTRODUCTION**

Gonorrhea has been a curable sexually transmitted infection since the introduction of antibiotics to treat the disease in 1937 (Barry & Klausner, 2009, p. 555). However, recent gonorrhea treatment failures related to the use of ceftriaxone, the last approved antibiotic to treat gonorrhea, raise the specter of a future of untreatable gonorrhea infections and a concomitant increase in morbidity from the disease (Cámara et al., 2012; Ohnishi et al., 2011a; Stoltey & Barry, 2012, p. 1412; Unemo, Golparian, & Hestner, 2011; Unemo, Golparian, Potocnik, & Jeverica, 2012; Unemo et al., 2012). This paper seeks to provide background on the emerging issue of antibiotic-resistant gonorrhea infection, including information on the history and epidemiology of gonorrhea as well as a critique of existing gonorrhea-specific public health plans created by the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC). This paper will also explore the relationship between gonorrhea and the evolutionary arms race between bacteria and antibiotics, and the possible future effects of an epidemic of untreatable gonorrhea infections.



## 2.0 EPIDEMIOLOGY

The term “gonorrhoea” was coined by a second-century physician, prompting some scholars to speculate that gonorrhoea has been afflicting human populations for millennia (Groopman, 2012, p.26). Other scholars question whether the disease described in ancient texts is modern day gonorrhoea or another type of sexually transmitted infection altogether as the expression of gonorrhoea in ancient times does not necessarily reflect the disease’s modern symptoms (Oriol, 1994, p. 6-7). The other well-known term for gonorrhoea, “the clap,” was first used in a 1378 document written by an English surgeon (Morton, 1977, p. 4). The etymology of the term is unknown and conjectures as to the word’s origin vary (Morton, 1977, p.4). Some suggest that it may have been gleaned from an Anglicization of the French word ‘clapisses,’ which was used to describe brothels in a particular district of Paris, whereas another theory is that it is derived from the clapping instruments that lepers used to announce their arrival (Morton, 1977, p. 4). In the pre-antibiotic era, treatments for gonorrhoea were often symptom-focused, especially in men (Lewis, 2010, p. 415). Specifically, treatments included urethral irrigation, catheterization and foregoing sex and alcohol (Lewis, 2010, p. 415). Little was known about the infection in women and it was not until 1876 that gonorrhoea was implicated as a cause of Pelvic Inflammatory Disease (PID) (Oriol, 1994, p. 125).

The bacterium that causes gonorrhoea, *Neisseria gonorrhoeae*, was discovered in 1879 by Albert Neisser (Barry & Klauser, 2009, p. 555). However, it was not until 1937 that a cure for

gonorrhoea was introduced in the form of the antibiotic, sulfanilamide (Barry & Klausner, 2009, p. 555). At the time of its introduction, sulfanilamide was shown to cure 80-90% of cases; however, by 1950, more than 90% of tested gonorrhoea bacteria exhibited resistance to sulfanilamide (Lewis, 2010, p. 415). In response to the decreased effectiveness of sulfanilamide, penicillin became the primary antibiotic used to treat gonorrhoea (Lewis, 2010, p. 416). Over time, increasingly larger doses of penicillin were needed to cure the disease; by 1976, the level of resistance was so high that penicillin was no longer considered a first line drug to treat gonorrhoea (Lewis, 2010, p. 417).

For people allergic to penicillin tetracyclines were developed in the late 1940s (Lewis, 2010, p. 417). By the mid-1980s, resistance to these drugs emerged and fluoroquinolones became the antibiotic of choice for gonorrhoea (Lewis, 2010, p. 418). As before, rising numbers of treatment failures due to growing resistance required higher doses of fluoroquinolones until resistant bacteria completely prevailed (Lewis, 2010, p. 418). Azithromycin, a type of macrolide preferred for its ability to treat both chlamydia and gonorrhoea, was subsequently adopted, but gonorrhoea also began to develop wide-ranging resistance to it by the 1990s (Ndowa, Lusti-Narasimhan, & Unemo, 2012, p. 317).

This history of antibiotic resistance in gonorrhoea is an instructive example of the evolutionary arms race between bacteria and antibiotics. While different antibiotics have been deployed against the *N. gonorrhoeae* bacterium, it continuously developed the necessary resistance to allow it to survive, flourish and continue infecting humans despite our most current antibiotic interventions. In this way, gonorrhoea is not unique, but, like all bacteria, is a complex organism with a high level of adaptability that is able to evolve in order to survive and selectively compete in an ever-changing environment. Just as viruses, such as influenza and

HIV, evolve constantly, preventing the development of an effective vaccine, bacteria are capable of even greater structural and chemical changes, given their far greater complexity. Antibiotics are just one more threat in a bacterium's environment, comparable to others confronted over thousands of years. Therefore, it should come as no particular surprise that antibiotics are not a permanent preventive fix, but, rather, a temporary solution to the permanent problem of bacterial infections. In this way, the evolutionary arms race with bacteria has become a sort of catch-22: antibiotics are a necessary and life-saving part of our medical interventions, yet the more we use them, the closer they become to being useless (Wright, 2010). In the case of gonorrhea, the medical community has exhausted many of our possible treatments for the disease, prompting the current uncertainty as to whether the bacteria, in the case of gonorrhea, have, at least temporarily, won the race and become an untreatable disease, just as it was a little over seven decades ago (Barry & Klausner, 2009, p. 555).

In light of these considerations, it is possible to provide a broad overview of post-World War II American trends in gonorrhea (Trotter, Hughes, & Ison, 2010, p. 234). During the late 1940s, gonorrhea rates increased dramatically, coinciding with the return of American troops from abroad (Trotter, Hughes, & Ison, 2010, p. 234). Rates declined in the 1950s, only to sharply increase in the 1960s, likely as a result of the sexual revolution (Centers for Disease Control and Prevention [CDC], 2007b; Trotter, Hughes, & Ison, 2010, p. 234). Rates peaked in 1975 at almost 500 cases per 100,000 and then decreased 74% through 1997 (CDC, 2007b). This downward trend was triggered by the initiation of the national gonorrhea control program in 1972 (Brown & Weisner, 1980). The program included innovations such as creating national treatment guidelines, implementing gonorrhea screening programs in health departments

throughout the country and initiating education of both the general public and clinicians about gonorrhea and screening programs (Brown & Weisner, 1980).

Gonorrhea is the second most frequently reported disease in the United States with 321,849 cases in 2011 (CDC, 2012c). The true number of cases may be much higher, due to the asymptomatic nature of many infections, with one estimate placing the accurate disease burden in the U.S. at 700,000 cases (Kirkcaldy, Bolan & Wasserheit, 2013, p.185). The disease burden data generates a rate of 104.2 cases per 100,000 in 2011, a 4% increase over the 2010 rate (CDC, 2012c). However, gonorrhea rates have been decreasing over the past few years with an 11.7% reduction occurring between 2007 and 2011 (CDC, 2012c).

The current low rates of gonorrhea infection in the general public obscure the disproportionate burden of the disease suffered by certain subpopulations. One important disparity in rates of gonorrhea infection occurs among people of different races and ethnicities. Blacks accounted for sixty seven percent of reported gonorrhea cases in which the patient's race or ethnicity was documented. The rate of gonorrhea infection for blacks in 2011, 427.3 per 100,000, is seventeen times higher than that of whites, 25.2 per 100,000. When teasing out differences among the sexes, black men have a gonorrhea rate that is 19.4 times higher than that of white men and black women have a rate that is 15.2 times higher than white women. In 2011, these disparities persisted across racial and ethnic groups with American Indians and Alaska Natives accounting for a rate that is 4.6 times higher than that of whites and Hispanics having a rate that is 2.1 that of whites. The only racial or ethnic minority that does not have higher rates of gonorrhea infection than whites is Asians and Pacific Islanders with a rate of 15.1 per 100,000 (CDC, 2012f).

A variety of different reasons for the racial and ethnic disparities exhibited in the epidemiology of many sexually transmitted infections (STIs) have been posited. One explanation for the difference is black sexual networks. In white and Hispanic sexual networks, people at high risk of contracting an STI tend to partner with other high risk individuals, isolating STI incidence among high-risk groups (Laumann & Youm, 1999). However, in black sexual networks, high risk individuals are more likely to partner with low risk individuals, causing STI transmission to be dispersed throughout the black community, even among people at comparatively low risk of infection (Laumann & Youm, 1999). This trend may be due to a disproportionate black male-to-female ratio caused by high levels of mortality and incarceration among black men, leading black women to choose high risk partners (Doherty, Schoenbach, & Adimora, 2009, p. 119). Blacks are also more likely to choose intra-racial sexual relationships than whites or Hispanics, maintaining high levels of STIs within the black community (Laumann & Youm, 1999). Minority sexual networks may often also have high rates of individual-level risk factors for gonorrhea infection, most notably concurrent sexual partnerships (multiple sexual partnerships during the same time span) or taking only brief pauses between terminating one sexual partnership and initiating another, with reinfection a major driver of gonorrhea incidence in these groups (Chen & Ghani, 2010). Poverty and lack of access to healthcare, which stems the treatment of infections and subsequent prevention of transmission, have also been cited as factors contributing to racial disparities in STI incidence (Aral, Adamora, & Fenton, 2008, p. 337-8).

The southern United States has higher gonorrhea rates than any other region with a rate of 135.5 cases per 100,000 (CDC, 2012c). The rates of gonorrhea also fluctuate widely by state or district, with Vermont having the lowest rate in 2011 (7.7 cases per 100,000) and D.C. having the highest (426.9 cases per 100,000) (CDC, 2012b). The higher gonorrhea rates in the southern

United States are likely due to the higher proportion of blacks in that region (Farley, 2006, p. S58).

In 2011, women had a higher prevalence rate than men (108.9 cases per 100,000 vs. 98.7 per 100,000) with women aged between twenty and twenty-four having the highest gonorrhea rates of any other group (584.2 per 100,000) (CDC, 2012d). The next highest prevalence rate by group was women aged fifteen to nineteen with a rate of 556.5 cases per 100,000 (CDC, 2012d). High prevalence rates among young adults may be the result of an inability to access healthcare services especially due to cost and absence of transportation as well as a dearth of public health interventions to address teen social norms around sex and sexually transmitted infections (CDC, 2012d). Young women may be especially at risk of contracting sexually transmitted infections, including gonorrhea, due to cervical ectopy, a condition wherein young women have greater numbers of columnar cells present on the ectocervix than older women (Boskey, 2010). Columnar cells are more vulnerable to infection by gonorrhea bacteria, putting young women at greater biological risk of infection (Boskey, 2010). Adolescents are also more likely to engage in high risk sexual behaviors than adults, including higher rates of unprotected sex, multiple sexual partnerships and brief sexual partnerships (Upchurch, Mason, Kusunoki, & Kriechbaum, 2004, p. 277).

Another at-risk population for gonorrheal infection is men who have sex with men (MSM). In 2011, among MSM who visited sexually transmitted disease (STD) clinics that were part of the STD Surveillance Network, the site specific prevalence of gonorrhea ranged from 2.8% to 21% with a median of 14.5%. In eleven of the twelve STD clinics, the prevalence of gonorrhea was higher than that of chlamydia. Higher rates of risk factors for STIs in MSM

groups, including greater numbers of sex partners and lower rates of protected sex, may account for this disparity (CDC, 2012e).

Worldwide gonorrhea incidence in 2008, the year of the most recent available data, was estimated to be 106.1 million cases and the prevalence was 36.4 million cases (World Health Organization [WHO], 2011a, p. 1).<sup>1</sup> In that year, gonorrhea had a higher estimated incidence rate than chlamydia or syphilis, likely due to upward adjustments in the estimated prevalence rate of gonorrhea in most WHO regions (p. 3). Based on these statistics, an estimated 440,000 Disability Adjusted Life Years (DALYs) were lost in 2008 due to gonorrhea infection (Ndowa & Lusti-Narismhan, 2012, p. 77). The WHO African region had the highest incidence and prevalence rates of gonorrhea in 2008, with an incidence rate of 60.3 cases per 1,000 for men and 49.7 cases per 1,000 for women (WHO, 2011a, p. 4). There was a 2% prevalence rate in men and a 2.3% prevalence rate in women (p. 4). The high rate of gonorrhea in the WHO Africa region may be due to a lack of surveillance, adequate screening methods and access to care and further compounded by a high prevalence in the general population (Low et al., 2006). Globally, up to 4,000 babies per year become blind due to mother-to-child transmission of either gonorrhea or chlamydia (p. 20). Many countries lack adequate surveillance systems for gonorrhea, and clinicians' attentiveness to antibiotic resistance may also be meager, causing concern that treatment failures may be more widespread than what has been already documented in developed country contexts (p. 11).

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<sup>1</sup> The WHO defines incidence as new cases of gonorrhea occurring in 2008 and prevalence as the total number of adults infected with gonorrhea at any point in 2008 (WHO, 2011a, p. 2).

### 3.0 SEXUAL TRANSMISSION, SYMPTOMS AND CONSEQUENCES

Gonorrhea is a bacterial infection caused by the *Neisseria gonorrhoeae* bacterium (Ndowa & Lusti-Narasimhan, 2012, p. 76).<sup>2</sup> It is most often spread through sexual contact, attaching to the urethra, cervix, rectum and pharynx (CDC, 2013; Groopman, 2012, p.27). The chance of a man passing on gonorrhea bacteria to a woman per episode of unprotected vaginal intercourse is approximately 50% whereas the probability of a woman giving gonorrhea to a man is closer to 20% per episode (Silverman & Geffen, 2008). If a woman has two or three exposures to an infected man through vaginal sex, the likelihood of her being infected is greater than 90% (Silverman & Geffen, 2008). A man, who has unprotected vaginal sexual intercourse with an infected woman four or more times has a 60 to 80% chance of becoming infected (Silverman & Geffen, 2008). There is inadequate information on gonorrhea transmission rates for oral and anal sex; however, rectal gonorrhea infections, especially symptomatic infections, have much higher bacterial loads than pharyngeal infections, suggesting that receptive partners

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<sup>2</sup> Lifetime medical costs associated with gonorrhea infection in the United States are estimated to be \$68 per case for an infected man and \$343 per case for an infected woman. Besides the direct medical costs associated with treatment, it is estimated that work-related productivity losses for untreated cases of gonorrhea are \$34 per infected man and \$171 per infected woman. This estimate of lost productivity does not include the opportunity costs of treatment for both patients and clinicians or the loss in work-related productivity caused by employees acting as caregivers for infected partners or adolescent children. PID is an even more costly outcome of gonorrhea infection with the estimated average lifetime cost as high as \$3,180 per case. For women who suffer the most severe effects associated with PID, costs are even higher, with lifetime costs of \$1,270 for infertility, \$6,350 for chronic pain and \$6,840 for costs related to an ectopic pregnancy (National Business Group on Health, 2011).



may transmit gonorrhea to insertive partners more easily through anal than oral sex (Bissessor et al., 2011).

Sexually transmitted gonorrheal infections in men can lead to urethritis or inflammation of the urethra which, if left untreated, can result in epididymitis in 10-30% of cases (CDC, 2007a; Ndowa & Lusti-Narasimhan, 2012, p.79). Epididymitis is characterized by pain and inflammation of the epididymis and can lead to serious complications, including testicular abscesses, low sperm count and infertility (CDC, 2011a; Ndowa & Lusti- Narasimhan, 2012 p. 79). Gonorrheal infections in men are asymptomatic in approximately 10% of cases (Leone, 2012).

In women, gonorrheal infection can also cause urethritis as well as cervicitis or inflammation of the cervix which can lead to PID, an infection of a woman's reproductive organs (Leone, 2012; Ndowa & Lusti- Narasimhan, 2012, p. 79; Medline Plus, 2013). Up to 40% of women infected with gonorrhea who do not receive treatment will develop PID and, of those, approximately 25% will suffer from infertility (WHO, p. 19). PID is the most common cause of infertility in the United States and can also result in ectopic pregnancies, chronic pain and abscesses (CDC 2011b; Medline Plus, 2013). About 50% of all cervical gonorrheal infections are asymptomatic (Leone, 2012). Gonorrhea is also associated with adverse birth-related events, including spontaneous abortion and premature births, problems that can occur in up to 35% of mothers with untreated infections (WHO, 2011b).<sup>3</sup>

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<sup>3</sup> A second mode of transmission for gonorrhea is that of mother-to-child transmission during vaginal childbirth, which may occur in as many as 30 to 40% of cases, where the mother is infected with cervical gonorrhea (CDC, 2011c). Infection of an infant's eyes with *N. gonorrhoeae* can lead to conjunctivitis, which if left untreated, may result in blindness (CDC, 2010a). Other, rarer, complications suffered by infected newborns include scalp abscesses, infection of the urethra, cervix, pharynx, or anus, septic arthritis, sepsis or meningitis (Speer, 2012).

Affecting both sexes are anal gonorrhea and pharyngeal gonorrhea (Ndowa & Lusti-Narasimhan, 2012, p. 79). While usually asymptomatic, one possible outcome of gonorrhea infection through anal sex is proctitis, inflammation of the rectum, which can cause pain, discharge and bleeding (U.S. National Library of Science, 2011). While also typically asymptomatic, pharyngeal gonorrhea, transmitted through oral sex may be one of the most significant reservoirs of gonorrhea bacteria (Stoltey & Barry, 2012, p. 1415). *N. gonorrhoeae* in the pharynx comingles with other *Neisseria* species, exchanging DNA with bacteria that may already be resistant to a variety of antibiotics (Ndowa & Lusti-Narasimhan, 2012, p.78; Stoltey & Barry, 2012, p. 1415). Another reason for concern about pharyngeal gonorrhea is that during treatment, the pharynx is likely to have lower concentrations of an antibiotic, making the antibiotic less effective against pharyngeal gonorrhea than genital gonorrhea (Ndowa & Lusti-Narasimhan, 2012, p. 78). Therefore, while genital gonorrhea and its symptoms may be cured after treatment, *N. gonorrhoeae* bacteria may continue living in the pharynx asymptotically, infecting other hosts through transmission from the pharynx to the urethra during oral sex (Ndowa & Lusti-Narasimhan, 2012, p. 78; Stoltey & Barry, 2012, p. 1415). Moreover, while pharyngeal infections were thought to be uncommon in the past, newer studies suggest that pharyngeal gonorrhea may be the most prevalent site of infection for MSM (Templeton et al., 2010, p. 90). Therefore, the importance of pharyngeal gonorrhea as a driver of new infections and of antibiotic resistance should not be underestimated.

Distinct from the localized conditions discussed above is when the *N. gonorrhoeae* bacteria leave the site of infection and spread throughout the body causing a condition known as disseminated gonococcal infection (DGI). More common in women than men and occurring in .5 to 3% of all gonorrhea cases, DGI can result in a variety of symptoms including skin lesions,

dermatitis, tenosynovitis (tendon-related inflammation), arthritis and joint pain. Two other clinically significant conditions that can result from gonorrhea traveling outside of the mucous membranes are endocarditis and meningitis (Goldenberg & Sexton, 2012).<sup>4</sup>

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<sup>4</sup> Gonococcal meningitis and endocarditis are both very rare outcomes of an untreated gonorrhea infection. Only 24 cases of gonococcal meningitis have been reported since 1922 (Martín et. al, 2008, p.1673). It is believed that gonococcal meningitis is less lethal than meningitis caused by other bacteria as 6 of 9 people, who suffered from the disease in the pre-antibiotic era, survived without antibiotic intervention (p.1673). Gonococcal endocarditis is somewhat more prevalent occurring in 1-2% of all DGI cases (Jackman & Glamann, 1991, p. 227). The mortality rate for gonococcal endocarditis, which tends to affect adolescents and young adults, is approximately 20%, even with antibiotic and surgical intervention (p. 229). Therefore, both conditions are notable for being potentially fatal, an outcome that is not associated with other manifestations of gonorrhea infection.

#### **4.0 CONTEMPORARY ANTIBIOTIC TREATMENT AND ANTIBIOTIC RESISTANT GONORRHEA**

Cephalosporins are now the last class of drugs known to effectively treat *N. gonorrhoeae* bacteria, and, like all other antibiotics before them, resistance to cephalosporins is increasing dramatically (Barry & Klausner, 2009, p. 555). The two major cephalosporin variants, which have been effective against gonorrhea infection, are cefixime, taken orally, and ceftriaxone, an injectable drug (Groopman, 2012, p.27). However, increasing resistance to cefixime, including documented treatment failures in North America and elsewhere, have led the United States, Europe and the United Kingdom to replace cefixime with ceftriaxone as the first line antibiotic to treat gonorrhea (Kirkcaldy, Bolan, & Wasserheit, 2013, p. 186). In the U.S. the standard regimen to treat gonorrhea is 250 mg ceftriaxone combined with either azithromycin or doxycycline (CDC 2010b; Stoltey & Barry, 2012, p. 1414). In Japan, where cephalosporin resistance is more pronounced, the standard dose is 1 g of ceftriaxone (Tapsall, 2009, p. 257). The U.S. could increase its standard dose of ceftriaxone over time to reduce resistance, as it upgraded from a 125 mg dose in 2010, though the maximum amount of ceftriaxone that can be given in a single dose is 2 g (American Society of Health-System Pharmacists, 2005; CDC, 2010b).

Some of the earliest documented treatment failures associated with a standard ceftriaxone regimen occurred in Australia in 2009. While two cases of urogenital gonorrhea were cured,

their pharyngeal infections remained after a 250mg dose of ceftriaxone was administered, necessitating higher doses of the drug to completely cure the infection (Stoltey & Barry, 2012, p. 1412).

Another major treatment failure was documented in Japan in 2009 when a Kyoto female sex worker's pharyngeal gonorrhea failed to respond to ceftriaxone (Ohnishi et al., 2011a, p. 3538; Ohnishi et al., 2011b, p. 148). In 2011, it was revealed that the strain of gonorrhea discovered in the woman, known as H041, was highly resistant to all types of cephalosporins and many other types of antimicrobials (Ohnishi et al., 2011a, p. 3538). Even though the sex worker's infection was believed to have spontaneously resolved after three months, there was concern that the H041 strain could spread swiftly through Japan, given the lack of a gonorrhea surveillance program in the country and the possibility that the infected sex worker transmitted the strain to a large number of other people (Ohnishi et al., 2011a, p.3541, 3543). However, secondary infections with the H041 strain were not reported, suggesting that the bacteria was not as fit as other strains and, therefore, could not be transmitted (Ohnishi et al., 2011a, p. 3543).

Like that case, many past strains of gonorrhea are believed to have originated in the WHO's Western Pacific Region and spread internationally via migration, long distance truck driving and sex tourism (Lewis, 2009, p. 418; Ohnishi et al., 2012a, p. 3539). Past antibiotic resistant strains of the disease have spread globally from the Western Pacific Region, which includes countries and territories stretching from China to French Polynesia, in only one to two decades (Ohnishi et al., 2011a, p. 3543; WHO, 2013). With the consistent increase in the speed and volume of global travel, a new antibiotic-resistant strain of gonorrhea may not even take that long to spread its reach internationally with some experts predicting that ceftriaxone-resistant gonorrhea will be prevalent within five to eight years (Groopman, 2012, p. 27). Already,

laboratory testing has shown decreased susceptibility to ceftriaxone in strains of gonorrhea taken from the West coast of the United States, as well as from men who have sex with men (MSM) populations (CDC, 2012a, p. 3). The trend in resistance spreading from the West and prominent among MSM echoes the spread of fluoroquinolone-resistant gonorrhea in the past (CDC, 2012a, p. 3). There is also concern that selective pressures associated with antibiotic use or genetic exchange between gonorrhea and other bacteria could cause resistance to emerge in the United States or other countries without a previous history of documented ceftriaxone treatment failures (CDC, 2012a, p. 1).

In June 2010, a second strain of extensively resistant gonorrhea, known as F89, was discovered in an MSM patient in Quimper, France (Unemo et al., 2012, p. 1274). The man suffered a treatment failure of his urethral gonorrhea after being treated with cefixime, and required a dose of gentamicin to be cured (Unemo et al., 2012, p. 1274). The man's sexual contact could not be reached for testing and treatment (Unemo et al., 2012, p. 1274). The two different resistant strains (H041 and F89) evolved from two different multilocus sequence typing clones<sup>5</sup> (Stoltey & Barry, 2012, p. 1414). These clones have already spread globally, making it possible that the resistant strains will also be easily spread or that novel resistant strains will be able to develop from the already wide-ranging clones (Stoltey & Barry, 2012, p. 1414).

Only a month after the French case presented to doctors, a Swedish man in his twenties, who had recently had protected vaginal and unprotected oral sex with a female Japanese partner, sought treatment for pharyngeal and urethral gonorrhea. After the man was given amoxicillin, a course that is not recommended for the treatment of gonorrhea, his urethral infection cleared, but

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<sup>5</sup> The terms clone refers to “bacterial cultures isolated independently from different sources, in different locations, and perhaps at different times, but showing so many identical phenotypic and genetic traits that the most likely explanation for this identity is a common origin” (Orskov & Orskov, 1983, p.346). Multilocus sequence typing is a means to compare the genetic variation between isolates (Woodford, Turton & Livermore, 2011, p. 737).

his pharyngeal symptoms remained. He was given increasingly high doses of ceftriaxone (250 mg and 500 mg) until, finally, a 1 g dose of ceftriaxone cured him of his infection. Though the man was exposed to the gonorrhea in Japan, the bacteria sequence type that he was infected with has only been previously reported in Australia (Unemo, Golparian, & Hestner, 2011).

In September 2011, a Slovenian woman in her thirties, who has sex with both men and women, required medical treatment after having unprotected vaginal and oral sex with a male partner, who could not be traced for treatment. She was found to have pharyngeal gonorrhea, which a 250 mg dose of ceftriaxone failed to treat. She was finally cured, after repeatedly returning to care for the gonorrhea and a concomitant chlamydia infection, with a dose of ceftriaxone combined with 1 g of azithromycin. The gonococcal clone responsible for this treatment failure has been linked to previous cefixime treatment failures internationally as well to the F89 strain from France, and a resistant strain that was later found in Spain in May of 2012 (Groopman, 2013, p. 27; Unemo, Golparian, Potocnik, & Jeverica, 2012).

This novel strain of resistant gonorrhea in Spain was discovered in urethral and rectal samples from two MSM, who had a sexual relationship (Cámara et al., 2012). These cases are the first documented instance of a highly resistant strain being transmitted from one person to another (Cámara et al., 2012). In many other documented cases of ceftriaxone-resistant gonorrhea, the cases' previous sexual partners could not be located to determine if the strain was transmitted from person to person (Ohnishi et al., 2011a; Unemo et al., 2012, p. 1274; Unemo, Golparian, Potocnik, & Jeverica, 2012). Therefore, it cannot be ruled out that previous cases' strains evolved independently inside of their bodies, possibly as a result of gonorrhea bacteria exchanging genetic information with other types of resistant bacteria, rather than the strains being transmitted from a sexual partner (Ndowa & Lusti- Narasimhan, 2012, p.78; Stoltey &

Barry, 2012, p. 1415). Therefore, the Spanish case is especially notable for documenting that ceftriaxone-resistant gonorrhea bacteria have been able to evolve both transmissibility and resistance concurrently (Cámara et al., 2012).

One of the infected Spanish men was cured with doxycycline while the other was given azithromycin. The strain in the Spanish MSM was related to that of the French MSM detected in 2010. It is unknown whether the Spanish strain evolved resistance independently or if there has been a spread of resistant gonorrhea among European MSM. However, no connection could be found between the French and Spanish cases of the disease (Cámara et al., 2012).

The documented cases of ceftriaxone-resistant gonorrhea in Australia, Europe and Japan vary widely. Affected cases included a sex worker and non-sex workers, men and women as well as people who engaged in heterosexual and homosexual sex acts. The sporadic and unrelated nature of the cases makes it difficult to predict where and in what populations future cases may appear. This complicates surveillance efforts as it is unknown how best to allocate resources to most effectively target the diversity of at-risk groups. There is also the possibility that undocumented ceftriaxone treatment failures have occurred, but have not been discovered through surveillance methods, making it difficult to know how widespread severely resistant strains may be.

The strains that have been documented, however, seem to portend a future of widespread ceftriaxone-resistant gonorrhea, especially given that the clones from which the Spanish and French cases derived have already spread globally (Stoltey & Barry, 2012, p. 1414). Because the clones are now rampant, there is a high probability that new ceftriaxone-resistant strains will arise from these clones in the future (p. 1414). New strains may also possess the high level of transmissibility of the existing clones, incorporating both ceftriaxone resistance and fitness, as



the Spanish strain does, increasing the likelihood of a ceftriaxone-resistant gonorrhea pandemic (p. 1414).

## 5.0 FUTURE TREATMENTS

All of these known cases of ceftriaxone treatment failure have been cured, either spontaneously or through the use of other antibiotics (Cámara et al., 2012; Ohnishi et al., 2011a; Unemo et al., 2012, p. 1274; Unemo, Golparian, & Hestner, 2011; Unemo, Golparian, Potocnik, & Jeverica, 2012). These cures suggest the possibility that additional antibiotics may be used if and when ceftriaxone-resistant gonorrhea becomes widespread to give humans a chance in the arms race with the gonorrhea bacterium. The World Health Organization defines a successful antibiotic for the treatment of gonorrhea as one that cures greater than 95% of infections (Newman, Moran, & Workowski, 2007, p. 585). The CDC has set even more stringent guidelines for antibiotic treatments, requiring antibiotics that cure greater than 95% of gonorrhea infections with the lower end of the confidence interval being greater than 95% (Newman, Moran, & Workowski, 2007, p. 585). Therefore, antibiotics must meet these criteria to be considered as a first line drug to treat gonorrhea in the United States (Newman, Moran, & Workowski, 2007, p. 585).

To achieve these standards, new antibiotics that have not been used to treat gonorrhea must be initiated, as gonorrhea bacteria often manage to retain resistance to past regimens long after these antibiotics are withdrawn (Tapsall, Ndowa, Lewis & Unemo, 2009). Besides proven effectiveness, a treatment for gonorrhea should be given in a single dose, so that patient

adherence is a non-issue. A treatment option that is orally administered, relatively cheap and available is also highly sought after (Newman, Maran, & Workowski, 2007, p. 585).

One antibiotic that has been proposed to take ceftriaxone's place as the first line drug to treat gonorrhea is azithromycin (Bignell & Garley, 2010, p. 422). Azithromycin is already being used in combination with ceftriaxone to treat gonorrhea in the U.S. (Stoltey & Barry, 2012, p. 1414). In a single 2 g dose, taken orally, it has been shown to meet CDC criteria for effectiveness (Bignell & Garley, 2010, p. 422). However, there are conflicting reports as to the gastrointestinal side effects that accompany an effective dose of azithromycin, with over 35% of patients experiencing side effects in one study (Bignell & Garley, 2010, p.422). Even more troubling is that gonococcal bacteria resistant to azithromycin have been documented in countries throughout Europe, the United States and in South America (Bignell & Garley, 2010, p.424). Many of the studies into azithromycin were conducted years before resistance to the antibiotic became as widespread as it is today, putting into question the effectiveness of azithromycin as a singular first line drug to treat gonorrhea (Bignell & Garley, 2010, p. 424). A 2 g dose of the drug may also promote even more resistance by causing low levels of the antibiotic to persist in the body over time, a condition thought to promote gonococcal resistance (Newman, Maran, & Workowski, 2007, p. 592).

Another possible antibiotic that has been suggested to replace ceftriaxone is spectinomycin (Barry & Klausner, 2009, p. 569). Spectinomycin has also been shown to meet the CDC criteria for effectiveness for anogenital infections, but is ineffective against pharyngeal infections (Newman, Maran, & Workowski, 2007, p. 585). As many of the past ceftriaxone treatment failures have involved pharyngeal infections, it is important that a new drug effectively treat such infections (Ohnishi et al., 2011a; Stoltey & Barry, 2012, p. 1412; Unemo, Golparian,

& Hestner, 2011; Unemo, Golparian, Potocnik, & Jeverica, 2012). Spectinomycin is also not currently available in the United States (Barry & Klausner, 2009, p.569). While gonococcal resistance to spectinomycin is currently meager, because it has been rarely used in the U.S., data from U.S. servicemen in Korea, who were given spectinomycin as a first line drug for gonorrhea infection in the 1980s, show that widespread resistance emerged within only four years of spectinomycin use (Lewis, 2010, p. 417). This rapid development of resistance suggests that if spectinomycin became the recommended antibiotic to treat gonorrhea infection, its effectiveness would be very short-lived (Lewis, 2010, p. 417).

Perhaps more promising is solithromycin, an antibiotic that is still undergoing research. In one in vitro study, solithromycin was shown to be more effective than azithromycin and a variety of other antibiotics in effectively killing a number of gonorrhea strains, including those that are resistant to cephalosporins. Much lower doses of solithromycin were needed to effectively kill gonorrhea bacteria as compared with the other antibiotics tested, suggesting that solithromycin could be the new first line drug to treat gonorrhea infection. However, more research would need to be done into solithromycin before it could become a recommended drug to treat gonorrhea, including clinical trials and investigations into the mechanisms by which gonorrhea bacteria may develop resistance to the antibiotic (Golparian, Fernandes, Ohnishi, Jensen, & Unemo, 2012, p. 2739-2741).

Already used in developing countries, gentamicin has also been put forth as a potential gonorrhea treatment for the developed world (Ross & Lewis, 2012, p. 6). Gentamicin has been used in Malawi for twenty years, but it has not met the stringent CDC or WHO criteria level for efficacy (Kirkcaldy, Ballard, & Dowell, 2011, p. 201; Ross & Lewis, 2012, p. 7). Accordingly, it has never been considered an option for gonorrhea treatment in developed countries (Brown et

al., 2007, p. 169). However, given the few treatment options available post-ceftriaxone, an option that is adequate, rather than exceptional, may need to be pursued (Kirkcaldy, Ballard, & Dowell, 2011, p. 201).

One study reported in 2007 that varying strains of gonorrhea bacteria tested in Malawi were 100% susceptible to the antibiotic, despite its extended use (Kirkcaldy, Ballard, & Dowell, 2011, p. 201). However, this finding is somewhat questionable (Kirkcaldy, Ballard, & Dowell, 2011, p. 201). Bacterial susceptibility to an antibiotic is typically measured by the concentration of the antibiotic that is needed to effectively kill the bacteria (Kahlmeter, et al., 2003, p. 145). Unlike for most other antibiotics, there is no recognized standard for how high concentrations of gentamicin must be to kill gonorrhea bacteria and still be considered an efficacious drug, making it difficult to compare the efficacy or levels of susceptibility of gentamicin to that of other antibiotics (Kirkcaldy, Ballard, & Dowell, 2011, p. 201) Most of the studies that support the efficacy of gentamicin were conducted thirty to forty years ago, and none were randomized (Ross & Lewis, 2012, p.7). The reported rates of cure for gentamicin in these studies ranged from as low as 65% to as high as 100% (Ross & Lewis, 2012, p.7). A clinical trial testing the effectiveness of gentamicin combined with azithromycin to treat gonorrhoeal infection is currently being conducted (Ross & Lewis, 2012, p.7).

A few other new or existing drugs have also been suggested including kanamycin, rifampin, ertapenem and tigecycline but, like many of the antibiotics discussed above, these drugs are either untested in vivo, or reduced gonococcal susceptibility to these drugs has already been shown (Barry & Klausner, 2009, p. 569). Therefore, more research would be needed to determine if any of these drugs would be suitable to replace ceftriaxone, and to investigate whether resistance to any of these drugs is so high as to be prohibitory (Barry & Klausner, 2009,

p. 569). Another proposed solution would be to use new combinations of existing drugs to treat gonorrhea; one clinical study is already underway to examine the efficacy of new drug combinations (Kirkcaldy, Bolan, Wasserheit, 2013, p. 186). The hypothesis behind using multiple drugs to treat gonorrhea is that it would be unlikely for the bacterium to develop resistance to two drugs simultaneously (Barry & Klausner, 2009, p. 570). Combinations of antibiotics are already being used to treat gonorrhea in the U.S. and elsewhere, however, and it has been suggested that this regimen has promoted azithromycin resistance (Barry & Klausner, 2009, p. 570). Moreover, using a multi-drug regimen increases costs as well as the likelihood of side effects and the difficulty of implementation, especially in developing country contexts (Barry & Klausner, 2009, p. 570; Ndowa & Lusti-Narismhan, 2012, p.77).

Even if any of these treatment options, singularly or in combination, prove sufficiently effective, safe and inexpensive for widespread use, they are unlikely to provide a long-term solution to the issue of gonorrhea resistance (Tapsall, Ndowa, Lewis & Unemo, 2009). For example, cefixime resistance became widespread in only five years, and the nature of gonococcal evolution is such that any new drugs used to treat the disease would only be reliable for a relatively short time (Ndowa & Lusti-Narismhan, 2012, p. 77). Therefore, the only certain, durable way to reduce gonorrhea infection in the future is to focus on prevention (Ison & Hughes, 2010, p. 410).

## 6.0 EXISTING PLANS: CDC, WHO, ECDC

In response to the possibility of the proliferation of untreatable gonorrheal infections, the CDC, the WHO and the ECDC have all released tentative plans for dealing with this potential threat (CDC 2012a; European Centre for Disease Prevention and Control [ECDC], 2012; WHO, 2012). The CDC's Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan, released in August of 2012, is designed to provide guidance to local and state health departments regarding the surveillance for, and initial response to, ceftriaxone resistant gonorrhea (CDC 2012a, p. 3). Most of the document focuses on surveillance and laboratory testing in order to identify treatment failures and resistant strains of gonorrhea (CDC, 2012a). The responses suggested by the CDC to the occurrence of treatment failures are to conduct an epidemiological investigation to track down and treat partners of known cases (CDC, 2012a). Within the forty three page document, only one paragraph is devoted to the issue of prevention, where the CDC advises that "public health authorities should also continue to scale up general gonorrhea prevention and control activities. These activities are designed to reduce the overall gonorrhea disease burden through prevention, early diagnosis, timely and effective treatment, and partner services" (CDC, 2012a, p. 18). However, specifics related to these activities are not elucidated in the response plan.

Therefore, the document is seemingly helpful to health departments, clinicians, and laboratory technicians, especially in its discussion of the difficulties associated with surveillance,

and the likelihood of not preventing the spread of ceftriaxone-resistant gonorrhea, given the past history of how rapidly and universally resistant bacteria have spread (CDC, 2012a, p.2). It also serves to codify and standardize procedures related to ceftriaxone-resistant gonorrhea (CDC, 2012a). However, there is no specific discussion of prevention activities that should be undertaken to help to avert infections that, in the future, may be untreatable (CDC, 2012a). Given that the CDC is tasked with providing policy guidelines and intervention recommendations to the public health community in the United States, it is unfortunate that they have not included such suggestions in advance of what they admit to be a major impending public health issue (CDC, 2012a, p. 2).

The WHO document, the Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae*, similarly places its focus on surveillance for the disease as well as on reducing inappropriate or harmful antibiotic use (WHO, 2012). The WHO differs slightly in their plan by stressing the importance of international and national funding for prevention and surveillance, gaining government officials' support for gonorrhea-related public health activities and communication messages targeted to both the general public and policymakers to educate these groups about the issue of antibiotic-resistant gonorrhea (WHO, 2012). In terms of prevention, the WHO stresses communication and education, involvement of people at highest risk of gonorrhea, such as MSM, and reducing stigma around STIs (WHO, 2012, p. 15-16). Overall, this document is mainly focused on managing infections, rather than preventing them (WHO, 2012). It is understandable why the WHO does not give specific recommendations in terms of policy or interventions for prevention, as member countries vary dramatically in terms of resources, culture and a variety of other factors important to public health actions to prevent the spread of gonorrhea. However, such general and tepid



suggestions in regards to prevention, such as the need to reduce stigma and improve education, are not likely to spark action among member countries in the way that a more specific plan, perhaps tailored to WHO regions, would.

In a separate document, the Global Strategy for the Prevention and Control of Sexually Transmitted Infections: 2006–2015, the WHO does get more specific about the importance of condoms (both male and female), better access to well-managed health care services, and targeted interventions and health care approaches for at-risk populations (WHO, 2006, p. 2-3). However, the document does not specify any STI, including gonorrhea, with the notable exception of HIV, which is mentioned numerous times throughout the text (WHO, 2006). While all STIs are certainly interrelated, both biologically and behaviorally, the symptoms, treatment, prognosis and even prevention activities vary between these diseases. For example, unprotected oral sex has often been suggested as a means to decrease one's risk of contracting HIV (Varghese, Maher, Peterman, Branson, & Steketee, 2002). However, as noted above, gonorrhea can be spread through unprotected oral sex (Groopman, 2012, p.27). Moreover, pharyngeal gonorrhea infections are often especially difficult to treat, the *N. gonorrhoeae* bacterium can exchange genetic information in the pharynx with other bacteria conferring resistance, the infection can remain asymptomatic preventing cases from seeking treatment, yet transmission can continue to occur through unprotected oral sex (Ndowa & Lusti- Narasimhan, 2012, p.78; Stoltey & Barry, 2012, p. 1415). Therefore, a more comprehensive exploration of the various STIs and tailored plans for each of them would have been better suited to dealing with the complicated and diverse public health problem of STIs.

The ECDC's document, The Response Plan to Control and Manage the Threat of Multidrug Resistant Gonorrhoea in Europe, is comparable to both the CDC and the WHO's

documents (ECDC, 2012). Large sections of the document are devoted to surveillance, case management, and data collection (ECDC, 2012). The one prevention activity mentioned in the plan is to inform at-risk subpopulations, such as MSM, about the threat of ceftriaxone-resistant gonorrhea (ECDC, 2012, p. 10). The plan claims that, “this can be achieved by distributing leaflets in dedicated clinical settings” (ECDC, 2012, p.10). Communication beyond these leaflets is not discussed, nor is the importance of behavioral or health care interventions (ECDC, 2012).

The dearth of information regarding a comprehensive prevention plan in all three of these documents would seem to put the public health effort to control gonorrhea infections beneath that of surveillance or other similar efforts. While understanding the epidemiology and detecting the presence of resistant gonorrhea is an incredibly important part of the public health response, it is only one part, and prevention activities need to be integrated into a more holistic plan to control the spread of the disease. The reluctance to include prevention activities in the documents reviewed above may be a result of an undue emphasis on a clinical and biomedical approach for treating gonorrhea rather than focusing on a public health or social ecological model to prevent the disease, which would include interventions at multiple levels, including addressing policy and community-level factors. However, with the seemingly imminent powerlessness of clinicians to adequately treat gonorrhea, a preventative focus is the only remaining option, and more will need to be done than distributing “leaflets” as advised by the ECDC (ECDC, 2012, p. 10). That leaflets are even the go-to public health communications response for a potential impending public health crisis is both laughable and tragic, and demonstrates how little the authors of the ECDC document understand about public health communications or addressing various ecological levels of health. Experts in the field of

prevention and communication efforts need to be brought on board to add their opinions and strategies to the existing plans for surveillance as soon as possible, especially since so often proper communication efforts or the translation of prevention interventions take a tremendous amount of time and effort. By failing to address this important piece of the gonorrhoea control puzzle, the WHO, CDC and ECDC have made a tremendous and, potentially, costly mistake that may harm members of the public, who could have been helped by a more inclusive and holistic response to the looming issue of ceftriaxone-resistant gonorrhoea.

## **7.0 OPPORTUNITIES FOR INTERVENTION**

Despite the CDC, the WHO and the ECDC's silence on the issue of prevention, there are prevention interventions and activities that are known to be effective in reducing rates of gonorrhea. As discussed above, gonorrhea incidence is clustered among specific subgroups, especially in the United States and other parts of the Western world. Therefore, targeting at-risk groups, which experience a high proportion of the burden of gonorrhea disease, rather than the general population, is the first step towards effective prevention (Chen & Ghani, 2010).

Interventions with proven efficacy in the United States to prevent the spread of gonorrhea vary widely, from individual-level small-group STI educational meetings for young minority women to community-based interventions to promote STI testing among adolescents (Shain et al., 2004; VanDevanter et al., 2005). Many screening interventions have also proven efficacious including screening students in middle school health centers, and calling patients to have them return to care for rescreening (Burstein et al., 1998; Malotte et al., 2004).

Another promising intervention is expedited treatment of sexual partners, which allows partners of the infected to receive treatment without an examination, either in a clinical setting or by giving the treated partner medication for the unexamined partner (Golden et al., 2005, p. 676). In the case of gonorrhea, given that ceftriaxone is an injected drug, partners would still need to present to the clinical setting for treatment. In one randomized controlled trial, the rate of persistent or recurrent gonorrhea infection among sexual partners was decreased from 11% in the

control group to 3% in those provided with expedited therapy (Golden et al., 2005, p.676). In another population-based intervention in King County, Washington, which utilized a triage method to give expedited partner therapy to patients who were most likely to benefit from it, an increase was reported in the percentage of index cases' sex partners who received therapy (Golden et al., 2007, p. 602). Therefore, expedited partner treatment could increase the amount of infected people treated for gonorrhea and prevent reinfection among those who have already sought treatment (Golden et al., 2005). However, there are some states where distributing prescription medication without a physical examination or physician-patient relationship is not legally permitted (Hodge, Pulver, Hogben, Bhattachray, & Brown, 2008, p. 240). Therefore, a change in policy would be needed to allow for a more widespread dissemination of expedited partner therapy.

Globally, there have been other successful gonorrheal prevention interventions. To prevent pharyngeal gonorrhea among sex workers in Singapore, a two part educational intervention targeted towards sex workers and brothel keepers resulted in a significant increase in condom use during oral sex and a significant decrease in pharyngeal gonorrhea among treatment group sex workers as compared to those in the control group (Wong, Chan, & Koh, 2012). Thai men, urban Malawian women, and urban Burkinabe have all experienced decreases in STI rates, including gonorrhea rates, most likely as a result of HIV prevention efforts in those countries (Celentano et al., 1998; Nagot et al., 2004; Taha et al., 1998). In both England and Sweden, rates of gonorrhea declined in the 1980s and into the 1990s, likely also a result of robust HIV prevention campaigns in those countries (Bergland et al., 2007; Nicoll et al., 2001). However, as those HIV prevention messages have waned, rates of gonorrhea have been on the rise, especially in MSM, suggesting a need for enhanced STI prevention and condom promotion

messages for a younger generation of sexually active individuals (Bergland et al., 2007.; Nicoll et al., 2001). HIV prevention efforts have been thought to reduce gonorrhea rates by increasing STI screening and treatment, promoting condom use and decreasing high-risk sexual behaviors (Celentano et al., 1998; Nagot et al., 2004; Nicoll et al., 2001; Taha et al., 1998).

While a systematic review of the literature as it relates to gonorrheal prevention is outside the scope of this paper, it may behoove the CDC, the WHO, and similar organizations to analyze and categorize such evidence-based interventions in a format similar to that used for the Diffusion of Effective Behavioral Interventions (DEBIs) for HIV/AIDS or to incorporate messages specific to gonorrheal infection into the already-approved DEBIs. Such guidance, recommendations and policy commitment coming from respected public health authorities may help to trigger more research, as well as translation of existing efficacious interventions. It is important to prioritize prevention now, while treatment of gonorrhea is still a possibility, rather than waiting until the conceivable day when prevention is our only reliable tool against the disease.

## **8.0 A FUTURE OF UNTREATABLE GONORRHEA**

If gonorrhea does become truly untreatable, with ceftriaxone no longer a viable option to treat the disease and only subpar options to take its place, what will the future of gonorrhea infection look like? Rather than curing gonorrhea with antibiotics, clinicians will be forced to return to attempting to ameliorate the symptoms associated with gonorrhea infection, as was done in the pre-antibiotic era. Yet, despite these interventions, the disease would remain. In individuals who are asymptomatic, the morbidity associated with gonorrhea infection would be low. However, for those suffering from a high-morbidity infection, such as women who develop PID, the consequences of untreated gonorrhea will be pronounced, including infertility, ectopic pregnancies and persistent pain (CDC 2011b). Men with high-morbidity infections may also suffer from infertility (CDC, 2011a; Ndowa & Lusti- Narasimhan, 2012 p. 79). An inability to treat gonorrhea infections and its related symptoms will cause an increase in DALYs associated with the disease, as well as costs, especially lost productivity due to missed work days or presenteeism.

In terms of transmission, mother-to-child transmission may become a more important means of transmission in such a future. While mothers in developed country contexts could undergo caesarian sections to avoid infection of their infants, mothers in the developing world may not have access to such procedures, increasing the likelihood that their babies will be infected, which can cause devastating health consequences, including blindness (CDC, 2010a).

It is more difficult to predict the effects of untreatable gonorrhea on sexual transmission. While reinfection is currently a major driver of incidence, reinfection would not occur in the future, if cures are not able to be meted out (Chen & Ghani, 2010). It is likely that subpopulations, which are currently acutely and disproportionately affected by gonorrhea infection, would continue to suffer from high incidence rates of the disease, given the high existing prevalence in these groups, as well as these groups' status as marginalized populations, who most likely will not receive adequate policy or structural supports to promote prevention.

The threat of untreatable gonorrhea and public health messages around the issue may encourage some people to reduce their risky sexual behaviors, which would, in turn, reduce incidence rates of the disease. However, it is unconvincing that many people will discontinue engaging in risky sexual behaviors. While the epidemic of HIV/AIDS, accompanied by prevention interventions, has been able to change some sexual behaviors, even the threat of a fatal infection has not been enough to completely reduce high risk behaviors (Celentano et al., 1998; Nagot et al., 2004; Taha et al., 1998). Therefore, a non-lethal infection, such as gonorrhea, which is often asymptomatic, will likely not be a sufficient impetus for widespread changes in sexual patterns. It is unlikely that without multiple levels of intervention, including those addressing poverty and other drivers of STI incidence, much will change in terms of sexual behaviors (Aral, Adamora, & Fenton, 2008, p. 337-8). However, even if incidence rates did decrease, the burden of morbidity caused by a pandemic of an untreatable bacterial infection would be unparalleled in the modern age, and a significant blow to our ability to compete with bacteria in the evolutionary arms race.



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