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Mini-Review

Chlamydia Trachomatis: Common Misperceptions and Misunderstandings

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Introduction

Responsible for more than three million infections each year in the United States, Chlamydia trachomatis (CT) poses a public health problem of epidemic proportions.[1–10] Unequivocal evidence of sexual transmission makes CT both the most commonly reported bacterial sexually transmitted disease (STD) in the US and the nation's most commonly reported bacterial infection.[1–10] Chlamydial infections are easy to cure.[1–10] However, because the infections so frequently go untreated, the CT epidemic has brought with it serious complications ranging from epididymitis and pelvic inflammatory disease (PID) to ectopic pregnancy, infertility, and chronic pelvic and genital pain.[1–9] Treating these complex, often chronic, medical problems and their psychological sequelae is costly both in financial and human terms.[1–10] In the US alone it is estimated that annual CT-related expenditures exceed $1.5 billion.[1,4,8,9] Moreover, with 75% of these costs devoted to treating the sequelae of initially uncomplicated cervical infections, racial disparities in the prevalence and treatment of this easy-to-cure lower genital tract infection, could be responsible for much of the excess reproductive morbidity among Black American women.[1,4,6,8,9]

The epidemiology, clinical presentation, diagnosis, and treatment of chlamydial infections have been reviewed so extensively that a compendium of relevant citations in the English medical literature alone (Medline, Embase, and the Cochran Database), would undoubtedly rival the global prevalence of this infection. Nonetheless, this paper makes a novel and hopefully useful contribution to this voluminous literature by drawing attention to several common misperceptions and misunderstandings (M & M) about CT. Our goal is to dispel the myths about contagion and treatment they have fostered. We anticipate that this endeavor will stimulate discussion and changes in clinical practice that will in turn minimize CT-related morbidity in the US.

Scope and Epidemiology of the Problem

M & M 1: The prevalence of chlamydial infections is increasing in the United States

The two-fold rise in the reported number of CT cases documented by passive US surveillance systems between 1990 and 1997 raised widespread concern that the prevalence of this infection was increasing.[1–9] These fears have subsequently been fueled by the growing awareness that there is a large reservoir of undiagnosed, asymptomatically infected individuals in the US.[1–9] For example, in 2000—the first year in which CT reporting was required in all 50 states and the District of Colombia—the fact that only 700,000 such reports were filed with public health authorities[1–3] reinforced the impression that the number of reported cases significantly underestimated the true prevalence of CT in the American population.[1–9]

In truth, owing to the focality of the CT epidemic in the US, estimates concerning the proportion of infected individuals depend upon the characteristics of the study population and the survey and testing methods employed.[3–9] As CT prevalence data from non-clinic

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population-based studies become increasingly available it should be possible to define the scope and magnitude of this epidemic in the US more precisely. However, at the present time it is difficult to give accurate prevalence figures or to obtain meaningful data regarding the kinetics of the CT epidemic and the effect of disease control and prevention efforts in the US.[3–9] On the one hand, the precipitous increase in CT reporting suggests that the epidemic is continuing unabated.[3–9] On the other hand, data collected at sentinel surveillance sites suggests that efforts to control this infection have been successful.[11–17] While there is still no reason for complacency, evidence that over the last decade the decreased prevalence of chlamydial infections documented at these locations has cut across all age, sex, and racial groups[11–17] may justify diminished concern. At a minimum it suggests the apparent escalation in the scope of the CT epidemic may simply be an artifact of improved test sensitivity, increased reporting, and expanded screening for this hyperendemic infection.[1–9,17,18]

M & M 2: The epidemiology of chlamydial infections parallels the epidemiology of condom use

Young age, female sex, and minority race/ethnicity are stronger, more reliable predictors of chlamydial infection than inconsistent condom use.[1–10,19–29] Indeed, variables that quantify risky sexual behavior add little to predictive algorithms that contain these traits,[1–11,18–29] because these sociodemographic characteristics are proxies for biological vulnerabilities and membership in sexual networks in which the risk of exposure to a core group of chlamydial infection transmission is so high that unsafe sexual behavior has little added effect on the risk of CT transmission between partners.[3,7,29–52] Rather, because the prevalence of this sexually transmissible pathogen is the most important predictor of infection, members of these high-risk networks are at increased risk for infection after treatment regardless of their subsequent sexual behavior.[29,53,52] Thus, *who* teenage girls have sexual relations has more effect on the risk for acquisition of CT than *how* they do so.

This makes it crucial for clinicians to thoroughly understand of the epidemiologic characteristics of this infection. In the US, two factors conspire to make teenage girls especially susceptible chlamydial infections. First, CT is an extremely contagious STD to which humans do not develop natural immunity.[37] The frequency of transmission by CT-infected adult males and females is nearly identical.[7] Regardless of prior contact, contagion ranges between 50% and 70% for those who are exposed to CT through multiple episodes of unprotected sexual intercourse.[7] However, STD transmission dynamics are not linear.[35] Rather, the number of infected potential sexual partners in the environment has a multiplicative effect on exposure risk.[35] Teenage girls are especially apt to be exposed to CT because their romantic relationships are typically serially monogamous at best and they tend to engage in unprotected sexual intercourse with older males whose sexual risk profiles they rarely investigate in advance.[1–3,6–9,17,19–27,30–44] The second reason teenage girls are so vulnerable to CT is that in the US, the most prevalent serotypes of this organism thrive in alkaline environments and have an affinity for columnar epithelium.[37] During adolescence, the vagina is relatively alkaline and columnar epithelium is prominent on the ectocervix.[1–3,6–9,17,19–27,30–44] Thus, as a group 13- to 19-year-old American females are likely at maximal biological and social risk for acquisition of this infection.

The prevalence of chlamydial infections in this sector of the US population is unknown. School- and clinic-based studies suggest a range of 3% to 27%, with the highest age-specific prevalence reported among 14- to 15-year-olds.[19–27,43–48] Higher rates have also been documented in inner-city than suburban communities, among minorities than non-minorities, in US-born than foreign-born Hispanics, and in pregnant and recently delivered teens than non-pregnant teens.[1–3,6–9,19–27,43–48] Teenage girls are significantly more likely to be screened and treated for chlamydial infections than teenage boys.[50–52] However, owing to their unique vulnerability to CT, girls this age are more likely to be infected with this organism than boys. This is true both at school (16.5% and 2%, respectively)[22] and in private pediatric offices (2.7% and 0.9%, respectively).[45] The prevalence of CT among teenage girls also exceeds the 1–5% infection rate reported for sociodemographically similar young adult women.[1–4,6–9,17,19–27,48] This is surprising, as the consistency of condom use decreases with age and absent a vaccine or natural immunity, treated patients remain at risk for re-infection. Thus, researchers have attributed the adolescent peak in CT prevalence to the fact that the alkalinity of the vagina, the size of the cervical ectropion, and the number of new sexual partners tend to decrease with increasing age.[3,17,19–27,37–40] This same mix of biological and social risk factors may explain why, even within behaviorally at-risk groups, the prevalence of CT is highest among pregnant, postpartum, and Black teenage girls. On the one hand, pregnancy is associated with an increase in the alkalinity of the vagina, the size of the cervical ectropion, and the odds of concurrency among sexual partners; on the other, Black women exhibit a higher vaginal pH than do White women.[37–40]

The practical implication of these epidemiological observations for care providers and program planners is that condoms are to STD prevention what emergency contraceptive pills are to pregnancy prevention: "Plan B." This does not mean that it is not important to teach teenagers about condoms and enhance their ability to use them by ensuring they have opportunities to learn and rehearse the requisite skills. Rather, it means that it is equally important that they learn how to choose low-risk sexual partners. Patients who acquire STDs are often unaware of their partners' sexual risk behavior.[41] Misconceptions about monogamy and normative behavior are especially common.[27–36,41–43,52–64] These misperceptions are problematic as related social pressures deter personal risk reduction.[41–44,52–64] Thus, the concerns about infidelity raised by the diagnosis of an STD provide a unique opportunity to promote dialogue about sexual health and disease transmission and prevention between sexual partners.[2,10,27–32,36,41–44,59–64] The optimal content and duration of such counseling is debatable and the number of relevant studies limited.[32,60,64] Nonetheless, brief (5-minute), personalized (provider-delivered-client-centered) counseling seems to be more effective than didactic groups and as effective as prolonged individualized sessions that are difficult to conduct in busy clinics.[32,60,64] Available data also suggests that it is best to focus on a narrow range of achievable behavioral goals (i.e., avoiding concurrent sexual relationships and seeking STD testing as soon as suspicious signs and symptoms appear or immediately after risky sexual encounters).[32,60,64] Finally, an effort should be made to dispel the misperceptions about normative group behavior that enhance the spread of STDs.[32,60,64] In this regard circumstantial evidence suggests that if properly channeled in the future, the media could provide an important context for social norm transmission.[65,66]

M & M 3: Pregnancy is the greatest public health threat posed by unprotected teen sexual activity

Chlamydial infections are more prevalent among American teenagers than pregnancy, but are ranked lower in importance by public health officials in the US.[67] Similarly, American teenagers are more likely to use condoms to protect themselves from pregnancy than from CT and other STDs.[68,69] The low priority this readily eradicable infectious disease receives in the US is surprising. Failure to recognize the staggering economic and human costs of chlamydial infections may explain why behavior interventions (i.e., condom distribution and monogamy counseling programs) have been so unmotivating and ineffective. The problem is particularly serious for women, among whom the majority of severe consequences of under-treatment occur.[1,4,8,9,34,70–72] At least two thirds of tubal factor infertility and a third of ectopic pregnancies in the US are attributable to inadequately treated chlamydial infections.[8,70–72] CT also facilitates the transmission of the human immunodeficiency virus.[73,74] Finally, it is clear that the huge reservoir of untreated, asymptomatic disease makes a disproportionately large contribution to the spread of CT and its costly sequelae.[1,4,8,9] Thus, it is estimated that every dollar spent on screening and treating asymptomatic young women and their sexual partners saves more than ten dollars in health expenditures.[1,4,8,9,70–74]

The tremendous cost savings associated with the early detection and eradication of chlamydial infections highlight the unique responsibility primary health care providers have to draw public attention to this problem. Systematically testing and treating sexually active patients and providing the anticipatory guidance needed to dispel denial and the misperceptions about monogamy and disease transmission that deter those with STD-related symptoms from seeking care, is helpful.[1,4,8,9] However, given the burgeoning number of teens in the US and their relatively weak connection to the traditional health care system, testing and treating is only the first step. To meet the therapeutic obligation to control CT transmission, providers must abandon their patient-centered testing and treating efforts in favor of protocols that approach the problem from a public health perspective. This means expanding office-based, symptom-driven genital testing practices to include urine-based screening for asymptomatic infections in the home and settings such as schools, juvenile detention centers, drug treatment facilities, military recruiting offices, and emergency departments where concerns about confidentiality and cost are less apt to pose a barrier to care.[1–9,17–28] Treatment guidelines must also be broadened.[29–36] Given the frequency and rapidity with which untreated partners undermine the efficacy of efforts to treat individual patients,[29–36,43,44,46,47] it is simply futile to continue to treat index cases in isolation of their sexual networks, or one infected individual at a time.[29]

Clinical Presentation

M & M 4: Lower genital tract chlamydial infections cause a classic clinical syndrome

Chlamydia trachomatis should always be suspected in men and women with dysuria and pyuria, men with purulent penile discharges (especially commencing 1 to 3 weeks after unprotected sexual intercourse with a new partner), women with lower abdominal or pelvic pain, dyspareunia, abnormal vaginal discharge, postcoital, irregular menstrual, or "break-through" contraceptive bleeding, and infants with conjunctivitis,

nasal congestion, or a staccato cough.[8,37] However, these signs and symptoms are of dubious clinical utility as they are neither sensitive nor specific indicators of this infection.[17–27,75–84] Rather, most infections caused by this organism are asymptomatic.[2–9,17–29] Moreover, when present even the most common clinical manifestations (i.e., mucopurulent cervicitis in women and urethritis in men) are non-specific syndromes, characterized by erythema, edema, and friability of the ectocervix and purulent endocervical or urethral exudates that are as likely to be caused by other infectious and non-infectious agents as by CT.[75–86] In truth, close to 90% of chlamydial infections are asymptomatic and CT is isolated from less than half of men with non-gonococcal urethritis, less than a third of women with mucopurulent cervicitis, and even fewer women with urethritis, bartholinitis, and bacterial vaginosis.[1,2,64] Thus, testing sociodemographically at-risk persons is the only reliable way to diagnose the infection.[1,2,64]

Chlamydial infections are an excellent example of the dependence of the clinical manifestations of disease on the intrinsic properties of the pathogen and host.[37] In western industrialized countries virtually all chlamydial infections are sexually transmitted or passed vertically at birth from mother to child.[37] Hence, non-genital clinical manifestations, such as conjunctivitis, tenosynovitis, and arthritis are uncommon in American adolescents and adults. Moreover, because prevalent serotypes have an affinity for columnar epithelium, lymphogranuloma venereum is rare and the endocervix, urethra, and rectum are preferentially infected by this organism in the US.[37] Finally, CT survives by a cytotoxic replicative cycle that evokes a variable immune response in the host.[37] Thus, clinical manifestations range from asymptomatic infections to florid inflammatory conditions with severe reproductive consequences.[8,37,70–72,87,88] For these reasons a symptom-based diagnostic approach to this infection is apt to be ineffective. Indeed, this tactic may actually be counterproductive. It is likely to distract patient and provider attention from the behavioral and environmental factors that should influence asymptomatic individuals to seek STD testing, thereby increasing (rather than decreasing) the risk of disease transmission and the odds of incurring the serious adverse personal and environmental consequences of over- and under-diagnosis and treatment.[85]

M & M 5: Asymptomatic, culture-negative CT-urethritis has severe health consequences

Untreated chlamydial urethritis can have devastating long-term reproductive and health consequence.[8] However, estimates concerning the prevalence of these complications reflect culture-proven disease. When positive, modern nucleic acid amplification tests (NAAT) often reflect very small inoculums of this bacterium.[2,8,17,64,89] It is not known if or how inoculum size affects disease presentation. Moreover, there are no data comparing the clinical consequences of chlamydial infections detected by NAATs and those detected by less sensitive traditional assays. Until the clinical significance of infections diagnosed only by these highly sensitive tests is fully explicated, it may be unwise to extrapolate from extant data to the consequences of culture-negative, NAAT-positive, chlamydial infections. Indeed, until further data become available, such inferences should probably be avoided as they might lead to inappropriate conclusions about risk and the costs and benefits of NAAT-based screening.

The frequent association between chlamydial cervicitis and vaginal clue cells or gram stain abnormalities indicative of an overgrowth of anaerobic bacteria has led to speculation that CT alters the normal vaginal ecology (or vice versa), thereby setting the stage for a complex polymicrobial upper genital tract infection, with clinical manifestations that range from uncomplicated PID to salpingo-oophoritis, perihepatitis (Fitz-Hugh-Curtis syndrome), infertility, ectopic pregnancy, and chronic pelvic pain.[8,14,37,70–72,87,88] Among untreated women with culture-proven chlamydial cervicitis, the estimated incidence of the most common suppurative complication, PID, ranges from 10% to 40%.[8,10,14,70–72,87,88] Young age and prolonged or recurrent infection significantly increases, whereas treatment of asymptomatic chlamydial infections significantly decreases, both disease severity and the risk of developing these sequelae.[8,14,70–72,86,87] Adverse outcomes associated with uncomplicated chlamydial cervicitis during pregnancy include preterm labor, premature rupture of the placental membranes, low birth weight delivery, neonatal death, postpartum or post-abortal endometritis, and vertical transmission to infants.[8,37,87,88] Among infants born to CT-infected mothers, 30–50% develop conjunctivitis, 15–20% develop nasopharyngitis, and 5–10% develop pneumonia.[8,37] The suppurative complication of lower genital tract chlamydial infections in men are less severe and less common.[8,37] Epididymitis, prostatitis, acute proctocolitis, and Reiter's syndrome (urethritis, conjunctivitis, arthritis, and mucocutaneous lesions), rarely require in-patient therapy.[8,37] Moreover, only 1% to 3% of males with culture-proven chlamydial urethritis develop the most common of these complication, epididymitis.[8,37] Nonetheless, approximately 75% of epididymitis in young sexually active men is caused by CT.[8,37] Long-term sequelae ranging from urethral strictures and chronic pain to infertility occur in men, albeit less frequently than in women.[8,37]

Diagnosis and Screening

M & M 6: Lower genital tract chlamydial infection is a clinical diagnosis

The signs and symptoms of a lower genital tract chlamydial infection are non-specific in both men and women and often persist for weeks after documented eradication of this pathogen.[2,8,10,64,75–85,90,92] For example, CT is rarely isolated from more than half of males with leukocyte esterase positive urine samples and females with leukocyte laden vaginal wet mounts and endocervical gram stains.[2,64,75–85] Thus, these non-specific clinical and laboratory findings should be regarded as a trigger for testing, not treatment.[8,10,64,85] Unfortunately, because concerns about the consequences of under-diagnosis typically overshadow concerns about the consequences of over-diagnosis, this important caveat about the clinical presentation of CT is often overlooked in practice.[85] While close follow-up is clearly indicated when CT is suspected clinically, empiric treatment is usually unnecessary.[85] Indeed, given the ramifications of over-diagnosis and over-treatment, failure to base diagnostic and therapeutic decisions on well-standardized tests is likely to cause more harm than good.[2,64,85] The diagnosis of an STD has pernicious psychological consequences and the indiscriminate use of antibiotics has detrimental environmental consequences.[2,64,85] Moreover, NAATs typically remain positive for 3 to 4 weeks after successful eradication of chlamydial infections.[64,89–91] Thus, empirical treatment makes it difficult to determine the cause of persistent symptoms.

In the US the consensus is that except in special situations, (i.e., when acquiring evidence for a potential legal investigation), NAATs that detect nucleic acids as targets are optimal for diagnosing both symptomatic and asymptomatic chlamydial infections.[2,8,17,64,89] These assays do not require the presence of intact organisms. Hence, specimens are stable and easy to transport and results can be obtained within a day.[89] Moreover, NAATs detect very low levels of this organism.[89] Thus urine or cervical, vaginal, or urethral fluids can be used as the analyte.[89] This is a major advantage over the stringent collection and transport requirements and three-day growth period needed to culture this fastidious organism.[37,89] Thus, with sensitivities and specificities fluctuating around 98% on male urethral and urine specimens and female endocervical samples, NAATs are currently the best CT tests available.[2,8,17,89] The only caveat is that the sensitivity of these assays for detecting infections in women varies significantly in relation to the analyte used.[17,89,93–99] Sensitivities are significantly lower when female urine samples (80–95%) and patient- or provider-collected specimens of vaginal fluid (70–85%) are tested.[17,22,27,64,82–85,89,93–99]

Hence, endocervical specimens should be used except in screening situation where the impracticality of performing pelvic examinations makes every asymptomatic case diagnosed on a urine or vaginal specimen a bonus. In truth, multiple site testing (i.e., endocervix, urethra, and rectum) is probably always optimal for females.[83] This is because some women with urethral or rectal CT infections do not have endocervical infections.[83] It is a particularly important to take this fact into account when the failure to identify an infection due to false negative test results represents a significant liability, for example, in the case of an asymptomatic woman who seeks testing prior to intercourse with a new partner. Conversely, in settings where false positive results represent a significant liability, culture specimens are recommended,[10,17,27,89] for example, when an examination is conducted following an alleged rape. Indeed, if an NAAT must be used for this purpose, positive test results should be confirmed by a second NAAT that targets a different nucleic acid sequence.[17] Finally, to avoid undue suspicion within romantic relationships and needless concerns about fidelity, all patients should understand that men and women can harbor CT unwittingly for months and that even when the appropriate screening precautions are taken false negative test results occur. Hence, the diagnosis of CT in a member of a monogamous couple ought to prompt discussion about its origin. However, it does not necessarily imply recent acquisition from another partner.

Non-culture, non-NAAT, and rapid tests that provide a diagnosis within 20 to 30 minutes are less costly but are usually a poor alternative to NAATs and cultures.[8,64,92,98–100] Indeed, with sensitivities ranging from 65% to 85%, none of these techniques is sensitive enough to be recommended for routine clinical use.[8,64,98–100] In settings where CT is prevalent and follow-up uncertain, on-site treatment of individuals with positive rapid test results and back-up NAAT testing for those with negative results should decrease transmission and the risk of incurring costly sequelae.[64,98,100] This is an attractive alternative to empiric treatment of suspected chlamydial infections as it enables patients and providers to avoid the negative consequence of over-diagnosis and over-treatment. Moreover, because because patients can be treated immediately, this approach has the added advantage of sparing the medical staff the work of contacting them.

However, patients often will not wait even 30 minutes for test results.[64,100] Since the reduction in follow-up time must be balanced against the work of conducting rapid tests, the utility of disease control strategies that incorporate rapid testing has been disappointing.[64,100] In truth, the usefulness of these algorithms will likely remain greater in theory than

practice until the accuracy and speed of rapid diagnostic tests is improved.[64,100]

M & M 7: Periodic urine-based CT screening is a cost-effective prevention measure

It is widely recognized that for reasons ranging from denial of personal and patient risk and low health literacy to embarrassment and anxiety about the implications of an STD diagnosis and concerns about confidentiality and cost, teens, young adults, and the health care professionals who care for them, rarely engage in routine periodic STD screening.[6,17,50–52,59–64,101–108] It is equally clear that the delayed diagnosis of asymptomatic chlamydial infections contributes disproportionately to the spread of this organism and the development of the costly suppurative manifestations of chlamydial infection.[1–10] Thus, the consensus in the public health community is that routine, periodic screening is key for disease control.[1–9,17,27,64] There is far less agreement about whom to screen and how and when to do it.[2,17,27,64]

Pregnant and sexually active women under 25 years of age are the only group for whom this approach is currently recommended.[2] Initial support for this policy came from the clinical observation that routine, periodic endocervical screening reduces CT transmission and the related morbidity enough at the community level and make the benefits of screening outweigh the harms.[2,11–16] The results of these studies have now been corroborated by mathematical models, increasing confidence in the efficacy of this approach to the control of CT.[2] Admittedly, screening is rarely conducted in isolation of risk-reduction counseling and other educational interventions that have been associated with safer sexual practices and a concomitant decrease in incident STDs.[17] The favorable individual- and community-level effects attributed to the identification and treatment of CT-infected young women might therefore be due to factors such as increased condom use, decreased numbers of sex partners, and less concurrency in relationships. However, this is unlikely.

Individuals who have been treated for CT remain at increased risk for this infection regardless of their subsequent sexual behavior.[7,27–36,42–44,53,54] Thus, the most likely explanation for the success of programs in which young, sexually active women undergo routine, periodic endocervical STD screening is that assiduous attention to the treatment of index cases and their sexual contacts reduces the prevalence of CT in communities.[17]

The same can not be said for screening strategies that target sexually active women over 25 years of age.[17] Indeed, the prevalence of CT among older women does not usually reach the 2% level at which routine, periodic screening of asymptomatic females becomes a cost-effective approach to disease control, unless there is a prior history of STDs.[2] Thus, symptom-based endocervical screening coupled with patient-initiated testing following risky sexual encounters (i.e., after sexual contact with a new partner who is suspected of having an STD or when involved in a non-mutually monogamous relationship), is recommended for most women this age.[2]

The utility of screening strategies that employ other analytes and those that target males and non-clinic populations is also unproven.[17] NAATs detect very low levels of viable and non-viable organisms.[89] Studies comparing CT transmission rates and the clinical consequences of chlamydial infections that are detected by these highly sensitive tests in urine and vaginal fluids to those detected by endocervical swab are still needed to define the clinical and public health significance of NAAT-diagnosed urethral and vaginal CT infections. Until this information becomes available, the usefulness of CT screening programs that employ these analytes will remain in question.[17] In the case of males, there is little empirical data upon which to base a screening policy.[2] This is because asymptomatic men were rarely tested for CT prior to the introduction of urine-based NAATs.[2] Moreover, because the cost of treating CT-infected males is lower than the cost of treating CT-infected females and a greater proportion of infected males are symptomatic than females, finding about the efficacy of screening females for CT cannot be extrapolated to males.[2] Thus, according to the US Preventive Services Task Force there is currently insufficient evidence to determine if the benefits of routine, periodic screening for asymptomatic male CT infections outweigh the costs of testing and the potential harms associated with misdiagnoses and unnecessary treatments.[2]

Instead, it is recommended that prevention efforts with males of all ages be directed toward promoting patient-initiated symptom- and situation-based screening.[2] However this policy may soon be changed.[6] Recent data suggest that the magnitude of the threat asymptomatic, CT-infected males pose to the efficacy of female screening programs is far greater than public health officials had imagined.[2,6,9,17,27–36,44,46,47,64] Finally, it is important to note that there is little empirical evidence that screening in non-clinic settings reduces infection rates and CT-related morbidity.[17] Patient satisfaction with NAAT-based testing at home, school, and other field locations suggests that this approach holds tremendous promise for increasing population penetration.[17] However, identifying infected individuals is only the first step to effective disease control. To reduce the prevalence of CT and its costly sequelae at the population level, individuals with positive test results and their partners must be treated. Projections about the costs and benefits of clinic-based CT-screening programs take into account the fact that many

patients who test positive for this infection are never notified of their test results or treated, and even fewer notify their sexual partners.[17,29,32,64,109–122] However, absent information about the follow-up of asymptomatic patients who test positive for CT on specimens they collect at home or they or their care providers collect in other non-clinic settings, findings about the efficacy of screening clinic populations cannot be extrapolated to non-clinic populations.[17] While such inferences are inappropriate, given the failure of current screening strategies to control this easily curable STD,[6] the data are sufficiently compelling to make further study of the factors that motivate asymptomatic individuals to seek STD testing and ways to help them overcome the numerous barriers they encounter if and when they decide to do so a matter of intense public health interest.[1,2,9,17,27,50,64]

Developing selective CT-screening algorithms is an attractive public health goal that has been vigorously pursued by the research community for decades.[17] However, with the exception of female sex and age less than 25 years, no single demographic or behavioral risk factor or combination of risk factors has been found that is generalizable from one demographic area to others.[1–3,8,9,17,21–29,50,64,76,86,93,109–116]

Rather, the benefits of more selective criteria in terms of screening cost savings is limited by the high proportion of missed infections.[111] Indeed, the only reliable way to consistently identify a group of young, sexually active females who should not be screened for CT is to develop site-specific algorithms. Where these are not available, the recommendation is to screen females on the basis of age alone.[2]

Determining how frequently individuals must be screened to lower the prevalence of chlamydial infections and CT-related morbidity at the population level is an even more complex task.[1–9,17,27,64,116–124] Mathematical models demonstrate two important facts about the process.[114–116] First, screening programs must run for a period of time to significantly lower the incidence of CT at the population level. Second, due to the progressive decrease in CT prevalence, each successive year becomes less cost-effective. The randomized controlled trials needed to test these models empirically have not been conducted. Nevertheless, based on the observation that the median time to first and repeat infection is approximately six months among sexually active teenagers, bi-annual screening algorithms have been proposed.[22,27,44,50,64] This is a reasonable starting point for further study. However, there is currently no evidence that this is a cost effective approach to disease control in adolescents.[50] Moreover, given the strong inverse relationship between age and the risk of re-infection with CT, there is even less reason to believe that it would be appropriate to extend this recommendation beyond the teenage population.[1,2,17,22,27,46,47,54,64,117] For example, in one study the prevalence of repeat CT infection fell precipitously from 16% among 10- to 14-year-olds to 11% among 15- to 19-year-olds and 4% among 20-year-olds.[54] In truth, dynamic, population-specific models that take into account the variable kinetics and manifestations of this infection within communities and sexual networks will probably be needed to determine the optimal screening interval for each phase in the evolution of the CT epidemic. Thus, it remains to be determined if it is possible to develop a broad national consensus about who should be screened when and where for this infection.

Treatment

M & M 8: Treating one CT-infected individual decreases the risk of infection in others

The primary goal of antibiotic treatment of chlamydial infections is to prevent complications and contagion.[1,10] This is a simple task that is easy to summarize in tabular form.[1,10] Moreover, when administered under medical supervision, the cure rate for single-dose azithromycin therapy is close to 100%.[10] Hence, there is little need for a "test-of-cure," except when antibiotic efficacy may be reduced, (i.e., during pregnancy) or compliance is in doubt.[1,10] However, given the futility of treating index cases in isolation of their sexual networks, therapy can not be considered complete until all individuals who have had sexual contact with the index case during the 60 days preceding the onset of symptoms or diagnosis have been treated.[1,10] This is a far more difficult and complex task.[1,10,27–36,41–44,46,47,53,54,64,114,117] Indeed, given the myriad of personal and environmental barriers that must be overcome, it is unlikely that it will ever be possible to summarize the requisite activities in tabular form. Even when CT-infected patients are counseled about future disease prevention, (i.e., the necessity of repeat testing and responding proactively to STD-related symptoms and risky sexual encounters by seeking immediate testing), it is estimated that only approximately a half to two thirds of those who test positive for the infection refer their sex partners for therapy.[17,29,32,64,114,125–127] This large reservoir of untreated partners is among the most important impediments to disease control. For example, investigators at the Colorado Health Department STD clinic found that repeat chlamydial infections were more than twice as common as new infections.[29] In another study bi-annual screening and treatment was associated with a dramatic decline in the prevalence of chlamydial infections in boys who patronized eight school-based clinics, but due to reinfection by partners who were

not students at the study schools it was impossible to sustain a similar screening-based decrease in CT among the girls.[44] The frequency with which repeat chlamydial infections occur is extremely concerning because they have been implicated in the pathogenesis of upper genital tract damage.[8,14,27,64,70–72,123,124] Indeed, given the magnitude of the problem, repeat infections and the untreated partners that usually cause them, may actually pose the greatest public health threat.[29] Thus, it is imperative that the next phase of research focuses on the development and implementation of network- and community-based treatments. Interventions that have the potential to impact the prevalence of CT-related morbidity at the population level are needed. Treatment programs that approach the problem from an ecological perspective and those that are grounded in Social Learning Theory[128] or other theories of human behavior are more effective than low-intensity, client-centered efforts, but they are extremely labor intensive.[17,27] For this reason, care providers often find the most successful models prohibitively complex and costly.[17,27] Thus, until more effective ways of communicating test results and counseling about treatment, partner notification, and risk reduction are developed it may be wise to retest infected individuals 3 to 4 months after treatment and periodically thereafter until their risk profiles change.[2]

Patients and their sexual partners are most likely to be treated if they are both informed by a professional.[17,27,64] However when this is impossible or impractical, patient delivered partner treatment is an attractive alternative to patient initiated partner notification as it is equally effective and can save both time and money.[127] The only caveat is that health care providers who adopt this approach run the risk that a patient who is not under their direct care and whose medical and allergy histories are unknown will develop an adverse reaction to the prescribed medication.[64] Finally, when treating teenagers, special care must be taken to stay within the confines of confidentiality and privacy provisions afforded by individual state and federal mandates and the Health Insurance Portability and Accountability Act.[64,129]

M & M 9: The risks of under-treatment exceed the risks of over-treatment

The risks of under-diagnosis and under-treatment are common themes in the CT-literature.[64,75–85] This is particularly true of the adolescent STD literature, as in comparison to most other groups, teenagers have higher STD prevalence rates, are especially vulnerable to the adverse reproductive consequences of untreated STDs, and are generally perceived as promiscuous and non-compliant with follow-up.[64] By contrast, the risks of over-diagnosis and over-treatment are rarely discussed.[85] This is surprising, as there is ample evidence that when it comes to the diagnosis and treatment of STDs, erring on the side of excess can create as many problems as erring on the side of temperance.[64,85,108,130–138] With the introduction of NAAT-based testing the practice of routinely treating leukocyte esterase positive urine dip sticks and inflamed, purulent cervixes empirically as STDs was rightfully denounced.[10,64]

However, in its place the Centers for Disease Control (CDC) has left us with the vague mandate to consider doing so only in "situations where there is a high prevalence of the infection, or where there is limited availability of testing and follow-up."[10,64] Unfortunately, precisely what should be considered a "high prevalence" of CT and who should be considered "unlikely" to follow-up has not been explicitly stated.[64] Thus health care professionals muddle along trying to avoid under- and over-treating suspicious signs and symptoms. More specific guidance than the advice offered in the most recent CDC STD treatment guidelines is clearly needed, particularly when it comes to caring for teenagers.[64] Cognizant of the unique concerns about confidentiality and numerous institutional and psychological barriers that deter STD treatment at this age, health care providers are especially apt to empirically treat boys with white blood cells in their urine and girls with mucopurulent endocervical discharge.[64,85] This is an unfortunate practice, given the low positive predictive value of common gynecologic and urologic complaints such as mucopurulent cervicitis and dysuria for CT.[2,64,75–85] Indeed, it is likely to result in over half of individuals who have these symptoms being misdiagnosed with STDs and prescribed antibiotics unnecessarily.[64,85] With antibiotic side-effects consisting of mild-to-moderate gastrointestinal discomfort occurring in less than a quarter of patients who take a gram of azithromycin, toxicity is uncommon and there is rarely any need for medical intervention.[85,139] However, by inducing bacterial resistance the indiscriminate use of antibiotics poses a serious public health threat in the community.[136–138] The adverse psychological effects of being diagnosed with an of STD, (i.e., dysphoric feelings, anxiety, depression, and decreased self-esteem, disruption of romantic relationships and domestic violence),[108,130–135] should also temper enthusiasm for the practice of treating CT empirically on the basis of characteristic symptom complexes or suggestive vaginal wet mounts or urine dip sticks.[85] Mathematical models demonstrate that knowledge about the prevalence of CT in individuals with these non-specific signs and symptoms is critical.[85] For example, one decision analysis found that the ratio of infection-related morbidity prevented to treatment-related morbidity inflicted did not approach one-to-one until the incidence of CT in symptomatic

persons was close to 70%.[85] This makes empirical treatment an attractive option for STD clinic patrons and recent sexual contacts of CT-infected individuals.[85] However, the benefit-to-risk ratio is far less compelling in other settings.[85] Hence, there is still no consensus concerning the meaning of the current CDC recommendations regarding empiric treatment of suspected chlamydial infections and even less agreement about how best to operationalize them in clinic and nonclinic settings.[64] Indeed, there may currently be no optimal approach to this problem. Rather, until further data become available, preventing the adverse consequences of chlamydial infections will likely require a variable definition of "optimal."[85] Moreover, what constitutes "best practice" is likely to remain dependent upon individual perspectives and values.[85] From a societal or third-party payer perspective, cost may be the predominant concern, whereas for some patients avoiding the misdiagnosis of an STD may be paramount and for others minimizing the risk of sequelae and disease transmission may take precedence. This leaves health care providers caught between Scylla and Charybdis: on one side facing the monstrous, two-headed problem posed by the anger, sorrow, and guilt the misdiagnosis of an STD engenders and the very real threat of community-wide antibiotic resistance and on the other the destructive whirlpool of untreated chlamydial infections and their costly sequelae. Thus, once tested it may be preferable to allow symptomatic and other high-risk patients to select between empiric and results-based treatment, the strategy that best conforms with their personal values.

Conclusions

The prevention of CT-related morbidity is a complex problem for which simple answers and solutions are unlikely.[140] Knowledge and understanding about the epidemiology, clinical presentation, diagnosis, and treatment of this and other STDs has evolved over the years but is still incomplete. Misperceptions and misunderstandings that have the potential to prolong infectiousness and increase the CT-related morbidity are still rampant among teenagers, young adults, and the professionals who care for them. If policy makers are to develop a cumulative and empirically based understanding of how to minimize CT-related morbidity, program developers must describe how their interventions prevent the antecedents of these problems and investigators must conduct theory-driven evaluations. Future studies of the efficacy of prevention programs must be held to standards of scientific inquiry that are as high as those for studies of the effectiveness of antibiotic treatment regimens. Rigorous evaluation tactics are a necessity or unproductive interventions may be misinterpreted as effective and valuable interventions may be prematurely dismissed as ineffective. Finally, since preventing the adverse consequences of chlamydial infections will likely require "a myriad of imperfect, cumulatively effective" population-level interventions,[140] we wholeheartedly support the suggestion that future investigations should focus on the identification of program components that build on each other and "not only shift high-risk individuals out of the danger zone, but also move society as a whole toward a lower level of risk for any sexual exposure."[140]

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