Sexually transmitted infections in Canada: A sticky situation

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The West African spider folktales describe triumphs of Anansi – a 'spider-man' who overcomes numerous challenges through his cunningness. One of Anansi's tasks is to capture an evasive character named Mmoatia; he catches Mmoatia using a doll covered in sticky gum (1). Mmoatia gets into a tussle with the doll; because of the sticky gum, the harder he struggles, the more he gets stuck. Echoes of this story appear in folklore from other countries including the Brer Rabbit tales recorded by Joel Chandler Harris in the American south (2).

What does this have to do with infectious diseases? The analogy is not a perfect one, but with reference to sexually transmitted bacterial infections, we find ourselves at a somewhat similar juncture this year in Canada. We struggle and struggle, and the more we struggle, the more we get stuck. For chlamydia and syphilis, accurate laboratory tests and highly effective antimicrobials theoretically make these threats controllable; indeed, we are only 10 years removed from an ambitious effort in the United States (US) to actually eliminate syphilis (3). Not only are these threats not controlled, but the incidence of both infections has risen sharply across Canada in recent years (4). Chlamydia rates in several countries have increased sharply with screening efforts, raising questions as to whether screening itself might somehow enhance chlamydia transmission or whether (as we believe) more intensive case finding efforts are simply uncovering an increasing fraction of the chlamydia 'iceberg'.

The situation with gonorrhea is less startling with respect to change in disease burden (4), but in some ways, it is even more concerning, with multidrug resistance now an established fact that complicates the management of this still common infection (5). In the present article, we describe emerging clinical and epidemiological facets of these important challenges in Canada and elsewhere.

CHLAMYDIA

Chlamydia trachomatis (CT) is a sexually transmitted pathogen that is the most common notifiable infectious disease in North America, accounting for more than 50% of all reported cases of infectious disease in Canada and the US (6,7). Medical consequences include pelvic inflammatory disease, infertility, ectopic pregnancy and chronic pelvic pain (8), enhanced rates of HIV transmission and acquisition (9), and eye and lung disease in newborn infants (10, 11). In Canada, the rate of CT infection has increased from 113.9 cases in 1997, to 248.9 cases per 100,000 in 2008 (12); the annual prevalence of infection is 2% in some northern communities (4). Asymptomatic infections are most common (perhaps accounting for 80% to 90% of all infections) (13), and insidious effects of asymptomatic CT infection may result in health and health economic impacts that exceed those associated with clinically apparent infections. While the costs associated with CT infections and its sequelae are difficult to measure with certainty, they are likely substantial; recent estimates suggest costs of $50 million to $120 million annually in Canada (14,15).

Chlamydia should be controllable through screening: it is common (16); detectable using a sensitive, specific and noninvasive test (17); and treatable when diagnosed, with reduction in pediatric infectious diseases risk in randomized controlled trials (16,18). Chlamydia screening in younger women is considered to be cost effective or cost saving (16,19). Although the Public Health Agency of Canada advocates that sexually active individuals undergo regular screening for chlamydia (7,20,21), the impact of heavily funded and widely applied screening programs in Canada has been disappointing, with CT rates continuing to rise, and increased time and resources being allocated at the local public health unit level to contact tracing and partner notification. After an initial decline, chlamydia prevalence increased 57% in Canada between 1991 and 2008 – a period during which screening was widespread (4). Similar 'rebound' has been observed in the US, Sweden and the United Kingdom, and has spurred calls for reduction or elimination of chlamydia screening (22). The tremendous burden of disease that has been identified through screening also requires a large volume of follow-up care, including contact tracing and partner notification activities by local public health units, which draws public health resources away from other programs.

Surging rates of chlamydia in Canada and the US, despite expanded screening, have been variously attributed to increased case finding, increased prevalence of infection risk due to behavioural 'risk compensation' (23) and immunologically mediated 'rebound' due to the increasing number of susceptible individuals (24,25). Furthermore, variability in sexual behaviour may be more important than average sexual behaviour in sustaining disease transmission, with the highest-risk individuals accounting for a disproportionate amount of transmission, making the control of infection in highly 'connected' individuals an extremely attractive disease control strategy (26). Understanding variability in sexual contact structure is emerging as a critical element in the design of public health interventions that can effectively control the spread of pathogens such as CT.

One potentially promising approach to management is to reach otherwise unreachable sex partners by having the patients themselves deliver antimicrobial therapy; this is referred to as 'patient-delivered partner therapy' or 'expedited partner therapy' (EPT) (27,28). In most randomized trials, EPT has been associated with a significant reduction (approximately 25%) in the risk of reinfection of patients (Figure 1), presumably because of a reduction in reinfection of untreated partners (28-31). While this approach is potentially challenging from both legal and ethical points of view (because the treated partner will not, in general, undergo medical assessment), evidence suggests that clinicians already provide EPT (27), and statutes that explicitly permit EPT have recently been passed in several US states (32); the legal status of EPT in each state can be viewed at http://1.usa.gov/qsrwgy. Perhaps a larger hurdle for EPT is the degree to which it relies on single-dose azithromycin (1 g orally) as an effective, convenient and therapeutic regimen. Emerging evidence suggests that single-dose azithromycin may be less effective than a seven-day course of doxycycline for uncomplicated lower genital tract CT infection (33). Additional work is needed to establish the optimal approach to patient and partner management given the potential trade-offs between these regimens.

SYPHILIS

Major urban centres in North America, Europe and Australia have witnessed a dramatic re-emergence of syphilis in recent years, with much of the epidemic focused on men who have sex with men (MSM) and HIV-infected individuals (34,35). In Ontario, syphilis case counts have surged in both Ottawa and Toronto, with infections disproportionately affecting MSM (36). In Toronto, the annual rate of diagnosed infectious (primary, secondary or early latent) syphilis has increased more than 40-fold since 2001, with HIV/syphilis coinfection commonly encountered. Many individuals with early syphilis are either truly asymptomatic or undiagnosed; in the absence of diagnosis and treatment, approximately one-third of individuals will progress to neurological complications, visual and hearing loss, psychiatric disease, cardiovascular disease and other forms of systemic disease (37). Infectious syphilis has also been associated with acquisition and transmission of HIV (9), highlighting the importance of syphilis control as a component of HIV prevention efforts (34,35).

Elsewhere in Canada, epidemics have been MSM focused, although nationally, the male to female ratio of cases remains well above 1 (4). In

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Alberta, a syphilis epidemic that began with an MSM focus is now associated with a surge in cases in women, and in a substantial burden of congenital syphilis cases (38). The response to syphilis in all regions has included increased testing and treatment campaigns targeting populations at risk. Novel treponema-specific assays, such as syphilis enzyme immunoassays (EIA) or chemiluminescence immunoassays, have both enhanced the ability of laboratories to perform high-throughput testing, and have likely also enhanced sensitivity of testing for early (rapid plasma reagin [RPR] negative) disease (39). Traditional testing algorithms have been replaced by 'reverse sequence' algorithms such that positive EIA and chemiluminescence immunoassays for syphilis are followed by a quantitative nontreponemal test, such as RPR, with RPR-negative cases subjected to traditional treponemal tests (such as *Treponema pallidum* particle agglutination) to rule out false-positive EIA results (40). Point-of-care tests for syphilis represent another very promising advance for rapid, onsite diagnosis and treatment of this disease (41). Benzathine penicillin remains a highly effective therapy for early-stage syphilis (outside the central nervous system and in nonpregnant individuals) (7); however, the recent emergence of *T pallidum* resistant to macrolides is a source of concern (42).

While it might be expected that enhanced testing and treatment would decrease syphilis case numbers, the epidemiology of syphilis is complex, and the lessons learned in Vancouver, British Columbia, in the early 2000s may be instructive. In Vancouver, a heterosexual syphilis outbreak was managed with aggressive empirical therapy targeted at populations at risk; while syphilis rates decreased transiently, there was subsequent 'rebound' in syphilis cases to a level beyond baseline (43). Researchers at the British Columbia Centre for Disease Control used mathematical models to evaluate plausible mechanisms for this rebound; best-fit models suggested that by truncating latent syphilis through antibiotic treatment, outreach may have cycled epidemiologically important individuals back into a state in which they could again acquire early (infectious) syphilis, thus contributing to rising case counts by transmitting infection (44).

A similar immune mechanism may account for the periodic rise and fall in syphilis cases observed during the past century. Because of the noninfectiousness of individuals with late latent syphilis, syphilis epidemics appear to 'burn out' when prevalence of latency crosses a threshold; as young (uninfected) individuals become old enough to become sexually active, a pool of susceptible individuals gradually reaccumulates, enabling epidemics of infectious syphilis to emerge (34,45,46). This is probably what we are currently experiencing in Canada.

GONORRHEA

Genital tract infection due to *Neisseria gonorrhoeae* (NG) remains an important sexually transmitted infection in North America, both in terms of burden and cost of disease, and with respect to disease sequelae including pelvic inflammatory disease and its complications in women; epididymo-orchitis and prostatitis in males; ophthalmic disease in neonates; enhanced risk of HIV transmission and acquisition; and rarely, disseminated infection (47,48). Gonorrhea incidence decreased sharply in North America at the end of the 20th century (49,50), representing an important public health success, and one that was predicted by mathematical models. The models demonstrated that a pathogen such as NG, characterized by a relatively brief duration of infectiousness, is strongly dependent on individuals with high rates of sex partner change or concurrency (so called 'core groups') for continued propagation, such that the antibiotic treatment of core groups precipitates a rapid decline in the incidence and prevalence of infection in the population as a whole (26). When antimicrobial treatment is provided to core groups, gonorrhea prevalence can be expected to collapse.

However, despite targeted treatment of core groups, gonorrhea incidence rates have remained stable but high in the US, while rates have been increasing in western Europe and Canada (4,51,52), nearly doubling in Ontario where rates have risen from 15 to 25 cases per 100,000 population between 1997 and 2007 (53).

As with the other sexually transmitted infections described above, it is likely that the rise in gonorrhea case counts is multifactorial. However, multidrug-resistant NG isolates are becoming increasingly common (53). Resistance of NG to tetracyclines, aminopenicillins and erythromycin

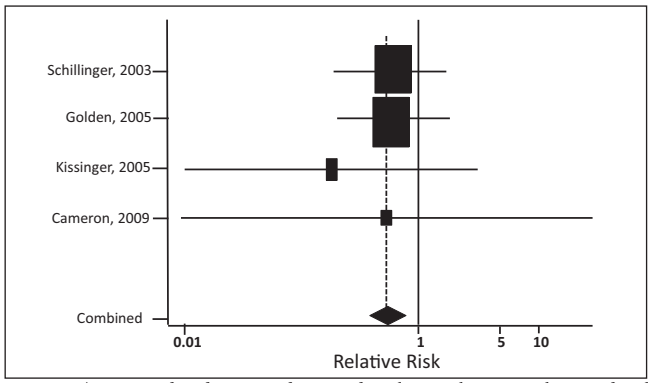

Figure 1) *Forest plot showing relative risks of noninfection in four trials of patient-delivered partner therapy. The diamond represents the summary estimate derived by pooling data from a summary of individual trials (RR 0.76, 95% CI 0.65 to 0.96 in fixed-effects model; P=0.005). There was no statistically significant between-trial heterogeneity (P=0.15). Box area is proportionate to the inverse of study variance*

was common by the 1990s (54). Fluoroquinolone antibiotics represented a promising single-dose therapy for uncomplicated NG, but resistance to these drugs emerged rapidly in the early 2000s; recent reports suggest that up to 30% of NG isolates in Ontario are fluoroquinolone resistant (53,55). With the loss of fluoroquinolones as a therapeutic option, third-generation cephalosporins, notably cefixime (400 mg orally) and ceftriaxone (125 mg intramuscularly), became the therapeutic regimens of choice. However, high-level NG resistance to third-generation cephalosporins has now been reported in Japan (56); recent reports note an increased frequency of NG isolates with reduced susceptibility to third-generation cephalosporins in the US and the Netherlands (57,58) in a manner that echoes changes that occurred with fluoroquinolones several years ago. Reduced susceptibility of NG to high-dose azithromycin (2 g orally) has now also been reported (59).

Clearly, novel strategies are needed to confront the threat of multidrug-resistant gonorrhea. The preponderance of NG testing performed through nucleic acid amplification means that frequently clinicians will not have antimicrobial susceptibility data to guide treatment decisions and, indeed, that such information will not be available for public health surveillance purposes. Point-of-care testing for both NG and antimicrobial susceptibility is an exciting prospect, but such assays are not yet clinically available (60). Proposals for enhancing the effectiveness of empirical treatment for gonorrhea may include revisions of guidelines so that multidrug treatment of NG infections becomes standard, and may also include the institution of routine cure tests in treated individuals. However, it is important to remember that regular condom use remains a mainstay of NG prevention (61). Efforts to develop a vaccine against NG have not been historically met with much success, but recent advances in synthetic biology and development of immune adjuvants suggest that future efforts may meet with greater success (62).

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