

Azithromycin resistance in *Treponema pallidum*

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Purpose of review

Although the recommended treatment for syphilis is penicillin, azithromycin has been used as an alternative. We discuss azithromycin-related treatment failures and resistance in *Treponema pallidum*, and propose ways to meet the resulting clinical and public health challenges.

Recent findings

Azithromycin treatment failures in syphilis were first noted in San Francisco in 2002 and result from an A→G mutation at position 2058 of the 23S rRNA gene of *T. pallidum*. This mutation confers resistance by precluding macrolide binding to the bacterial 50S ribosomal subunit, of which 23S rRNA is a structural component. Azithromycin resistance has also been identified in *T. pallidum* specimens from elsewhere in the United States, Ireland, and Canada, and the amount of resistant specimens has increased with time. Treatment with azithromycin or other macrolides appears to be a risk factor for presenting with a resistant *T. pallidum* strain.

Summary

Although *T. pallidum* remains sensitive to penicillin and certain other antibiotics, azithromycin resistance in *T. pallidum* has emerged and is increasing in the United States, Canada, and Ireland. This poses clinical and public health challenges, and indicates a need for further antibiotic drug development and surveillance for resistance in *T. pallidum*. If azithromycin is used to treat syphilis, clinicians and public health practitioners should remain vigilant for treatment failures.

Keywords

antibiotic resistance, azithromycin, syphilis, *Treponema pallidum*

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Introduction

Be a whore still: they love thee not that use thee;
Give them diseases, leaving with thee their lust.
Make use of thy salt hours: season the slaves
For tubs and baths; bring down rose-cheeked youth
To the tub-fast and the diet.

Timon, to the harlot Timandra,
in Shakespeare's *Timon of Athens* (Act IV, Scene III)

Treatment of syphilis has changed dramatically since Elizabethan times, when remedies included hot baths, mercury, and a Spartan diet [1]. The discovery of antibiotics and recognition that *Treponema pallidum* subsp. *pallidum* (*T. pallidum*), the spirochete that causes syphilis, is sensitive to penicillin revolutionized treatment of syphilis [2–4]. Intramuscularly administered penicillin G benzathine is the preferred treatment for syphilis (except for neurosyphilis and certain types of congenital syphilis) [5], although other antibiotics, including tetracyclines, macrolides, and cephalosporins, have also been used [5–11]. These alternatives have been useful in treating penicillin-allergic patients, and certain ones

can be administered orally, which is often more convenient or acceptable than intramuscular administration. During the past 3 decades, and especially since 2004, reports of treatment failures and antibiotic resistance associated with macrolides — first erythromycin and then azithromycin — have been reported. This article reviews the epidemiology and treatment of syphilis, describes the trends in and mechanisms that underlie antibiotic resistance in *T. pallidum*, and outlines ways to meet the clinical and public health challenges posed by azithromycin resistance in *T. pallidum*.

Epidemiology of syphilis in the USA

Incidence of primary and secondary (P&S) syphilis in the United States is increasing. In 2000, a year after the launch of the National Plan to Eliminate Syphilis [12], the US P&S syphilis rate reached its lowest level — 2.1 cases/100 000 population — since national reporting began in 1941 [13]. By 2005, however, the rate had increased to 3.0/100 000 population, with 46.4% of cases occurring in the south [14]. Through 11 August 2007 a total of 6025 cases of P&S syphilis were reported, compared with 5674

during a comparable period in 2006 [15]. The increases in P&S syphilis incidence have occurred primarily among men [13,14]. Rates among blacks and Hispanics are higher than among whites [14].

Gay men or other men who have sex with men (G/MSM) accounted for 64% of all US cases of P&S syphilis in 2004 and comprised larger proportions of cases in the west and northwest than in the south and midwest [13]. Syphilis among G/MSM has been associated with HIV co-infection, high-risk sexual behavior, methamphetamine use, and acquisition of sex partners through the internet [16–18]. Risk factors for heterosexual transmission include crack cocaine use, prostitution, socio-economic deprivation, and inadequate access to health care [18,19].

Syphilis treatment options and considerations

Penicillin G benzathine, administered intramuscularly in a single dose of 2.4 million units in adults, is the preferred treatment for P&S syphilis, according to US Centers for Disease Control and Prevention (CDC) guidelines (Table 1) [5]. For certain penicillin-allergic patients, alternative therapies can be used; these include doxycycline, tetracycline, ceftriaxone, and azithromycin [5]. Although use of penicillin to treat syphilis is supported by > 50 years of clinical experience, data supporting use of nonpenicillin treatments for syphilis are limited [5]. As a result, patients receiving nonpenicillin therapies should be observed closely; in particular, such therapies should be undertaken with caution among HIV-infected persons [5]. In addition, because no proven alternatives to penicillin exist for treating syphilis during pregnancy, penicillin-allergic pregnant women with any stage of syphilis should not receive a nonpenicillin treatment; rather, they should be desensitized to and then treated with penicillin [5].

Azithromycin is the only antimicrobial that can be administered as a single-dose, oral treatment for syphilis. Azithromycin is a semisynthetic azalide, a subclass of macrolides that are structurally distinguished by the addition of nitrogen at position 9a of the lactone ring [20]. That structural difference enables azithromycin to resist acid degradation, penetrate tissues, have greater activity against Gram-negative organisms, and have a longer half-life [20].

In-vitro and animal tests published in 1990 first indicated that azithromycin was effective against *T. pallidum* [21,22]. Clinical effectiveness in syphilis was supported by nonrandomized studies [10,23–26] and by three randomized controlled trials – two in the United States [7,8] and one in Africa [9] – that compared azithromycin with penicillin (Table 2) [7–9,54]. From clinical and public health perspectives, azithromycin was an attractive syphilis treatment because of its equivalent effectiveness with penicillin [7–9], cost-effectiveness [27], and favorable adverse event profile [27,28**]. Additionally, the simple oral regimen for azithromycin was acceptable when used in syphilis control efforts in San Francisco to increase partner treatment through patient-delivered partner therapy [28**]. For those reasons, azithromycin was used for syphilis treatment in the mid-1990s in Uganda [10] and for targeted chemoprophylaxis in 2000 in Vancouver [29] and Los Angeles [30]. The San Francisco Department of Public Health (SFDPH) began to use azithromycin as an alternative treatment for preventing syphilis in patients exposed to contacts with syphilis in 1999 and as an alternative treatment for P&S syphilis in 2000 [28**].

Syphilis treatment failures and *Treponema pallidum* antibiotic resistance

As in other infectious diseases, treatment failures in patients with syphilis (i.e. failure of a prescribed therapy

Table 1 Treatment options for patients with primary and secondary syphilis and their sex partners

Antibiotic	Dose	Route	Frequency	Duration
Preferred regimen [5]				
Penicillin G benzathine	2.4 million units (adults) or 50 000 units/kg (children; not to exceed 2.4 million units)	Intramuscular	Single dose	Single dose
Other regimens (not recommended by CDC but sometimes used to treat syphilis) ^a				
Doxycycline	100 mg	Oral	Twice daily	14 days
Tetracycline	500 mg	Oral	Four times daily	14 days
Ceftriaxone	1 g	Intramuscular or intravenous	Once daily	8–10 days
Azithromycin	2 g	Oral	Single dose	Single dose

^a Penicillin-allergic pregnant women should be desensitized and receive penicillin G benzathine. Follow up of patients receiving nonpenicillin therapies is essential. Azithromycin should not be used in areas where resistance is widespread, and should be used with caution in areas where the prevalence of resistant specimens is unknown. Because data on use of nonpenicillin therapies in HIV-infected persons are limited, nonpenicillin therapies in HIV-infected persons should be used with caution. Penicillin-allergic patients who might not comply with therapy or who might not return for follow up should be desensitized and receive penicillin G benzathine. Certain penicillin-allergic patients might also be allergic to ceftriaxone. For additional details on treatment of sex partners of patients with primary and secondary syphilis and for treatment recommendations for other stages of syphilis, see US Centers for Disease Control and Prevention guidelines (CDC) [5].

Table 2 Clinical trials comparing azithromycin to penicillin for syphilis treatment

Authors (year) [ref.]	Location(s)	Types of syphilis studied	Regimens compared (number of subjects evaluated)	Duration of follow-up	Primary endpoint	Results
Hook <i>et al.</i> (1999) [7]	Birmingham, Alabama	Persons with a nonreactive RPR result who had been sexually exposed to patients with primary, secondary, or early latent syphilis within 30 days of presentation	Penicillin G benzathine 2.4 million units administered intramuscularly in a single dose (23) Azithromycin 1 g administered orally in a single dose (40)	3 months	Clinical or serologic evidence of progression to syphilis	No evidence of progression to syphilis in any evaluable patient
Hook <i>et al.</i> (2002) [8]	Birmingham, Alabama, and New Orleans, Louisiana	Persons in whom primary, secondary, or early latent syphilis was diagnosed	Penicillin G benzathine 2.4 million units administered intramuscularly once in Birmingham or twice, 7 days apart, in New Orleans (14) Azithromycin 2 g administered as a single oral dose (17) Azithromycin 2 g administered as two oral doses 6–8 days apart (29)	Up to 12 months	Cure defined as resolution of all signs and symptoms of syphilis, including all suspicious lesions present at baseline, and either a negative RPR titer or a fourfold or greater decrease in RPR titer	Cure achieved in 12/14 (86%) participants treated with penicillin, 16/17 (94%) participants treated with a single dose of azithromycin, and 24/29 (83%) participants treated with two doses of azithromycin
Riedner <i>et al.</i> (2005) [9]	Mbeya, Tanzania	Persons in whom primary or high-titer (defined as at least 1 : 8 on an RPR test) latent syphilis was diagnosed	Penicillin G benzathine 2.4 million units administered intramuscularly as a single dose	9 months	Cured defined serologically as a decline in the RPR titer of at least two dilutions by 9 months after treatment and, for patients with primary syphilis, epithelialization of ulcers within 1–2 weeks	Cure rates were 95% in the penicillin G benzathine group and 98% in the azithromycin group
Klausner <i>et al.</i> (2006) [54]	San Francisco	Individuals who were sexual contacts of persons with infectious syphilis	Azithromycin, 2 g administered as a single oral dose Penicillin G benzathine 2.4 million units administered intramuscularly as a single dose	3 months	Treatment failure defined as a positive VDRL test	In the azithromycin-treated group, 2/12 (16.7%) participants were treatment failures; in the penicillin-treated group 0/13 (0.0%) participants were treatment failures ($P = 0.18$). On the basis of these data, the study was terminated early by a data safety monitoring board

RPR, rapid plasma regain; VDRL, venereal disease research laboratory.

to achieve the intended result) can result from different causes, including factors related to the patient, the therapy, or the organism itself. Treatment failure related to therapy can result from inappropriate antibiotic choice, as in the use of nonrecommended penicillin preparations to treat syphilis [31]. Treatment failure related to *T. pallidum* can result from antibiotic resistance (i.e. the ability of an organism to evade an antibiotic's antimicrobial actions) [32,33]. In *T. pallidum*, as in other organisms [34], molecular tests for the presence of specific genetic mutations that confer resistance have been developed [32,35].

Penicillin

Syphilis treatment failures after recommended treatment courses of penicillin were first reported in the 1960s [36–40], although penicillin resistance *per se* in any *T. pallidum* specimen has never been documented [6]. Concerns regarding the potential for penicillin resistance in *T. pallidum* were heightened by a report published in 1981 [41] that described the presence of plasmid DNA in a *T. pallidum* strain; plasmids are extrachromosomal DNA in which antibiotic resistance genes in bacteria commonly reside. Despite those molecular findings, plasmid-mediated antibiotic resistance in *T. pallidum* has not been reported. Another potential mechanism for penicillin resistance in *T. pallidum* was discovered in 2004, when researchers described a novel β -lactamase, an enzyme that can degrade the β -lactam ring of penicillins, in a membrane-bound protein called Tp47 [42]. Tp47 is strongly inhibited by products of the β -lactamase reaction, however; therefore, *T. pallidum* remains sensitive to penicillin [42]. Theoretically, mutations in Tp47 resulting in a failure of those reaction products to inhibit Tp47 might lead to penicillin resistance in *T. pallidum* [42].

Erythromycin

Before azithromycin, erythromycin was an alternative treatment for syphilis among penicillin-allergic patients [43]. Both erythromycin and azithromycin are macrolides, bacteriostatic antibiotics that reversibly bind to 50S ribosomal subunits of susceptible micro-organisms, thereby inhibiting bacterial protein synthesis [44].

Treatment failure with erythromycin was first reported in 1976, in a penicillin-allergic pregnant woman aged 24 years. She was treated with a 12-day course of erythromycin but, despite serologic evidence of a response, delivered an infant with congenital syphilis [45]. In 1977, new syphilitic lesions developed in another patient who was receiving erythromycin [46]. In the 1980s, two additional failures of erythromycin treatment were reported, one in a pregnant woman aged 21 years whose child had congenital syphilis [47] and another in an HIV-infected man aged 32 years [48].

Unlike treatment failures with penicillin, molecular evidence exists that indicates that genetic mutations in certain strains of *T. pallidum* confer resistance to erythromycin. This resistance was demonstrated in 'street strain 14', which was isolated from the syphilis patient whose failure to respond to erythromycin therapy was reported in 1977 [46]. Chromosomally mediated resistance in this strain was demonstrated first by an in-vitro assay for antibiotic susceptibility [49] and then confirmed by a molecular analysis that revealed the presence of an A→G mutation at the A2058 position in the 23S rRNA gene [33], which encodes a structural component of the 50S ribosomal subunit [50]. Also identified in other bacteria [50], this mutation (hereafter referred to as A2058G) alters the 23S rRNA, precluding macrolide binding and thereby conferring resistance to erythromycin and other macrolides [33,50].

Azithromycin

In 2002, the SFDPH [51] began noting azithromycin treatment failures in patients with incubating or P&S syphilis (Table 3) [28^{**},32,52^{*},53^{**},55^{*},56]. The first of those treatment failures occurred from September 2002 to July 2003 in eight self-reported G/MSM, three diagnosed with primary syphilis and five initially asymptomatic serologically negative contacts of syphilis patients. Penile ulcers persisted or worsened in the three patients with ulcerative disease, who each had received single 2 g oral azithromycin doses. The five contacts who each had received 1 g oral azithromycin doses either became serologically positive or experienced clinical disease. All patients subsequently responded clinically and serologically to treatment with either penicillin or doxycycline.

Gene sequencing of *T. pallidum* specimens from two San Francisco patients who failed azithromycin treatment revealed presence of the same A2058G mutation present in street strain 14 [32]. This mutation was also identified in specimens obtained from four patients from Dublin and two patients from Seattle [32]. A novel PCR-based assay that uses restriction-digestion to detect that mutation was then developed and used to assess a convenience sample of 114 specimens obtained from patients with primary syphilis lesions or moist secondary syphilis lesions from San Francisco, Seattle, Baltimore, and Dublin [32]. The A2058G mutation was present in 12/55 (22%) isolates from San Francisco, 3/23 (13%) isolates from Seattle, 2/19 (11%) isolates from Baltimore, and 15/17 (88%) isolates from Dublin. The mutation was also present in street strain 14 but none of the other 17 historical isolates of *T. pallidum*, collected between 1912 and 1987. Rabbits infected with street strain 14 were successfully treated with penicillin G benzathine, but not azithromycin or erythromycin, further demonstrating the relation between the mutated *T. pallidum* genotype and a phenotype of macrolide resistance [32].

Table 3 Reports of azithromycin treatment failures in syphilis patients and/or studies of azithromycin resistance in *T. pallidum*

Authors (year) [ref.]	Location(s)	Azithromycin treatment failures, <i>T. pallidum</i> resistance to azithromycin, or both	Patients and dates studied	Prior antibiotic use
CDC (2004) [51]	San Francisco	Treatment failures	Treatment failure in eight patients September 2002–July 2003	Not reported
Lukehart <i>et al.</i> (2004) [32]	San Francisco, Baltimore, Seattle, Dublin, and historical isolates	Both	One treatment failure reported. Convenience sample of 114 isolates assayed. Proportion of resistant isolates was 12/55 (22%) in San Francisco, 2/19 (11%) in Baltimore, 3/23 (13%) in Seattle, and 15/17 (88%) in Dublin. Of 18 historic isolates assayed, 1 (6%) was resistant ('street strain 14'; see text)	Not reported
Morshed and Jones (2006) [52*]	British Columbia	Resistance	Proportion of resistant isolates was 1/47 (2%) 2000–2003 and 4/9 (44%) in 2004	Not reported
Mitchell <i>et al.</i> (2006) [28**]	San Francisco	Both	Six treatment failures from 2000 to 2004. Proportion of resistant isolates was 1/25 (4%) from 2000 to 2002, 13/32 (41%) in 2003, and 37/66 (56%) in 2004	7/52 (14%) with resistant isolates took 1 g oral azithromycin for nonsyphilis-related reasons during the 30 days before onset of symptoms or diagnosis versus 1/72 (1%) without resistant isolates ($P < 0.01$)
Marra <i>et al.</i> (2006) [53**]	Seattle	Resistance	Percentage of resistant isolates was 0 in 2001, 9% in 2002, 23% in 2003, 50% in 2004, and 56% in 2005	Isolates were resistant in 10/18 (56%) patients who had taken macrolides during the prior 12 months versus 10/40 (25%) of those who had not ($P = 0.024$)
Zhou <i>et al.</i> (2007) [55*]	Shanghai	Treatment failures	Congenital syphilis in five neonates whose penicillin-allergic mothers had been treated with azithromycin during pregnancy	No additional antibiotics received during pregnancy or after delivery
Behets <i>et al.</i> (2007) [56]	Madagascar	Resistance	None of 103 isolates assayed was resistant	Not reported

CDC, Centers for Disease Control and Prevention.

A larger investigation into *T. pallidum* isolates from San Francisco assayed 124 specimens obtained during 2000–2004 by using the technique previously described [32]. A2058G mutations were present in 46/118 (39%) specimens with amplifiable DNA. Notably, the mutation was identified in 1/25 (4%) isolates during 2000–2002, 13/32 (41%) from 2003, and 37/66 (56%) from 2004 [28**]. The mutation has since been identified in 13/17 (76.5%) specimens from 2005 and 17/22 (77.3%) specimens from 2006. The increase since 2004 occurred despite a September 2004 decision by SFDPH, based on those increasing proportions, to cease using azithromycin to treat patients with syphilis in its own clinics and to cease recommending azithromycin as a treatment alternative to penicillin for patients in San Francisco. Similar temporal increases in proportions of A2058G *T. pallidum* specimens have been documented in other areas. In British Columbia, 1/47 (2%) specimens obtained from 2000 to 2003 harbored a mutation, as compared with 4/9 (44%) in 2004 [52*]. In Seattle, 1/14 (7%) specimens from 2000 to 2001 harbored a mutation, as compared with 5/9 (56%) in 2005 [53**].

Additionally, an SFDPH-conducted randomized controlled trial comparing azithromycin (1 g given orally as a single dose) with penicillin G benzathine (2.4 million units intramuscularly) in sexual contacts of persons with infectious syphilis was begun in June 2004. It was terminated in November 2004 by a data safety monitoring board after treatment failures were noted in 2/12 azithromycin-treated participants and 0/13 penicillin-treated participants (Table 2) [54].

There has also been a report from China of azithromycin-associated syphilis treatment failures in five penicillin-allergic pregnant women during 1998–2004; the total number of pregnant women treated with azithromycin during that period was not reported [55*]. One of those patients had secondary syphilis; three had early latent syphilis; and one had latent syphilis. Each woman received treatment with at least 1 g azithromycin, administered orally or intravenously, and exhibited declining rapid plasma reagin titers over the course of pregnancy; all sex partners of those women were treated with penicillin. Despite treatment of the women, all five infants born to those mothers developed clinical and serologic evidence of syphilis. Assays for the A2058G mutation were not performed.

Azithromycin treatment failures and *T. pallidum* resistance have not been reported in Africa. In the Tanzanian trial comparing azithromycin with penicillin [9] no azithromycin treatment failures in patients with confirmed primary syphilis. Molecular studies were not performed during this trial or during the Ugandan trial [10]. Additionally, no A2058G mutations were identified in

molecular analyses of 103 *T. pallidum* specimens obtained in Madagascar during an ongoing trial of the effectiveness of azithromycin for treatment of early syphilis [56].

Clinical presentation with A2058G *T. pallidum* has been associated with use of azithromycin or other macrolides by syphilis patients before receiving a syphilis diagnosis. In Seattle, A2058G specimens were obtained from 10 out of 18 (55.6%) of patients who had been administered any macrolides during the previous 12 months, as compared with 10/40 (25.0%) in those who had not ($P = 0.024$) [53**]. In San Francisco, 7/52 (13.5%) patients with A2058G specimens had been administered 1 g oral azithromycin for reasons unrelated to syphilis during the 30 days before onset of symptoms or diagnosis, as compared to 1/72 (1.4%) with sensitive specimens ($P < 0.01$) [28**].

Association with recent the use of azithromycin or other macrolides, and the increasing frequency of A2058G isolates, indicate that resistance probably reflects pressure on *T. pallidum* generated by use of macrolides for other indications, rather than the increased spread of a single mutant A2058G *T. pallidum* strain. Further support for this hypothesis is derived from molecular analyses, in which investigators in Seattle were able to distinguish two different strains of A2058G *T. pallidum* by presence or absence of an additional DNA sequence in the *T. pallidum* genome [53**]. The stability of that additional sequence over time was demonstrated in historic isolates of *T. pallidum*, supporting the hypothesis that the difference between the two strains was not the result of a recently acquired mutation [53**].

In San Francisco syphilis is commonly diagnosed in G/MSM and in persons co-infected with HIV. Not surprisingly, A2058G *T. pallidum* specimens have commonly been obtained from syphilis patients who are G/MSM and those who are co-infected with HIV. No data exist that indicate persons in those groups are at higher risk for acquiring A2058G strains. The largest sample of *T. pallidum* isolates from San Francisco included 118 patients, of whom 112 (95%) were MSM. All azithromycin treatment failures and all A2058G specimens were obtained from MSM [28**]. The proportion of MSM among patients with A2058G *T. pallidum* [46/46 (100%)], however, was not statistically significantly different from that among patients with azithromycin-sensitive specimens, of whom 66/72 (91.7%) were MSM ($P = 0.09$) [28**]. In that same sample, 13 out of 46 patients (28.3%) with A2058G *T. pallidum* were co-infected with HIV, as compared with 24/72 patients (33.3%) with sensitive specimens ($P = 0.53$).

Nonmacrolide alternatives

Resistance of *T. pallidum* to nonmacrolide alternatives to penicillin has not been reported.

Clinical and public health challenges

The emergence of resistance to macrolides poses clinical and public-health challenges to syphilis treatment and control efforts [57]. This is especially true for azithromycin, because simple, cost-effective treatment regimens are important components of a therapeutic armamentarium [57]. Such regimens might be especially useful in increasing access to syphilis treatment in developing countries, where injection equipment and medically trained personnel to administer penicillin injections might be scarce [9].

Antibiotic resistance in *T. pallidum* indicates that there is a need for continuous clinical and laboratory surveillance for antibiotic resistance. That surveillance need also reflects the continued, appropriate use of azithromycin and other macrolides for nonsyphilis indications. Such use has been associated with increasing proportions of resistance in *T. pallidum* specimens and is unlikely to decline on the basis resistance in *T. pallidum* alone.

Recently, the assay for azithromycin resistance has been enhanced, allowing use of real-time PCR to detect the A2058G mutation in hours without a required restriction-digestion step [35]. In areas where azithromycin might be used to treat syphilis, use of that enhanced PCR-based assay [35] for azithromycin resistance for surveillance and, possibly, for clinical management of patients with syphilis might be feasible. Data from the Gonorrhea Isolate Surveillance Program led the US CDC to recommend against continued use of quinolones to treat gonorrhea in MSM in 2004 [58] and in all patients in 2007 [59]. In areas where azithromycin might be used, the Gonorrhea Isolate Surveillance Program can serve as a model for azithromycin resistance surveillance efforts for syphilis and could contribute to ongoing national efforts to eliminate syphilis in the United States [12,18]. Additionally, rapid emergence of azithromycin resistance in *T. pallidum*, which has already precluded use of azithromycin in many areas of the USA, underscores the continued need to emphasize antibiotic drug development to treat syphilis and other infectious diseases [60,61].

Syphilis affects < 200 000 persons in the United States, and therefore new drugs being developed to treat syphilis can receive an 'orphan drug designation' from the Food and Drug Administration [62]. Such a designation confers certain advantages on the drug's developer, including tax incentives for clinical research, eligibility for grant funding, assistance with protocol development, waiver of Food and Drug Administration user fees, and 7 years of marketing exclusivity after approval or licensure [63]. Those benefits have not been sufficient in encouraging development, however. Further reforms in federal regu-

lations, funding priorities, or funding procedures might be necessary [60,61].

Conclusion

Penicillin G benzathine remains the treatment of choice for syphilis [5], but its administration requires intramuscular injection and desensitization of penicillin-allergic patients before treatment [5]. Other treatment options include tetracycline, doxycycline, azithromycin, and ceftriaxone, which can be useful in treating penicillin-allergic patients (not pregnant women). Except for ceftriaxone these treatments are oral therapies that do not require injections. Azithromycin has been the only antimicrobial that offers the possibility of single-dose, oral treatment for syphilis. Azithromycin might still be an appropriate treatment in areas—unlike San Francisco—where macrolide resistance is uncommon [5]. Treatment failures after azithromycin therapy (including documented azithromycin resistance in *T. pallidum* specimens obtained from patients who failed azithromycin therapy), however, indicate that use of azithromycin to treat syphilis should be undertaken with careful follow up and within the context of surveillance for treatment failures and azithromycin resistance. New drug development can lead to development of a single-dose, oral syphilis treatment that might increase compliance, improve partner treatment, and offer safe and cost-effective therapy for the United States and developing world. In the meantime, clinicians and public health practitioners should remain vigilant for treatment failures in syphilis.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 106–107).

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