Treatment Effectiveness of Azithromycin and Doxycycline in Uncomplicated Rectal and Vaginal Chlamydia trachomatis Infections in Women: A Multicenter Observational Study (FemCure)

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Background. Rectal infections with Chlamydia trachomatis (CT) are prevalent in women visiting a sexually transmitted infection outpatient clinic, but it remains unclear what the most effective treatment is. We assessed the effectiveness of doxycycline and azithromycin for the treatment of rectal and vaginal chlamydia in women.

Methods. This study is part of a prospective multicenter cohort study (FemCure). Treatment consisted of doxycycline (100 mg twice daily for 7 days) in rectal CT-positive women, and of azithromycin (1 g single dose) in vaginally positive women who were rectally untested or rectally negative. Participants self-collected rectal and vaginal samples at enrollment (treatment time-point) and during 4 weeks of follow-up. The endpoint was microbiological cure by a negative nucleic acid amplification test at 4 weeks. Differences between cure proportions and 95% confidence intervals (CIs) were calculated.

Results. We analyzed 416 patients, of whom 319 had both rectal and vaginal chlamydia at enrollment, 22 had rectal chlamydia only, and 75 had vaginal chlamydia only. In 341 rectal infections, microbiological cure in azithromycin-treated women was 78.5% (95% CI, 72.6%–83.7%; n = 164/209) and 95.5% (95% CI, 91.0%–98.2%; n = 126/132) in doxycycline-treated women (difference, 17.0% [95% CI, 9.6%–24.7%]; P < .001). In 394 vaginal infections, cure was 93.5% (95% CI, 90.1%–96.1%; n = 246/263) in azithromycin-treated women and 95.4% (95% CI, 90.9%–98.2%; n = 125/131) in doxycycline-treated women (difference, 1.9% [95% CI, –3.6% to 6.7%]; P = .504).

Conclusions. The effectiveness of doxycycline is high and exceeds that of azithromycin for the treatment of rectal CT infections in women.

Clinical Trials Registration. NCT02694497.

Keywords. women; Chlamydia trachomatis; rectal; treatment effectiveness.

There is an ongoing debate regarding the widespread use of a single dose of azithromycin for uncomplicated Chlamydia trachomatis (CT) infections [1], and especially for CT infections at the rectal site [2]. Rectal infections are commonly found in women [3–6]. In a meta-analysis, the summary prevalence of rectal CT in women attending sexual health services was 6% (95% confidence interval [CI], 3%–9%), and among those who tested positive for vaginal chlamydia, it was 68% (95% CI, 57%–80%) [7]. In women, rectal CT may indirectly pose a risk for adverse reproductive outcomes if rectal CT, by autoinoculation, infects the genital area [8, 9].

A 1-g single dose of azithromycin was found to be slightly less effective than 7 days of doxycycline (100 mg twice per day) for urogenital chlamydia (94% vs 97%) in randomized controlled clinical trials (RCTs) [10, 11]. Azithromycin was found substantially less effective than doxycycline for rectal chlamydia (83% vs 99%) in a meta-analysis of observational studies [12]. Nevertheless, in these rectal CT treatment studies, women are largely underrepresented and no rectal RCT data are available [12–15].

We assessed rectal and vaginal CT infections by nucleic acid amplification test (NAAT) in a large prospective multicenter
cohort (FemCure) of female patients treated with azithromycin or doxycycline. Treatment effectiveness by microbiological cure at week 4 was evaluated for both anatomical sites, adjusting for confounders. In addition, follow-up measurements, proxies for bacterial load, and culture were included to explore clinically relevant variations in the cure estimates. Findings contribute to CT management in women in the context of current clinical care.

METHODS

Study Design
This was a prospective cohort study (Figure 1) as part of the FemCure study, 2016–2017 [16].

Regular Sexually Transmitted Infection Clinic Care
Patients were recruited from regular sexually transmitted infection (STI) clinic care at 3 public health STI clinics in the Netherlands [17]. At the regular care STI clinic testing consultation (T−1), women were vaginally tested by NAAT, and women reporting unprotected anal sex (in the past 6 months) or current anal symptoms were also rectally tested by NAAT. At enrollment (T0), treatment was provided, based on the test result at T−1 [17]. Women who were rectally CT positive were treated with a 7-day course of oral doxycycline 100 mg twice daily. Vaginal CT–positive women who were rectally untested or rectally negative received a 1-g single oral dose of azithromycin; some patients with vaginal CT received doxycycline because of a contraindication to azithromycin. Azithromycin and the first doxycycline dose were directly observed.

Enrollment at Regular Care Treatment
Women were enrolled at T0, the treatment visit. Eligible were nonpregnant adult women (aged ≥18 years) who had a vaginal or rectal CT infection; were not infected with human immunodeficiency, syphilis, or Neisseria gonorrhoeae; and who had not used antibiotics since T−1. Participation started after written informed consent.

Study Sample Collection and Laboratory Analyses
Women collected rectal and vaginal swabs at enrollment (T0) immediately prior to treatment, and after 4 weeks (T1) at the STI clinic; women also collected samples at week 1 and week 2 at home [16]. Individual test results were not available to clinic staff and participants. Samples were tested using commercial NAAT platforms according to manufacturers’ instructions (COBAS 4800; Roche Diagnostics, Basel, Switzerland). The NAAT quantitation cycle (Cq) values were taken as a proxy for bacterial load [18]. Positive week 0 and 4 samples were cultured [19]. Week 4 NAAT-positive samples with a low Cq value (<31) were genotyped by multilocus sequence typing; the accompanying week 0 sample was also genotyped [20].

Demographic, Clinical, and Sexual Behavior Data
Data were collected [16] using structured online patient-administered questionnaires (weeks 0, 2, and 4) regarding antibiotic use, symptoms, and sexual practices in the 2 weeks preceding enrollment. At week 1, vomiting and doxycycline pill intake were assessed using an online questionnaire; participants were encouraged to notify the study nurse in case they had vomited or forgotten to take the doxycycline treatment. Clinical data were extracted from the patient registries.

Primary Outcome
The primary outcome was microbiological cure (ie, a negative NAAT at week 4) [12, 13].

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Figure 1. Study design. Abbreviations: STI, sexually transmitted infection; T−1, STI clinic testing consultation; T0, enrollment; T1, follow-up (week 4).
Statistical Analyses

Aim
To assess and compare the proportion of microbiological cure after doxycycline and azithromycin treatment, separately for rectal and vaginal chlamydia.

Infections Studied (Main Population)
The rectal and vaginal infections studied were based on the $T_0$ sample test results. Numbers of patients by their $T_1$ and $T_2$ results and treatment are presented in Supplementary Table 1.

Proportion of Microbiological Cure and Difference Between Treatments
The proportions of women with rectal chlamydia reaching microbiological cure were assessed for azithromycin and doxycycline. Proportions were compared between the 2 treatment groups, using 2-sided exact tests. Similar analyses were done for women with vaginal chlamydia. We present the difference in proportions with exact 95% CIs.

Potential Confounders for Treatment Effect
Treatment allocation was based on regular clinic care test results (at $T_0$), possibly leading to differences in enrollment characteristics between the treatment groups. To test for such differences, we compared treatment groups using the Mann-Whitney U test for continuous variables (age and Cq value) and a $\chi^2$ test for other variables. Also, using logistic regression analyses, the association between enrollment characteristics and the outcome (“not reaching microbiological cure”) was tested. Characteristics that were associated ($P < .10$) with treatment or with the outcome were considered possible confounders for the treatment effect.

Treatment Effect
Univariate logistic regression analyses were used to assess the association between treatment type and the inverse of the outcome (ie, “not reaching microbiological cure”) defined by a week 4 positive NAAT. In multivariate models, we adjusted for the identified potential confounders. Subgroup heterogeneity of associations was tested by including interaction terms (between age, education, migration background, and treatment type), but all interaction terms were not statistically significant.

Analyses in a Restricted Subset of the Main Population
To minimize potential bias. In some women, a positive NAAT at week 4 may indicate a reinfection after having unprotected sex or due to suboptimal antibiotic treatment intake. Conversely, additional antibiotic treatment during the study could have contributed to a negative NAAT at week 4. To minimize such potential bias, the main population was restricted to a subset that included only those women who reported the treatment according to the regular care protocol [16, 17]—that is, patients had to report at least a compliance of 10 doxycycline pills without direct (<3 hours) vomiting [11] or no vomiting after azithromycin intake. Furthermore, the subset did not include women who reported unprotected vaginal or anal sex, had missing questionnaire data, or received additional antibiotics after enrollment. In the subset, we evaluated microbiological cure as described above.

To assess and compare secondary outcomes in sensitivity analyses. We assessed secondary outcomes to explore clinically relevant variations in the estimates. A positive NAAT at week 4 possibly only indicates the presence of remnant CT DNA originating from dead chlamydia bacteria [21], and we hypothesized that a positive week 4 NAAT may in that case reflect an actual “true cure.” To approach this hypothetical situation, we redefined microbiological cure in 3 separate secondary outcomes:

1. Week 4 NAAT negative or week 4 NAAT positive with week 1 or week 2 NAAT negative [22, 23].
2. Week 4 NAAT negative or week 4 NAAT positive with a high Cq value (>36) as a proxy for low bacterial load [18].
3. Week 4 NAAT negative or week 4 NAAT positive with a negative culture, appreciating that this does not prove absence of viable CT, due to the low sensitivity of culture [19, 21].

All 3 secondary outcomes were taken as imperfect proxies for “true cure” and were used to compare proportions of microbiological cure.

Analyses were performed using SPSS package version 21 (IBM Corporation, Armonk, New York) and Stata version 13.1 software (StataCorp, College Station, Texas).

Ethical Considerations
All participants provided written informed consent. This study was approved by the Medical Ethical Review Committee from the Maastricht University Medical Centre, the Netherlands (NL51358.068.15/METC153020, 20-01-2016). This study was monitored by the Clinical Trial Centre Maastricht (Maastricht University).

RESULTS

Main Population
In total, 1763 women were invited to participate and 560 (31.8%) were enrolled. Of the participants, 36 were excluded from further analyses as they were NAAT negative at enrollment (some due to spontaneous clearance or perhaps initial remnant CT DNA detection). Of the 524 remaining women, 102 patients did not provide follow-up samples, and 6 patients had a missing sample at week 1, 2, or 4. After excluding these 108 women (20.6%), 416 women remained for analyses. Women included and excluded did not differ regarding care diagnosis, treatment type, reported anal or vaginal sex, and symptoms. However, in excluded women the proportion of
women with a medium or low education (87.0%) and with non-Western migration background (12%) was higher than in included women (69.7% [P < .001] for education and 6.0% [P = .042] for migration background). Excluded women were younger (median age, 21 years [interquartile range {IQR}, 20–23 years]) than included women (median, 23 years [IQR, 20–24 years]) (P < .001).

Of the 416 patients included in analyses, the median number of days between T₀ and T₁ was 8 (IQR, 7–12 days). Of the 416 patients, all sampled within 6 days of the planned 4-week time point (at 28 days posttreatment), and 407 (98%) patients sampled within 3 days. Of the 416 patients, 319 (76.7%) had a rectal and vaginal CT, 22 (5.3%) had a single rectal CT, and 75 (18.0%) had a single vaginal CT. In total, the women contributed 341 rectal infections and 394 vaginal infections (Figure 2). Table 1 and Supplementary Table 2 present characteristics at enrollment.

**Microbiological Cure in the Main Population**

Microbiological cure was 78.5% (95% CI, 72.6%–83.7%; n = 164/209) in azithromycin-treated rectal infections and 95.5% (95% CI, 90.1%–96.1%; n = 126/132) in doxycycline-treated rectal infections. The difference was 17.0% (95% CI, 9.6%–24.7%; P < .001) (Table 2).

Microbiological cure was 93.5% (95% CI, 90.1%–96.1%; n = 246/263) in azithromycin-treated vaginal infections and 95.4% (95% CI, 90.9%–98.2%; n = 125/131) of the doxycycline-treated vaginal infections (Table 2). The difference was 1.9% (95% CI, –3.6% to 6.7%; P = .504).

Supplementary Figure 1 shows the percentages of microbiological cure at the patient level.

**Treatment Effect Adjusted for Confounders in the Main Population**

In rectal CT, in the univariate logistic regression analyses, the odds for not reaching microbiological cure were 5.8 (95% CI, 2.4–13.9; P < .001) times higher for those treated with azithromycin than for those treated with doxycycline (Table 2). Adjusting for potential confounders (see next section) in the multivariate analyses, the odds ratio (OR) increased (OR, 9.4 [95% CI, 3.2–27.2]; P < .001). In vaginal CT, treatment type showed no association in univariate analyses (OR, 1.4 [95% CI, 0.6–3.7]; P = .455) or in multivariate analyses (OR, 1.4 [95% CI, 0.5–4.0]; P = .528) (Table 2).
Table 1. Characteristics of the Main Population at Enrollment by *Chlamydia trachomatis* Infection Site and by Treatment Regimen

| Characteristic at Enrollment | Rectal Infection at Enrollment | Vaginal Infection at Enrollment |
|-----------------------------|-------------------------------|--------------------------------|
|                             | Azithromycin (n = 209)        | Doxycycline (n = 132)          | PValue* |
|                             | Doxycycline (n = 131)         |                                |         |
| Study site                  |                               |                                |         |
| Clinic 1: South Limburg     | 91 (43.5)                     | 41 (31.1)                      | <.001   |
| Clinic 2: Rotterdam         | 65 (31.1)                     | 23 (17.4)                      |         |
| Clinic 3: Amsterdam         | 53 (25.4)                     | 68 (51.5)                      |         |
| Age, y, median (IQR)        | 22 (20–24)                    | 23 (21–25)                     | <.001   |
| Age, y, median (IQR)        | 22 (20–24)                    | 23 (21–25)                     | <.001   |
| Migration background        | .244                          | .365                           |         |
| Western                     | 193 (92.3)                    | 126 (95.5)                     |         |
| Non-Western                 | 16 (7.7)                      | 6 (4.5)                        |         |
| Educational level           |                               |                                | .001    |
| Low or medium               | 158 (75.6)                    | 78 (59.1)                      |         |
| High                        | 51 (24.4)                     | 54 (40.9)                      |         |
| Number of sex partners      |                               |                                | .099    |
| preceding 3 mo              | 78 (37.3)                     | 44 (33.8)                      |         |
| 0–1                         | 102 (48.8)                    | 56 (43.1)                      |         |
| 2–3                         | 29 (13.9)                     | 30 (23.1)                      |         |
| Previous episode of chlamydia reported | .822 | .888 | |
| No                          | 159 (76.1)                    | 99 (75.0)                      |         |
| Yes                         | 50 (23.9)                     | 33 (25.0)                      |         |
| Vaginal sex 2 wk preceding enrollment | .978 | .922 | |
| No                          | 100 (47.8)                    | 62 (47.7)                      |         |
| Yes                         | 109 (52.2)                    | 68 (52.3)                      |         |
| Anal sex 2 wk preceding enrollment | .003 | .015 | |
| No                          | 207 (99.0)                    | 121 (93.1)                     |         |
| Yes                         | 2 (1.0)                       | 9 (6.9)                        |         |
| Vaginal chlamydia at         |                               |                                | <.001   |
| enrollment                  | 1 (0.5)                       | 21 (15.9)                      |         |
| No                          | 208 (99.5)                    | 111 (84.1)                     |         |
| Yes                         | 55 (20.9)                     | 20 (15.3)                      |         |
| Rectal chlamydia at         |                               |                                | .172    |
| enrollment                  | NA                            | NA                             |         |
| No                          |                               |                                |         |
| Yes                         | 208 (79.9)                    | 111 (84.7)                     |         |
| Genital symptoms at         |                               |                                | .976    |
| enrollmentb                 | NA                            | NA                             |         |
| No                          |                               |                                |         |
| Yes                         | 153 (58.2)                    | 76 (58.0)                      |         |
| Anal symptoms at enrollmentb |                               |                                | <.001   |
| No                          | 193 (92.3)                    | 90 (68.2)                      |         |
| Yes                         | 16 (7.7)                      | 42 (31.8)                      |         |
| Vaginal CT NAAT Cq value at |                               |                                | .034    |
| enrollment, median (IQR)    | NA                            | NA                             |         |
| Rectal CT NAAT Cq value at  |                               |                                |         |
| enrollment, median (IQR)    | 35 (32–38)                    | 34 (30–37)                     |         |
| Vaginal CT culture positive  |                               |                                | .679    |
| at enrollment               | NA                            | NA                             |         |
| No                          |                               |                                |         |
| Yes                         | 204 (77.6)                    | 104 (79.4)                     |         |
| Rectal CT culture positive  |                               |                                | .182    |
| at enrollment               | NA                            | NA                             |         |
| No                          | 152 (72.7)                    | 87 (65.9)                      |         |
| Yes                         | 57 (27.3)                     | 45 (34.1)                      |         |
| Included in subsetc         |                               |                                | .852    |
| No                          | 96 (45.9)                     | 62 (47.0)                      |         |
| Yes                         | 113 (54.1)                    | 70 (53.0)                      |         |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Cq, quantitation cycle; CT, *Chlamydia trachomatis*; IQR, interquartile range; NA, not assessed; NAAT, nucleic acid amplification test.

*P* values for differences between the 2 treatment groups were determined using the Mann-Whitney U test for continuous variables (age and Cq value) and χ² test for all other characteristics.

Symptoms for vaginal CT: dysuria, irregular menstruation, lower abdominal pain, pain during intercourse, vaginal discharge; symptoms for rectal CT: anal discharge, anal blood loss during or after intercourse, pain during or after intercourse.

took azithromycin without direct vomiting (<3 hours) or took at least 10 doxycycline pills without direct (<3 hours) vomiting and did not receive additional treatment. They also had no unprotected anal sex, no unprotected vaginal sex, and no missing data on sexual practices during the 4 weeks after treatment.
TABLE 2. Proportions and Differences of Microbiological Cure for Azithromycin- or Doxycycline-treated Rectal and Vaginal Chlamydia trachomatis Infections, and the Treatment Effect (ie, the Odds of Azithromycin Compared to Doxycycline in Not Reaching Microbiological Cure) in the Main Population and the Restricted Subset

| Patients | Azithromycin | Doxycycline | Difference in % Cured | Treatment Effect |
|----------|--------------|-------------|-----------------------|------------------|
| Rectal chlamydia | | | | |
| All patients | 164/209 | 78.5 (72.6–83.7) | 126/132 | 95.5 (91.0–96.2) | 17.0 (9.6–24.7) | < .001 | 5.76 (2.38–13.93) | 9.38 (3.24–27.17) |
| Subsetb | 89/113 | 78.8 (70.6–85.6) | 68/70 | 97.1 (91.4–99.5) | 18.4 (8.7–27.5) | < .001 | 9.17 (2.09–40.14) | 18.51 (3.20–106.96) |
| Vaginal chlamydia | | | | |
| All patients | 246/263 | 93.5 (90.1–96.1) | 125/131 | 95.4 (90.9–98.2) | 1.9 (3.6 to 6.7) | .504 | 1.44 (0.55–3.74) | 1.40 (0.49–3.96) |
| Subsetb | 134/143 | 93.7 (88.9–96.9) | 69/72 | 95.8 (89.5–98.3) | 2.1 (–6.1 to 9.1) | .755 | 1.55 (0.41–5.89) | 0.89 (0.19–4.11) |

For rectal chlamydia, the OR was adjusted for study site, age, education, number of sexual partners, anal sex, vaginal Chlamydia trachomatis at enrollment, anal symptoms, prior chlamydia reported, quantitation cycle (Cq) value of the rectal nucleic acid amplification test (NAAT), and culture result of the rectal sample. For vaginal chlamydia, the OR was adjusted for study site, age, education, anal sex, number of sexual partners, Cq value of the vaginal NAAT test, and culture result of the vaginal sample.

Abbreviations: aOR, odds ratio adjusted for characteristics measured at enrollment; CI, confidence interval; no., number of patients with microbiological cure; No., total number of patients; OR, unadjusted odds ratio.

bThe subset included only participants who were treated according to the protocol and who reported no sex or safe sex only. This means that the subset (compared to all participants in analyses) did not include those who directly vomited after azithromycin, who did not take at least 10 doxycycline pills without direct vomiting, who received additional treatment, who reported unprotected anal sex, who reported unprotected vaginal sex, and those who had missing data on sexual behavior.

Confounders Adjusted for in Multivariate Analyses

Treatment groups differed regarding study site, age, education, number of sex partners, anal sex, single rectal infection, anal symptoms, and Cq NAAT value for rectal CT and regarding study site, age, education, and anal sex for vaginal CT (Table 1). Characteristics associated with “not reaching microbiological cure” were for rectal CT: no history of chlamydia, a lower Cq value, and a positive culture; for vaginal CT, these were a low or medium educational level, more sex partners, a lower Cq value, and a positive culture (Table 3).

Analyses in a Restricted Subset of the Main Population

Fourteen patients with CT at week 4 could be evaluated by sequence typing (13 rectal infections and 2 vaginal infections). All evaluated patients had the same genotype at week 4 compared with their week 0 sample (Supplementary Table 3). Excluding 190 patients from the main study population who were not treated according to the protocol or who reported unprotected sex, 226 patients remained in the subset analyses who contributed 183 rectal CT infections and 215 vaginal CT infections (Figure 2). Proportions of microbiological cure and differences between treatments were similar as described before for the main study population.

The week 1 and 2 NAAT results, the week 4 NAAT Cq values, and the week 4 culture results (Supplementary Table 3) were used to construct 3 secondary outcomes. Evaluating secondary outcomes (Supplementary Table 4), cure proportions for azithromycin-treated cases were 82%–91% for rectal CT and 94%–99% for vaginal CT. Cure proportions for doxycycline-treated cases were 97%–100% for rectal CT and 96%–100% for vaginal CT. The difference between treatments was 9%–15% for rectal CT and 1%–2% for vaginal CT.

DISCUSSION

This prospective observational multicenter study in outpatient STI clinic women assessed the effectiveness of doxycycline and azithromycin for the treatment of rectal and vaginal chlamydia. We observed high proportions of microbiological cure for doxycycline in rectal and vaginal CT and for azithromycin in vaginal CT. The proportion of rectal CT infections reaching microbiological cure was substantially and significantly lower for women treated with azithromycin.

Strengths of this study include the study population (women) for whom scarce rectal treatment data are available, the rigorous and detailed data collection conducted by assessing both rectal and vaginal CT, the comparison of 2 treatments within one study, and adjustment for putative confounders. With analyses in a subset, we aimed to further reduce bias due to suboptimal treatment compliance and possible CT reexposure. A unique feature of this study was the genotyping, the multiple time sequential sampling, Cq value assessment, and culture of week 4 samples. This allowed us to evaluate secondary outcomes that perhaps approximate more clinically relevant definitions of “true cure” as NAAT tests are highly sensitive and may detect remnant CT DNA from dead chlamydia. Doing so, the cure proportions remained substantially lower for azithromycin compared with doxycycline in rectal CT. Several posttreatment samples, especially in the azithromycin group, had consistent preceding positive samples, higher loads, or culture-positive results, which suggested or proved presence of viable posttreatment CT. Moreover, viable infections may have been missed by culture due to its low sensitivity. Enhanced viability testing may provide more clues on these issues, as planned in our future research [16, 19, 21].
We also recognize limitations. First, treatment was neither randomized nor blinded and confounding cannot be ruled out [12, 13]. Participants originated from STI clinic regular care practice [17], and this practice reflected in the study population (eg, doxycycline users more often reported anal sex and symptoms). We aimed to minimize confounding by performing analyses that adjusted for various potentially important determinants. Doing so, the treatment effect increased even more (rectal CT) or remained similar (vaginal CT).

Second, under- or overreporting of behaviors may have affected the findings. If doxycycline pill intake by participants was overreported, the actual proportion “cured” in doxycycline-treated cases may even be higher. Differential underreporting of anal sex in rectally positive azithromycin-treated women, women with a low educational level, and those with a non-Western migration background were less represented in the study population. This did, however, not affect the internal validity of the study as there was no subgroup heterogeneity of associations.

Third, as our NAAT did not have an internal human control, we could not rule out the possibility that negative NAAT results were due to inadequate self-sampling. However, a previous study showed that the majority (98.4%) of CT-negative samples contained human DNA and thus were considered as being adequately sampled [22].

Fourth, it is unknown whether our findings are generalizable to other STI clinic or non-STI clinic settings. Young women, women with a low educational level, and those with a non-Western migration background were less represented in the study population. This did, however, not affect the internal validity of the study as there was no subgroup heterogeneity of associations.

In both treatment groups and both anatomic sites there were cases with CT DNA detection after treatment. For azithromycin and doxycycline, it is yet unknown whether antibiotic concentrations are sufficiently high to cure high pretreatment bacterial loads. Heterotypic resistance has been previously associated with a higher bacterial load [25], in agreement with the observed association with the pretreatment Cq value in our study and in other studies [21, 26]. Still, the reasons for a lower cure proportion in azithromycin-treated rectal CT are unknown. In vitro,
CT strains showed higher minimum inhibitory concentration values of macrolides in colorectal compared with endocervical cells; this was not the case for doxycycline [27]. Others have suggested that a longer duration of azithromycin treatment may be the key to better target the specific CT life cycle [28].

The observed proportions of microbiological cure correspond with previous findings [10–12, 14, 15]. For azithromycin-treated rectal chlamydia, proportions are below the World Health Organization threshold of 95% recommended for a first-line treatment [29]. Rectal chlamydia is widely treated with azithromycin in the United States, but also in Europe and Australia where doxycycline is recommended [17]. This is because selective rectal testing policies result in many untested rectal infections that are coincidentally azithromycin-treated for vaginal CT [3, 6, 7]. Rectal testing is highly acceptable [4–6], and universal rectal testing has been found to be cost-effective in the STI clinic context [30]. Pooling of samples may contribute to reduced costs. When selective rectal testing of women remains the practice of choice, doxycycline use for vaginal CT may be considered as this would treat most rectal CT infections. Universal rectal testing as well as universal doxycycline use would provide a comprehensive (ie, vaginal and rectal) CT clinical management [4]. However, doxycycline use has limitations. It is contraindicated in pregnant women, which hampers its use as a simple treatment for all women. Furthermore, photosensitivity may occur with doxycycline use, although the occurrence of main side effects (minor gastrointestinal upset) was found to be similar between azithromycin (24%) and doxycycline (23%) [10]. Even though studies show consistently high doxycycline microbiological cure rates [10, 11, 14, 15] in the context of possible incomplete doxycycline pill intake, in routine clinical settings, compliance is a major issue in antibiotic regimens that require twice-daily administration for multiple days [31, 32]. We may need to seek practical care strategies to improve adherence, such as the use of text message reminders or online applications.

In conclusion, the results of this observational study indicate that the microbiological cure proportion of doxycycline exceeds that of azithromycin for the treatment of rectal CT infections in women.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. N. D. drafted the report and performed the statistical analyses. N. D., M. S., C. H., H. G., and H. V. designed the statistical analysis. P. W., M. L., and S. B. set up and performed the laboratory analyses. All authors reviewed the results; provided guidance on the method; and drafted, reviewed, and provided critical feedback on the report.

Acknowledgments. The authors thank the staff at the Public Health Service (GGD) South Limburg (Ronald van Hoorn, Marta Margelsberg, Mandy Saalmans, Emily Suijlen, Bianca Penders, Helen Sijstersmans, Ine de Bock, Julien Weijers, Patricia Zaamdant, Jeanine Leenen, Jeanne Heil, Stephanie Brinkhues, and Genevieve van Liere); the staff at GGD Rotterdam-Rijnmond (Astrid Wielemaker, Angie Martina, Roselyne Uwimana, Mieke Ildidge, and Klaas de Ridder); and the staff at GGD Amsterdam (Dicie Martini, Myra van Leeuwen, Claudia Owusu, Jacqueline Woutersen, Princella Felipa, Mayam Amezian, Arjdal Khadija, and Iris Deen), who were involved in the logistics, recruitment, and enrollment of the study. They also thank Martijn van Rooijen for data management, and Anders Boyd for statistical advice. They thank the staff at the laboratories of medical microbiology of the Maastricht University Medical Center, especially Judith Veugen, Laura Saelmans, and Kevin Janssen. Additionally, they thank the staff of the microbiological laboratory of the GGD Amsterdam, especially Esther Heuser and Michelle Himschoot. Finally, they thank the members of the advisory committee of this study for providing excellent input on the design of the study and feedback on this paper, from the National Institute for Public Health and the environment (Ian van Bergen, Birgit van Benthem) and from the University of Maastricht (Gerjo Kok and Servaas Moree).

Disclaimer. The funding source had no role in the writing or publication of this paper.

Financial support. This work was funded by a governmental organization grant from the Netherlands Organization for Health Research and Development (ZonMW Netherlands); ProjectID: 50-53000-98-109.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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