Routine universal testing versus selective or incidental testing for oropharyngeal *Neisseria gonorrhoeae* in women in the Netherlands

Citation for published version (APA):

van Liere, G. A. F. S., Dukers-Muijters, N. H. T. M., Kuizenga-Wessel, S., Wolffs, P. F. G., & Hoebe, C. J. P. A. (2021). Routine universal testing versus selective or incidental testing for oropharyngeal *Neisseria gonorrhoeae* in women in the Netherlands: a retrospective cohort study. *Lancet Infectious Diseases*, 21(6), 858-867. [https://doi.org/10.1016/S1473-3099\(20\)30594-6](https://doi.org/10.1016/S1473-3099(20)30594-6)

Document status and date:

Published: 01/06/2021

DOI:

[10.1016/S1473-3099\(20\)30594-6](https://doi.org/10.1016/S1473-3099(20)30594-6)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Routine universal testing versus selective or incidental testing for oropharyngeal *Chlamydia trachomatis* in women in the Netherlands: a retrospective cohort study

Ymke J Evers, Geneviève A F S van Liere, Nicole H T M Dukers-Muijters, Jan van Bergen, Sophie Kuizenga-Wessel, Christian J P A Hoebe

Summary

Background Pharyngeal *Chlamydia trachomatis* in women might contribute to autoinoculation and transmission to sexual partners. Data for effectiveness of different testing practices for pharyngeal *C trachomatis* are scarce. We therefore aimed to assess the prevalence of pharyngeal *C trachomatis*, determinants, and effectiveness of different testing practices in women.

Methods We did a retrospective cohort study, in which surveillance data for all women visiting sexually transmitted infection clinics in all regions in the Netherlands between Jan 1, 2008, and Dec 31, 2017, were used. We collected consultation-level data and individual-level data from 2016 onwards for sociodemographic characteristics, sexual behaviour in the past 6 months, self-reported symptoms, and STI diagnoses. The primary outcome was the positivity rate of pharyngeal *C trachomatis* infection compared between routine universal testing (>85% tested pharyngeally per clinic year), selective testing (5–85% tested pharyngeally per clinic year), and incidental testing (<5% pharyngeally tested per clinic year). We calculated the number of missed infections by extrapolating the positivity rate assessed by routine universal testing to all selectively tested women. We used multivariable generalised estimating equations logistic regression analyses to assess independent risk factors for pharyngeal *C trachomatis* and used the assessed risk factors as testing indicators for comparing alternative testing scenarios.

Findings Between Jan 1, 2008, and Dec 31, 2017, a total of 550 615 consultations with at least one *C trachomatis* test was recorded, of which 541 945 (98·4%) consultations (including repeat visits) were included in this analysis. Pharyngeal *C trachomatis* positivity was lower in the routine universal testing group than in the selective testing group (1081 [2·4%; 95% CI 2·2–2·5] of 45 774 vs 3473 [2·9%; 2·8–3·0] of 121 262; $p < 0·0001$). The positivity rate was also higher among consultations done in the incidental testing group (44 [4·1%; 95% CI 3·1–5·5] of 1073; $p < 0·0001$) than in the routine universal testing group. Based on extrapolation, selective testing would have hypothetically missed 64·4% (95% CI 63·5–65·3; 6363 of 9879) of the estimated total of *C trachomatis* infections. The proportion of pharyngeal-only *C trachomatis* was comparable between routinely universally tested women (22·9%) and selectively tested women (20·4%), resulting in a difference of 2·5% (95% CI –0·3 to 5·3; $p = 0·07$). When using risk factors for pharyngeal *C trachomatis* as testing indicators, 15 484 (79·6%) of 19 459 women would be tested to detect 398 (80·6%) of 494 infections.

Interpretation No optimal testing scenario was available for pharyngeal *C trachomatis*, in which only a selection of high-risk women needs to be tested to find most pharyngeal *C trachomatis* infections. The relative low prevalence of pharyngeal-only *C trachomatis* (0·5%) and probably limited clinical and public health effect do not provide support for routine universal testing.

Funding Public Health Service South Limburg.

Copyright © 2021 Published by Elsevier Ltd. All rights reserved.

Introduction

Chlamydia trachomatis is the most reported bacterial sexually transmitted infection (STI) in the world, with highest occurrence in people younger than 25 years.^{1,2} *C trachomatis* is a bacterium that can be easily transmitted and can result in pelvic inflammatory disease, ectopic pregnancy, tubal infertility, and chronic abdominal pain in women.^{3,4} The control of *C trachomatis* remains a continuous public health challenge as many infections remain hidden to care and ongoing transmission is still ubiquitous.

Extragenital infections, in this case pharyngeal *C trachomatis*, might contribute to ongoing transmission to sexual partners from the male pharynx to the male urethra⁵ and from the female pharynx to the male urethra.⁶ Some studies in animals suggest that pharyngeal *C trachomatis* possibly also transmits to their own genital or rectal site via the gastrointestinal tract.^{7,8} Evidence for autoinoculation in humans is absent. Pharyngeal exposure can be operationalised as unprotected oral sex, which is highly prevalent in women. A large representative Dutch cohort study

Lancet Infect Dis 2021

Published Online
December 14, 2021
[https://doi.org/10.1016/S1473-3099\(21\)00465-5](https://doi.org/10.1016/S1473-3099(21)00465-5)

See Online/Comment
[https://doi.org/10.1016/S1473-3099\(21\)00581-8](https://doi.org/10.1016/S1473-3099(21)00581-8)

Department of Sexual Health, Infectious Diseases and Environmental Health, South Limburg Public Health Service, Heerlen, Netherlands (Y J Evers PhD, G A F S van Liere PhD, N H T M Dukers-Muijters PhD, Prof C J P A Hoebe PhD); Department of Social Medicine and Medical Microbiology (Y J Evers, G A F S van Liere, Prof C J P A Hoebe) and Department of Health Promotion (N H T M Dukers-Muijters), School of Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, Netherlands; Faculty of Medicine, University of Amsterdam, Amsterdam, Netherlands (Prof J van Bergen PhD); Department of Sexual Health, Public Health Service Haaglanden, Hague, Netherlands (S Kuizenga-Wessel PhD)

Correspondence to:
Dr Ymke J Evers, Department of Sexual Health, Infectious Diseases and Environmental Health, South Limburg Public Health Service, Heerlen 6411 TE, Netherlands
ymke.evers@ggzdl.nl

Research in context

Evidence before this study

We searched PubMed from database inception to Feb 22, 2021, for studies of pharyngeal testing for *Chlamydia trachomatis* in women published in English. Search terms related to infection ("chlamydia", "chlamydia trachomatis", "C trachomatis") were combined with anatomic site terms ("oral", "pharyngeal diseases", "pharynx", "oropharyngeal", "oropharynx") and gender ("women", "female"). Additionally, we searched reference lists of selected studies. Our search yielded 18 studies. Few studies assessed pharyngeal *C trachomatis* in women, with the few published studies focusing on certain risk groups, such as female sex workers and women reporting extragenital exposures. No studies included routine universal testing of a large, non-selected group of women attending sexual health-care services. This gap in evidence hinders thorough evaluation of the testing policy for pharyngeal *C trachomatis* in women.

Added value of this study

This study used a large cohort of national sexually transmitted infection (STI) clinic data of the Netherlands (2008–17). Several Dutch STI clinics have implemented routine universal pharyngeal testing in women. These data provide the unique opportunity to assess the prevalence based on all pharyngeal *C trachomatis* infections in women, including the proportion of pharyngeal-only *C trachomatis* infection; evaluate three currently used testing practices in Dutch STI clinics, including routine universal testing (>85% tested pharyngeally per clinic-year), selective testing (5–85%), and incidental testing (≤5%); and compare alternative testing scenarios based on

independent risk factors for both pharyngeal *C trachomatis* and pharyngeal-only *C trachomatis* by estimating the proportion tested and the proportion missed for pharyngeal *C trachomatis* infections per scenario. This study hereby provides a comprehensive overview of pharyngeal *C trachomatis* in women.

Implications of all the available evidence

Our study shows that pharyngeal *C trachomatis* positivity was lower using routine universal testing (2.4%) compared with selective testing (2.9%). However, selective testing in practice would hypothetically have missed two-thirds of the estimated total of pharyngeal *C trachomatis* infections. Approximately one-in-five of these missed infections would have been pharyngeal-only *C trachomatis* cases and four-in-five would have been concurrent with an anogenital infection. Most pharyngeal *C trachomatis* infections would have been treated concurrently with anogenital infections. When comparing alternative testing scenarios based on independent risk factors of pharyngeal *C trachomatis*, no optimal testing scenario is available in which only a selection of high-risk women needs to be tested to find the vast majority of infections. Only routine universal testing would be able to detect all pharyngeal *C trachomatis* infections. However, the probably limited clinical and public health effect and risk of overtreatment do not support choosing routine universal testing as the best testing strategy. The benefit-to-risk ratio of finding and treating all pharyngeal *C trachomatis* infections needs to be further studied to determine whether routine universal testing should be preferred to no testing at all.

showed that 34% of adolescents and 69% of young adults had experience with oral sex, and almost all oral sex was without consistent condom use.⁹ In a US study using a national probability sample, 75% of women aged 15–44 years reported oral sex and only 6% reported condom use at last oral sex.¹⁰ The prevalence of pharyngeal *C trachomatis* has been estimated to be 0.2–3.2% (median 1.7%) among women, mostly based on STI clinic sites.¹¹ Pharyngeal *C trachomatis* can cause symptoms of a mild pharyngitis or lymphadenitis in 2–5% of cases, but pharyngeal infections mostly remain asymptomatic.¹² Pharyngeal *C trachomatis* can be detected by nucleic acid amplification tests (NAAT)¹³ and can effectively be treated with azithromycin or doxycycline.¹⁴ Pharyngeal-only *C trachomatis* infections—ie, without concurrent anogenital *C trachomatis*—are most important as they are not coincidentally treated with concurrent anogenital infections. In a Dutch study among 164 women being diagnosed with pharyngeal *C trachomatis*, pharyngeal-only *C trachomatis* was present in 32%.¹² When only testing at the genital or rectal site, these isolated infections remain undetected and untreated. Detection of pharyngeal *C trachomatis* and treatment of pharyngeal-only *C trachomatis* fully depend on testing policy and practice.

International STI guidelines for pharyngeal *C trachomatis* testing in women differ per country and health-care provider,^{15–17} but mostly recommend selective pharyngeal *C trachomatis* testing based on pharyngeal exposure risk groups such as sex workers.¹⁸ Data for effectiveness of selective screening practices in terms of established, missed, and untreated infections are scarce. Since 2010, several Dutch STI clinics have implemented routine universal pharyngeal testing in women. Data from these clinics provide a unique opportunity to assess the optimal testing practice for pharyngeal *C trachomatis* in men who have sex with men visiting STI clinics.

In this study, we aimed to provide insight in all pharyngeal *C trachomatis* infections in women visiting the STI clinic, including the positivity rate of pharyngeal *C trachomatis* and the proportion of pharyngeal-only *C trachomatis*; evaluate testing practices in Dutch STI clinics, including routine universal testing, selective testing, and incidental testing; and compare alternative testing scenarios based on independent risk factors.

Methods

Study design

We did a retrospective cohort study, in which we used coded surveillance consultations from all STI outpatient

clinics in the Netherlands (25 public health services with 38 STI clinic locations; also known as Centers for Sexual Health) that were submitted to the National Institute for Public Health and Environment via an electronic patient registry between Jan 1, 2008, and Dec 31, 2017. Reporting of data to this national institute is standardised and mandatory for all STI clinics. The publicly funded Dutch STI clinics serve high-risk groups, including individuals who are 24 years or younger, men who have sex with men, sex workers, individuals with a history of an STI diagnosis in the past year, individuals from STI-endemic countries, individuals notified for any STI, and individuals with STI-related symptoms. We extracted consultation-level data, and individual-level data from 2016 onwards, for sociodemographic characteristics, sexual behaviour in the past 6 months, self-reported symptoms, and STI diagnoses for the entire study period. Data for self-reported oral sex were available from 2016. Consultations with at least one *C trachomatis* test were included in this study. Exclusion criteria were the use of pooled samples—ie, mixing genital, rectal, and pharyngeal test samples in one sample—and implausible values on used variables.

Before 2015, Dutch guidelines advocated selective testing for pharyngeal *C trachomatis* in women who reported receptive, unprotected oral sex, or pharyngeal symptoms. Since 2015, pharyngeal testing has been recommended in women who were notified for any STI, reported sex work, or reported protected anogenital sex in combination with unprotected oral sex. Regardless of these guidelines, we classified three testing practices based on the proportion of consultations in which a pharyngeal test was done in an STI clinic during 1 clinic year. The classification was based on practical experience used in previous research.¹⁹ A clinic calendar year was defined as routine universal testing when more than 85% of the women attending the clinic that year (starting in January) were tested for pharyngeal *C trachomatis*. A clinic calendar year was defined as selective testing when 5–85% of women were tested pharyngeally and a clinic calendar year was defined as incidental testing when less than 5% was tested. Although routine universal testing implies pharyngeal testing of all women, achieving 100% coverage has been proven unfeasible in practice—eg, in individuals opting out of pharyngeal testing.

The Medical Ethics Committee of Maastricht University (METC 2017-0251) waived the requirement for ethical approval and written informed consent because the data used were coded, originated from standard care, and were analysed anonymously.

Procedures

All women who presented to the STI clinic were tested for *C trachomatis* at the genital site. The testing policy for rectal *C trachomatis* is comparable to the testing policy of pharyngeal *C trachomatis* except that all women reporting

receptive anal sex have an indication for rectal testing. *C trachomatis* positivity at any site was defined as being positive on NAAT. Although commercial *C trachomatis* assays had not yet been licensed to test pharyngeal specimens at the time of data collection for this study, NAATs had been shown to have sufficient sensitivity for the detection of pharyngeal infections.¹³ All STI clinics used NAAT for diagnoses. All women who presented to the STI clinic were also tested for *Neisseria gonorrhoeae*, according to the same testing procedures as for *C trachomatis*. Only women from high-risk groups were tested for syphilis (any stage) and HIV infection. High-risk groups included sex workers, women from STI-endemic countries, and women who were notified for any STI. Specimens were tested in regional laboratories using different commercially available diagnostic assays. All tests were done according to the manufacturers' protocols.

Outcomes

The primary outcome was the positivity rate of pharyngeal *C trachomatis*, defined as the number of positive tests divided by the total number of tests. For the secondary outcome, pharyngeal infections were categorised as pharyngeal-only or concurrent with genital or rectal infections, which was defined as the proportion of pharyngeal-only *C trachomatis* in the total number of pharyngeal *C trachomatis* infections. Primary and secondary outcomes were assessed among the total number of included consultations and compared between different testing practices. Additionally, in the routinely universally tested group, the positivity rate of pharyngeal *C trachomatis* and the proportion of pharyngeal-only *C trachomatis* in the total number of *C trachomatis* infections were calculated. Additional prespecified analyses that assessed risk factors for pharyngeal and pharyngeal-only *C trachomatis* and compared alternative testing scenarios based on these risk factors were done on a subset of the data, including consultations in the routinely universally tested group between Jan 1, 2016, and Dec 31, 2017. From 2016, two additional variables were available in the electronic patient registry: self-report of oral sex and a personal identifier, which enabled us to control for repeated measurements of patients that visited the STI clinic multiple times during the study period.

Statistical analysis

We calculated the positivity rate of pharyngeal *C trachomatis* using the following equation:

$$\text{Positivity rate of pharyngeal } C \text{ trachomatis} = \left(\frac{\text{Number of positive tests}}{\text{Total number of tests}} \right) \times 100$$

The positivity rate was calculated per testing practice and we compared the positivity rates between testing practices using χ^2 tests.

	Routine universal testing (51 293 consultations)	Selective testing (411 636 consultations)	Incidental testing (79 016 consultations)
Proportion of consultations with pharyngeal testing	45 774 (89.2%)	121 262 (29.5%)	1073 (1.4%)
Age (years)	23 (22–25)	23 (22–25)	23 (21–25)
Age group (years)			
<31	16 758 (32.7%)	136 494 (33.2%)	27 255 (34.5%)
31–43	18 411 (35.9%)	154 873 (37.6%)	30 043 (38.0%)
>43	16 124 (31.4%)	120 269 (29.2%)	21 718 (27.5%)
Ethnicity			
Western	35 125/51 251 (68.5%)	338 693/408 852 (82.8%)	70 925/78 771 (90.0%)
Non-western	16 126/51 251 (31.5%)	70 159/408 852 (17.2%)	7846/78 771 (10.0%)
Number of sexual partners in the past 6 months			
<4	16 890/51 291 (32.9%)	121 603/411 631 (29.5%)	28 290/79 014 (35.8%)
4–8	20 530/51 291 (40.0%)	170 785/411 631 (41.5%)	32 764/79 014 (41.5%)
>8	13 871/51 291 (27.0%)	119 243/411 631 (29.0%)	17 960/79 014 (22.7%)
Sex worker	4767/44 984 (10.6%)	34 419/359 432 (9.6%)	3780/70 433 (5.4%)
Swinger*	961/32 998 (2.9%)	14 727/187 316 (7.9%)	3454/44 074 (7.8%)
Notified of any STI	7186/51 072 (14.1%)	53 594/409 928 (13.1%)	8954/78 812 (11.4%)
STI-related symptoms	15 308/51 040 (30.0%)	136 289/408 595 (33.4%)	19 662/77 878 (25.2%)
Condom use during last anogenital sex	12 746/49 284 (25.9%)	93 992/387 670 (24.2%)	16 551/66 480 (24.9%)
Oral sex†	18 150/20 879 (86.9%)	70 578/84 729 (83.3%)	7390/9020 (81.9%)
<i>C trachomatis</i>			
Pharyngeal	1081/45 774 (2.4%)	3473/121 262 (2.9%)	44/1073 (4.1%)
Pharyngeal-only	248/45 774 (0.5%)	708/121 262 (0.6%)	25/1073 (2.3%)
Urogenital	6886/51 237 (13.4%)	49 968/411 178 (12.2%)	9604/78 969 (12.2%)
Anorectal‡	2418/18 848 (12.8%)	9875/83 958 (11.8%)	474/4175 (11.4%)
Any site	7558/51 293 (14.7%)	52 514/411 636 (12.8%)	9734/79 016 (12.3%)
<i>Neisseria gonorrhoeae</i>			
Urogenital	1074/51 231 (2.1%)	4584/388 932 (1.2%)	685/73 794 (0.9%)
Anorectal§	314/18 821 (1.7%)	1216/96 554 (1.3%)	76/4254 (1.8%)
Pharyngeal	620/45 759 (1.4%)	1734/123 886 (1.4%)	94/3888 (2.4%)
Any site	1420/51 293 (2.8%)	5764/411 636 (1.4%)	754/73 839 (1.0%)
HIV			
Untested	13 597 (26.5%)	122 675 (29.8%)	23 553 (29.8%)
Negative	37 651 (73.4%)	288 392 (70.1%)	55 361 (70.1%)
Known positive	26 (0.1%)	415 (0.1%)	72 (0.1%)
First positive test	19 (<0.1%)	154 (<0.1%)	30 (<0.1%)
Syphilis			
Untested	13 490 (26.3%)	114 798 (27.9%)	20 644 (26.1%)
Negative	37 774 (73.6%)	296 663 (72.1%)	58 332 (73.8%)
Positive	29 (0.1%)	175 (<0.1%)	40 (0.1%)

Data are n (%), median (IQR), or n/N (%). STI=sexually transmitted infection. *A swinger was someone who self-identified as part of a heterosexual couple who had sex with each other and as a couple with other heterosexual couples and self-identified heterosexual sex partners. These individuals were classified as men who have sex with men, as they reported male-to-male sex in the past 6 months. †Data for oral sex was only available between 2016 and 2017. ‡The proportion tested for anorectal *C trachomatis* was 5.3% (4175 of 79 016) for incidentally tested women, 20.4% (83 958 of 411 636) for selectively tested women, and 36.7% (18 848 of 51 293) for routinely universally tested women. §The proportion tested for anorectal *N gonorrhoeae* was 5.4% (4254 of 79 016) for incidentally tested women, 23.5% (96 554 of 411 636) for selectively tested women, and 36.7% (18 821 of 51 293) for routinely universally tested women.

Table 1: Characteristics of consultations (n=541 945) attended by women at STI clinics in the Netherlands for 2008–17 by pharyngeal *Chlamydia trachomatis* testing practice

The proportion of pharyngeal-only *C trachomatis* was calculated with the following equation:

$$\text{Proportion of pharyngeal-only } C \text{ trachomatis} = \left(\frac{\text{Number of pharyngeal-only } C \text{ trachomatis}}{\text{Total number of pharyngeal } C \text{ trachomatis}} \right) \times 100$$

The proportion was calculated per testing scenario and we compared the proportions between testing practices using χ^2 tests. The number of pharyngeal *C trachomatis* infections missed using selective testing in clinic years, including 95% CIs, was estimated by extrapolating the positivity rate found using routine universal testing in clinic years to that of all consultations in clinic years defined as selective, including those without pharyngeal testing. Routine universal testing is considered the reference testing practice because results represent all women visiting STI clinics without any preselection on the basis of risk behaviour. For this extrapolation, all consultations in clinic years defined as selective testing were weighted to match all consultations in clinic years defined as routine pharyngeal testing for the following variables: ethnicity (western vs non-western), sex work in the past 6 months, and being notified for any STI. Missing values for these variables were imputed with age as a predictor variable using chained equations imputation. The weighted dataset was analysed using the complex sample module in SPSS (version 21.0.0).

Univariable and multivariable logistic regression analyses using generalised estimating equations were used to identify independent determinants for pharyngeal *C trachomatis* and pharyngeal-only *C trachomatis* in the routinely universally tested group. These analyses were done on a subset of the data, including consultations in the routinely universally tested group between Jan 1, 2016, and Dec 31, 2017. A personal identifier enabled us to control for repeated measurements of patients that visited the STI clinic multiple times during the study period by using generalised estimating equations.²⁰ The variables assessed were age (≤ 21 years vs 22–25 years vs ≥ 26 years, based on tertile distribution), ethnicity (western vs non-western), number of sexual partners in the past 6 months (none or one vs two or three vs ≥ 4 , based on tertile distribution), reporting sex work in the past 6 months, being notified for any STI by a previous partner (partner notification), condom use during last receptive anogenital sex, reporting any symptoms, reporting oral sex, co-infection with *N gonorrhoeae*, and concurrent *C trachomatis* infection. Ethnicity was based on self-reported country of birth by clients and country of birth of their parents. Western ethnicity included those who were born in Europe (excluding Turkey), North America, Oceania, Indonesia, or Japan. Non-western ethnicity included individuals who were either born in or at least one of their parents

was born in Africa, Latin America, Asia (excluding Indonesia and Japan), or Turkey, as defined by Statistics Netherlands.²¹ If the proportion of missing data for a variable was more than 5%, a separate category was included in the analyses. If the proportion of missing data was less than 5%, user-missing values were excluded from analyses. All variables were entered in the multivariable analyses and all multivariable analyses were adjusted for STI clinic region and year of testing.

To compare alternative testing scenarios for selective testing, we constructed three hypothetical testing scenarios: (1) according to the current Dutch guidelines, (2) variables independently associated with pharyngeal *C trachomatis* determined in this study, and (3) reported sexual behaviour (presumably condomless oral sex). The current Dutch guidelines had three indicators: being notified for any STI, reported sex work, or reported condom use during anogenital sex in combination with no condom use during oral sex. We operationalised the third indicator of this guideline as condom use during last anogenital sex and having oral sex. No data were available for condom use during oral sex, but we expected this omission to be an appropriate operationalisation, as condom use is expected to be low during oral sex.¹⁰ These testing scenarios were compared for on the basis of the number of pharyngeal *C trachomatis* tests needed, the proportion of infections diagnosed, and the proportion of infections missed for both pharyngeal *C trachomatis* and pharyngeal-only *C trachomatis* infections in the 2016–17 subset of data.

We did all analyses using SPSS (version 21.0.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2008, and Dec 31, 2017, 550 615 consultations with at least one *C trachomatis* test was recorded, of which 541 945 (98.4%) consultations (including repeat visits) were included in this analysis. 8670 (1.6%) consultations were excluded because they were from STI clinics that used only pooled samples in testing (n=8612) or because of an implausible age value (eg, >100 years; n=58). The median age in the included consultations was 23.0 years (IQR 21.0–27.0 years) and 444 743 (82.5%) of 538 874 had a western ethnicity (table 1). A median of two sexual partners (IQR 1–4) in the past 6 months was reported. Overall, 168 109 consultations involved a pharyngeal test, of which 4598 (2.7%) consultations reported a positive test result. Of 541 945 consultations, 51 293 (9.5%) were done in clinic years defined as routine universal pharyngeal testing (>85% pharyngeally tested), 411 636 (76.0%) in clinic years defined as selective testing (5–85% pharyngeally tested), and 79 016 (14.6%) in clinic years defined as incidental testing (<5% pharyngeally tested). The mean proportion of

Figure: Anatomic site distribution of all pharyngeal *Chlamydia trachomatis* infections in women stratified by testing practice

1081 (2.4%) of 45 774 women in the routine testing group, 3473 (2.9%) of 121 262 women in the selective testing group, and 44 (4.1%) of the 1073 women in the incidental testing group were positive for pharyngeal *C trachomatis*.

consultations tested for pharyngeal infection per clinic year was 89.2% (SD 0.31) for routine universal testing, 29.5% (0.46) for selective testing, and 1.4% (0.12) for incidental testing.

The positivity rate of pharyngeal *C trachomatis* infection was lower in the routine universal testing group than in the selective testing group (1081 [2.4%; 95% CI 2.2–2.5] of 45 774 vs 3473 [2.9%; 2.8–3.0] of 121 262; $p < 0.0001$). The positivity rate was also higher among consultations done in the incidental testing group (44 [4.1%; 95% CI 3.1–5.5] of 1073; $p < 0.0001$) than in the routine universal testing group. In routinely universally tested women, pharyngeal infections comprised 1081 (14.3%) of 7558 of all *C trachomatis* infections. The positivity rate of the routine universal testing group (2.4%) was extrapolated to all consultations in clinic years defined as selective testing, including those without pharyngeal testing (n=411 636). This extrapolation resulted in 9879 estimated infections, of which 3516 (35.6%) were diagnosed using selective testing in clinical practice. Based on this extrapolation, selective testing would have hypothetically missed 64.4% (95% CI 63.5–65.3; 6363 of 9879) of the estimated total number of pharyngeal *C trachomatis* infections. Weighted estimates were fully comparable to unweighted samples (appendix), by showing that 65.2% of infections were missed in the selective testing group.

Of the 1081 consultations in the routine universal testing group in which a pharyngeal *C trachomatis* infection was identified, 248 (22.9% [95% CI 20.5–25.5]) included pharyngeal-only infections. Of 3473 consultations with pharyngeal *C trachomatis* in the selectively tested group, 708 (20.4% [95% CI 19.1–21.8]) included pharyngeal-only infections. A difference of 2.5% (95% CI –0.3 to 5.3; $p = 0.07$) was assessed between the routine universal testing group and the selectively tested group for the proportion of pharyngeal-only *C trachomatis*. The proportion of pharyngeal-only infections was higher in incidentally tested women compared with routinely

See Online for appendix

	Pharyngeal <i>C trachomatis</i> positive			Pharyngeal-only <i>C trachomatis</i> positive		
	Number of infections	OR (95% CI)	Adjusted OR (95% CI)	Number of infections	OR (95% CI)	Adjusted OR (95% CI)
Age (years)						
≤21	237/6254 (3.8%)	2.9 (2.2–3.8)	1.7 (1.3–2.3)	31/6254 (0.5%)	1.1 (0.6–1.9)	1.1 (0.7–1.9)
22–25	181/7556 (2.4%)	1.8 (1.4–2.4)	1.5 (1.1–2.0)	39/7556 (0.5%)	1.2 (0.7–1.9)	1.2 (0.7–2.1)
≥26	76/5649 (1.3%)	1 (ref)	1 (ref)	25/5649 (0.4%)	1 (ref)	1 (ref)
Ethnicity						
Non-Western	150/6372 (2.4%)	0.9 (0.7–1.1)	1.0 (0.8–1.3)	33/6372 (0.5%)	1.1 (0.7–1.7)	1.2 (0.8–1.9)
Western	344/13 077 (2.6%)	1 (ref)	1 (ref)	62/13 077 (0.5%)	1 (ref)	1 (ref)
Number of sexual partners in the past 6 months						
1	124/5880 (2.1%)	1 (ref)	1 (ref)	26/5880 (0.4%)	1 (ref)	1 (ref)
2–3	211/8168 (2.6%)	1.2 (0.9–1.5)	1.1 (0.9–1.4)	41/8168 (0.5%)	1.1 (0.7–1.9)	1.2 (0.7–1.9)
≥4	159/5411 (2.9%)	1.4 (1.1–1.8)	1.5 (1.2–2.0)	28/5411 (0.5%)	1.2 (0.7–2.0)	1.3 (0.7–2.6)
Sex worker						
Yes	30/1985 (1.5%)	0.6 (0.4–0.8)	1.1 (0.7–1.8)	9/1985 (0.5%)	0.9 (0.4–2.0)	1.1 (0.5–2.7)
No or unknown	464/17 437 (2.7%)	1	1	86/17 437 (0.5%)	1 (ref)	1 (ref)
Notified of any STI						
Yes	194/3512 (5.5%)	3.1 (2.5–3.7)	1.7 (1.4–2.0)	21/3512 (0.6%)	1.3 (0.8–2.1)	1.3 (0.8–2.2)
No	300/15 929 (1.9%)	1 (ref)	1 (ref)	74/15 929 (0.5%)	1 (ref)	1 (ref)
Condom used during last anogenital sex						
Yes	82/4306 (1.9%)	1 (ref)	1 (ref)	13/4306 (0.3%)	1 (ref)	1 (ref)
Unknown	38/1076 (3.5%)	1.9 (1.3–2.8)	1.8 (1.1–2.8)	4/1076 (0.4%)	1.1 (0.3–4.0)	0.9 (0.2–3.5)
No	374/14 077 (2.7%)	1.4 (1.1–1.8)	1.1 (0.8–1.4)	78/14 077 (0.6%)	1.8 (1.0–3.3)	2.0 (1.1–3.7)
Oral sex						
Yes	465/18 028 (2.6%)	1.3 (0.9–1.9)	1.2 (0.8–1.8)	89/18 028 (0.5%)	1.2 (0.5–2.9)	1.2 (0.5–2.7)
No	20/1114 (1.8%)	1 (ref)	1 (ref)	5/1114 (0.4%)	1 (ref)	1 (ref)
Symptoms						
Yes	168/5930 (2.8%)	1.2 (1.0–1.4)	1.0 (0.8–1.2)	24/5930 (0.4%)	0.8 (0.5–1.2)	0.7 (0.5–1.2)
No	326/13 502 (2.4%)	1 (ref)	1 (ref)	71/13 502 (0.5%)	1 (ref)	1 (ref)
<i>C trachomatis</i>						
Urogenital						
No	125/16 593 (0.8%)	1 (ref)	1 (ref)	NA	NA	NA
Yes	369/2855 (12.9%)	19.6 (15.9–24.1)	10.4 (7.7–14.3)	NA	NA	NA
Anorectal†						
No	89/10 284 (0.9%)	1 (ref)	1 (ref)	NA	NA	NA
Yes	227/1608 (14.1%)	21.0 (16.1–27.3)	2.5 (1.7–3.6)	NA	NA	NA
<i>Neisseria gonorrhoeae</i>						
Urogenital						
No	475/19 048 (2.5%)	1 (ref)	1 (ref)	94/19 048 (0.5%)	NA	NA
Yes	19/399 (4.8%)	2.0 (1.2–3.1)	1.0 (0.6–1.7)	1/399 (0.3%)	NA	NA
Anorectal‡						
No	299/11 709 (2.6%)	1 (ref)	1 (ref)	63/11 709 (0.5%)	NA	NA
Yes	7/164 (4.3%)	1.7 (0.8–3.7)	0.5 (0.2–1.2)	0/164	NA	NA
Pharyngeal‡						
No	485/19 239 (2.5%)	1 (ref)	1 (ref)	94/19 239 (0.5%)	NA	NA
Yes	8/214 (3.7%)	1.5 (0.8–3.1)	1.1 (0.5–2.2)	1/214 (0.5%)	NA	NA

Data are n/N (% within groups), unless otherwise specified. The variables swinger, co-infection with HIV, and co-infection with syphilis were not included in the analyses due to too few cases. All multivariable analyses were adjusted for STI clinic region (of which there were two) and year of testing. The intraclass correlation coefficient of –0.006 when using pharyngeal *C trachomatis* as an outcome and –0.003 when using pharyngeal-only *C trachomatis* indicated no clustering within STI clinic regions. NA=not applicable. STI=sexually transmitted infection. Ref=reference. *19 459 (91.7%) of 21 213 were tested pharyngeally. †These data included 4543 (21.4%) of 21 213 repeated visits. The pharyngeal *C trachomatis* positivity was 2.1% in repeated consultations and 2.7% in women that visited the STI clinic once during this period (p=0.06). ‡The proportion of women with missing data or not tested was higher than 5% and these were included in the analyses as a separate category.

Table 2: Risk factors for pharyngeal and isolated pharyngeal *Chlamydia trachomatis* in women routinely universally tested between 2016 and 2017 (n=21 213)* using generalised estimating equations logistic regression analyses†

universally tested women (25 [56·8%] of 44 vs 248 [22·9%] of 1081; $p < 0.0001$). The overall proportion of pharyngeal-only infections in all consultations in which a pharyngeal *C trachomatis* infection was diagnosed was 21·3% (981 of 4598). The proportion of pharyngeal-only *C trachomatis* per testing scenario is shown in the figure. In the routinely universally tested group, the positivity rate of pharyngeal-only *C trachomatis* was 0·5% (248 of 45774 pharyngeal tests) and this value comprises 3·3% (248 of 7558 *C trachomatis* infections) of all *C trachomatis* infections.

Among the 19459 consultations in the routine universal testing group between 2016 and 2017, 494 (2·5%) were positive for pharyngeal *C trachomatis* and 95 (0·5%) were positive for pharyngeal-only *C trachomatis*. Independent risk factors for pharyngeal *C trachomatis* were young age (≤ 25 years), having had four or more sexual partners in the past 6 months, being notified for any STI, and having concurrent urogenital or anorectal *C trachomatis* (table 2). Condomless anogenital sex was independently associated with pharyngeal-only *C trachomatis* (adjusted odds ratio 2·0 [95% CI 1·1–3·7]).

Table 3 shows the comparison of alternative testing scenarios. When testing women who report oral sex, 18028 (94·2%) of 19142 women would have to be tested and 465 (94·1%) of 494 pharyngeal *C trachomatis* infections would have been detected. Testing on the basis of independent risk factors would have been more specific, by having to test 15484 (79·6%) of 19459 women and detecting 398 (80·6%) of 494 infections. Testing on the basis of the current Dutch guidelines would have been most specific, having to test 7790 (40·0%) of 19459 women, but would have detected fewer infections (257 [52·0%] of 494; table 3).

Discussion

This large study provides a comprehensive overview of pharyngeal *C trachomatis* in women visiting STI clinics. Routine universal testing was used in almost 10% of Dutch STI consultations. These routine universal testing data offered the unique opportunity to estimate the prevalence of pharyngeal and pharyngeal-only *C trachomatis*, risk factors for pharyngeal *C trachomatis*, and the potential number of missed pharyngeal *C trachomatis* infections when using selective testing. Comparable to previous research,¹¹ pharyngeal *C trachomatis* was prevalent in 2·4% of women when routinely universally tested and the prevalence of pharyngeal-only *C trachomatis* was 0·5%.

Selective testing based on risk groups and risk behaviour was most often used in Dutch STI clinics. Selective testing in clinical practice would have missed approximately two-thirds of the estimated total of pharyngeal *C trachomatis* infections. One-in-five of these missed infections would have been pharyngeal-only *C trachomatis* and four-in-five would have been concurrent infections. This finding suggests that the majority of pharyngeal *C trachomatis* infections would

	Tested	Positive	Missed pharyngeal <i>C trachomatis</i> infections
All pharyngeal <i>C trachomatis</i>			
Number of women	19 459	494	..
Dutch testing policy			
Sex work*	1985/19 422 (10·2%)	30 (6·1%)	464/494 (93·9%)
Notified for any STI†	3512/19 441 (18·1%)	194 (39·3%)	300/494 (60·7%)
Condom use during last anogenital sex and reported oral sex‡	4021 (20·7%)	79 (16·0%)	415/494 (84·0%)
One or more of the criteria above	7790 (40·0%)	25 (52·0%)	237/494 (48·0%)
Independent risk factors			
Age ≤ 25 years	13 810 (71·0%)	418 (84·6%)	76/494 (15·4%)
Number of sex partners ≥ 4	5411 (27·8%)	159 (32·2%)	335/494 (67·8%)
Notified for any STI	3512 (18·0%)	194 (39·3%)	300/494 (60·7%)
Concurrent urogenital <i>C trachomatis</i>	2855/19 448 (14·7%)	369 (74·7%)	125/494 (25·3%)
Concurrent anorectal <i>C trachomatis</i>	1608 (8·3%)	227 (46·0%)	267/494 (54·0%)
One or more of the criteria above without urogenital or anorectal <i>C trachomatis</i> §	15 484 (79·6%)	398 (80·6%)	96/494 (19·4%)
Behaviour based			
Reported oral sex¶	18 028/19 142 (94·2%)	465 (94·1%)	29/494 (5·9%)
Pharyngeal-only <i>C trachomatis</i>			
Number of women	19 459	95	..
Dutch testing policy			
Sex work*	1985/19 422 (10·2%)	9 (9·5%)	86/95 (90·5%)
Notified for any STI†	3512/19 441 (18·1%)	21 (22·1%)	74/95 (77·9%)
Condom use during last anogenital sex and reported oral sex‡	4021 (20·7%)	13 (13·7%)	82/95 (86·3%)
One or more of the criteria above	7790 (40·0%)	36 (37·9%)	59/95 (62·1%)
Independent risk factors			
Condomless anogenital sex‡	14 077 (72·3%)	78 (82·1%)	17/95 (17·9%)
Behaviour based			
Reported oral sex¶	18 028/19 142 (94·2%)	89 (93·7%)	6/95 (6·3%)

Data are n, n (%), or n/N (%). STI=sexually transmitted infection. *Data were missing for 37 (0·2%) of 19 459 consultations. †Data were missing for 18 (0·1%) of 19 459 consultations. ‡Data were missing for 1202 (6·2%) of 19 459 consultations. §This testing scenario is based on those who are 25 years or younger, having four or more sexual partners, and being notified for any STI. Concurrent urogenital *C trachomatis* and concurrent anorectal *C trachomatis* are not considered relevant indicators, as it is not possible to triage on these indicators in an STI consultation and treatment of urogenital and anorectal *C trachomatis* leads to concurrent treatment of pharyngeal *C trachomatis*. ¶Data were missing for 317 (1·6%) of 19 459 consultations.

Table 3: Estimated ability of three alternative testing scenarios to detect pharyngeal and pharyngeal-only *Chlamydia trachomatis* among women who were routinely universally tested in 2016–17 (n=21 213) based on sexual behaviour and independently associated variables identified by multivariable logistic regression analyses using generalised estimating equation

have been coincidentally treated with anogenital infections. In theory, testing according to the Dutch guidelines would have missed half of pharyngeal *C trachomatis* infections. The discrepancy indicates that guidelines are not always fully implemented in clinical practice. Independent risk factors for pharyngeal *C trachomatis* suitable for selection were a younger age (≤ 25 years), four or more sexual partners, and being notified for any STI. A younger age and a higher number of sexual partners are general risk factors for *C trachomatis* in women.²² Following these risk factors as testing

indicators, 79·6% of women would need to be tested and 80·6% of pharyngeal *C trachomatis* would be diagnosed. Using the found independent risk factor for pharyngeal-only *C trachomatis*, condomless anogenital sex, as an indicator, resulted in theoretically testing the majority of clients (72·3%) and finding 82·1% of isolated pharyngeal *C trachomatis* cases. Our results suggest that condom use during anogenital sex in combination with condomless oral sex, currently used as indicator in testing guidelines, might not be effective in finding pharyngeal-only *C trachomatis*. No testing scenario is available, in which only a selection of high-risk women needs to be tested to find most *C trachomatis* infections. Of the Dutch testing indicators, being notified for any STI, might be the most cost-effective indicator in finding pharyngeal *C trachomatis* by testing 18·0% and finding 39·3% of pharyngeal *C trachomatis* and 22·1% of pharyngeal-only *C trachomatis*. Only routine universal testing would be able to detect all infections. When deciding on a testing strategy, considerations about the clinical and public health effect and possible risks of overtreatment should be taken into account in addition to the effectiveness of a strategy in finding the majority of infections. The clinical effect of untreated pharyngeal *C trachomatis* and public health effect of these infections on *C trachomatis* transmission are under debate.

Regarding the clinical effect, concerns have been raised that pharyngeal *C trachomatis* cases might initiate a reservoir of infection via the gastrointestinal tract based on evidence in animals.^{7,8} However, previous pharyngeal *C trachomatis* infection has not been determined to be a risk factor for anorectal *C trachomatis* in humans using epidemiological methods,²³ thereby not supporting the gastrointestinal tract theory. Recently, concerns have been raised whether all pharyngeal *C trachomatis* infections should be treated.²⁴ Pharyngeal *C trachomatis* infections have been considered low bacterial load infections that are frequently self-limiting within a short period.^{12,25} Spontaneous pharyngeal *C trachomatis* clearance has been estimated to be 36–57% within a median time of 9–10 days,^{14,12,25} and this proportion seems to be higher than for genital or rectal infections.^{12,26–28} The percentage viable in pharyngeal *C trachomatis* samples (26%) has been much lower than in genital (94–96%) or rectal (58–67%) positive samples.^{14,23} Regarding the public health effect, some evidence suggests that pharyngeal *C trachomatis* might contribute to ongoing transmission to sexual partners.^{5,6} However, the prevalence of pharyngeal-only *C trachomatis* assessed in our study (0·5%) is relatively low and also the proportion of pharyngeal *C trachomatis* infections in the total of *C trachomatis* infections (estimated 14·3% in our study) is limited. The relative low prevalence and self-limiting character of pharyngeal *C trachomatis* suggests limited public health effect. These considerations imply that detecting and treating all pharyngeal *C trachomatis* infections involve a risk of overtreatment, which might

contribute to increased antimicrobial resistance. The probably limited clinical and public health effect and risk of overtreatment do not support choosing routine universal testing as the recommended testing strategy. In clinical practice, diagnostics for *C trachomatis* are often combined with *N gonorrhoeae*. A previous study showed that routine universal testing would be needed to detect most pharyngeal *N gonorrhoeae* infections in women.¹⁹ When this testing strategy would be implemented for *N gonorrhoeae* in women, costs for pharyngeal *C trachomatis* testing would be covered. However, pharyngeal *C trachomatis* and *N gonorrhoeae* infections are different in their prevalence, anatomical site distribution, and implications. Pharyngeal *N gonorrhoeae* has a higher proportion of pharyngeal-only infections¹⁹ and entails stronger evidence for transmission.^{29,30} Therefore, recommendable testing strategies could be different for pharyngeal *C trachomatis* and *N gonorrhoeae*. Our study showed that for pharyngeal *C trachomatis*, the benefit-to-risk ratio of testing and treating pharyngeal *C trachomatis* needs to be further studied to determine whether routine universal testing should be preferred to no testing at all.

This study has some limitations. First, the cutoffs to define testing practice were based on empirical study data and the authors' expertise, as no standardisation is available. Results could have been slightly different when using different cutoffs. Second, although the dataset is large and represents all women visiting STI clinics in one country, women visiting other sexual health-care providers, such as general practitioners, were not included. General practitioners diagnose about two-thirds of all *C trachomatis* infections in women in the Netherlands. However, such diagnoses are based almost entirely on genital testing, thus the number of missed pharyngeal infections is likely to be higher than estimated in this setting. Third, STI clinics are likely to serve a population at high risk for STIs and therefore the prevalence of pharyngeal *C trachomatis* and other data obtained in this clinic-based data might not be representative of all women. Fourth, condom use during oral sex was not available in our data. We could not assess the proportion tested and the proportion positive among women reporting unprotected oral sex. However, we assumed that most women who reported oral sex in this study did not use a condom, as previous studies indicated very low condom use among heterosexual oral sex.¹⁰ Furthermore, data specifying which NAAT platform was used in which test consultation were not available. However, laboratory analysis for all Dutch STI clinics is done at ISO 15189-accredited laboratories, which use commercially available, approved, and validated NAAT platforms for clinical diagnoses. Finally, false positives could not be ruled out in this study because most manufacturers' protocols do not advocate confirmatory testing for pharyngeal *C trachomatis*. Whether increased pharyngeal testing such as implementing routine

universal testing would lead to more false positives is not known.

In summary, routine universal testing assessed low prevalence of pharyngeal *C trachomatis* in women visiting the STI clinic (2.4%) and 23% were pharyngeal-only infections. Selective testing would have missed two-thirds of the estimated total of pharyngeal *C trachomatis* infections, of which one-in-five would be isolated and four-in-five would be concurrent with an anogenital infection. Most of these missed infections would have been treated coincidentally with anogenital infections. When comparing alternative testing scenarios based on risk factors, no optimal testing scenario is available, in which only a selection of women at high risk needs to be tested to find the majority of pharyngeal-only *C trachomatis* infections. Only routine universal testing would be able to detect all infections. However, the probably limited clinical and public health effect and risk of overtreatment do not support choosing routine universal testing as the recommended testing strategy.

Contributors

CJPAH and GAFSvL conceptualised and designed the study. YJE and GAFSvL analysed the data. YJE, GAFSvL, and CJPAH accessed and verified the data. YJE and CJPAH wrote the first draft of the manuscript. All authors contributed to drafting of the manuscript and read and approved the final version of the manuscript for submission. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data used were explicitly made available for this study by the National Institute for Public Health and the Environment. Any data sharing requests should be directed to the National Institute for Public Health and the Environment (soap@rivm.nl).

Acknowledgments

This study was funded by the Public Health Service South Limburg. We thank the Dutch Centres for Sexual Health (also referred to as sexually transmitted infection [STI] clinics) and Fleur van Aar and Maartje Visser from the National Institute of Public Health and the Environment for providing the national STI clinic surveillance data used in this study.

References

- Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One* 2015; **10**: e0143304.
- Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2013. Atlanta: US Department of Health and Human Services, 2014. <https://www.cdc.gov/std/stats/archive/Surv2013-Print.pdf> (accessed on March 20, 2021).
- Haggerty CL, Gottlieb SL, Taylor BD, et al. Risk of sequelae after *Chlamydia trachomatis* genital infection in women. *J Infect Dis* 2010; **201** (suppl 2): 134–55.
- Hoenderboom BM, van Benthem BHB, van Bergen JEAM, et al. Relation between *Chlamydia trachomatis* infection and pelvic inflammatory disease, ectopic pregnancy and tubal factor infertility in a Dutch cohort of women previously tested for chlamydia in a chlamydia screening trial. *Sex Transm Infect* 2019; **95**: 300–06.
- Bernstein KT, Stephens SC, Barry PM, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* transmission from the oropharynx to the urethra among men who have sex with men. *Clin Infect Dis* 2009; **49**: 1793–97.
- Marcus JL, Kohn RP, Barry PM, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* transmission from the female oropharynx to the male urethra. *Sex Transm Dis* 2011; **38**: 372–73.
- Yeruva L, Spencer N, Bowlin AK, et al. Chlamydial infection of the gastrointestinal tract: a reservoir for persistent infection. *Pathog Dis* 2013; **68**: 88–95.
- Bavoil PM, Marques PX, Brotman R, Ravel J. Does active oral sex contribute to female infertility? *J Infect Dis* 2017; **216**: 932–35.
- De Graaf H, Verbeek M, Van den Borne M, Meijer S. Offline and online sexual risk behaviour among youth in the Netherlands: findings from 'Sex under the age of 25'. *Front Public Health* 2018; **12**: 72.
- Leichter JS, Chandra A, Liddon N, et al. Prevalence and correlates of heterosexual anal and oral sex in adolescents and adults in the United States. *J Infect Dis* 2007; **196**: 1852–59.
- Chan PA, Robinette A, Montgomery M, et al. Extragenital infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: a review of the literature. *Infect Dis Obstet Gynecol* 2016; **2016**: 5758387.
- van Rooijen MS, van der Loeff MF, Morré SA, et al. Spontaneous pharyngeal *Chlamydia trachomatis* RNA clearance. A cross-sectional study followed by a cohort study of untreated STI clinic patients in Amsterdam, The Netherlands. *Sex Transm Infect* 2015; **91**: 157–74.
- Ota KV, Tamari IE, Smieja M, et al. Detection of *Neisseria gonorrhoea* and *Chlamydia trachomatis* in pharyngeal and rectal specimens using the BD Probetec ET system, the Gen-Probe Aptima Combo 2 assay and culture. *Sex Transm Infect* 2009; **85**: 182–86.
- Dukers-Muijters NHTM, Wolffs P, Lucchesi M, et al. Oropharyngeal *Chlamydia trachomatis* in women: spontaneous clearance and cure after treatment (FemCure). *Sex Transm Infect* 2020; **97**: 147–51.
- Workowski KA BG. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015; **64**: 1–137.
- Fifer H, Saunders J, Soni S, Sadiq ST, Fitzgerald M. British Association for Sexual Health and HIV national guideline for the management of infection with *Neisseria gonorrhoeae*. 2019. <https://www.bashhguidelines.org/media/1208/gc-2019.pdf> (accessed on Sept 19, 2019).
- Australasian Sexual Health Alliance. Australian STI management guidelines for use in primary care. 2018. <http://www.sti.guidelines.org.au/> (accessed Sept 12, 2019).
- Lanjouw E, Ouburg S, De Vries HJ, et al. 2015 European guideline on the management of *Chlamydia trachomatis* infections. *Int J STD AIDS* 2016; **27**: 333–48.
- Van Liere GAFS, Dukers-Muijters NHTM, Kuizenga-Wessel S, Wolffs PFG, Hoebe CJPA. Routine universal testing versus selective or incidental testing for oropharyngeal *Neisseria gonorrhoeae* in women in the Netherlands: a retrospective cohort study. *Lancet Infect Dis* 2021; **21**: 858–67.
- Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003; **157**: 364–75.
- Statistics Netherlands. Wat verstaat het CBS onder een allochtoon? <https://www.cbs.nl/nl-nl/faq/specifiek/wat-verstaat-het-cbs-onder-een-allochtoon-> (accessed Feb 15, 2021).
- Araújo RSC, Guimaraes EMB, Alves MFS, et al. Prevalence and risk factors for *Chlamydia trachomatis* infection in adolescent females and young women in central Brazil. *Europ J Clin Microb Infect Dis* 2006; **25**: 397–400.
- Leenen J, van Liere GAFS, Hoebe CJPA, Hogewoning AA, de Vries HJC, Dukers-Muijters NHTM. A longitudinal study to investigate previous *Chlamydia trachomatis* infection as a risk factor for subsequent anorectal infection in men who have sex with men (MSM) and women visiting STI clinics in the Netherlands. *Epidemiol Infect* 2019; **147**: e214.
- van Bergen J. Can we control chlamydia? Tallinn: Keynote speech IUSTI-Europe Congress, 2019. <https://piv.lend.ee/iusti2019videogallery/#video25> (accessed on March 20, 2021).
- van Liere GAFS, Hoebe CJPA, Dirks JA, et al. Spontaneous clearance of urogenital, anorectal and oropharyngeal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in women, MSM and heterosexual men visiting the STI clinic: a prospective cohort study. *Sex Transm Infect* 2019; **95**: 505–10.
- Dukers-Muijters NHTM, Janssen KJH, Hoebe CJPA, et al. Spontaneous clearance of *Chlamydia trachomatis* accounting for bacterial viability in vaginally or rectally infected women (FemCure). *Sex Transm Infect* 2020; **96**: 541–48.

- 27 Wijers JNAP, Dukers-Muijters NHTM, van Liere GAFS, et al. Men and women have an equal oropharyngeal and anorectal *Chlamydia trachomatis* bacterial load: a comparison of three anatomic sites. *J Infect Dis* 2019; **223**: 1582–89.
- 28 Apewokin SK, Geisler WM, Bachmann LH. Spontaneous resolution of extragenital chlamydial and gonococcal infections prior to therapy. *Sex Transm Dis* 2010; **37**: 343–44.
- 29 Hui B, Fairley CK, Chen M, et al. Oral and anal sex are key to sustaining gonorrhoeae at endemic levels in MSM populations: a mathematical model. *Sex Transm Infect* 2015; **91**: 365–69.
- 30 Hook EW, Bernstein K. Kissing, saliva exchange, and transmission of *Neisseria gonorrhoeae*. *Lancet Infect Dis* 2019; **19**: e367–69.