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Trends in *Chlamydia trachomatis* IgG seroprevalence in the general population of the Netherlands over 20 years

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ABSTRACT

Objectives To report sex and age-specific *Chlamydia trachomatis* (Ct) seroprevalence estimates in the general population of the Netherlands between 1996 and 2017 and identify risk factors associated with Ct seropositivity.

Methods Participants (n=5158, aged 15–59 years) were included from three independent nationwide population-based serosurveillance studies in 1996, 2007 and 2017. Participants completed a questionnaire on demographics and sexual behaviour. Serum antibodies were analysed using Medac Ct IgG ELISA test. Census weights were assigned to achieve seroprevalence estimates representative of the general Dutch population. Weighted seroprevalence estimates were stratified by gender, age and birth cohort. Trends and risk factors in men and women were identified using multivariable logistic regression.

Results Weighted overall Ct seroprevalence was 10.5% (95% CI: 9.2% to 12.0%) in women and 5.8% (95% CI: 4.7% to 7.0%) in men. Among women <25 years, there was a non-significant increase in seroprevalence from 5.9% (95% CI 3.7% to 9.2%) in 1996, to 7.6% (95% CI 5.1% to 11.1%) in 2007 and 8.8% (95% CI 5.5% to 13.9%) in 2017. Among women ≥25 years, the seroprevalence significantly decreased from 15.6% (95% CI: 12.2% to 19.7%) in 1996 to 9.5% (95% CI: 7.2% to 12.4%) in 2007 but did not further drop (11.2% (95% CI 8.1% to 15.3%) in 2017). In men, we did not observe trends between study rounds. In both men and women, having a non-Western migration background was a risk factor for seropositivity. In women, having had a prior sexually transmitted infection and ≥2 recent sex partners were risk factors for seropositivity as well.

Conclusions We have not found evidence for a decrease in population seroprevalence in those under 25 years old despite decades of intensified testing-and-treatment efforts in the Netherlands. This suggests further monitoring of Ct burden in the general population is needed. If serum banks are used for this, specifically individuals <25 years old and with diverse migration backgrounds should be included.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Nationwide chlamydia seroprevalence surveys are a tool for understanding the impact of control activities in countries.
⇒ In the Netherlands, chlamydia reporting rates are rising, but it is unclear if this is due to increased transmission or better case finding.

WHAT THIS STUDY ADDS

⇒ There was no evidence for a decrease in population chlamydia seroprevalence in people under 25 years old, despite decades of targeted chlamydia testing-and-treatment efforts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In settings with targeted chlamydia testing, repeated population-based serology studies provide essential insight in chlamydia exposure in the general population.
⇒ Future seroprevalence studies for monitoring of chlamydia should specifically include individuals <25 years old and with diverse migration backgrounds.

INTRODUCTION

Widespread testing and treatment of *Chlamydia trachomatis* (Ct) in asymptomatic women and heterosexual men are under debate in various Western countries.[1 2] The goals of Ct control can be twofold: first, to curb transmission of Ct infection in the population and second, to reduce reproductive tract sequelae. While there is evidence from trials that Ct control programmes can reduce the risk of pelvic inflammatory disease (PID) in women, there is a lack of evidence supporting a reduction in population prevalence.[1–3]

To estimate population prevalence, Ct serology can be used in addition to nucleic acid amplification tests (NAATs), as it estimates cumulative exposure over time. Recent studies of Ct serology using existing serum banks have provided valuable insights into the impact of Ct control activities.[4–6]

In the Netherlands, Ct is monitored by surveillance in all Sexual Health Centre (SHC) clinics, where free-of-charge sexually transmitted infection (STI) testing and treatment are provided for high-risk groups (eg, heterosexuals aged <25 years, those who report STI symptoms or are notified of STI exposure), and in a representative sample of general practitioners (GPs). Reported Ct infections have increased steeply between 2010 and 2021 by 51% in GPs and 77% in STI clinics, adding up to around 63.000 reported Ct infections in 2021.[7 8] However, surveillance estimates cannot be used as indicators of population incidence and prevalence as Ct infections are often asymptomatic and diagnosis depends on client-initiated testing behaviour

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and client characteristics, which changed over time. Repeated nationwide surveys are needed to put these surveillance data into perspective.

Ct seroprevalence in the Netherlands was previously assessed using a national biobank for population-based seroprevalence studies from 1995/1996 and 2006/2007.[9] We now have seroprevalence data from 2017 available. This allows us to study trends and gain more insight in Ct prevalence following the implementation of a uniform national testing policy in 2006.[8] The aim of this study was to report sex and age-specific Ct seroprevalence, evaluate trends between 1996–2017 and risk factors for seropositivity.

METHODS

Study design

Samples were used from large serum banks in the Netherlands, collected from three consecutive cross-sectional serological surveys conducted in 1995–1996 (Pienter 1, referred to as 1996), 2006–2007 (Pienter 2, '2007') and 2016–2017 (Pienter 3, '2017'). The primary objective of the Pienter studies was to periodically monitor seroprevalence of national immunisation programme-targeted diseases. The designs of the Pienter studies were described in detail elsewhere.[10–12] In summary, a representative national sample was drawn from the Dutch population. In randomly sampled municipalities (selected from geographical regions proportional to size), an age-stratified sample was randomly drawn from the register (age 0–79 years). Participants were invited to fill in a questionnaire and provide a blood sample.

We included participants aged 15–39 years as this group is most relevant for Ct transmission and bears the largest burden of sexual and reproductive ill-health due to Ct. A sufficient number of samples were included to detect a 3% change in overall Ct prevalence across concurrent Pienter rounds.[9] This resulted in including all Pienter samples from 2007 with sufficient serum and from the samples collected in 1996, a random selection was made matched for age and sex to 2007.[9] In 2017, the age group was expanded to 15–59 years to describe birth cohort effects. Samples from 2017 were randomly selected to achieve a similar age distribution as in 1996 and 2007.

Laboratory methods

The Medac Ct IgG ELISA (Wedel, Germany) test was used to test for Ct IgG antibodies. This test was the most used serology test in clinical practice in the Netherlands.[13 14] The ELISA uses a synthetic peptide from the immuno-dominant region of the major outer membrane protein (MOMP) as antigen, providing minimal cross-reactivity with other Ct species and therefore high specificity (97%).[14 15] Sensitivity of the Medac was found to be 71% as compared with the Microimmunofluorescence assay, and varied between 38% and 66% in comparison with NAAT, depending on time since infection.[14 16] Levels of Ct IgG antibodies (arbitrary units (AU)/mL) were calculated per manufacturer's instructions, and outcomes were classified as negative (IgG concentration <22 AU/mL), grey zone (IgG concentration 22–28 AU/mL) or positive (IgG concentration ≥28 AU/mL).

Questionnaire data

From all participants, information on age, sex, urbanisation, country of birth and country of birth of both parents was available from the population register. Migration background was based on country of birth of the participant and both parents and was categorised as Dutch if both parents and participant were born in the Netherlands. First and second-generation migrants were grouped together and further divided into Western non-Dutch (West European countries, Australia, North America, Indonesia and Japan); Morocco and Turkey; Suriname, Aruba and the former Dutch Antilles; and non-Western (other countries). Other demographic and sexual risk behaviour variables were self-reported and definitions can be found in online supplemental table 1. Education was divided into theoretical (higher professional level, university level) or practical (all other levels). No data on previous STI testing were available, only on diagnosis which was included in the analyses as 'STI diagnosed ever' and 'Ct diagnosed ever'.

Weighting of the data

We incorporated census weights to achieve estimates representative for the general Dutch population. The weights were obtained using census data for the Netherlands by sex, age and migration background, for each survey period. Weights were obtained by dividing the proportion of the population in the Netherlands in a specific group (eg, women aged 25–29 years with a Turkish or Moroccan migration background) by the proportion of survey participants in the same group.

Statistical analyses

We first determined differences between participants in study rounds by comparing demographic and behavioural variables using the χ^2 test. Prevalence of IgG antibodies against the Ct MOMP (hereafter 'seroprevalence') was calculated with corresponding 95% CIs. Antibody levels in Ct seropositives stratified by age group and sex were compared between study rounds using the Mann-Whitney U test. P values below 0.05 were considered significant.

Ct IgG seroprevalence

Numbers of Ct seropositives and seroprevalence were all estimated taking into account weights. Analyses were stratified by sex, age group, study round and birth cohort. Strata were compared using the χ^2 test. Trends between three or more groups were assessed using the χ^2 test for trends. P values below 0.05 were considered significant. Several comparisons were made among participants 15–39 years old, all stratified by sex and age group. Age was divided into: (1) binary variable corresponding to high-risk triage criterion in Dutch SHC clinics[7] (<25 years and ≥25 years), and (2) in 5-year age bands (15–19, …, 35–39 years) to assess trends in more detail.

First, we compared overall seroprevalence between women and men by age group. Second, we compared seroprevalence between age groups by study round. Last, we compared seroprevalence between study rounds by age group, which we plotted against the yearly number of tests conducted in SHC based on national surveillance data.[7 8]

In addition, we compared seroprevalence between study rounds by cross-sectional birth cohorts for which participants 15–59 years were included. For example, for women born in 1977–1981, we compared seroprevalence between 1996, 2007 and 2017, when they were, respectively, 15–19, 25–29 and 35–39 years.

Determinants of Ct seropositivity

To identify determinants of Ct seropositivity, logistic regression analyses were performed stratified by sex. Due to low number of seropositives per study round, the data from all rounds were combined. We excluded variables which were highly correlated (condom use: regular partner vs casual partner and last sexual

Table 1 Sociodemographic characteristics and sexual risk factors of the study population (15–39 years old) in 1996, 2007 and 2017

	1996	2007	2017	1996 vs 2007	2007 vs 2017	1996 vs 2017
Characteristics	**N (%)**	**N (%)**	**N (%)**	**P value**	**P value**	**P value**
Total	1568 (100)	1590 (100)	1146 (100)			
Fully observed variables						
Sex				>0.9	<0.001	<0.001
Female	953 (61)	966 (61)	562 (49)			
Male	615 (39)	624 (39)	584 (51)			
Age				0.6	<0.001	<0.001
15–24	589 (38)	610 (38)	430 (27)			
25–39	979 (62)	980 (62)	716 (46)			
Migration background*				<0.001	0.024	<0.001
Dutch	1386 (88)	1320 (83)	944 (82)			
Moroccan or Turkish	41 (2.6)	41 (2.6)	21 (1.8)			
SAN	24 (1.5)	40 (2.5)	76 (6.6)			
Western, non-Dutch	98 (6.2)	120 (7.5)	33 (2.9)			
Non-Western	19 (1.2)	69 (4.3)	72 (6.3)			
Urbanisation				<0.001	<0.001	<0.001
(Very) low	765 (49)	344 (22)	339 (30)			
Moderate and high	803 (51)	1246 (78)	807 (70)			
Variables with missing data						
Education†				<0.001	<0.001	<0.001
Practical	1153 (74)	1107 (70)	652 (57)			
Theoretical	246 (16)	464 (29)	420 (37)			
Unknown	169 (11)	19 (1.2)	74 (6.5)			
Sexual practice‡				>0.9	–	–
Women (all sexual practices)	953 (61)	966 (61)	562 (49)			
Heterosexual men	410 (26)	409 (26)	422 (37)			
Homosexual/bisexual men	5 (0.3)	6 (0.4)	21 (1.8)			
Unknown	200 (13)	209 (13)	141 (12)			
Ct diagnosed ever				<0.001	<0.001	<0.001
No	1327 (85)	1485 (93)	999 (87)			
Yes	11 (0.7)	31 (1.9)	46 (4.0)			
Unknown	230 (15)	74 (4.7)	101 (8.8)			
STI diagnosed ever§				<0.001	<0.001	<0.001
No	1316 (84)	1469 (92)	975 (85)			
Yes	42 (2.7)	64 (4.0)	79 (6.9)			
Unknown	210 (13)	57 (3.6)	92 (8.0)			
Age at first time sex				<0.001	<0.001	<0.001
<18	479 (31)	578 (36)	482 (42)			
18 and above	568 (36)	563 (35)	394 (34)			
Unknown	521 (33)	449 (28)	270 (24)			
Number of recent sexual partners¶				<0.001	0.007	0.4
0–1	1221 (78)	1143 (72)	826 (72)			
2 and more	78 (5.0)	72 (4.5)	68 (5.9)			
Unknown	269 (17)	375 (24)	252 (22)			
Regular partner**				–	0.14	–
No	n.c.	456 (29)	387 (34)			
Yes	n.c.	1091 (69)	717 (63)			
Unknown	n.c.	43 (2.7)	42 (3.7)			
Condom use last sexual contact**				–	<0.001	–
No	n.c.	848 (53)	640 (56)			
Yes	n.c.	236 (15)	261 (23)			
Unknown	n.c.	506 (32)	245 (21)			
Condom use regular partner**††				–	0.017	–
Always	n.c.	179 (11)	149 (13)			
Sometimes	n.c.	69 (4.3)	45 (3.9)			
Never	n.c.	734 (46)	532 (46)			

Continued

Table 1 Continued

Characteristics	1996 N (%)	2007 N (%)	2017 N (%)	1996 vs 2007 P value	2007 vs 2017 P value	1996 vs 2017 P value
Unknown	n.c.	608 (38)	420 (37)			
Condom use with casual partner**††				–	<0.001	–
Always	n.c.	68 (4.3)	141 (12)			
Sometimes	n.c.	12 (0.8)	25 (2.2)			
Never	n.c.	40 (2.5)	90 (7.9)			
Unknown	n.c.	1470 (92)	890 (78)			

P values are based on χ^2 test. Participants 40–59 years old were excluded (n=844).
An extra category was created for missing data. Missing data are shown as 'unknown'. Missing data are a mix of 'I don't know', 'I don't want to say' and not filled in.
*Migration background was based on the country of birth of the participant and both parents and categorised as Dutch, Western non-Dutch (West European countries, Australia, North America, Indonesia and Japan), Morocco and Turkey, SAN and non-Western (other countries).
†Education was classified as theoretical (higher professional education, university-level education) or practical (all other educations).
‡1996: based on sex of sexual partners in the past year; 2007: based on sex of sexual partners in the past 6 months; 2017: based on sex of sexual partners lifetime.
§1996: chlamydia, hepatitis B, gonorrhoea, herpes, genital warts (HPV), syphilis; 2007 and 2017: chlamydia, hepatitis B, gonorrhoea, herpes, genital warts (HPV), syphilis, HIV.
¶1996: number of partners in the past year; 2007 and 2017: number of partners in the past 6 months.
**Data not collected in 1996.
††2007: with partners in the past year and 2017: with partners in the past 6 months.
Ct, *Chlamydia trachomatis*; HIV, human immunodeficiency virus; HPV, human papillomavirus; n.c., not collected; SAN, Suriname, Aruba and the former Dutch Antilles; STI, sexually transmitted infection.

contact) or which had an inconsistent definition across study rounds (sexual practice). We included the following categorical sexual risk behaviour variables: STI diagnosed ever, age at first time sex, number of recent sexual partners, having a regular partner and condom use with regular partner (online supplemental table 1). If a variable had more than 5% missingness, a separate missing category was included in the analyses to avoid loss of information.

We first performed univariable logistic regression. We then performed multivariable logistic regression. The multivariable model was built via backward stepwise selection based on Akaike Information Criterion (AIC). Age and migration background could affect seropositivity differently across study periods, for example, because access to sexual healthcare has become more available to certain groups over time. To account for potential bias introduced by combining study rounds, interaction terms for age and migration background with study round were included. Interaction terms were checked one by one by comparing the AIC with and without. Variables with subgroups with less than 15 cases were excluded from the multivariable analyses. Weighted ORs and weighted adjusted ORs with 95% CIs were calculated.

Statistical analyses were performed using R V.4.2.0, and weights were incorporated in Ct seroprevalence estimates and logistic regression analyses using the R survey package.[17]

RESULTS

Characteristics of the study population

We included a total of 5158 participants. For ages 15–39 years, we included 958 women and 620 men from 1996, 972 women and 625 men from 2007, and 569 women and 587 men from 2017. For ages 40–59 years, we included additional participants from 2017 (431 women and 413 men). Participants with Ct grey zone results were excluded from all analyses (n=32, 0.6%).

Characteristics are described for participants aged 15–39 years (table 1). The majority of participants had a Dutch

Table 2 Weighted numbers of Ct IgG positives and weighted Ct IgG seroprevalence in the general population in the Netherlands in 1996, 2007 and 2017

	Overall	1996	2007	2017	χ^2 test between rounds*		
	CAT+N; % (95% CI)	CAT+N; % (95% CI)	CAT+N; % (95% CI)	CAT+N; % (95% CI)	1996 vs 2007 (p value)	2007 vs 2017 (p value)	1996 vs 2017 (p value)
Women							
Overall	225; 10.5 (9.2 to 12.0)	92; 12.3 (9.9 to 15.0)	61; 8.8 (7.0 to 11.0)	70; 10.3 (7.9 to 13.0)	**<0.05**	0.37	0.29
15–24 years	59; **7.5 (5.7 to 9.6)****	15; **5.9 (3.7 to 9.2)*****	19; 7.6 (5.1 to 11.1)	24; 8.8 (5.5 to 13.9)	0.40	0.62	0.23
25–39 years	166; **12.2 (10.4 to 14.3)****	77; **15.6 (12.2 to 19.7%)*****	42; 9.5 (7.2 to 12.4)	46; 11.2 (8.1 to 15.3)	**<0.01**	0.42	0.10
Men							
Overall	126; 5.8 (4.7 to 7.0)	34; 4.5 (3.1 to 6.0)	51; 7.1 (4.9 to 10.0)	40; 6.0 (4.2 to 8.0)	0.08	0.50	0.28
15–24 years	44; 5.5 (3.9 to 7.7)	11; 4.4 (2.4 to 7.7)	20; 7.4 (4.2 to 13.0)	12; 5.0 (2.5 to 8.9)	0.20	0.29	0.86
25–39 years	82; 6.0 (4.6 to 7.8)	23; 4.5 (2.8 to 7.2)	31; 6.9 (4.4 to 10.7)	28; 6.7 (4.4 to 10.3)	0.21	0.96	0.23

Weighted number of study participants for each group can be found in online supplemental table 2. Please note that these numbers are weighted and do not necessarily correspond to the numbers in table 1.
P values of <0.05 are indicated in bold. P values for χ^2 test between age groups by study round are indicated as: *p<0.05, **p<0.01, ***p<0.001.
*P value for χ^2 test for a linear trend in proportions between study rounds by age group.
CAT, chlamydia antibody test; Ct, *Chlamydia trachomatis*.

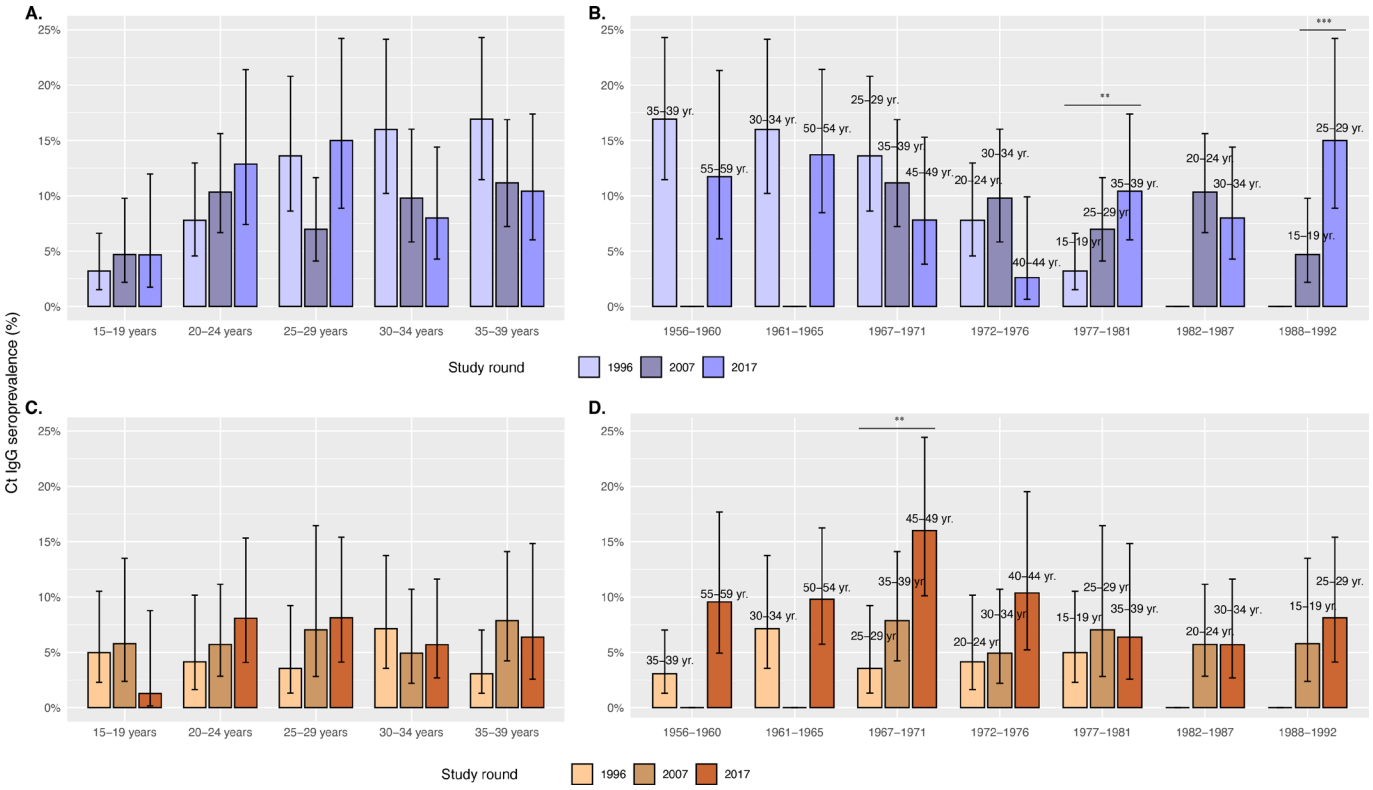

Figure 1 *Chlamydia trachomatis* (Ct) IgG seroprevalence by study round and by age strata for women (A) and men (C). Ct IgG seroprevalence by birth cohort for women (B) and men (D) for 1967–1971, 1972–1976 and 1977–1981, with corresponding 95% CI for seroprevalence. Flat lines in B and D indicate no data were collected for this birth cohort and age group. P value is given for χ^2 test between two strata or linear trend in proportions between three strata. P values are indicated as: *p<0.05, **p<0.01, ***p<0.001.

migration background, but this decreased from 88% in 1996 to 83% and 82% in 2007 and 2017, respectively. Participants in 1996 were more often from low urbanisation municipalities and practically educated as compared with 2007 and 2017. The proportion of participants with a known history of STI increased over time from 2.7% in 1996 to 4.0% in 2007 and 7.3% in 2017. More participants reported first sexual contact <18 years over time from 31% in 1996 to 42% in 2017. Most participants (70–80%) had <2 recent sexual partners. Condom use increased between 2007 and 2017 with last sexual contact, with regular partner and casual partner (p<0.05).

Ct IgG seroprevalence

In total, 347 chlamydia seropositives were identified. Among both women and men, median Ct antibody levels by age group did not differ significantly between study rounds (online supplemental figure 1).

Overall, the weighted Ct seroprevalence was 10.5% (95% CI: 9.2% to 12.0%) in women and 5.8% (95% CI: 4.7% to 7.0%) in men (table 2).

Between women and men

Overall seroprevalence was significantly lower in men compared with women ≥25 years (6.0%; 95% CI: 3.9% to 7.7% men vs 12.2%; 95% CI: 10.4% to 14.3% women). Among those <25 years, seroprevalence was not significantly different between men and women (5.5% men vs 7.5% women).

Between age groups by study round

In 1996, seroprevalence was significantly lower in women <25 years than in women ≥25 years (5.9%, 95% CI: 3.7 to 9.2 vs 15.6%, 95% CI: 12.2 to 19.7, p<0.001), but this difference diminished in 2007 and 2017 (table 2). In more detail, figure 1A showed seroprevalence increases with each 5-year age band in 1996. On the contrary, in 2017, this increase with age is only visible in women <30 years. Among men, within each study round, seroprevalence was not significantly different between those below and above 25 years (table 2 and figure 1C).

Between study rounds by age group

Among women ≥25 years, the seroprevalence significantly decreased from 15.6% (95% CI: 12.2% to 19.7%) in 1996 to 9.5% (95% CI: 7.2% to 12.4%) in 2007 (p<0.01), but did not further drop with 11.2% (95% CI 8.1% to 15.3%) in 2017 (p=0.42 for 2007 vs 2017). The decrease is especially visible in women 30–34 and 35–39 years (figure 1A). Among women <25 years, there was a non-significant increase in seroprevalence from 5.9% in 1996, to 7.6% in 2007 and 8.8% in 2017, during a period of intensified Ct testing and treatment in this group (online supplemental figure 2). This increase is especially visible in women 20–24 years (figure 1A). Among men ≥25 years, there is a non-significant increase in seroprevalence from 4.5% in 1996 to 6.9% in 2007 and 6.7% in 2017 (table 2), which is not observed in men <25 years.

Table 3 Determinants for Ct IgG seropositivity among women and men aged 15–39 years old in the Netherlands in 1996, 2007 and 2017

	Women			Men		
	Weighted Ct IgG positive	Univariable	Multivariable	Weighted Ct IgG positive	Univariable	Multivariable
Characteristics	N (%)	OR (95% CI)	aOR (95% CI)	N (%)	OR	aOR (95% CI)
Total	224 (10.5)			126 (5.8)		
Study round						
1996	92 (12)	1	1	34 (4.4)	1	
2007	61 (9)	0.7 (0.5 to 1.0)	1.3 (0.7 to 2.5)	50 (7.0)	1.6 (0.9 to 2.8)	
2017	70 (10)	0.8 (0.6 to 1.2)	1.5 (0.7 to 3.1)	41 (6.0)	1.3 (0.8 to 2.3)	
Age group						
15–24 years	59 (7.5)	1	1	44 (5.6)	1	
25–39 years	166 (12.3)	**1.7 (1.2 to 2.4)**	**3.0 (1.6 to 5.6)**	82 (6.0)	1.1 (0.7 to 1.1)	
Age×study round 2007			**0.4 (0.2 to 0.9)***			
Age×study round 2017			**0.4 (0.2 to 0.9)***			
Migration background†						
Western	167 (9.5)	1	1	84 (4.6)	1	1
Non-Western	57 (15.3)	**1.7 (1.1 to 2.7)**	**2.1 (1.3 to 3.5)**	41 (12.3)	**2.9 (1.7 to 5.1)**	**3.3 (1.7 to 6.1)**
Level of urbanisation						
Very (low)	67 (10.3)	1		31 (4.4)	1	
Moderate and high	157 (10.6)	1.0 (0.8 to 1.4)		95 (6.5)	1.5 (1.0 to 2.4)	
Level of education‡						
High	54 (9.8)	1		30 (5.2)	1	
Moderate and low	163 (11.1)	1.1 (0.8 to 1.6)		93 (6.3)	1.2 (0.7 to 2.0)	
STI diagnosed ever§						
No	177 (9.6)	1	1	102 (5.3)	1	
Yes	32 (27.6)	**3.6 (2.3 to 5.7)**	**3.3 (2.0 to 5.4)**	13 (17.6)	**3.7 (1.8 to 7.8)**††	
Age at first time sex						
<18	106 (12.8)	1	1	47 (7.4)	1	1
≥18	74 (10.1)	0.8 (0.5 to 1.1)	0.7 (0.5 to 1.0)	43 (5.5)	0.7 (0.4 to 1.2)	0.7 (0.4 to 1.3)
Number of recent sexual partners**						
0–1	175 (10.8)	1	1	84 (5.7)	1	
≥2	17 (19.1)	**2.0 (1.1 to 3.4)**	**2.3 (1.3 to 4.1)**	10 (7.8)	1.3 (0.7 to 2.7)	
Regular partner¶						
Yes	89 (9.7)	1		54 (6.4)	1	
No	38 (9.1)	0.9 (0.6 to 1.4)		30 (6.0)	0.9 (0.5 to 1.7)	
Condom use with regular partner¶						
Always	15 (8.8)	1		11 (7.0)	1	
Sometimes/never	70 (10.6)	1.3 (0.6 to 2.5)		41 (6.2)	0.9 (0.4 to 2.1)	

An extra category was created for missing data so that these could be included in the analyses. Missing data are not shown. Missing data are a mix of 'I don't know', 'I don't want to say' and not filled in. Missing values included in the analysis as a separate category (ORs not shown).
ORs with p values of <0.05 are indicated in bold.
*P=0.024 for the interaction term 'age group×study round 2007'; p=0.027 for the interaction term 'age group×study round 2017'.
†Migration background was combined into Western (Dutch and Western non-Dutch (West European countries, Australia, North America, Indonesia and Japan)) and non-Western (Morocco and Turkey, SAN and non-Western (other countries)).
‡Education was classified as theoretical (higher professional education, university-level education) or practical (all other educations).
§1996: chlamydia, hepatitis B, gonorrhoea, herpes, HPV, syphilis; 2007 and 2017: chlamydia, hepatitis B, gonorrhoea, herpes, genital warts (HPV), syphilis, HIV.
¶Data not collected in 1996, univariable association from 2007 and 2017 data only. Not included in multivariable model.
**1996: reported number of partners in the past year; 2007 and 2017: reported number of partners in the past 6 months.
††Variables could not be tested in multivariable model due to low numbers (<15 cases per group).
aOR, adjusted OR; Ct, *Chlamydia trachomatis*; HIV, human immunodeficiency virus; HPV, human papillomavirus; SAN, Suriname, Aruba and the former Dutch Antilles; STI, sexually transmitted infection.

Between study rounds by birth cohort

A significant increase in seroprevalence by age was found within the female birth cohorts of 1977–1981 and 1988–1992 (p=0.01 and p=0.007, figure 1B) and within the male birth cohort of 1967–1971 (p=0.001, figure 1D). The largest significant increase within a birth cohort is found for women born in 1988–1992 from 4.7% (95% CI: 2.2% to 9.8%) at 15–19 years to 15.0% (95% CI: 8.9% to 24.2%) at 25–29 years (online supplemental table 3).

Determinants of Ct seropositivity

Having a non-Western migration background, ever prior STI and ≥2 recent sex partners were associated with Ct

seropositivity in women (table 3). Furthermore, consistent with previous analyses, we found that the odds of Ct seropositivity among women aged ≥25 years differed between 1996 and 2007/2017. Among men having a non-Western migration background was associated with Ct seropositivity.

DISCUSSION

Based on three nationwide population-based probability surveys in the Netherlands, we found an overall chlamydia seroprevalence of 10.5% (95% CI: 9.2% to 12.0%) among women 15–39 years over the time period from 1996 to 2017. Seroprevalence in women ≥25 years was highest in 1996, dropped in 2007, but plateaued by 2017. In women <25 years, seroprevalence has increased non-significantly but consistently between 1996 and 2017. Within birth cohorts, the strongest effect was observed in women born 1988–1992 where seropositivity tripled between those 15–19 years and 25–29 years old. For men, seroprevalence was half of that of women. We did not observe trends within and between study rounds.

This is the first Ct seroprevalence study in the Netherlands to assess trends during decades of increased Ct control efforts. There are several limitations to this study. First, response rates of Pienter decreased from 55% to 16% between 1996 and 2017,[10–12] similar to falling rates in European health surveys.[18] Although participation determinants were consistent across Pienter surveys, healthy responder bias could be present which may result in underestimating Ct seroprevalence.[19 20] We (partly) corrected for this by weighting for demographic characteristics, but generalisability might be decreased in subgroups at a population level. Second, no gold standard exists for Ct serology, making any serology test suboptimal, particularly in men who often do not develop a detectable antibody response after infection.[4 21] Due to sensitivity of the used serology test (38–66%), our estimates are likely an underestimation of prior Ct infections.[14 15] Furthermore, it is known that individuals with repeated infections and recent infections are more likely to develop and maintain detectable antibodies.[16 22] As a consequence, people with first or non-recent infections might be missed in our seropositives. Third, because of the relative low number of identified seropositives, few stratified analyses could be conducted and a certain degree of uncertainty was observed around our estimates. For women, we did observe consistent trends, but these were often not significant, likely due to low numbers. For men, the uncertainty is largest due to relatively lower sensitivity of serology to detect past infection in males.[4 21]

Our results on prevalence are as expected when compared with a Dutch study among participants of a prior Ct screening implementation trial, in which the same antibody test was used as in our study.[22] Among women 25–39 years, a seropositivity of 15% (95% CI 14% to 16%) was found in the cohort study in 2016,[22] whereas 11% (95% CI 8% to 15%) was found in our study. The difference is likely explained by the self-selection of high-risk participants into the Ct screening implementation trial. In an English study in 2010/2012, a seroprevalence of 25% was found in women using an in-house Pgp3 antibody test, while our study found 9–10% in 2007/2017.[4] A comparison study among women with a prior Ct infection, in which the Pgp3 assay found 74% seropositives and the Medac assay found 45%, suggests the difference likely reflects the higher sensitivity of the Pgp3 test and not necessarily a higher prevalence of Ct infection in England compared with the Netherlands.[4 16] Both the English study and our study observed an increase in seroprevalence with age in women, which levelled out around age 30 years.[4]

Identified risk factors for Ct seropositivity found in our study are largely consistent with those found in other population-based studies.[4 22 23] We found an association between migration background and Ct seropositivity, with similar effect size as found for race/ethnicity in a study in the USA.[23] Reasons for this association might be that immune response to Ct differs across ethnic groups.[24 25] It could also be that migration background is a proxy of lower socioeconomic status. However, we did not find an association with level of education or urbanisation and Ct seropositivity.

For women, we identified trends across study rounds which could be explained by differences in Ct exposure.

Among women ≥25 years, seropositivity was highest in 1996 and significantly decreased in in 2007. This suggests that exposure to Ct was historically high before 1990 and subsequently decreased, possibly as a consequence of changes in sexual behaviour following extensive AIDS/HIV media coverage.[26] Other explanations might include Ct control efforts, though the absence of a further decline from 2007 to 2017 contrasts with increased control efforts in the Netherlands in this period. In 2017, seroprevalence increased with age, as expected for cumulative exposure, but levelled out around age 30 years. This may suggest reduction of exposure or waning of Ct antibodies in women >30 years, relative to those <30 years.

Among women aged <25 years, we observed no significant changes in age-specific seroprevalence between 1996 and 2017, which is surprising given increased control efforts during that time. Multiple explanations could explain this. First, it could be that due to limited statistical power, a change could not be detected in this age group. However, if anything, we observe an increase in seroprevalence over time rather than a decrease in women <25 years. This is supported by the birth cohort results which suggest the strongest increase by age is in the most recent cohort of young women (1988–1992). Second, targeted testing and treatment of high-risk populations could have an effect in that group, but that effect cannot be observed in a sample of low-risk individuals. Finally, seroprevalence trends may not directly indicate changes in exposure, but rather relate to factors such as treatment, frequency or duration of infections influencing seroconversion or reversion,[22 27 28] for which no data were collected in this study.

If test and treat of current Ct infection is scaled down in the foreseeable future, serology could be used to obtain reliable estimates of general population exposure.[1] Based on this study, we would recommend samples to be collected more frequently to be able to assess trends (eg, every 5 years), focus on those under 25 years old (because interpretation is closer to incidence) and include sufficient numbers from different migration backgrounds. Furthermore, it should be considered that scaling back Ct control programmes may not necessarily impact transmission but could lead to an increase in sequelae. Therefore, monitoring of sequelae is crucial, and biomarkers to predict the progression to scarring sequelae, such as PID and infertility, are needed. Assays that use Ct antibody profiles as predictors for disease progression are currently under development and could be incorporated into Ct serosurveillance.[21 29 30]

We have not found evidence for a decrease in population seroprevalence in those under 25 years old despite decades of intensified testing-and-treatment efforts in the Netherlands. Repeated seroprevalence studies in the future would be useful to monitor Ct burden in the general population.

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