Aus dem Robert Koch-Institut, Berlin

DISSERTATION

Surveillance von Infektionen mit *Chlamydia trachomatis* und von Antibiotika-Resistenzen von *Neisseria gonorrhoeae* in Deutschland

zur Erlangung des akademischen Grades

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von

Sandra Dudareva

aus Riga, Lettland

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1. Zusammenfassung

1.1. Abstract auf Deutsch

Sexuell übertragbare Infektionen (*sexually transmitted infections*, STI) verursachen eine hohe Krankheitslast (1). Durch fehlende Meldepflichten für Chlamydien- und Gonokokken-Infektion ist die Datenlage zu diesen Infektionen in Deutschland sehr eingeschränkt.

In Deutschland können Personen bei Vorliegen von Symptomen oder aus anamnestischen Gründen mit Kostenübernahme auf STI getestet werden (2). Zusätzlich gibt es zwei Screening-Programmen für Frauen. Seit 1995 werden schwangere Frauen und Frauen, die einen Schwangerschaftsabbruch durchführen, auf Chlamydien getestet (3-6). Für junge Frauen unter 25 Jahren wurde im Jahr 2008 ein Screening auf Chlamydien eingeführt (3-7). Die Bestimmung der *Neisseria gonorrhoeae*-Antibiotikaresistenzen (NG-AMR) spielt für eine erfolgreiche Therapieentscheidung eine wesentliche Rolle (8).

Informationen zu Chlamydien-Testungen und NG-AMR-Bestimmungen werden im Rahmen von zwei durch das Robert Koch-Institut koordinierten Labornetzwerken gesammelt. Das **Chlamydien-Laborsentinel** ist ein freiwilliges Laborbasiertes Sentinel System, in dessen Rahmen Daten zu den in teilnehmenden Laboren durchgeführten Chlamydien-Testungen an das RKI übermittelt werden (4-6). Die Daten können auf dem Detaillierungsgrad einzelner Tests sowie einzelner Personen ausgewertet werden (4, 6, 9). Im Rahmen des Gonokokken-Resistenz Netzwerks (**GORENET**) werden dem RKI seit 2014 Daten zu auf NG-AMR getestete Proben übermittelt (10, 11). Zusätzlich senden die teilnehmenden Labore einen Teil der Isolate für eine zentralisierte NG-AMR-Testung an das Konsiliarlabor für Gonokokken (10, 11).

Das RKI hat durch das **Chlamydien-Laborsentinel** zwischen den Jahren 2008 und 2014 Daten zu 3.877.588 Chlamydien-Tests erhoben (5, 6). Der Großteil der übermittelten Chlamydien-Tests (93%) stammte von Frauen (5, 6). Insgesamt 3,9 % der Untersuchungen bei Frauen und 11,0 % der Untersuchungen bei Männern waren positiv auf *Chlamydia trahomatis* (5, 6). Bei jungen Personen war der Anteil positiv getesteter Proben am höchsten: 6,8 % bei 15-19 und 5,9 % bei 20-24 Jahre alten Frauen sowie 15,4 % bei 15-19, 19,2 % bei 20-24 und 14,8 % bei 25-29 Jahre alten Männern (5, 6). Für 2.574.635 Chlamydien-Tests war die Auswertung auf Personen-Ebene möglich (9). Insgesamt 23,1 % der Frauen und 11,9 % der Männer wurden mehrfach getestet (9). Unter den Mehrfachtestern wurde eine Reinfektion bei 2,0 % der Frauen und 6,6 % der

Männer beobachtet (9). Unabhängig vom Testgrund und in allen Altersgruppen war es wahrscheinlicher positiv getestet zu werden (ORs 1,9-22,3), wenn in der Vergangenheit bereits ein positiver Vortest vorlag (9). Die Resultate aus dem Chlamydien-Laborsentinel betätigen, dass Präventionsmaßnahmen sowohl auf junge Frauen als auch auf junge Männer ausgerichtet werden sollen (5, 6). Neben dem bereits eingeführtem Chlamydien-Screening für junge Frauen, könnte ein Risiko-adaptiertes Screening auch für junge Männer erwogen werden (5, 6).

Durch **GORENET** konnten in den Jahren 2014-2015 Informationen zu 1.654 auf NG-AMR getesteten Proben erhoben werden und 537 Isolate wurden im Konsiliarlabor für Gonokokken auf NG-AMR getestet (10, 11). Resistenzen gegenüber Ceftriaxon wurden nicht beobachtet (10, 11). Gegen Cefixim wiesen 1,9 % (2014) und 1,4 % (2015) der Isolate Resistenzen auf, gegen Azithromycin entsprechend 11,9 % (2014) und 9,8 % (2015) (10, 11). Somit konnten wir feststellen, dass die Therapieempfehlung entsprechend der Leitlinie (8, 12) weiter umgesetzt werden kann (10, 11). Da die NG-AMR-Situation schnell wieder verändern kann, muss sie kontinuierlich beobachtet werden und die Therapieleitlinien entsprechend zeitgerecht angepasst werden (10, 11). Um die Überwachung sowohl von Chlamydien-Infektionen als auch der NG-AMR-Situation in Deutschland zu ermöglichen, sollten die aufgebauten Systeme weiter geführt werden (6, 10, 11).

1.2. Abstract auf English

Sexually transmitted infections (STIs) cause significant disease burden (1). As chlamydia and gonococcal infections are not reportable, data on these infections in Germany is very limited.

In Germany persons are tested for STI in the presence of symptoms or due to anamnestic reasons. In addition, there are two screening programs for women. Pregnant women are tested for chlamydia since 1995 (3-6). For women below 25 years of age the screening was introduced in year 2008 (3-7). The determination of *Neisseria gonorrhoeae* antibiotic resistance (NG-AMR) plays an essential role in an appropriate therapy decision (8).

Information on chlamydia testing and NG-AMR determination is collected through two laboratory-based projects at the RKI. The **Chlamydia Laboratory Sentinel** is a voluntary laboratory-based sentinel collecting data on performed chlamydia tests in the participating laboratories (4-6). The data can be analysed on level of tests and on level of tested persons (4, 6, 9). The Gonococcal Resistance Network (GORENET) is collecting since

2014 information on samples tested for NG-AMR and collects isolates for centralised NG-AMR testing towards ceftriaxone, cefixime, azithromycin, penicillin and ciprofloxacin in Conciliar Laboratory (10, 11).

For the period 2008-2014 RKI has collected data on 3,877,588 chlamydia tests were collected in frame of the **Chlamydia Laboratory Sentinel** (5, 6). Majority of the chlamydia tests (93 %) were performed in women (5, 6).For women, the proportion positive was 3.9 %, for men 11.0 % (5, 6). The proportion positive was highest among younger persons: 6.8 % among 15-19 and 5.9 % among 20-24 years old women, and 15.4 % among 15-19, 19.2 % among 20-24 and 14.8 % among 25-29 year old men (5, 6). A total of 2,574,635 chlamydia tests could be included in the analysis at the level of tested persons (9). Altogether 23.1 % of women and 11.9 % of men were tested multiple times (9). Among the multiple testers, reinfection was observed for women in 2.0 % and for men in 6.6 % (9). Regardless of reason for getting tested and across all age groups, it was more likely to test positive (ORs 1.9-22.3) if the person has been tested positive previously (9). The results from the Chlamydia Laboratory Sentinel showed that preventive measures are necessary, especially for young women and men (5, 6). A risk-adapted screening for chlamydia infection for women and men should be considered (5, 6).

For the period 2014-2015 GORENET collected information on 1,654 samples tested for NG-AMR and 537 isolates were centrally tested in the Consiliary Laboratory for NG-AMR (10). None was resistant towards ceftriaxone (10, 11). In 2014 and 2015, 1.9 % and 1.4 % of the isolates, respectively, were resistant to cefixime and 11.9 % and 9.8 %, respectively, to azithromycin (10, 11). These results mean that antibiotics recommended for gonorrhea therapy (8, 12) can continue to be used (10, 11). Since the NG-AMR situation can rapidly change, it must be monitored continuously and the therapy guidelines adjusted in a timely manner (10, 11). In order to ensure continuous monitoring of chlamydia infection and NG-AMR development in Germany, it seems appropriate to continue the data and isolate collection established by the two systems (6, 10, 11).

1.3. Einführung

1.3.1. Sexuell übertragbare Infektionen

Chlamydien-, Gonokokken-, Trichomonaden-Infektionen und Syphilis sind mit jährlich rund 356 Millionen neuen Infektionen für eine hohe Krankheitslast verantwortlich (13). Davon entfallen 127 Millionen Infektionen auf Chlamydien-, 87 Millionen auf Gonokokken-, 156 auf Trichomonaden-Infektion und 6.4 Millionen auf Syphilis (13). Für die genannten STI stehen wirksame Prävention-Möglichkeiten und Therapieoptionen zur Verfügung (14). Unbehandelte STI können zu Folgeerscheinungen führen (15-19). Rektale Chlamydien- und Gonokokken-Infektionen können die Übertragung von HIV-Infektionen erhöhen (20).

Dadurch, dass die STI Infektionen, insbesondere die Chlamydien-Infektion, asymptomatisch verlaufen können, ist die Anzahl der durch das Meldesystem erfassten Infektionen stark von Screening-Maßnahmen und der Testhäufigkeit abhängig (21, 22). Daten des ECDC (European Centre for Disease Prevention and Control) zeigen, dass die jährliche Meldeinzidenz der Chlamydien- und Gonokokken-Infektionen je nach europäischem Land zwischen 0 und 662 Infektionen pro 100.000 Einwohner*nnen für Chlamydien-Infektionen variiert, sowie zwischen 0,1 und 75 für Gonokokken-Infektionen und 0,6 und 15 für Syphilis (21). Da sich die Surveillancesysteme und Teststrategien in verschiedenen Ländern stark unterscheiden, sind die Daten aus unterschiedlichen Ländern nur sehr eingeschränkt vergleichbar (21, 23). Eine zuverlässige Aussage zur tatsächlichen epidemiologischen Situation in Europa kann anhand der Daten des ECDC nicht getroffen werden.

In Deutschland, existiert mit Ausnahme von Sachsen keine Meldepflicht für Chlamydien- und Gonokokken-Infektionen. Daher ist die Datenlage zu diesen Infektionen sehr eingeschränkt. Die Daten aus Sachsen zeigen einen ständigen Anstieg bei Chlamydien- und Gonokokken-Infektionen in den letzten Jahren: von 41 Chlamydien-Infektionen und 8 Gonokokken-Infektion pro 100.000 Einwohner*nnen im Jahr 2004 auf entsprechend 97 und 21 Infektionen im Jahr 2017 (24, 25). Diese Zunahme könnte sowohl durch vermehrtes Testen, als auch durch eine reale Zunahme der Inzidenz erklärbar sein.

Infektionen mit Syphilis (Nachweis von *Treponema pallidum*) sind in Deutschland gemäß § 7 Abs. 3 Infektionsschutzgesetz (IfSG) meldepflichtig (26). Die Syphilis-Daten werden regelmäßig am RKI gesammelt und ausgewertet (27-29).

Zwischen den Jahren 2003 und 2009 hat das Robert Koch-Institut (RKI) eine bundesweite STI-Sentinel-Studie durchgeführt (30). In den teilnehmenden Einrichtungen wurde im Zeitverlauf ein leicht ansteigender Positivanteil zwischen 3,3 % im Jahr 2003 und 4,5 %

im Jahr 2008 beobachtet (30). Da nur ein kleiner Anteil entsprechender Einrichtungen in Deutschland an dieser Sentinel-Erhebung teilgenommen hat, sind die Daten nicht repräsentativ für Gesamt Deutschland (30). Die KiGGS Studie, die unter Kindern und Jugendlichen in Deutschland durchgeführt wurde, untersuchte unter anderem auch die Chlamydien-Prävalenz bei sexuell aktiven Jugendlichen (31, 32). In den Jahren 2003 bis 2006 wurde bei 17 Jahre alten Mädchen eine Prävalenz von 4,6 % (95 % KI 1.4-7.7 %) beobachtet (31). In den Jahren 2014 bis 2017 zeigte sich eine Prävalenz an Chlamydien-Infektion von 9,6 % (95 % KI 0,0-23) bei 15-17 Jahre alten Mädchen und zwischen 0,1 % und 3,4 % bei 15-17 Jahre alten Jungen (32). Die DEGS Studie, die unter Erwachsener in Deutschland in den Jahren 2008-2011 durchgeführt wurde, zeigte eine Prävalenz von 2,3 % (95 % KI 1,0-5,3 %) bei 18-24 und 1,2 % (95 % KI 0,4-3,5 %) bei 25-29 Jahre alten Frauen sowie 1,9 % (95 % KI 0,8-4,2 %) bei 18-24 und 3,5 % (95 % KI 1,6-7,7 %) bei 25-29 Jahre alten Männern (32).

Vor diesem Hintergrund und parallel zu anderen westeuropäischen Ländern mit Meldepflicht ist davon auszugehen, dass Infektionen mit Chlamydien und Gonokokken in Deutschland eine hohe und steigende Krankheitslast verursachen. Diese Lage wird verstärkt durch die Problematik der bereits bestehenden und sich stetig ausweitenden Antibiotika-Resistenz bei Gonokokken-Infektionen.

Um die Datenlage zu Chlamydien- und Gonokokken-Infektionen zu verbessern, wurden im Rahmen der vorliegenden Doktorarbeit Daten zu Chlamydien- und Gonokokken-Infektionen in Deutschland aus den teilnehmenden Laboren erhoben und ausgewertet.

1.3.2. Chlamydien-Infektion

Chlamydien-Infektionen der Serotypen D-K können einen asymptomatischen Verlauf haben und somit unentdeckt bleiben, wenn nur symptomatische Personen getestet werden (15, 22). Eine unerkannte und unbehandelte Infektion kann zu schweren Folgeerkrankungen führen (15-17). Die Prävalenz der Chlamydien-Infektionen sind am höchsten unter jungen Erwachsenen unter 30 Jahren (16, 33). Die häufigsten schwerwiegende Folgen bei Frauen sind Unterleibsentzündungen, die zu Verklebungen der Eileiter, chronischen Schmerzen, extrauterinen Schwangerschaften und letztlich zu Infertilität führen können (16, 17). In der Literatur wird das Ausmaß dieser Folgeerkrankungen sehr unterschiedlich eingeschätzt (33-36). So wird zum Beispiel aus prospektiven Studien berichtet, dass 0 bis 30 % mit Chlamydien infizierte Frauen Unterleibsentzündungen entwickeln. Diese Folgen treten bis zu 6-mal häufiger auf als bei Frauen, die keine Chlamydien-Infektion hatten (33-36). Auch bei Männern treten

Folgeerscheinungen auf, wie zum Beispiel Epididymitis, was auch zu einer Unfruchtbarkeit führen kann (16).

Die *Chlamydia trachomatis* Serotypen L1-L3 verursachen eine zum Teil invasive Infektion (18). Lymphogranuloma venreum (LGV) Häufungen sind bei HIV positiven MSM in mehreren Europäischen Ländern inklusive Deutschland beschrieben (37-43). In der PARIS Studie wurden in circa 10 bis 15 % aller rektalen Chlamdien Infektionen von L-Serotypen gefunden (44).

Um mögliche schwerwiegende Folgen von Chlamydien-Infektionen zu vermeiden und die weitere Übertragung der Infektion zu stoppen, muss es möglichst frühzeitig diagnostiziert und behandelt werden. Für Behandlung sind gut wirksame Antibiotika verfügbar (14). Auch Sexualpartner*innen sollten untersucht und ggf. behandelt werden um eine wiederholte Infektion zu vermeiden (14). Wegen des häufig asymptomatischen Verlaufs soll die Testung nicht nur basierend auf Symptomen, sondern verstärkter auch anhand anamnestischer Angaben angeboten werden. Für besonders betroffenen Bevölkerungsgruppen, wie z.B. junge Erwachsene, kann ein opportunistisches Screening helfen, unentdeckte Infektionen zu finden und somit die Krankheitslast zu reduzieren (45).

In Deutschland werden Personen auf Chlamydien getestet, wenn entsprechende Symptome vorliegen oder bei einer Sexualpartner*in eine Chlamydien-Infektion diagnostiziert wurde (2). Seit 1995 werden schwangere Frauen und Frauen, die einen Schwangerschaftsabbruch durchführen, auf Chlamydien getestet (3-6). Für junge Frauen unter 25 Jahren wurde im Jahr 2008 ein Screening auf Chlamydien eingeführt (3-7).

1.3.3. Gonokokken-Infektion

Gonokokken-Infektionen kommen ähnlich wie Chlamydien-Infektionen insbesondere bei jungen Erwachsenen vor (46, 47). MSM weisen eine höhere Prävalenz auf (48, 49). So wurde bei MSM in der PARIS-Studie (*Pharyngeal And Rectal Infection Screening*), die zwischen den Jahren 2009 und 2010 durchgeführt wurde, ein Positivanteil von 4,6 % in rektalen Abstrichen gefunden (50). Eine typische klinische Manifestation bei Frauen ist die Zervizitis, welche zu Entzündung des kleinen Beckens, Eileiterverschluss und extrauteriner Schwangerschaften führen kann (51, 52). Bei Männern kommt es häufig zu einer eitrigen Urethritis (18, 19). Besonders problematisch ist allerdings der häufig auftretende asymptomatische Verlauf der Infektion. Rektale und pharyngeale Infektionen verlaufen deutlich häufiger asymptomatisch als die genitalen Infektionen (50). Bei Frauen verläuft eine urethrale Gonokokken-Infektion in etwa 30-80 % asymptomatisch, bei Männern in etwa 5 % (19, 53).

Neisseria gonorrhoeae hat die Fähigkeit, in kurzer Zeit Resistenzen gegen alle gängigen Antibiotika zu entwickeln (54). In Europa und auch weltweit wurden zwischen den Jahren 2010 und 2014 immer mehr Antibiotikaresistenzen (AMR) bei Gonokokken beobachtet, auch gegenüber Cephalosporine der dritter Generation (55-59). Diese besorgniserregende Entwicklung trug dazu bei, dass sowohl die WHO als auch das ECDC die Überwachung und Kontrolle von Infektionen mit antibiotikaresistenten Gonokokken hoch priorisiert haben (1). In den Jahren 2009 bis 2013 berichtete das europäische Netzwerk Euro-GASP wiederholt über Ceftriaxon und Cefixim resistente Isolate (46). AMR bei Gonokokken wird durch Messung der minimalen Hemmkonzentration (MHK) wie z.B. mit E-Test bestimmt (60). Häufig wird für den Nachweis einer Gonokokken-Infektion auf eine Anzucht verzichtet, stattdessen werden zumeist sensitivere molekularbiologische Testverfahren verwendet, die aber keine Resistenztestung ermöglichen (10, 11, 61).

Bis 2018 wurde bei einer Gonokokken-Infektion eine gleichzeitige Behandlung mit Ceftriaxon (ggf. Cefixim) und Azithromycin als Therapie der erster Wahl empfohlen (12). Die in dem Jahr 2018 veröffentlichte Leitlinie sieht bei adhärenten Patient*innen eine Monotherapie mit Ceftriaxon (ggf. Cefixim) vor. Nicht-adhärente Patient*innen erhalten als First-Line weiterhin die duale Therapie (8).

1.3.4. Chlamydien-Laborsentinel

Im Jahr 2010 etablierte das RKI ein freiwilliges laborbasiertes Sentinel, welches das Screening Programm für Frauen unter 25 Jahren (7) evaluieren sollte (4). In Rahmen dieses Labor-Sentinels wurden Daten zu den in teilnehmenden Laboren sei dem Jahr 2008 durchgeführten Chlamydien-Tests nach Geschlecht, Alter, und Testgrund erhoben und ausgewertet (4-6).

1.3.5. Gonokokken Resistenz Netzwerk (GORENET)

Im Jahr 2013 etablierte das RKI und das Konsiliarlabor für Gonokokken das Gonokokken Residenz Netzwerk (GORENET) (10, 11, 61). Ziel war es, die NG-AMR Situation in Deutschland mit Hilfe einer einheitlichen Methodik abzubilden (10, 11, 61). Die am GORENET teilnehmenden Labore übermitteln dem RKI Daten zu in den Laboren durchgeführten NG-AMR Testungen. Zusätzlich werden ausgewählte Isolate an das Konsiliarlabor für eine zentralisierte AMR Testung mit einheitlicher Methodik gesendet (10, 11).

1.3.6. Doktorarbeit

Im Rahmen der Doktorarbeit wurden Daten aus dem Chlamydien-Laborsentinel und aus GORENET gesammelt und ausgewertet. Die Ergebnisse wurden in Publikationen dargestellt:

- die Publikation 1 mit dem Titel ***„Establishment of a voluntary electronic Chlamydia trachomatis laboratory surveillance system in Germany, 2008 to 2014“*** (6) widmet sich der Bewertung des Chlamydien-Laborsentinels als Daten-Erhebungsinstrument zu Chlamydien in Deutschland sowie der Analyse der erhobenen Daten anhand der in der Studie verfügbaren Merkmalen;
- in der Publikation 2 mit dem Titel ***„Not again! Effect of previous test results, age group and reason for testing on (re-)infection with Chlamydia trachomatis in Germany“*** (9) sind Daten aus dem Chlamydien-Laborsentinel auf Personenebene dargestellt. Hier werden die Anzahl der durchgeführten Tests pro Person beschrieben und Zusammenhänge zwischen früheren und darauffolgenden Testergebnissen untersucht;
- in der Publikation 3 mit dem Titel ***„Antimicrobial resistance of Neisseria gonorrhoeae in Germany: low levels of cephalosporin resistance, but high azithromycin resistance“*** (10) werden Ergebnisse aus Resistenz-Testungen der teilnehmenden Labore sowie AMR-Test-Ergebnisse aus dem Konsiliarlabor für Gonokokken analysiert.

Auf dieser Grundlage wurden im Rahmen der Doktorarbeit folgende Fragestellungen untersucht:

- Wieviele Untersuchungen auf Chlamydien werden insgesamt und pro Labor übermittelt und wie vollständig sind die durch das Chlamydien-Laborsentinel erhobenen Daten?
- Wie ist die geographische Abdeckung des Chlamydien-Laborsentinels?
- Wie repräsentativ sind die Daten zu Chlamydien-Tests im Chlamydien-Laborsentinel im Vergleich zu allen Chlamydien-Tests in Deutschland?
- Wie hoch ist die Anzahl der durchgeführten Chlamydien-Tests und der Anteil der positiven Ergebnisse nach Geschlecht, Alter und Untersuchungsgrund?
- Wie hoch ist die Anzahl der Chlamydien-Tests pro Person, und in welchen Abständen werden Untersuchungen bei Mehrfachtestungen durchgeführt?
- Wie häufig findet eine Reinfektion mit Chlamydien statt?
- Welche Faktoren sind damit assoziiert, positiv auf Clamydien getestet zu werden?
- Wie ist die geographische Abdeckung der GORENET?
- Wie hoch ist die Anzahl der durchgeführten Gonokokken-Antibiotika-Resistenz-Testungen im Rahmen der Studie und welche epidemiologische Merkmale machen diese aus?

- Welche Resistenzen weisen die im Konsiliarlabor für Gonokokken nachgetesteten Isolate auf, und gibt es Veränderungen im Zeitverlauf?

1.4. Material und Methodik

1.4.1. Chlamydien-Laborsentinel

Chlamydien-Laborsentinel erhebt anonymisierte Daten zu in den Laboren durchgeführten *Chlamydien*-Tests (4-6). Das Labor Sentinel wurde im Jahr 2010 aufgebaut und hat Daten retrospektiv ab 2008 erhoben (4-6). Labore, die zu einem späteren Zeitpunkt dazukamen haben soweit möglich Daten ab 2008 übermittelt (4, 6). Es wurden Informationen zu Testergebnissen, zu Testgründen und weitere patientenbezogenen Informationen (z.B. Geschlecht, Geburtsjahr, 3-stellige Postleitzahl des Wohnortes, Krankenversicherung, Probenmaterial) erhoben. Die Daten wurden von den Laboren in verschlüsselter Form übermittelt (6).

Die teilnehmenden Labore wurden anhand der Anzahl der übermittelten Chlamydien-Tests pro Jahr beschrieben (4, 6). Die Vollständigkeit der Informationen in den erhobenen Variablen wurde insgesamt und pro Labor ausgewertet. Anhand von KBV (Kassenärztliche Bundesvereinigung) Daten wurde die Repräsentativität der erhobenen Daten berechnet (4, 6). Anhand der übermittelten Postleitzahlen wurde die geographische Abdeckung pro 100.000 Einwohner*innen in Deutschland für den Zeitraum 2008-2014 dargestellt (4, 6). Die bei Frauen und Männern durchgeführten Chlamydien-Tests wurden nach Alter, Geschlecht, Testgrund, Bundesland und untersuchtem Material ausgewertet (4, 6). Diese Auswertungen wurden auf Grundlage der Anzahl durchgeführter Untersuchungen vorgenommen und somit ist es möglich, dass von einer Person mehrere Untersuchungen in den Auswertungen eingeschlossen wurden (4, 6).

Für die Auswertung zu Mehrfachtestungen wurden Daten herangezogen, die es erlaubten, die Patient*innen Daten anhand der Patienten-ID für drei und mehr Jahre zu berücksichtigen (9). Basierend auf Literatur zu falsch positiven Testergebnissen aufgrund residualer DNA wurden nur Tests, die in einem Abstand von mindestens 30 Tagen durchgeführt wurden, als separate Testungen definiert (9).

Für die Beschreibung der Mehrfachuntersuchungen wurde die Anzahl der Tests pro Person nach Geschlecht, Altersgruppe, Testgrund und Testergebnis ausgewertet (9). Hierfür wurden die von den Laboren übermittelten pseudonymisierten Personenkennzahlen genutzt (9). Bei den Wiederholungstestern wurde die mittlere Zeit zwischen den

Untersuchungen anhand des ersten und des nachfolgenden Untersuchungsergebnisses berechnet (9). "Erstes Untersuchungsergebnis" ist definiert als die erste Chlamydien-Testung, die im Laborsentinel erfasst wurde (9). Dies ist jedoch möglicherweise nicht die erste Chlamydien-Testung des Individuums (9).

1.4.2. GORENET

Das GORENET-Labornetzwerk wurde im Jahr 2013 gegründet und erhebt seit dem Jahr 2014 Daten zu NG-AMR-Testungen (10, 11, 61). Für diese Testungen werden Informationen zu Geburtsjahr, Geschlecht, dreistellige Postleitzahl, Einsendedatum der Probe, Probenmaterial, Angaben zum Einsender, Testmethode, Interpretationsstandard und NG-AMR-Testergebnis übermittelt (10, 11). Zusätzlich senden die teilnehmenden Labore Isolate an das Konsiliarlabor für Gonokokken für eine wiederholte Testung mit E-Test (10, 11). Die Daten werden Fall-Basiert und anononymisiert an das RKI übermittelt (10, 11).

Das Konsiliarlabor führt eine wiederholte zentralisierte NG-AMR Testung für die relevanten Antibiotika mit E-Test durch (10, 11). Die NG-AMR wurde für Ceftriaxon, Cefixim, Azithromycin, Ciprofloxacin und Penicillin bestimmt (10, 11). Beta-Lactamase Produktion wurde mit Nitrocefin-Tests überprüft (10, 11). Die Ergebnisse wurden nach EUCAST 4.0 (European Committee on Antimicrobial Susceptibility Testing 2014) Kriterien (62) interpretiert (10, 11).

Für an das RKI übermittelte NG-AMR-Testergebnisse wurden folgende Merkmale dargestellt: Anzahl der an das RKI übermittelten Proben pro Labor, geographische Abdeckung der teilnehmenden Labore und Proben, Alter, Geschlecht, Testmaterial, Organisationsform und Spezialisierung des Einsenders (10, 11). Für die im Konsiliarlabor wiederholt getesteten Isolate wurden MHK-Verteilung und der Anteil von sensiblen, intermediären und resistenten Isolaten berechnet (10, 11).

1.4.3. Statistische Methoden

Die genauen statistischen Methoden können aus den jeweiligen Publikationen und Berichten entnommen werden (4, 6, 9, 10).

1.4.4. Ethische Aspekte und Datenschutz

Im Rahmen des Chlamydien-Laborsentinels wurden vollständig pseudonymisierte und im Rahmen von GORENET vollständig anonymisierte Daten erhoben. Es wurde keine patientenidentifizierenden Daten erhoben oder übermittelt (4, 6, 9, 10). Die Daten wurden ausschließlich vom dem Projektpersonal bearbeitet. Alle Maßnahmen zum Datenschutz sind vom Datenschutzbeauftragten des RKI begutachtet und genehmigt worden.

1.5. Ergebnisse

1.5.1. Chlamydien-Laborsentinel

Für die Jahre 2008 bis 2014 (Datenstand 24. November 2015) wurden von den 24 teilnehmenden Laboren insgesamt 3.877.588 Chlamydien-Testungen durchgeführt und berichtet (5, 6). Fünfzehn dieser Labore haben die Daten für den gesamten Untersuchungszeitraum berichtet, andere nahmen erst ab einem späteren Zeitpunkt an der Studie teil (6). Untersuchungen aus einem einzelnen deutschlandweit arbeitenden Labor machten 42 % aller übermittelten Untersuchungen aus (6). Berechnet auf die Gesamtzahl aller übermittelten Tests fehlten in weniger als 1 % der Pflichtvariablen und zwischen 10 % und 80 % der optionalen Variablen die jeweiligen Informationen (6).

Die Auswertung zur Repräsentativität konnte mit KBV-Abrechnungsdaten aus den Jahren 2011-2012 durchgeführt werden (6). Auf Grundlage von KBV-Abrechnungsdaten konnte geschätzt werden, dass das Chlamydien-Laborsentinel insgesamt 34,3 % aller Chlamydien-Tests der gesetzlich versicherten Personen in Deutschland repräsentiert (6). Das Chlamydien-Laborsentinel erfasste zwischen 4,4 % (Baden-Württemberg) und 60,9 % (Thüringen) aller durchgeführten Chlamydien-Test (6).

Bei insgesamt 3.330.628 Chlamydien-Tests wurde eine Postleitzahl übermittelt, die die Zuordnung zum Wohnort ermöglicht (6). Es bestehen erhebliche regionale Unterschiede in der geographischen Abdeckung. Insbesondere die südwestlichen Bundesländer zeigten eine niedrige Abdeckung (Abbildung 1, Seite 2 in Publikation 1 (6)).

1.5.1.1. Auswertung aller Chlamydien Testungen

Von den insgesamt 3.877.588 berichteten Chlamydien-Tests wurden 92,8 % (3.599.821) bei Frauen durchgeführt (5, 6). Der größte Anteil aller durchgeführten Tests wurde aus den Altersgruppen 20-24 Jahre (Frauen) und 20-34 Jahre (Männer) berichtet (4, 6). Siehe Abbildung 2, Seite 3 in Publikation 1 (6).

Insgesamt 41,9 % aller Tests bei Frauen wurden im Rahmen des „Screenings in der Schwangerschaft“ durchgeführt (5, 6). Weitere 26,9 % aller Tests fanden in Rahmen des „Screening für Frauen unter 25 Jahren“ und 28,7 % wegen Beschwerden oder aus anamnestischen Gründen statt (5, 6). In die Auswertung zum getesteten Material wurden Chlamydien-Tests von Männern eingeschlossen (6). Als Testmaterial wurde „Abstrich nicht näher bezeichnet“ am häufigsten angegeben (49,0 %), gefolgt von „Urin“ (32,5 %).

Weitere 5,3 %, 3,1 % und 1,9 % konnte entsprechend Abstrichen aus Urethra, Rektum und Pharynx zugeordnet werden (6).

Im gesamtem Untersuchungszeitraum konnte ein Positivenanteil von 3,9 % (95 % KI 3,9-4,0 %) bei Frauen und 11,0 % (95 % KI 10,9-11,2 %) bei Männern beobachtet werden (5, 6). Die höchsten Positivenanteile wurden bei 15 und 19 Jahre alten Frauen (6,8 %) beobachtet (5, 6). Dabei war der Positivenanteil am höchsten (10,0 %) in der Gruppe für Frauen, die im Rahmen des Schwangerschaftsscreenings getestet worden sind (5, 6). Bei Männern war der Positivenanteil am höchsten in den Altersgruppen 15-20 (15,4 %), 20-24 (19,2 %) und 25-29 (14,8 %) Jahre (5, 6). Der Positivenanteil bei Männern war am höchsten in Rektalabstrichen (12,3 %) und in nicht näher bezeichneten Abstrichen (13,4 %) (6). Der Positivenanteil bei Frauen und Männern nach Altersgruppe und Testgrund ist in Abbildung 3 in der Publikation 1 dargestellt (6).

1.5.1.2. Auswertung zu Mehrfachtestungen

Die 2.574.635 Chlamydien-Tests von 16 Sentinel-Laboren, die in die Auswertung zu Mehrfachuntersuchungen eingeschlossen wurden, stammen von 123.033 Männern und 1.815.494 Frauen (9). Insgesamt 23 % der Frauen sowie 12 % der Männer wurden mehrfach untersucht, hiervon die Mehrheit (70 % bzw. 74 %) zweimal (9).

Bei 2 % der Frauen und 7 % der Männer, die bereits einmal positiv getestet wurden, wurde eine Reinfektion mit Chlamydien festgestellt (9). Die mediane Zeit vom ersten zum zweiten positiven Test (Reinfektion) betrug 4,2 Monate (IQR 2,1-13,0 Monate) bei Frauen und 4,0 Monate (IQR 2,3-16,6 Monate) bei Männern (9).

Die Wahrscheinlichkeit, positiv getestet zu werden, war höher für Personen, die schon einmal positiv getestet waren ($p < 0,01$) (9). Die Ergebnisse sind in der Tabelle 3 auf Seite 5 sowie in den Abbildungen 2, 3 und 4 auf Seite 6 in Publikation 2 dargestellt (9).

1.5.2. GORENET

Am GORENET nahmen 21 Labore im Jahr 2014 und 23 Labore im Jahr 2015 23 teil (10, 11). Insgesamt wurden Informationen zu 1656 NG-AMR Testungen übermittelt (10, 11). Die Anzahl der Proben, zu denen Informationen an das RKI übermittelt wurden variierte zwischen 2 und 305 Proben pro Labor, der Median lag bei 43 Proben (10, 11). Die Abbildung 1 auf Seite 4 der Publikation 3 zeigt die regionale Verteilung aller an das RKI übermittelten Daten (10). Die Abdeckung im Norden, Osten und Westen von Deutschlands war im Vergleich zu Mitteldeutschland, Süden und Südosten als gut zu bewerten (10, 11).

Am häufigsten (84 %) wurden die Proben aus dem niedergelassenen Bereich eingesendet (10, 11). Die Mehrheit der Proben (90 %) stammten von Männern (10, 11). Der Altersmedian bei Männern ((32 (IQR 25-44) Jahre) war höher als bei Frauen (25 (IQR 22-40) Jahre), $p < 0.001$ (10, 11). Der Großteil der Proben von Männern wurde aus dem Fachbereich Urologie (74 %) und von Frauen aus dem Fachbereich Gynäkologie (80 %) eingesendet (7, 8). Das am häufigsten untersucht Material bei Männern war ein „urethraler Abstrich“ und bei Frauen ein „endozervikaler Abstrich“ oder „vaginaler Abstrich“ (10, 11).

Im Konsiliarlabor wurden insgesamt 537 Isolate zentralisiert untersucht (10, 11). Keiner der getesteten Isolate zeigte Resistenzen gegen Ceftriaxon (10, 11). In 2014 ggf. 2015 waren 1,9 % bzw. 1,4 % der Isolate resistent gegen Cefixim, 11,9 % bzw. 9,8 % gegen Azithromycin, 72,0 % bzw. 58,3 % gegen Ciprofloxacin ($p < 0,05$) und 29,1 % bzw. 18,8 % gegenüber Penicillin ($p < 0,05$) (10, 11). Weitere 33,7 % und 28,3 % der Isolate zeigten 2014 bzw. 2015 eine mittlere Empfindlichkeit gegenüber Azithromycin (10, 11). 60,5 % (2014) und 66,1 % (2015) der Isolate zeigten eine mittlere Penicillinempfindlichkeit (10, 11). Auswertungen der sensitiven, intermediären und resistenten Stämme sind in Tabelle 2 auf Seite 6 in Publikation 3 dargestellt (10).

1.6. Diskussion

1.6.1. Chlamydien-Laborsentinel

Mit dem Chlamydien-Laborsentinel wurde ein funktionierendes Datenerhebungsinstrument aufgebaut, das circa ein Drittel aller Chlamydien-Tests in Deutschland repräsentiert (6). Die erhobenen Daten konnten gut die Chlamydien-Testungen und deren Ergebnisse deutschlandweit darstellen (6).

Die Positivenanteile waren bei jungen Frauen und Männern am höchsten, ähnlich, wie in den Bevölkerungsbasierten Studien des RKI in Deutschland und in den Internationalen Studien (6, 63-69). Die Daten legen nahe, dass Präventionsmaßnahmen insbesondere auf junge Frauen und Männer ausgerichtet werden müssen (6, 9).

Die im Chlamydien-Laborsentinel durchwegs niedrigeren Positivenanteile unter Frauen im Vergleich zu Männern ist vermutlich durch die Testung der Frauen im Rahmen der verschiedenen Screening-Programme erklärbar (6). Mit Hilfe der Screening-Untersuchungen konnten auch asymptomatische Infektionen gefunden und somit klinische Spätfolgen vermieden werden. Das Screening für junge Frauen ist somit eine

notwendige und wichtige Maßnahme individuellen gesundheitlichen Nutzens wie auch aus Public Health Sicht (6).

Da es für Männer keine Screening Programme gibt, werden Männer häufiger nur beim Vorliegen der Symptome getestet. Darüber hinaus ist vermutlich eine wesentliche Anzahl aller Proben von MSM in dem Datensatz erhalten (6, 70). In der PARIS-Studie wurden MSM, die ein Test- und Beratungszentrum aufsuchten, auf Chlamydien und Gonokokken untersucht (50). Dabei wurde eine Chlamydien-Prävalenz von 9,4 % gefunden; 57 % der urethralen und 88 % der rektalen Infektionen waren in dieser Studie asymptomatisch (50). Daher ist ein Risiko basiertes Screening auch für Männern zu erwägen (2, 9).

Mit der Auswertung zu Mehrfachtestungen und Einflussfaktoren auf Infektionen mit Chlamydien konnte gezeigt werden, dass zuvor positiv auf Chlamydien getestete Frauen und Männer häufiger wieder positiv getestet wurden (9). Daher sind gezielte Präventionsmaßnahmen notwendig, die insbesondere auf junge Frauen und Männer gerichtet sind (9). Ein ausreichendes Bewusstsein über Infektion, Reinfektion und Prävention ist insbesondere deshalb wichtig, weil in Deutschland keine standardisierte Partnerbenachrichtigung stattfindet. Um Komplikationen zu vermeiden bzw. den Therapieerfolg zu bestätigen, ist für junge Freuen eine erneute Testung innerhalb von 3 bis 6 Monaten nach der Therapie empfohlen (9, 71). Darüber hinaus sollte jede unter 25-jährige Frau einmal pro Jahr auf Chlamydien gescreent werden (3). Die geringe Testanzahl pro Person bei Frauen deutet auf eine mangelhafte Abdeckung durch das Screening hin (9).

Das Chlamydien-Laborsentinel trägt zum epidemiologischen Wissen über Chlamydien in Deutschland bei. Die durch das Laborsentinel gesammelten Daten haben eine gute Abdeckung und ermöglichen detaillierte Auswertungen (6).

Die Erhebung von positiven wie negativen Testergebnissen macht es möglich, im Gegensatz zu Meldedaten statt der Anzahl an Fällen auch die Positivenanteile zu berechnen (4, 6). Da STI, insbesondere die Chlamydien-Infektion, oft asymptomatisch verlaufen und daher oft kein Test durchgeführt wird, stellen Meldedaten die wahre Inzidenz dieser Infektion nicht dar. Ein weiterer Vorteil des Chlamydien-Laborsentinels ist, dass darin Wiederholungsuntersuchungen ausgewertet werden und der Anteil von Reinfektionen bestimmt werden kann (9).

So tragen die Ergebnisse des Chlamydien-Laborsentinels dazu bei, Test- und Therapieempfehlungen sowie Präventionsmaßnahmen für Frauen und Männer in Deutschland möglichst gut zu evaluieren und evidenzbasiert anpassen zu können. Die

Daten können darüber hinaus als Instrument zur Begleitevaluation der unterschiedlichen Chlamydien-bezogenen Interventionsmaßnahmen in Deutschland dienen.

1.6.2. GORENET

In Rahmen von GORENET konnten Informationen zu NG-AMR Proben aus ganz Deutschland erhoben werden. Mit Hilfe der im Konsiliarlabor nachgetesteten Isolate konnte die NG-AMR-Resistenzsituation in Deutschland beschrieben werden (10, 11). Die Überwachung der Resistenzsituation ist wichtig, um zeitnah auch kleine Veränderungen in der Resistenzentwicklung zu erkennen. Insbesondere betrifft dies First-Line-Therapie von Ceftriaxon, Cefixim und Azithromycin (10, 11).

Die Mehrheit aller NG-AMR-Tests wurden bei Männern durchgeführt (10, 11), ähnlich wie in anderen Datenerhebungen aus Deutschland von Horn et.al (72). In Euro-GASP Daten, die aus vielen europäischen Ländern gesammelt werden, wird diskutiert, dass mindestens etwa 50 % der Isolate von Männern aus der Gruppe der MSM stammen (73, 74). In GORENET wurde beobachtet, dass der Altersmedian von getesteten Männern höher war als der von Frauen (10, 11). Ähnliche Ergebnisse wurden sowohl in den Studien von Horn et.al als auch in Euro-GASP Daten beobachtet (72, 73).

Die Ceftriaxon und Cefixim Resistenz bei den in GORENET getesteten Isolaten blieb auf einem niedrigen Niveau. Es wurde bei keinem der wiederholt getesteten Isolate Resistenzen gegenüber Ceftriaxon beobachtet (10, 11). Die Cefixim Resistenz war bei weniger als 2 % der Isolate nachweisbar (10, 11). In den Jahren 2014 und 2015 wurde eine Abnahme der resistenten Stämmen auch in Euro-GASP beobachtet (46, 73), ähnlich wie in anderen Europäischen Ländern und weltweit (46, 58, 75-78). In den Jahren 2016 bis 2018 wurde in GORENET nur ein Isolat mit Resistenz gegen Ceftriaxon beobachtet, die Abnahme des Anteils resistenter Stämmen gegenüber Cefixim setzte sich fort (79). 2016 und 2017 zeigten sich in den Euro-GASP Daten keine Resistenzen gegen Ceftriaxon (46). Die Abnahme der Cefixim Resistenz ist möglicherweise mit einer entsprechenden Änderung der Therapierichtlinie erklärbar, die als Firstline-Substanz nicht mehr Cefixim, sondern Ceftriaxon vorsieht (8, 10, 11). Eine weitere Erklärung könnte sein, dass es zu Veränderungen in den zirkulierenden Sequenztypen gekommen ist. Die Ceftriaxon und Cefixim Resistenzen wurden in Zusammengang mit dem Sequenztyp ST1407 berichtet (80-82). Dieser Stamm wurde in den letzten fünf Jahren durch andere Stämme ersetzt (83). Die Resistenz sowie intermediäre Empfindlichkeit gegenüber Azithromycin war bedeutsam hoch in den in GORENET untersuchen Isolaten (10, 11). In den Jahren 2016-2017 ging der Anteil resistenter Stämme zurück (< 4 %), stieg jedoch 2018 wieder an (8,4 %) (79). Azithromycin wird oft für die Behandlung anderer

Infektionen, einschließlich der Behandlung von anderen STI, eingesetzt. Durch vermehrte Exposition und Anpassung des Erregers kann die Zunahme der Resistenzen gegenüber Azithromycin vermutet werden (84, 85). Im Jahr 2018 wurde eine neue Genogruppe identifiziert, die mit erhöhten MHK-Werten gegenüber Azithromycin verbunden sind (86). Weltweit sind Fälle von *High-Level*-Azithromycin-Resistenz berichtet worden (87-91). Auch in Deutschland wurde ein Isolat mit NG *High-Level*-Azithromycin-Resistenz (MHK > 256 mg/L) in Rahmen von GORENET beobachtet (11, 92). Daher sollte vor der Gonorrhö Behandlung mit Azithromycin ein AMR-Test durchgeführt werden.

Die Anteil der Isolate mit einer Resistenz gegenüber Ciprofloxacin und Penicillin war in GORENET insgesamt hoch (10, 11). Auch bei Ciprofloxacin und Penicillin wird in Europäischen Ländern und weltweit Resistenzen seit Längerem beobachtet (73). Ciprofloxacin und Penicillin sollte daher für die Gonorrhö Behandlung nicht mehr zum Einsatz kommen (10, 11).

Neisseria gonorrhoeae entwickelte in der Vergangenheit Resistenzen gegen jedes für die Therapie eingesetzte Antibiotikum (54) Mit der Einführung der Therapieleitlinie in 2014 wurde die Therapie mit zwei Substanzen – Ceftriaxon (ggf. Cefixim) und Azithromycin - in Deutschland implementiert (12). Wegen der sich rasch entwickelnden Resistenzlage gegenüber Azithromycin wurde in der Leitlinie von 2018 für Patient*innen mit gesicherter Adhärenz eine Monotherapie mit Ceftriaxon (ggf.Cefixim) eingeführt (8).

Um die Veränderungen der Antibiotika-Resistenzen von Gonokokken schnell zu erfassen und die Therapieleitlinien zeitgerecht zu aktualisieren, ist eine Surveillance der NG-AMR notwendig (10, 11). Das im Rahmen von GORENET aufgebaute Netzwerk sollte daher weiter ausgebaut und die Anzahl der jährlich getesteten Proben weiter gesteigert werden (10, 11). Um dauerhaft die NG-AMR Surveillance in Deutschland zu gewährleisten, wurde kürzlich eine Meldepflicht für NG-AMR mit Beginn zum 01.03.2020 eingeführt (93). Diese wird dabei helfen, ein vollständigeres Bild über die Lage der NG-AMR in Deutschland zu liefern. Die in GORENET bereits aufgebaute Isolatesammlung könnte auf wissenschaftlicher Ebene mit Daten aus der Meldepflicht verknüpft werden.

Durch das Chlamydien-Laborsentinel und GORENET konnte in Deutschland die Datenlage zu diesen zwei sehr bedeutsamen STI verbessert werden. Das Chlamydien-Laborsentinel liefert robuste Daten im Quer- und Längsschnitt. Daten aus GORENET haben bereits dazu beigetragen, die Therapie-Richtlinien evidenzbasiert anzupassen. Die Weiterführung sowie der Ausbau der Datenerhebung können wichtige und belastbare Daten für die Surveillance und Response von Chlamydien- und Gonokokken-Infektion in Deutschland liefern.

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2. Eidesstattliche Versicherung

„Ich, Sandra Dudareva, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Surveillance von Infektionen mit *Chlamydia trachomatis* und von Antibiotika-Resistenzen von *Neisseria gonorrhoeae* in Deutschland (Surveillance of *Chlamydia trachomatis* infections and antibiotic resistance of *Neisseria gonorrhoeae* in Germany) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autor*innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

3. Anteilserklärung

Sandra Dudareva hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Sandra Dudareva-Vizule, Karin Haar, Andrea Sailer, Klaus Jansen, Osamah Hamouda, Hilmar Wisplinghoff, Carsten Tiemann, Eberhard Pape, Viviane Bremer, Chlamydia trachomatis laboratory sentinel team, *Establishment of a voluntary electronic Chlamydia trachomatis laboratory surveillance system in Germany, 2008 to 2014,* Euro Surveillance, 2017.

Beitrag im Einzelnen:

- Mitwirkung bei der Planung des Chlamydien-Laborsentinels;
- Koordinierung der Datensammlung und der Plausibilitätskontrolle;
- Federführung bei der Konzeption des Artikels;
- Durchführung der Literaturrecherche und Auswahl der relevanten Literatur;
- Federführende Konzipierung der Datenauswertung;
- Federführende Auswertung der Daten;
- Vorbereitung der Daten für die Erstellung der Abbildung 1, Konzipierung der Abbildung 1
- Erstellung der Abbildungen 2, 3, 4 und Tabellen 1, 2 und 3
- Interpretation der Ergebnisse in Zusammenarbeit mit den Koautor*nnen;
- Entwurf und Fertigung der Publikation als Erstautorin.

Publikation 2: Alexandra Sarah Lang, Matthias an der Heiden, Klaus Jansen, Andrea Sailer, Viviane Bremer, Sandra Dudareva & Chlamydia trachomatis laboratory sentinel team, *Not again! Effect of previous test results, age group and reason for testing on (re-) infection with Chlamydia trachomatis in Germany*. BMC Infectious Diseases, 2018.

Beitrag im Einzelnen:

- Mitwirkung bei der Planung des Chlamydien-Laborsentinels;
- Koordinierung der Datensammlung und der Plausibilitätskontrolle;
- Mitarbeit bei der Konzeption des Artikels;
- Mitkonzipierung der Datenauswertung;
- Betreuung der Datenauswertung und Betreuung der Erstellung aller Abbildungen und Tabellen
- Mitwirkung bei der Interpretation der Ergebnisse;
- Mitwirkung bei der Fertigung der Publikation als Letztautorin.

Publikation 3: Susanne Buder, Sandra Dudareva, Klaus Jansen, Anna Loenenbach, Sergejs Nikisins, Andrea Sailer, Eva Guhl, Peter K. Kohl, Viviane Bremer & GORENET study group, Antimicrobial resistance of Neisseria gonorrhoeae in Germany: low levels of cephalosporin resistance, but high azithromycin resistance. BMC Infectious Diseases, 2018.

Beitrag im Einzelnen:

- Geteilte Erstautorschaft mit Susanne Buder
- Federführende Planung des Gonokokken Resistenznetzwerks;
- Koordinierung der Daten- und Isolaten-Sammlung und der Plausibilitätskontrolle;
- Zusammen mit zweiter Erstautorinn (S. Buder) Federführung bei der Konzeption des Artikels;
- Durchführung der Literaturrecherche und Auswahl der relevanten Literatur;
- Federführende Konzipierung der Datenauswertung;
- Federführende Auswertung der von Laboren und Kosiliarlabor berichteten Daten;
- Vorbereitung der Daten für die Erstellung der Abbildung 1, Konzipierung der Abbildung 1
- Erstellung der Abbildungen 2, 3, 4, 5 und Tabellen 1, 2 und 3
- Interpretation der Ergebnisse in Zusammenarbeit mit den Koautor*innen;
- Zusammen mit zweiter Erstautorinn (S. Buder) Entwurf und Fertigung der Publikation als Erstautorin.

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Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

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Unterschrift des Doktoranden/der Doktorandin

4. Druckexemplare der ausgewählten Publikationen

Establishment of a voluntary electronic *Chlamydia trachomatis* laboratory surveillance system in Germany, 2008 to 2014

S Dudareva-Vizule [1,2], K Haar [1], A Sailer [1], K Jansen [1], O Hamouda [1], H Wisplinghoff [3,4,5], C Tiemann [6], E Pape [1], V Bremer [1], Chlamydia trachomatis laboratory sentinel team [7]

1. Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
2. Charité University Medicine, Berlin, Germany
3. Wisplinghoff Laboratories, Cologne, Germany
4. Institute for Medical Microbiology, University of Cologne, Cologne, Germany
5. Institute for Microbiology, University Witten/Herdecke, Witten, Germany
6. Labor Krone, Bad Salzuflen, Germany
7. The Chlamydia trachomatis laboratory sentinel team is listed at the end of the article

Correspondence: Sandra Dudareva-Vizule (Dudareva-VizuleS@rki.de)

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Chlamydia trachomatis (CT) infections are not reportable in Germany and limited data on prevalence are available. CT screening has been offered free of charge to pregnant women since 1995 and to all women under 25 years since 2008. For symptomatic women and men, diagnostic testing is covered by statutory health insurance. We describe the establishment of a nationwide, laboratory-based, voluntary sentinel that electronically collects information on all performed CT tests with test results, test reason and patient information. The sentinel represents one third of all performed CT tests in Germany. In the period from 2008 to 2014, 3,877,588 CT tests were reported, 93% in women. Women aged 20–24 years and men aged 25–29 years were the most frequently tested age groups. The overall proportion of positive tests (PPT) among women was 3.9% and among men 11.0%. The highest PPT among women was in the age groups 15–19 (6.8%) and 20–24 years (5.9%), and among men in the age groups 20–24 (19.2%), 15–19 (15.4%) and 25–29 years (14.8%). The PPT for CT was high among women and men younger than 25 years. Prevention is urgently needed. Monitoring of CT infection in Germany should be continued.

Introduction

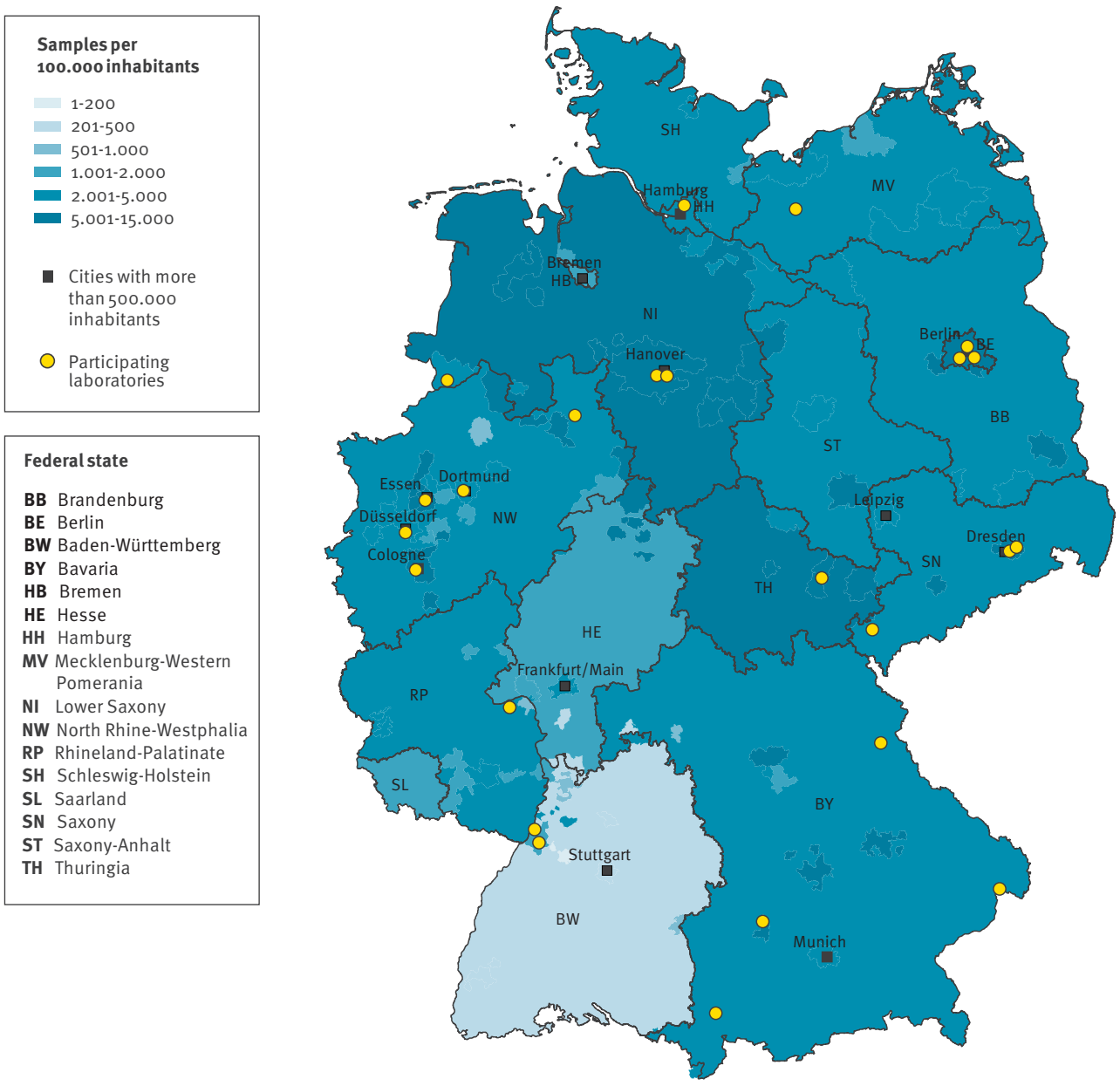
Infections with *Chlamydia trachomatis* (CT) rank among the most frequent sexually transmitted infections (STI) in Europe and worldwide [1,2]. According to European data, the most affected age groups are women aged 15–24 years and men aged 20–24 years [2,3].The CT infection may be asymptomatic and can, if not detected and treated, result in complications such as pelvic inflammatory disease, chronic abdominal pain, ectopic pregnancy, tubal sterility, a higher risk of adverse pregnancy outcomes for women and of epididymitis for men [3-10]. Evidence whether CT screening can prevent these complications is, however, controversial [3].

CT infections are not reportable in Germany, except for one federal state (Saxony), where we observed a continuous increase from 40.8 reported CT infections per 100,000 population in 2004 to 101.0 in 2012 [11]. However, only detected infections are reported. The true incidence in the population might be higher owing to the large proportion of asymptomatic infections that might remain undetected. In population-wide studies in Germany performed between 2003 and 2006, we observed a prevalence of up to 4.5% among women aged 17–19 years and 4.9% among men aged 25–29 years [12-14]. Between 2003 and 2009, data on CT were collected through the STI sentinel surveillance system from 247 sites (mainly local municipality counselling centres for STI, followed by STI outpatient clinics, general practitioners and other specialists) situated all over Germany but not representative of the general population in Germany. CT was the most frequently diagnosed STI, with a positivity of 6.0% among performed tests [15-17]. Sixty-seven per cent of the diagnosed CT infections were among women, many of them working as sex workers who attended the free-of-charge local municipality counselling clinics. The median age of infected women was 25 years and of men 31 years [15,16].

Health insurance in Germany is compulsory and individuals are covered either by statutory health insurance (ca 90%) or private health insurance. Private

Figure 1

Number of reported *Chlamydia trachomatis* tests per 100,000, by federal state, Germany, 2008–14 (n = 3,220,628)



health insurance is available only to some segments of the population [18].

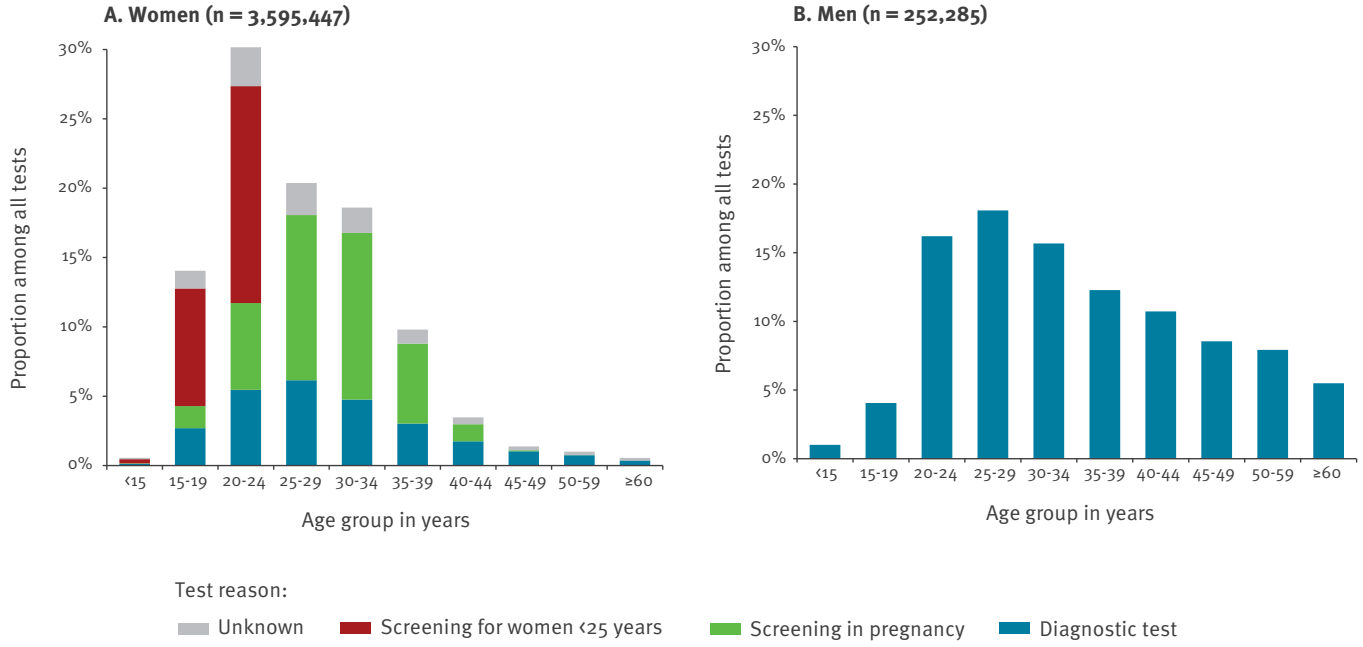
Patients in Germany can freely choose their medical practitioner, i.e. not based on place of residence. Laboratories do not have a defined catchment area, thus, there are laboratories serving only surrounding areas as well as laboratories receiving samples from all over Germany.

Since 1995, opportunistic CT screening for pregnant women with statutory insurance has been in place, and in 2008, yearly CT screening for sexually active women under the age of 25 years with statutory insurance, as well as a CT test before planned abortion, was introduced in Germany [19]. Up until now, there have been no CT screening programmes for men. Health insurance companies can reimburse men and women for the costs of testing if they report specific symptoms or unspecific symptoms together with risk behaviour or if a sex partner has been tested positive for CT (diagnostic testing). Otherwise, the CT test can be requested and paid by the patient.

CT has been classified in the highest priority group of pathogens in Germany [20]. However, data on the proportion of positive tests (PPT) in different age groups and regions are limited. Furthermore, there are no data on the frequency of the different test indications for CT in women and on the coverage of the screening programme for women younger than 25 years. Except for Saxony, there is no information on the CT infection trend over time.

Figure 2

Proportion of reported *Chlamydia trachomatis* tests by age group, test reason and sex, Germany, 2008–14



To close this knowledge gap, we introduced a new laboratory-based CT surveillance system, the 'CT laboratory sentinel' in Germany in 2010. The aim of the CT laboratory sentinel was to monitor CT testing data and infections in Germany and to evaluate the newly introduced CT screening for women under 25 years of age, in order to develop public health recommendations for targeted prevention measures.

Before the laboratory-based CT-surveillance was set up, all laboratories testing for CT in Germany were mapped [21]. Of 1,504 contacted facilities, 725 (48%) responded to a questionnaire; 143 reported that they performed CT diagnostics and of those 143, 60 reported that they would be interested in reporting data [21].

In this paper, we report on how the CT laboratory sentinel was established and present the first results.

Methods

Establishment of the *Chlamydia trachomatis* laboratory sentinel

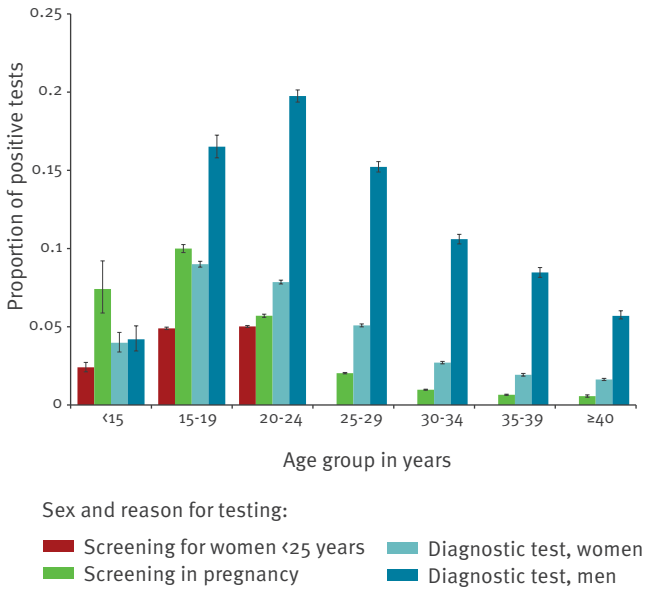
In September 2010, we started implementing a voluntary laboratory-based sentinel system in Germany for electronic and, where possible, automated collection of information that is routinely available in laboratories on CT tests. Mapping of the laboratories performing CT diagnostics [21] provided us with a list of laboratories that expressed interest in participation and with information on the number of CT tests per quarter and catchment area. We recruited laboratories based on the number of performed CT tests and on the size of the catchment area. Our aim was to recruit laboratories performing many CT tests and to reach equally good geographical distribution in each federal state. After review of the geographical distribution and coverage in our sample, we decided to recruit additional laboratories with catchment areas from underrepresented regions.

Through the CT laboratory sentinel, we collected retrospective (back to 2008) and continuous data on the performed CT tests up to 31 December 2014. Data were reported on a quarterly basis. The laboratories indicated that not all variables could be selected from their data systems or the selection would be very time consuming. To keep the effort reasonable, we defined a standard common set of mandatory and optional variables. Mandatory variables were sample and patient identification number, date of laboratory testing, test result, sex, and year of birth. Optional variables included date of sampling, the first three digits of the standard five-digit postal code of the patient, the first three digits of the postal code of the submitting medical practitioner, month of birth, reason for testing or billing codes (used for invoicing health insurance), pregnancy status, tested material, health insurance status (statutory or private) and method of testing.

If the three-digit postal code of the patient was not available, we used the three-digit postal code of the submitting medical practitioner. We generated information on the test reason from the reported reason for testing or respective billing codes. Samples from female patients, who were tested because of symptoms or suspicion of infection, were categorised as 'Diagnostic testing'. Samples from female patients who were tested during pregnancy or before a planned abortion were categorised as 'Screening in pregnancy'.

Figure 3

Proportion of positive *Chlamydia trachomatis* tests with 95% confidence intervals, by sex, age group and test reason, Germany, 2008–14, among women (n = 3,577,935) and men (n = 249,857)



Women who were screened as part of the screening for under 25 years of age were categorised as 'Screening for women under 25'.

On the basis of the year of birth, we calculated patient age at the time of testing. Laboratories reported the CT tests for the complete time period, or less if reporting for the complete time period was not possible.

Data were transmitted electronically. The data were sent to us either via email as extensible markup language (.XML) files, comma-separated values (.CSV) or Excel spreadsheet (.XLS) files or in XML format via secure sockets layer (SSL)-encrypted Internet connection to a web service. After performing predefined automated plausibility checks, the received data were combined in a structured query language (SQL) database. Unplausible variables were set to missing. The sample and patient numbers were MD5-encrypted and transmitted as 32-digit hash codes. Decryption of this code was not possible. If patients were tested more than once at the same laboratory, the 32-digit hash code enabled us to assign data from several samples over time to one patient. However, samples from the same patient tested in different laboratories could not be assigned to the same patient. If laboratories used different input data (for example, surname and date of birth in one quarter and name plus surname and date of birth in the subsequent quarter) to generate the 32-digit hash codes, we were not able to trace those patient numbers over time. In order to understand if person-related analysis, such as testing frequency and time intervals between tests, is possible for this way of data collection, we proved the traceability of the patient identification numbers by laboratory over time. There was no financial compensation for laboratories to participate in the study. The data collection protocol was confirmed by the data protection officer at the Robert Koch Institute, Berlin. Additional approval from an ethics committee was not deemed necessary, as no patient-identifying data were collected.

Data analysis

We analysed all CT tests available for the time period between 1 January 2008 and 31 December 2014. For the reported CT tests, we calculated counts and proportions of the available and missing variables. We calculated the duration of the reporting period by laboratory as well as counts and proportions of the CT tests by laboratory.

We defined coverage as the proportion of CT tests from individuals with statutory insurance collected through the sentinel among all CT tests from individuals with statutory insurance. The National Association of Statutory Health Insurance provided us with data on all performed CT tests from individuals with statutory insurance for the years 2011 and 2012. We are not able to individually link patients or tests in the two data sources. Instead, we first calculated the proportion of individuals with statutory insurance among the CT tests with available information on health insurance status. Then, we extrapolated this proportion to all CT tests collected within the laboratory sentinel in the years 2011 and 2012 and calculated the total number of CT tests from individuals with statutory insurance. Finally, we assessed the coverage of the laboratory sentinel by comparing the total number of CT tests from persons with statutory insurance in Germany and from persons with statutory insurance collected in the CT laboratory sentinel. We assumed that the coverage of CT tests for privately insured persons was similar.

The geographical distribution of the reported CT tests based on the postal codes was described as the number of CT tests per 100,000 population by federal state in Germany.

We described CT tests in the laboratory sentinel and the PPT by age group, sex, reason for testing (diagnostic testing because of symptoms, screening in pregnancy or screening for women under 25 years of age) and tested material (for men).

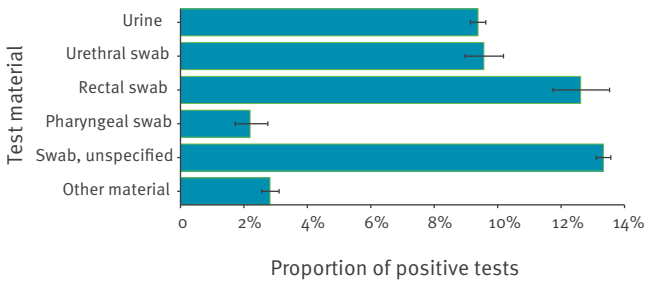
Results

Participating laboratories and collected data

Of the 60 laboratories selected for recruitment, 24 agreed to participate and have been reporting data to the CT laboratory sentinel. The reasons for refusing to participate were: data selection in the requested format was not possible (n = 10), too much effort was required (n = 12), CT samples were forwarded to a partner/alliance laboratory or organisational changes

Figure 4

Proportion of positive *Chlamydia trachomatis* tests with 95% confidence intervals among men, by tested material, Germany, 2008–14 (n = 174,346)



(n = 7), refusal without a specific reason (n = 4), other reasons (n = 3). Three of the laboratories refusing to participate were large laboratories with a nationwide catchment area. Currently, two laboratories are reporting data by using the web service; three send the data as XML, five as CSV and 14 as Excel spreadsheets via email.

By 24 November 2015, a total of 3,877,588 CT tests had been reported for the period from 1 January 2008 to 31 December 2014. A total of 15 laboratories have reported data for each quarter of the entire study period. A further nine laboratories have reported data for a minimum of 1 month and a maximum of 4 years and 7 months (Table 1).

Information on the mandatory variables was missing in less than 1% of all reported CT tests and on optional variables between 13% and 80% (Table 2). Patient number was consistently coded and therefore traceable over the entire reporting time in 15 laboratories, consistently coded only for part of the time in seven laboratories, and two laboratories did not report patient identification numbers (Table 1).

Coverage

In total, 91.1% and 78.1% of CT tests with information on health insurance were attributable to, respectively, the women and men with statutory health insurance. We estimated that 34.3% of all CT tests performed among statutorily insured persons in Germany were reported to the CT laboratory sentinel. These estimates varied by federal state from 4.4% in Baden-Wurttemberg to 60.9% in Thuringia (Table 3). The coverage was 34.6 for CT tests among women and 28.7% for CT tests among men (Table 3).

Regional distribution

The number of reported CT tests with information on the three-digit postal code for the entire period per 100,000 of the population varied by region between 141 and 14,901 (Figure 1). Based on information on the catchment areas provided from laboratories that did not report information on postal code, ca 50% of CT tests with missing postal codes would be from Saxony, around 40% from the western part of the country (Bremen, Lower Saxony, North Rhine-Westphalia, Hesse, Rhineland-Palatinate, Saarland and Baden-Württemberg) and the rest from Berlin.

CT testing

Of the total of 3,877,588 reported CT tests for the period 2008 to 2014, 92.8% (3,599,821) were done in women and 6.6% (255,634) in men. Among women with information on age (3,595,447), the most frequently tested age groups were women aged 20–24 years, and among men (252,285) those aged 25–29 years, followed by those aged 20–24 years and 30–34 years. The proportion of CT tests by age group among men and women are reported in Figure 2.

Reason for testing in women

Among CT tests in women with information on the reason for testing, 41.9% were attributable to screening in pregnancy, 26.9% to screening of women under 25 years of age and 28.7% to diagnostic tests (Figure 2).

Tested material in men

Among CT tests in men with information on tested specimen, 49.0% were unspecified swabs, 32.5% urine, 5.3% urethral, 3.1% rectal and 1.9% pharyngeal swabs. In 8.2% of tests, other materials were tested.

Proportion of positive tests

Among tests with valid test results (n = 3,827,792), 3.9% (95% confidence interval (CI): 3.9–4.0) of tests among women and 11.0% (95% CI: 10.9–11.2) of tests among men were positive. PPT varied by federal state from 3.0% in Saarland to 6.8% in Mecklenburg-Western Pomerania among women and 9.0% in Saarland to 17.0% in Mecklenburg-Western Pomerania among men.

The PPT among women differed by reason for testing and age (Figure 3). Overall, the highest PPT was observed among women aged 15–19 years and 20–24 years (Figure 3). The PPT when screening women under 25 years was 4.9% in 15–19 and 5.0% in 20–24 year-olds. While screening tests in pregnancy and diagnostic testing revealed, respectively, a PPT of 10.0% and 9.0% among 15–19 year-olds and 5.7% and 7.9% among 20–24 year-olds, PPT among pregnant women decreased to 2.0% among women 25–29 years of age and was < 1% in those 30 years and older. The PPT in diagnostic tests also decreased with increasing age (Figure 3).

Among men, the highest PPT was observed among the age groups 20–24 years (19.2%), 15–19 years (15.4%) and 25–29 years (14.8%). The PPT among women and men decreased with age (Figure 3).

Among men, the PPT was higher in rectal (12.3%) and in unspecified swabs (13.4%) (Figure 4).

Table 1

Number of reported *Chlamydia trachomatis* tests, proportion of tests in women, data reporting period, catchment area and patient traceability period by laboratory, Germany 2008–2014 (n = 3,877,588)

Laboratory	Reported CT tests n[a]	Tests in Women %	Reporting period (number of CT tests)							Patient traceability period
			2008	2009	2010	2011	2012	2013	2014	
1	1,629,040	98.0	78,770	183,085	211,571	244,480	268,823	309,423	332,888	Partly
2	450,368	93.0	49,184	59,628	66,939	63,678	63,383	70,182	77,374	Complete
3	342,929	91.1	41,451	51,327	51,190	50,430	48,649	50,946	48,936	Complete
4	268,248	86.2	15,821	33,004	34,360	39,379	47,893	47,990	49,801	Partly
5	200,204	90.4	15,366	27,885	29,839	29,859	31,142	33,842	32,271	Complete
6	132,726	92.4	ND	ND	ND	ND	ND	282	132,444	Partly
7	126,170	96.6	2,609	19,884	19,836	20,892	21,919	21,663	19,367	Complete
8	95,022	74.0	8,964	10,618	11,548	12,336	14,261	15,805	21,490	Complete
9	92,824	80.2	12,162	12,882	11,529	11,746	11,998	15,684	16,823	Partly
10	83,715	92.3	8,338	11,924	12,025	12,973	12,282	13,236	12,937	Complete
11	64,806	94.9	ND	ND	ND	ND	ND	29,906	34,900	Patient number missing
12	64,133	96.6	7,705	8,449	8,894	8,937	9,482	10,118	10,548	Complete
13	59,098	99.9	5,834	14,592	15,013	14,583	9,076			Complete
14	51,755	90.7	6,524	7,371	7,128	7,857	7,715	7,460	7,700	Complete
15	49,839	84.1	3,219	7,594	7,452	7,533	7,162	7,926	8,953	Complete
16	45,708	94.7	ND	ND	ND	ND	15,816	14,951	14,941	Partly
17	39,969	70.3	ND	ND	ND	ND	64	20,017	19,888	Complete
18	29,573	90.9	ND	ND	ND	7,849	7,296	7,251	7,177	Partly
19	28,636	32.9	3,569	3,541	3,549	3,849	4,573	4,782	4,773	Complete
20	12,398	63.9	1,587	1,437	1,411	1,769	1,822	2,065	2,307	Complete
21	8,105	66.8	766	895	995	1,198	1,053	1,260	1,938	Complete
22	1,590	69.7	ND	ND	ND	422	397	391	380	Partly
23	564	97.2	ND	ND	ND	554	10	ND	ND	Patient number missing
24	168	92.3	ND	ND	ND	ND	168	ND	ND	Complete
Total	**3,877,588**	**92.8**	**261,869**	**454,116**	**493,279**	**540,324**	**584,984**	**685,180**	**857,836**	

CT: Chlamydia trachomatis; ND: no data reported.

[a] Laboratories sorted by number of reported CT tests.

Discussion

We established a CT laboratory sentinel in Germany that electronically collects data that are routinely available in laboratories on performed CT tests; the CT laboratory sentinel serves as a surveillance system. In the period from 2008 to 2014, we reached good coverage and collected a large number of samples representing one third of all performed CT tests in Germany, together with epidemiological information and data on testing. In total, 24 laboratories reported data on a voluntary basis; for the majority of the data, we had information for a complete time period (January 2008 to December 2014). Completeness of the five mandatory variables was more than 99%, while completeness of the eight optional variables varied by laboratory and variable.

We estimate that we have collected 34% of all CT tests of individuals with statutory health insurance in the CT laboratory sentinel. This was possible because we were able to recruit some very large laboratories. Although this estimate is based on data from 2011 and 2012, we assume that we have reached at least the same coverage in the following years 2013 and 2014. We also assume that the coverage of CT tests from individuals with private health insurance was similar. The coverage was slightly better for statutorily insured women than men. The reason for this is unclear. One possible explanation may be that statutorily insured men are being tested at specialist HIV centres or at centres targeting men who have sex with men (MSM), and that these centres might be cooperating with local laboratories not included in the sentinel.

We were able to collect data from samples from all over Germany. Baden-Wurttemberg contributed the lowest number of reported CT tests per 100,000 population and also reached the lowest coverage compared with the other federal states. A substantial proportion of the CT tests with missing information on postal codes was reported from one laboratory with a catchment area in Baden-Wurttemberg, Hesse and Rhineland-Palatinate. We therefore assume that the geographical

Table 2

Number of *Chlamydia trachomatis* records with information on collected variables, and number and proportion of records with unknown, missing or implausible information, Germany, 2008–2014 (n = 3,877,588)

Variable	Type of variable	Available	Unknown, missing or unplausible	
		n	n	%
Sample number	Mandatory	3,877,588	0	0.0
Patient number	Mandatory	3,877,588	0	0.0
Test result	Mandatory	3,856,972	20,616	0.5
Sex	Mandatory	3,855,455	22,133	0.6
Year of birth	Mandatory	3,859,684	17,904	0.5
Month of birth	Optional	3,313,251	564,337	17.0
Three-digit postal code[a]	Optional	3,220,557	657,031	20.4
Date of sampling	Optional	776,349	3,101,239	80.0
Test reason	Optional	3,496,011	381,577	9.8
Pregnancy status	Optional	2,954,620	922,968	23.8
Tested material	Optional	3,378,347	499,241	12.9
Method of testing	Optional	2,126,643	1,750,945	45.2
Health insurance status	Optional	1,207,750	2,669,838	68.9

[a] For 3,097,980 records (96.2%), patient three-digit postal codes were reported, and for 122,577 records (3.8%), postal codes of practitioners were reported.

distribution of tested persons in these federal states or neighbouring areas is better than that estimated based on the postal codes. To obtain better regional data and better coverage of the CT tests from men, we are recruiting further laboratories for participation. An update of the laboratory mapping exercise would be desirable to indicate further potential laboratories covering Baden-Wurttemberg that were not reached in the first mapping.

In several laboratories, the number of performed CT test has increased over the years. Based on information provided from laboratories, a substantial part of the observed increase can be attributed to merging or expansion of the laboratories. However, we are not able to quantify this. We believe that there has been a real increase in CT testing activity in Germany. Further analysis of the statutory insurance registry can clarify if the number of performed CT tests has risen since 2008.

The majority of the reported CT tests were from women, as CT screening is offered to women under 25 years of age and pregnant women. Women aged 20–24 years were by far the most frequently tested age group, followed by women aged 25–34 years. Men aged 20–34 years were most frequently tested compared with other age groups. We also observed the highest PPT in age groups with the highest test frequency. PPT among both men and women was high among tests from younger people and decreased with age. In order to analyse the PPT variation by region further, sociodemographic information is necessary.

We observed the highest PPT among women and men aged 15–24 years, which is similar to several population-based studies in Europe [12-14,22-28]. National chlamydia testing data with information on denominator from England and Norway report PPT of, respectively, 7.8% and 11.5% among 15–24 year-old women and of 10.0% and 17.1% among 15–24 year-old men [27,28]. Opportunities for testing free of charge, especially for men, are scarce in Germany, comparison with England and Norway [27,28]. This impacts testing rates, the groups tested and the PPT.

The PPT was high among very young women screened during pregnancy (these data include also CT tests before abortion). This might be explained by a young age at first sexual intercourse, which several studies have linked to having more partners, more diverse sexual experiences, less frequent use of condoms, and increased risk for bacterial STI, pregnancy and abortion [29]. The PPT among CT tests in pregnancy decreased with increasing age and was less than 1% among women older than 30 years. Our data suggest that it is more rational to screen younger pregnant women, especially those under 25 years of age, than older ones. Furthermore, it is likely that with the given PPT in older pregnant women, some tests may be false positive and will lead to unnecessary treatment. With the current data collected in the laboratory sentinel, we cannot determine what proportion of positive CT tests can be explained by risk behaviour, such as new or multiple sexual partners, other STI or history of sex work. Testing groups with higher prevalence is more effective in terms of detection rate. Age- and risk behaviour-indicated screening in pregnancy in Germany instead of screening of all pregnant women should be further discussed. A cost–benefit analysis taking into account estimates of age-specific adverse health outcomes in

Table 3

Proportion of *Chlamydia trachomatis* tests from men and women with statutory health insurance (n = 2,964,346), collected in the Chlamydia trachomatis laboratory sentinel, by federal state, Germany, 2011–12 (n = 1,016,231)

Federal state (total population[a])	Proportion of CT tests collected through the sentinel (%)			
	Women	Men	Unknown	Total
Baden-Wurttemberg (n = 10,786,227)	4.3	6.3	18.4	4.4
Bavaria (n = 12,595,891)	29.6	16.1	19.2	28.9
Berlin (n = 3,501,872)	57.9	53.2	177	57.3
Brandenburg (n = 2,495,635)	37.2	8.8	3.5	35.7
Bremen (n = 661,301)	12.2	1.9	0.0	11.5
Hamburg (n = 1,798,836)	15.3	2.4	0.7	13.5
Hesse (n = 6,092,126)	19.7	22.9	44.6	20.0
Lower Saxony (n = 7,913,502)	24.7	12.2	1.4	23.8
Mecklenburg-Western Pomerania (n = 1,634,734)	53.9	25.9	17.7	52.4
North Rhine-Westphalia (n = 17,841,956)	39.6	34.9	66.4	39.4
Rhineland-Palatinate (n = 3,999,117)	29.8	18.9	1170	29.5
Saarland (n = 1,013,352)	19.6	8.8	90.5	19.0
Saxony (n = 4,137,051)	27.7	35.4	49.0	28.4
Saxony-Anhalt (n = 2,313,280)	36.1	6.9	1.4	33.8
Schleswig-Holstein (n = 2,837,641)	22.6	3.3	5.5	21.1
Thuringia (n = 2,221,222)	60.1	82.6	41.5	60.9
Total	**34.6**	**28.7**	**177.3**	**34.3**

CT: Chlamydia trachomatis.

[a] Population by federal state in 2011 (Source: German Federal Statistical Office).

pregnancy due to chlamydia infection would facilitate these discussions.

PPT was higher in men than in women also when comparing only diagnostic CT tests. This was not unexpected, as we only reported on CT tests performed among men presenting with symptoms. The PPT in rectal swabs compared with urethral samples was high. Therefore we believe that a substantial proportion of positive CT tests among men might be attributable to MSM. Although almost half of the samples tested were unspecified swabs, we believe based on the PPT that a substantial proportion can be attributable to rectal swabs. Among MSM screened for STI in Germany, a CT prevalence of 9.4% (95% CI: 7.1–12.0) has been previously reported [30].

The majority of countries in the European Union and European Economic Area have a system for reporting and monitoring diagnosed CT cases at the population level [31]. These are however limited to infections that have been diagnosed and reported. The CT detection rates are influenced by populations tested and testing volume [31]. The CT laboratory sentinel provides information on both positive and negative test results which allows us to calculate the PPT and monitor it over time.

The limitations of this study are that the laboratories did not have an equal chance to be included in the sentinel, as we were selecting laboratories based on the interest to participate, number of performed CT tests and catchment area. There may be other large laboratories that were not reached in the mapping phase [21] and thus not considered for the laboratory sentinel. Although we evaluated our data for coverage at least once per year and selected for recruitment additional laboratories with catchment areas in regions underrepresented in the sentinel, we could not obtain an even coverage in all regions. Few laboratories reported the optional variables, which could have resulted in a selection bias in these data. However, owing to the large number of reported CT tests, analyses describing these variables are still possible. Efforts are continuing to improve completeness of the optional variables. We are unable to collect more detailed epidemiological information such as route of transmission and symptoms through the CT laboratory sentinel. Usually, laboratories in Germany have only very limited epidemiological information and there is no legal basis to collect these data. Laboratories that have more information need to treat this information confidentially.

Conclusion

The implementation of our CT laboratory sentinel has shown that it is feasible in Germany to collect, electronically and continuously, readily available data from laboratories with a reasonable effort that can for now be used instead of mandatory surveillance. We managed to collect a large amount of data from all regions in Germany that represented around one third of all performed CT tests. In contrast to mandatory surveillance, the CT laboratory sentinel collects information

on all performed CT tests which allows analysis of PPT over time. In addition, regularly conducted population-based prevalence surveys, although costly, could help determine the true prevalence of CT infection in the population and evaluate prevention strategies.

A large PPT among young men and women and low awareness of CT in Germany [32] support the need for further prevention efforts. The CT laboratory sentinel should continue to collect data and expand the base of participating laboratories in order to monitor and describe CT infection in Germany and guide public health strategies. The participating laboratories should be continuously evaluated and the coverage and representation of different groups tested should be improved.

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Conflict of interest

None declared.

Authors' contributions

Viviane Bremer, Sandra Dudareva-Vizule, Karin Haar, Andrea Sailer and Osamah Hamouda were mainly responsible for the development of the methods and first implementation of the Chlamydia trachomatis laboratory sentinel. Eberhard Pape, Hilmar Wisplinghoff and Carsten Tiemann contributed to the methods of data collection, the initial data collection and supported the implementation of the electronic data transfer. Viviane Bremer, Osamah Hamouda and Klaus Jansen were mainly responsible for the supervision of the roll-out and continuation of the Chlamydia trachomatis laboratory sentinel. Sandra Dudareva-Vizule, Karin Haar and Andrea Sailer were in charge of the data analysis. Sandra Dudareva-Vizule drafted the paper and all the authors revised it.

The Chlamydia trachomatis laboratory sentinel team

Michael Baier, Eberhard Straube (Institut für Medizinische Mikrobiologie, Universitätsklinikum Jena), Armin Baillot (Niedersächsisches Landesgesundheitsamt, Hannover), Patricia Bartsch (MVZ Dr Eberhard & Partner, Dortmund), Thomas Brüning (LADR GmbH MVZ Nord-West, Schüttorf), Josef Cremer (Medizinisch-Diagnostisches Labor Kempten, Kempten), Helga Dallügge-Tamm, Arndt Gröning (amedes MVZ wagnerstibbe, Hannover), Stephan Eicke (Labor Dr Eicke, Berlin), Dagmar Emrich (MVZ Labor 28 GmbH, Berlin), Gundula Fritsche (Labor MVZ Westmecklenburg, Schwerin), Rosi Gjavotchanoff (Labor Alfredstraße, Essen), Peter Gohl (Bioscientia Institut für Medizinische Diagnostik GmbH, Ingelheim), Matthias Götzrath, Axel Meye (Medizinisches Labor Ostsachsen MVZ GbR, Dresden), Ingrid Ehrhard, Beate Köpke (Landesuntersuchungsanstalt Sachsen, Dresden), Birgit Henrich (Institut für Medizinische Mikrobiologie und Krankenhaushygiene, Universitätsklinikum Düsseldorf), Caroline Kastilan (MVZ Labor Diagnostik Karlsruhe GmbH, Karlsruhe), Susanne Lehmann (Diagnosticum, Plauen), Anneliese Märzacker (Labor Schottdorf MVZ GmbH, Augsburg), Bernhard Miller (Labor PD Dr Volkmann und Kollegen GbR, Karlsruhe), Gerrit Mohrmann (Labor Lademannbogen MVZ GmbH, Hamburg), Christian Pache (MVZ Dr Engelschalk, Dr Schubach, Dr Wiegel und Kollegen, Passau), Roland Pfüller (MDI Laboratorien GmbH, Berlin), Thomas Müller, Christian Aepinus – (synlab MVZ Weiden GmbH, Weiden).

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RESEARCH ARTICLE Open Access

Not again! Effect of previous test results, age group and reason for testing on (re-)infection with Chlamydia trachomatis in Germany

Alexandra Sarah Lang[1*], Matthias an der Heiden[1], Klaus Jansen[1], Andrea Sailer[1], Viviane Bremer[1], Sandra Dudareva[1,2], Chlamydia trachomatis laboratory sentinel team

Abstract

Background: Infection with *Chlamydia trachomatis* (Ct) is the most commonly reported sexually transmitted infection in Europe. In Germany, Ct screening is offered free of charge to pregnant women since 1995 and to women < 25 years of age since 2008. For symptomatic individuals, testing is covered by statutory health insurance. Study results have shown that repeat Ct infection occurs in 10–20% of previously infected women and men. Our aim was to describe persons tested for Ct and to investigate the determinants of (repeat) Ct infection in women and men in Germany.

Methods: We analysed Ct test results from men and women tested between 2008 and 2014 in laboratories participating in the German *Chlamydia trachomatis Laboratory Sentinel surveillance*. Reinfection was defined as at least 2 positive laboratory tests within more than 30 days. We performed logistic regression stratified by sex and, for women, reason for testing to determine the effect of previous test results and age group on subsequent test results.

Results: In total, 2,574,635 Ct tests could be attributed to 1,815,494 women and 123,033 men. 5% of women and 14% of men tested positive at least once. 15–19- and 20–24-year-old women tested positive at least once respectively in 6.8 and 6.0%, while men respectively in 16.6 and 21.2%. Altogether, 23.1% of tested women and 11.9% of tested men were tested repeatedly between 2008 and 2014. Among those who previously tested positive, reinfection occurred in 2.0% of women and 6.6% of men. Likelihood to be tested Ct positive was higher in women and men with a positive Ct test in the past compared to previously tested Ct negative, odds ratios 4.7 and 2.6 ($p < 0.01$) respectively. Odds ratios ranged by age group and test reason.

Conclusion: A history of Ct infection increased the likelihood of infection with Ct in women and men taking into account the result of the previous test. Health education, safer sex and treatment of partners are necessary for women and men who have tested positive to prevent reinfection and complications and to interrupt the chain of transmission. To identify potential reinfection repeat testing after treatment should be performed.

Keywords: Chlamydia trachomatis, Sexually transmitted infections, STI, Reinfection, Screening, Infertility, Sentinel

* Correspondence: LangAl@rki.de
[1]Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
Full list of author information is available at the end of the article

Background

Infection with *Chlamydia trachomatis* (Ct) is the most commonly reported sexually transmitted infection (STI) in Europe [1]. According to data of the European Center for Disease prevention and control (ECDC), young people are particularly affected, with two-thirds (67%) of the 384,555 reported cases in 2013 diagnosed amongst 15 to 24-year-olds [2]. This is however strongly influenced by testing practices in reporting countries [2]. In contrast to other STIs, Ct infection is very common in the general population with prevalence ranging from 3.0 to 5.3% among women 18–26-years old and 2.4–7.3% among men 18–26 years old [3]. Population-based estimations for Germany showed prevalence of 4.4% for sexually active 17-year-olds, 4.5% for 18- to 19-year-old women and 4.9% for 25- to 29-year-old men [4]. Overall, women aged 20 to 24 years are the group most frequently diagnosed with Ct [5, 6]. The most consistent risk factors associated with Ct infection in other studies are young age and a high number of sexual partners [5, 7–9].

Ct causes infection in the lower genital tract. Untreated infected women may suffer from ascending infection, which can lead to complications such as chronic pain, inflammation and occlusion of the fallopian tubes, which may result in infertility and ectopic pregnancy [10, 11]. Ct increases the susceptibility and transmission of HIV-infection [12]. The infection is asymptomatic in up to 50% of women and 80% of men or may only display mild symptoms. Therefore, Ct infection often remains unnoticed and undiagnosed, and thus untreated [13].

Because of the considerable burden of Ct infection and its sequelae, particularly in young women, many countries have implemented Ct-related public health activities to enhance detection and to prevent negative consequences by treating infected individuals as soon as possible. Approximately half of the European countries offer opportunistic testing as a measure for Ct control. Only a few countries have a systematic approach with standard guidance for treatment and repeated testing [14]; however, there are guidelines on the management of Ct infection available for Europe [15]. Germany published a guideline in 2016 to enable optimal diagnostics and therapy of Ct [16]. In Germany, opportunistic screening has been offered free of charge for statutory insured pregnant women since 1995 and once annually for statutory insured sexually active women under 25 years of age since 2008. Currently, tests for men are refunded by statutory health insurance if carried out for diagnostic purposes, i.e. suspect infection based on symptoms or anamnesis. There is no screening program for men in Germany. There are no regulations for the contract tracing in Germany and usually it is performed. With the aim of gathering representative data on Ct tests, the Robert Koch-Institute (RKI) established a voluntary nationwide, laboratory-based Ct surveillance system, the 'Ct laboratory sentinel', in 2010 that accompanied the implementation of the Ct screening programme for women under 25 years old. Information on routine Ct-testing in combination with test results, reason for testing and patient-related information were collected from 24 microbiological laboratories in Germany offering Ct-diagnostics. The Ct laboratory sentinel covers 34% of all Ct tests performed in Germany. Study results based on the sentinel data found an overall positive result rate of 3.9% amongst women and 11.0% amongst men of all age groups [17]. Reinfection with Ct is possible and increases the likelihood of complications and future acquisition and transmission of the disease [18]. Based on international studies it was estimated that 13.9% of women and 11.3% of men have repeatedly been infected with Ct [19, 20] .

The association of previous infections, age and test reason on reinfection have not yet been analysed yet in Germany. The main aims of this study were to gather evidence on whether current infection was more frequent in women and men who had tested positive previously compared to those who had tested negative previously and, furthermore, to identify whether the age group and, for women, the reason for testing, along with previous test results, influences the result of a subsequent test. Our findings will contribute to identify special risk groups for Ct who are in need of health education and to generate evidence for targeted Ct testing programmes.

Methods

The study population was composed of women and men who were tested for Ct in Germany between January 1, 2008 and December 31, 2014 and whose assays were tested in one of the laboratories participating in the Ct Laboratory Sentinel that provided traceable patient-IDs for a minimum of 3 years. The patient-IDs consisted of an encrypted 32-digit hash code. If patients were tested more than once within the same laboratory, data from several samples could be assigned by this unique identifier to one patient [16].

The following variables were used for analysis: patient-ID, assay-ID, laboratory code, testing date, age, sex, test result and test reason.

If information on sex or age was missing for some of the assays with the same patient-ID, the missing values were replaced by the information on sex and birth date available from the other assays. If sex was missing in all assays with the same patient-ID, these assays were excluded from analysis.

Multiple assays with the same patient-ID that were examined on the same day or within 7 consecutive days were considered as only one test. In this case, the test result was recorded as positive if at least one assay tested positive and recorded as negative if all assays were

negative. The decision to summarize multiple assays was based on information regarding the time difference between the date when the sample was taken (available for 26% of all assays in the sample) and the date of testing. Assays taken the same day by the physician were tested within 7 days. Thus, multiple assays (such as vaginal and rectal swabs) belonging to the same test-event might have been tested in the laboratory on different days.

Assays with missing information on the test result were excluded from analysis. Assays with missing information on age group or reason for testing were kept in the analysis.

The nucleic acid amplification test (NAAT) that is predominantly used in Germany for Ct testing is very sensitive and can still be detected 3 weeks after therapy even though the pathogen is no longer vital [21, 22]. Thus, we included only those tests with a time interval of at least 30 days from the preceding test in the analysis. Reinfection was consequently defined as at least 2 positive laboratory tests within a time interval of more than 30 days, following the definition of Brunham et al. [23] and the European Guideline for the management of Ct which recommends a test of cure 4 weeks after completion of therapy [15].

We described the number and proportions of performed Ct tests, the number of tested persons and the number of tests per person by sex, age group, reason for testing and test result. Among repeat testers we calculated median time between Ct tests by initial and subsequent test result. "Initial test result" is defined as the first Ct test that we have captured in the sentinel, however, this might not be the first test of the individual.

We tested the association between the variables *previous test result* and *age group* and the outcome variable *test result* by using logistic regression. Because of the large sample size a p-value less than alpha = 0.01 was considered significant in all calculations. We included only tests from women and men at least 15 years old. Separate models were calculated for men and women, and for women, the analysis was additionally stratified according to the reason for testing. The persons tested only once in the surveillance period contribute to the calculation of the proportion tested positive. To include these persons into regression analysis, we defined the variable *previous test result* as "unknown" as this group is mixture of those previously never tested and those tested positive or negative. The stratified univariable analysis was compared to the results of a multivariable logistic regression model. We tested improved goodness of fit by using likelihood ratio tests (LRTs), and we calculated odds ratios (OR), probabilities (Pr), and the according 99% confidence intervals. Including the interaction in a model with two variables means that every combination of age group and previous test result was estimated separately. Since the result is a single odds it can directly be transformed into a probability ($P = O/(O + 1)$). We chose to present the probabilities, since for most people this is the more familiar measure. This implied that the probability of a positive test result had to be estimated separately in all strata. The data were extracted from an SQL dataset and analysed using STATA 14.

Results

Study population

General characteristics of Ct testing in Germany

During 2008–2014, 3,877,589 Ct tests were reported. Of those, 2,574,635 tests were analysed, including 2,429,942 in women and 144,693 in men (Fig. 1). These tests could be attributed to 1,815,494 women and 123,033 men. The median age at the first Ct test was 26 years in women (IQR: 22–32) and 33 years (IQR: 25–43) in men. Note that this might not be the first test of the individual. In women, most tests (45.0%) were performed because of screening in pregnancy, followed by screening under 25 years (27.9%) and diagnostic testing (27.2%). The median age at the time of the first positive test was 22 years for women (IQR: 19–25) and 28 years for men (IQR: 23–36). Number of Ct tests and proportion of positive Ct tests by reason of testing and age group among women and men is given in Table 1.

Altogether, 23.1% (n = 420,220) of tested women and 11.9% (n = 14,680) of tested men were tested more than once during the 7-year-surveillance period. Most of those were tested twice (69.5% of women and 73.6% of men). While 20.1 and 10.4% of women and 16.4 and 10.0% of men were tested 3 and 4 or more times, respectively.

Amongst women and men tested more than once 13.6% (n = 57,133) and 34.6% (n = 5073) respectively had at least one positive Ct test. In women and men, the median time until the date of the subsequent test was shorter if the previous test was positive (Table 2).

Overall, in 0.5% (n = 8369) of women and in 0.8% (n = 963) of men in all the tested men and women reinfection was detected. Amongst repeatedly tested women and men, reinfection was detected in 2.0 and 6.6%, respectively. The median time from the first to the second positive test (reinfection) was 4.2 months in women (IQR: 2.1–13.0) and 6.7 months in men (IQR: 2.3–16.6).

Uni- and multivariable analysis

In the univariable logistic regression, the variables *age group* and *previous test result* were significantly associated with a positive result in a subsequent test (for detailed results of univariable analysis for women see Additional file 1: Table S1). A multivariable logistic regression model including the variables *age group* and *previous test result*

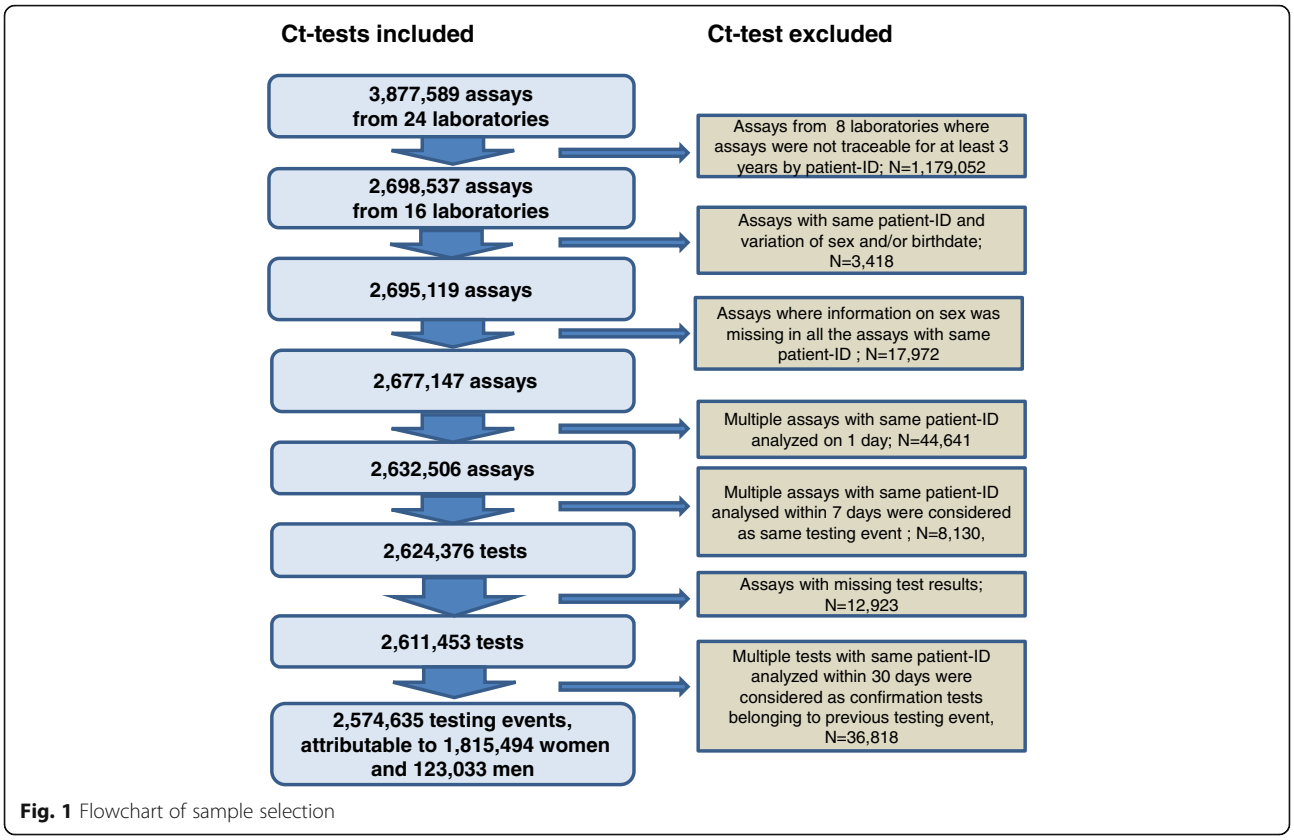

Fig. 1 Flowchart of sample selection

Table 1 Number of Ct tests and proportion of positive Ct tests by reason of testing and age group among women and men, 2008–2014, *n* = 2,574,635

	Women		Men	
	Number (Proportion in %)	Proportion Ct positive in %	Number (Proportion in %)	Proportion Ct positive in %
Tests				
Total	2,429,942 (100)	4.0	144,693 (100)	12.4
Reason for testing (tests)				
Screening under 25 years	571,054 (23.5)	5.0	n. a.	n. a.
Screening in pregnancy	920,133 (37.9)	2.5	n. a.	n. a.
Diagnostic testing	555,853 (22.9)	4.6	144,693 (100)	12.4
Unknown	382,902 (15.8)	5.1	n. a.	n. a.
Age group (tests)				
0–15 years	13,106 (0.5)	3.4	1048 (0.7)	3.0
15–19 years	342,892 (14.1)	6.8	6634 (4.6)	16.6
20–24 years	736,040 (30.3)	6.0	24,545 (17.0)	21.2
25–29 years	494,432 (20.4)	3.3	24,924 (17.2)	17.1
30–34 years	445,559 (18.3)	1.6	21,165 (14.6)	12.1
35–39 years	238,306 (9.8)	1.2	17,211 (11.9)	9.3
40+ years	157,824 (6.5)	1.3	46,868 (32.6)	5.7
Unknown	1783 (0.1)	5.1	2298 (1.6)	7.7

Table 2 Median time interval until subsequent test in women and men stratified by previous test result, 2008–2014, $n = 1{,}074{,}430$

Time interval until subsequent test	Women	Men
	Median time in months (IQR)	Median time in months (IQR)
Negative test	15.5 (IQR: 9.4–25.6)	7.4 (IQR: 3.1–15.2)
Positive test	3.0 (IQR: 1.7–8.9)	2.8 (IQR: 1.5–8.1).

showed that their interaction had a significant effect (Likelihood-Ratio-Test: $p < 0.01$). In regard to the probability of a positive test result, a similar result was reported in women for each test reason. Women and men of all age groups who had previously tested positive showed a higher probability of testing positive compared to their peers who had previously tested negative. The estimated probabilities for women and men are shown in Table 3 and Figs. 2, 3 and 4. A different presentation of the results for women and men in odds ratios can be found in Additional file 2: Figure S1 and Additional file 3: Figure S2.

In women who were tested in the frame of screening programmes (Table 3, Fig. 2), the probability to test positive generally decreased with increasing age. The proportion of previously positive pregnant women testing positive again was highest amongst the 15–19 and 20–24-year-olds. However, the difference in regard to the previous test result was most pronounced in pregnant women in older age groups. Previously positive tested women aged 35–39 years were 21.1 times and women aged 40+ 20.5 times more likely to test positive compared to their previously negative tested peers.

Amongst diagnostic tests the probability to test positive was highest in the age groups 15–19 and 20–24 years in women who had previously tested positive. Overall, the probability to test positive decreased with increasing age, regardless of the previous test result. We observed a slight increase in the probability of a positive test result in the group of previously positive 35- to 39-year-olds. The difference between women who had previously tested positive and their previously negative tested peers was most pronounced in the age groups 35–39 and 40+ years (OR: 7.1 and 5.4, respectively).

The probability to test positive in men (Table 3, Fig. 4) was highest amongst 15–19 and 20- to 24-year-olds who had previously tested positive. The probability to test positive decreased with increasing age; however, amongst men who had previously tested positive, we observed a slight increase in the age group 40+. The difference between previously positive and previously negative tested men was most distinct in the age groups 35–39 and 40+ years (OR: 2.6 and 2.8, respectively).

Table 3 Probability (Pr) of positive test result by previous test result and age group among women according to reason for testing and men, 2008–2014

Previous test result	Age group, years	Pr to test positive in % (99%-CI)			
		Women			Men
		Screening under 25 years	Screening in pregnancy	Diagnostic testing	All tests
Negative	15–19	4.3 (4.1–4.6)	6.5 (6.0–8.1)	5.3 (4.8–5.8)	9.2 (5.9–14.1)
	20–24	3.4 (3.2–3.5)	3.0 (2.9–3.4)	4.6 (4.3–4.9)	10.7 (9.0–12.6)
	25–29	–	1.1 (1.0–1.3)	3.1 (2.9–3.4)	9.5 (8.0–11.2)
	30–34	–	0.4 (0.4–0.5)	1.6 (1.4–1.9)	7.8 (6.5–9.3)
	35–39	–	0.3 (0.2–0.4)	1.2 (1.0–1.5)	6.4 (5.2–7.9)
	40+	–	0.3 (0.1–0.6)	1.1 (0.9–1.3)	5.5 (4.8–6.3)
Positive	15–19	12.6 (11.3–14.0)	28.4 (34.3–45.7)	16.8 (15.7–18.1)	18.6 (12.7–26.4)
	20–24	9.8 (9.1–10.4)	18.5 (20.6–24.9)	12.7 (12.0–13.4)	19.2 (16.7–22.0)
	25–29	–	10.4 (10.0–13.3	10.1 (9.2–11.0)	16.6 (14.3–19.3)
	30–34	–	7.9 (6.8–10.8)	7.1 (6.0–8.4)	16.4 (13.8–19.5)
	35–39	–	6.4 (4.3–10.7)	8.8 (6.9–11.0)	15.4 (12.3–19.1)
	40+	–	5.9 (2.3–17.2)	5.9 (4.3–8.1)	16.9 (14.7–19.4)
Unknown	15–19	4.9 (4.7–5.0)	9.7 (10.2–11.3)	8.1 (7.7–8.4)	16.9 (15.7–18.2)
	20–24	5.7 (5.6–5.8)	5.8 (6.0–6.4)	8.3 (8.0–8.6)	22.3 (21.6–23.1)
	25–29	–	2.2 (2.1–2.3)	5.1 (5.0–5.3)	18.0 (17.3–18.7)
	30–34	–	1.1 (1.0–1.1)	2.9 (2.7–3.0)	12.4 (11.8–13.1)
	35–39	–	0.7 (0.6–0.8)	1.9 (1.8–2.1)	9.4 (8.8–10.1)
	40+	–	0.6 (0.5–0.8)	1.6 (1.5–1.7)	6.1 (5.8–6.4)

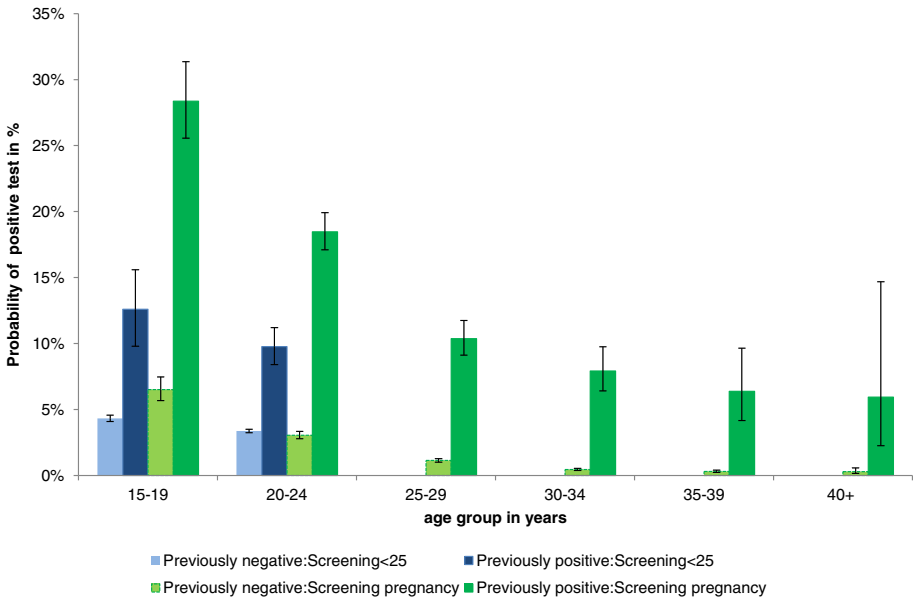

Fig. 2 Probability and 99%-CI of positive test results according to age group and previous test results in women tested in the frame of screening programmes by age group, 2008–2014

Discussion

To our best knowledge, this was the first German study using a comparably large dataset of routine Ct tests to examine the likelihood of infection while taking into account the result of the previous test.

The likelihood of being diagnosed with Ct differed based on the reason for testing and age in women. In particular, young pregnant women who had a history of Ct infection were at a high risk to test positive. As in Germany the mean age of women at the time of the birth of their first child was 29.3 years in 2015 [26], it is possible that many pregnancies in the age group 15–19 years were unwanted and screening for Ct has been carried out in the context of an abortion and can be related to behaviour with higher risk to acquire a STI as discussed before [17].

The proportion of positive tests was considerably higher in men compared to women.

This can be explained by the fact that men are usually tested because of symptoms or anamnestic reasons. Furthermore, past analysis of the Ct laboratory sentinel showed

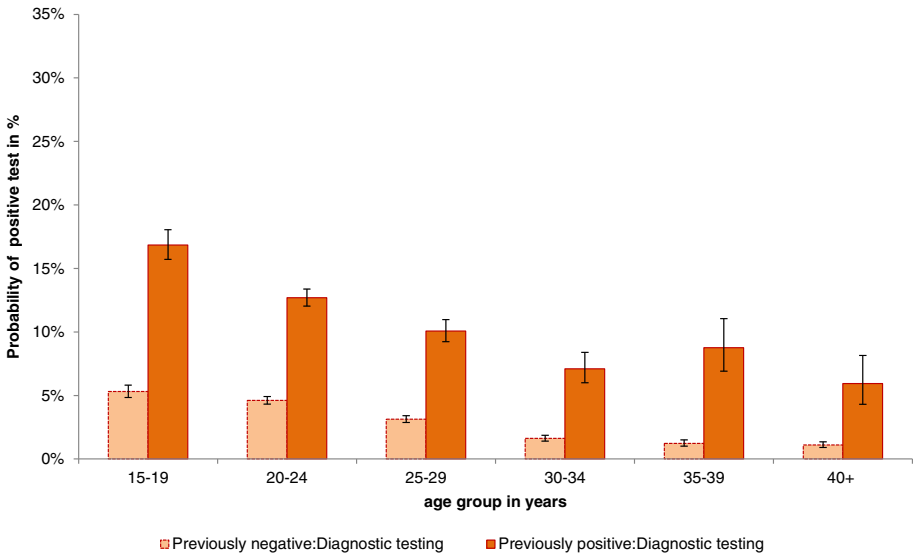

Fig. 3 Probability and 99% CI of positive test result according to age group and previous test results in women tested for diagnostic reasons, 2008–2014

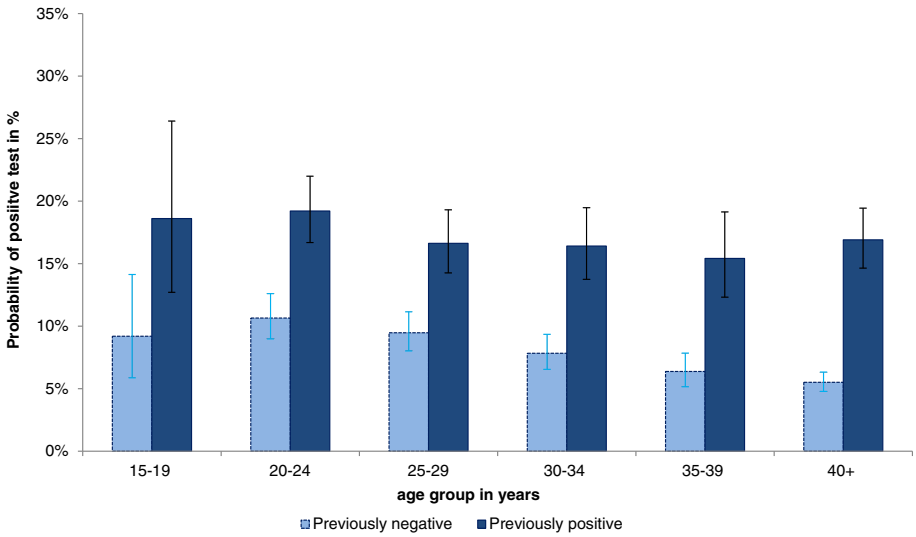

Fig. 4 Probability and 99% CI of positive test result according to age group and previous test results in men, 2008–2014

that a substantial proportion of tested material is rectal swabs [27] . Based on previous national and international studies, it is known that the proportion of positive tests is higher among MSM than heterosexual men [13, 29]. This aspect might have influenced the data we observe.

Less than one fourth of all tested women and men were tested repeatedly during the study period. Because screening for women < 25 years of age should be performed annually, and women can also be tested because of screening in pregnancy and for diagnostic reasons, we expected higher proportion of repeatedly tested women. The small proportion of repeatedly tested women suggests that screening programmes might not be sufficiently implemented in Germany yet. To tackle insufficient coverage of the existing screening programs, the Federal Agency for Health Education (BZgA) designed an information campaign and information materials on chlamydia screening for physicians and attendees of medical praxes, in addition to an ongoing poster campaign on STIs and corresponding symptoms [28].

In all age groups and regardless of the reason for testing, women and men with prior Ct infection had a high probability to be tested positive for Ct (women: Pr: 5.9–28.4%, men: Pr: 15.4–19.2%). The probability of reinfection varied substantially among women by age and test reason with highest probabilities in young women, especially if tested within screening in pregnancy. Studies have shown that early first intercourse was associated with subsequent sexual risk behavior [9, 24] which also leads to a higher probability of acquiring an STI. We observed less age-related variation for reinfection among men, though younger men had a higher probability for reinfection. We believe that this might be related to a mixed population of men in our data set. The group that repeatedly tested positive might be more at risk of infection, for example HIV positive MSM. Bacterial STI are more common in HIV positive MSM [13, 30]. However, we lack data in current study to analyse this in more detail. Additionally, the detection rate of STI, especially asymptomatic infections, among men frequently accessing testing might be higher.

Currently, evidence remains insufficient to recommend routine Ct-screening for all sexually active young men in Germany, partially because men rarely develop sequelae [31]. Nonetheless, the benefit of a screening programme for high-risk populations of men has been supported, for example Gift et al. found that Ct-screening programme targeting high-risk men was cost-saving compared to programme expanding screening of lower-risk women [32].

Interestingly, previously positive tested women and men in the older age groups showed the highest odds ratios to test positive; women especially when screened in pregnancy. This finding could indicate that these women and men aged 30 years and older with repeat infection, may represent a small group with ongoing sexual risk behavior that is thus more likely to contract repeat infection than their previously negative tested peers. Nevertheless, the absolute risk differences (in percent points) between previously positive and previously negative tested women and men by age group are much higher in the young age groups. The increased probability of infection for women and men with a history of Ct infection has been found by several other studies. In a study population of adolescent girls, Batteiger et al. found that incident Ct infections occurred in 78.1% of participants with infections at baseline compared to 51.7% of participants without infection at baseline [33]. The results of Dunne et al. showed a 1.2-fold risk for men with previous Ct infection amongst

men screened for Ct infection [34], whereas Rietmejer et al. found a 2.4-fold increased risk of reinfection for women and men with Ct infection at baseline amongst female and male patients of an STI clinic [25]. However, because of wide variations amongst the definitions of reinfection, the study designs and the composition of study populations, it is difficult to compare these numbers directly to our results.

Untreated infections of current partners and unprotected sex with new partners contribute to repeated infections [17, 35]. Although treatment with antibiotics is highly effective [33], a small proportion of alleged reinfection might be ongoing infections after treatment failure or insufficient adherence to treatment. Several studies have shown that persons with prior Ct infection were at a high risk of reinfection [9, 20, 25, 33, 34]. However, a link between previously diagnosed and treated Ct infections and the development of immunity against Ct has also been discussed [23].

The testing interval was considerably shorter if a previous Ct test was positive. A median time to repeat testing after a positive test result of approximately 3 months might indicate compliance to European guideline that recommends repeat testing in women and men < 25 years of age within 3 to 6 months after a positive Ct test result [15]. Additionally, test of cure is recommended for pregnant women, if symptoms persist, if non-compliance is suspected or if second- and third-line treatments have been used [15]. However, the median time to the reinfection depends largely on the testing patterns and cannot directly be related to the natural history of infection.

The relatively small proportion of persons with reinfection we found in our whole sample was likely a consequence of the small proportion of repeatedly tested persons in our sample. While among those tested repeatedly during the study period, the reinfection was observed in 2% of women and 6.5% of men. The median time to reinfection was 4.2 month in women and 6.7 months in men. Similar to our results, studies from the United States and Australia have found a median time to reinfection of 5.2 months amongst 19-year-old women [29] and of 4.6 months amongst women aged 16 to 25 years [9]. The treatment failure can still be observed 7–8 weeks after antibiotic treatment. Therefore, it is important to be able to distinguishing between actual reinfection with Ct and treatment failure [36]. As we have no information on treatment and detailed follow up data, we cannot distinguish between treatment failure and reinfection. Therefore, our approach to define a reinfection as each infection that occurs after a 30 days period is sensitive and potentially misclassifies those with treatment failure. In a sensitivity analysis, where we defined a reinfection as a subsequent positive test occurring after 42 days, we observed a reinfection in 1.9% (instead of 2.0%) of repeatedly tested women and in 6.4% (instead of 6.6%) of repeatedly tested men. With this approach, it is probable that some of the true reinfections are misclassified treatment failures.

Limitations

First, because several samples of a person only received the same patient-ID if tested in the same laboratory, the true number and proportion of reinfection in the study population may have been underestimated. If samples of one person were sent to different laboratories, e.g., because someone changed physician or the physician changed the diagnosing laboratory, these persons were either lost to follow-up or their tests were sampled in the Ct laboratory sentinel again, but with a new patient-ID. However, we expect that the proportion of previously tested persons having received a new patient-ID represents only a small fraction of the analysed tests.

Another limitation is that the *Ct laboratory sentinel* dataset offers no information on whether a person who tested positive received therapy and whether the treatment was successful. Thus, ongoing Ct-infections due to non-compliance or treatment failure could have been falsely classified as reinfection in this study. Furthermore, there is no information on behavioural factors that may influence the likelihood to be tested positive.

Finally, the Ct Laboratory Sentinel data might lack representativeness for the target population in Germany, even though the sentinel generally reached a good coverage in the period 2008–2014 and it was possible to collect a large number of samples representing one third of all performed Ct tests in Germany [17]. Still, the participation of laboratories was voluntary and it is unclear whether participating laboratories differed systematically from the non-participating laboratories, e. g. in terms of tested population. Data from the laboratories with continuous follow-up for at least 3 years used in current analysis did not substantially differ from rest of the participating laboratories regarding distribution of sex, age and proportion tested positive.

Conclusions

We describe how history of Ct infection increased the likelihood of infection with Ct in women and men, taking into account age and reason for testing (in women). This helps to identify groups in need of health education and generates evidence for a more targeted testing strategy.

The high proportion of positive tests and of reinfection found amongst men supports risk-based screening of sexually active young men. However, future studies must determine all potential risk factors and identify the categories of transmission in men to identify for which group Ct screening is most beneficial.

We recommend that women and men who have been diagnosed positive with Ct should be consulted on prevention, symptoms and possible consequences of Ct infection to avoid reinfection.

To identify potential reinfection – and persisting infection – repeat testing after treatment should be performed. To increase the number of those getting tested, preventive measures for young women and men like awareness campaigns on Ct infection and testing opportunities as well as sex education in schools should be implemented. Till now, preventional campaigns for Ct in Germany do not address a higher risk for infection of persons who were tested positive before specifically. On basis of our data, we recommend to adjust the respective materials to emphasize this. Awareness about Ct infection, increased risk of reinfection for person tested Ct positive before, and adaequate screening should also be raised amongst physicians and gynaecologists to enhance the coverage of the screening programmes. Further studies are necessary to examine whether these measures show the desired effect.

Additional files

Additional file 1: Table S1. Univariable association of previous test result and age-group with "tested Ct positive" by test reason among women, 2008–2014. (DOCX 15 kb)

Additional file 2: Figure S1. Odds Ratio and 99%-CI: Positive test results in previously positive vs. previously negative tested women by age group and test reason. Source: Ct Laboratory Sentinel 2008–2014. (DOCX 47 kb)

Additional file 3: Figure S2. Odds Ratio and 99%-CI: Positive test results in previously positive vs. previously negative tested men by age group and test reason. Source: Ct Laboratory Sentinel 2008–2014. (DOCX 37 kb)

Abbreviations

CDC: Centers for Disease Control and Prevention; Ct: Chlamydia trachomatis; ECDC: European Center for Disease Control and Prevention; LRT: Likelihood ratio test; MSM: Men having sex with men; NAAT: Nucleic acid amplification test; OR: Odds ratio; Pr: Probability; STI: Sexually transmitted infection

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Patricia Bartsch (MVZ Dr. Eberhard & Partner, Dortmund)
Thomas Brüning (LADR GmbH MVZ Nord-West Schüttorf)
Josef Cremer (Medizinisch-Diagnostisches Labor Kempten, Kempten)
Helga Dallügge-Tamm (amedes MVZ wagnerstibbe, Hannover)
Arndt Gröning (amedes MVZ wagnerstibbe, Hannover)
Stephan Eicke (Labor Dr. Eicke, Berlin)
Dagmar Emrich (MVZ Labor 28 GmbH, Berlin)
Florian Mielack, Martina Woitkowiak (MVZ Labor 28 GmbH, Berlin)
Gundula Fritsche (Labor MVZ Westmecklenburg, Schwerin)
Rosi Gjavotchanoff (Labor Alfredstraße, Essen)
Peter Gohl (Bioscientia Institut für Medizinische Diagnostik GmbH, Ingelheim)
Matthias Götzrath, Axel Meye (Medizinisches Labor Ostsachsen MVZ GbR, Dresden)
Ingrid Ehrhard, Beate Köpke (Landesuntersuchungsanstalt Sachsen, Dresden)
Birgit Henrich (Institut für Medizinische Mikrobiologie und Krankenhaushygiene, Universitätsklinikum Düsseldorf)
Caroline Kastilan (MVZ Labor Diagnostik Karlsruhe GmbH, Karlsruhe)
Susanne Lehmann (Diagnosticum, Plauen)
Anneliese Märzacker (Labor Schottdorf MVZ GmbH, Augsburg)
Stefan Odenbreit, Claudio Perocco (Labor Schottdorf MVZ GmbH, Augsburg)
Bernhard Miller (Labor PD Dr. Volkmann und Kollegen GbR, Karlsruhe)
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Christian Pache (MVZ Labor Passau)
Thomas Miedl (MVZ Labor Passau)
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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

AL, SD and VB developed the concept of the analysis of repeated testers in the Chlamydia trachomatis laboratory sentinel study. AL, MadH and SD developed data analysis plan. AL performed the data analysis. SD and MadH supervised the data analysis. AS supported the data management. AL, SD, KJ, VB, AS and MadH critically discussed study results and data interpretation. AL drafted the paper. SD, KJ, VB, AS and MadH revised the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The data-collection protocol was confirmed by the Federal Commissioner for Data Protection and Freedom of Information (https://www.bfdi.bund.de). Additional approval from an ethics committee was deemed not necessary as no patient-identifying data were collected. As only routine in laboratories readily available testing data were collected a no additional testing of the samples were performed, consent to participate was deemed not necessary. According to the German Data Protection Act the study complies with the national guidelines, and no formal ethical committee approval was necessary (available under https://www.gesetze-im-internet.de/bdsg_1990/index.html).

Consent for publication

Not applicable.

Competing interests

KJ is member of the editorial board member at BMC Infectious Diseases. However, there are no competing interests of all authors.

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Author details
[1]Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany. [2]Charité Universitätsmedizin Berlin Berlin, Germany.

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RESEARCH ARTICLE Open Access

Antimicrobial resistance of *Neisseria gonorrhoeae* in Germany: low levels of cephalosporin resistance, but high azithromycin resistance

Susanne Buder[1*†], Sandra Dudareva[2,3*†], Klaus Jansen[2], Anna Loenenbach[2], Sergejs Nikisins[2,4,5], Andrea Sailer[2], Eva Guhl[1], Peter K. Kohl[1], Viviane Bremer[2] and GORENET study group

Abstract

Background: The widespread antimicrobial resistance of *Neisseria gonorrhoeae* is a serious problem for the treatment and control of gonorrhoea. Many of the previously effective therapeutic agents are no longer viable. Because *N. gonorrhoeae* infections are not reportable in Germany, only limited data on disease epidemiology and antimicrobial susceptibility patterns are available. The Gonococcal Resistance Network (GORENET) is a surveillance project to monitor trends in the antimicrobial susceptibility of *N. gonorrhoeae* in Germany in order to guide treatment algorithms and target future prevention strategies.

Methods: Between April 2014 and December 2015, data on patient-related information were collected from laboratories nationwide, and susceptibility testing was performed on 537 *N. gonorrhoeae* isolates forwarded from the network laboratories to the Conciliar Laboratory for gonococci. Susceptibility results for cefixime, ceftriaxone, azithromycin, ciprofloxacin and penicillin were defined according to EUCAST 4.0 standards. Percentages, medians and interquartile ranges (IQR) were calculated.

Results: Altogether, 90% of isolates were from men. The median age was 32 (IQR 25–44) years for men and 25 (IQR 22–40) years for women (p-value < 0.001). The most frequently tested materials among men were urethral (96.1%) and rectal swabs (1.7%), and among women, it was mainly endocervical and vaginal swabs (84.3%). None of the isolates were resistant to ceftriaxone. Furthermore, 1.9% (in 2014) and 1.4% (in 2015) of the isolates were resistant to cefixime, 11.9% and 9.8% showed resistance against azithromycin, 72.0% and 58.3% were resistant to ciprofloxacin, and 29.1% and 18.8% were resistant to penicillin.

Conclusions: Resistance to ceftriaxone was not detected, and the percentage of isolates with resistance to cefixime was low, whereas azithromycin resistance showed high levels during the observation period. The rates of ciprofloxacin resistance and penicillin resistance were very high across Germany. Continued surveillance of antimicrobial drug susceptibilities for *N. gonorrhoeae* remains highly important to ensure efficient disease management.

Keywords: *Neisseria gonorrhoeae*, Gonorrhoea, Antimicrobial resistance, Resistance surveillance

* Correspondence: dr.susanne.buder@web.de; DudarevaS@rki.de
†Equal contributors
[1]German Consiliary Laboratory for Gonococci, Department of Dermatology and Venerology, Vivantes Hospital Berlin, Berlin, Germany
[2]Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
Full list of author information is available at the end of the article

Background

The worldwide development of antimicrobial resistance in *Neisseria gonorrhoeae* is a serious problem for the treatment and control of gonorrhoea. Treatment opportunities are dramatically limited because many of the previously recommended therapeutic agents are no longer effective.

The World Health Organization (WHO) [1], the Centers for Disease Control and Prevention (CDC) [2], and the European Centre for Disease Prevention and Control (ECDC) [3] have called for action to confine the spread of multidrug-resistant *N. gonorrhoeae* by enhancing the surveillance system of *N. gonorrhoeae* susceptibility testing and by strengthening laboratory capacities to perform culture and antimicrobial resistance testing. Representative coverage of collected data, unified *N. gonorrhoeae* susceptibility testing methods and interpretation standards are of great importance [4–6].

Extended spectrum cephalosporins (ESCs) are the last agents effective against *N. gonorrhoeae*. However, resistance to ESCs is increasingly common [7–13], causing concern that the efficacy of this substance group could expire in the near future [5–10]. Due to the worldwide rising resistance of *N. gonorrhoeae* against cefixime in recent years, the treatment guidelines needed to be changed accordingly. Thus, cefixime is no longer recommended as first-line therapy in many countries [14–16] and new therapy guidelines and action plans have been developed to keep gonorrhoea a treatable disease. In 2014 the German STI Society implemented new therapy guidelines for Germany. These guidelines recommend the use of the ESC ceftriaxone (1000 mg single dose i.m. or i.v.), now in combination with azithromycin as dual therapy (1.5 g single dose p.o.), as the first-line treatment [17]. The use of cefixime (800 mg single dose p.o.) should be reserved for cases where parenteral treatment is not possible and ideally after susceptibility testing.

Because gonorrhoea is not a notifiable disease in Germany, only very limited data about epidemiology and antimicrobial resistance against *N. gonorrhoeae* are available. Furthermore, no standard operating procedures or unified protocols for *N. gonorrhoeae* susceptibility testing have been established in Germany. To date, information about *N. gonorrhoeae* susceptibility can be derived from several cross-sectional, regionally limited studies [18–21] through the German antibiotic resistance surveillance programme (ARS) and 100–120 isolates submitted to Euro-GASP yearly through the Consiliary Laboratory (CL) for gonococci [22]. Within this Euro-GASP collection, isolates resistant against ceftriaxone (MIC >0.125 mg/L) have been observed in Germany. Resistance against ceftriaxone was shown by 6.5% ($n = 7$) of all German Euro-GASP isolates in 2011, while in the following years 2012–2014, one isolate per year (1%) could be identified with ceftriaxone resistance. Cefixime resistance (MIC >0.125 mg/L) in German Euro-GASP isolates ranged between 5.7% and 12.9% ($n = 13$, 11.9% in 2010; $n = 11$, 10.2% in 2011; $n = 6$, 5.7% in 2012; $n = 13$, 12.9% in 2013) [22]. In 2014, there was no detection of cefixime-resistant isolates in Euro-GASP.

To implement continuous routine data collection on epidemiology and antimicrobial susceptibility testing for *N. gonorrhoeae* in German laboratories (aim 1) and to collect isolates for testing in the German CL for gonococci with unified methodology (aim 2), we set up a *N. gonorrhoeae* resistance network (GORENET).

We analysed the data and isolates collected through GORENET in 2014 and 2015 to guide treatment algorithms and targeted prevention strategies in Germany.

Methods

To characterise laboratories testing for *N. gonorrhoeae* in Germany and indicate laboratories for recruitment, we performed a cross-sectional survey between June and August 2013, as described previously [23]. From the laboratories that expressed an interest in participating, we recruited private and hospital laboratories for GORENET, prioritizing those with a wider catchment area and a higher number of *N. gonorrhoeae* tests per quarter. The laboratories in Germany have no predefined catchment areas, and practitioners are free to choose laboratories for cooperation. For a better geographical coverage of the data, we strove to recruit laboratories from all regions in Germany and laboratories that use any gradient Etest for *N. gonorrhoeae* susceptibility testing, at least for azithromycin, ceftriaxone and cefixime. Participation was voluntary, and there was no financial compensation for laboratories to participate in the study. The data collection protocol was confirmed by the data protection officer at the Robert Koch Institute (RKI), Berlin. Additional approval from an ethics committee was deemed to be unnecessary.

Continuous routine data collection

From GORENET network laboratories, continuous routine data on all samples tested for *N. gonorrhoeae* antimicrobial susceptibility were collected between April 2014 and December 2015. The network laboratories submitted data to the RKI (further labelled as samples). The collected data included sample identification number, information on test results, sampled material (urethral swab, urine, vaginal swab, cervical swab, rectal swab, pharyngeal swab, and other material), date of sampling, date of testing, district code, gender and year of birth. If the district code of the patient was not available, we used the code of the laboratory instead. Based on the year of birth, we calculated the person's age at the time of sampling. If the date of testing was

not available, we used the date when the isolate was received in the CL.

Data were transmitted electronically to the RKI. Laboratories entered the data either in an online questionnaire (VOXCO Command Center 3) or in a preformatted Excel spreadsheet (.xls). Data on *N. gonorrhoeae* susceptibility from laboratories willing to participate in GORENET but already submitting their susceptibility data (including data on a wide range of other agents) to the German Antibiotic Resistance Surveillance Programme (ARS) were extracted from the ARS database. We performed plausibility checks on all reported data.

Based on the district codes, we described the geographical distribution of the samples tested for *N. gonorrhoeae* antimicrobial susceptibility. Each district code or respective 3-digit postal code corresponded to one district in Germany. We used samples tested for susceptibility from participating laboratories to describe tested persons by gender, age, sampled material and treating specialist. Susceptibility results from participating laboratories are used for national surveillance, but not presented in this paper.

An overview of the analysis of samples tested for *N. gonorrhoeae* susceptibility in network laboratories is given in Table 1.

Isolate collection and susceptibility testing

The network laboratories were asked to send *N. gonorrhoeae* isolates from the samples tested for antimicrobial susceptibility between April 2014 and December 2015 to the CL for extended and comparative susceptibility testing (further labelled as isolates). There were no criteria used to preselect isolates that should be sent to CL. The sample identification number was used to link isolates to samples. For all received isolates, we confirmed *N. gonorrhoeae* by using a combination of culture on non-selective agar medium, rapid oxidase production assays and determining the presence of Gram-negative diplococci using microscopy and the Phadebact Monoclonal GC OMNI Test (Pharmacia Diagnostics, Piscataway, NJ, USA). Susceptibility testing was performed and MIC were detected by using Etest (bioMérieux SA, Marcy-l'Étoile, France) according to the manufacturer's instructions for ceftriaxone, cefixime, azithromycin, penicillin and ciprofloxacin. To define resistance, we used the criteria of the European Committee on Antimicrobial Susceptibility Testing EUCAST 4.0 (2014) [24]. The presence of beta-lactamase enzyme production, which provides high-level resistance to penicillins, was detected by using the nitrocefin test (BBL DrySlide™, Becton, Dickinson, NJ, USA). Isolates testing positive for beta-lactamase were defined as penicillinase-producing *N. gonorrhoeae* (PPNG).

The working stock of *N. gonorrhoeae* isolates was stored at −80 °C. *N. gonorrhoeae* strains ATCC 49226 and WHO-reference strains G, K, M, O and P were used with each batch of Etest as quality controls [25]. Ceftriaxone and cefixime were tested twice when the MIC was ≥0.125 mg/L. Isolates tested in the CL were characterized by their resistance patterns.

An overview of the analysis of isolates tested in CL is given in Table 1. Note that a direct comparison of historical German data with current GORENET data was not possible because different methods for isolate collection were in place before GORENET was rolled out and the geographical coverage was different.

For categorical variables we calculated percentages and, for continuous variables, medians together with interquartile ranges (IQR) were determined. Percentages were compared by Chi-squared or Fisher's exact tests, and medians were compared with the Wilcoxon-Mann-Whitney test, where applicable. The Kruskal-Wallis test was used to compare continuous variables between more than two categories. Significance level was set at a p-value < 0.05.

Results

Of the 100 laboratories that were interested in participating in GORENET, 31 were selected for recruitment, and 23 agreed and reported data to GORENET. The reasons for declining participation in GORENET were not using the Etest for *N. gonorrhoeae* susceptibility

Table 1 Isolates tested for susceptibility in network laboratories and in CL, number of laboratories and isolates included in analysis and description of performed analysis for each data source

	Number of laboratories	Number of samples or isolates			In manuscript referred as	Performed analysis
		Total	2014	2015		
Samples tested for *N. gonorrhoeae* susceptibility in network laboratories	23	1654	727	927	Samples	Geographical, age and gender distribution. Sampled material and treating specialist
Isolates tested in CL	16	537	261	276	Isolates	Susceptibility for ceftriaxone, cefixime, azithromycin, penicillin and ciprofloxacin. Presence of beta-lactamases

testing (n = 5) and too much time and effort needed for participation (n = 3).

Continuous routine data collection

Twenty-three participating laboratories reported to the RKI in total 1654 *N. gonorrhoeae* samples tested for susceptibility. Of them, 727 were collected from April to December 2014, and 927 were collected from January to December 2015. Overview of the reported samples is given in Table 1.

The number of reported samples varied between 2 and 305 per laboratory, with a median of 43 samples (IQR 24–86). In total 47.1% of the samples were reported by three laboratories, which provided information on 209 (in Hamburg), 265 (in Berlin) and 305 (in North Rhine-Westphalia) samples, respectively.

The number of reported *N. gonorrhoeae* samples varied by administrative district between 1 and 209 (Fig. 1). The three laboratories submitting the majority of the data were located in the areas with >50 samples.

Central and northern Germany were represented equally. Data from southern Germany mostly originated from the larger cities.

Overall, 90.0% of samples tested for susceptibility in network laboratories were from men; 9.5% were from women and in nine samples, information on gender was not available. The median age of tested men and women was 33 (IQR 25–44) and 27 (IQR 22–40) years respectively (p-value < 0.001). The distribution of

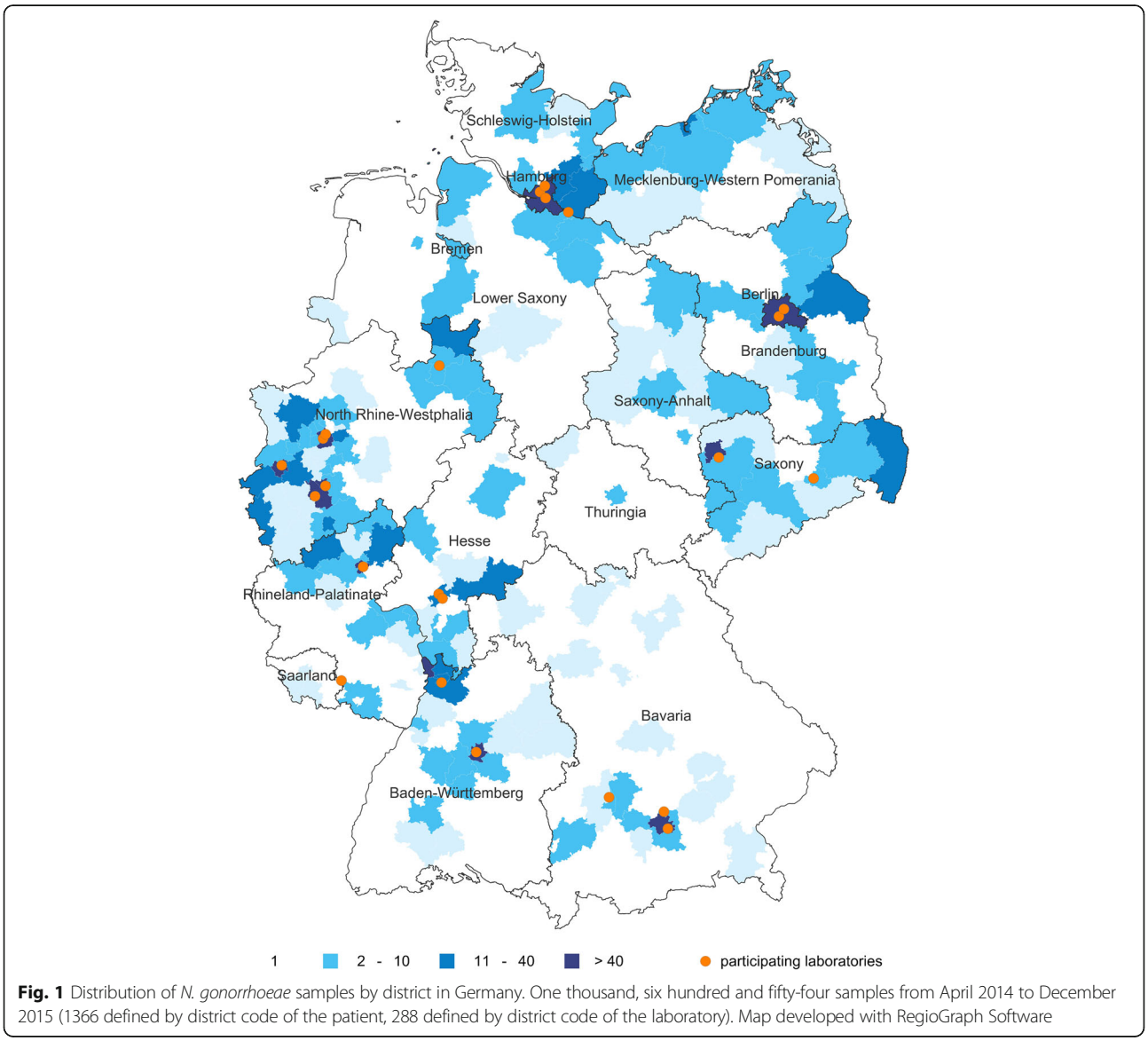

Fig. 1 Distribution of *N. gonorrhoeae* samples by district in Germany. One thousand, six hundred and fifty-four samples from April 2014 to December 2015 (1366 defined by district code of the patient, 288 defined by district code of the laboratory). Map developed with RegioGraph Software

N. gonorrhoeae susceptibility testing by age group and gender is displayed in Fig. 2.

Most tested samples from men were from urethral (96.1%) and rectal swabs (1.7%), while among women samples came from predominately endocervical or vaginal swabs (84.3%). Most of the samples tested from men were ordered by urologists (74.4%) and from women by gynaecologists (79.7%). Distribution by gender (p-value = 0.25), age (p-value = 0.28 for men and p-value = 0.87 for women), tested material (p-value = 0.15 for men and p-value = 0.07 for women) and ordering specialist (p-value = 0.63 for men and p-value = 0.73 for women) did not differ between the years 2014 and 2015.

Isolate collection and susceptibility testing

From the recruited 23 laboratories submitting information on samples tested for *N. gonorrhoeae* susceptibility, 16 sent isolates to the CL. We received 261 viable isolates collected between April and December 2014 and 276 viable isolates collected between January and December 2015. It was determined that 91.4% of isolates were from men, 8.4% were from women, and for one of the samples the gender was unspecified. The median age was 33 (IQR 26–43) for isolates from men and 28 (IQR 23–41) for isolates from women. These 537 isolates were tested for susceptibility in the CL. An Overview of the isolates tested in CL is given in Table 1. The results of the AMR testing of all isolates are summarized in Table 2. The percentage of resistant, intermediate and susceptible isolates did not significantly differ by age or gender.

No resistance to ceftriaxone (MIC >0.125 mg/L) was detected in 2014 or 2015 (Fig. 3). In 2014, two isolates showed MICs at the estimated breakpoint of 0.125 mg/L. One of these isolates displayed further resistance to cefixime, azithromycin and ciprofloxacin and showed an intermediate test result to penicillin (isolate 1, Table 3). Another isolate displayed resistance to ciprofloxacin and penicillin, while it was intermediate to azithromycin and had a MIC value at the breakpoint for cefixime (isolate 10, Table 3).

Altogether, 1.9% (n = 5) in 2014 and 1.4% (n = 4) in 2015 of the isolates displayed resistance (MIC >0.125 mg/L) to cefixime. The majority of isolates (62.5% in 2014 and 77.9% in 2015) showed low MICs of ≤0.016 mg/L to cefixime (Fig. 4). In 2014, 3.8% (n = 10) and in 2015, 1.4% (n = 4) of the isolates had a MIC of 0.125 mg/L at the estimated breakpoint.

All isolates with resistance to cefixime displayed resistance to ciprofloxacin. Three of the nine cefixime-resistant strains also showed resistance to azithromycin. No cefixime-resistant strain was susceptible to penicillin (3 resistant, 6 intermediate).

One cefixime-resistant isolate (MIC 0.25 mg/L) displayed additional resistance against azithromycin and ciprofloxacin, intermediate susceptibility against penicillin and showed reduced susceptibility to ceftriaxone at the breakpoint of MIC 0.125 mg/L (isolate 1, Table 3).

All isolates displaying resistance to cefixime were from men.

A total of 11.9% (2014) and 9.8% (2015) of the isolates showed resistance against azithromycin (MIC >0.5 mg/L). In addition, there was a high percentage of *N. gonorrhoeae* strains with intermediate susceptibility (33.7% in 2014 and 28.3% in 2015) and the MIC distribution of the susceptible strains appeared closer to intermediate breakpoint (MIC >0.38 mg/L) (Fig. 5). The MICs of resistant strains were mostly low and showed a distribution concentrating around the breakpoint (MIC >0.5 mg/L).

In 2015, one isolate displayed high-level resistance to azithromycin (MIC >256 mg/L). This isolate also showed high-level resistance to penicillin and resistance to ciprofloxacin, but was susceptible to ceftriaxone and cefixime.

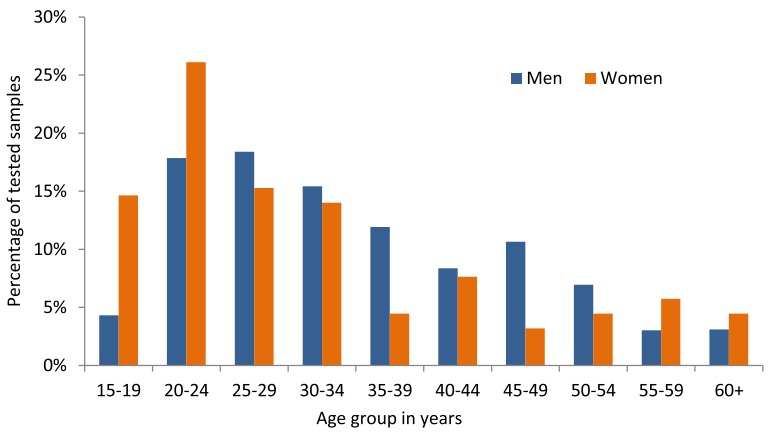

Fig. 2 *N. gonorrhoeae* samples tested in participating laboratories, by age group and gender, n = 1642

Table 2 Number and percentage of *N. gonorrhoeae* isolates testing susceptible, intermediate and resistant against cefixime, ceftriaxone, azithromycin, penicillin and ciprofloxacin, $n = 261$ for year 2014 and $n = 276$ for year 2015, *p-value < 0.05

	Susceptible		Intermediate		Resistant	
	Number (percentage, %)		Number (percentage, %)		Number (percentage, %)	
	2014	2015	2014	2015	2014	2015
Cefixime	256 (98.1)	272 (98.6)	/	/	5 (1.9)	4 (1.4)
Ceftriaxone	261 (100)	276 (100)	/	/	0 (0)	0 (0)
Azithromycin	142 (54.4)	171 (62.0)	88 (33.7)	78 (28.3)	31 (11.9)	27 (9.8)
Ciprofloxacin*	73 (28.0)	114 (41.3)	0 (0)	1 (0.4)	188 (72.0)	161 (58.3)
Penicillin*	27 (10.3)	40 (14.5)	158 (60.5)	184 (66.7)	76 (29.1)	52 (18.8)

The percentage of strains with resistance to ciprofloxacin (MIC >0.06 mg/L) was 72.0% in 2014 and 58.3% in 2015 (Table 2).

Overall, 29.1% of the isolates in 2014 and 18.8% in 2015 displayed resistance to penicillin. In addition, there was a very high rate of intermediate *N. gonorrhoeae* strains (Table 2).

Nitrocefin testing for the detection of beta-lactamase activity in *N. gonorrhoeae* was performed in 83.5% ($n = 218$) of isolates in 2014. All 276 isolates (100%) were tested for beta-lactamase activity in 2015. High-level plasmid-mediated resistance against penicillin (penicillinase producing *N. gonorrhoeae*, PPNG) was found in 25% of all tested strains in 2014 and in 14% of the strains in 2015.

Discussion

Using GORENET we aimed at two targets concerning gonococcal infections: data collection on disease epidemiology and monitoring of resistance patterns with unified methodology.

We were able to implement a nationwide data collection of all performed *N. gonorrhoeae* susceptibility testing in the participating laboratories. Routine data collection on all performed *N. gonorrhoeae* susceptibility tests together with epidemiological information, like age and gender, was not in place until GORENET surveillance.

Before starting GORENET, the CL collected isolates from a range of laboratories. This pre-existing network was expanded within GORENET, and the number of collected isolates increased substantially.

We were able to set up electronic data collection for all samples tested for *N. gonorrhoeae* susceptibility in the participating laboratories. Timely transmitted data are a good tool for monitoring *N. gonorrhoeae* susceptibility dynamics. Due to data protection issues, the collected epidemiological information was limited and important information, such as data regarding the transmission route, therapeutic regimen and therapeutic success, could not be gathered.

We reached a relatively even geographical representation of all regions, but the coverage in central and southern Germany should be increased further.

In routine data collection from the network laboratories, we found that over 90% of all samples tested for *N. gonorrhoeae* susceptibility were from men, similar to several other European countries [22]. This percentage

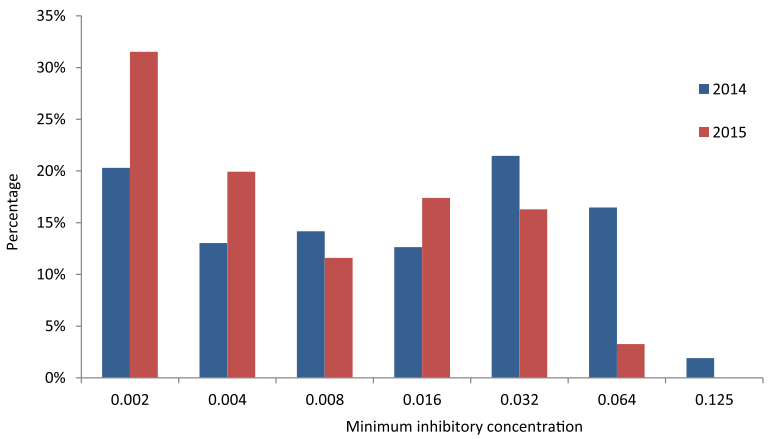

Fig. 3 Distribution of minimum inhibitory concentrations for ceftriaxone, $n = 261$ for year 2014 and $n = 276$ for year 2015

Table 3 Minimum inhibitory concentrations (MIC) of cefixime, ceftriaxone, azithromycin, ciprofloxacin and penicillin for isolates with resistance to cefixime or with MICs at the breakpoint for resistance to cefixime ($n = 24$)

	Minimum inhibitory concentration (MIC)				
Isolate	Cefixime	Ceftriaxone	Azithromycin	Ciprofloxacin	Penicillin
1	0.25	0.125	0.75	32	1
2	0.19	0.047	1	0.25	32
3	0.19	0.094	0.75	32	3
4	0.19	0.023	0.19	32	0.75
5	0.19	0.047	0.125	32	0.75
6	0.19	0.032	0.19	32	1.5
7	0.19	0.032	0.094	12	0.75
8	0.19	0.032	0.19	16	1
9	0.19	0.023	0.125	16	0.75
10	0.125	0.125	0.5	32	2
11	0.125	0.064	1	32	1
12	0.125	0.064	1	32	2
13	0.125	0.032	0.19	32	0.75
14	0.125	0.032	0.19	32	0.75
15	0.125	0.032	0.19	32	0.5
16	0.125	0.032	0.125	32	1.5
17	0.125	0.023	0.125	32	0.38
18	0.125	0.023	0.19	32	0.75
19	0.125	0.023	0.19	32	0.5
20	0.125	0.023	0.125	16	0.75
21	0.125	0.023	0.094	12	0.75
22	0.125	0.016	0.25	32	0.75
23	0.125	0.012	0.125	12	0.38
24	0.016	0.006	256	12	32

was 84% in previous studies in Germany [15], and we can assume that at least half of all isolates from men are attributable to men having sex with men (MSM), comparable to other European countries [22]. Nevertheless, women might still be underrepresented in our sample. This seems possible because men are more often symptomatic and might therefore be tested more often than women [14]. We aim to collect data on transmission routes from physicians to better interpret the collected data.

We also found that the median age of tested men was slightly higher than that of tested women. Again, Euro-GASP data and other previous data from Germany have reported findings [18, 21, 22] similar to our results. In countries that reported the risk of transmission, the proportion of men aged >25 years was higher among MSM than among heterosexual men. This might explain the higher median age of the tested men in our sample. As *N. gonorrhoeae* is not reportable in Germany, we were not able to compare whether the *N. gonorrhoeae* AMR test distribution by age corresponded to the age groups most affected by gonorrhoea.

We exclusively analysed susceptibility data from the CL testing because presently Germany lacks a standard operation protocol and regular quality assurance for *N. gonorrhoeae* testing for all laboratories. From a cross-sectional survey among laboratories performing *N. gonorrhoeae* diagnostics we know that 55% of all laboratories (76% of private laboratories) are accredited and 19% are certified [23]. However, due to the use of different methods, standards and test panels it is unknown if there are substantial differences in quality of testing, and GORENET will be a useful tool for quality assurance in the future.

Susceptibility testing in the CL enabled the monitoring of *N. gonorrhoeae* antimicrobial resistance detected by a unified methodology. Age and gender distribution of the

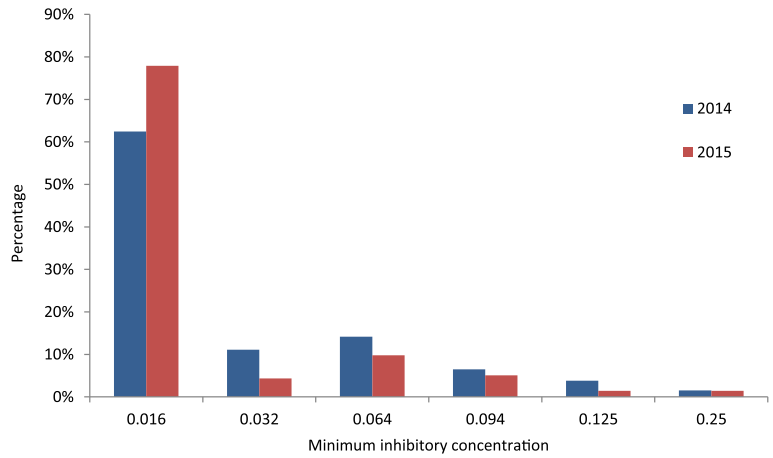

Fig. 4 Distribution of minimum inhibitory concentration for cefixime, $n = 261$ for year 2014 and $n = 276$ for year 2015

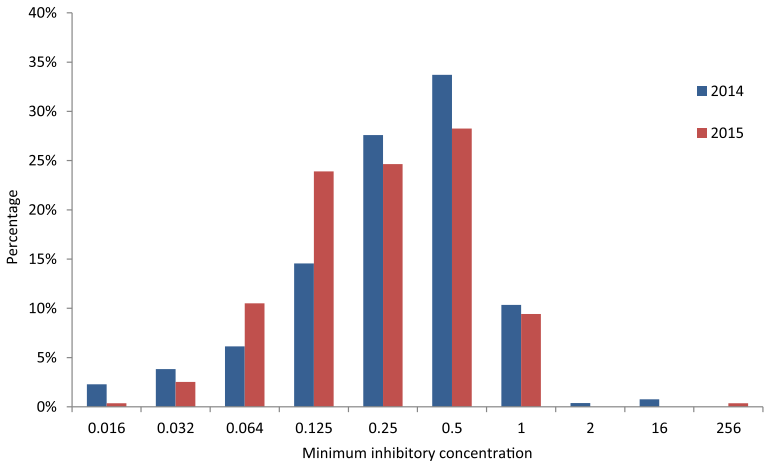

Fig. 5 Distribution of minimum inhibitory concentration for azithromycin, $n = 261$ for year 2014 and $n = 276$ for year 2015

tested isolates did not differ from all samples tested for susceptibility in the participating laboratories.

No resistance to ceftriaxone was detected in 2014 and 2015 in isolates collected with GORENET, and only two isolates showed MICs at the estimated breakpoint of 0.125 mg/L.

Previous German publications also did not show notable levels of ceftriaxone resistance or ESC resistance [18–21] in Germany. However, within the Euro-GASP collection, there was one exception in 2011, when 6.5% of German strains were resistant against ceftriaxone. In the following years 2012–2014, there were no notable levels of ceftriaxone resistance observed [18, 21, 22] in Germany by the Euro-GASP surveillance.

Currently, parenterally administered ceftriaxone remains an effective treatment option for gonorrhoea in Germany. Similar data have been published from surveillance systems in other countries [13, 26].

The percentage of strains with resistance to cefixime remained moderate within the GORENET (<2%), and low MIC values were predominant. German Euro-GASP data from 2014 correspond to this GORENET observation. In 2014 no cefixime-resistant isolate from Germany was detected within the Euro-GASP surveillance [22]. Compared with previous German data from Euro-GASP, this is a decrease from the years 2009–2013, when resistance rates from 5.7% to 12.9% were detected [22]. The decreasing number of strains resistant to cefixime could be observed not only in GORENET: European Euro-GASP data from 2014 and surveillance reports from the United Kingdom, the United States and Canada showed the same trend to less ESC-resistant isolates [26–29]. The decrease in gonococcal resistance to cefixime in 2014/15 suggests that clinicians in Germany may have avoided prescribing this antibiotic as a first-line treatment after the new therapy guidelines were published. However, changes in resistance patterns develop incrementally and are usually not detected so fast.

A presumptive explanation for this observation is the eradication of previously undetected reservoirs [27, 30]. Especially extragenital infections, which are oftentimes asymptomatic, difficult to culture and difficult to treat, are a constant reservoir for the spread of gonorrhoea [9, 30, 31]. Due to regular use of highly sensitive molecular diagnostic tests, like nucleic acid amplification tests (NAAT), in the routine diagnostic, detection of gonococcal infections was improved. Extragenital infections and subclinical urogenital infections are therefore more often confirmed and can be successfully treated [31]. The adjustment of treatment guidelines for ceftriaxone as first-line therapy seems to provide here an additional benefit. Sufficient treatment of these infections prevents a selection of resistant clones and might be a reason for the decrease of cefixime-resistant gonococci [27, 28, 30].

Molecular typing studies, performed with *N. gonorrhoeae* multiantigen sequence typing (NG-MAST, http://www.ng-mast.net) [32], showed one sequence type (ST1407), which was the most frequently observed sequence type associated with ESC- and multi-resistance [33–35]. Therefore, a further reason for the decrease of cefixime resistance could be a replacement of this multidrug-resistant *N. gonorrhoeae* clone ST1407 by clones with different resistance patterns within the infected population [27]. This could be an effect of the sufficient treatment or, as the Euro-GASP authors pointed out, be caused by impaired reinfection with the same clone due to a partial immunity and needs to be evaluated by future typing studies [27]. Additional monitoring and a molecular typing study within GORENET in the next years are therefore intended.

Multidrug resistance was not detected regularly in GORENET. Only one cefixime-resistant isolate displayed further resistance to azithromycin and ciprofloxacin,

intermediate susceptibility to penicillin and a reduced susceptibility to ceftriaxone at the breakpoint MIC of 0.125 mg/L. Nevertheless, the combination of resistances is particularly alarming and should be monitored further.

A high prevalence of resistance was detected for azithromycin. Although we observed mostly resistance near the breakpoint (MIC >0.5 mg/L), this trend is concerning. In addition, there was a high rate of intermediate *N. gonorrhoeae* strains: 40–45% of the strains were not fully susceptible to azithromycin. Germany's data from previous years [22] shows that the level of azithromycin resistance was mostly under 5%. The first-line use of azithromycin is very common in STI treatment regimes, especially as a syndromic treatment before or without confirmation of the pathogenic agent. This might explain the increase in azithromycin resistance in the last several years, but data on prescriptions in Germany are not published.

In 2015, we detected the first case of a high-level azithromycin resistant *N. gonorrhoeae* strain in Germany, with a MIC >256 mg/L. This isolate was susceptible to ceftriaxone and cefixime but showed high-level resistance to penicillin and resistance to ciprofloxacin. As rising resistance rates to azithromycin are increasingly observed globally [22, 26] and high-level azithromycin resistance is reported worldwide [35–43], azithromycin is not suitable for first-line treatment. If azithromycin is used as a single-drug treatment in cases of severe penicillin/cephalosporin anaphylaxis, susceptibility testing prior to treatment should be performed.

According to current treatment guidelines, dual therapy with ceftriaxone and azithromycin is recommended, using two antimicrobial agents with different mechanisms of action [5, 44]. Currently, there is no alternative to this dual treatment regime. Ultimately, we will need to discuss whether we have to abandon dual therapy with azithromycin if the trend of increasing azithromycin resistance remains in the years to come [9, 45].

The resistance rates to ciprofloxacin were constantly high in Germany, although a drop was detectable in the surveillance period. A high prevalence of resistance to ciprofloxacin has also been found in Europe and worldwide since the late 1990s [22]. The drug is therefore not recommended for therapeutic use in Germany.

Resistance to penicillin has been prevalent for many decades worldwide. Nearly 25% of all isolates displayed resistance to penicillin and an additional 64% showed intermediate susceptibility in the GORENET surveillance data. Accordingly, approximately 90% of the strains were not fully susceptible to penicillin in Germany. High-level plasmid-mediated resistance to penicillin was also regularly observed but decreased within the surveillance period from 25.9% to 14%, an observation that requires further monitoring.

We have several limitations in our data. First, within the GORENET data collection scheme, we were unable to collect more detailed epidemiological information, such as the risk of transmission, special symptoms, therapy strategies and treatment success rates. Usually, laboratories in Germany have very limited epidemiological information available, provided by the physicians in charge, and need to treat these data confidentially due to strict data-protection regulations.

Second, our data analysis was limited by the small number of isolates collected compared to the overall population of Germany.

Third, we cannot exclude selection bias in our data, because we recruited laboratories based on their catchment area, number of tested *N. gonorrhoeae* samples and use of the Etest from a pool of laboratories that expressed an interest to participate. However, with selected and established network laboratories, which forwarded all of their received isolates, we diminished a collection bias from laboratories being more prone to submit isolates with interesting resistance patterns.

Conclusions

Using GORENET, we were able to implement a nationwide collection of all performed *N. gonorrhoeae* susceptibility data in the participating laboratories and increase the number of collected isolates retested at the CL for confirmation and quality assurance. The majority of susceptibility tests are performed among young men. More detailed epidemiological information would be beneficial.

The resistance rate to ceftriaxone remains low in Germany. Therefore, ceftriaxone is still an appropriate treatment for gonorrhoea at present. In 2014 and 2015, we found low resistance rates for cefixime in Germany. However, this needs further monitoring. Resistance to azithromycin is common and should continue to be monitored in the future. Except for a small decrease in AMR towards ciprofloxacin and penicillin, no substantial changes in the susceptibility patterns between 2014 and 2015 could be detected.

In conclusion, GORENET as a gonococcal antimicrobial surveillance in Germany is highly needed. Current data and ongoing collection of data will be used to update national treatment guidelines and, if necessary, implementation of future prevention measures.

To continue to monitor *N. gonorrhoeae* susceptibility, particularly against ESC and azithromycin, the yearly number of isolates tested in the CL should be substantially increased. Molecular surveillance of the circulating strains is important for monitoring the current situation, the evolving resistances and the transmission networks.

Surveillance of susceptibility is essential to ensure efficient patient management and keep gonorrhoea a treatable disease.

Abbreviations
AMR: Antimicrobial resistance; ARS: Antibiotic resistance surveillance programme; ATCC: American Type Culture Collection; CDC: Centers for Disease Control and Prevention; CL: Consiliary Laboratory for gonococci; ECDC: European Centre for Disease Prevention and Control; ESC: Extended spectrum cephalosporin; EUCAST: European Committee on Antimicrobial Susceptibility Testing; Euro-GASP: European Gonococcal Antimicrobial Surveillance Programme; GORENET: Gonococcal Resistance Network; i.m.: Intramuscular; i.v.: Intravenous; IQR: Interquartile ranges; MSM: Men having sex with men; *N. gonorrhoeae*: *Neisseria gonorrhoeae*; NAAT: nucleic acid amplification test; NG MAST: *Neisseria gonorrhoeae* multiantigen sequence typing; PPNG: Penicillinase producing *N. gonorrhoeae*; RKI: Robert Koch Institute; ST: Sequence type; STI: Sexually transmitted infection; WHO: World Health Organization

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**GORENET study group.*
Thomas Back (Labor Schottdorf MVZ GmbH, Augsburg).
Anja Berger (Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit, Oberschleißheim, Sachgebiet GE 2.2 Infektiologie, Humanbakteriologie, Mykologie und Konsiliarlabor Diphtherie).
Valerie Chapot, Jörg Steinmann (Institut für Medizinische Mikrobiologie, Universitätsklinikum Essen).
Stephan Eicke (Labor Dr. Eicke, Berlin).
Claudia Friedrichs (Medizinisches Labor Ostsachsen MVZ GbR, Görlitz).
Andreas Groß, Hans-Jochen Hagedorn (Labor Krone, Bad Salzuflen).
Alexander Halfmann (Institut für Medizinische Mikrobiologie und Hygiene, Universitätsklinikum des Saarlandes, Homburg).
Britt Hornei (MVZ Synlab Leverkusen GmbH, Leverkusen).
Ralf Ignatius (Labor Enders und Kollegen MVZ, Stuttgart).
Simone Korten, Hany Sahly (Labor Lademannbogen MVZ GmbH, Hamburg).
Elzbieta Kozub-Witkowski (LADR GmbH Medizinisches Versorgungszentrum Dr. Kramer & Kollegen, Geesthacht).
Sabine Krämer (MVZ Labor Eveld & Kollegen, Essen).
Margit Kühn (Labor Becker, Olgemöller und Kollegen, München).
Anke Liebetrau (MVZ Labor Dr. Reising-Ackermann und Kollegen, Leipzig).
Thomas Meyer (Institut für Medizinische Mikrobiologie, Virologie und Hygiene, Universitätsklinikum Hamburg-Eppendorf).
Klaus Oberdorfer (Labor Dr. Limbach und Kollegen, Heidelberg).
Roland Pfüller (MDI Laboratorien GmbH, Berlin).
Caroline Ruckert (MVZ für Laboratoriumsmedizin und Mikrobiologie Koblenz-Mittelrhein, Koblenz).
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Authors' contributions
SB, SD, PKK and VB developed the concept and methods of the Gonococcal Resistance Network (GORENET). SB, SD, KJ, AL, AS, SN, PKK and VB were responsible for implementation of the GORENET. SB, EG and PKK were responsible for laboratory testing. SD, AS, KJ, SN and VB were in charge of the data collection and analysis. SB and SD drafted the paper and share the first authorship in equal parts. All authors revised the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The data-collection protocol was confirmed by the data-protection officer. Additional approval from an ethics committee was deemed not necessary, as no patient-identifying data were collected. According to the German Data Protection Act the study complies with the national guidelines, and no formal ethical committee approval was necessary (available under https://www.gesetze-im-internet.de/bdsg_1990/index.html)

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Competing interests
Klaus Jansen is a member of the editorial board (Associate Editor) of this journal. All other authors declare that they have no competing interests.

Publisher's Note

Author details
[1]German Consiliary Laboratory for Gonococci, Department of Dermatology and Venerology, Vivantes Hospital Berlin, Berlin, Germany. [2]Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany. [3]Charité University Medicine Berlin, Berlin, Germany. [4]Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany. [5]European Public Health Microbiology Training (EUPHEM) programme, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden.

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5. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6. Publikationsliste

6.1. Publikationen in wissenschaftlichen Zeitschriften mit Peer-Review

Boes L, Houareau C, Altmann D, An der Heiden M, Bremer V, Diercke M, **Dudareva S**, Neumeyer-Gromen A, Zimmermann R. Evaluation of the German surveillance system for hepatitis B regarding timeliness, data quality, and simplicity, from 2005 to 2014. Public Health. 2020;180:141-8.

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6.3. Publikationen in Zeitschriften ohne Peer-Review

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