

Introduction of *Chlamydia trachomatis* screening for young women in Germany

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- mass screening
- urogenital diseases
- pelvic inflammatory disease (PID)

Summary

Screening for genital *Chlamydia trachomatis* infections for young sexually active women was incorporated into routine medical care of German statutory health insured patients starting in January 2008. The primary goal of this new preventive measure is the reduction of severe sequelae for women such as tubal infertility and ectopic pregnancies. The course of the deliberations leading to the Federal Joint Committee's decision is summarized in this review.

Introduction

Genital *Chlamydia trachomatis* (CT) infection is the most frequent sexually transmitted disease worldwide [1]. The predominantly asymptomatic infection in women carries with it the risk of inflammatory processes in the small pelvis (pelvic inflammatory disease – PID). Serious possible sequelae of the inflammatory disorder are tubal infertility, chronic lower abdominal pain and ectopic pregnancy. The risk of subsequent infertility is estimated at about 15 % for a single episode of PID [2]. Chlamydial infections during pregnancy are associated with complications for the child (premature birth, underweight child, premature rupture of membranes, conjunctivitis and pneumonia). In association with an induced abortion a pre-existing chlamydial infection can lead to ascending infections such as endometritis

A test for CT infection in pregnant women has been part of the maternity guidelines in Germany since 1995. Outside of pregnancy the test is a component of the curative benefits catalogue of the statutory health insurance. Screening outside of pregnancy has not yet been available in the statutory health insurance system.

Since January 1, 2008 all women with statutory health insurance up to the 25th birthday are eligible for yearly screening for urogenital CT infections as well as women preceding a planned induced abortion. The background for introducing this new offer into the statutory health insurance system in the sense of an opportunistic screening is explained in the following.

Initiation of deliberations in the Federal Joint Committee

After prior research by the German Association of Statutory Health

Insurance Physicians (Kassenärztliche Bundesvereinigung, KVB) into the current status of scientific evidence, especially with regard to the benefits of screening young women (independent of pregnancy), the subject was presented by the KBV in the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) in 2003 and the necessity of deliberation was explained. Application for deliberation by the KBV of December 2003 was approved and a working group containing representatives of the physicians and the statutory health insurances as well as patient representatives was formed. As foreseen in such deliberations expert opinions from the medical community were called for through publication in the Federal Gazette (Bundesanzeiger) and the German Physicians' Gazette (Deutsches Ärzteblatt) in May and June 2004.

Expert opinions of the medical community

The G-BA publishes themes to be deliberated in the Federal Gazette, the German Physicians' Gazette and in the internet in order to provide experts in medical science and practice, confederations of specialty professional societies, national confederations of self-help groups and patient representatives as well as national confederations of manufacturers of medical products and instruments the opportunity of making statements. The interest shown by the medical community was relatively small with only three statements (two from manufacturers of diagnostic tests as well as one by a university department of gynecology). All statements including the references cited were considered and evaluated.

Systematic information search

The working group first gained a detailed oversight of information syntheses on this theme complex. A systematic search of Health Technology Assessment (HTA) reports and guidelines was undertaken; the results were compared with information of the expert opinions. This extensive basic information was supplemented by specialized research of the primary literature for the discussion of concrete single aspects. Further, members of the working group included additional (found even by handsearch) relevant publications in the deliberation process.

The results of the search were analyzed in a two-step process by two independent reviewers for relevant studies and filtered according to previously set inclusion and exclusion criteria.

As a result eight HTA reports and further information syntheses as well as 14 international guidelines on the subject Chlamydia screening were included in the individual evaluation.

Specialized and additional searches were done on the question of Chlamydia testing or treatment in women before a planned induced abortion with nine clinical studies being analyzed. Another 22 studies on Chlamydia testing in pregnant women and 4 studies on the quality of NAATs (nucleic acid amplification test) with pooling of samples were individually analyzed.

Results of the deliberation

Prevalence in Germany

Prevalence of *Chlamydia trachomatis* varies in different populations. As much

published data come from selected patient groups, interpretation and generalization are limited. The WHO estimates worldwide prevalence rates from under 3 to 27 % depending on the targeted group examined [1]. Risk factors for infection vary with the population tested. Reported factors include, among others: more than two sex partners in the last twelve months or one new partner in less than three months, sex without the use of condoms, women with certain symptoms at the time of the clinical examination, area of residence (rural, city).

Current data for Germany are found in the publication of Gille and Klapp et al. for girls aged 14 to 21 years in a district of the city of Berlin in 2005 with a prevalence of 10 % for 17-year-olds [3]. A publication by Koch and Kirschner et al. from 1997 focused on an older target group (10- to 40-year-old women) reported a rate of 3.6 % [4]. In the Epidemiologic Bulletin of the Robert Koch Institute (RKI, the Federal Institute for Communicable and Noncommunicable Diseases) Nr. 39 of 2004 [5] the number of new cases of genital chlamydiosis is estimated at 300,000 annually. The prevalence rate estimated from the reviewed publications lies around 5 % for Germany. How representative these data are for the general population remains unclear. In summary, the prevalence rate depends on the individual risk profile, but in Germany, too, an increased rate of infection in younger age groups is apparent.

Screening in sexually active women under 25 years of age

The evidence base for screening of non-pregnant sexually active women under the age of 25 years was evaluated so clearly and homogeneously in the reviewed HTA reports and information syntheses [6–12], that no further search of primary studies was deemed necessary. Altogether the working group coincided with the generally positive benefit evaluation as found in the information syntheses. Further, the benefit of screening for non-pregnant women in a high-risk population is verified with high evidence [13]. In a randomized controlled trial (RCT) from the USA (1996), criteria such as age under 25 years, Afro-American ethnicity, nulligravidity, vaginal douching in the previous year, two or more sexual partners in the previous

year were assessed by a questionnaire. For each criterion a number of points were assigned. The points were used to calculate a score. Unmarried women with a score over three points were selected for the study. In this population, a 50 % reduction of PID cases in the screened group versus the non-screened group was confirmed after one year of follow up. Data from epidemiologic studies from Sweden show comparable results. A screening program has been established in Sweden since the mid 1980s. A continual decline in PID cases was seen after 1987, with the largest effect in the age group 15–19-year-olds [14]. Epidemiologic indications of a reduced prevalence of urogenital *Chlamydia trachomatis* infections due to screening exist.

Among the questions not yet answerable with sufficient evidence is the optimal test interval, with the vast majority of included information syntheses recommending annual screening (the RCT of Scholes and Stergachis et al. from 1996 considers a time period of one year after the screening test with regards to PID reduction).

Whether the results of the RCT of Scholes and Stergachis et al. are applicable to women under 25 years of age (without further risks) in a German context, cannot be answered definitively at present. Nonetheless, the authors of the information syntheses and of the expert opinions consider "age under 25 years" unanimously as the most valid indicator for inclusion in a screening program. Screening programs limited to a high-risk collective cannot be viewed as capable of implementation due to the limited validity of sexual histories. Therefore, an opportunistic screening of sexually active women under 25 years of age is generally recommended.

As previously mentioned, the working group agreed with this assessment. As the disease represents a significant health problem, diagnoses are available and effective treatment of genital *Chlamydia trachomatis* infection is possible, the question on benefit and necessity of such a screening can be affirmed. Essential criteria demanded internationally for screening tests [15, 16] are fulfilled. Airtight data for Germany, especially on prevalence, incidence and on a whole on disease burden and the natural disease course, are missing.

Test before planned abortion

A further target group that could especially profit from screening consists of women before a planned abortion, as a particularly high prevalence has been observed and the abortion is coupled with an increased risk of ascending infection. The studies evaluated in addition to the information syntheses (all therapy studies) convincingly prove benefit and necessity of therapy of chlamydial infections during abortion. The prevalence of infection varies in an age-dependent manner and is especially high in the younger age groups (in the evaluated study up to 16 %). The risk of PID in association with an abortion is substantial in untreated infection (in the evaluated studies up to 43 %). The question if a preventive antibiotic treatment is superior to a strategy with testing and targeted treatment cannot be answered by the evaluated studies.

Testing allows for examination and treatment of the partner so that reinfection or new infection of further partners can be avoided. With blind prophylaxis this option is lost. Therefore, testing for *Chlamydia trachomatis* in all women before a planned abortion is prudent.

Screening in the context of maternity care

Neither in the individual analysis of the studies cited in the information syntheses nor in the update search after 1998 could studies be found with high-quality proof of the benefit of Chlamydia screening in the context of maternity care. Likewise, no studies were found upon which an evidence-based determination of the optimum time point for testing in pregnancy could be made. Indications do exist that screening in the context of maternity care is capable of improving certain pregnancy outcomes, but the data base is weak and not consistent in itself. Altogether, the existing proofs of benefit of screening during pregnancy are significantly weaker than for sexually active women under 25 years of age.

Screening in men

Even though the application for deliberation was explicitly directed towards screening for women, the appropriate literature in connection with the entire complex was viewed. Presently available data for the establishment of screening for men are inadequate. The fact that

men vary rarely develop sequelae, among others, plays a role. However, partners of infected women must be treated, especially to prevent reinfection.

Test methods

Analyzed HTA reports and metaanalyses on test quality comparison unanimously come to the conclusion that nucleic acid amplification techniques (NAATs) are superior to other evaluated test methods. No significant differences between test results from urine and cervical samples were found (Table 1).

Pooling in NAATs

The working group followed indications in the evaluated literature for economic use of NAATs by means of pooling strategies by performing a special systematic search of primary studies.

In pooling several samples from different subjects are mixed (pool) and are examined using a single test kit. If the test is negative, this result is valid for all subjects involved. In the case of a positive result, the samples of all subjects must be tested individually with one test kit each. In view of the superiority of NAATs in terms of test quality and significantly increased costs, on the other hand, in a screening program with a high number of samples, this strategy can be of special, particularly economic, importance. In Germany, experience exists in the field of testing banked blood for diverse pathogens (for example, hepatitis B, C, HIV) employing pooling and tests with NAATs. Here, due to the low prevalence of the target disease, substantially large pools (up to 96 samples) are used in comparison to the studies existing on pooling for Chlamydia [17].

A total of 14 studies [18–31] were included, with various NAATs examined. The reference test was the single

test. Various pool sizes were evaluated. Cost savings depend on the CT prevalence in the population and on the pool size employed.

Statements on reproducibility cannot be found. Pooling had no effects on test quality, neither for endocervical samples nor for urine samples. Some studies report of reflex testing for discrepancies between single tests and pooling as an adaptation of the sample to cut-off (S/CO). Due to the same algorithm (all samples of a positive pool are re-tested as individual tests) used in all studies no study shows a loss of specificity caused by pooling in comparison to individual testing.

When qualitative prerequisites called for in the studies are fulfilled, only slight loss of test quality due to pooling is to be expected. Even with pessimistic estimates a significantly better test quality of NAATs in pooling in comparison to other available non-amplified methods exists. The results of the studies are transferable to the German health care situation (Figure 1).

Establishment of Chlamydia screening for young women in Germany

The Federal Joint Committee, on the base of the preparatory work of the working group, in its meeting on September 13, 2007 decreed changes in the guidelines of the National Committee of Statutory Health Care Physicians and Statutory Health Insurance Funds on birth control and on planned abortion as well as maternity care guidelines.

The decree which was not objected to by the Federal Ministry of Health was published on 12/12/07 in the Federal Gazette and on 22/02/08 the German Physicians' Gazette. The decree is in force since January 1, 2008.

Table 1: Test quality of polymerase chain reaction (PCR) versus enzyme immunoassay (EIA) for the detection of *Chlamydia trachomatis* in urogenital samples.

	Sensitivity	Specificity
PCR/endocervical swab	88.6 %	98–100 %
PCR/urine	85.6 %	99–100 %
EIA/endocervical swab	65 %	bis 99 %
EIA/urine	38 %	bis 99 %

Central question for determining savings potential on test kits in a pooling strategy are:

- What is the optimum pool size for a known prevalence?
- Up to which prevalence can a predetermined pool size retain savings effects on test kits?

Number of tests:

without pooling: number of patients = number of tests

with pooling: $\frac{\text{number of tests}}{\text{pool}} + \text{number of tests} * \text{prevalence} * \text{pool}$

Optimum pool size for known prevalence:

$$f(\text{pool}) = \text{number of tests} - \left(\frac{\text{number of tests}}{\text{pool}} + \text{number of tests} * \text{prevalence} * \text{pool} \right)$$

$$f'(\text{pool}) = \text{number of tests} * \left(1 - \frac{1}{\text{pool}} - \text{prevalence} * \text{pool} \right), \text{ then :}$$

$$f''(\text{pool}) = \frac{1}{\text{pool} * \text{pool}} - \text{prevalence}$$

when $f''(\text{pool}) = 0$, then

$$\text{pool} * \text{pool} = \frac{1}{\text{prevalence}}$$

$$\text{pool} = \sqrt{\frac{1}{\text{prevalence}}}$$

Not taken into consideration in these thoughts is the probability of distribution of positive samples. A maximum retest requirement is assumed, so that the optimum pool size is overrated – just as the maximum prevalence in a fixed pool size is underrated.

Thus for the optimum pool size:

(that has to be appropriately corrected and rounded for real use)

$$\text{pool} = \sqrt{\frac{1}{\text{prevalence}}}$$

Prevalence	1 %	2 %	3 %	4 %	5 %	6 %	7 %	8 %	9 %	10 %
Pool	10.00	7.07	5.77	5.00	4.47	4.08	3.78	3.54	3.33	3.16
Prevalence	11 %	12 %	13 %	14 %	15 %	16 %	17 %	18 %	19 %	20 %
Pool	3.02	2.89	2.77	2.67	2.58	2.50	2.43	2.36	2.29	2.24

Maximum prevalence in fixed pool size:

$$\text{prevalence} = \frac{1}{\text{pool} * \text{pool}}$$

Pool	2	3	4	5	6	7	8	9	10
Prevalence	25.00 %	11.11 %	6.25 %	4.00 %	2.78 %	2.04 %	1.56 %	1.23 %	1.00 %

In comparison to these calculations study results exist that in summary show that by using adequate quality standards for pool sizes up to five no relevant loss of test quality is to be expected.

Figure 1: Calculation of pool size in dependence on prevalence.

Table 2: Course of the scientific evaluations.

- Young, sexually active women profit from testing for *Chlamydia trachomatis* infections. Treating asymptomatic diseases reduces serious sequelae. Annual screening for the age group under 25 years using NAAT is therefore established.
- Sample pooling with use of NAATs is a reliable, cost-saving and secure method with no significant loss of test quality.
- In addition to the physician's consultation the women receive an information sheet which explains in an understandable manner why women in Germany up to their 25th birthday are offered an annual test for Chlamydia.
- Convincing proof of the benefit of testing before a planned abortion exists. Therefore, testing for Chlamydia in this situation is also a part of the benefits catalogue.
- Since 1995 screening pregnant women for *Chlamydia trachomatis* infections has been a component of the maternity care guidelines in Germany.

As to the question of scientific evaluation of the opportunistic screening for sexually active women under 25 years of age, talks, are presently being held between representatives of the Robert Koch Institute (Federal Institute for Communicable and Noncommunicable Diseases) and the Federal Ministry of Health.

A summarized review of the course of the scientific evaluation is given in Table 2. The comprehensive final report as well as the decree text can be found under:

<http://www.g-ba.de/informationen/beschluesse/zum-unterausschuss/4/>
http://www.g-ba.de/downloads/40-268-533/2008-01-30-Abschluss_Chlamydien.pdf

http://www.g-ba.de/downloads/39-261-483/2007_09_13-Empfaengnis-Chlamydien_BAnz.pdf
Detailed lists of reference are published in the final report under www.g-ba.de/informationen/beschluesse/zum-unterausschuss/4/. <<<

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