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Epidemiology of *Chlamydia trachomatis* infection in women and the cost-effectiveness of screening

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BACKGROUND: The majority of *Chlamydia trachomatis* infections in women are asymptomatic, but may give rise to pelvic inflammatory disease (PID) and tubal infertility. Screening programmes aim at reducing morbidity in individuals by early detection and treatment, and at decreasing the overall prevalence of infection in the population. A number of modelling studies have tried to calculate the threshold prevalence of chlamydia lower genital tract infection above which screening becomes cost-effective. There is considerable debate over the exact complication rates after chlamydia infections, and more precise estimates of PID and tubal infertility are needed, for instance to be inserted in economic models.

METHODS: With reference to key studies and systematic reviews, an overview is provided focusing on the epidemiology of chlamydia infection and the risk-estimates of its late complications.

RESULTS: In the literature, the generally assumed risk of developing PID after lower genital tract chlamydia infection varies considerably, and is up to 30%. For developing tubal infertility after PID the risks are 10–20%. This implies that the risk of test-positive women of developing tubal infertility would range between 0.1 and 6%. We included chlamydia IgG antibody testing in a model and estimated a risk of tubal infertility up to 4.6%.

CONCLUSION: The risk of developing late complications after chlamydia lower genital tract infection appears low. High quality RCTs dealing with the transition from cervicitis to infertility are needed to broaden the evidence. In screening programmes, chlamydia antibody testing, as an intermediate marker for potential adverse sequelae, might enable more precise estimates.

Key words: *Chlamydia trachomatis* / infertility / epidemiology / screening / cost-effectiveness

Background

Although *Chlamydia trachomatis* is considered the most prevalent sexually transmitted disease (STD) worldwide, its true incidence and prevalence are not known. The WHO estimate that annually almost 100 million new cases occur worldwide (WHO, 2006a), but the majority of women with lower genital tract infections remains asymptomatic and therefore undiagnosed (WHO, 1995; Peipert, 2003). In a systematic review reporting on *C. trachomatis* among asymptomatic European women the prevalence ranged from 1.7 to 17% (Wilson *et al*., 2002). Among young women attending STD clinics rates are well above 10% (Van Bergen *et al*., 2006), and in population-based studies among under 30-year-old prevalence was between 2 and 6% in the Netherlands (Van Bergen *et al*., 2005), Denmark (Andersen *et al*., 2002) and the UK (Macleod *et al*., 2005). Reported rates of genital chlamydia infections are rising, but it is unclear whether this is due to increased testing or to a true increase in incidence (Low *et al*., 2008). The chlamydia prevalence and test rates reported in European countries vary and depend highly on the population tested or screened, and on the national reporting system of chlamydia positive cases (Fig. 1).

Reports on the incidence of *C. trachomatis* infections are rare, as to study incidence subjects should be tested at regular intervals. In young women who were followed for 18 months and were tested every 6 months, of those tested negative at baseline 4.9% became positive (LaMontagne *et al*., 2007). In a Dutch study, women aged 15–29 who tested negative at a population-based screening 2.9% were positive after 1 year (Veldhuijzen *et al*., 2005).

If recognized, a chlamydia infection in the lower genital tract can be treated effectively and easily by antibiotics. Even if the infection remains unrecognized it does not always cause serious sequelae. Studies on the natural course of untreated *C. trachomatis* lower genital tract infections in women show spontaneous clearance rates of 30–50% in the first 2–3 years (Golden *et al*., 2000; Morré *et al*., 2002a; Molano *et al*., 2005; Geisler *et al*., 2008). Experimental studies in primates have shown that single upper genital tract infections are often self-limiting and do not produce tubal scarring (Patton *et al*., 1987). For tubal tissue damage to occur, prolonged exposure to chlamydia is considered a major predisposing factor, either by chronic persistent infection or by frequent reinfections (Brunham and Peeling, 1994; Mardh, 2004). It has been hypothesized that this prolonged or repeated exposure of the host to the micro-organism evokes a chronic low-grade auto-immune response which leads to chronic inflammation and subsequent tissue damage (Brunham and Peeling, 1994; Ness *et al*., 2008). In young adolescents, reinfection rates of 10–30% have been found (Veldhuijzen *et al*., 2005; LaMontagne *et al*., 2007), and sexual risk behaviour is an important determinant. Host genetic variations have been shown to play a role in the risk of persistence of infection (Morré *et al*., 2003; Den Hartog *et al*., 2006; Morré *et al*., 2009). Besides behavioural factors and host genetics, specific chlamydia strains, called serovars, have also been suggested to affect the course of infection (Morré *et al*., 2000).

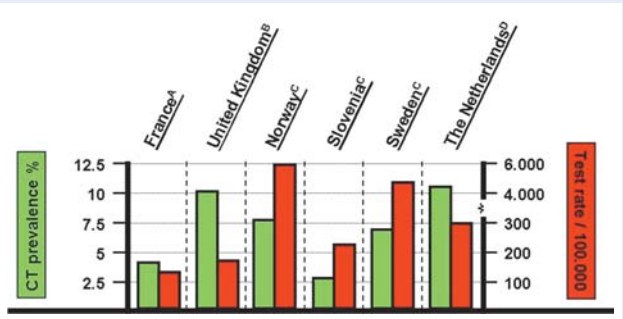

Figure 1 *Chlamydia trachomatis* (CT) prevalence and test rates in European countries based on data reported in 2005–2006 (Adapted from ECDC, 2008).

[a]Compulsory reporting of chlamydia infections diagnosed by central reference laboratories only (i.e. 3% of laboratories). Test rate calculated at the population level; [b]Data from the UK National Chlamydia Screening Programme, compulsory reporting of chlamydia infections diagnosed in screenings settings. Test rate calculated at the population level; [c]Compulsory reporting of chlamydia infections diagnosed in any setting; [d]Compulsory reporting of chlamydia infections diagnosed in selected settings (i.e. STD clinics). Number of tests is reported in all settings.

Chlamydia infections have been associated with a wide spectrum of complications. After chlamydia urethritis, males may develop epididymitis (Peipert, 2003), but the contribution of epididymitis to male infertility is not well understood. Adverse pregnancy outcomes which have been associated with uncomplicated chlamydia cervicitis include sporadic and recurrent miscarriage, preterm labour, premature rupture of the membranes and low birthweight, although reports show conflicting results (reviewed in Baud *et al*., 2008). In the pathogenesis of obstetric complications immunologic reactions of the host to the micro-organism are considered a more important trigger than the direct effect of the micro-organism itself (Karinen *et al*., 2005). Chlamydia cervicitis may cause conjunctivitis, nasopharyngitis and pneumonia in newborns by vertical transmission (Peipert, 2003). In women, ascending cervical infections may cause pelvic inflammatory disease (PID), and untimely tubal pathology, which increases the risk of ectopic pregnancy, tubal infertility and chronic abdominal pain.

Treating PID and tubal infertility is costly both in psychosocial and in financial terms. In order to decrease these costs screening programmes have been introduced. The primary aim of chlamydia screening is to reduce morbidity in individuals by early detection and treatment of uncomplicated lower genital tract infections. The secondary aim is to decrease the overall prevalence of chlamydia infections and subsequently reduce transmission in the population. Screening is cost-saving when the costs related to diagnosing and treating the late sequelae exceed or at least largely offset the costs related to the logistics of screening and treatment of positive cases. A number of modelling studies have tried to calculate the threshold prevalence of lower genital tract chlamydia infection above which screening becomes cost-saving or cost-effective. On the basis of various assumptions threshold prevalences between 3.0 and 14% have been suggested (Genc and Mardh, 1996; Paavonen *et al*., 1998; Honey *et al*., 2002). Some investigators reported that screening has been estimated to be cost-effective or even cost-saving in selected populations (Postma *et al*., 1999, 2000; Welte *et al*., 2000; Andersen *et al*., 2006; De Vries *et al*., 2006). Others, using empirical estimates of screening uptake and incidence of complications, found that screening was not cost-effective (Roberts *et al*., 2007). There is considerable debate, however, on the exact complication rates after chlamydia infections,

and there is a need for more precise estimations of PID and tubal infertility. These estimates can be inserted in economic models, in which currently used estimates of tubal infertility vary from 0.02 to 20%. No study has yet demonstrated that chlamydia screening can significantly reduce the prevalence of tubal infertility.

Methods

This review focuses on the epidemiology of *C. trachomatis* infection and the estimates of the prevalence of chlamydia related complications in women, and highlights the controversies with reference to selected key studies and systematic reviews. The main focus is on PID and tubal infertility, with the aim to propose more accurate estimates of these risks, which can be used in patient counselling and inserted in future cost-effectiveness analyses of different screening strategies. A brief overview of chlamydia test characteristics is given to enable assessment of the reliability of estimates of *C. trachomatis* infections. No systematic literature search was performed to review the evidence for chlamydia screening, as a current review has recently been published (Low *et al*., 2009).

Testing

After the detection of chlamydia inclusions by Giemsa staining in 1907, detection methods have improved with respect to sensitivity, specificity, time per assay and laboratory standardization. The technical developments in *C. trachomatis* detection from culture to enzyme-immuno assay (EIA) and direct fluorescent-antibody assay (DFA) to the more recently developed nucleic acid amplification test (NAAT) will be described. Test characteristics and providers of the most widely used commercially available tests are summarized in Table I.

Table I Sensitivities and specificities of *C. trachomatis* detection assays (based on Bianchi *et al*., 1998) and most widely used commercially available tests

Test	Sensitivity (%)	Specificity (%)	Detection limit (no. of organisms)
NAAT[a]	90–95	>99	1–10
DFA[b]	80–85	>99	10–500
EIA[c]	60–85	99	500–1000
DNA-probe[d]	75–85	>99	500–1000
Cell culture	50–85	100	5–100
POC[e]	25–55	>90	>10 000

[a]Nucleic Acid Amplification Test. DNA-based: PCR Amplicor assay (Roche Diagnostics, Basel, Switzerland), LCR (Abbott Laboratories, Abbott Park, IL, USA), currently the Abbott m2000rt; SDA (Becton Dickinson, Franklin Lakes, NJ, USA), currently BD ProbeTec. RNA-based: TMA, AMP-CT (Gen-Probe, San Diego, CA, USA), current system from Gen-Probe is named TIGRIS; NASBA (Organon Teknika, Boxtel, the Netherlands, currently BioMerieux, Marcy l'Etoile, France).
[b]Direct Fluorescence Assay. Syva MicroTrak (Syva Co, Palo Alto, CA, USA).
[c]Enzyme Immuno Assay. Vidas (BioMérieux, Craponne, France).
[d]DNA-based: hybrid capture assay (Qiagen, Hilden, Germany), Ampliprobe system (ImClone Systems, New York City, NY, USA); RNA-based: PACE 2 assay (Gen-Probe, San Diego, CA, USA).
[e]Point of care test. Handilab-C (Zonda Incorporated, Dallas, TX, USA), Biorapid Chlamydia Ag test (Biokit, Barcelona, Spain), QuickVue Chlamydia test (Quidel Corporation, San Diego, CA, USA).

Giemsa staining and culture

The typical chlamydia inclusions were described for the first time in Giemsa stained epithelial cells in the infected conjunctivae of primates (Halberstaedter and Von Prowazek, 1907). As compared with the more recently developed chlamydia detection systems, Giemsa staining is insensitive and detects only 15% of culture-proven chlamydia infections in the male urethra and 41% in the female cervix and single slide evaluation is labour intensive (Schachter and Dawson, 1977). Fifty years after the Giemsa staining, isolation of chlamydia was reported using the 'yolk-sac' method, i.e. inoculation of *C. trachomatis* in eggs (T'ang *et al*., 1957). This culture method was replaced by the more convenient isolation of chlamydia in cell culture (Gorden *et al*., 1969), which made large scale application of chlamydia culture possible and enhanced the study of chlamydia biology. Although cell culture is the definite proof of a chlamydia infection, making the assay 100% specific, it has some major disadvantages. The technique is very laborious, expensive and relatively insensitive (50–85%) as compared with the more recently developed NAATs (Goessens *et al*., 1997; Puolakkainen *et al*., 1998). Furthermore, for culturing the clinical material has to be handled in a way (regarding time, transport and storage conditions) that does not affect the viability of the organism. Cell culture has been regarded as the gold standard for chlamydia infections but has lost this status due to the introduction of the NAATs.

Antigen detection: DFA and EIA

The development of monoclonal antibodies enabled the direct detection of chlamydia in clinical specimens (Stephens *et al*., 1982; Tam *et al*., 1984). The demanding requirements of cell culture do not apply and a broad spectrum of clinical specimens can be used. The two target antigens used in DFA and EIA are the chlamydia species-specific major outer membrane protein (MOMP) and the genus-specific lipopolysaccharide (LPS) (Fig. 2). Cross reactivity is noticed on the basis of MOMP (Fox *et al*., 1991) and LPS (Nurminen *et al*., 1983), and non-specific binding occurs by reactions with host proteins. The sensitivity of DFA is 80–90% and the specificity 98–99% relative to culture (Chernesky *et al*., 1986; Quinn *et al*., 1987; Smith *et al*., 1987). The DFA test was widely used as a confirmation test of positive results of other non-culture tests and in discrepancy analysis schemes for DNA amplification tests because of its high specificity (Chan *et al*., 1994; Kellogg *et al*., 1993).

The EIA technique has been applied in many commercially available diagnostic tests for chlamydia. Most of them are based on the immunochemical detection of LPS genus-specific antigen. To improve the specificity, some manufacturers have developed a blocking assay in order to verify positive EIA results (Newhall *et al*., 1994). Currently DFA and EIA have been replaced by NAATs.

Rapid tests or Point of Care (POC) tests have been developed as tests which do not require sophisticated equipment and can be completed in about 30 min. Most POC tests employ EIA technology and use antibodies against LPS. They give rise to false-positive results due to cross-reactivity with LPS from other micro-organisms. In general the POC tests are significantly less sensitive and specific than laboratory-performed EIA and DFA. POC tests have been suggested to be of value for high prevalence ocular *C. trachomatis*

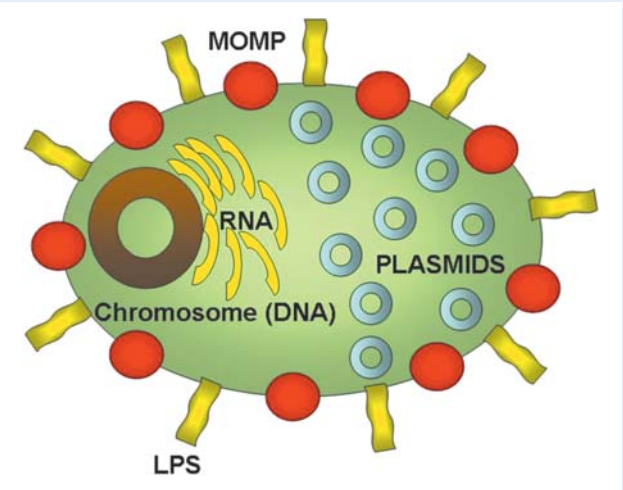

Figure 2 Schematic representation of a chlamydia particle with different targets for diagnostic tests: major outer membrane protein (MOMP), lipopolysacharide (LPS), chlamydia plasmids (DNA and RNA), chlamydia chromosome (DNA and RNA).

detection, but for urogenital *C. trachomatis* infections these tests have too low a sensitivity (Michel *et al*., 2006).

DNA and RNA detection: amplification and non-amplification systems

Besides identifying chlamydia by culture or by detecting parts of its membrane, *C. trachomatis* can be identified by detecting the nucleic acids (either DNA or RNA) (Fig. 2). Initially, direct detection of nucleic acid used to be performed without its amplification, and later techniques were developed to amplify nucleic acid to make even the detection of very low amounts of DNA or RNA possible by the so-called NAAT technology.

In the non-amplification systems for the detection of chlamydia DNA (Yang *et al*., 1991; Clavel *et al*., 1998) and RNA, for which the PACE 2 (Iwen *et al*., 1991) is the best available test, sensitivity is 85–98% as compared with cell culture with a specificity of around 99%. PACE 2 was developed for the simultaneous detection of *C. trachomatis* and *Neisseria gonorrhoeae* (Doing *et al*., 1999).

In the past 25 years NAATs have been developed. In these amplification tests the original amount of nucleic acid (either DNA or RNA) present in the clinical sample is multiplied. NAATs are far more sensitive compared with culture, EIA and DFA. Due to the increased sensitivity NAATs generate 25–40% more chlamydia positive results as compared with cell culture (Jespersen *et al*., 2005).

The first commercially available NAAT was a PCR amplification assay for the detection of *C. trachomatis* DNA. This assay detected the extra-chromosomal *C. trachomatis* plasmid DNA existing in 10 copies per chlamydia particle. Besides the commercially available PCR assays numerous so-called 'in-house' or 'home brew' PCR assays have been published in the literature (Dutilh *et al*., 1989; Bobo *et al*., 1990; Ossewaarde *et al*., 1992; Roosendaal *et al*., 1993; Ossewaarde *et al*., 1994). They vary greatly in performances and specificity, and are often used in discrepancy analysis in comparing commercially available assays. A few years after the introduction of the PCR, other detection techniques were developed in part to circumvent PCR patent rights. These include the ligase chain reaction (LCR) (Dille *et al*., 1993) and the strand displacement amplification (SDA) (Walker *et al*., 1992; Walker, 1993). NAAT comparisons show in general comparable test sensitivities for male and female urine, urethral and cervical swab specimens (Van der Pol *et al*., 2001; Gaydos *et al*., 2004).

For the detection of chlamydia RNA in amplification systems template mediated amplification (TMA) is used. Other RNA amplification techniques include the nucleic acid sequence based amplification (NASBA), which is formerly called 3'SR (Self-sustained sequence replication) (Guatelli *et al*., 1990; Fahy *et al*., 1991) and transcription-based amplification system (TAS) (Kwoh *et al*., 1989). The NASBA showed to be 100 times more sensitive for the detection of chlamydia as compared with the PCR from Roche and LCR from Abbott (Morré *et al*., 1996, 1998).

Antibody detection in serum

Different serological assays have been developed for the detection of antibodies to *C. trachomatis*, including the complement fixation test, micro-immunofluorescence assay, EIA and immunoblotting. In these assays cross reaction occurs if LPS is used.

Little is known about antibody profiles during acute or chronic genital chlamydia infections. Superficial infections are considered to provide a poor stimulus for antibody formation. However, a correlation between antibody titres and the severity of tubal inflammation has been shown (Treharne *et al*., 1979; Akande *et al*., 2003). IgG antibodies persist for years (Gijsen *et al*., 2002) even after antibiotic treatment (Piura *et al*., 1993; Henry-Suchet *et al*., 1994), and are considered as markers of a past infiltrating *C. trachomatis* infection. Immunoglobulin (Ig) M production is transient and rises in IgM titres are infrequently found. Therefore, IgM titres are of no significance in diagnosing current or previous disease. IgA antibodies are also of little diagnostic value except for highly invasive Lymphogranuloma venereum (LGV) infections caused by the LGV serovars of *C. trachomatis*, as recently detected among men having sex with men (Spaargaren *et al*., 2005; Van der Snoek *et al*., 2007).

In the 1970s chlamydia antibody testing (CAT) was developed for use in epidemiologic studies, but this application remained limited. Recently it was recommended that CAT might deserve a more prominent place in epidemiologic research, as in retrospective case control studies with infertility as an outcome measure, an immunologic response might be a useful marker of a previous chlamydia infection (Garnett, 2008). Among women with clinical signs and symptoms of mild to moderate PID, antibodies to *C. trachomatis* were shown to be associated with reduced pregnancy rates (Ness *et al*., 2008). In fertility clinics CAT was introduced as a screening test for tubal infertility (Mol *et al*., 1997; Land *et al*., 1998) after it had become evident that an association exists between chlamydia IgG antibodies in serum and tubal pathology (Punnonen *et al*., 1979). The most accurate tests for CAT have a sensitivity of ~60% for tubal pathology, whereas their specificity is 85–90% (Land *et al*., 2003).

In conclusion, when comparing the performances of chlamydia detection assays, taking the above mentioned discussion points into account, NAAT is most sensitive (90–95%) and highly specific, followed by the new generation of DFA, EIA and the PACE 2

DNA-probe assays which are more or less equally sensitive (up to 85%), followed by culture (up to 80%), and finally the POC or rapid tests, which are quite insensitive (25–55%) (Table I). When using literature-derived prevalence and incidence data for either asymptomatic, symptomatic or complicated infections the test type and the year in which the data were generated should be taken into account in interpreting the validity of the data reported. Chlamydia IgG antibody testing in serum is applied in reproductive medicine in the fertility work-up on a large scale, but it has no place in early diagnosis of chlamydia infections.

Cost-effectiveness of screening

Many national guidelines incorporate (annual) screening of young (<25 years) sexually active women as good medical practice. The appropriateness of screening for disease prevention is usually assessed according to the Wilson and Jungner principles (Wilson and Jungner, 1968) and chlamydia has been judged to fulfil these criteria either in whole, or in part (Low and Egger, 2002; Meyers *et al*., 2008). However, in a recent systematic review critical questions have been raised about the effectiveness of chlamydia screening, since in the literature available no strong evidence could be found supporting opportunistic screening (Low *et al*., 2009).

Screening can be opportunistic or register-based. In opportunistic screening individuals visiting health professionals are offered screening whereas attending, and the professional is supposed to repeat the test-offer at regular intervals. Individuals who do not access health services have no opportunity for testing. The Swedish experiment (Egger *et al*., 1998) and the National UK Chlamydia Screening Programme (Department of Health, 2004) are examples of opportunistic screening. Screening can also be provided in a pro-active, systematic manner, in which registers are used to identify and invite individuals for screening. This form of systematic screening is currently being piloted in the Netherlands.

Mathematical modelling is a method for the investigation of the epidemiology of sexually transmitted infections and the effects of screening. In cost-effectiveness analysis, costs, savings and health gains are generically related to each other within the context of a formal model. It is of importance whether these cost-effectiveness evaluations used static or dynamic models (Welte *et al*., 2005). Static models typically only include the savings and health gains for the index cases being screened and treated, whereas dynamic models go beyond these direct impacts in also considering indirect savings and health gains in the broader population through reduced transmission. To date, only a few health-economic studies have applied the preferred—but highly complex—approach of dynamic modelling (Townshend and Turner, 2000; Welte *et al*., 2005; Evenden *et al*., 2005; De Vries *et al*., 2006; Adams *et al*., 2007; Roberts *et al*., 2007), in which the transmission of *C. trachomatis* in populations is explicitly modelled using mathematical designs. Also only few studies have attempted to quantify health outcomes in terms of quality-adjusted life-years (QALYs), enabling the comparison of chlamydia screening with other health-care interventions or with explicit thresholds for cost-effectiveness, as have been specified now for various countries such as the USA, the UK and the Netherlands (Hu *et al*., 2004; Adams *et al*., 2007; De Vries *et al*., 2008). For example, De Vries *et al*. (2008) estimated that screening every 2 years for chlamydia in the Netherlands would cost €3300 per QALY gained, whereas Adams *et al*. (2007) estimated that this screening would cost €27 000 in the UK if performed on an annual basis if the screening was designed as recommended by the UK National Chlamydia Screening Programme (Adams *et al*., 2007; Postma *et al*., 2008). Both studies investigated screening men as well as women within the population-dynamical model structure. Hu *et al*. (2004) found cost-effectiveness ratios all well below US$10 000 per QALY for a variety of specific screening strategies for young women only. In particular, screening of various age categories was considered in detail. Their model, however, was based on a static rather than the preferred population-dynamic structure.

Given the preference for modelling chlamydia screening using dynamic models (Welte *et al*., 2005; Low *et al*., 2007), as a crude quality selection we applied the absence or presence of such a model structure to select individual studies for further analysis regarding specific aspects of tubal infertility risks, costs and QALYs in the models (Table II). Additionally, we show the discount rates for monetary costs and savings. Discount rates are applied to correct for time preference. As generally known for health-economic models, discount rates are highly influential on the cost-effectiveness of screening programmes (Brouwer *et al*., 2005), and the lower the discount rates are, the more favourable cost-effectiveness (note that QALYs are also subject to discounting; not shown in the table). Table II shows some variety in the indicators that were selected. Generally, the probability of developing tubal infertility was inserted in the models as a risk following PID and derived from Weström *et al*. (1992), who previously estimated this risk at ~11%. Two studies used deviating assumptions, one based on expert opinions (Townshend and Turner, 2000) and one using a submodel directly relating tubal infertility risk to chlamydia infection, rather than to the clinical signs of PID (Roberts *et al*., 2007). In this latter study an estimated progression per day from infection to tubal infertility was used, with an increasing rate for repeated infections. Over a 20-year time horizon, their assumptions would correspond to approximately 18 cases of tubal infertility averted for every 100 cases of PID averted by screening. This is relatively high, but still relevantly lower than the assumption applied by Townshend and Turner (2000). One study (Evenden *et al*., 2005) neglected discounting of costs and savings, an approach that is not according to any international nor national guideline for health-economic research. Neglecting these potentially biased studies by Townshend and Turner (2000) and Evenden *et al*. (2005), the share of averted costs for tubal infertility in total cost savings ranges from ~6% in two Dutch studies (Welte *et al*., 2005; De Vries *et al*., 2006) to approximately 4-fold of this in two UK-studies (Adams *et al*., 2007; Roberts *et al*., 2007). The final column in Table II shows the variation in unit costs applied per case of tubal infertility, partly explaining the aforementioned difference between the Dutch and the UK-studies. Striking differences between both UK-studies concern the risk of tubal infertility and the unit costs of tubal infertility, although (estimated) costs for infertility work-up are considerably higher in both UK-studies than the costs applied in both Dutch studies. Whether this is related to the specific sources used for cost estimation or does reflect real differences in the respective economies of the UK and the Netherlands is left for further research. It should be noted that differences in discount rates applied are only minor and would not contribute to major differences in those estimates.

Table II Assumptions and outcomes on cost-effectiveness of screening for *C. trachomatis*: probability of developing tubal infertility (TI), expressed as risk after pelvic inflammatory disease (PID) unless stated otherwise; share related to averted cases of TI in discounted cost savings, as percentage of total cost savings on all complications considered; undiscounted costs per case of TI, medical costs only unless stated otherwise (all as reported in the papers or derived by the authors), all recalculated in €'s using the exchange rate of 2004–2005 (1€ = £0.67), with original price year between brackets; and the discount rate used for costs and savings

Authors	Probability TI	Share[a] (%)	Unit costs (€)	Discount rate (%)
Townshend and Turner (2000)	0.10[b]	62	3134[c]	6
Welte *et al.* (2005)	0.11	5.6	4703 (1996)[d]	4
Evenden *et al.* (2005)	0.12	17[e]	3731[f]	None
Adams *et al.* (2007)	0.11	24	16 103 (2004)	3.5
De Vries *et al.* (2006)	0.11	6.8	4703 (2002)[d]	4
Roberts *et al.* (2007)	0.18[g]	24	10 000 (2005)[h]	3.5

[a]This share was exactly defined as the cost savings estimated to be achieved on reduced numbers of TI cases divided by all cost savings estimated in the respective papers.
[b]As risk of infection.
[c]Price year not stated, however, discounted figure given (6%).
[d]Reflecting outpatient infertility work-up and one formal round of IVF, inclusive indirect costs of production losses.
[e]No discounting of costs applied in the model structure resulting in overestimation of this share.
[f]Costing year not given.
[g]Derived from the paper, using the simulation results over a 20-year period (men and women versus no screening; 0.18 being 7/40 directly taken from the paper).
[h]Not explicitly reported in the paper, but can be approximated.

From the study by De Vries *et al.* (2008) it may additionally be derived that the share of QALYs attributable to averted tubal infertility in the total of QALYs gained, ranges from 27 to 33%. The range corresponds to discount rates applied to QALYs of 4 and 1.5% respectively, with 4% reflecting the previous Dutch guideline for discounting and 1.5% reflecting the updated guideline that is now in place (ISPOR guidelines, 2009).

In conclusion, to date only a few non-biased studies have been performed estimating cost-effectiveness of screening and treatment of chlamydia infections. Two potentially non-biased studies each have been performed for both the Netherlands and the UK, respectively, all using the preferred dynamic modelling approach and two of them using the preferred outcome of net costs per QALY. Studies indicate that shares in total savings and in QALY gains due to prevented cases of tubal infertility are 6–24% and 33%, respectively.

Risk of complications

Thus far, all cost-effectiveness models have been based on assumptions for the prevalence of the complications of chlamydia infections. There are no prospective controlled studies available on how frequently women tested positive for chlamydia will develop tubal infertility. The best available evidence is obtained from a few RCTs and several retrospective cohort and case–control studies, in which either the progression from cervicitis to PID or from PID to tubal infertility has been addressed. Systematic reviews dealing with the estimates for complications have been summarized in Table III.

From cervicitis to PID

Two systematic reviews on this topic concluded that the risk of PID after chlamydia lower genital tract infection varied from 0–30% (Risser and Risser, 2007) to 0–72% (Boeke *et al.*, 2005), respectively, and suggest a differential between the exact risk, dependent on symptoms and risk-category. In the latter study the PID risk was estimated at 0–4% in asymptomatic PCR positive women from a low risk population, 12–30% in symptomatic women from a high risk population and 27–72% in women requesting legal abortion.

In a retrospective population based cohort study in Sweden, with over 700 000 woman years of follow-up, the cumulative incidence of PID by age 35 was 5.6% (95% CI 4.7–6.7%) in women who ever tested positive for chlamydia, 4.0% (3.7–4.4%) in those with negative tests and 2.9% (2.7–3.2%) in those who were never screened (Low *et al.*, 2006a). The incidence of hospital diagnosed PID was 1.9 (1.8–2.0) per 1000 women years (Low *et al.*, 2006a). This is in agreement with data from prospective studies suggesting that the overall incidence of hospital diagnosed PID is 5–7 per 1000 woman years (Ostergaard *et al.*, 2000; Clark *et al.*, 2002; Van Valkengoed *et al.*, 2004). This estimated incidence rate of PID might be an underestimation as PIDs diagnosed in primary care were not taken into account. When cases diagnosed in primary care are included, incidence rates of PID of 17–31 per 1000 women years have been estimated (Scholes *et al.*, 1996; Simms *et al.*, 1999; Ostergaard *et al.*, 2000). Data from two RCTs show that the absolute annual risk of (symptomatic) PID in the studied population was 2% (Scholes *et al.*, 1996) and 5.3% (Ostergaard *et al.*, 2000).

A major drawback in all studies refers to the diagnosis of PID, which is neither particularly sensitive nor specific. It is estimated that of all PID cases only 4% are the typical 'severe' cases, 36% are mild to moderate and 60% are subclinical (Weström and Eschenbach, 1999). Suggestive features (pelvic or lower abdominal pain) and signs (uterine or adnexal tenderness) and supportive tests (CRP and positive tests for *C. trachomatis* or *N. gonorrhoeae*) have been used for diagnosing PID (UK guideline, 2005; CDC guideline, 2006), and if available laboratory tests (leucorrhoea or mucopurulent exudates in cervical swabs) and

Table III Estimated probabilities for pelvic inflammatory disease (PID) and tubal infertility (TI) after chlamydia lower genital tract infection (LGTI) (based on systematic reviews by Van Valkengoed *et al.*, 2004; Boeke *et al.*, 2005; Risser and Risser, 2007)

Authors	From LGTI to PID (%)	From PID to TI (%)	From LGTI to TI (%)
Van Valkengoed *et al.* (2004)	0.43		
Rahm *et al.* (1986)	1.8		
Scholes *et al.* (1996)	5		
Rees (1980)	7.5		
Paavonen *et al.* (1980)	20		
Stamm *et al.* (1984)	30		
Ostergaard *et al.* (2000)	31		
Weström *et al.* (1992)		11.4	
Marrazzo *et al.* (1997)		10–20	
Howell *et al.* (1998)		12	
Paavonen *et al.* (1998)		20	
Van Valkengoed *et al.* (2004)			0.02
Summary estimate based on literature			0.1–6
CAT[a]-based calculations in present review			0.1–4.6

[a]CAT, Chlamydia IgG antibody testing.

clinical data (fever >38°C or pelvic abscess) have been added (Ness *et al.*, 2005; Oakeshott *et al.*, 2008). Endometritis has been suggested as a surrogate marker for salpingitis, as asymptomatic plasma cell endometritis has been found in 30% of chlamydia-infected women (Wiesenfeld *et al.*, 2002), but endometrial biopsies are not practiced on a wide scale. Laparoscopy is considered the gold standard for diagnosing PID, but for obvious reasons not all women in whom PID is suspected will undergo this invasive, diagnostic procedure. Furthermore, in only 70% of women presenting with signs of acute salpingitis this could be confirmed at laparoscopy (Bevan *et al.*, 1995).

Studies available in the literature all refer to symptomatic PID. Of all women with tubal infertility, 30–60% does not report a history of PID. Many tubal infections are severe enough to cause tubal pathology but give rise to no or only mild symptoms. This leaves us with the question about the exact proportion of (asymptomatic) lower genital tract infections progressing to PID.

From PID to tubal infertility

Some cost-effectiveness studies have estimated probabilities of developing tubal infertility after chlamydia PID, and the modelled estimates vary between 10 and 20% (Marrazzo *et al.*, 1997; Paavonen *et al.*, 1998; Howell *et al.*, 1998; reviewed in Van Valkengoed *et al.*, 2004). Most models were based on data obtained from populations at high risk for developing complications, or on data from case–control studies.

Another approach to obtain data on late complications after chlamydia infection is by observational studies. Weström *et al.* (1992) followed over 1200 women with laparoscopically verified PID for several years. On average 11.4% of women became infertile: <4% after one episode of mild/moderate PID and 40% after three PID episodes. Weström *et al.*'s study is a large prospective study but refers to a hospital population and symptomatic patients. It refers to all PID and not just that caused by chlamydia, but it has been suggested that the outcome of PID on fertility does not differ if the PID is caused by *C. trachomatis*, *N. gonorrhoeae* or both (Wolner-Hanssen *et al.*, 1985). Furthermore, in Weström *et al.*'s study microbiological detection was done by culture. Currently used NAATs are much more sensitive and pick up also low grade infections which seem to contribute less to transmission and less to complications (Rogers *et al.*, 2008).

From cervicitis to infertility

A systematic review (Wallace *et al.*, 2008) on the excess risk of infertility in women after genital chlamydia infection did not find valid evidence of the attributable risk. The authors found only one study that satisfied their inclusion criteria. The validity of this study, however, is limited by the small sample size and by cell culture being applied as the laboratory test for C. *trachomatis*.

In a retrospective cohort study performed in Sweden, containing over 700 000 women-years of follow-up, the infertility risk was estimated in women stratified by their previous chlamydia status (Low *et al.*, 2006a). The cumulative incidence of hospital diagnosed infertility in women who ever tested positive was 6.7% (5.7–7.9%) and in those with negative tests 4.7% (4.4–5.1%), but the cause of infertility was not specified.

Van Valkengoed *et al.* (2004) constructed a model for the estimation of complication rates after asymptomatic chlamydia infections. They used data obtained from a screening programme and from local registrations in primary and secondary care, and arrived at an estimate of 0.02% for the probability of tubal infertility after an asymptomatic chlamydia infection.

If the risk of developing PID after lower genital tract infection is considered 1–30% (Boeke *et al.*, 2005; Risser and Risser, 2007) and of developing tubal infertility after PID is considered 10–20% (Marrazzo *et al.*, 1997; Howell *et al.*, 1998; Paavonen *et al.*, 1998), the risk for

developing tubal infertility after lower genital tract chlamydia infection ranges between 0.1 and 6%.

How to arrive at the best estimate of late sequelae

Assessing and quantifying a causal relationship between chlamydia lower genital tract infection and tubal infertility is a challenge for several reasons. The majority of women with chlamydia infections are asymptomatic. PCR testing is seldom performed at regular intervals, and therefore a positive test does not provide information about the moment of infection. Once infected, a number of women will clear the micro-organism, and it is not known in whom the infection will ascend and cause tubal scarring. Many women with a positive PCR test will be treated by antibiotics, and early detection and prompt antibiotic treatment may prevent long-term complications (Hillis *et al*., 1995). Late sequelae will become evident at a later age, and the delay to infertility diagnosis is too long to make it a feasible end-point in clinical trials. In couples who do not conceive there may be other causes of infertility, and to diagnose tubal pathology invasive diagnostics, i.e. laparoscopy, is required. A number of possible approaches have been suggested to address the existing gap in the evidence on the risk of tubal infertility after chlamydia infection.

A prospective study to monitor long-term adverse events in women with treated and untreated chlamydia infections would now be considered unethical as treatment of positive cases is generally recommended. Retrospective studies have been performed in screened adolescents, in which time to pregnancy and cumulative incidences for birth rates in test-positive and test-negative women have been compared. In historical register-based follow-up studies no differences in birth rates by chlamydia infection status could be found (Andersen *et al*., 2005; Bakken *et al*., 2007), and time to pregnancy was comparable between women who tested positive and negative (Andersen *et al*., 2005). A shortcoming of this study design is that the primary outcome (i.e. pregnancy or delivery) is determined by many other chlamydia-unrelated factors which cannot be taken into account. Moreover, only a very limited proportion of these women underwent annual chlamydia screening and most women had only been screened once or twice.

Ideally one should obtain results from high quality RCTs on valid outcome indicators like PID and infertility. In the Netherlands currently a register-based screening programme, that is introduced in a cluster randomized stepped wedge design, is attempting to measure the impact of chlamydia screening on the prevalence of chlamydia and self reported PID (Van Bergen *et al*., 2007). In the UK a RCT has commenced in 2500 females $<$27 years, who provide self-administered vaginal swabs (Oakeshott *et al*., 2008). In the intervention group the swabs are analysed for chlamydia and positive cases are treated. In the control group the swabs are stored and analysed 1 year later. The primary outcome of the study is the incidence of clinical PID in 12 months in both groups. The results of this RCT are not yet available.

Role of serology?

Although CAT was originally developed for epidemiological research purposes, CAT has not been incorporated in cost-effectiveness models addressing the risk of tubal infertility after chlamydia infection. It is tempting to do so, as the prevalence of chlamydia IgG antibodies in infertile women is high (35–60%) (Mol *et al*., 1997; Fiddelers *et al*., 2005) as compared with healthy blood donors (6–12%) (Verkooyen *et al*., 2002) and pregnant women (10–20%) (Lyytikäinen *et al*., 2008), and there is good evidence for an association between CAT positivity and tubal infertility (Mol *et al*., 1997; Land *et al*., 1998; Akande *et al*., 2003; Ness *et al*., 2008). Most data on CAT and tubal pathology are only available in selected groups of patients, i.e. infertile couples who seek medical care. There are no reports on chlamydia IgG antibody formation and the development of late complications in an unselected, asymptomatic population. Furthermore, the results reported in the literature on the prevalence and diagnostic accuracy of CAT are heterogeneous because of differences in CAT tests applied and definitions of tubal infertility (Land *et al*., 1998).

We have constructed two hypothetical models for estimating the risk of tubal infertility after lower genital tract chlamydia infection in the general population. There is still poor insight in the precise pathophysiology of antibody formation in chlamydia infections, and therefore our models had to be based on several assumptions. One of our assumptions is that only PCR positive women will eventually develop chlamydia IgG antibodies, although CAT positivity has been reported in women who are PCR negative (Morré *et al*., 2002b; Verkooyen *et al*., 2002). We have based our assumptions on data reported in selected or symptomatic patients and the available data might not be representative for the general population, but it is the best estimate which can currently be made.

Model 1

Infertility affects ~10% of couples and in 10–30% of these couples infertility is due to tubal pathology (review in Evers, 2002). Among women with tubal pathology at laparoscopy, 60–70% has been shown to be CAT positive (WHO, 1995; Land *et al*., 2003). When the presence of chlamydia IgG antibodies is considered a marker of a previous infection, it can be concluded that maximally 0.6–2.1% of women might have tubal infertility due to chlamydia infection.

Model 2

Among screened adolescents, 1.7–10% are PCR test positive (Wilson *et al*., 2002; Van Bergen *et al*., 2005). Superficial infections are considered to provide a poor stimulus for antibody formation, whereas scarring disease is assumed to be associated with seroconversion (Tayler-Robinson, 1997). The prevalence of seroconversion has been reported to be significantly higher in PCR test positive patients than in women with negative tests (Morré *et al*., 2002b). Seroconversion was found in 20% of women suspected to have PID who tested positive by PCR (Ness *et al*., 2008), and in 70% of women visiting STD clinics (Verkooyen *et al*., 2002). If 1.7–10% of asymptomatic women tested for chlamydia are PCR positive, then 0.34–7% (20–70% of 1.7–10%) of women tested positive by PCR might be CAT positive. In 30–65% of CAT positive women tubal pathology has been identified at laparoscopy (Eggert-Kruse *et al*., 1997; Mouton *et al*., 2002; Veenemans and Van der Linden, 2002; Akande *et al*., 2003; Land *et al*., 2003; Logan *et al*., 2003). Therefore, 0.1–4.6% of women (30–65% of 0.34–7% PCR test positives) might have tubal infertility due to chlamydia infection.

Our two hypothetical models would indicate a risk for tubal infertility after chlamydia infection in the range up to 4.6%, which corresponds with assumptions made in most economic analyses reporting a risk of PID after chlamydia infection up to 30% and a risk of developing infertility after PID of 10–20%. Obviously, our calculations are crude and many shortcomings remain. More studies based on antibody levels are needed in order to be able to calculate a risk of tubal infertility after lower genital tract chlamydia infection. Moreover, serum antibodies are products of the humoral immune response, whereas it is the cell-mediated immune response that is mainly involved in tissue scarring causing tubal pathology (Tiitinen *et al*., 2006). Recently, in a study in pregnant Finnish women it was shown that seropositivity decreased from 20.8 to 10.6% over a period of 20 years in spite of an increase in chlamydia prevalence in Finland (Lyytikäinen *et al*., 2008). It was hypothesized that this might be an effect of early treatment, which might lead to a poor humoral immune response and low antibody levels with rapid loss (Brunham *et al*., 2005). It remains to be proven whether the decrease in seropositivity is associated with a decrease in incidence of PID.

Lessons from current screening programmes

A recent review on existing chlamydia screening in Europe showed a considerable variation in chlamydia management and screening activities (Low *et al*., 2008). Although a lot of screening activities occur in clinical practice and in pilot interventions, few organized screening programmes are in place, though several countries are considering implementation.

Existing screening programmes, like the UK National Screening Programme and the US Infertility Prevention Program are organized in an opportunistic way. The Swedish experience is not seen as a screening programme by health officials because there is no national programme, as different activities are undertaken by different counties. In the Netherlands a pro-active systematic screening programme is being piloted.

As the objectives of a screening programme not only target the individual level (reducing complications by early diagnosis and treatment), but also the public health level (reducing transmission within the population), a critical issue is programme uptake. Even though acceptance rate after a test-offer might be high, if coverage and regular uptake of the screening is low, only a minority of the eligible population is reached.

In the USA the annual screening rate in sexually active women aged 15–25 has increased from 25% in 2000 to 41% in 2007 (CDC, 2009). In Sweden 71% of women had at least one chlamydia test in a 10 year period, but only 1% had ten or more tests which would reflect annual testing (Low et al., 2006a). In the UK, the national coverage in 2008 was 9.5%, and the target for 2010 is 25% (NCSP, 2009). In a single-round home-based population screening in the Netherlands using postal delivery of test kits, participation was 37–41% in high urban areas (Van Bergen *et al*., 2005). Prevalence was strongly related to risk-profiles (Götz *et al*., 2005) and currently a systematic, internet-based, selective screening program in 16–29 year olds is piloted in the Netherlands with multiple screening rounds. In the first 2 months of the program 20% of eligible women requested a test package, and of these 80% returned specimens for chlamydia testing (J. Van Bergen, personal communication). The programme is implemented in a stepped wedge design and intends to measure impact on prevalence of chlamydia infections and complications after repeated screening rounds.

The body of evidence on the impact of screening at the individual and at the public health level is limited. Although there are many studies that show the association between chlamydia infection and sequelae like PID and infertility, most of these studies are retrospective, cross-sectional and in selected patient populations. Evidence for impact of screening should preferably come from high-quality randomized trials. Today, there is limited evidence from only two RCTs that systematic screening reduces PID in the intervention group. One randomized intervention study (selective population screening) in the USA showed that the incidence of PID at 1 year was 56% lower (95% CI: 10–80%) in the intervention than in the control group (Scholes *et al*., 1996). The other randomized trial, in Denmark, evaluated screening in school students and young people in the general population by self-taken specimens for chlamydia testing (Ostergaard *et al*., 2000). Amongst women in the school-based study the incidence of PID at 1 year was reduced by 50%. However, both studies are subject to criticism on study design and case ascertainment (Low and Egger, 2002; Low *et al*., 2008). There are no randomized trials that show effectiveness of opportunistic chlamydia screening on PID-incidence in non-pregnant women.

Ecological studies, both in Sweden and in the USA, showed that chlamydia prevalence and its complications (PID, ectopic pregnancy) did decrease after implementing screening, but its causal relation is questioned as in other countries without screening programmes the STD rates also fell in the 1980s due to HIV campaigns (Hillis *et al*., 1995; Egger *et al*., 1998; Kamwendo *et al*., 1998; Bachmann *et al*., 2003). Evidence from three trials in schools in Canada showed some impact on reduction of chlamydia prevalence after the intervention (Hodgins *et al*., 2002), but the strength of the evidence of these studies is limited (Low *et al*., 2009).

An interesting human experiment occurred in Sweden recently. A chlamydia variant occurred, the Swedish Variant with a 377 base pair deletion in the *C. trachomatis* plasmid. This deletion is located in the target area of several commercially available tests to diagnose urogenital chlamydia infections, including the COBAS Amplicor system from Roche and the LCx from Abbott. In regions in which these diagnostics were used, diagnoses and (partner) treatment was discontinued, since cases tested false-negative. After correction of the diagnostic, a rebound chlamydia epidemic could be demonstrated, showing evidence that early diagnosis and treatment does have effect on community transmission (Ripa and Nilsson, 2006; Catsburg *et al*., 2007).

Alternatives for screening

Ideally, primary prevention of infection would make chlamydia screening redundant. The WHO recommends implementation of evidence-based strategies for primary prevention and surveillance of sexually transmitted infections (WHO, 2006b), and governments have been convinced to invest in campaigns for safer sex to increase awareness of risk-taking behaviour and early symptoms of infections (Low

et al., 2006b). In spite of this the prevalence of chlamydia has been increasing in the latest decade (Low et al., 2008).

The development of a chlamydia vaccine could significantly reduce the prevalence of infection. In a scenario in which 80% of individuals are vaccinated by a 100% efficacious chlamydia vaccine which is assumed to provide long-term (10 years) immunity, chlamydia infection would be eradicated within 5 years after widespread introduction of the vaccine (Brunham and Rey-Ladino, 2005). Since many studies have shown that previous exposure to *C. trachomatis* does not provide significant immunity against re-infection, an effective vaccine against *C. trachomatis* would have to elicit an immune response that is superior to that which is provoked by natural infection.

In the 1960s, a human vaccine trial for trachoma was carried out suggesting that immunity is serovar-specific and short-lived. In addition, post-vaccination exposure to chlamydia in some individuals resulted in more severe disease than that seen in unvaccinated individuals (Grayston and Wang, 1978). Following these disappointing results, subunit vaccine approaches with (amongst others) the MOMP as a primary candidate were initiated but also obtained disappointing results, potentially based on lack of the native conformation of MOMP in the experiments performed (Pal et al., 2001). Other adaptive immune effectors, such as CD4+ and CD8+ T cells, might have to be stimulated by a (subunit) vaccine to generate an immune response that is sufficiently potent to protect humans against *C. trachomatis* infections (Loomis and Starnbach, 2002; Morrison and Caldwell, 2002). The major challenge in developing a vaccine for *C. trachomatis* is generating one that can elicit sterilizing immunity, presumably by stimulating multiple immune effector responses, whereas avoiding immunopathology (Loomis and Starnbach, 2002; Roan and Starnbach, 2008). Currently it is not expected that a *C. trachomatis* vaccine will be available within the next 10 years.

Presumptive treatment, a one-time or periodically given treatment for a presumed infection, has been suggested as a strategy to reduce prevalence of infections in high risk populations in which other curative and preventive services are not (yet) available. For trachoma it has been shown that biannual single dose azithromycin-treatment in preschool children can eliminate ocular infection from severely affected areas (Melese et al., 2008). Three RCTs have been performed in female sex workers who were given monthly antibiotics. In only one was a reduction in chlamydia infections achieved (review in Manhart and Holmes, 2005).

The efficacy of prophylactic treatment has been studied in women undergoing induced abortion. A meta-analysis showed that post-abortion infection could be reduced by half (RR 0.58; CI 0.47–0.71) and that prophylaxis is to be preferred over a screen-and-treat strategy. In a randomized study comparing prophylaxis against chlamydia, gonorrhoea and bacterial vaginosis versus a screen-and-treat strategy, antibiotic prophylaxis was concluded to be at least as effective as a screen-and-treat policy in minimising post-abortion infections and to be more cost-effective (Sawaya et al., 1996; Penney et al., 1998). In a model to evaluate cost-effectiveness in women seeking induced abortion, at a chlamydia prevalence of 4.8% prophylaxis was shown to provide a cost savings over screen-and-treat (Chen et al., 2007). A disadvantage of universal prophylaxis is that infected women remain unnoticed and cannot be offered the benefits of partner notification and treatment. Therefore, a third strategy has been proposed, involving prophylaxis at the time of abortion followed by screening for gonorrhea and chlamydia to ensure adequate follow-up of treatment results and partner notification (Penney, 1997).

Studies in women presenting at fertility clinics have shown that the prevalence of lower genital tract chlamydia infections is low (1.8%) (Eggert-Kruse et al., 1997; Macmillan and Templeton, 1999; review in Land et al., 2002). Several years after chlamydia infections viable micro-organisms may still be present in the upper genital tract (Dieterle et al., 1998; Gérard et al., 1998), which may be reactivated after uterine instrumentation (e.g. hysterosalpingography and laparoscopy with dye testing). In subfertile women the presence of viable micro-organisms in the upper genital tract cannot be excluded by non-invasive means. Therefore, single dose azithromycin as a prophylaxis has been recommended in all subfertile women before uterine instrumentation, instead of endocervical screening and treatment of positive cases only (Land et al., 2003).

In conclusion, primary prevention by safer sex campaigns, positive attention for sexual health and proper counselling remain a cornerstone in STD prevention. If uptake is sufficient, vaccination will decrease the prevalence of chlamydia infections, but it will take several more years before effective vaccines will be available. Early diagnosis and proper treatment will prevent onward transmission and development of sequelae. This will require interventions increasing early health care seeking behaviour and proper case management (diagnosis, counselling and partner treatment). Prophylactic treatment has been shown to be cost-effective in induced abortion, but it remains to be determined in uterine instrumentation for other procedures.

Further developments

More research is required to broaden the evidence on (cost-) effectiveness and impact of chlamydia screening programmes. In particular, high quality RCTs dealing with the transition from cervicitis to tubal infertility are needed. Antibody testing, as a marker of a previous infection, alongside PCR testing in screening programmes might be an alternative for a time to pregnancy cohort and could potentially be a surrogate marker for adverse sequelae in such studies.

For cost-effectiveness analysis, application of existing and new evidence should be performed within the frameworks of dynamic mathematical models, despite the relative complexity of the approaches. In particular, dynamic approaches explicitly model the spread of chlamydia in populations with the advantage that effectiveness of screening is not only estimated in the actually screened population but additionally the effects are included on populations that are not screened, yet potentially indirectly protected. Modelling this indirect protective effect—often labelled herd protection—is crucial for enhancing valid cost-effectiveness estimates. The relevance of dynamic mathematical modelling has been shown for chlamydia screening (Welte et al. 2005), but also applies for other interventions in infectious diseases, for example vaccinations (Rozenbaum et al., 2008).

To limit consequences of chlamydia infection, concerted actions from different specialities (e.g. researchers, clinicians and policy makers) are needed, as the course of infection is determined by the interplay between host, pathogen and environmental factors. Potential gains achieved by immunogenetic studies of *C. trachomatis* infections include the identification of genetic markers of the susceptibility to

and clearance of *C. trachomatis* infections, which can be used to develop diagnostic tools to determine an individual's predisposition to infection and the risk to develop late complications. The current chlamydia genome sequencing on clinical isolates is expected to provide information on strain specific immunopathologic differences. In the EpiGenChlamydia consortium (www.EpiGenChlamydia.eu), funded by the European Union, a number of research groups collaborate on epidemiologic and immunogenetic studies on *C. trachomatis* in order to move forward to effective chlamydia control at the individual and societal level.

Conclusions

The majority of chlamydia-infected individuals are asymptomatic, and remain unnoticed and untreated. Infected women may be at risk of gynaecological complications (e.g. PID and tubal infertility), and determine the reservoir for onward transmission in the population. Strategies for the control of infection and prevention of its complications are only partially effective (safer sex campaigns) or not yet available (vaccine). Screening programmes have been introduced as an additional strategy for early detection and treatment of infected cases. Cost-effectiveness of screening is largely determined by the rates of complications prevented. Evidence on the impact of screening on the prevalence of chlamydia infections at a population level is still limited, as is the impact on the prevalence of complications in screened women.

We reviewed the literature for estimates of the prevalence of chlamydia related complications, to be used in patient counselling and in estimating the cost-effectiveness of screening. The risk of developing PID after lower genital tract infection varies considerably and is estimated between (less than) 1% up to 30%. Difference in estimates is largely determined by the characteristics of the tests used (e.g. PCR or culture) and the populations tested (e.g. symptomatic versus asymptomatic, high-risk versus low-risk). Risk of low-load PCR detected infections in low-risk populations will be rather at the lower than at the upper estimate. The risk of developing tubal infertility after PID is estimated at 10–20%, and from this it can be concluded that the risk to test-positive women of developing tubal infertility ranges between 0.1 and 6%. We tried to estimate this risk by including chlamydia IgG antibody testing in hypothetical models. Our analyses indicate a risk of tubal infertility after lower genital tract chlamydia infection in the range up to 4.6%, which is in line with assumptions in published cost-effectiveness analyses that generally indicate potentials for favourable cost-effectiveness for chlamydia screening.

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