Screening programmes for chlamydial infection: when will we ever learn?

With more countries recommending screening programmes for chlamydial infection, **Nicola Low** argues that such programmes are not underpinned by sound evidence

The notion that a programme of widespread screening[1] in Sweden controlled transmission of chlamydial infection and reduced morbidity of the female reproductive tract is commonly cited as fact.[2-4] Unfortunately, this assertion and similar claims about screening in the United States[3-5] and Canada[6] are not supported by rigorous research or practice. Here, I will show how misinterpretation of what comprises a screening programme led to uncritical acceptance of the effectiveness of chlamydia screening, and the funding of a National Chlamydia Screening Programme in England,[3] before the benefits and harms were evaluated.

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Screening for chlamydial infection in Sweden

Swedish researchers were key players in demonstrating the importance of sexually transmitted chlamydial infection in the 1970s and 1980s. They were instrumental in developing diagnostic tests[w1] and defining the role of *C trachomatis* in pelvic inflammatory disease and infertility.[w2] The first documented "program to identify asymptomatics" started in 1982 and tested women under 30 years seeking contraception, abortion, or antenatal care and male partners of infected women.[7] In 1988, a change in the Swedish infectious diseases law required doctors to provide free testing, treatment, and partner notification for anyone with suspected chlamydia and to report cases.[7] There were educational campaigns, and young people's clinics were established to make testing easily available.[8]

Rates of chlamydia and its complications decreased up to the mid-1990s, at the same time as widespread testing was introduced (fig 1).[7-9] Financing services,[8] strong infrastructure,[8] open attitudes to sexual health,[1] and a small population[1] were suggested to contribute to this success. Studies such as these have now been cited as evidence of success of organised chlamydia screening programmes up to 80 times in Web of Science indexed journals[w3] and in official reports.[3]

In fact, the fall in rates of chlamydia infection in Sweden coincided with the national campaign to prevent HIV (fig 1).[10] Desire to believe in chlamydia screening seems to have displaced alternative explanations, such as changing sexual behaviour,[8 10] even though parallel decreases in sexually transmitted infections in countries with no efforts to control chlamydia were attributed to HIV prevention campaigns.[11] Reports of the effectiveness of screening in Sweden persist,[3 4] despite increasing rates of diagnosed chlamydia since 1995 (fig 1).[w4]

SUMMARY POINTS

- Lack of an agreed concise definition of a screening programme has contributed to beliefs about the effectiveness of opportunistic screening for chlamydial infection
- Opportunistic screening as currently implemented in the National Chlamydia Screening Programme in England has not been evaluated in randomised controlled trials
- Criteria for assessing the appropriateness for introducing a screening programme have not been rigorously applied to chlamydial infection
- Countries implementing or contemplating national chlamydia screening should conduct research to determine if such screening programmes do more good than harm at reasonable cost

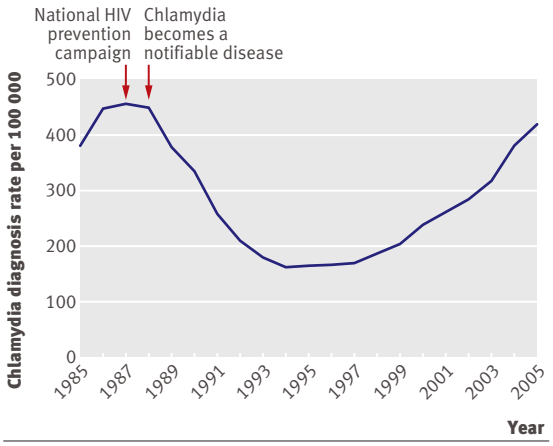


Fig 1 | Rate of laboratory diagnosed chlamydial infection in Sweden 1985 to 2005

Screening for chlamydia in the US

In the US, opportunistic screening was also credited with decreases in rates of chlamydial infection.[4 5] The Centers for Disease Control and Prevention have supported screening programmes since 1988.[5] A federally funded national Infertility Prevention Program that provides chlamydia screening for women on low incomes attending certain healthcare settings was established by 1995.[5] The most recent report showed that chlamydia positivity in women aged 15-24 years screened in family planning clinics decreased in two of 10 regions from 2003 to 2004, increased in six, and remained the same in two.[5]

The National Chlamydia Screening Programme in England

A programme offering opportunistic chlamydia screening (box 1) to all sexually active women and men under 25 years attending a variety of healthcare settings in England is due to be implemented by 2008.[3] One-off screening opportunities in commercial pharmacies, universities, colleges, and other venues are also encouraged.[16] The programme aims to, "control genital chlamydial infection through the early detection and treatment of asymptomatic infections and prevention of sequelae and onward transmission."[3 16] In two pilot sites, all general practitioners took part, were paid for each patient enrolled,[4] and generated the highest proportion of tests and cases, achieving an effective screening rate (box 1) of 50%.[3] In the programme itself, participation of general practitioners

is optional and largely unremunerated. In 2005-6, the effective screening rate was less than 5% in more than half of programme areas.[16] Performance indicators do not measure key outcomes of repeat screening, prevalence of chlamydial infection, or morbidity.[3]

What is a screening programme?

A "screening programme" has no agreed concise definition, although "screening" (box 1) is well defined. Any health service activities that facilitate early disease detection could therefore be called a programme, if certain criteria are fulfilled.[12-14] I suggest that it should be defined as a continuing organised service that ensures that screening is delivered at sufficiently regular intervals to a high enough proportion of the target population to achieve defined levels of benefit at the population level, while minimising harm (box 1).

In fact, no national chlamydia screening programme exists in Sweden, and "national strategies for the entire area of sexual health and sexuality are presently lacking."[12] Locally funded activities that promote testing for chlamydial infection for case finding, underpinned by legislation, were widely described and interpreted as screening programmes.[1 8] Reliance on the obligations of individual doctors without national coordination, objectives, or outcome standards does not fulfil the suggested definition and is unlikely to achieve the aims of screening.

Box 1 | Definitions of screening programmes

Screening
Members of a defined population, who may not know they are at risk of a disease or its complications, are asked a question or offered a test to identify those who are more likely to be helped than harmed by further tests or treatment (UK National Screening Committee[12 13])

Screening programme
A continuing public health service that ensures screening is delivered at sufficiently regular intervals to a high enough proportion of the target population to achieve defined levels of benefit at the population level, while minimising harm (my definition, based on previous work[12-14])

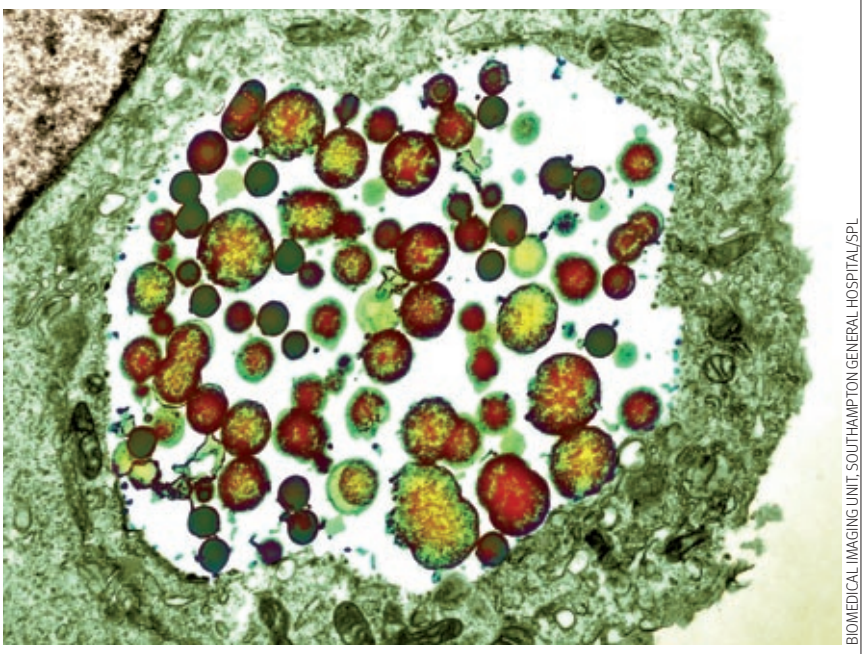
Proactive screening
Population registers are used to invite members of the population at risk for screening at appropriate intervals; also known as population, register based, call-recall, cyclical, active, or systematic screening[12 w5]

Opportunistic screening
A health professional offers a screening test to patients attending health care or other defined settings for unrelated reasons; the onus is on the health professional to repeat the test offer at appropriate intervals; also known as case finding[12 w5]

Acceptance rate
Number of people who accept a screening test as a proportion of those offered the test; measures acceptability of the test in the population receiving the offer[15 w6]

Effective screening rate
Number of people screened as a proportion of those eligible for screening; measure of screening coverage at population level[15 w6]

Offer rate
Number of people offered the screening test as a proportion of those eligible for screening[15 w6]



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***Chlamydia trachomatis* bacteria inside a cell**

Appropriateness of a chlamydia screening programme

Chlamydia would seem to be an ideal candidate for screening. *Chlamydia trachomatis* is a common, curable, easily diagnosed, sexually transmitted infection that usually causes no symptoms. It can, however, cause devastating complications, including infertility, ectopic pregnancy, neonatal infection, and facilitation of HIV transmission.[w7]

Agreed standards should be applied to all diseases for which screening is in place or is being considered.[2] Screening programmes approved by the National Screening Committee require registers that allow proactive invitations (box 1) to be sent to people in the target population to ensure regular uptake.[17] The alternative is opportunistic screening, which reaches people attending health or other services (box 1). A health professional is responsible for offering the test at regular intervals. Cervical cancer screening in the United Kingdom was initially opportunistic, but screening was poorly targeted and consistent reductions in mortality only occurred after a proactive programme increased regular coverage.[17]

Opportunistic screening is widely assumed to be the only acceptable model of service delivery for chlamydia.[4 5] In England, postal invitations to young people who were not yet sexually active were deemed inefficient and the coverage of opportunistic screening stated to be adequate[4] before alternatives had been investigated. The assumption about coverage was based on high acceptance (box 1) once chlamydia screening had been offered. However, not everyone uses the services that provide testing and not everyone who uses those services is offered a test. Subsequent research has shown that effective screening rates (box 1) are 30-40% for both proactive and opportunistic approaches,[15] and costs per screening invitation are similar.[18]

Gray has suggested another important difference between chlamydial infection and chronic diseases: that a person's risk of acquiring an infection depends on its prevalence in the population.[13] A chlamydia screening programme must therefore control

transmission through both regular screening and partner notification to reduce morbidity. Thus, the model for chlamydia screening might differ from that for a non-communicable disease, but standards for the organisation and appropriateness of screening should be the same. Key criteria of the National Screening Committee, outlined below, have not been stringently applied to chlamydia.[18]

Natural history should be adequately understood

Increasing evidence shows that the rate of progression of endocervical chlamydia to pelvic inflammatory disease is lower than previously thought.[19] Population based studies consistently estimate lower incidence rates of pelvic inflammatory disease than clinic based studies.[19] Infections detected by screening asymptomatic people might therefore have a better prognosis than symptomatic infections, because of differences in the burden of the organism. Descriptions of chlamydial infection and its consequences,[3] and models of the impact of screening,[18] however, nearly always cite the higher estimates.

Evidence from high quality randomised controlled trials

The Department of Health funded pilot studies of opportunistic chlamydia screening,[2-4] even though no randomised controlled trial had shown that this intervention reduced long term morbidity.[4] The National Screening Committee accepted that, "In Scandinavia, screening for chlamydia has been found to reduce the risk of infertility and ectopic pregnancy,"[2] on the basis of only uncontrolled ecological studies. A systematic review, commissioned after the National Chlamydia Screening Programme was introduced, has confirmed that no randomised controlled trial has evaluated opportunistic chlamydia screening as it is currently practised.[15] Evidence from trials of proactive screening cannot be extrapolated to opportunistic screening and is limited by methodological biases that overestimate the benefits.[15] No trial evidence about the effects of more than one round of screening for either approach is available.

Value for money

Most studies cited as showing that chlamydia screening is cost effective do not satisfy accepted quality criteria for economic evaluations.[18] The need for dynamic mathematical modelling has been largely ignored, in contrast with work on other infections.[18] Furthermore, most studies make two assumptions that overestimate the cost effectiveness of chlamydia screening—that the incidence of pelvic inflammatory disease and regular screening rates are higher than are seen in practice.[3] Under realistic assumptions, introducing a chlamydia screening programme is likely to be an expensive intervention.[18]

Lessons to be learnt

Belief in the success of opportunistic screening persists,[3 6] despite an absence of evidence of effectiveness[15] and increasing rates of chlamydia in countries that are assumed to have such programmes.[5 6 w4] Increased testing with highly sensitive tests explains only part of the observed rise. In Sweden, rates of chlamydial infection in 15-19 year olds began to increase before nucleic acid amplification tests were available, and rates were also increasing in some laboratories before they changed diagnostic methods.[w8] Reasons that have been suggested to explain the resurgence of chlamydia include inadequate partner notification,[20] and a loss of immunity after widespread early treatment.[6] The possibility that the opportunistic screening approach has not achieved regular screening has not been widely discussed.[w9] Unsubstantiated belief also seems to have allowed the requirements of the National Screening Committee and the experience of other UK screening programmes to be over-ridden. Uncertainty about the status of chlamydia screening is, however, emerging. National Screening Committee policy is that screening should not be offered to pregnant women[w10] owing to insufficient evidence of effectiveness, whereas the National Chlamydia Screening Programme recommends screening in antenatal clinics.[3] Countries currently considering introducing screening policies or programmes include France, Romania and Slovenia,[7] Ireland,[w11] the Netherlands,[w12] and Australia.[w13] Policy makers and researchers in these countries need to learn from the past and move forward by generating the evidence required (Box 2) to determine whether this intervention does more good than harm at reasonable cost.

Box 2 | Research needed to establish benefits and harms of chlamydia screening programmes

Validity of screening tests

- Systematic review of diagnostic studies of nucleic acid amplification tests to determine if higher observed yields of *Chlamydia trachomatis* in vulval or vaginal specimens than in urine specimens is clinically important

Epidemiology and natural history of the condition

- Cohort studies to track progression of lower genital tract *C trachomatis* infection (detected with nucleic acid amplification) to pelvic inflammatory disease and other reproductive tract morbidity. Stored repeated endocervical specimens (such as those from human papillomavirus vaccine trials), with linkage to medical records, could be used
- Cohort studies to estimate the incidence of neonatal complications after perinatal maternal chlamydial infections detected with nucleic acid amplification tests
- Prospective studies of the associations between quantitative measures of chlamydial organism load, symptomatic and asymptomatic lower and upper genital tract disease, and transmission of infection
- Prospective studies to define appropriate screening intervals more accurately

Effectiveness of screening for reducing morbidity

- Randomised controlled trials to examine the effectiveness of opportunistic and proactive chlamydia screening, including more than one round of screening and measuring uptake of initial and repeat invitations, and biological outcomes
- Randomised trials to examine ways of increasing the uptake of regular repeat screening

Value for money

- Cost effectiveness analysis using economic and epidemiological data collected in randomised controlled trials and dynamic mathematical models to examine the impact of interventions on transmission of chlamydia and incidence of complications
- Prospective studies to determine utility values for quality adjusted life years with pelvic inflammatory disease, ectopic pregnancy, tubal infertility, and epididymo-orchitis

Contributors: NL is an epidemiologist and accredited physician in genitourinary medicine and public health with a research interest in screening programmes for sexually transmitted infections. This article uses information that emerged from a longstanding collaboration on *Chlamydia* in Uppsala, Sweden with Björn Herrmann and Matthias Egger, and is based on plenary talks at the Australasian Sexual Health Conference 2006 and the 22nd IUSTI-Europe Conference on Sexually Transmitted Infections 2006. Discussions and research collaborations with Judith Stephenson, University College London, and Jackie Cassell, Brighton and Sussex Medical School, also informed the present discussion.

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