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Point-of-care management of sexual transmitted infections
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Citation for published version (APA):

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INTRODUCTION

This thesis is about the usability and cost-effectiveness of point-of-care (POC) testing of sexual transmitted infections (STI’s). All studies described in this thesis are about POC testing of urogenital chlamydia and gonorrhoea infections, except one study, which evaluates POC testing of HIV infections.

The World Health Organization (WHO) estimates that 131 million chlamydia and 78 million gonorrhoea infections occur annually worldwide, the majority of them in developing countries. Though curable, those infections present a major burden of disease. Untreated infections can lead to long-term sequelae in both men and women, especially among pregnant women and their children. Both infections can cause preterm birth, fetal growth retardation, low birth weight, pelvic inflammatory disease (PID) which can lead to ectopic pregnancy or infertility, epididymitis among men and perinatal complications such as conjunctivitis and pneumonia among infants. Moreover, chlamydia and gonorrhoea infections are important drivers of the HIV epidemic by facilitating the acquisition and transmission of HIV. Diagnostic testing is particularly critical, as most infected individuals, especially females, are asymptomatic.

POC testing is defined as rapid medical testing carried out by a professional at or near the site of patient care. In contrast with laboratory-based testing the result of a test is directly available and enables prompt management if indicated.

The first paragraph of this introduction will start with a short history of medical diagnosis and POC testing, including the current available POC tests for STI’s. The second part will briefly discuss the cost-effectiveness of POC testing and the outline of this thesis.

History of medical diagnosis and POC testing

The concept of using bodily fluids for diagnostic tests dates back to ancient history. One of the earliest recorded urine based test was a home-based pregnancy test described on an Egyptian papyrus document from 1350 BC. In this test a woman had to urinate on wheat and barley seeds; if nothing happened the conclusion was that she was not pregnant; if the wheat sprouted it was believed she was having a girl, if the barley sprouted, a boy. The Greeks used a less pleasant test to prove whether a woman was pregnant; in the vagina of a woman a onion was left overnight, and if the next day the mouth breath did not smell of onions she was believed to be pregnant.

The history of POC testing for diabetes mellitus is also documented extensively in ancient documents. Doctors from Persia to China diagnosed the disease by
simply tasting the urine of their patients; the Indian doctors used an indirect method, and observed whether ants were attracted by the sweet urine. For many centuries doctors adhered to the observation of urine as the only available tool to diagnose diseases (Figure 1). The theory behind visual examination of urine, uroscopy, is well described by Hippocrates in the 4th century BC and is based on diagnosing disease and determining a prognosis by observing the color and consistency of the urine.

Until the mid 19th century uroscopy remained the central paradigm of Western medicine and was commonly accepted and practiced throughout Europe. Doctors were also called piss-prophets (‘piskijkers’) in these days. The club-shaped urinal known as ‘matula’ became the guild symbol of the doctor and can be found back in many images and paintings. A famous example is the painting “The dropsical woman” of the Dutch painter Gerard Dou on which a doctor is examining the urine of a suffering women in the background (Figure 2).
The discovery of microscopic lenses was the beginning of a paradigm shift; a closer look at body fluids with lenses revealed the real cause of infectious diseases. The earliest microscopist was a Jesuit priest from Germany, Athanasius Kirchner (1602-1680), who observed with lenses how maggots and other living creatures developed in decaying matter. In the following centuries microscopic lenses were further optimized. Robert Hooke (1635-1703), an English scientist, could reach a magnification of 30 times with his microscope and described for the first time the existence of ‘little boxes’ or cells in vegetables.\textsuperscript{7} In the same period the Dutch scientist Anthoni van Leeuwenhoek (1632-1723) constructed a single lens microscope that could magnify objects until 480 times. With this microscope he was one of the first scientists who described the existence of bacteria (Figure 3).\textsuperscript{12}
It took until the 19th century before a link was made between bacteria and infectious diseases. In the 19th century famous scientists like Louis Pasteur, Robert Koch, Ignaz Semmelweis and Joseph Lister realized major breakthroughs by the isolation of organisms responsible for infectious diseases and by introducing ways of preventing these with vaccination, pasteurization or sterilization.\textsuperscript{14,15} The German physician Albert Ludwig Sigesmund Neisser discovered the pathogen of gonorrhoea in 1879 when he saw the typical pared bacteria (diplococci) under his microscope and linked this with the symptoms of a clap.\textsuperscript{16} In 1882, Hans Christian Gram developed the Gram stain, a method of staining to differentiate bacterial species into two large groups (Gram positive and Gram negative bacteria).\textsuperscript{17} Two associates of Neisser, the scientists Halberstaedter and von Prowazek, were the first who described the presence of inclusion bodies, later known as \textit{Chlamydia trachomatis}. During a experimental expedition on Java in 1907, they took scrapings from individuals infected with trachoma (an eye infection), and inoculated orangutans eyes with the samples to prove the infectious nature of the disease (Figure 4). It took until 1976 that chlamydia was recognized as a sexual transmitted disease.\textsuperscript{18}
From the beginning of the 20th century clinical laboratories were established in hospitals. Besides microscopy, additional diagnostic tools became available such as immunological staining for syphilis (Wasserman test). But at that time most of the diagnostics for infectious diseases were not POC tests because mostly it took hours to days before the results were available.

The invention of immunochromatographic assays, also called lateral flow tests (LFT’s) or dipstick tests, was a breakthrough in the field of rapid testing in the mid of the 20th century. LTF’s are simple devices intended to detect the presence of a target analyte (antibodies or proteins) in sample (matrix) without the need for specialized and costly equipment. The technical basis of the lateral flow immunoassay was derived from the latex agglutination assay, developed in 1956 by Plotz and Singer. In the following decades the main application driving the development of the LFT’s was the pregnancy test, which represented a continued historical interest in the use of urine for medical diagnostic purposes. In 1971, the first home-based commercial pregnancy tests were developed.

**Current POC tests of STI’s**

Presently, LFT’s remain the dominant form of POC tests in the field of infectious diseases. LFT’s are widely used in the POC management of STI’s. They have a
high sensitivity and specificity for the detection of systemic infections like HIV and syphilis.\textsuperscript{22-24} Numerous LFT’s are available for chlamydia and gonorrhea, unfortunately, they all have a poor performance because these infections are usually limited to local anatomic sites with low levels of bacterial analytes and without a systemic immunological response with substantial antibody responses.\textsuperscript{25,26}

Gram stained smear (GSS) analysis with microscopy is still of value for the detection of gonorrhea, especially among men. Indirectly, the GSS is also used as POC test for chlamydia among men (chlamydia bacteria are too small to observe directly with light microscopy). The presence of polymorph nuclear leucocytes is used as a marker to detect a non-gonococcal urethritis as a proxy for urogenital chlamydia.\textsuperscript{26-28}

Currently, the most accurate POC tests for STI’s are nucleic acid amplification technique (NAAT) based tests. An example is the GeneXpert\textsuperscript{®} (Cepheid) test, a cartridge-based, automated test that can identify different infections by nucleic acid amplification technique (NAAT) in 90 minutes.\textsuperscript{29} The GeneXpert\textsuperscript{®} cartridge can be analyzed in machines of different sizes (also as bench top and handheld devices) and are also used in mobile clinics to reach rural communities.\textsuperscript{30} The GeneXpert\textsuperscript{®} CT/NG detects chlamydia and gonorrhea simultaneously. It has been evaluated in studies in Europe, the USA and Australia with one study showing a very accurate diagnostic performance with sensitivities and specificities above 97\%.\textsuperscript{31,32} In London there are STI clinics that run on theses platforms and often offer treatment the same day a person is tested.\textsuperscript{33} Barriers are the high costs and relative long waiting time of 90 minutes for the patients associated with these tests although an augmented version is under development with a turnaround time of 30 minutes (personal communication with Cepheid).

Cost-effectiveness of POC testing

Due to budget cuts and the generally increasing number of consultations and positivity rates of STI’s, decision makers are forced to optimize the effectiveness of test policies. Point-of-care (POC) management has the potential to be more effective by averting new infections that could occur during the interval between testing and treatment or due to lost to follow-up. Moreover, earlier treatment of gonorrhea and chlamydia can avoid long-term complications like pelvic inflammatory disease, ectopic pregnancy and infertility among women and epididymitis among men and also can potentially reduce HIV transmission because most STI’s increase HIV acquisition and transmission.

Nonetheless, depending on the test characteristics, relying solely on results of POC tests with a suboptimal performance can lead to overtreatment and missed infections.\textsuperscript{2,4,34,35} Moreover, in most developed settings, POC manage-
ment generates additional costs for extra tests and staff time added to the costs of confirmatory molecular tests. There are also other barriers for POC tests, especially in low-and middle-income countries (LMIC), such as the required information system integration and the inadequate infrastructure.\textsuperscript{36,37}

For this reason most healthcare settings in LMIC’s are dependent on syndromic management, an approach with a very poor performance because most STI infections are asymptomatic.\textsuperscript{38,39} In these settings the need for an affordable and accurate POC test is urgent.

The World Health Organization (WHO) has developed guidelines for an ideal POC test, the so called ASSURED criteria. ASSURED stands for: Affordable by those at risk for infection, Sensitive, very few false negatives; Specific, very few false positives; User-friendly, very simple to perform; Rapid and Robust, to enable treatment at first visit (rapid) and does not require refrigerated storage (robust), Equipment-free, easily collected non-invasive specimens and not requiring complex equipment and Delivered to end users.\textsuperscript{36}

With the introduction of a new POC test, policymakers have to weigh all these criteria in a pragmatic manner. The desire to achieve a maximum sensitivity and specificity must be balanced against practical considerations. This can differ from setting to setting depending on the available budget, but also on the

\textbf{Figure 5.} Considerations for the appropriate selection and use of laboratory tests\textsuperscript{40}
epidemiological and behavioral characteristics of the population (Figure 5). A cost-effectiveness analysis (CEA) can help to make a decision by weighing all these factors in a structured way.⁴⁰

For some CEA’s, mathematical models are needed to calculate the potential impact of an intervention in the future. Mathematical models for STI’s are frequently complex frameworks that describe the sexual networks of individuals, since these networks determine the transmission dynamics STI’s in a specific population.

Often compartmental models are used, where individuals are categorized according to the stage of infection (for instance, susceptible, symptomatic, asymptomatic) and can be stratified by sexual activity level, age, or other characteristics (Figure 6).⁴¹ If the intervention is the introduction of a POC test the total costs and effects of POC testing have to be compared with the standard testing procedure.

A mathematical model can provide the long-term effects for both procedures. Effects that are usually considered are the infections at each stage of infection/disease, the future prevalence and adverse reproductive complications. From the mathematical model, also the total numbers of tests and treatments can be calculated, which are used to calculate the total costs of each testing procedure.

**Outline of this thesis**

Chapters 2 and 3 of this thesis report on the evaluation of the cost-effectiveness of light microscopic examination of Gram stained smears as a POC test for uro-

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**Figure 6. The transmission dynamics of gonorrhoea.** Schematic illustration of the model of gonorrhoea used by Hethcote & Yorke (1984).⁴¹ Men and women have three states with respect to infection, which are shown as boxes with the arrows representing the movement between states. The population is also divided into sexual-activity groups according to rates of sex-partner change⁴¹
genital gonorrhoea (chapter 2) and chlamydia (chapter 3) at the STI outpatient clinic of the Public Health Service (PHS) of Amsterdam. In both chapters the diagnostic accuracy, costs and public health implications like overtreatment and loss to follow-up are compared between two POC algorithms: Gram stain testing for all patients compared with Gram stain testing for symptomatic patients only.

Chapter 4 reports on the evaluation of the diagnostic performance of the leucocyte esterase test (LET), a lateral flow POC test, in the detection of urogenital chlamydia among male patients at STI outpatient clinics in Paramaribo and Amsterdam.

In chapter 5 the impact of POC management on the transmission of anogenital gonorrhoea among men who have sex with men (MSM) is predicted with a mathematical modelling and cost-effectiveness study. The potential influence of POC testing on the transmission of anogenital gonorrhoea is modelled with data collected from self-reported questionnaires regarding the sexual behaviour of MSM in the period between testing and treatment. In three different POC scenarios the prevalence of gonorrhoea after five years are estimated; the costs of each scenario is calculated.

In chapter 6 the results of the HIV Testing Week (HTW) 2015 in Amsterdam are described. During the HTW anonymous POC tests for HIV were offered free of charge at different locations. The analyzed outcomes are the number of (positive) tested persons, characteristics and testing history of the tested population, and the healthcare workers’ experiences and opinions concerning the HTW.

Finally, in chapter 7 the results of all chapters are summarized and discussed.
REFERENCES


Introduction


