Point-of-care management of sexual transmitted infections

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Publication date
2017
Document Version
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CHAPTER 7

General discussion

GENERAL DISCUSSION

The World Health Organization (WHO) estimates that the global incidences of bacterial STI's like chlamydia, gonorrhoea and trichomonas have been steadily rising since 1995 and increased from 2005 to 2008 by 11.7%.[1] These findings are consistent with the situation in the Netherlands where there is a yearly increase in the incidence of chlamydia and gonorrhoea. In addition, other STI's like syphilis and hepatitis C are also on the rise.

The increasing number of consultations at STI clinics led the Dutch government to limit the budget for STI care and to change the national testing policy in 2012. A restriction was put on the total number of consultations and more focus was directed towards high-risk groups like men who have sex with men (MSM) and young heterosexuals (<24 year old).[2] Since then, people who do not belong to these risk-groups are referred to the general practitioner for STI testing and treatment. As a consequence, the high costs for STI testing, mostly paid by patients themselves, may hinder their access to care.

Growing healthcare expenditures and subsequent budget cuts have become a major challenge affecting almost all fields of healthcare. It is increasingly important to incorporate economical aspects in the evaluation of health interventions in order to help allocate scarce health resources in the most effective way.[3] A cost-effectiveness analysis (CEA) may help policy makers whether to implement a certain health intervention, mostly by comparing a new intervention with the existing one in terms of costs and consequences.[4]

In the first two studies of this thesis (chapter 2 and 3) CEA's were used to evaluate the economical consequences of the restriction of light microscopic examination of Gram stained smears (GSS) as point-of-care (POC) test for urogenital gonorrhoea and chlamydia.

We also (chapter 4) evaluated the diagnostic performance of the leucocyte esterase test (LET), a dipstick POC test, as a proxy for the detection of urogenital chlamydia among men in both Suriname and the Netherlands.

We modelled (chapter 5) the effect of POC testing on the on-going transmission of gonorrhoea among MSM (by preventing transmissions during the period between sampling and treatment or due to lost to follow-up) in three testing scenarios; POC testing for all, POC testing for only symptomatic and no POC testing. Per scenario also the total healthcare costs over 5 years were calculated.

In chapter 6 the HIV Testing Week 2015 in Amsterdam was evaluated with respect to the total number of participants tested, the total number of positives found and the characteristics and testing history of the participants.

This final chapter provides a summary of all findings of the studies, discusses these findings in a broader context and looks forward to the future perspectives of POC testing.

GSS as POC test for gonorrhoea and chlamydia

In 2010 the indication and use of light microscopic examination of urogenital GSS was restricted at the STI outpatient clinic of the PHS of Amsterdam due to an increasing workload that could no longer be handled in combination with structural understaffing. Since then on only high-risk patients with urogenital symptoms were tested with light microscopic examination of GSS.

The rationale of our initial studies (chapter 2 and 3) was to evaluate the consequences of this policy changes on the diagnostic performance of light microscopic examination of urogenital GSS for chlamydia and gonorrhoea respectively, the associated healthcare costs and public health outcomes like overtreatment and lost to follow-up.

GSS examination to detect urogenital gonorrhoea had a high specificity among both sexes (≥99.8%), a high sensitivity among men (≥95.4%) but a poor sensitivity among women (≤32.0%). When GSS examination was offered to symptomatic patients only, the cost per consultation was reduced by 8% without a significant difference in diagnostic accuracy or numbers of overtreatment and lost to follow-up.

These outcomes justified retrospectively the change of the testing policy. The study also confirmed the outcomes of earlier studies[5;6]; GSS examination is a reliable POC test for men but not for women due to the low sensitivity.

The cost-effectiveness of GSS examination for the detection of urogenital chlamydia among men was investigated with a similar design and during the same time periods. In both periods the sensitivity was fairly high: 83.8% when all men were tested and 91% when only symptomatic men were tested. On the other hand, the specificity was relatively low in both periods; 74.1% and 53.1% respectively.

Ultimately, POC testing of symptomatic men only resulted in a higher sensitivity but a lower specificity of the GSS examination and a cost reduction of 14.3% per correctly managed consultation.

Although also other causative micro-organisms of urethritis (like *Mycoplasma genitalum*) could have been treated incidentally, the high rate of overtreatment due to the low specificity is a major concern. Overtreatment is not only a waste of money but it also may enhance emerging antimicrobial resistance. For this reason GSS examination is not an ideal POC test for chlamydia among men, but is still used by lack of a better alternative in STI clinics.

POC testing in low-and middle-income countries

Ideally, a POC test should meet the ASSURED criteria of the World Health Organization; Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, Deliverable to those who need them.[7] When applying these criteria, microscopic examination of GSS is a suboptimal test recommendation, since most healthcare settings in low-and middle-income countries (LMIC) lack the required laboratory infrastructure. Lateral flow dipstick tests are much easier to perform and do not require laboratory conditions, but tend to have low diagnostic accuracy in the detection of chlamydia and gonorrhoea.[1;8;9]

An example of a lateral flow dipstick test is the LET, which detects inflammatory cells, a non-specific proxy for infection. The diagnostic accuracy of the LET to detect urogenital chlamydia among men was evaluated, both at STI clinics in Paramaribo, Suriname and Amsterdam, the Netherlands (chapter 4).

In both countries the sensitivity was reasonable high, 92.6% in Suriname and 77.3% in the Netherlands, but the specificity was low, 38.1% and 58.1% respectively. Modelling studies have shown that in settings were a lot of patients do not return for treatment even a POC test with a moderate sensitivity can be more effective in averting transmissions than a sensitive molecular test were patients have to come back for, with the chance of being lost to follow-up. On the other hand, the poor specificity of the LET, may cause overtreatment. Whether the advantages of direct management based on LET outweigh the disadvantages of overtreatment is a subject for further studies.

Impact of POC testing on transmission

Little is reported in the literature about the sexual behaviour of patients in the period between sampling and treatment, the period in which POC management potentially can avert transmissions.

We collected data with a self-reported questionnaire concerning the sexual behaviour of patients in the period between testing and treatment. This data was used as input for a deterministic mathematical model to predict the impact of POC testing on averted anogenital gonorrhoea transmission among MSM in Amsterdam. The prevalence of gonorrhoea, the number of consultations and the total healthcare costs over five years were calculated for three testing scenarios: POC testing for symptomatic MSM only, POC testing for all MSM, and no POC testing for MSM. Because GSS examination was used as POC test in this study, part of the diagnostic accuracy and cost data came from the previous study described in chapter 2. POC testing of only symptomatic MSM was considered the baseline scenario and the consequences of both expansion of this scenario

to POC testing for all MSM as well as the abandonment of POC testing were investigated.

Expanding the POC policy to all MSM irrespective of symptoms had a modest effect on the prevalence rate (decline of 11%) at a rise in costs per consultation and was not considered an attractive option in times of declining health care budgets. The abandonment of POC testing of symptomatic MSM resulted in a high increase of 60% in the gonorrhoea prevalence in 5 years. Although this policy resulted in a cost reduction per consultation, we neither considered this justifiable from a public health point of view.

In a future study we want to address to which extent (a specific trade-off) a certain decline of prevalence could be cost-effective whereby also indirect costs and effects of testing and treatment would have to be taken into account. Indirect parameters associated with sequelae like long-term complications of gonorrhoea, facilitative effects on HIV transmission and loss of productivity will be needed to calculate the costs changes per quality adjusted life year (QALY) expressed in an incremental cost-effectiveness ratio (ICER).

Lowering the barriers of STI testing: the role of POC tests

In the Netherlands an estimated number of 22,100 individuals are infected with HIV, of whom about 2700 (12%) are unaware of their infection.[10] Detecting and treating HIV infected individuals at an early stage is an important public health challenge; in addition to individual prognostic benefits, there is growing evidence that early detection and treatment is also crucial for the reduction of HIV transmission in the population.

Since 2015, multiple stakeholders engaged in HIV prevention and treatment, joined forces in the 'HIV Transmission Elimination Amsterdam' (H-TEAM) initiative, with the aim to eliminate the HIV epidemic in Amsterdam and improve the prognosis for those people living with HIV.[11]

One of the initiatives of the H-TEAM was an HIV Testing Week (HTW) in Amsterdam that takes place yearly in the week of World AIDS Day. In 2015 from 28 November through to 4 December the HTW mainly focussed on two high-risk groups: MSM and migrants from non-western countries.

In chapter 6 we presented the results of an evaluation of the HTW 2015. In total 1231 participants were tested with free-of-charge POC HIV tests at the different locations. With three positive POC HIV tests the detection rate was 0.3%. Over 60% of the participants belonged to one of the targeted risk-groups, about one third of the tested participants was tested for HIV for the first time and about one third of the participants was previously tested more than one year ago.

Community involvement of different cultural ethnic organizations played an important role in the organization and campaign of the HTW. From previous studies it is known that among migrants there are more barriers to HIV testing such as a lower risk-perception, lack of general knowledge about HIV, fear of the consequences of a positive HIV result, negative social norms and costs of HIV tests.[12-17] As a consequence, the estimated percentage HIV infected individuals that is unaware of their HIV infection is higher than in the 12% in the general population; respectively 33% and 25% among HIV infected migrants from sub-Sahara Africa and the Caribbean.[10;18]

The HTW was an initiative to lower barriers for HIV testing for the population in general, and specifically for the targeted risk-groups. Lowering barriers for migrants is not only needed for HIV testing but for STI testing in general.

A study by van Rooijen et al. revealed a discrepancy of the positivity rates and test uptake between inhabitants of different quarters in Amsterdam: in the Southeastern quarter of Amsterdam, an area with a high percentage of migrants, the highest chlamydia positivity rates were found while the percentage of tested inhabitants was one of the lowest (information provided by M. van Rooijen; data not yet published). To better reach out for this group, the STI outpatient clinic opened a satellite testing site in the Southeastern quarter in 2015.

Lowering barriers by decentralization of STI testing services can still be further improved and POC testing can play an important role in this process. The need to make healthcare more patient-centered is a global trend and is based on the premise that healthcare should be organized more around the patient rather than the provider.[19] A strategy is to invest more in STI self-testing within communities (e.g. at pharmacies) or online. This will not only lower barriers but also has the potential to be cost-saving because the majority will not need to be seen in a clinical setting.

An evaluation of a recent Dutch trial using the online HIV self-test (Time2test) demonstrated it was successful in reaching first-time and infrequent testers.[20] Other studies investigating home-based and in-pharmacy POC testing of HIV in different European countries and the USA also show promising results.[21;22] Unfortunately, officially it is not yet allowed to offer HIV self-tests online in the Netherlands.

New POC technologies

With the trend of miniaturization it is becoming possible to incorporate complex technologies in small devices.[23] The newest developments are microfluidic based diagnostics, the so-called labs-on a chips (LOC's). LOC's are devices that integrate multiple laboratory functions on a single chip of only millimeters to a

few square centimeters in size and are capable of handling extremely small fluid volumes down to less than pico liters.[24;25]

The GeneXpert platform, a cartridge based real-time PCR system (already described in the introduction), is available in bench top and handheld devices and is already used in clinical settings.[26]

A step further is the integration of POC tests with mobile phones. The development of cellphone-based devices is promising but still is in its infancy.

In Rwanda a phone attachment using disposable cartridges was evaluated as part of a United States Agency for International Development (USAID) program on maternal health for the rapid detection of HIV and syphilis. A low-cost dongle performed a triplex immunoassay: HIV antibody, treponemal-specific antibody for syphilis, and nontreponemal antibody for active syphilis infection. The test analyzed whole blood obtained from a fingerprick and the smartphones showed the results after 15 minutes. In the Rwandese study 96 pregnant women provided samples and the POC test had a sensitivity of 92 to 100% and specificity of 79 to 100%.[27]

Likewise, in other fields of medicine there has been a rapidly growing trend toward the use of cellphone-based devices. For example in Ghana two different phone based microscopes were evaluated for the detection of *Schistosoma haematobium* infection: the mobile phone-mounted Foldscope and reversed-lens CellScope had sensitivities of 55.9% and 67.6%, and specificities of 93.3% and 100.0%, respectively, compared with conventional light microscopy.[28]

The changing landscape of STI care

Globally, all regions of the world are gaining access to internet and mobile phones (figure 1). In 2014, nearly 60% of the population worldwide already owned a mobile phone. The mobile phone penetration is forecasted to continue to grow, rounding up to 67 percent by 2019.[29;30] This trend facilitates the possibilities of mobile health.

Besides the above described cellphone-based devices, the concept of mobile health is much broader; the rapidly evolving field includes the development of mobile phone applications concerning medication adherence, health worker communication, health education, drug supply chain, health cost payments, partner notification and emergency and disaster response.

Especially in LMIC's, mobile health has the potential to enhance equitable distribution of healthcare to the marginalized areas and vulnerable populations groups.[31;32] But also in high-income countries like the Netherlands equal accessibility to STI care is not optimal and mobile health may help to improve this.

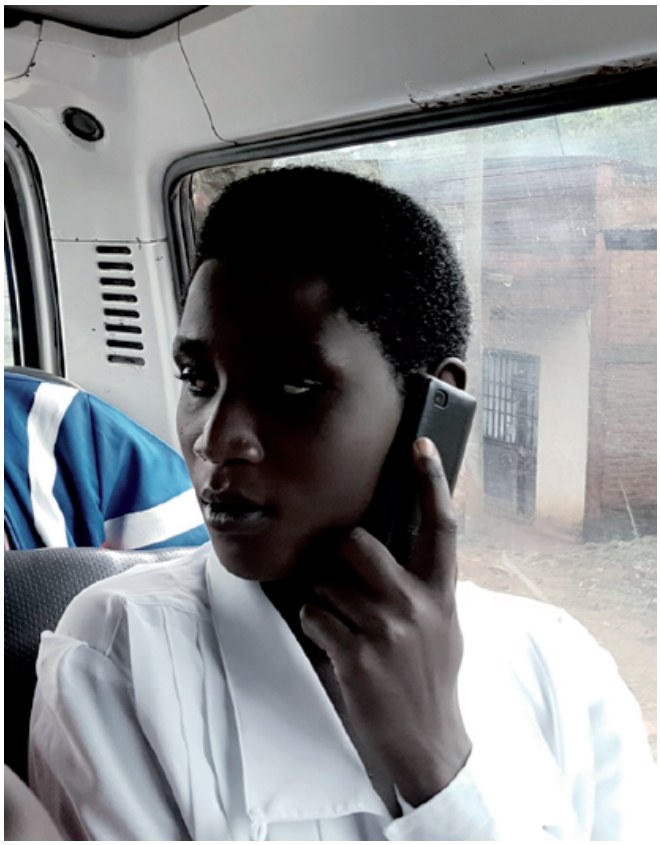

Figure 1. Worldwide people are gaining access to internet and mobile phones. Self-tests for STI's that are connected with mobile phones, the so-called cellphone-based devices, are under development. These technologies have the potential to make diagnostic testing broader accessible in the future (photo made by Menne Bartelsman in Rwanda).

POC self-tests for various STI's are increasingly offered online, unfortunately also by non-reliable commercial parties. In contrast to HIV, hepatitis C virus and syphilis, no reliable antibody-based POC tests are available for chlamydia and gonorrhoea as these infections are confined to mucosal tissue and normally invoke little to no production of antibodies.[8;33] In spite of their low diagnostic accuracy, various commercial POC self-tests for chlamydia and gonorrhoea are offered online and even in drug stores in the Netherlands. Although the manufacturers claim high sensitivities and specificities found in an artificial laboratory setting, independent confirmation of these results in a real-life trial setting failed.[8;34] Even more disturbingly, when these criticized tests are taken from the market they subsequently reappear under different commercial names.[35] Unfortunately there is not sufficient legislation that restricts the proliferation of these misleading self-tests.

As long as no reliable and simple POC tests for chlamydia and gonorrhoea are available, the only acceptable current alternative for self-testing is to offer molecular self-sampling, and samples subsequently have to be send to a central

laboratory. This service is already implemented for asymptomatic patients at the STI outpatient clinic in Amsterdam. However, these patients still have to visit the clinic for self-testing and stigmatization and embarrassment related to clinical attendance can be a barrier.[36]

In England online clinical pathways are explored (eSTI2 consortium[37]) whereby all steps in STI care like self-testing, partner notification and electronic prescription can be arranged with a smartphone application. A qualitative study was conducted about the acceptability of this service among young adults in London. In-depth interviews revealed that young adults were enthusiastic about online self-testing service and suggested that they would use it and test more often if it were routinely avialable.[36] A cost-effectiveness study from the USA suggested that internet STI testing and electronic prescription cost less per STI detected than a standard clinic-based STI testing.[38]

In the near future, self-testing of chlamydia, gonorrhoea and other STI's will probably further improve with the commercialization of new emerging smaller POC techniques, like the cellphone-based devices described earlier in this chapter.

A challenge when offering online POC self-tests for STI's will be to guarantee a proper surveillance, partner services, privacy and linkage to care and treatment.[33;39] Nevertheless, the shift to more online POC self-testing is inevitable in an era in which younger generations are used to do almost everything with their mobile phone.

These trends will change the traditional STI outpatient clinic as we know it today; most likely the STI outpatient clinics of the future will follow the trend of 'clicks an bricks' that a lot of other customer services like stores are already gone through.[40] A smart integration of both offline (bricks) and online (clicks) presence will be needed to secure the cost-effectiveness and quality of care. While electronic health has the potential to be cost saving (less staff and overhead costs), new technological advanced POC platforms will demand extra investment costs for clinics.

Patient contributions towards the costs of STI care should also be further explored. Although in the Netherlands patient contributions are not allowed legally within public health care settings, this option can be a solution of equal access to STI care for all risk-groups. Nowadays, the current policy in the Netherlands just guarantees free unlimited access of higher risk-groups (mainly MSM and young heterosexuals). A relative big group with lower risk for STI's are excluded now and are forced to pay costly STI tests at the general practitioner clinics. It is questionable if this current system is fair and if own responsibility should not be addressed to all risk-groups. More research is needed to investigate alternative

online clinical pathways in which willingness to pay for a STI (self) tests should be an important outcome.

Although this thesis is about POC testing of STI's, a few comments addressing therapeutic perspectives for STI's should be added. In contrast to the encouraging development of diagnostics, the development of novel treatments for STI's (and for bacterial infections in general) are lagging far behind. The discovery of penicillin in 1928 by Alexander Fleming was the start of the so called 'Golden Age' of antibiotic development that longed until the 1980's. Since then the development pipeline is constrained, especially for those that tackle lethal multidrug-resistant Gram-negative bacteria like *Neisseria gonorrhoeae*. The number of U.S. Food and Drug Administration (FDA) approvals of systemic antibiotics has declined by 90% during the past 30 years. Pharmaceutical and biotechnology firms are reluctant to invest in the development of novel antibiotics because the market return is risky and relatively unprofitable.[41;42]

Concluding remarks

The global burden of STI's is increasing and current approaches to STI control like syndromic management in LMIC's are inadequate to control the spread of STI's. POC tests can play a future role in improving STI care and controlling the epidemics.

In LMIC's syndromic management of STI's causes a lot of under- and overtreatment and there is an urgent need for affordable and reliable POC tests for STI's like chlamydia and gonorrhoea. Also in high-income countries like the Netherlands POC tests can play a major role in improving future STI care. In both settings POC management of STI's has the potential to be more effective; prompt treatment can reduce STI transmission, avert long-term sequelae of untreated infections, improve partner notification and treatment and reduce overtreatment (in case of syndromic management) and associated induction of antimicrobial resistance.

Mobile health has the potential to further expand the scope of POC testing and can be advantageous by removing cultural and geographical barriers. Whether online clinical POC pathways are a strategy to tackle these barriers has to be further explored.

In the current political climate, where there is a tendency to economize on (public) health care and shift towards more self-reliance, equal access to STI care is under constraint. A fair system whereby all patients equally contribute a small amount of money for their tests could be a possible solution. In the dynamic and evolving landscape of public STI care cost-effectiveness studies will be increasingly important.

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