Gonorrhoea in Indonesia and the Netherlands

*Diagnostics and antimicrobial resistance*

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CHAPTER I: INTRODUCTION

*Neisseria gonorrhoeae* and gonorrhoea – Definition and diagnosis

Gonorrhoea is a sexually transmitted infection (STI) caused by *Neisseria gonorrhoeae*.\[1-3\] *N. gonorrhoeae* are aerobic, Gram negative diplococci bacteria that belong to the *Neisseriaceae* family, together with *N. meningitidis* and several other commensal bacteria of human pharynx, such as *N. lactamica, N. subflava, N. cinerea*, and *N. sicca*.\[4-5\]

In humans, *N. gonorrhoeae* can infect the mucosal tissue of the genitalia, rectum, and pharynx.\[2-3\] A total of 78 million new gonococcal infections worldwide are estimated to occur annually.\[1\] Overall, urogenital infections comprise the majority of the total gonorrhoea cases.\[2,6\] Yet, extra-genital infections also play significant roles in sustaining the gonorrhoea epidemiology, especially in men who have sex with men (MSM).\[6-7\]

Muco-purulent discharge is a typical symptom of uncomplicated gonorrhoea, while several possible complications may occur, including pelvic inflammatory disease (PID), infertility, and life-threatening disseminated gonococcal infections.\[2-3\] A syndromic approach is a method to diagnose gonorrhoea based on the presence of symptoms or signs in genitalia, rectum, or pharynx.\[8\] This method is frequently practiced in resource-limited settings, e.g. in developing countries such as Indonesia, or in outreach health services.\[8-10\]

Yet, gonococcal infections are often clinically asymptomatic, especially among women, and in rectal and pharyngeal infections.\[1-3\] Asymptomatic individuals play an important role in ongoing gonococcal transmission, as they tend to remain undiagnosed and untreated while remaining sexually active.\[11\]

To improve gonorrhoea diagnostics, several laboratory methods are used, i.e. light microscopic examination, bacterial culture, and nucleic acid amplification tests (NAAT).\[4,12\] The variety of diagnostic methods may influence the observed epidemiological patterns of gonorrhoea in different settings and regions.
For light microscopic examination, samples are obtained from possibly infected sites. A smear is produced, stained (commonly using the Gram method) and examined under a microscope using 1000x magnification and oil immersion. *N. gonorrhoeae* will appear as pink diplococci inside polymorphonuclear leucocytes (known as intracellular Gram-negative diplococci [IGND]).[4,9,13] Light microscopy is a simple, cheap, and quick laboratory method to diagnose gonorrhoea. Yet, its accuracy is often questioned, especially when examining endocervical, rectal, or pharyngeal (i.e. non-urethral) samples.[4,13]

For bacterial culture to isolate *N. gonorrhoeae*, samples are obtained and inoculated onto a growth medium and incubated under appropriate conditions (37°C, 5% CO₂) for about 48 hours.[4,14] Several methods are used to identify colonies grown in culture, i.e. morphology (macroscopy and microscopy), biochemistry (e.g. oxidase and peroxidase tests), and genotypic tests (for example deoxyribonucleic acid [DNA]-probing). Strains isolated via bacterial culture can be used for antimicrobial susceptibility determination, either via a dilution or via a diffusion method.[15-16] However, the culture requires more time than direct microscopy. In addition, the culture procedure requires more complex instruments and an appropriate laboratory setting.[4,12]

NAAT is nowadays considered the standard diagnostic for gonorrhoea because of its high sensitivity and specificity.[4,17-18] In NAAT, samples are tested to detect the presence of specific parts of *N.gonorrhoeae* DNA or ribonucleic acid [RNA], for example 12 *opa* genes.[18] However, NAAT is not available everywhere, due to its high prices, the required infrastructure and the need for qualified personnel.

**Treatment failure and antimicrobial resistance**

Extended spectrum cephalosporins (ESCs), such as ceftriaxone, cefixime, and cefotaxime, are currently the first line treatment for *N. gonorrhoeae* infections.[2] In general, ESCs show good clinical efficacy. Yet, the emergence of *N. gonorrhoeae* strains with reduced susceptibility or resistance to ESCs have been reported from studies in various countries.[19-21] For this reason, cefixime and cefotaxime have
been abandoned in most treatment guidelines, leaving ceftriaxone the sole first line option.

*N. gonorrhoeae* is one of the antimicrobial-resistant (AMR) pathogens which are prioritized by the World Health Organization. This implies that it is considered an emerging and global potential threat that requires intensified research, surveillance, and the development of new antimicrobials.[22] *N. gonorrhoeae* has a capacity to develop antimicrobial resistance against various drugs in a relatively short period.[23] In the past, several older drugs like penicillin, tetracycline and quinolones had to be abandoned due to emerging AMR *N. gonorrhoeae* strains.[2,23] AMR bacteria are assumed to be a consequence of inappropriate use of antimicrobial drugs, especially in settings where accurate diagnostic tools are not available.[12] Gonorrhoea treatment may become problematic, as no alternative is available when cephalosporin resistance will become widely prevalent.

Pharyngeal gonococcal infections may play an important role in the emergence of AMR strains.[23-24] This is probably caused by the unfavourable pharmacological and pharmacodynamical conditions in the pharynx that hamper effective eradication of infections with *N. gonorrhoeae*. Horizontal transfer of resistance genes can occur across species, especially in locations where genetically-related strains reside. As the pharynx is the natural environment for many *Neisseria* species,[5-6] this may occur in the pharynx.

**Current situation in Indonesia**

The Ministry of Health of Republic of Indonesia (MoH-RI) organizes a periodic national surveillance in sexual health (the Integrated Biological and Behavioral Survey [IBBS]).[25] In 2013, the Indonesian IBBS report showed a continuing high prevalence of gonococcal infection, especially among MSM (21.2%), transwomen (19.6%), and female sex workers (17.7-32.2%). The IBBS reports also mentioned a low proportion of consistent condom use in the Indonesian population (20-40%) that might contribute to the epidemiology of gonorrhoea and other STDs in Indonesia. However, the IBBS reports lack important data such as epidemiology of asymptomatic cases, risk factors for gonorrhoea and antimicrobial susceptibility.
To diagnose gonorrhoea and other STDs, syndromic approach is generally implemented in Indonesian health care facilities.[9] The approach is not only used in outreach settings, but also in institutional settings (such as community health centers, known as “puskesmas”, private clinics, and hospitals). In addition to syndromic approach, light microscopic examination of Gram-stained samples to support a urogenital gonorrhoea diagnosis is recommended by the Indonesian national guideline for the management of STI.[9] A routine bacterial culture is not recommended by the guideline, and is only performed in large facilities, such as some academic hospitals. NAAT is generally absent, and presumably is used for research purposes only.

According to the Indonesian guideline, gonorrhoea is to be treated with cefixime (400 mg, single dose, oral), or ceftriaxone (250 mg, single dose, intramuscular injection).[9] The guideline also recommends additional treatment with azithromycin (1 gram, single dose) or doxycycline (200 mg daily, for 7 days) for the presumptive treatment of chlamydia.[9]

In Indonesia self-medication using “over-the-counter” drugs is a common practice. As a result, antimicrobial drugs are used frequently without proper medical guidance, resulting in the emergence of AMR pathogens in the community.[26] This undesired practice might have implications for the spread of AMR gonorrhoea strains.

In Indonesia, several key populations such as sex workers, men who have sex with men, and transwomen are strongly stigmatized by the society.[27-28] This hampers the access of these groups to institutionalized health care facilities (e.g. puskesmas or hospitals). The delivery of health care services to these groups is often only possible through outreach services performed in collaboration between clinics and community-based non-governmental organizations.

**Impact of sexual networks on the spread of gonorrhoea and antimicrobial resistant strains**
For a successful control of gonorrhoea and STDs in resource-limited settings, key populations need to be identified. In addition, the overall risk to contract gonorrhoea in the population is largely determined by the characteristics of sexual networks.[29] It is therefore important to examine the spread of STIs and antimicrobial resistance in the light of population mobility. For example, in the 1980s, quinolone-resistant *N. gonorrhoeae* emerged first in the South-East Asian region and consecutively spread globally within 10 years.[23]

Traditionally, sexual networks are identified through clients’ self-reported sexual history.[30] However, this approach is limited by recall bias, socially desirable responses, and privacy issues.[30-31] To provide information on the spread of bacterial strains in different populations, molecular typing techniques, such as Multiple-Locus Variable Number Tandem Repeat (VNTR) Analysis (MLVA) and Ng Multi-Antigen Sequence Typing (NG-MAST), are nowadays used.[31-33]
Thesis outline and data source

The studies in this thesis were performed to provide additional insights in the diagnostics of gonorrhoea and antimicrobial resistance of *N. gonorrhoeae*, in two contrasting settings, i.e. a resource-limited setting in Indonesia and a resource-rich setting in the Netherlands.

Part I (consisting of chapters 2 to 5) elaborates on aspects of gonococcal infection (diagnostics, epidemiology, antimicrobial resistance [AMR] and prevention) in the Indonesian population.

Chapter 2 assesses the value of light microscopy to diagnose urogenital gonorrhoea, using NAAT as the reference. Chapter 3 describes the epidemiology of asymptomatic urogenital gonorrhoea and the antimicrobial resistance profile of *N. gonorrhoeae* strains in Indonesia. Chapter 4 describes the molecular epidemiology of *N. gonorrhoeae* strains circulating in three major Indonesian cities as reported in chapter 3, and its relation to strains circulating in Amsterdam, the Netherlands. Chapter 5 examines condom use among Indonesian MSM and transwomen populations and analyses the characteristics of sex partners in relation to condomless anal sex.

In Part II (consisting of chapters 6 and 7), we focused on pharyngeal gonorrhoea, based on studies in patients at the STI clinic, Amsterdam, the Netherlands. Chapter 6 describes spontaneous clearance in untreated pharyngeal gonorrhoea at the STI clinic, Amsterdam, the Netherlands. Chapter 7 describes persistence among pharyngeal gonorrhoea cases that were treated using a standard treatment of 500 mg ceftriaxone (intramuscular injection) at the STI clinic, Amsterdam, the Netherlands.

In general discussion in chapter 8, the main findings of the studies are discussed and related to relevant literature. Suggestion and recommendations for future studies are presented.
Table 1. Summary of design and data source of studies included in the thesis
“Gonorrhoea in Indonesia and the Netherlands: diagnostics and antimicrobial resistance

<table>
<thead>
<tr>
<th>Chapter Number</th>
<th>Main Research Questions</th>
<th>Study Design</th>
<th>Source of Study Population</th>
<th>Period of Data Collection</th>
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<tbody>
<tr>
<td>2</td>
<td>What is the accuracy of syndromic approach and light microscopy of Gram-stained urogenital smears (detection of intracellular Gram negative diplococci, IGDN; and polymorphonuclear leukocytes count, PMNL) to diagnose urogenital gonococcal infections, compared to nucleic acid amplification tests (NAAT)?&lt;br&gt;&lt;br&gt;Is there variability in the accuracy of light microscopy to diagnose urogenital gonococcal infections (by infections locations, symptomatology, and format of clinic services)?</td>
<td>Cross-sectional, diagnostic test study</td>
<td>Males (including transwomen who did not undergo genital reconstructive surgery) and females who visited clinic-based and outreach STI service facilities in Jakarta, Yogyakarta, and Denpasar, Indonesia.</td>
<td>January-December 2014</td>
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<td>3</td>
<td>What is the prevalence of asymptomatic urogenital gonorrhoea in Indonesia?&lt;br&gt;&lt;br&gt;What are factors associated with asymptomatic urogenital gonorrhoea in</td>
<td>Cross-sectional study</td>
<td>Patients (males, females, and transwomen) who visited clinic-based</td>
<td>January-December 2014</td>
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<td>Question</td>
<td>Study Type</td>
<td>Study Details</td>
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<td>How is the antimicrobial resistance profile of <em>N. gonorrhoeae</em> strains circulating in Indonesia?</td>
<td>Cross-sectional study</td>
<td>1) Patients of clinic-based and outreach STI service facilities in Jakarta, Yogyakarta, and Denpasar, Indonesia. 2) Patients at the STI clinic, Amsterdam, the Netherlands, with a positive <em>N. gonorrhoeae</em> culture which were fully susceptible</td>
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<tr>
<td>How is the distribution of Indonesian <em>N. gonorrhoeae</em> strains typed using Multi-Antigens Sequence Typing (NG-MAST) and Multi-locus Variable Number Tandem Repeat Analysis (MLVA) techniques, by age groups, geographical locations, and risk groups of the patient?</td>
<td>Cross-sectional study</td>
<td>1) Patients of clinic-based and outreach STI service facilities in Jakarta, Yogyakarta, and Denpasar, Indonesia. 2) Patients at the STI clinic, Amsterdam, the Netherlands, with a positive <em>N. gonorrhoeae</em> culture which were fully susceptible</td>
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<td>Is there any relation between <em>N. gonorrhoeae</em> strains circulating in Indonesia and in Amsterdam, the Netherlands?</td>
<td>Cross-sectional study</td>
<td>1) Patients of clinic-based and outreach STI service facilities in Jakarta, Yogyakarta, and Denpasar, Indonesia. 2) Patients at the STI clinic, Amsterdam, the Netherlands, with a positive <em>N. gonorrhoeae</em> culture which were fully susceptible</td>
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<td>How is the concordance between NG-MAST and MLVA techniques in Indonesian <em>N. gonorrhoeae</em> strains?</td>
<td>Cross-sectional study</td>
<td>1) Patients of clinic-based and outreach STI service facilities in Jakarta, Yogyakarta, and Denpasar, Indonesia. 2) Patients at the STI clinic, Amsterdam, the Netherlands, with a positive <em>N. gonorrhoeae</em> culture which were fully susceptible</td>
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<td>Question</td>
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<td>Time Period</td>
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<td>5</td>
<td>What is the prevalence of condomless anal intercourse (penetrative and receptive) among MSM and transwomen in Indonesia?</td>
<td>Cross-sectional study</td>
<td>MSM and transwomen who visited clinic-based and outreach STI service facilities in Jakarta, Yogyakarta, and Denpasar, Indonesia.</td>
<td>January-December 2014</td>
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<td></td>
<td>What are characteristics of sex partners associated with condomless anal intercourse (penetrative and receptive) among MSM and transwomen in Indonesia?</td>
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<td>6</td>
<td>What is the prevalence of spontaneous clearance in untreated pharyngeal gonococcal infections?</td>
<td>Retrospective cohort study</td>
<td>Patients at the STI clinic, Amsterdam, the Netherlands with pharyngeal gonococcal infections who were not treated immediately at the first consultation and returned for a follow up visit (had a new sample collected for a second NAAT) prior to administration of antibiotics treatment.</td>
<td>January 2012-August 2015</td>
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<td>What are factors associated with spontaneous clearance in untreated pharyngeal gonococcal infections?</td>
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<td>7</td>
<td>What is the prevalence of persistence in pharyngeal gonococcal infections that were treated using 500 mg ceftriaxone intramuscular injection?</td>
<td>Retrospective cohort study</td>
<td>Patients at the STI clinic, Amsterdam, the Netherlands, who were diagnosed with pharyngeal gonococcal infections (between January 2012 and August 2015) and received a treatment of intramuscular injection of 500 mg ceftriaxone (as monotherapy or was combined with other antibiotics), and returned for a test-of-cure 7-28 days after treatment administration.</td>
<td>January 2012-August 2015</td>
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