PUBLIC HEALTH ECONOMICS OF CHLAMYDIA AND OTHER STIs

- Aspects of risk, prevention and resources

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ABSTRACT

The overall aim of this thesis was to increase the knowledge of the public health economic aspects of chlamydia and other STIs, in terms of risk, prevention and resources.

In Study I, we examined the association between demographic, socioeconomic and lifestyle factors and the risk of self-reported chlamydial infection among young adults in the Stockholm public health cohort. We found that the risk of self-reported chlamydia infection among young adults in Sweden was associated with lower age, high alcohol consumption, lower educational level and being employed or unemployed, on sick leave or pre-retired compared to being a student.

In Study II, we identified potential key factors for successful regional prevention of chlamydia and other STIs by a case study including seven Swedish counties. We found that potential key factors include adequate programme- and county council investments, suitable organizational structure, strong leadership, management of regional networks, research connection, multiple local collaborations, high testing coverage and a strategic risk approach.

In Study III, we analyzed the cost-effectiveness of the intervention Chlamydia Monday by estimating costs, savings and health gains generated by the intervention and analyzed whether the cost-effectiveness varied between men and women. We found that this testing intervention of a self-selected sample of individuals was cost-effective for both sexes with a discounted average cost of €8,346 per QALY. Sensitivity analyses showed consistent results for changes in parameters, and all scenarios except exclusion of contact tracing for males, generated a cost per QALY below the established threshold.

In Study IV, we estimated the additional resources required to scale up adolescent-friendly health services to universal coverage in 74 low-and middle-income countries. We found that the financial costs for scaling up key adolescent-friendly health services was US$ 15.4 billion through 2015. The cost for STI management was approximately US$ 226.97 million of which approximately 20% constituted management of chlamydia. The estimated required resources illustrate a substantial investment gap in relation to current expenditure.

In conclusion, the thesis illustrates a public health economic approach to studying STI-prevention. The findings show that chlamydia in young adults in Stockholm is associated with social and lifestyle factors, that greater consideration should be taken to the structural factors of prevention, that one of the common testing interventions implemented in many parts of Sweden is cost-effective and finally that considerable investment is required to improve quality and expand reproductive health care services to universal coverage for adolescents in the least developed countries in the world.
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<tr>
<td>AFHS</td>
<td>Adolescent-friendly health services</td>
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<td>AFR</td>
<td>WHO African Region</td>
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<td>AIS</td>
<td>Aids Indicator Survey</td>
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<td>AMR</td>
<td>WHO Region of the Americas</td>
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<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<td>CHW</td>
<td>Community health worker</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CMO</td>
<td>County medical officer</td>
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<td>DHS</td>
<td>Demographic health survey</td>
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<td>EMR</td>
<td>WHO Region of the Eastern Mediterranean</td>
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<td>EUR</td>
<td>WHO European Region</td>
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<td>GBD</td>
<td>Global burden of disease</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HTC</td>
<td>HIV testing and counseling</td>
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<td>HUI</td>
<td>Health utility index</td>
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<td>IEC</td>
<td>Information, education and communication</td>
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<td>IPV</td>
<td>Intimate partner violence</td>
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<td>MDG</td>
<td>Millennium development goal</td>
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<td>MI</td>
<td>Motivational interviewing</td>
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<td>NICE</td>
<td>National Institute of Clinical Excellence (UK)</td>
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<td>NAP</td>
<td>National action plan</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PID</td>
<td>Pelvic inflammatory disease</td>
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<td>PMTCT</td>
<td>Prevention of mother-to-child transmission (of HIV)</td>
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<td>QALY</td>
<td>Quality adjusted life years</td>
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<td>SBU</td>
<td>Swedish Council on Health Technology Assessment</td>
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<td>SEAR</td>
<td>WHO South East Asian region</td>
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<td>SNBHW</td>
<td>Swedish National Board of Health and Welfare</td>
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<td>SMI</td>
<td>Swedish Institute of Infectious Disease Control (Smittskyddsinstitutet)</td>
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<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
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<tr>
<td>TLV</td>
<td>Swedish Dental and Pharmaceutical Benefits Agency</td>
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<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<tr>
<td>USD</td>
<td>United States Dollar ($)</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WPR</td>
<td>WHO Region of the Western Pacific</td>
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<td>WTP</td>
<td>Willingness to pay</td>
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1 INTRODUCTION

The major health burden and economic consequences of sexually transmitted infections (STI) and related disease are in women of reproductive age. STIs present a short term problem but may also be a future threat to reproductive capacity. Genital chlamydia trachomatis, a major STI burden worldwide, is largely asymptomatic which means that diagnosis and treatment is often delayed, increasing the risk of complications. The burden for individuals and health services is large with women being particularly disadvantaged as the major complications in women include pelvic inflammatory disease, ectopic pregnancy and infertility. I initially got engaged in sexual and reproductive health issues because of this particular reason. In my opinion, contemporary young women experience enough added pressure regarding reproduction compared to their male peers, and chlamydia being a preventable and treatable infection, should not be yet another additional, unfairly distributed, burden. Additionally, given the range of sophisticated interventions and technologies for prevention and treatment now available, effective and affordable, much of the ill health and suffering due to STIs in low-and middle-income countries is, in theory, unnecessary.

Later, my interest grew towards the weight that economic evidence can provide in illustrating the societal benefits compared to the costs of prevention. This led me to Anna Månsdotter who involved me in fascinating discussions on economics, health, feminism and life.

Several scientific fields of research contribute to the understanding of prevention of STIs. Medicine, public health, behavioural science, economics and more, all highlight different aspects of this prevalent public health problem. This thesis takes on a public health economic perspective to STI prevention.
2 BACKGROUND

2.1 PUBLIC HEALTH ECONOMICS

There is lack of information about the economic aspects of public health. Costs for public health efforts are commonly determined or monitored based on what the cost is, rather than what the goal of the cost is. Economic decision-making generally describes what alternative actions are relevant and their differential costs. However, public health interventions are rarely adequately linked to determined outcomes before implementation. Hence, to achieve a realistic and appropriately determined course of decision-making, some classical aspects of public health and economic evaluation need to be addressed. This requires approaching a public health problem with economic theory and methodology in mind, taking into account the aspects needed to bridge public health research and public health economic analysis and ultimately feed decision-making with economic rationales.

‘Public health economics’ was first used in 1944 when the journal Public Health Economics was published by the Bureau of Public Health Economics of the University of Michigan’s School of Public Health. The term then encompassed items on governmental health programmes, health insurance plans, public health education and legislation regarding public health. In the foreword of the first issue, the editor Dr Nathan Sinai stated that the publication was a “contribution towards the development of a new and vital blending of the medical and the social sciences” (1). Later, Carende-Kulis proposed an expansion of the scope of health economics research in an area characterized as public health economics—the study of the economic role of government in public health, particularly, but not exclusively, to account for market failures. Public health economics in Sweden has been loosely defined as economics in the sphere of public health. This encompasses measurement of public health by indexes such as Quality-adjusted life years (QALY) and Disability-adjusted life years (DALY), calculations of the societal costs of ill-health, consequence analysis based on determinants of health, gainful and harmful preferences with regard to health, as well as economic evaluations of public health efforts (2).

Economics in public health has mainly focused on the efficiency and effectiveness of programmes by cost-effectiveness or net present value measures, summarized as ‘economic evaluation’ This is performed by methods such as cost analysis, cost-minimization analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). The science of economics could be positive (seeking answers to how it is and why) as well as normative (seeking answers to how it should be). Economic evaluations represent the normative approach since they aim to provide recommendations on societal action with the point of departure in a particular ethical guidance. For interventions aimed at health, the main ethical principle refers to maximizing health given available resources (3). Other ethical principles of relevance to public health economics may refer to Pareto optimum, welfare maximization, and health equality (4).
2.2 PUBLIC HEALTH

Public health has been defined as a ‘social and political concept aimed at improving health, prolonging life and improving the quality of life among whole populations through health promotion, disease prevention and other forms of health intervention’ (5). Thus, public health programmes and interventions target risk factors of disease and factors of health. Health, as defined by the constitution of the World Health Organization (WHO) ‘is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’ (6). Some classical principles of public health provide a useful framework for addressing a public health problem by five steps: surveillance and monitoring of a problem; identification of risk factors; development and implementation of interventions; evaluation; and finally reproduction and expansion of effective policy and programmes (7). Figure 1 illustrates the disciplinary position of the thesis, bridging some of the steps in the classic public health approach with four of the health economic areas defined by Culyer and Newhouse’s (2000) schematic of health economics (8). The black squares represent the public health approach, the blue circles public health economic activities and the green circles represent the thesis.

Figure 1. Disciplinary position of the thesis.
In Sweden, national public health policy is largely governed by the National Public Health Strategy Bill (*En förnyad folkhälsopolitik*, Govt Bill 2007/08:110) and partly by the EU health programme *Together for health 2008-2013*. There are 11 national overarching goals for public health of which mainly No. 6, (health promoting health care), No. 7 (protection against communicable diseases) and No. 8 (sexual and reproductive health) concern STIs.
ECONOMIC THEORY OF RESOURCE ALLOCATION

The fundamental principle behind all economic problems is that resources are always limited and can be used in different ways while need is infinite. Hence, there is the issue of how resources should be allocated. Every time a choice is made, as resources are limited, there is also the cost of the best alternative choice. The estimation of the alternative value depends on which perspective is assumed, since the value for the individual, the health care service or the society is different. These issues of resource allocation have traditionally been addressed by the norms of welfare economics. According to welfare economics, society’s resources should be allocated in a way that maximizes social welfare, which in this context is defined as the sum of the welfare of all the individuals in the society (overall welfare). Individual welfare is measured in utility, which is supposed to represent preference and is judged by the individuals themselves. If the individuals are rational they will attempt to maximize their own welfare by using their own limited resources to consume goods or services that give them the maximum possible utility (9). This understanding is however disputed by some health economists, (Culyer, 1989) who suggests that the welfarist approach could consider other aspects such as equality (referring to similarity) and equity (referring to the principle of fairness) thus taking on an ‘extra-welfarist’ viewpoint.

How social welfare can be maximized is usually described through the competitive market model (10) in which it is assumed that all producers and consumers on the market act as price-takers (i.e. they cannot influence price). This is because of the many other agents on the market competing in selling and buying goods and services. The prices are determined by the equilibrium, when demand equals supply. On the competitive market, consumers try to make decisions on how to use their limited resources that will maximize their utility while producers are trying to produce as much as they can at the lowest possible cost. Their different production possibilities are determined by a production function representing different ways of combining production factors. If there is a fully competitive market it has been demonstrated that the economy will in itself, without any governmental interference, reach an optimum state where no allocation of resources can be made without reducing the welfare (utility level) of any individual. This is known as the First Optimality Theorem and is the grounds for the Pareto criterion, which states that a reallocation of resources is only beneficial to society if it improves the welfare (utility) of at least one individual without reducing the welfare of anyone else (11).

There are various reasons why the competitive model does not hold for the health care market (12). In particular, consumers of health services are often unable to assess either their need or the quality of the service which makes consumers dependent on medical experts (asymmetric information). Additionally, the effects of health services may often concern other people than the consumer (patient, individual at risk etc.) which is generally the case regarding infectious diseases where other people may be exposed to infection if an individual is not vaccinated (externalities). (For more information on this, see Reference 12).

Regarding the consumption of health-enhancing goods and services, the consumers demand is not for the good or service in itself but rather for good health (13).
Individuals invest in themselves in terms of human capital such as education in order to increase their productivity (in their work life in order to increase their income but also to be able to better enjoy their leisure time). While education increases productivity, there are two reasons for demand for health. Firstly, it directly affects their utility (as a consumption commodity) and secondly it affects the total time disposable for work or leisure. Thus, in the Grossman model of human capital, people are not merely consumers but also producers of health. Each individual is born with a certain level of health (health stock) that depreciates with increasing age (time). However, with the use of health investments (health goods and services), people can affect their lifetime by increasing their health level and thus also increase their productivity as well as utility.

2.4 HEALTH ECONOMIC EVALUATION IN PUBLIC HEALTH

2.4.1 Cost-effectiveness analysis

Market failures may generate inefficient outcomes which is why policy interventions or public regulation are used to improve welfare by guiding resource allocation and decision-making. Cost-effectiveness analyses are used to comparatively analyse alternative interventions in terms of costs and benefits and the results are generally presented as an incremental cost per health outcome gained. Usually this is done by presenting the ratio between incremental costs and health gains, which is called the incremental cost-effectiveness ratio (ICER), summarized in the following formula;

\[
ICER = \frac{C_I - C_C}{E_I - E_C}
\]

where Cost\textsubscript{I} represents the cost of the new intervention, Cost\textsubscript{C} represents cost of the best available alternative (usually the standard intervention or procedure), Effect\textsubscript{I} represents the health gains of the new intervention and Effect\textsubscript{C} represents health gains of the best available alternative. The results of the ratio may mean that the intervention is less expensive and more effective than the alternative, which means it is clearly the most cost-effective choice. However the most common scenario usually means that the new intervention is more expensive but generates more health gains, which may imply more as well as less cost-effective. The rationale for decision-making also includes comparing the cost-effectiveness ratio against a threshold value representing the budget constraint or ‘willingness to pay’ (WTP) of that certain health gain. If the ICER is lower than the threshold then the intervention is considered cost-effective.

QALYs have been recommended by the National Institute for Health and Clinical Excellence (NICE) as the main effect outcome measure in health economic evaluations (14). QALYs are calculated by multiplying the remaining life years after an intervention (or the period of time during which the patient would be affected by the disease) by a weight representing the health-related quality of life during those years. One instrument for measuring quality of life is the Health Utility Index (HUI) Mark II. This is a multi-attributable health status classification system and a scoring formula consisting of seven core attributes (sensation, mobility, emotion, cognition, self-care, pain and fertility). This scoring formula is based on standard gamble utilities measured on the general public and scores range from 0 to 1, with 0 representing death and 1 full
health. Thus, the quality-adjustment weight for each health state is multiplied by the time in the state and then summed to calculate the number of quality-adjusted life-years, (for more details on HUI and QALYs see (15) and (16)).

How much one is prepared to pay per QALY generally varies depending on considerations of the principles of need-solidarity and human value. This implies, for instance, that the threshold is dependent on the budget available for health sector investments in a particular country. Within traffic safety in Sweden, decisions on investments have been made on an estimated statistical value of a human life of 16.3 million SEK which generates a willingness to pay of SEK 655,000 per QALY by Persson et al (17). Other estimates have also been applied such as SEK 400,000 per QALY by Hjalte et al (18), and SEK 500,000 per QALY by the Swedish National Board of Health and Welfare (SNBHW) and SBU (19-20). In the UK, NICE suggests a threshold of ~£20-30,000 per QALY as a reference for determining whether or not an intervention is cost-effective and proposes that programmes with an incremental cost-effectiveness ratio of more than £30,000 are unlikely to be considered based on cost-effectiveness (14).

2.4.2 Societal perspective

The most widespread recommendation in Sweden (by for example the Swedish Dental and Pharmaceutical benefits agency (TLV), SNBHW, the Swedish Council on Health Technology Assessment (SBU) and the Swedish National Institute of Public Health (SNIPH) as well as in other countries (NICE) is that economic evaluations should be performed with a societal perspective, although sometimes together with relevant restricted perspectives (21). This includes all relevant costs and benefits regardless of payer or beneficiary. This means that costs and consequences for all sectors are included in the analysis such as patients, local authorities and participants in public health programmes and not merely the health sector (16).

2.4.3 Productivity losses

Productivity losses are the value of production foregone due to an individual’s unperformed work (16). The productivity losses are born not solely by the individual but also to a great extent by other members of society because of social insurance coverage for example. Productivity loss is commonly calculated as the work time foregone multiplied by the value per time unit of this work. The value of the work time can be estimated as the employee’s gross income including social fees, which is usually based on average salaries of the patient group. There are two main methods of estimating the work time: the human capital approach and the friction cost method. Using the human capital approach, the total time that the employee is unable to work is considered and multiplied by the value per time unit. Using the friction method, the amount of production lost due to disease depends on the time-span organizations need to restore the initial production level, (for more details see Reference (22)). Given that the most common recommendation in Sweden is the societal perspective for evaluations, productivity costs should be included in the analysis.
2.4.4 Estimation of costs and benefits

The cost estimation needed for cost-effectiveness analysis and cost-projections summarizes the costs for the intervention that is being assessed. There are different types of costs related to health interventions; resource use within the health care sector (direct health care costs), resource use by patients and their families such as time spent and out-of-pocket expenses (direct non-health care costs) and productivity changes such as sick leave (indirect costs). The perspective of the analysis determines which costs should be included (16). According to the societal perspective, all costs are accounted for regardless of who experiences them while the health care perspective only accounts for health care costs (and not costs for other sectors or agents). Costs of the intervention are usually calculated by quantifying the resource use following the intervention and then multiplying this by the unit costs or prices (ingredients approach) (23).

2.4.5 Models in health economic evaluation

Health economic evaluations can be based on intervention data from implemented scenarios or combined data from interventions, previous studies or estimates from models. In order to evaluate the long term costs and benefits of the intervention, modelling is often required. The increasing use of economic evaluation for decision making has placed increased requirements on researchers in terms of analytic methods. These include the need to incorporate all relevant evidence into the analysis (24). The majority of existing evidence on the cost-effectiveness of chlamydia screening has commonly used decision analysis models including decision trees and Markov models. These models are ‘static’ meaning they assume a constant rate of infection and treat individuals independently from each other in the model structure (25). This makes them particularly suitable when there is a continuous risk of events. Models should strive to depict reality using appropriate estimates according to the disease process and its consequences (24). In the evaluation of an infectious disease, the model must hence be capable of covering all its effects, including the potential for transmission (26). Dynamic models may more accurately reflect the reality of infectious diseases in that they can account for the risk of re-infection or the effects on disease risk over time due to screening activities.

2.5 CHLAMYDIA TRACHOMATIS

Chlamydia trachomatis (throughout the thesis referred to as chlamydia infection or in short chlamydia) is the most common bacterial sexually transmitted infection in the world with an estimated 92 million new cases each year (27). The number of reported cases is increasing in Sweden and many European countries, partly due to increased testing and improved sensitivity of tests. After a steady increase, the number of reported cases stabilized in 2005. However, the decline was shown to be due to a new variant that was discovered the year after, which was not detected by some of the tests used in Sweden at that time. Reports from different counties in Sweden showed a proportion of the new variant of 20–65 % (28). In 2007, the number of reported cases reached a peak in Sweden with about 47,000 reported cases (Swedish Institute of Infectious Disease (SMI)) (29). Figure 2 shows the number of reported cases from year 1997 to 2012.
Sweden was the first country to establish national laboratory surveillance of chlamydia incidence in 1983, and in 1988 the infection was included in Act of Communicable Disease Control and Prevention as a notifiable disease, classified as dangerous to the public. As a result, testing and treatment were offered free of charge and contact tracing and notification to the county medical officer (CMO) and SMI was made mandatory for the testing physician.

The nature of and the proportion of complications following a chlamydia infection is of crucial importance when estimating the severity of the problem, and hence also the cost-effectiveness of prevention programmes. Complications for women include pelvic inflammatory disease (PID), chronic pelvic pain, ectopic pregnancy and infertility. Ectopic pregnancy and tubal infertility are not generally discovered until several years later. PID progression due to chlamydia varies depending on particular population, setting and time but has been estimated to range from approximately 1% among the general population (31-32) to around 30% among high-risk groups (33). Weström et al (1992) showed that the risk of developing complications varies considerably depending on the severity of the PID (34). Some of the major complications of PID include acute and chronic inflammation of the Fallopian tubes (salpingitis). Tubal infertility due to PID has been estimated at 10-12% for first episodes and up to 24% for second episodes (34-35). The risk of chronic pelvic pain due to PID has been estimated to 18% and ectopic pregnancy to 7.8% (34).
However, there are still gaps in the current knowledge about the natural course of a chlamydia infection due to the methodological and ethical difficulties in performing long-term follow-ups. Poor understanding of the incidence of complications and the latent period of chlamydia is still one of the main obstacles in assessing whether chlamydia control activities are likely to be effective or not. A majority of cost-effectiveness analyses of screening of women for asymptomatic chlamydia have commonly used the best existing estimates, which in some cases may be based on case-controls or populations at greater risk of infection or complication than the population for which the programme is designed (for more on this, see Reference (32)).

### 2.6 OTHER STIs

The number of diagnosed cases of gonorrhoea has been increasing in Sweden since early 2000 and diagnosis is more common among men due to an increased spread among men who have sex with men. In 2011, 951 cases of gonorrhoea were reported (incidence of 10 cases per 100,000 inhabitants). Syphilis is relatively rare in Sweden while it is more common in some low-and middle-income countries. In 2011, 206 cases of syphilis were reported (incidence of 2 cases per 100,000 inhabitants). During the last couple of years, a slight increase was seen in Sweden among men who have sex with men, primarily in the urban areas of the country. Regarding HIV, there are approximately 6,200 people with known HIV in Sweden which corresponds to a prevalence of around 65 cases per 100,000 inhabitants (0.06 %). In 2012, 441 new cases were reported of which 69% were infected outside of Sweden. Of all new cases in 2012, 225 (51%) were infected heterosexually, 137 (31%) by sex between men, 22 (5%) via injecting drug use, 13 (3%) were children born outside of Sweden and infected via transmission from mother to child and 3 cases were infected outside of Sweden via blood or blood product (36).

### 2.7 THE SWEDISH NATIONAL ACTION PLAN FOR CHLAMYDIA PREVENTION

In 2009, SNBHW developed a National Action Plan for Chlamydia Prevention focusing on adolescents and young adults (NAP) (37). The NAP recommendations underline improved counselling and partner tracing and increased availability and accessibility to health services, particularly for most at risk groups. Schools and youth centres are mentioned as main arenas for effective prevention. Uniform communication and information is emphasized as well as improved collaboration within and outside the health care sector.

### 2.8 PREVENTION

There are many different strategies to reduce the exposure to STIs including classical primary prevention efforts such as condom promotion and distribution as well as secondary prevention such as testing and treatment. The concept of the reproduction number ($R_0$) (38-39), has been crucial to the understanding of the epidemiology of STIs and helped rationalize prevention strategies (40). $R_0$ describes the average number of secondary infections generated by an infected individual when entering a fully susceptible population and is determined by three parameters: $\beta$, which represents the per-capita transmissibility of the agent; $c$, the pattern of contact between susceptible
and infectious individuals; and D, the average annualized duration of infection: $R_0 = \beta cD$. When the reproduction number is greater than 1, it defines an increase of infection in the population (i.e., ecological success of the pathogen). STI prevention programmes can be linked with each of these parameters. Increased condom use reduces transmissibility ($\beta$), behavioural interventions aim at reducing the number of individuals exposed by increased condom use and reduced number of sexual partners (c), and treatment reduces the duration of infection via screening, testing and contact tracing (D). Transmission of STIs in the population is thus largely dependent on large scale testing or screening programmes and sexual health units offering individuals the possibility for testing and treatment.

Traditionally in Sweden, standard preventive measures applied include contact tracing, different types of increased access to testing via drop-in and opening hours specifically for testing and condom distribution with information to adolescents and young people. Opportunistic screening is provided in STI- and youth clinics when patients come for example contraceptive counselling, but no official screening programme is in place.

### 2.9 ADOLESCENTS AND YOUNG ADULTS

The bulk of the STI burden, both in Sweden and globally, is carried by adolescents and young adults. In 2012 in Sweden, 85.6% of reported chlamydia cases were in 15-29 year olds. Globally, this particular group is generally perceived as healthy (41) but faces several different health issues such as sexual and reproductive health problems, substantial barriers to health care, endemic diseases and increasing mental ill-health (42). The UNICEF (2011) call for continued investment in youth health argues that “adolescence is an age of opportunity for children and a pivotal time for us to build on their development in the first decade of life, to help them navigate risks and vulnerabilities, and to set them on the path to fulfilling their potential.” In general, there is a trend in international policy making to focus a disproportionate emphasis on targeting resources at the under 5s as means of securing the health of future generations (43). Despite substantial overall improvement in health, global health inequalities still exist and are likely to affect adolescents and young people to a great extent. Research shows that important changes occur beyond the age of 5, and early adolescence and that investment in early years will not be fully effective unless followed up (44). This underlines the UNICEF call that adolescence represents a time of opportunity.

### 2.10 HEALTH CARE SYSTEMS

#### 2.10.1 Provision of health care

The core of all health systems is health care, which accounts for one of the largest areas of spending by both governments and individuals. The primary objective of health systems is to ensure the quality of care and safety of the people it serves. The main goals are good health, responsiveness to the expectations of the population, and fair financial contribution (45). The report “Everybody’s business: Strengthening Health Systems to Improve Health Outcomes” deconstructs health systems into six operational building blocks: service delivery, human resources, health information systems, access to essential medicines, financing, and leadership/governance (46-47). Service delivery
is a direct output of the inputs into the health system, such as the financing, the health care workforce and the procurement and supply of essential medicines.

2.10.2 Coverage of health care

The World Health Assembly Resolution 58.33 from 2005 (48) states that everyone should be able to access health services and not be subject to financial hardship in doing so. ‘Universal coverage’ requires that all people obtain the health services they need without the risk of severe financial problems linked to paying for them. Furthermore, the resolution states that the health services people receive need to be of good quality (49-50).

Tanahashi’s conceptual framework for coverage proposes five different ways of measuring coverage: **Availability** (the proportion of health facilities providing health services to adolescents); **Accessibility** (the proportion of adolescents who can reach and use the service); **Acceptability** (who are willing to use the service); **Contact** (the proportion of adolescents who actually use the service); and **Effective** (the number of people who have received satisfactory service) (51). Coverage is thus the proportion of the population in need for whom services are available/ accessible/ acceptable or being used by them. For adolescents, coverage is hence the number of adolescents for whom services are available/ accessible/ acceptable/ being used, divided by the number of adolescents who need the services. In sexual and reproductive health, indicators such as unmet need for family planning, adolescent fertility rates, contraception rates, births attended by skilled health personnel and antenatal care attendance are often used to estimate coverage rates.

2.10.3 Quality of health care

Quality of care has been defined as ‘the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge’ (52). Donobedian conceptualized three quality-of-care dimensions. **Structure** (the attributes of settings where care is delivered) refers to how the context in which care is delivered affects processes and outcomes. For instance, if the facility is an unpleasant place to be, patients will not come, workers will not do a good job, and children will not be immunized. **Process** (whether or not good medical practices are followed), for example, whether the waiting room is clean. **Outcome** (impact of the care on health status) indicates the combined effects of structure and process, for example if children are up to date on vaccinations (for further reading see reference (53)). In Sweden, SNBHW proposed ‘National indicators for quality care’ including regulation for quality and patient safety (54). Internationally, the WHO-Recommended Quality-of-Care Framework (55) suggests that a health system should seek to make improvements in six areas or dimensions of quality (effective, efficient, accessible, acceptable/patient-centred, equitable and safe). Based on the WHO-recommended quality-of-care framework, the adolescent-friendly health services approach (AFHS) was developed (56-58). To be considered adolescent-friendly, services should be **equitable, accessible, acceptable, appropriate and effective**. AFHS defines a detailed list of adolescent-friendly characteristics that could contribute

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1 In Swedish: Nationella indikatorer för god vård. Socialstyrelsen (2009)
to making health facilities and other points of health service delivery more adolescent-friendly. They are organized according to the five broad dimensions of quality listed above. This list was created from a longer list of characteristics developed at the WHO Global Consultation in 2001 and in following discussions (58). Box 1 illustrates a case example of the need for AFHS.

Box 1. Case example of the need for adolescent-friendly health services.

The nurse who prescribed blame for young patients

Dr Kaya, a specialist in reproductive health at a city hospital, is on secondment at a rural health centre 200 kilometres away. She is travelling with an outreach worker as part of a Ministry of Health quality improvement programme. Her task is to observe the work and to identify the needs for staff, equipment and training. Dr Kaya is with the nurse, a woman in her late 30s who has a reputation for being forceful and energetic. Dr Kaya is impressed with the efficient way she keeps the patients flowing. Her brusque manner is probably a result of the pressure. The next patient, a girl of 16, stares at the ground and says in a hardly audible voice, that she hurt herself ‘down there’. She shows the nurse sores around her vagina and says she has been having a discharge. This is clearly a sexually transmitted infection and the nurse tells her so loudly, so that her voice carries to the queue still waiting in the corridor outside. The girl utters something inaudible. “Don’t tell me you did it just once,” says the nurse. “That’s what you all say. You got this from a man who has been sleeping around.” All this time she is giving the girl an injection and making up a package of pills. She gives her instructions on how to take the pills, although it seems to Dr Kaya the girl is not listening, but wishing she was somewhere else. As the girl stands up to leave, the nurse stands in front of her and waves her finger. “Listen to me. When an unmarried girl has sex it is a sin. When she has sex with a married man, the disease is her punishment. Next time it could be worse — you could get AIDS and die. It will be your fault.” The girl leaves weeping and clutching her medicine, and the nurse glares at the doctor. “I can see you think I am being a bit hard,” she says. “That’s how it is with these up-country girls who have no morals. I have to scare them — and it works,” she says defiantly. “How do you know it works?” Dr Kaya asks gently. “Because they never come back,” says the nurse, triumphantly.

2.11 PREVIOUS RESEARCH

2.11.1 Risk groups by social and lifestyle factors

Strong risk factors for chlamydia and other STIs include a young age at first sexual intercourse, multiple lifetime sexual partners, and a history of STIs. Furthermore, health risk behaviours such as smoking, drinking and substance use may affect the risk of STIs by association with sexual risk behaviour (60-63). Low educational level (64) and starting smoking or drinking at an early age have also been shown to be associated with increased risks of STIs (65). Research from the US and the UK shows that groups with high prevalence of chlamydia infection are more often non-white, belong to ethnic minorities (66-67) and have a lower socioeconomic status (68). In Sweden, little research has been published on the risk factors for chlamydia among young adults and, currently, no distinct groups have been identified for targeted intervention aimed at reducing the spread of this disease. A study of adult patients (mean age 27.8 years) attending a drop-in STI clinic in Umeå, showed that socioeconomic factors (education level and occupation) were highly correlated with present chlamydia infection among women, when adjusted for sexual behaviour factors (69). Regarding adolescents, a Swedish study of upper secondary school students showed that girls and boys in vocational programmes displayed substantially more risky sexual behaviour than peers in theoretical (more academic) programmes (70). Low socioeconomic status, generally indicated by low income, low education or low occupational status, is known to be of importance in a range of negative health outcomes such as smoking and hazardous drinking. These individuals may be more prone to taking sexual risks as well. Unfavourable social determinants of health add to the context in which multiple factors indirectly contribute to infectious disease. The epidemiologic context hence mediates the relationship between social position and STIs.

2.11.2 Effective prevention

A review of reviews of the effectiveness of non-clinical interventions (71) shows there is sufficient review-level evidence to conclude that interventions are more likely to be effective if theoretical models are used in developing interventions, interventions are targeted and tailored, provide basic, accurate and unambiguous messages and use behavioural skills training. Furthermore, the most successful interventions are multicomponent interventions that address a range of personal and structural determinants of risk simultaneously. A review of the effectiveness of interventions to prevent STI and HIV in heterosexual men concludes however, that few existing studies are methodologically rigorous and that no consistently effective approach to reduce infections or change behaviour has been identified (72).

Sex education in schools has been shown to be an effective tool to increase young people’s ability to protect themselves from STIs, increase their knowledge and enable them to communicate about sex (73). Sexual educative programmes in schools including visits to health care clinics with information about health care- and contraceptive availability are potentially effective to increase health care utilization (74). Condom distribution in combination with information and education or counselling could be an effective way to reduce STIs considering the price sensitivity
of the target group (73,75). Information campaigns aiming to increase awareness and/or increase condom use and testing can be effective during the period the campaign is active. However, research indicate that positivity rates during campaigns decrease compared to ‘normal’ testing periods suggesting that testing campaigns seem to fail to attract high-risk groups (76-78).

Increased access to testing, treatment and counselling for adolescents and young people is likely to prevent spread of STIs, and partner tracing and notification have proven essential measures for the control of STIs (79-81). In Sweden, testing via internet has proven an effective strategy by which men are tested to a higher extent than regular testing (82). There is varying evidence whether patient or provider referral of partner notification is most effective and contextual differences may exist. Improved partner tracing by skilled investigators has proved effective in Sweden (83). With very few exceptions (84), studies rarely declare the costs for partner notification however, costs must be determined in order to inform decisions on adequate selection of notification method at the local level. Behavioural change counselling in connection to partner tracing, testing or contraceptive counselling may reduce sexual risk-taking (85-86).

Insight into what makes an effective prevention mix against STIs is still lacking as well as information on organizational factors, the structures and functions of service organisations and their capacity to sustain prevention programmes, including availability of and accessibility to health services. Bernard et al (2008) (87) identified some key factors in dealing with HIV increases in Australia. By key informant interviews with major stakeholders, the study found that type of prevention strategy and level of financial investment in prevention activities appeared to be related to the effectiveness of the efforts. Further, building and maintaining a partnership with collaborative partners from governmental as well as non-governmental bodies and community sector together with appropriate and flexible resource allocation were identified as key factors for the successful response to the HIV increase among men who have sex with men (MSM). In an editorial response to Bernard’s study, Griew emphasizes the importance of policy and the structural prerequisites in which preventive activities are initiated and organized, which could be decisive for the execution of activities and maintenance of funding (88).

2.11.3 Cost-effectiveness

Regarding the cost-effectiveness of chlamydia testing and screening, health economic evaluations have broadly reported screening to be cost-effective (89-90). Partner tracing has been found to improve cost-effectiveness compared to no partner tracing (91). Screening of high-risk women (92) and extended screening of both high risk men and women have also proven to be cost-effective (93). There is significant controversy over whether testing asymptomatic patients can in fact reduce prevalence and/or prevent reproductive ill-health (94). An Irish study recently determined opportunistic screening to not be cost-effective (95) while a study by Welte et al (2000) illustrated non-selective opportunistic screening and contact tracing to be cost-effective (96). Welte et al, as well as Townshend et al (2000) (97), used dynamic models and Welte suggests that their screening programme would eventually save costs for the society but
in the early stages costs will outweigh savings, and it will take several years to reach the point of saving and longer to reach the break-even point. Roberts et al (2007) showed chlamydia screening using posted home collected specimens, at uptake levels achieved in empirical studies, and assuming a low incidence of chlamydia-associated complications, was not cost effective (98).

Conclusions of cost-effectiveness are highly dependent on basic assumptions of the health benefits of testing and treatment, which in chlamydia testing is highly dependent on the risk of PID progression. The randomized control trial by Oakeshott et al provides further evidence of the uncertainties of the natural history of chlamydia and its effect on PID. Studies further highlight the ambiguities regarding the effectiveness of screening by illustrating the lack of knowledge about effective delivery of chlamydia control interventions in general (31,99).

2.11.4 The scale-up of services

Based on existing knowledge about risk groups in need of services, current coverage, effective prevention factors and cost-effective prevention and treatment, cost estimations of service expansions are produced to determine the financial commitment required to reduce morbidity and mortality due to specific disorders. During the progress of the Millennium Development Goals (MDGs), such illustrations have mainly focused on either specific health outcomes such as HIV reduction or particular target groups such as children under the age of five. Several ‘global price tags’ have been published on the costs to reach the MDGs, (100-103) however, explicit identification of the resources required to scale up adolescent-friendly health services, and furthermore based on bottom-up country-by-country costing, is still lacking.
3 AIMS

The overarching aim of this thesis was to increase the knowledge of the public health economic aspects of chlamydia and other STIs.

Specific aims:

- to examine the association between demographic, socioeconomic and lifestyle factors and the risk of self-reported chlamydial infection among young adults in Stockholm, Sweden (Paper I),
- to identify potential key factors for successful regional prevention of chlamydia and other STIs in Sweden (Paper II),
- to analyse the cost-effectiveness of the 2007 Chlamydia Monday in terms of estimating costs, savings and health gains generated by the intervention, and to determine whether cost-effectiveness varies between men and women (Paper III),
- to estimate the additional resources required to scale up adolescent-friendly health service interventions with the objective to reduce mortality and morbidity among individuals aged 10 to 19 years in 74 low- and middle-income countries (Paper IV).
4 MATERIAL AND METHODS

An overview of the domains of the studies, the research questions, material and outcomes is shown in Figure 3.

Figure 3. Summarizing overview of the studies included in the thesis.

<table>
<thead>
<tr>
<th>Domains</th>
<th>Research Questions</th>
<th>Papers</th>
<th>Data</th>
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<tr>
<td>Implemented activities, structures &amp; allocated resources</td>
<td>What are potential key factors of successful regional prevention of chlamydia and other STIs?</td>
<td>II</td>
<td>Regional: survey and interview data from key stakeholders, and data from seven county council records (2006-2009)</td>
<td>STIs in Swedish regions</td>
</tr>
<tr>
<td>Scale up of effective policy and interventions</td>
<td>What is the additional resource need to scale-up adolescent-friendly health services (to universal coverage) in low- and middle-income countries?</td>
<td>IV</td>
<td>Global: country-specific data from numerous sources (2000-2011)</td>
<td>STIs + in low- and middle income countries</td>
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4.1 STUDY I

4.1.1 Material

The study was based on the Stockholm County Council’s Public Health Survey of 2006, which covers diverse questions regarding public health and risk factors. The survey population comprised a randomly selected sample of 57,009 persons aged 18 to 84 years, living in the Stockholm County area, of whom 34,707 (61%) responded. The selected study population was limited to the population at high risk of chlamydia, namely young adults of age 20 to 29 (N=4,278: 1,743 men and 2,508 women). The response rate among 18-25 year olds was 51% and among 26-35 year olds 56% (104). Figures on income level, personal and parental educational levels, and country of birth, were based on registry data linked to the survey results. Two registries were used: the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA is the Swedish acronym), and the Swedish Register of Education, both held by Statistics Sweden.

4.1.2 Methods

4.1.2.1 Independent variables

The independent variables consisted of demographic, socioeconomic, and lifestyle factors. Demographic factors taken into consideration were sex (male, female), age (20-22, 23-25, and 26-29 years), and country of birth. In order to ensure an informative sample size, country of birth was recoded as Sweden or ‘Other’.

Socioeconomic factors included personal and parental educational levels, income level and employment status. Personal and parental educational levels were divided into three categories: compulsory (completed 9th grade), secondary school, and university level. The principle for categorising parental education was that the highest reported level of parental education of the two parents was taken into account. When data were missing about one parent’s educational level (mostly because the Swedish Register of Education lacks data on foreign academic degrees), the other parent’s educational level was used. Income was categorised in three levels: low (amounting to <60% of median); high (>150% of median); and medium (60%-150% of median). Employment status was also divided into three categories: university student, employed and a third category that included unemployed, on sick leave or pre-retired. Pre-retired persons were few but did exist even in this young age group, since the Swedish welfare system classifies individuals with no future possibility of being able to work as ‘pre-retired’.

Lifestyle factors comprised body mass index (BMI), mental health, alcohol consumption, and partnership status. Alcohol consumption and partnership status were used to indicate the level of sexual risk-taking. BMI and mental health were utilised as potential explanatory factors for higher or lower risk-taking due to their connection with self-esteem, self-care, social interaction, and sexual activity (105-107). BMI was calculated as the subject’s weight in kilograms divided by the square of his or her height in meters, and grouped into low/normal weight (BMI <25) and overweight (BMI >25). Mental health was measured by the General Health Questionnaire 12 (GHQ12), where a cut-off point >3, referring to poor or very poor self-reported health, was used to indicate mental ill-health. High alcohol consumption was defined as a daily
consumption of at least 35 g of 100% alcohol for men and 25 g for women, corresponding to three standard glasses (87.5 ml of 40% alcohol) per day for men and two standard glasses (62.5 ml of 40% alcohol) for women. Partnership status was indicated by living with a partner or living with others/alone since ‘marital status’ was not considered inclusive enough for this young study population.

4.1.2.2 Outcome variable

The outcome variable was self-reported chlamydial infection based on the question: “Have you been diagnosed with chlamydia by a doctor in the past 12 months? Yes/No”. This question was answered by 99% of the study population (n=4,251; 1,743 men and 2,508 women).

4.1.2.3 Statistical modelling

Differences in proportions of chlamydial infection between individuals in the different demographic, socioeconomic and lifestyle categories were assessed by means of the chi-square test, while the association between age and chlamydial infection was explored with an independent t-test. Multivariate logistic regression was used to determine the association between the included factors and self-reported chlamydial infection, and the results were presented by means of Odds Ratios (ORs) with 95% confidence intervals (CIs). Because of the low prevalence of the outcome variable, the direction and magnitude of the associations (ORs) were interpreted as Relative Risks (RRs). The regression analysis only took into account subjects with complete information on the included independent variables. The regression analyses included the following four successive steps for each factor: a crude analysis, adjustments for demographic factors: age, sex and country of birth, additionally adjusted for socioeconomic factors: personal and parental educational levels, income level and employment status and finally we also adjusted for lifestyle factors, including partnership status, mental health, BMI, and alcohol consumption.

Statistical significance was set at p<0.05. The Statistical Package for Social Sciences (SPSS) version 20 was used for all analyses.

4.2 STUDY II

4.2.1 Material

The study was based on a selection of seven Swedish counties. These were selected based on their use of the same diagnostic test of chlamydia (Becton Dickinson ProbeTec) that was able to detect the new chlamydia variant. The different sources for data collection were for prevention structure and activities: survey, interviews and county council records (2006-2009), for condom use: survey data from Gothenburg University (2009), and for reported cases of chlamydia: national surveillance registers (2006-2009).

4.2.1.1 Survey

In April 2010, a survey was sent by e-mail to two key informants in each county: STI-coordinators and CMOs. In some cases, surveys were passed on to colleagues within the Units for Communicable Disease Control (county CDC units) resulting in answers
from STI-coordinators (all counties), four CMOs (counties B, E, F & G), and two CDC unit nurses (counties A & D). The informants were selected for holding strategic positions in STI prevention from which they could take an overall view of the case. Before the questionnaires were sent out, the informants were informed by letter about the study and its aims. The questions in the survey considered prevention factors of structure corresponding to: program- and county council investments, organizational structure, leadership, role in regional network, competencies, research connections, collaborations, regional action plans and implementation of NAP; and activity corresponding to: testing characteristics, testing coverage, partners tracing, risk approach, information efforts, internet based communication, outreaching activities and condom distribution. The survey is provided in the supplementary material in Paper II.

4.2.1.2 Interview

Following the retrieval and reading of the completed surveys (received from all counties), telephone interviews with the 13 key informants were conducted during the period from April to June 2010. An additional five persons were interviewed based on recommendations by the original informants (1 CDC unit nurse in county C, 4 counsellors in STI-, dermatology-, and venereology clinics in counties A, C, E and F). The purpose of this step was to further explore the preventive efforts and their implementation based on the same factors (structures and activities) as in the questionnaires. The answers from the interviews, which were audio recorded and ranged in length between 30 – 45 minutes, were condensed by county in a written document for all informants to read and comment on. This lead to a few additions and corrections in all cases, after which all informants, except one in county A that could not be reached after repeated attempts, approved.

4.2.1.3 County council records

The survey and interview data regarding prevention factors was complemented with county council data regarding programme investments from the governmental grant for prevention of STI (obtained from SNBHW), and county council investments in STI prevention (obtained from county council records).

4.2.1.4 Indicators of successful prevention

Successful preventive response was indicated by high proportion of condom use (2009) and decreased number of chlamydia cases (2006-2009) for each county. The first indicator was measured by condom use at latest vaginal intercourse among youth and young adults 15-29 years, retrieved from a large survey study on young people, sex and health by Gothenburg University (UNGKAB) (108). The survey was conducted partly as an overview of representative samples of persons aged 16, 20, 24 and 28 years in Sweden, and partly via various online communities (a self-selected sample). In total, the material comprised approximately 15,000 (15-29 years) individuals of which 77.5% answered the question on condom use at last intercourse (n 11,625). In the representative sample, the response rate was 24%.
The second indicator considered was the decrease in number of reported cases of chlamydia over the period from 2006 to 2009. The annual number of reported cases was retrieved from SMI (109).

4.2.2 Methods

4.2.2.1 Case study methodology

The research question for this study could be explored in many different ways. The case study method usually involves the use of multiple sources and techniques in data collection and analysis in order to explore and generate understanding of a phenomenon based on a restricted number of cases (110). Hence, the method was judged suitable for the current study with the aim of enabling open comparison of counties.

4.2.2.2 Analysis

A single researcher performed the interviews while the analysis was done by two researchers to improve robustness. Factors of structure and activities were identified for each county, and rated as strengths or weaknesses compared to standard preventive measures. The performance of the majority of counties was referred to as the standard (rating 3), whereas deviations were referred to as strengths (rating 4-5) and weaknesses (rating 1-2). The rating was data-based, meaning it was solely and consistently based on a comparison with other cases in the study. The rating was done by each of the researchers independently (CD and CM). This resulted in similar ratings except for one of the factors for two of the cases, which were then reviewed by a third researcher (AM). Potential key factors for successful prevention were finally identified by strengths (rating 4-5) corresponding to a high proportion of condom use and a decrease in number of reported chlamydia cases.

4.3 STUDY III

The study was based on an intervention aiming to increase chlamydia testing, and hence ultimately reduce prevalence, in the county of Stockholm, Sweden. Since materials, methods, assumption and calculations are closely incorporated in each other, the descriptions of material and methods are kept summarized under one headline.

4.3.1 Material and methods

A cost-effectiveness model was constructed in Excel and a societal perspective was adopted meaning that all costs and savings were included regardless of who experienced them. Avoided future production-loss was accounted for in the sensitivity analysis. The analysis considered the Chlamydia Monday in 2007 versus the alternative of no Chlamydia Monday; hence, average cost-effectiveness and incremental cost-effectiveness were considered the same. All costs and savings were transformed from Swedish krona (SEK) to euros (€) by the mean exchange rate of January to November 2008 (Sweden’s central bank), and when relevant, adjusted to the average price level of 2007 (including the Swedish inflation rate) by the consumer price index (Statistics Sweden). Savings and health gains were presented in both discounted (3%) and undiscounted values, in accordance with the TLV general recommendations on economic evaluations. The time from a chlamydia infection to various medical sequels
is not well established. However, the largest disease burden is caused by chronic pelvic pain, ectopic pregnancy and infertility, of which the latter two occur during pregnancy or attempts to become pregnant. Savings and health gains were therefore assumed to occur 10 years after diagnosed chlamydia, i.e. when a majority of the patients would be around 34 years old. The duration of the loss in health caused by chronic pelvic pain and infertility was conservatively set at 30 years, which implies a time horizon extending to the age of retirement in Sweden.

4.3.1.1 Estimating effectiveness

The effectiveness of the intervention was measured by how many additional patients came to get tested, and was determined by data from a questionnaire that every tested individual was invited to answer. The overall response rate was 83.4% (1,234 individuals out of 1,480 tested), and one question was: ‘If there had not been a Chlamydia Monday, would you still have had a test done?’ The share of individuals (22.25%) who answered that they would not have had a test if there had been no Chlamydia Monday was assumed to represent the effectiveness of the intervention. The patient survey showed that the study group (those who would not have tested without the intervention) included a lower proportion of women (53.1% versus 60.8%), and a higher mean age (25 years compared to 24) compared to those who reported they would have got tested anyway. Furthermore, individuals in the study group stated symptoms or unprotected sex as a reason for being tested to a lesser extent, 59%, compared to 73.3% among those who would have had a test done regardless of the Chlamydia Monday. Hence, among individuals who answered ‘no’, the prevalence of chlamydia was estimated at 5% compared to 8% in the total group of screened individuals. No statistically significant difference in prevalence between men and women was found at the 5%-level of significance.

4.3.1.2 Estimating the costs

The advertisement campaign costs were obtained from the accounts of the Stockholm County Council. Staff costs were based on the Swedish Association of Health Professionals’ wage statistics (110) and on social and employers’ fees, which were at 32.42% in 2007 (Swedish Tax Authorities) (112). The cost was calculated by the average wage for nurses and social workers in the County of Stockholm including social fees, multiplied by the time of testing. According to the Stockholm Unit of Infectious Disease Control (113), contact-tracing takes on average 30 minutes per diagnosed individual. Cost of treatment (doxycycline) was retrieved from the Swedish Pharmaceutical Board. The production loss due to testing was based on the human capital approach based on average income (114) and time for transport and testing.

4.3.1.3 Estimates of savings

The savings (defined as prevented health care costs due to undiagnosed chlamydia) was based on the risk of progression for various sequels. The total cost of an undetected case of chlamydia was made up of the treatment of the chlamydia infection, plus the risk of sequels multiplied by their treatment costs. The inpatient costs were based on estimates for Stockholm public hospitals in 2007 (Stockholm County Council), while the outpatient costs were obtained from the price list of Umeå University Hospital
When the risk estimates were found to vary in the literature, the middle point of the risk interval was used. See Figure 1, Paper III for the estimates used on sequel progression for women, men and new-borns.

4.3.1.4 Estimates of health gains

The health gains in QALYs were based on a study by the Institute of Medicine (116) in which health-related quality of life regarding aspects of chlamydia was estimated by the HUI Mark II. The HUI weights for the various medical sequels were combined with duration to estimate the loss in quality of life. This loss was then multiplied by the number of prevented cases in order to obtain gained QALYs.

4.3.1.5 Screening and treatment of traced sexual contacts

Testing and treatment of partners found in contact tracing was included as costs, savings and health gains. A previous Swedish study found that a mean of 2.5 sex-contacts per index patient were found in contact tracing; 1.9 of them showed up for screening; of whom 65% tested positive for chlamydia (117). Additionally, in 98% of the cases chlamydia was transmitted heterosexually. Hence, the costs and savings of 1.21 traced female sex-contacts (1.9 x 0.65 x 0.98) were assumed to be generated by screening and treating one male participant, and vice versa.

4.3.1.6 Cost-effectiveness and sensitivity analyses

In the calculation of the cost-effectiveness ratio, the net monetary cost for society was put in the numerator and the health change in QALYs in the denominator. The concluding result is always relative, but the threshold value of €50,000 for the Swedish context was used according to TLV. Sensitivity analyses included eight scenarios; effectiveness rates of 34.9%, 22.25% and 10%, PID progression rate of 10%, inclusion of prevented future production loss, prevalence rates of 8% and 3%, exclusion of contact tracing and finally shortened duration of chronic sequels to 10 years. The interaction of the parameters effectiveness and prevalence was also explored.

4.4 STUDY IV

Since materials, methods, assumption and calculations are closely incorporated in each other, the descriptions of material and methods are kept summarized under one headline.

4.4.1 Material and methods

In contrast to Study III, that assumed a societal perspective, the analysis of Study IV was conducted from a health care perspective and assessed financial costs. The development of a global price tag for the scale-up of AFHS required the selection of countries, priority interventions and estimation of the population in need of each intervention, and of current and target coverage of interventions. Adolescent-specific data was used when possible, however at times adult estimates were applied or adjusted by expert opinion. Input data were largely based on country-specific data but were complemented with regional as well as global estimates when needed. The underlying assumptions are described in a technical report available from the authors upon request (118).
Countries included in this study were those defined as having a high disease burden for maternal, child and reproductive health, as included in the ‘Countdown to 2015 - Maternal, newborn and Child Survival’ (68 countries) and/or low income countries as defined by the UN Secretary General’s list of least developed countries in 2009 (49 countries), resulting in a total of 74 countries (119-120). Hence, the cost estimate includes low- and middle-income countries from all WHO regions with high maternal and child mortality. The 74 countries included have a total adolescent population aged 10-19 years, of approximately 954 million in year 2015. A complete list of countries is found in Paper IV, Table 1.

4.4.1.1 Health care interventions

A standard set of effective priority interventions were chosen based on expert opinion of WHO staff in combination with WHO guidelines on interventions and strategies to address the major causes of burden of disease among adolescents in these countries, with a focus on reproductive health (121-123). Identified interventions were assumed to be implemented in all 74 countries with adjustments made for different epidemiological circumstances. Interventions were assumed to be delivered at three delivery points, including hospital care, health facility care and the community. A list of interventions, delivery points and population in need is provided in Paper IV, Table 2.

4.4.1.2 Contraceptive services and STI management

Contraceptive services were assumed to be delivered at facility level and in communities through outreach activities. Contraceptives included oral contraceptives, emergency contraceptives and injectables. Condoms were provided by means of a package of 15 male condoms through a variety of channels including health care facilities and outreach by community health workers. For STI management, a visit included testing and treatment of infection and was assumed to be delivered at facility and hospital level.

4.4.1.3 Population in need

The population in need was identified per intervention and estimated based on population size (UN Populations Division's 2008 Revision projections) and incidence or prevalence of a condition based on various data sources (124-131). For contraceptive services, the population in need was defined based on sexual activity while for STI management, need was based on regional prevalence estimates on STIs. Due to lack of adolescent data, adult prevalence was applied for both sexes (125). Occurrence of PID was estimated by a global average of 2% and 4% in adolescent girls 10-14 and 15-19 years respectively. Both interventions were costed by one health care visit per case.

4.4.1.4 Estimating current coverage levels

Coverage was defined as the proportion of adolescents receiving the interventions from those in need. Country-specific current coverage levels were estimated using a variety of data sources (131-133). For most interventions, data from Demographic health

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2 South Sudan is also a high burden country but since data is scarce, South Sudan was not included in this analysis.
surveys (DHS) or AIDS Indicator Survey (AIS) was used. For countries for which there was no coverage data available, regional averages were applied (population weighted when possible). For interventions for which no data was available, experts within WHO and UNAIDS were consulted. Current coverage of STI services was estimated based on country-specific data from DHS regarding the percentage of adolescents reporting symptoms of STIs in the last 12 months who sought care at a service provider. Current coverage of contraceptive services was based on use of any modern contraceptive among sexually active adolescents as reported by DHS.

4.4.1.5 Programme activities for Adolescent-Friendly Health Services

Programme activity costs are expenses incurred at the levels of facility, district or national level (134), and here refer to improving the management and quality of care provided to adolescents. Programme activities were identified based on the quality of care characteristics as mentioned earlier in the background (56-58) and classified into programme management, training, supervision, information, education and communication (IEC), infrastructure and equipment.

4.4.1.6 Costing the scale-up

The incremental scale-up of coverage was estimated using the target of universal coverage (95%) as per other ‘universal coverage’ targets that have been costed (135) minus the current coverage levels per country and intervention. Intervention costs refer to direct costs of service delivery and include drugs, laboratory tests, medical supplies and consultation time based on guidelines and recommendation of health care delivery (124, 126, 136-141). For programme costs, the quantities of investments were determined based on the WHO Quality of Care model and discussions with the WHO staff.

Three different kinds of models were used. To estimate costs for the majority of the interventions, a new costing model was created containing assumptions for all interventions on coverage rates, population in need, and ingredients of health care. For maternity care, an existing model was used with adaptation to adolescent population data and updated prices (142). For programme costs, a new costing model was created containing assumptions for components of programme activities. The scale-up trajectory to 2015 is assumed to be linear for all countries. Prices were taken from the WHO-CHOICE database (WHO CHOosing Interventions that are Cost Effective) (143) and the Management Sciences for Health’s International drug price guide (144). Costs are presented in US dollars (2008), and estimated by cost category, country and year.

4.5 ETHICS

The ethical committee at Karolinska Institutet, Stockholm approved Studies I-III. Study IV was based on aggregate data and did not require ethical review.
5 RESULTS

5.1 SOCIAL AND LIFESTYLE FACTORS OF CHLAMYDIA IN SWEDEN
(STUDY I)

The aim of this analysis was to examine the association between demographic, socioeconomic and lifestyle factors and the risk of self-reported chlamydial infection among young adults in Stockholm, Sweden.

Results showed that 3.1% of surveyed individuals aged 20 to 29 years reported they had been diagnosed with chlamydial infection during the preceding 12 months. Compared to individuals aged 26-29 years, risks of self-reported chlamydial infection were doubled and tripled among individuals aged 23-25 years and 26-29 years, respectively. Individuals with secondary school level had an almost twofold increased risk compared to individuals with university level education. Furthermore, compared to students, increased risk of self-reported chlamydial infection was obtained among those being employed (twofold increased risk) and unemployed, on sick leave or pre-retired (threelfold increased risk). High alcohol consumption also proved to be associated with a twofold risk of self-reported chlamydial infection. The reported associations remained strong and statistically significant after mutual adjustment of demographic, socioeconomic and lifestyle factors.
Table 1. Odds ratios (ORs) of chlamydial infection and 95% confidence intervals (CIs) in relation to significant independent variables.

<table>
<thead>
<tr>
<th></th>
<th>Number (n=3442)</th>
<th>Self-reported chlamydia infection (n=111) %</th>
<th>Crude OR (95% CI)</th>
<th>Final model* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-29</td>
<td>1497</td>
<td>1.6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>23-25</td>
<td>995</td>
<td>3.6</td>
<td>2.03 (1.28-3.23)</td>
<td>2.03 (1.16-3.53)</td>
</tr>
<tr>
<td>20-22</td>
<td>950</td>
<td>5.4</td>
<td>3.40 (2.21-5.22)</td>
<td>2.99 (1.58-5.70)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>1172</td>
<td>1.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Secondary school</td>
<td>1567</td>
<td>4.2</td>
<td>3.18 (1.83-5.52)</td>
<td>1.88 (1.01-3.49)</td>
</tr>
<tr>
<td>Compulsory</td>
<td>703</td>
<td>4.1</td>
<td>3.11 (1.68-5.77)</td>
<td>1.34 (0.64-2.82)</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>1108</td>
<td>2.2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Employed</td>
<td>2124</td>
<td>3.5</td>
<td>1.65 (1.04-2.63)</td>
<td>2.02 (1.23-3.32)</td>
</tr>
<tr>
<td>Unemployed/sick leave/pre-retired</td>
<td>210</td>
<td>5.7</td>
<td>2.74 (1.35-5.56)</td>
<td>2.98 (1.41-6.29)</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not high</td>
<td>2107</td>
<td>2.2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>High</td>
<td>1335</td>
<td>4.8</td>
<td>2.21 (1.51-3.24)</td>
<td>2.05 (1.38-3.06)</td>
</tr>
</tbody>
</table>

* Final model: Adjusted for demographic factors (sex, age and country of birth), socioeconomic factors (parental education, personal education, income level, and employment status) and lifestyle factors (partnership status mental health, body mass index, and alcohol consumption).
5.2 POTENTIAL KEY FACTORS FOR SUCCESSFUL REGIONAL PREVENTION (STUDY II)

The aim of this analysis was to identify potential key factors of successful regional prevention of chlamydia and other STIs in Sweden.

Figure 4 shows variations in number of reported cases of chlamydia between counties. During the period from year 2006 to 2007, most counties (A, D, E, F & G) experienced an increase, whilst during 2008 to 2009, most counties experienced a decrease (A, C, D, E, F & G). Regarding the whole period (2006-2009), county F had the strongest decrease in reported number of chlamydia cases by 21.03%, whereas counties A, B, D and E had moderate decreases (5.55%, 7.05%, 5.28% and 9.84%). Figure 5 shows the proportion of condom use by county. In counties C, E and F, the use of condom at last intercourse among youth and young adults were 29%, 26.5% and 27.6%, respectively, while in other counties the use was lower, spanning from 15.5-23.0%. Two counties (E and F) fulfilled the criteria of successful prevention based on the combined consideration of high proportion of condom use and decreased number of reported chlamydia cases.

Figure 4. Number of reported cases of chlamydia per 100,000 inhabitants, 2006-2009 (SMI).
Results showed that the prevention factors differed between counties. Identified potential key factors are summarized in Table 2: adequate programme- and County council investments, suitable organizational structure, strong leadership, managing regional networks, research connection, multiple local collaboration, high testing coverage and strategic risk approach. In all, strong counties with strengths in preventive measures were E and F, weak counties with weaknesses were A and G, and undifferentiated counties with standard preventive measures were B, C, D.

More specifically, high investments in primary and secondary prevention, legitimate and clear leadership and collaboration with multiple cross-sectional regional agents, and scientific foundation for action seemed vital. Furthermore, comprehensive testing with high ratios of tested men versus women, high numbers of tested per positive case and of tested per 100 000 inhabitants were identified as important. Finally, implementing a broad mix of efforts simultaneously was recognised as successful, including targeting risk individuals in testing and counselling, and potentially using innovative approaches like internet-based communication and health care services.

Regarding resources allocated for STI-prevention, investments were significantly higher per capita in county F with a larger proportion provided from the county council than in the other counties. County F deviated from the rest of the counties with a combination of high investments via the governmental grant (programme investment) and high investments in, not only STI prevention, but also general public health and health care issues via the county council. This generated a need-based and flexible resource allocation where the CMO and the STI-coordinator had the possibility to initiate prevention activities where and when a need was identified.
Table 2. Potential key factors of successful prevention: strengths (4, 5) and weaknesses (1, 2) compared to standard (3) in the seven counties (A-G).

<table>
<thead>
<tr>
<th>Data</th>
<th>Cases</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programme investment</td>
<td>(3)</td>
<td>Rather high (4)</td>
<td>Low (1)</td>
<td>(3)</td>
<td>(3)</td>
<td>High (5)</td>
<td>Rather low (2)</td>
<td></td>
</tr>
<tr>
<td>County council investment</td>
<td>(3)</td>
<td>Saving package (1)</td>
<td>Favourable (4)</td>
<td>(3)</td>
<td>(3)</td>
<td>High (5)</td>
<td>Tight budget (2)</td>
<td></td>
</tr>
<tr>
<td>Organization structure</td>
<td>STI-group meet ≤3times/year (1)</td>
<td>(3)</td>
<td>(3)</td>
<td>STI-group meet ≤4times/year (2)</td>
<td>STI-group meet 6-8 times/year (4)</td>
<td>STI-group meet ≥6 times/year, Network meetings (5)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Leadership</td>
<td>STI-coordinator 20% (1)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>Good leadership (4)</td>
<td>Strong &amp; clear leadership (5)</td>
<td>No STI-coordinator, Good leadership (2)</td>
<td></td>
</tr>
<tr>
<td>Role regional network</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>Responsible (4)</td>
<td>Responsible (4)</td>
<td>(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competencies</td>
<td>Little training (1)</td>
<td>(3)</td>
<td>Restricted training (2)</td>
<td>(3)</td>
<td>(3)</td>
<td>Extensive MI training, High education to health care &amp; school staff (4)</td>
<td>Extensive MI training, High education to health care &amp; youth contexts, Innovative training (5)</td>
<td></td>
</tr>
<tr>
<td>Research connection</td>
<td>None mentioned (1)</td>
<td>(3)</td>
<td>None mentioned, Systematic evaluation (2)</td>
<td>(3)</td>
<td>Strong &amp; broad (5)</td>
<td>Strong (4)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Collaborations</td>
<td>≤3 regional agents (2)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>≥5regional agents (4)</td>
<td>≥7regional agents (5)</td>
<td>≤2regional agents (1)</td>
<td></td>
</tr>
<tr>
<td>Testing coverage</td>
<td>Low male/female ratio &amp; test per case (2)</td>
<td>(3)</td>
<td>Low male/female ratio, test/case &amp; test/100,000 inhabitants (1)</td>
<td>(3)</td>
<td>(3)</td>
<td>High male/female ratio, test/case &amp; test/100,000 inhabitants (5)</td>
<td>High male/female ratio &amp; test/case &amp; moderate test/100,000 inhabitants (4)</td>
<td>No male/female ratio, low test/case &amp; test/100,000 inhabitants (1)</td>
</tr>
<tr>
<td>Risk approach</td>
<td>MI for risk patients (2)</td>
<td>Poor MI use (1)</td>
<td>(3)</td>
<td>(3)</td>
<td>Strategies, Consistent MI use some clinics (4)</td>
<td>Risk assessment tools &amp; strategies, Consistent MI use (5)</td>
<td>(3)</td>
<td></td>
</tr>
</tbody>
</table>
5.3 COST-EFFECTIVENESS OF THE CHLAMYDIA MONDAY (STUDY III)

The aim of this analysis was to assess the cost-effectiveness of the 2007 Chlamydia Monday by estimating costs, savings and health gains generated by the intervention, and to determine whether cost-effectiveness varies between men and women.

The point of departure for the calculation of costs, savings, and health gains of the intervention was that a total of 1,480 individuals were tested (864 women and 616 men) of whom 22.25% would not have undergone any testing if the Chlamydia Monday had not been available (effectiveness). The prevalence of chlamydia was 5% for both sexes in the group. As illustrated in Table 3, the total cost of the Chlamydia Monday in 2007 was estimated at €66,787 of which €39,014 related to women and €27,773 related to men. The total savings due to prevented health care costs were €20,598 of which €11,630 related to women and €10,968 related to men (discounted figures). Health gains in total number of QALYs gained were 5.29 (discounted figure) of which the largest part was generated by PID and its sequels. Consequently, the main alternative demonstrates a discounted cost-effectiveness ratio of €8,346 per QALY, €10,811 per QALY for women and €6,085 per QALY for men.

Table 3. Main alternative: costs, savings, QALYs gained and cost per QALY.

<table>
<thead>
<tr>
<th></th>
<th>Costs</th>
<th>Savings</th>
<th>QALYs gained</th>
<th>Cost per QALY</th>
<th>Cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>39,013</td>
<td>15,630</td>
<td>6.140970</td>
<td>3,808</td>
<td>&lt; WTP</td>
</tr>
<tr>
<td></td>
<td>(11,630)</td>
<td>(2.533002)</td>
<td></td>
<td>(10,811)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>27,773</td>
<td>14,740</td>
<td>3.711354</td>
<td>3,512</td>
<td>&lt; WTP</td>
</tr>
<tr>
<td></td>
<td>(10,968)</td>
<td>(2.761596)</td>
<td></td>
<td>(6,085)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>66,787</td>
<td>30,370</td>
<td>9.852324</td>
<td>3,696</td>
<td>&lt; WTP</td>
</tr>
<tr>
<td></td>
<td>(22,598)</td>
<td>(5.294598)</td>
<td></td>
<td>(8,346)</td>
<td></td>
</tr>
</tbody>
</table>

Furthermore, the sensitivity analyses show almost consistent cost-effectiveness defined as less than €50,000/QALY. When avoided future production loss was included, the result generated a net saving while, when costs and savings of contact tracing were excluded, the intervention proved to be cost-effective in total and for women, but not for men. The sensitivity analysis illustrated the “break-even” point (meaning the lowest acceptable level of prevalence and effectiveness based on a willingness to pay €50,000) to be 3.5% for both variables. Figure 6 shows the cost-effectiveness by parameters effectiveness and prevalence.
Assuming a reduced PID progression rate of 10% and 22.25% effectiveness, the cost per QALY remains below the threshold until prevalence falls below ~2% (see Figure 7).
5.4 RESOURCE NEEDS FOR ADOLESCENT-FRIENDLY HEALTH SERVICES (STUDY IV)

The aim of this analysis was to estimate the additional resources required to scale up adolescent-friendly health service interventions with the objective to reduce mortality and morbidity among individuals aged 10 to 19 years in 74 low- and middle-income countries.

The 5-year total cost of scale up was estimated at US$ 15.41 billion, of which US$ 1.86 billion for year 2011, increasing to US$ 4.31 billion for the year 2015 (see Table 4). This corresponds to approximately US$ 1.02 per adolescent in 2011, increasing to US$ 4.70 in 2015. The cost estimates indicate the additional financial resources required to scale up health service interventions to adolescents towards universal coverage levels.

Table 4. Cost per year of scale-up (total for 74 countries, US$ billion 2008).

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>Total scale-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFHS Programme activity costs</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>5.96</td>
</tr>
<tr>
<td>Intervention costs</td>
<td>0.67</td>
<td>1.28</td>
<td>1.89</td>
<td>2.50</td>
<td>3.12</td>
<td>9.45</td>
</tr>
<tr>
<td>Total costs</td>
<td>1.86</td>
<td>2.47</td>
<td>3.08</td>
<td>3.69</td>
<td>4.31</td>
<td>15.41</td>
</tr>
</tbody>
</table>

The largest cost category is programme activities, of which information, education and communication is the largest cost accounting for 24.48%. Contraceptive services and maternity care are the most costly interventions, accounting for 33.02% and 10.04% of total costs, respectively, followed by HIV care and treatment (7.74%). The population in need for contraceptive services and maternity care is proportionately larger than for the other interventions while HIV care and treatment generate high commodity costs.
The essential service package (including contraceptive services, maternity care, HTC, management of STIs and safe abortion) constituted US$ 7.21 billion of which the cost for contraceptive services constituted US$ 5.09 billion while STI management constituted US$ 226.97 million (Figure 8). Contraceptive services account for the largest investment in all regions, except for the African region where costs for HIV care are slightly higher. As shown in Figure 9, information about contraceptives, STIs/HIV and pregnancy prevention accounts for the largest proportion of the cost for contraceptive services (54%).
As shown in Figure 10, the investment need is greatest in South East Asia region (28% of total STI costs) followed by the African and the region of the Americas (24% of total STI costs respectively). Figure 11 shows that the total cost for management of chlamydia amounted to US$ 44.58 million (approximately 20% of the total cost for STI management).
6 DISCUSSION

6.1 STUDY I

In Study I, we found that the risk of self-reported chlamydia infection among young adults in Sweden was associated with lower age, high alcohol consumption, lower educational level and being employed or unemployed, on sick-leave or pre-retired compared to being a student. The results generally confirm previous international studies as well as Swedish findings among adolescents. Further, the results are in line with the notion of investing in human capital for improving general health (Grossman).

6.1.1 Limitations

There are several weaknesses in the study.

Firstly, the use of cross-sectional data precludes any causal interpretation regarding the relationships between social and lifestyle factors, and chlamydial infection.

Secondly, self-reported data on chlamydia infection are not optimal for measuring outcome and are affected by recall bias as well as by unwillingness or embarrassment to answer the question due to subject sensitivity. However, the internal response rate of the question is very high (over 99%) and relates to diagnosis, not merely symptoms of disease. The self-reported rate of chlamydial infection was 3.2% in both men and women which corresponds to previously published self-reports of chlamydia among Swedish teenagers and young adults (15–29 years) (145). Studies also indicate substantial agreement between medical diagnosis and self-reported STI in adolescents (146).

Thirdly, the data lacked information on testing. Respondents who do not report having been diagnosed with a chlamydial infection could either have had a negative test or not have been tested at all. Regarding health care behaviour and access to testing, socio-economically deprived groups tend to be less influenced by public awareness campaigns, confronted with more barriers, and less likely to seek health care. If students, individuals with a higher education and those who are not high alcohol consumers are tested more often than others, our results are more likely to be underestimated rather than overestimated. Neither did the data include information on sexual behaviour which could have explained some of the associations between exposures and chlamydia infection. The risk of STIs ultimately also depends on the epidemiologic context in which people live. Unfavourable social determinants of health form a hostile environment in which several factors contribute indirectly to infectious disease. The epidemiologic context therefore typically mediates the association between social position and STIs (147).

Fourthly, in the comparison of subjects with missing data (excluded from the regression analysis) with those with no missing data, we found slight differences in self-reported chlamydia rates. This indicates that some selection bias may be distorting these particular findings, and affecting the risk level of these variables. However, the
direction of the differences (age, partnership status and alcohol consumption) confirms our findings. Furthermore, our data did not show any statistically significant differences between the proportions of self-reported chlamydial infection in non-missing versus missing data per category. Taken together, we find it unlikely that selection bias may have substantially distorted our results.

Finally, measuring socio-economic position in young adults is complex, as it requires ascribing a class status to adolescents or young adults who have not yet transitioned fully to adult roles. Employment status was used to stratify between students, employed and unemployed, on sick leave or pre-retired, and together with parental educational level (as well as personal educational and income levels), it was judged to be an accurate assessment of social position in the study population.

### 6.1.2 Policy implications

Our findings can contribute to the planning of public health programmes and the implementation of community prevention efforts. Indicators of risk-taking behaviours, especially in settings with generally little educational ambition or possibility, could be incorporated in the design of STI prevention strategies. Specifically, high alcohol consumption may be used to identify and target risk groups, and deprived areas should be prioritized in the allocation of resources and preventive programmes. From a human capital approach, especially young people with lower educational or occupational status, with many productive years ahead, would benefit from increased attention.

### 6.1.3 Future research

Official STI reporting systems are constrained by the lack of demographic and behavioural information on infected individuals. Hence, further analysis of self-reporting of reproductive disease to study the association with socioeconomic and lifestyle factors is warranted. For future research, there is great potential in clinical studies linking diagnosis to socio-epidemiological data.

### 6.2 STUDY II

The main findings of Study II illustrate potential key factors of successful regional chlamydia prevention, including; adequate program- and county council investments, suitable organizational structure, strong leadership, managing regional networks, research connection, multiple local collaborations, high testing coverage and strategic risk approach.

Recent trials of chlamydia screening not only provide evidence of the ambiguities regarding the benefits of screening but also illustrate how little we know about how best to deliver prevention activities in general (31,99). Exploring factors potentially associated with successful prevention is hence of considerable scientific interest. Attempting to link prevention input to outcome can be done in many ways. Identifying key prevention factors, by linking structure and prevention activities to the reported number of chlamydia cases, was based on the underlying assumption that the outcome is affected by the input and that condom use is the main mediating factor. STI
prevalence as well as reported number of cases will ultimately depend on a range of contextual, demographic, epidemiological as well as prevention factors.

6.2.1 Results in relation to earlier research

The main findings are somewhat similar to a study from Australia on HIV/AIDS indicating that the involvement of key stakeholders and adequate allocation and release of resources are important factors for a successful HIV response (87). The study included interviews with key stakeholders in three Australian states. The noteworthy case was New South Wales, the state hardest hit by the HIV epidemic since its arrival in Australia, but with notifications among gay men falling since a spike in 2001 and flat overall since 1998. Additionally, after a mapping of the investments and a workshop by the ministerial advisory committee on HIV/AIDS strategy, Australian researchers emphasized the importance of policy and investments for effective HIV prevention (88,148). In lack of knowledge and more relevant references within chlamydia control, HIV prevention research is useful however considerations are needed since HIV is different from chlamydia in terms of severity, stigma and health care response for example.

Resources allocated to primary and secondary prevention were identified as a key factor for successful prevention. Logically, resource allocation enables the implementation of activities which may help in developing a suitable underlying organization and collaboration around activities. Further insight into the resource allocation process would be of value.

6.2.2 Limitations

There are several limitations with the study.

Firstly, prevention factors were assessed by survey and interview data. Since the study was commissioned by SNBHW, informants were likely to try to answer as positively about their efforts as possible. This needs to be considered in open comparisons with counties excluded from the study, however counties included were assumed to be evenly affected by this bias.

Secondly, the analysis assumed all prevention factors were of equal importance for the outcome, regardless of whether, for example, partner tracing is more decisive for success than condom distribution. The analysis included a relative comparison to the standard (the performance of the majority of counties). This was done by me (CD) and one of the co-authors (CM), that is, the analysis was not blinded which could have possibly improved objectivity and reduced information bias since subjective ratings were assigned to cases.

Thirdly, regarding the outcome, the reduction in number of reported chlamydia cases and the proportion of condom use at last vaginal intercourse were used. The number of reported cases of chlamydia is merely an indicator of chlamydia prevalence and incidence and furthermore a very difficult one to interpret. While the true incidence can only be estimated if general screening is in place, the number of reported cases largely depends on testing rates. Regional condom use was based on the UngKAB09 survey,
which was conducted partly as a representative sample with low response rate (24%) and partly as a self-selected sample (total n=11,625). The low response in the representative sample makes it difficult to generalise the results for people in this age group in Sweden. Persons who replied to the survey online (the self-selected sample) are somewhat more sexually experienced than people in the representative sample. Furthermore, the survey was not originally designed to detect between county differences. In summary, both outcomes include considerable limitations, however in lack of other appropriate indicators, the combination was considered an accurate illustration of the effects of the regional response.

6.2.3 Policy implications

The Swedish national as well as regional action plans should consider including clear recommendations regarding ownership and accountability of STI prevention at the regional level to avoid this issue falling between the cracks in existing budgetary systems. Furthermore, greater consideration should be taken by regional authorities to structural factors of prevention such as for instance research connections, leadership and the flexibility of resource allocation.

6.2.4 Future research

In order to confirm these findings, further studies on the structural factors of STI prevention is encouraged. Key factors of successful response are likely to be identified by studies considering the implementation of a mix of key prevention activities, however this requires multidisciplinary competence as well as detailed input and output data over time.

6.3 STUDY III

In Paper III, we illustrate that a testing intervention including a self-selected sample of individuals was cost-effective. The main result showed a discounted cost of €8,346 per QALY, which is well below the threshold of €50,000 per QALY considered as point of reference for cost-effectiveness in a Swedish context. Sensitivity analyses showed consistent results for changes in parameters, and all scenarios, except exclusion of contact tracing for males, generated a cost-effective result.

6.3.1 Limitations

One of the critical limitations is that the effectiveness was based on a patient questionnaire in which the individual was asked to report awareness and impact of the Chlamydia Monday on his/her decision to have a test done. This self-reported information may have underestimated the results. Survey statements regarding behaviour are known to be unreliable (149) and most likely biased towards answering “yes”, in this case that one would have had a test done regardless of the intervention. The increase in testing rates compared to the week before the Chlamydia Monday (34.9%) was included as the upper boundary in the sensitivity analysis but this figure needs to also consider potential substitution effects (rate of consumption falls as the price of the good rises, meaning patients who would have normally attended the week before may postpone their visit to the day of the intervention due to the decreased time price of seeking care). However, this figure seems to be similar to that from other parts
of the country with similar interventions. According to an evaluation report, similar interventions in Malmö showed a 22% increase (2005) and Västra Götaland (Göteborg) a 25% increase (2004) compared to “a regular week” (150). Furthermore, the sensitivity analyses proving acceptable cost-effectiveness at the carefully assumed effectiveness of 5% to the highest alternative of 34.9% (compared to 22.25% in the main alternative) indicates validity.

The demand for health care increases with increased availability and especially with decreased costs (12). The Chlamydia Monday increases availability and accessibility by providing testing without having to make an appointment and it may also decrease the cost for the patient due to reduced time spent on seeking care. Previous research has shown that young people are more sensitive to price than older people (151), which corresponds to the target group of the intervention. Further, it has been reported that patients who perceive their health as good/excellent have a more elastic demand for health care than patients with fair/poor health (who are less sensitive to monetary and time costs) (152). This confirms the finding that the Chlamydia Monday attracted a relatively high proportion of individuals without symptoms. The prevalence among individuals attracted by the intervention was lower, 5% compared to 8%, than among individuals who would have had a test done in any case. This confirms previous findings that testing campaigns and screening interventions of this kind find more cases but fail to attract high-risk groups (76-77).

The main difference in comparison to the majority of the body of knowledge is that this intervention is based on a self-selected sample of adolescents and young people and not a defined group for complete screening. However, regarding models fitting reality, no official screening of chlamydia is in place in Sweden but rather opportunistic testing and other testing activities of similar characteristics.

The contentious literature on the risk of PID due to chlamydia makes this parameter highly uncertain. Since the majority of health benefits from chlamydia control activities depend on this, the cost-effectiveness is also substantially determined by the PID risk estimate. According to Swedish data from Malmö, approximately 30–45% of all PID cases in women below 35 years of age are associated with a chlamydia infection (153). The analysis was based on a 20% PID progression in the main alternative, which in the sensitivity analyses was reduced to 10% with consistent results.

The model did not take into account the risk of re-infection, which considerably limits the validity of the results. In a retrospective cohort study of 3,568 patients in Colorado, USA that were tested repeatedly, 13.8% had a positive result at their first visit (baseline infection) and 10.8% had a positive test at a subsequent visit (incident infection). The incidence of repeated infections was 23.6% and repeat infections accounted for 26% of all incident infections (154). In a home-based setting in Denmark it was found that the cumulative recurrence of urogenital chlamydia infections after antibiotic treatment was 29% over a 24-week period, presumably by reinfection from sexual partners (155). Swedish data from Malmö has shown a re-infection rate of 15% in 2003.
Essentially, someone who is successfully tested and treated for chlamydia infection may be re-infected which means the benefits of preventing long-term squeal is lost and the person may infect others. If they are successfully treated without reinfection, they will not transmit infection. The two possible scenarios have opposing effects on the cost-effectiveness ratio, it could overestimate or underestimate the cost-effectiveness. Economic evaluations that do not incorporate these effects are hence unlikely to model the outcome of chlamydia testing in an accurate way. As recommended by Roberts et al (2004) (26), the correct method for economic evaluations of chlamydia screening should use a dynamic modelling approach. The current results were generated based on a static model and hence the validity of the cost-effectiveness is difficult to assess. However, assuming that the current risk estimates used are accurate for first time as well re-infections, and that each infection may potentially cause a PID, then the estimated benefits and cost-effectiveness would be considered valid.

The strength of the study is that it adds an illustrative example of costs, savings, health gains and cost-effectiveness transferable to similar interventions (which are implemented yearly in a majority of the counties of Sweden) that decision- and policy-makers could consider in decision-making and further programme planning. Results were explored by an extensive sensitivity analysis including best and worst alternatives of critical parameters such as estimates of medical sequel progression, effectiveness and prevalence rates.

6.3.2 Results and methods in comparison to earlier research

Our results both confirm and contradict earlier studies. Regarding larger screening efforts, Roberts et al (2007) (98) used a transmission dynamic model and determined that home based population screening in a hypothetical population of 50,000 men and women was not cost-effective. However, findings by Welte et al (2000) (96) showed that screening asymptomatic women aged 15-24 was cost saving using a dynamic approach. In a comparing study, Welte et al (2005) illustrated that when compared with static modelling, dynamic modelling yielded different cost-effectiveness ratios and identified other optimal screening strategies as it considers changes in the force of infection caused by screening. Dynamic modelling is however, more complex, data- and time-demanding, and more sensitive to some parameters affecting the force of infection than static modelling (156).

6.3.3 Policy implications

The normative foundation in cost-effectiveness analyses is that society should strive to achieve the maximum possible health benefit based on existing resources (16). This study showed that the Chlamydia Monday was likely to contribute to this vision since the cost-effectiveness ratios were stable and well below the Swedish threshold of acceptance. In the absence of evidence for the long-term effectiveness of testing interventions and screening, providing accessible chlamydia testing and treatment widely with equality/equity aspects in mind may be an appropriate approach.

The effectiveness of the intervention indicates a large space for improvement in which similar interventions could find more cases and attract more high-risk individuals within the budget constraints. Ultimately, self-selecting testing interventions may have
the potential to widen existing health inequalities in sexual health since the service fails to attract the individuals most at risk. In line with the results of this study and Study I and in order to reduce the risk of increasing inequalities, it is wise to target risk groups and design testing to the particular characteristics of disadvantaged groups.

6.3.4 Future research

In order to determine the effectiveness and cost-effectiveness of chlamydia interventions, investment in further knowledge of the complications of chlamydia and the benefits of testing and screening in terms of quality of life as well as long term consequences is required. Further research on the mathematical modelling of chlamydia control activities is also needed, as well as studies on how to target risk groups and engage individuals most at risk in testing activities. So far in Sweden, no cost-effectiveness analysis based on a transmission dynamic model has been done on Swedish data, which would be of value.

6.4 STUDY IV

Study IV estimated the financial costs for scaling up adolescent friendly health services to universal coverage in 74 low- and middle-income countries to approximately US$15.4 billion through 2015. This corresponds to approximately US$ 1.02 per adolescent in 2011, increasing to 4.70 in 2015. Out of the total cost, 39% constitutes programme costs and the rest is intervention costs. Contraceptive services represent the largest intervention cost (33% of total costs). The total cost for STI management was US$ 226.97 million of which US$ 44.58 million (approximately 20%), is for management of chlamydia.

6.4.1 Results in comparison to earlier research

Almost no studies explicitly compare the cost of providing interventions to adolescents versus adults. In this study we assume that unit costs for direct service delivery are the same, regardless of target group while the programme costs represent the additional efforts needed to improve quality. Another approach would be to calculate different unit costs for different target groups based on estimates or additional mark-ups. Differential service delivery costs specific to particular target groups are sometimes referred to as incremental costs for specific target interventions. This is similar to Paper III in which the intervention costs for increased availability and accessibility to testing and for demand creating activities (the awareness campaign) was estimated. Recent efforts by countries to explicitly include adolescent health in their national strategic plans demonstrate some progress in this area (157). At the family planning summit 2012, pledges of US$ 4.6 billion were made for improving delivery of family planning services from 2013-2020. Our estimate is higher (US$ 5.1 billion 2011-2015), but includes a more extensive definition of contraceptive services with information, counselling and provision, scaled up to universal coverage for all adolescents regardless of sexual activity.

6.4.2 Limitations

The estimates aimed at reflecting WHO’s recommended clinical guidelines, protocols and quality framework to the largest extent possible. However, assumptions were
applied to enable estimates of the nature and extent of health conditions and current coverage. The baseline data of current coverage and population in need was mostly based on country-specific estimates retrieved from DHS or AIS but also, in lack of better data, on regional and sometimes global averages. Lack of appropriate adolescent data of current coverage or PIN for any one intervention or country is unlikely to significantly affect the findings on the total resource need of the scale up but may have an impact on the findings related to that particular intervention or country.

No sensitivity or uncertainty analysis was undertaken. Such assessments would increase our understanding of the uncertainty of the results. However, based on data used, the results are more likely to be underestimated since adult coverage in the majority of countries is higher than for adolescents. The estimates are only indicative, as many different factors may influence the expansion of services and the actual cost of services.

The impact on disease epidemiology of service expansion was not accounted for in the estimation of costs. Ideally, risk of disease, influence on health care need and the changing need over time would be included. However, considering the five year time horizon, it is acceptable to assume limited effect on population epidemiology. The impact will however be larger for interventions that currently have low coverage if they can be scaled up, compared to interventions with already relatively high coverage.

The feasibility of scale-up largely depends on the country-specific health care context. The different health care sector characteristics and capacities of specific countries were not considered in this exercise. Consequently, programme activities and interventions were assumed to be implemented in all countries regardless of context. Investment in advocacy is needed, however we do not know how much advocacy is needed in different countries. Furthermore, the analysis took a provider perspective and does not account for opportunity or time costs for patients, or other implications related to the demand side of a health care analysis.

The proportion of STI management costs does not indicate the severity or size of the problem nor the impact of service expansion. STIs pose a prominent problem in this context since coexisting STIs increase susceptibility of acquiring and transmitting HIV by two- to fivefold. STI management and contraceptive services are important components in the HIV response in these countries and studies show that aggressive STI prevention, testing, and treatment reduces transmission of HIV (158).

6.4.3 Policy implications

The analysis illustrates a substantial investment gap in adolescent health services that needs to be bridged in order to reach universal coverage. Compared to current average health expenditure levels in the 74 countries, the additional costs would be equivalent to a significant increase in total expenditure on health in these countries. In the 35 low-income countries with 19% of the population and currently spending 23.80 per capita, 2.94 billion would be needed. On the other hand in the 39 middle-income countries with 81% of the population and currently spending on average 136.76 per capita, 12.47 billion would be needed until 2015 (159).
This paper does not consider financing scenarios, nor does it seek to advocate that the additional resources must necessarily be channelled through the government system. It should be noted that in the short run the public sector may not be able to bear the full costs for expanding coverage and there may be need for investment from private sector actors as well as investments by external donors where appropriate. The US$ 15.41 billion estimated here could be financed in a number of ways, including pre-paid health financing systems such as government tax-based health financing systems, or health insurance schemes; external donor support for specific programmes and services; or direct out-of-pocket payments. It is likely that in most countries, the package of services outlined in this paper would be financed from a combination of these.

6.4.4 Future research

The programme costs for the AFHS represent a holistic approach to health system expansion and improvement. Future studies should preferably focus on integrating these costs in the estimation of price tags in order to assure that total costs represent the improvement and tailoring of interventions to the specific target group. A useful next step would be to validate these estimates at country level and incorporate the financial requirements in strategic plans for health care expansion. Sensitivity assessments may also be better performed at the national level, where scenarios can be adapted to local contexts.

6.5 SUMMARIZING DISCUSSION

Studying chlamydia and other STIs from a public health economic perspective faces some methodological limitations. One challenge in economic analysis of chlamydia prevention is the lack of disaggregated and fully traceable data regarding testing, the number of reported cases stratified by age and sex as well as adolescent estimates of prevalence and service coverage. More reliable data on the long-term sequel associated with chlamydia are also needed to perform modelling studies with less uncertain parameters. This thesis lies in the border zone between public health and health economics which is also why analyses are sometimes based on ‘best-available’ data. This could be seen as a needed trade-off in order to produce these estimates and push the development forward.

Figure 12 illustrates the different aspects of the thesis and their possible connections to each other. STI prevalence and incidence is affected by many different factors of which risk groups, coverage of services and condom use are some. Prevention activities, aiming at reducing transmission (and incidence) by increasing condom use, define the cost-effectiveness. Cost-effectiveness of interventions affects resource allocation, which consequently affects prevention activities and coverage, which in turn ultimately influences STI outcomes. Coverage highly affects groups at most risk, which normatively should affect choice and design of prevention activities.
What does this thesis add? This thesis supplements information on risk according to social factors among young adults in Sweden, provides indications that structural factors are of importance for the outcome of chlamydia prevention, shows that one of the most common chlamydia interventions across Sweden is potentially cost-effective and that in order to expand quality and coverage of health care for adolescents in the least developed countries in the world, a substantial increase in current investments is required. Furthermore, the thesis illustrates a public health economic approach to the public health problem of sexually transmitted infections, applicable to low-, middle- and high-income countries.
7 CONCLUSIONS

This thesis offers new knowledge on the public health economic aspects of risk, prevention and resource allocation regarding chlamydia and other STIs. The results should be useful for decision-makers in the financial and operational planning of prevention programmes and health care.

The specific conclusions and recommendations are:

Similar to many other health outcomes, the risk of chlamydia infection is increased among the youngest adults, among individuals with low education or with high alcohol consumption. With the aim of eradicating differences in health and target risk groups, preventive measures should focus on risk-taking in general and deprived areas should be prioritized in allocation of resources and prevention activities.

Prevention structures and activities across counties of Sweden vary in scope, strategy and systematization. The differences point to the importance of structural factors for the outcome of prevention activities. National guidelines should consider increased focus on structural factors and thus potentially improve outcomes by assuring appropriate settings and prerequisites for prevention activities.

The Chlamydia Monday, a testing intervention of a self-selected sample of adolescents and young adults in Stockholm was proven cost-effective. The validity of the cost-effectiveness is difficult to ascertain since re-infection was not included in the model. The cost-effectiveness of testing interventions such as the Chlamydia Monday would be further improved if risk groups were successfully attracted by these interventions. According to the results of our study, the intervention should be considered a wise use of society’s resources.

The cost of scaling up a package of adolescent-friendly health services to universal coverage in 74 low- and middle-income countries was estimated at approximately US$ 15.4 billion. The total cost for management of chlamydia amounted to US$ 44.58 million, which consequently indicates the approximate cost of managing the majority of the global disease burden of chlamydia in adolescents. These estimates are essential to guide the advocacy for raising funds. In order to provide health care according to the specific needs of people at this critical stage of their lives, national and international organizations and countries need to fund and implement adolescent focused interventions.

Resource allocation in STI prevention depends on the risk of disease in the relevant population and the effectiveness and cost-effectiveness of prevention activities. A public health economic approach to STI prevention may help bridge the public health understanding of the problem with the health economic response to it.
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