Economic aspects of public health programmes for infectious disease control
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chapter 1

General Introduction
OVERVIEW

Payers of healthcare services constantly strive to efficiently use the limited resources they have. This is often done via strategic policy planning activities, which are especially relevant for public health services as they usually cover a wider population. Infectious diseases present one core area for public health activities. This thesis focuses on the use of different economic evaluation methods to inform public health policy decision making related to two sexually transmitted viruses, 1) the human immunodeficiency virus, HIV; and 2) the human papillomavirus, HPV.

THE ROLE OF ECONOMIC EVALUATIONS IN PUBLIC HEALTH INFECTIOUS DISEASE CONTROL PROGRAMMES

Economic evaluations are vital components of evidence-based decision making, applicable to the assessment of both new and existing public health control programmes. Such evaluations typically consider costs and/or outcomes associated with the interventions, and guide policy decision makers in optimal use of limited resources to achieve both allocative and technical efficiency [1]. The analytical methods in this thesis range from full economic analyses, such as cost-effectiveness analysis, or partial analyses, which only consider either costs or outcomes, for example a cost of illness/disease analysis [2].

PARTIES RESPONSIBLE FOR ADVISING COMMISSIONING DECISIONS

Public health strategies to control transmission require careful consideration of their clinical and economic impact. This requires an understanding of the disease epidemiology and which intervention strategy relating to the local population needs will optimise the limited resources required to implement them, ensuring greatest value for money.

In England, assessment of the clinical and cost-effectiveness of technologies are carried out by either the National Institute for Health and Care Excellence (NICE), or by other expert groups such as the Joint Committee for Vaccination and Immunisation (JCVI), or the Clinical Priorities Advisory Group (CPAG) of National Health Service (NHS) England. NICE typically considers technologies with marketing authorisation for an indication being appraised, with their final appraisal recommendation mandated to be commissioned within 3 months of the decision publication, with certain exemptions such as an affordability challenge. JCVI on the other hand, considers the clinical and economic evidence around immunisation programmes and makes policy recommendations to the Department of Health. CPAG, finally, considers off-label indications, and have historically taken on all evaluations of HIV interventions and haemophilia care.

The methods for economic evaluation of health care technologies generally follow the economic reference case specified by NICE [3], although JCVI and CPAG may adopt their own value assessment protocol to decide whether to recommend funding of a technology. For instance, JCVI has their own code of practice that is similar to the NICE reference case, but adopts their own interpretation of uncertainty based on findings from probabilistic
sensitivity analyses [4] Whilst NICE generally accepts a threshold of between £20,000 and £30,000 for interventions to be considered cost-effective, JCVI defines a vaccination strategy to be cost-effective if 90% scenarios fall within £30,000 threshold. CPAG, on the other hand, uses a complex relative prioritisation process to determine which technologies are funded within a defined budget. The process considers both patient benefits and financial impact.

ECONOMIC EVALUATION PERSPECTIVE
Having defined evaluation methodologies allow for standardised assessment of different technologies. Important criteria to define in any economic evaluations include the analytical perspective – typically the commissioner’s perspective i.e. who pays, the time horizon, the clinical pathways of intervention(s) and relevant comparator(s). Whilst Austria, Belgium (outcomes only), the Netherlands and the World Health Organization adopt a societal perspective, which includes consideration such as time off work, other countries including Australia, Canada, England, and Wales take a narrower perspective of cost to the healthcare system and outcomes affecting patients, and occasionally (e.g. NICE in England) the carer’s perspectives [5]. Specifically, the perspective taken in England in terms of cost is usually that of the NHS and personal social services.

COMMISSIONING LANDSCAPE IN ENGLAND
To fully understand the context and potential impact of my analyses, which focused mostly on England, it is important to have an overview of the commissioning landscape in this country. The provision of health services in England, including that of public health, falls under the commissioning responsibility of either the Department of Health, NHS England, or local authorities, depending on the specific technology and disease area. The evaluation perspective corresponds to this commissioning responsibility. In accordance with the Health and Social Care Act 2012, commissioning of public health services in England falls under the responsibility of either the NHS or local authorities. Some of the defined public health functions are commissioned by NHS England, through an annually renewed arrangement with the Secretary of State for Health, under a Public Health functions agreement (Section 7A) [6]. Programmes covered under this commissioning arrangement include, inter alia, vaccination, and certain screening programmes, including cancer screening. Under the same act, local authorities have statutory public health responsibilities, which comprise commissioning of sexual health services, e.g. testing and treatment of sexually transmitted infections (STIs) including HIV testing, and HIV prevention initiatives [7]. HIV treatment, however, remains the commissioning responsibility of NHS England, under its specialised services. Such arrangement means that, depending on the disease area, commissioning responsibilities could rest with either NHS England or local authorities or be jointly commissioned based on prior agreement.

Thus, the assessment of cost-effectiveness of new or existing technologies may be undertaken by the commissioners locally, for instance at a local authority level or at a national
level, as done through the JCVI in their deliberations of value for money of new or alternative national vaccination strategies or occasionally via NHS England’s Clinical Priorities Advisory Group (CPAG) [8].

ROLE OF PUBLIC HEALTH INFECTIOUS DISEASES CONTROL INTERVENTIONS

Public health infectious diseases interventions generally aim to control infections either through prevention of new infections (i.e. primary prevention) or diagnosis and treatment of cases (i.e. secondary prevention). Such programmes are often designed with the aim of achieving the greatest net value, i.e. considering value to both population’s health and monetary benefits to the commissioner, within budgetary constraints. Sometimes this can be best achieved through high population coverage and occasionally through targeted delivery to a population at greater risk of contracting an infection and/or onward transmission to others. Examples include i) the HIV immediate antiretroviral treatment policy [9], where all newly diagnosed persons are offered antiretroviral treatment immediately regardless of CD4+ count, primarily to reduce onward HIV transmission and secondarily to prevent disease progression; ii) national immunisation programmes such as hepatitis B vaccination that are offered to populations at higher risk of infection e.g. people who inject drugs (PWID) and men who have sex with men (MSM), and more recently to infants and children under 10 years old, born after 1 August 2017 [10]. These policy decisions were guided by their cost-effectiveness evidence. Many countries have their own immunisation schedule that caters to local disease epidemiology.

INFECTIOUS DISEASES & THE POLICY QUESTIONS – HIV & HPV

This thesis focuses on preventive interventions against two viruses that can be transmitted sexually: 1) the human immunodeficiency virus, HIV; and 2) the human papillomavirus, HPV. HIV incidence has remained relatively stable over 2006 to 2015, with some indication of declining in more recent years attributed to existing public health control initiatives [11]. On the other hand, national school-based HPV vaccination programme covers girls only. Further opportunities exist to provide primary and secondary prevention to complement existing public health control interventions in England. Both viral infections usually have long periods where the infected host remain asymptomatic, which increases the probabilities of onward transmission without knowledge of those infected. As such, public health infection control programmes aim to reduce those undiagnosed and prevent new infections. Existing interventions include national HIV screening recommendations for local areas with high diagnosed HIV prevalence, antiretroviral treatment as prevention policy, and the HPV vaccination programme for adolescent girls. This thesis covers three different public health programmes aimed at reducing the incidence of HIV or HPV infections.
HIV

HIV is transmissible through body fluids, including blood, semen, and breast milk. Persons infected with HIV may have mild flu-like symptoms during the initial weeks after contracting the virus (acute phase), before becoming asymptomatic for a long period. The virus gradually destroys an infected person’s immune system over many years [12]. In later stages, as the person’s immune system is progressively damaged, they become more likely to get opportunistic infections. The advanced stage of HIV infection is commonly known as AIDS – acquired immune deficiency syndrome. The risk of transmission is highest during the acute and advanced phases of the infection [13].

Laboratory-based serology, as well as point-of-care tests, are used to diagnose HIV [14]. The general testing algorithm is to screen using a test that has high sensitivity and if the result is reactive, to confirm with a different test that has high sensitivity and specificity. For persons diagnosed with HIV, treatment using daily highly active antiretroviral therapy (HAART) reduces viral load and could result in near normal life expectancy [15]. Reductions in viral load mean that those on antiretroviral treatment have substantially reduced risk of transmitting the virus [16]. The current formulation of antiretrovirals requires daily intake for the remaining life of an infected person. There is currently no known cure for HIV.

Over a 10 years period from 2008 to 2017, the annual number of new diagnoses in England has declined, from 6,637 in 2008 to 3,973 in 2017 [11]. During this decade, as treatment and life expectancy continued to improve, the number of persons accessing HIV specialist care in England increased, from 56,353 in 2008 to 85,537 in 2017, with most infections acquired through sex between men or heterosexual contact. Meanwhile, the proportion of those seen in care who received antiretroviral treatment increased from 78% to 98%. The reduction in HIV incidence observed over the past decade has been attributed to increased HIV testing and improved access to antiretroviral treatment [17] [18].

In this thesis, I evaluate two public health strategies for the control of HIV. The first is the introduction of pre-exposure prophylaxis (PrEP). Towards the end of 2014, as evidence on high PrEP efficacy was beginning to emerge and to follow-up on the promising results of the UK PROUD pilot trial [19], I evaluate the introduction of this programme within the NHS. To inform the commissioning decision by NHS England and local authorities around the introduction and costs I focussed on both cost-effectiveness and budgetary impact of the programme. Therefore, the aim of chapter 2 is phrased as: to analyse whether the provision of HIV pre-exposure prophylaxis to persons at higher risk of contracting the virus is cost-effective in England and whether such introduction presents an affordability challenge to the commissioner [20].

As the cost-effectiveness of HIV interventions such as PrEP prevention depends on the life time treatment cost of HIV, I performed a subsequent analysis of the possible change in life time costs of HIV in the changing environment of drugs coming off patent. Consequently, Chapter 3 investigates how this lifetime care cost look like as generics have become available [21].
The second strategy I evaluated to control HIV concerned HIV screening. An important outstanding question for local authorities in England, who are responsible for commissioning of local public health initiatives including HIV prevention, is the optimal setting to deliver screening. Screening could be delivered via local general practice when patients attend clinic for first time, for example, where they have a brief registration check-up, or in hospital settings where patients have their blood withdrawn for testing prior to acute admissions. Thus, I looked at the cost consequence of investing screening in these two settings in Chapter 4 [22], to help local commissioners identify optimal setting for HIV screening based on local HIV prevalence. The cost builds on micro-costing information collected as part of a pilot study, whilst consequence is number of reactive tests.

HPV

HPV is a very common viral infection that is transmitted via skin to skin contact and is generally asymptomatic. There are more than 100 different HPV subtypes; most are not known to be carcinogenic. However, at least a dozen are believed to cause cancer, such as HPV-16, -18, and -33 [23] [24]: these are referred to as “high-risk” (HR) HPV types. Almost all cervical cancers have detectable HR HPV DNA and HR HPV infection is considered a necessary (though not sufficient) cause of all cervical cancers. HR HPV also plays a role in cancers of the vulva, vagina, anus, penis, oropharynx, oral cavity, and larynx. Not all persons infected with HR HPV will progress to cancers later in life.

Of the “low-risk, LR” types, two, HPV-6 and -11, cause the majority of genital warts, a very common symptomatic and troublesome, though not life-threatening, STI.

One of the earliest public health interventions related to HPV in England was the secondary prevention intervention of cervical cancer screening programme aimed at diagnosing and treating cervical pre-cancers and cancers. Diagnosis methods have evolved over time, from cytology testing initially that subsequently used HPV testing as an adjunct to cytology in order to triage cytology borderline results and as a test of cure and moving to HPV primary testing by 2020 [25]. Women who are HPV positive or has high-grade dyskaryosis are referred to colposcopy for further cervical examination [26]. The Papanicolau (pap) smear test was invented in the 1920s but organised call-recall mechanism for universal cervical screening only began in England in 1988. Each year over 2005 and 2014, in women aged between 20 and 64 years, around 175,000 to 200,000 borderline or low-grade abnormalities and ~45,000 high-grade abnormalities or worse have been recorded, with ~2,300 to 2,600 cases of cervical cancer registered for all ages [27]. Although cervical screening has been shown to reduce late stage diagnoses and deaths, screening does not necessarily prevent occurrence of cervical abnormalities in the first instance [28].

Although screening has been successful in reducing risks of cervical disease progression, HPV infection and cervical cancer remained an important public health issue. The remaining disease in countries with effective screening programmes as well as the disease in countries without cervical screening motivated vaccine development as a means of
primary prevention. Two HPV vaccines became available around 2006/07 [29] [30], offering protection from infections with HPV types 6, 11, 16, and 18 (quadrivalent) or HPV 16 and 18 only (bivalent). England began a national HPV vaccination programme in September 2008, covering girls only, with three-dose vaccination offer for those aged 12-13 years old (plus a catch-up programme to age 18). This followed a JCVI recommendation that was informed by cost-effectiveness analyses that showed when female vaccination coverage was high, adding boys to the vaccination programmes would be unlikely to be cost-effective [31]. The programme used the bivalent vaccine initially, before transitioning to the quadrivalent vaccine. In September 2014, the programme adopted a two-dose schedule for under 15s instead of the originally licenced three-dose schedule [32].

Males having sex with women were expected to gain considerable indirect benefit from the female HPV vaccination programme. However, men would be far less protected if they engage in sex with men. Men who have sex with men represent a high-risk group with ongoing exposure, with higher risk of HIV infection acting as a co-factor for HPV infection and disease progression. In England, the attendance of MSM at genitourinary medicine clinics, also known as sexual health clinics, offered the opportunity to offer HPV vaccination to MSM – ideally at their first attendance. Therefore, in Chapter 5, a previously published heterosexual dynamic cohort model is adapted to consider HPV transmission among MSM, adjusted by HIV status, to inform whether and which strategy of HPV vaccination for MSM could be cost-effective [33].

A related question on the cost-effectiveness of MSM HPV vaccination, having performed a cost-effectiveness model in England, is whether my findings are in agreement with other published work. Hence, a systematic review was conducted to allow for this comparison (Chapter 6) [34].

Finally, with an increasing number of HPV models including non-cervical outcomes, it was necessary to ensure that models used updated and relevant cost and utility estimates. Thus, in Chapter 7 [35], I conduct a systematic review and meta-analysis of the cost and utility of HPV-related non-cervical outcomes so as to better inform economic parameter values input to future HPV models.

REFERENCES

5. Rival perspectives in health technology assessment and other economic evaluations for investing in global and national health.


part 1

Human Immunodeficiency Virus (HIV)