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## Economic aspects of public health programmes for infectious disease control

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# chapter 8

**Discussion & Concluding Remarks**



## DISCUSSION

The work in this thesis successfully informed major public health policy directions in England – HIV PrEP and MSM HPV vaccination. It also provided analyses that will inform future economic evaluations, HIV testing policy directions, and proposals for consideration of changes to health technology methodology around use of generic comparators.

The objective of Chapter 2 was to assess whether and how a PrEP policy can deliver value for money for the NHS in England (1). Using a decision analytical model coupled with surveillance data, I found that although PrEP may be cost-effective under certain scenarios, its cost-effectiveness is highly dependent on risk of HIV in those given the drug, real world effectiveness of the drugs linked to treatment adherence, and the cost of the drug. As its cost-effectiveness is dependent on the absolute expected HIV incidence of a person given PrEP, but this risk of HIV based on future behaviour is a subjective estimate, dependent on clinician judgment of risk of the patients in their care, and patients' own assessment of risk and anticipated behavioural change, this estimate of risk is uncertain, resulting in corresponding uncertainty around the cost-effectiveness. The budgetary impact of a large scale public health programme is also substantial, especially at list price of the proprietary product. Thus, the policy conclusion is that although PrEP has very promising clinical potential, its cost-effectiveness is highly uncertain especially in the context of considering its substantial budget impact to deliver value for money. These findings resulted in an NHS England decision to fund the world's largest PrEP implementation trial from September 2017 (2), in order to assess its value for money when delivered at scale.

The analysis explored different plausible scenarios of PrEP delivery, specifying that although PrEP could be cost-effective when given to those subgroups with an HIV incidence of greater than 3.3 per 100 person-years, the pragmatism of identifying this subset of patients would be challenging, as sexual behaviour will likely change over time. Ergo, the subgroups to be targeted are dynamic. The incidence of 3.3 per 100 person-years was a proxy measure of risk, estimated from the cohort of patients recorded in GUMCAD with a history of STI diagnosis, on the reasoning that STIs are transmitted in the context of sex without condom. Notably, this is a measure of past risk and not future risk. Moreover, it would not be possible to limit PrEP only to those who have had a STI diagnosis in practice as it would not be feasible to apply this criterion nor would it be an equitable option.

Additionally, at its proprietary price, there was uncertainty on its budgetary impact, as uptake and duration on PrEP in the real-world was unknown. During the pilot UK PrEP trial of 500 participants, uptake was slow initially but as evidence on its efficacy, related to adherence (higher efficacy observed in those who adhered to treatment, compared with lower level of efficacy of 44% initially reported in the intention to treat analysis of an earlier international PrEP trial – the iPrEx study (3)), began to emerge, uptake rates substantially increased. In the absence of surveillance data on sexual behaviour, it would be challenging to provide an accurate estimate of plausible uptake. This is particularly important as there is an estimated half a million MSM in England, and a 10% coverage would translate to 50,000 MSM on PrEP, resulting in a significant corresponding budget impact.

In terms of the cost-effectiveness modelling approach, a deterministic decision analytical model was used. This approach was justified on the basis of the likely small population that would be given daily PrEP initially for as long as they were considered at high risk, limited by feasibility of programme delivery at scale over a short period, coupled with the notion that high drug cost due to market exclusivity protection would be for a time-limited period, necessitating important policy commitment to high upfront investment during this initial period time. Subsequently, as the programme builds up over time and as the combination antiretroviral used as PrEP loses market exclusivity (by February 2020), prices would be lower as generics become available, under which most scenarios evaluated were found to be cost-effective even in the context of a static model. However, dynamic modelling would be a useful to inform policy decisions as PrEP usage expands, whereby it would then be important to capture the indirect effect on infection transmission, and when the force of infection begins to fall as incidence declines, to inform future delivery of a programme that maintains its value. This represents an important area for future research.

A specific area to monitor is whether PrEP introduction would lead to increased STIs as individuals reduce condom usage. These should be captured in epidemiology surveillance data. It will be especially important to maintain close scrutiny of STIs such as hepatitis C and gonorrhoea, the former can be asymptomatic for a long time and is costly to treat, and the latter has a high risk of antimicrobial resistance.

A learning outcome from this analysis was the approach to presenting uncertainty. Economic models are founded on their background assumptions and methods to test the uncertainty in modelling assumptions include one-way, two-way or probabilistic sensitivity analysis, or scenario analysis. In this particular example, the main uncertainty was the drug cost, which is relatively fixed (dependent on commercial agreement), and around HIV incidence in those given PrEP, which, as mentioned, is subjective to how the programme will be delivered in real world and unknown at the time of analysis. Both could not be reasonably presented as uncertainty distribution to be applied to a probabilistic sensitivity analysis. Consequently, tornado diagrams representing one-way sensitivity analysis and multivariate sensitivity analysis considering progressive changes in plausible scenario assumptions were presented.

Another important learning outcome from this chapter is the need to consider budgetary impact alongside any cost-effectiveness analysis. Ultimately, cost-effectiveness is linked to the budget, as cost-effectiveness threshold should relate to opportunity cost of replacing least cost-effective care at the margin of the whole healthcare budget spend (4) (5). As the results show, PrEP could be very cost-effective but still unaffordable. In an ideal world, the cost-effectiveness threshold should link to the amount of budgetary resources an intervention displaces. After all, the concept of opportunity cost in a fixed budget setting meant that decisions to invest in something translates to funding being displaced elsewhere. Several other authors have previously discussed this (6) (4) (7). More recently, NHS England introduced a policy where pharmaceutical companies may enter into commercial discussions with them as the commissioner should the introduction of a new technology

generate substantial affordability challenge i.e. very high budget impact (over £20 million in a single year) (8). This was subsequent to the situation observed with hepatitis C directly acting antivirals, drugs that are curative, hence justified high upfront cost against lifetime disease management cost, but representing a high financial burden to the payer upfront. Similar scenarios are likely to occur in the future, especially with upcoming gene therapies with curative potential, and questions around budget impact as treatments are provided upfront and potentially substantial, which would be a major consideration for policy makers and commissioners. A future consideration of the practicalities of translating this economic concept is whether NICE appraisal committees would begin to at least mention the budget impact of new technology introduction to committee, which is not currently done.

In Chapter 3, I addressed the question of how much lifetime HIV care cost would change in the context of anticipated generic availability for currently used antiretrovirals, with a view for these estimates being used in future economic evaluations (9). Average lifetime HIV care cost was estimated to be ~£200,000 with 3.5% annual discounting applied, at current BNF list price i.e. not considering generic availability for most antiretrovirals. However, the lifetime care cost could be lowered by more than half of this estimate (~£70,000; 3.5% annual discounting of costs) when I considered generics' availability for antiretrovirals with sufficient usage and prices at 10% of current proprietary list price. This is because most commonly used antiretrovirals would lose market exclusivity within the next decade, whilst a person infected today at an average age of 35 years old is expected to live for the next 45 years i.e. the latter 35 years potentially on generic antiretrovirals. As lifetime HIV cost consists of both the cost of antiretroviral and HIV care, reduction in antiretroviral cost by 90% does not reduce total lifetime cost to a corresponding 10% of unadjusted estimates, as non-drug cost was around £1,450 per person per year, which is approximately 65% of total care cost (antiretroviral at 10% list price plus non-drug). Yet, an important methodological learning from this chapter concerned the impact of including future generic availability in cost analysis (and cost-effectiveness analysis, for that matter). Although actual level of commercial discount for each antiretroviral is different and will likely change over time, I have reviewed historical published procurement prices to guide my assessment, and explored scenarios of discounting at 20%, 30%, and 50% so that the reader could have a sense of how this lifetime cost changes.

An important implication of this research is the proposal that future appraisal of new technologies such as potentially transformational treatment in the future, not limited to HIV only but as an example a new HIV gene therapy (10) or even consideration of use of tenofovir alafenamide with better renal side-effect profile in place of tenofovir disoproxil as PrEP, economic evaluations should consider lifetime cost scenarios of intervention under consideration as well as comparators under assumptions of generic availability, which has implications on the maximum allowable price of new technologies. Although it would be debated that new technologies may come in that would cost more in the future, their total cost should only be higher when they either provide additional incremental benefit to current treatment, but not when their prices were set based on higher price of comparators

without incorporating generic pricing of comparators. This approach should be acceptable in the particular disease area of HIV, given many generics are used widely globally in the fight against HIV with US Abbreviated New Drug Application (ANDA) license for generics (11), giving some certainty on generic availability and supply. In future iterations of appraisal methodology in e.g. NICE reviews, it would be worthwhile to be explicit about situations where out of patent savings could be considered.

In chapter 4, I addressed the question of how much each HIV screen would cost when offered as part of hospital acute general medical admissions (ACUs) or in general practice settings (GPs) (12). Using pilot study data, I reported shorter time spent per offer and higher uptake in ACUs (2 minutes, 90% uptake) compared with GPs (5 minutes, 60% uptake). Cost per test ranged from £8.55 to £13.50 in the pilot settings, and was more than 50% cheaper in ACUs compared with GPs, due to less time needed for test offer and lower laboratory diagnostic test cost. Cost per reactive result was lowest at high local HIV positivity rate. Scenario analyses of different staff pay levels, test uptake rate, and local HIV positivity were presented to allow local assessment of a scenario most reflective of their local arrangements.

This work successfully addressed questions from local commissioners on how screening could be optimised in the context of a constrained budget, a question around allocative efficiency, when current national guidelines are available on local prevalence threshold to begin screening. It would not be straightforward to consider cost-effectiveness of screening within the context of a fragmented healthcare commissioning landscape, as HIV diagnoses and onward transmission prevented (benefits accrued) through population screening funded via local budgets would lead to cost-saving in a separate budget – that of the commissioners of HIV treatment i.e. NHS England. A whole system approach would be needed to address this. Thus, the analysis presented various scenarios that could be applied dependent on local set-up, as it was recognised that with 152 local authorities, each would have its own, unique local commissioning arrangements and requirements. The main uncertainties for a national HIV screening cost figure were around human resource involved in screening and population HIV prevalence. These uncertainties and their impact on screening cost were presented as scenarios, which would allow local commissioners to choose which applied to their specific local context. The analysis is straightforward and provides a clear illustration to local commissioners of the cost implications of implementation, potentially helping them make an informed decision on how screening should be arranged in accordance to their local needs.

In Chapter 5, I explored the cost-effectiveness of a three-dose HPV vaccination programme offered via sexual health clinics (also known as genitourinary medicine, GUM, clinics) to MSM, to address policy deliberations of offering vaccination to this population in the proposed setting (13). As a relatively high proportion of MSM could have been previously exposed to HPV by the time they first attend a GUM clinic (~30% with HPV 16/18 (14)), HPV vaccination offers prevention from repeat infections and protection of naïve individuals at very high ongoing risk of exposure. This strategy is slightly different to national girls vaccination programme, where vaccination delivery before sexual debut is important.

A dynamic compartmental model, adapted from previous work (15), suggested vaccination to be most cost-effective when offered to all MSM up to age 40. Interestingly, cost-effectiveness of vaccination strategies of all MSM by age groups (16 to 25, 30, 35, and 40 years) improved as the age groups widen. This was likely due to the higher HIV disease burden as they age and the corresponding risk of cancers and greater QALY gained offered by vaccination of MSM up to age 40 years. Following findings from this cost-effectiveness analysis, a pilot MSM HPV vaccination programme was introduced in England from 2016, and subsequently expanded to a national programme from April 2018 (16). The programme offered coverage for MSM indeed up to a higher age limit; i.e. up to and including those aged 45 years old.

As alluded to earlier, GUM-based HPV vaccination strategies serve to prevent repeat infections as well as protect naïve individuals. However, I anticipate that further impact on disease incidence could still come from universal vaccination of boys prior to sexual debut. At the same time, introduction of gender-neutral vaccination i.e. adding boys to current girls' programme, does not preclude continued offer of HPV vaccination to MSM GUM attendees, as MSM could have only moved to England post adolescent years or they may have missed vaccination. For example, based on 2015-16 GUMCADv3 enhanced surveillance data, about 28% of MSM reported country of birth outside of the UK (17). It would be important for periodic review of cost-effectiveness, informed by epidemiological data e.g. warts episodes to assess need, and inform future policy directions.

In Chapter 6 (18), a systematic review was conducted to identify published economic evaluations on MSM HPV vaccination to allow comparison with the work done in Chapter 5. The review found three other models that considered HPV vaccination in this population. All three were deterministic models. Other variations included consideration of anal cancer only, the use of HPV vaccination not as primary prevention but tertiary prevention after high-grade anal intraepithelial neoplasia. Base case results were different, as the papers considered different vaccination strategies. One paper (19) found vaccination to be cost saving when offered to HIV positive MSM. Two papers (20) (13) suggest MSM HPV vaccination to be likely cost-effective within ICER values of under US\$20K (2016 values). The fourth paper (19) found vaccination offered to HIV negative MSM treated for high grade anal intraepithelial neoplasia to likely be cost-effective with ICER nearing US\$100K (2016 values).

Despite limited models, different modelling approach and assumptions, a general theme from these studies reveal modelling outcomes to be most sensitive to assumptions around vaccine efficacy and price. However, as the models are from US or UK perspectives only, translation of their recommendation warrants further consideration to other countries with different epidemiology.

Future studies could consider synchronising parameter assumptions to test output generated by different models, similar to work done by Brisson et al. on models of HPV in heterosexuals (21).

In the final chapter (Chapter 7), I aimed to improve the understanding of published evidence on cost and (dis)utility associated with non-cervical HPV-related outcomes in order



to inform parameter input assumptions in future economic evaluations (22). This systematic review and meta-analysis on published cost and utility estimates found 61 papers (35 on costs, 24 on utilities, and 2 on both) and substantial variations in cost and utility estimates for all diseases considered, where there was more than one publication. These variations in value estimates could result from the differences in cancer site, disease stages, study population, treatment pathway/settings, treatment country and utility elicitation methods used. I conclude that although these estimates have now been collated, which could improve transparency in assumptions applied in future models, it must be recognised that as patient disease management changes over time, there will be corresponding effects on both cost and utility. Furthermore, some diseases such as head and neck cancer can be very variable with different disease stages and rapidly changing management pathways, again necessitating future updates to the estimates. These must be considered when applied to future economic evaluations, to ensure that assumptions are up-to-date and closely reflect the case mix of patients being evaluated.

## CONCLUDING REMARKS

The analyses in this thesis identified strategies for national public health control programme, such as HIV PrEP, MSM HPV vaccination, and HIV screening that could be optimised to deliver most value for money, such as targeted HPV vaccination of MSM up to a defined age group. The thesis demonstrated how economic evaluations could provide important input to guide policy deliberations. Different methods of evaluations could be applied, depending on the policy question posed. Findings around cost-effectiveness should not be considered independently of budget impact and affordability considerations, as the two are interlinked. Furthermore, health economists providing these economic analyses need to be mindful of the evolving and dynamic disease management landscape, including foresight of market dynamics, which affects cost of treatment. Ergo, in this thesis, I only demonstrate some aspect of one – yet crucial - piece of the overall puzzle of public health decision making.

## REFERENCES

1. Economic evaluation of HIV pre-exposure prophylaxis among men-who-have-sex-with-men in England in 2016. Ong, K.J., et al. 42, 2017, *Eurosurveillance*, Vol. 22. 10.2807/1560-7917.ES.2017.22.42.17-00192.
2. NHS England. News, NHS England announces world's largest single PrEP implementation trial to prevent HIV infection. s.l. : NHS England, 2017.
3. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. Grant, Robert M, et al. 27, 2010, *New England Journal of Medicine*, Vol. 363, pp. 2587-2599. 10.1056/NEJMoa1011205.Preexposure.
4. The NICE Cost-Effectiveness Threshold - What it is and What that Means. McCabe Christopher, Claxton Karl and Culyer Anthony J. 9, 2008, *PharmacoEconomics*, Vol. 26, pp. 733–744.
5. Lomas James, Martin Stephen and Claxton Karl. Estimating the marginal productivity of the English National Health Service from 2003/04 to 2012/13. Centre for Health Economics, University of York, UK. York, United Kingdom : s.n., 2018.

6. When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. Bilinski, Alyssa, et al. 10, s.l. : Public Library of Science (PLoS), 2 10 2017, PLOS Medicine, Vol. 14, p. e1002397. 10.1371/journal.pmed.1002397.
7. Determinants of Change in the Cost-effectiveness Threshold. Paulden, Mike, O'Mahony, James and McCabe, Christopher. 2, s.l. : SAGE Publications Inc STM, 23 8 2016, Medical Decision Making, Vol. 37, pp. 264-276. doi: 10.1177/0272989X16662242. 10.1177/0272989X16662242.
8. National Institute for Health and Care Excellence. Budget impact test. NICE guidance NICE technology appraisal guidance. [Online] 2019. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/budget-impact-test>.
9. HIV care cost in England: a cross sectional analysis of antiretroviral treatment and the impact of generic introduction. Ong KJ, et al. 2019, HIV Medicine (in press).
10. Passaes, Caroline P. and Sáez-Cirión, Asier. HIV cure research: Advances and prospects. Virology. s.l. : Academic Press Inc., 2014. Vols. 454-455, 1, pp. 340-352. 10.1016/j.virol.2014.02.021.
11. U.S. Food and Drug Administration. Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan. International Programs. [Online] 2019. <https://www.fda.gov/internationalprograms/pepfar/ucm119231.htm>.
12. Estimated cost per HIV infection diagnosed through routine HIV testing offered in acute general medical admission units and general practice settings in England. Ong, K.J., et al. 4, 2016, HIV Medicine, Vol. 17. 10.1111/hiv.12293.
13. Impact and cost-effectiveness of selective human papillomavirus vaccination of men who have sex with men. Lin, A., et al. 5, 2017, Clinical Infectious Diseases, Vol. 64. 10.1093/cid/ciw845.
14. King, Ellie. Human papillomavirus infection in men who have sex with men attending a sexual health clinic: prevalence, risk behaviours & vaccine acceptability. 2014.
15. Transmission dynamic modelling of the impact of human papillomavirus vaccination in the United Kingdom. Choi, Yoon Hong, et al. 24, s.l. : Elsevier Ltd, 28 5 2010, Vaccine, Vol. 28, pp. 4091-102. 10.1016/j.vaccine.2009.09.125.
16. Public Health England. Guidance, HPV vaccination pilot for men who have sex with men (MSM). GOV.UK. [Online] 2016. <https://www.gov.uk/government/publications/hpv-vaccination-pilot-for-men-who-have-sex-with-men-msm>.
17. Predicting STI Diagnoses Amongst MSM and Young People Attending Sexual Health Clinics in England: Triage Algorithm Development and Validation Using Routine Clinical Data. King, Carina, et al. s.l. : Elsevier BV, 28 11 2018, EClinicalMedicine, Vols. 4-5, pp. 43-51. 10.1016/j.eclinm.2018.11.002.
18. Cost Effectiveness of Human Papillomavirus Vaccination for Men Who have Sex with Men; Reviewing the Available Evidence. Setiawan, D., et al. 2018, Pharmacoeconomics. 10.1007/s40273-018-0649-y.
19. Clinical effectiveness and cost-effectiveness of quadrivalent human papillomavirus vaccination in HIV-negative men who have sex with men to prevent recurrent high-grade anal intraepithelial neoplasia. Deshmukh, Ashish A, et al. 51, 2014, Vaccine, Vol. 32, pp. 6941-6947. <https://doi.org/10.1016/j.vaccine.2014.10.052>.
20. Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis. Kim, Jane J. 12, s.l. : Elsevier, 1 12 2010, The Lancet Infectious Diseases, Vol. 10, pp. 845-852. doi: 10.1016/S1473-3099(10)70219-X. 10.1016/S1473-3099(10)70219-X.
21. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Brisson, Marc, et al. 1, s.l. : Elsevier Ltd, 1 11 2016, The Lancet Public Health, Vol. 1, pp. e8-e17. 10.1016/S2468-2667(16)30001-9.

22. Systematic review and evidence synthesis of non-cervical human papillomavirus-related disease health system costs and quality of life estimates. Ong, Koh Jun, et al. 1, 1 2 2019, *Sexually Transmitted Infections*, Vol. 95, p. 28. 10.1136/sextrans-2018-053606.



