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Cost-utility analysis of screening high-risk groups for anal cancer

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ABSTRACT

Objectives Cost-utility analysis of screening for anal cancer in high-risk groups from a UK perspective.

Methods Criteria for the assessment of screening programmes were combined in a Markov model representing the natural history of anal cancer and HIV infection in the UK population of men who have sex with men (MSM). Alternative screening programmes were overlaid on the natural history model to evaluate their impact. The model was populated using data derived from a systematic review of the literature, and calibrated probabilistically to represent joint uncertainty in the input parameters.

Results Reference case results showed screening is unlikely to be cost-effective. Sensitivity analyses identified two important parameters: regression from low-grade anal intra-epithelial neoplasia (AIN) and utility effects. Increased AIN regression rates resulted in a minimum incremental cost per QALY gained of £39 405, whereas a best case scenario reduced the ratio to £20 996.

Conclusions There are major areas of uncertainty. New analyses of existing primary data, undertaken specifically to inform regression rates may usefully update key parameters at little additional cost. If these analyses increase the likelihood that screening is cost-effective, further studies of the utility effects of treatment for high-grade AIN, and potential screening attendance rates may be justified.

Keywords cancer, economics, screening

Introduction

Anal cancer is a rare neoplasm that has been etiologically related to a sexually transmitted agent, the human papillomavirus.[1,2] In 2003, there were 722 registrations of newly diagnosed malignant neoplasm of the anus and anal canal in England.[3] The low-incidence rate means that mass population screening is not indicated for anal cancer. However, if identifiable high-risk groups could be defined, then it may be effective and cost-effective to offer a targeted screening programme. Men who have sex with men (MSM) are a high-risk group, due to the increased risk of exposure to the HPV virus.[4] Immunosuppression is also an observed risk factor, when combined with the elevated risk in MSM, an obvious high-risk sub-group is HIV positive MSM.[4] The latter group may be at particular risk since the advent of highly active antiretroviral therapy (HAART) has reduced deaths from competing causes.[5]

Goldie *et al.*[6,7] have published separate cost-effectiveness analyses of screening programmes for HIV positive and negative MSM. They found that screening either of these high-risk groups was a cost-effective strategy. However, issues remain around the applied modelling approach, such as the separate analysis of HIV positive and negative MSM, and the estimation of key parameter values. The previous models were also developed from a US perspective, and so the aim of this study is to assess an alternative modelling approach and to estimate the lifetime costs and consequences of screening for anal cancer in high-risk MSM groups from a UK NHS perspective.

Methods

The cost-effectiveness of a screening programme is a function of well-rehearsed criteria for defining whether a condition is

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suitable for screening in a defined population: the importance of the health problem, the understanding of the natural history and epidemiology, and the safety, simplicity, accuracy and acceptability of the screening test to the general population.[8] These issues were combined using a cohort-based Markov model to represent the natural history of anal cancer, alongside the natural history of HIV in a UK MSM population.

The model was populated using data derived from a review of the literature, and then calibrated probabilistically to represent the joint uncertainty in the input parameters. Alternative screening programmes are overlaid on the natural history model to predict their impact on health service costs and quality-adjusted life years (QALYs) gained over the lifetime of a cohort of MSM. A full probabilistic sensitivity analysis was undertaken, and costs and QALYs were discounted at 3.5% per annum. Cost estimates were uprated (where necessary) to 2007 values.

Model structure

The model structure, shown in Fig. 1, describes the simultaneous incidence and progression of HIV infection and anal cancer HIV negative MSM with no anal intra-epithelial neoplasia (AIN) may develop HIV infection with a CD4 count >500, which may then progress to a CD4 count of 200–500, and then to <200. AIDS was not explicitly modelled as relevant data sources expressed the linkage between HIV infection and mortality, and anal cancer, as functions of CD4 count. In any of the HIV states, individuals may be diagnosed and start to receive appropriate treatment that reduces their transition probabilities to subsequent CD4 count states and death, as well as to the anal cancer states. The choice of CD4 count categories was informed by data available to populate the model, as described in the model population section.

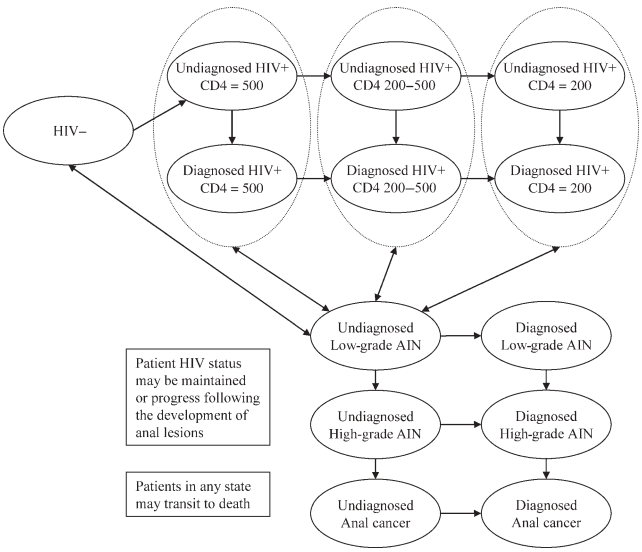

Fig. 1 Cost-effectiveness acceptability frontier for increased AIN regression sensitivity analysis.

At the same time as individuals may be progressing through the HIV states, they may also be progressing through the AIN states, which are the precursors to anal cancer. Individuals without AIN in the seven HIV-related states are assigned alternative probabilities of developing either low- or high-grade AIN. They may then progress through the high-grade AIN state to develop invasive anal cancer. Only a single anal cancer state is represented primarily due to data limitations that are discussed in Model Population section.

The model was developed as a cohort-Markov model using an annual cycle (chosen because an annual screening programme was the shortest interval tested). The time horizon of the model followed MSM to a maximum age of 100 years.

Model population

Systematic literature reviews were undertaken of the epidemiology and natural history of anal cancer, and screening technologies for anal cancer. The following sections briefly describe the data sources and methods of analysis informing the model's input parameters. Probability distributions were specified for each parameter, which are presented in Tables 1–3. Further details on the methods of analysis are presented in Appendix.

MSM and HIV parameters

Age-specific prevalence rates for MSMs were informed by questions about whether male respondents had had sex with a man in the last year (upper estimate) and in the last three months (lower estimate) from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) II.[9] Age-specific data on the number of diagnosed HIV positive MSM were informed by data provided by the Survey Of Prevalent HIV Infections Diagnosed (SOPHID) team at the Health Protection Agency (HPA), with only minor adjustments required to assign those cases for which CD4 count was not reported. Only an aggregate estimate of the number of undiagnosed HIV-infected MSM in the UK was available, from which age- and stage-specific rates were modelled on the basis of relative likelihoods of remaining undiagnosed informed by clinical opinion.

Age-specific HIV infection incidence rates were fitted to estimated aggregate incidence rates,[10] using a sub-Markov

Table 1 . Age-specific input parameters

Age	*Number of MSM*	*HIV incidence in MSM*	*Untreated HG-AIN to cancer*	*Treated HG-AIN to cancer*	*Anal cancer incidence*	
					HIV negative	*HIV positive*
16–24	30 151–38 927	0.003–0.007	0.0004–0.0008	0.0001–0.0003	0.009–0.255	0.094–2.158
25–34	89 979–93 440	0.014–0.018	0.0004–0.0008	0.0001–0.0003	0.046–0.939	0.187–3.398
35–44	61 801–72 707	0.020–0.033	0.0006–0.0012	0.0001–0.0005	1.638–5.430	2.545–6.647
46–55	51 993–61 168	0.002–0.007	0.0020–0.0040	0.0004–0.0016	1.909–5.671	7.276–14.520
56–65	32 563–38 309	0.001–0.004	0.0020–0.0040	0.0004–0.0016	0.985–2.950	7.347–14.145
66–75	1633–1921	0.000–0.000	0.0020–0.0040	0.0004–0.0016	0.191–0.585	0.897–1.844
Distribution*	Uniform	Non-parametric†	Uniform	Uniform	Uniform	Uniform
Source	[9]	[10,11]	[20–22]	[20–22]	[3,9,SOPHID‡]	[3,9,SOPHID‡]

*Probability density function used to represent data in model calibration analysis

†Calibrated using HIV incidence sub-Markov model (see Appendix for details)

‡Data on the number of diagnosed HIV positive MSM provided by the Survey Of Prevalent HIV Infections Diagnosed (SOPHID) team at the Health Protection Agency.

model that described transitions from the 'CD4 count >500' state to another CD4 state or death.[11]

Separate sets of HIV transition probabilities were required for diagnosed and undiagnosed HIV positive individuals. The former were informed by modelling using cross-sectional marker surveys,[10,12] while Goldie *et al.*[6] report transition data reflecting the impact of HAART.

Sweeting *et al.*[10] use Bayesian back-calculation to estimate median estimates of the quarterly probabilities of HIV diagnosis by CD4 count category states for homosexual men. Age-specific clinical presentation rates were estimated by applying subjectively defined weights that increased the likelihood of older MSM presenting clinically.

Risks of AIDS-related mortality and other cause deaths in HIV positive MSM, by CD4 count, were informed by a separate modelling exercise that combined: the overall relative risk (RR) of death in HIV patients (4–7),[13,14] the proportion of AIDS-related deaths in HIV patients post-HAART (0.07),[14] the RR of developing AIDS by CD4 count (0.57 for a 100 point increase in CD4 counts), and the RR of developing a non-AIDS illness (0.84 for a 100 point increase in CD4 counts).[15] RRs of death for non-diagnosed HIV patients used the aggregate RR for death observed in 1997 (17.5–27.5) in combination with the proportion of deaths due to AIDS in 1997 (0.84).[13]

Anal cancer natural history parameters

The natural history of anal cancer includes progression through the pre-invasive stages of the disease (low- and high-grade AIN), and from high-grade AIN to invasive anal cancer.

Transition probabilities between health states describing no AIN, low-grade AIN and high-grade AIN were informed by two US studies, published in the mid to late 1990s.[16–18] UK studies were excluded on account of the absence of any histological follow-up.[19]

Alternative ranges describing progression from high-grade AIN to anal cancer were tested during the full model calibration process. Progression rates in HIV-negative and -positive MSM were assumed to be similar, though age-specific transition probabilities were specified as a proxy for time-dependent transition probabilities.

AIN and anal cancer treatment parameters

Treatment of low-grade AIN was not modelled because treatment effectiveness is not established. All detected high-grade AIN lesions were assumed to receive treatment: 20–30% of detected high-grade AIN was assumed to be treated non-surgically, with the remainder receiving radical surgery. HIV-positive patients were assumed to receive treatment for recurrence every 2 years, and HIV-negative patients every 10 years.[20–22]

The anal cancer model initially differentiated between early stage (primary) and late stage (metastatic) anal cancer. Data informing progression from early stage disease to late stage disease were of limited value as the absolute rate of progression was unclear and no information on the timing of progression was presented.[23,24] As most studies presented survival rates after the treatment of early stage anal cancer,

Table 2 CD4 count-specific input parameters

Parameter	*HIV negative*	*CD4 >500 Treated*	*CD4 200–500 Treated*	*CD4 <200 Treated*	*CD4 >500 Untreated*	*CD4 200–500 Untreated*	*CD4 <200 Untreated*	*Distribution**	*Source*
Annual diagnosis probability	n/a	n/a	n/a	n/a	0.060–0.091	0.189–0.381	0.570–0.984	Uniform	[10]
Mortality RR†	n/a	1.490–5.410	3.570–7.160	5.890–11.620	1.360–10.520	10.650–22.640	39.510–69.880	Log normal	[13–15]
Transition probabilities									
to 200–500 CD4 count	n/a	0.135–0.215	n/a	n/a	0.135–0.215	n/a	n/a	Beta	[7,10]
to <200 CD4 count	n/a	n/a	0.198–0.307	n/a	n/a	0.181–0.283	n/a	Beta	[7,10]
Normal to LG-AIN	0.029–0.154	0.084–0.406	0.084–0.406	0.279–0.918	0.084–0.406	0.084–0.406	0.279–0.918	Beta	[16–18]
Normal to HG-AIN	0.005–0.047	0.016–0.091	0.016–0.091	0.039–0.238	0.016–0.091	0.016–0.091	0.039–0.238	Beta	[16–18]
LG-AIN to Normal	0.000–0.132	0.000–0.132	0.000–0.132	0.000–0.132	0.000–0.132	0.000–0.132	0.000–0.132	Beta	[16–18]
LG-AIN to HG-AIN	0.031–0.354	0.015–0.255	0.059–0.276	0.165–0.812	0.015–0.255	0.059–0.276	0.165–0.812	Beta	[16–18]

*Probability density function used to represent data in model calibration analysis.
†Relative risk, compared to HIV negative individuals.

the model structure was adapted to describe only a transition to death from a single anal cancer state.

Study populations included few HIV-positive patients, and so survival post-anal cancer was estimated in two parts. First, non-anal cancer-related mortality rates were estimated separately for HIV-positive and -negative patients.[13–15] Secondly, treated anal cancer-specific mortality was informed by the radiotherapy with chemotherapy arm of the largest and only UK study identified.[25] An assumption of equal anal cancer mortality in HIV positive MSM was informed by a matched comparison of 10 HIV positive patients treated with HAART with 10 HIV negative patients.[26] Untreated anal cancer mortality was subjectively informed by survival in the radiotherapy arm of the UKCCCR trial (which was defined as the upper 95% CI interval).[25]

Anal-screening test and clinical presentation parameters

Clinical presentation rates are not observable (at least, the denominator is not observable), and so subjective ranges were specified as inputs to the calibration analysis.

The review of studies investigating the characteristics of screening tests for AIN and anal cancer revealed significant variation in the estimated sensitivity and specificity rates,[27–30] which is probably due to differences in the definition of a positive test and in the study populations. The studies included very few cases of high-grade AIN and so similar test characteristics were assumed for all grades. The model does differentiate between test characteristics in HIV-negative and -positive MSM, and assumes that an 'Atypical Squamous Cells of Undetermined Significance' (ASCUS) test result would be considered a positive test.

The second category of screening parameters describes the likelihood that individuals eligible for screening will attend for screening. Cranston *et al.*[31] reported that ~10% of 125 MSM who were invited to take part in a screening study refused. However, as Knight[32] suggests, the more limiting factor is likely to be the identification of MSM to whom screening can be offered. MSMs indicate, their preferred sources of safer sex support are predominantly friends, the gay press and sexual peers rather than formal HIV services.[32] Findings from these studies were qualitatively considered to inform subjective parameter estimates.

Cost and utility weight parameters

Screening cost estimates were based on detailed costs estimated for the provision of cervical cancer screening in the UK.[33] Costs of diagnostic follow-up (including false positive cases) and treatment of pre-cancerous AIN lesions were estimated by applying UK unit costs to clinical care algorithms

Table 3 Other input parameters

Parameter	*Mean (range)*	*Distribution**	*Source*
Anal cancer annual mortality probabilities			
Not treated	0.159 (0.086–0.226)	Log normal	[25]
Treated	0.085 (0.035–0.136)	Log normal	[25]
Screening attendance			
HIV negative	0.44 (0.32–0.64)	Uniform	[28,31]
HIV positive	0.74 (0.57–0.85)	Uniform	[28,31]
Sensitivity (screening for AIN or anal cancer)			
HIV negative	0.47 (0.3–0.65)	Triangular	[27,30]
HIV positive	0.68 (0.6–0.85)	Triangular	[27,30]
Specificity (screening for AIN or anal cancer)			
HIV negative	0.93 (0.6–0.98)	Triangular	[27,30]
HIV positive	0.58 (0.3–0.7)	Triangular	[27,30]
Treatment costs‡			
Screening (per screen)	£23 (£20.52–£28.17)	Log normal	[33]
AIN diagnosis (anascopy and biopsy)	£107 (£47–£214)	Log normal	[6]
Follow-up (anascopy)	£94 (£47–£187)	Log normal	[6]
Treatment of detected HG-AIN lesions	£1804 (£902–£2705)	Log normal	[6]
Screen detected anal cancer	£8895 (£6671–£11 119)	Log normal	[34]
Non-screen detected anal cancer	£13 334 (£10 001–£16 668)	Log normal	[34]
HIV positive CD4 count >200 (annual cost)	£9655 (£8630–£10 938)	Log normal	[35]
HIV positive CD4 count <200 (annual cost)	£10 598 (£9362–£11 810)	Log normal	[35]
Utility weights			
HIV negative	1		
CD4 >500	0.94 (0.9–0.98)	Triangular	[38]
CD4 200–500	0.87 (0.84–0.9)	Triangular	[38]
CD4 <200	0.80 (0.76–0.84)	Triangular	[38]
High-grade AIN (multiplier†)	0.98 (0.95–0.99)	Triangular	[38]
Anal cancer	0.58 (0.5–0.7)	Triangular	[38]

*Probability density function used to represent data in model calibration analysis.

†HIV negative or HIV positive health state utility weights are multiplied by the high-grade AIN utility value.

‡Costs were uprated to 2007 values (where necessary) using the NHS Pay and Prices Indices.

developed by the University of California at San Francisco Faculty Practice.[6] In the absence of unit costs for procedures specific to anal cancer, unit costs reported for similar procedures for the diagnosis and treatment of cervical cancer were applied.

Goldie *et al.*[6] based treatment costs for anal cancer on published costs for colorectal cancer. A similar process was used in the current model, using a UK cost study.[34] As a proxy for the cost effects of screen-detected cases presenting at an earlier stage than clinically presenting cases, lifetime costs associated with diagnosis at Dukes stage A (£8895) and Dukes stage B (£13 334) were assumed to represent the cost of screen detected and clinically presenting anal cancers, respectively.

Relevant UK costs for treating HIV infection by CD4 count were derived from the National Prospective Monitoring System ± HIV Health Economics Consortium (NPMS ± HHC) study.[35]

Utility weights for individuals with anal cancer were derived from a rating scale valuation undertaken by patients.[6] The utility decrements were applied to both diagnosed and undiagnosed individuals (undiagnosed patients may have slightly higher utility than diagnosed patients, but later diagnosed patients may have lower utility during their treatment period). Goldie *et al.* used the same process to estimate a utility value for patients receiving treatment for high-grade AIN lesions of 0.98,[6] which was specified as a utility multiplier. The utility effects of HIV infection were

sourced from a number of studies that reported patient-based elicitation of utility values.[36–38]

Model calibration

The anal cancer screening model was calibrated to age-specific estimates of the incidence of anal cancer in 2003 as reported by the Cancer Registries.[3] As anal cancer is a rare and relatively slow progressing cancer, it was assumed that the cancer registry estimates for anal cancer had 77% completeness, at the low end of observed completeness rates.[39,40]

Age-specific incidence rates in the MSM populations were fitted to sampled values for aggregate incidence, and RRs for anal cancer in HIV-positive[5] and -negative men,[41] as well as to age-specific RRs.[42] This process was repeated for 5000 iterations in order to represent the joint uncertainty in these parameters.

For each of 5000 sampled sets of input parameter values, the calibration model collected the age-specific incident rates of anal cancer in HIV-negative and -positive MSMs in 2003. A two-stage calibration process was adopted. The first stage identified 4515 eligible input parameter sets that predicted aggregate incidence rates within the observed 95% confidence intervals (CIs). The second stage estimated the sum of differences between the predicted outputs and the observed 95% CIs for the incidence rates by age group and HIV status. The relative accuracy of the predicted outputs informed the assignment of sampling probabilities to each of the eligible input parameter sets.[43]

Model analysis

Ten programmes were analysed, included five programmes for HIV-positive MSM only, and five programmes for all MSM. Screening intervals of 1, 2, 3, 4 and 5 years were analysed for both eligible populations. The reference case analysis involved the random sampling of 5000 sets of input parameter sets based on the ranking probabilities estimated as part of the calibration process.

Results

The mean results from the reference case analysis of the model are presented in Table 4, which show that screening MSM is actually more costly and less effective than providing no screening, i.e. no screening dominates screening MSM for anal cancer. The reduced number of QALYs gained is due to the utility decrements associated with false positive screening results, and particularly the adverse side effects from treatment of HG-AIN. The probabilistic analysis shows that in all iterations no screening has the highest net benefits and is 100% certain to be the most cost-effective option (given the model, inputs and assumptions) up to a QALY value of £50 000.

Sensitivity analyses were defined in the context of the reference case results that showed screening to have little chance of being cost-effective. The estimates of anal cancer incidence used to calibrate the model were not excessively uncertain. A more uncertain parameter was the rate of regression of low-grade AIN, for which Goldie *et al.* had estimated higher regression rates.[6] The calibration and main models were re-run incorporating upwardly revised annual regression rates (30% in HIV-negative MSM, 2–5% in HIV-positive MSM). Table 5 presents the results that show that the minimum incremental cost per QALY (ICQ)

Table 4 Mean results from the reference case analysis

Model	*Costs:*						*QALYs (Aggregate)*	
	Aggregate	*Screening*	*False positives*	*AIN treatment and monitoring*	*Cancer treatment*	*HIV treatment*		*ICER compared to no screening*
No screening	£27 915	£0	£0	£2604	£60	£25 251	17.7950	
HIV positive 5-yearly	£28 350	£3.29	£1.80	£2997	£58	£25 290	17.7874	Dominated
HIV positive 4-yearly	£28 375	£3.50	£2.00	£3020	£58	£25 292	17.7870	Dominated
HIV positive 3-yearly	£28 433	£4.02	£2.52	£3075	£54	£25 298	17.7860	Dominated
HIV positive 2-yearly	£28 523	£4.93	£3.98	£3155	£54	£25 305	17.7843	Dominated
HIV positive annual	£28 607	£6.41	£7.62	£3239	£42	£25 312	17.7826	Dominated
All MSM 5-yearly	£32 653	£69	£33	£5050	£74	£27 427	17.7582	Dominated
All MSM 4-yearly	£32 870	£73	£35	£5176	£74	£27 511	17.7567	Dominated
All MSM 3-yearly	£33 579	£89	£43	£5522	£73	£27 853	17.7517	Dominated
All MSM 2-yearly	£35 233	£107	£69	£6228	£76	£28 753	17.7429	Dominated
All MSM annual	£37 135	£159	£130	£6972	£62	£29 812	17.7348	Dominated

Table 5 Mean results from analyses incorporating increased regression rates from low-grade AIN

	Costs:						QALY:		
Screening option	*Aggregate*	*Screening*	*False positives*	*AIN treatment and monitoring*	*Cancer treatment*	*HIV treatment*	*Aggregate*	*Average ICQ*	*Incremental ICQ*
No screening	£33 096	£0	£0	£2601	£233	£30 263	17.6354		
HIV positive 5-yearly	£34 072	£5.80	£10.72	£3218	£204	£30 634	17.6500	£66 831	Ext. dominated
HIV positive 4-yearly	£34 181	£8.04	£21.10	£3308	£161	£30 683	17.6517	£66 385	Ext. dominated
HIV positive 3-yearly	£33 810	£3.67	£4.46	£3046	£223	£30 532	17.6460	£67 462	Ext. dominated
HIV positive 2-yearly	£33 852	£3.97	£5.37	£3073	£220	£30 550	17.6467	£66 722	Ext. dominated
HIV positive annual	£33 945	£4.62	£7.02	£3132	£212	£30 588	17.6484	£65 182	Ext. dominated
All MSM 5-yearly	£37 631	£78	£52	£4739	£286	£32 476	17.7482	£40 198	Ext. dominated
All MSM 4-yearly	£37 811	£86	£58	£4836	£289	£32 542	17.7550	£39 405	£39 405
All MSM 3-yearly	£38 497	£107	£74	£5140	£290	£32 885	17.7709	£39 842	£43 129
All MSM 2-yearly	£40 127	£139	£116	£5787	£294	£33 791	17.8069	£41 000	£45 371
All MSM annual	£42 074	£229	£223	£6484	£243	£34 895	17.8460	£42 621	£49 720

for screening is £39 405. Screening all MSM is more effective than screening HIV-positive MSM due to gains from the early detection of undiagnosed HIV-positive MSM. The cost-effectiveness acceptability frontier in Fig. 2 shows that at higher QALY values the screening programmes for all MSM have higher mean net benefits (though no screening retains the highest probability of cost-effectiveness).

Other sensitivity analyses tested the assumption that false positive screen results and the treatment for HG-AIN incurred no utility decrements, which reduced the minimum ICQ to just over £60 000. Reducing the costs of screening by 50% did not alter the reference case results that all screening programmes are dominated by no screening.

Combining the effects of the three sensitivity analyses (all of which tested alternative assumptions that favoured screening), the minimum ICQ for screening is £20 996 (for 4-yearly screening of all MSM). Looking only at HIV positive MSM, the minimum ICQ is predicted to be £29 442 (for annual screening of HIV positive MSM).

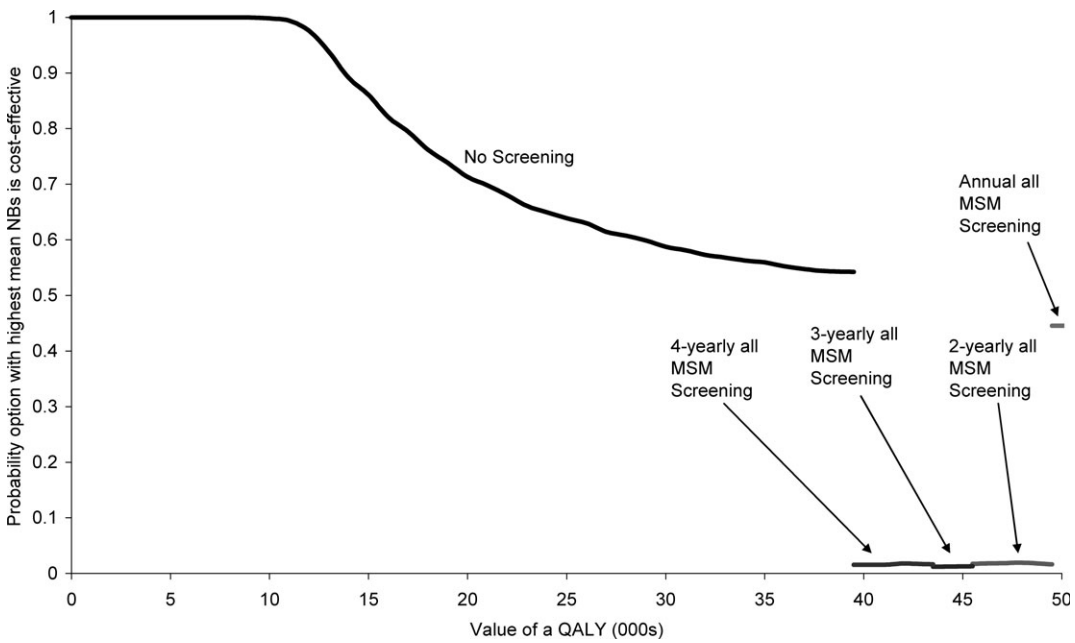

Fig. 2 Anal cancer screening model structure.

Discussion

Main finding of this study

The reference case cost-effectiveness model found that screening for anal cancer is very unlikely to be cost-effective. A key determinant of this finding was the low observed incidence of anal cancer in the UK population to which the model was calibrated. Estimated anal cancer incidence in the MSM population (by HIV status) was not conservative, incorporating upper ranges of the RRs of anal cancer in HIV-negative and -positive MSM compared with the general population of 45 and 272, respectively, and a low estimate of completeness in the observation of cases of anal cancer by the Cancer registries.

Sensitivity analyses showed that the reference case results were not overly robust to alternative assumptions around two parameters in particular: the probability of regression from low-grade AIN, and the utility effects of false positive cases and adverse effects of treatment of high-grade AIN. Other key areas of investigation include the modelled consequence that screening for anal cancer leads to the detection and the treatment of additional HIV positive MSM. The model assumes undiagnosed HIV-positive MSM are equally likely to be screened as HIV-negative MSM, though a specific mode of operation for a screening programme was not defined due to the unique issues around identifying and inviting different categories of MSM to a screening programme.

New analyses of existing primary data, undertaken specifically to inform regression rates may usefully update some key parameters at little additional cost. If these analyses increase the likelihood that anal cancer screening is cost-effective, further studies of the utility effects of treatment for high-grade AIN, and potential screening attendance rates may be justified.

What is already known on this topic

The only other identified cost-effectiveness analyses of screening for anal cancer found screening to be extremely cost-effective in both HIV-negative MSM (3-yearly) and HIV-positive MSM (annually), from a US perspective.[6,7]

What this study adds

Compared with previous models,[6,7] the main structural development of the current study is the combined representation of HIV negative, undiagnosed HIV positive and diagnosed HIV-positive MSM in the same model, so allowing for the transition from HIV-negative to HIV-positive status. The model analysis also included a probabilistic sensitivity analysis and a process of recalibration to test the impact of specific input parameters (e.g. regression rates).

In the directly comparable analyses, the total cost differences in the US and UK analyses are similar, but the estimated QALY gain per HIV-positive MSM from an annual screening programme compared with no screening was 0.2 and 0.01, respectively. The US study appears to use similar incidence rates of anal cancer to calibrate the models, but the calibrated transition probabilities from high-grade AIN to cancer are significantly higher than those estimated in the current study (3.6–5%).

The regression rates assumed in the current model led to higher rates of high-grade AIN, with extremely low rates of transition to anal cancer. The model predicted that a high proportion of population prevalent high-grade AIN would either not progress to anal cancer in the lifetime of the patient or would not present clinically if it did progress (i.e. patients die of other causes). Thus, screening is predicted to detect many latent cases. Increased regression rates reduce the proportion of latent screen-detected cases.

In the current model, the high incidence of high-grade AIN leads to greater utility decrements due to the side effects of treatment (including treatment of recurrent lesions). The UK model also incorporates higher mortality effects for HIV infection, such that the potential for benefit from screening for anal cancer is reduced. Finally, the UK model assessed the cost-effectiveness of screening in the current population of MSM in the UK, not in a cohort of 30-year-old MSM, which reduces the scope for benefit as older MSM have fewer QALYs to gain.

Limitations of this study

The anal cancer screening model was complicated, jointly modelling HIV and AIN progression. More flexibility to represent this complexity would have been afforded by an individual sampling model (ISM), but previous experience in the development of complex screening models with limited data informed our efforts to apply the model as a cohort-based model.[43,44] To apply the probabilistic calibration methods described in this report, ISMs require model running times several orders of magnitude higher than cohort models.

The main limiting assumptions of the cohort model include the use of non-time dependent transition probabilities, which meant that proxies for time dependency were incorporated, for example, transition probabilities were assumed to increase with age. The model also adopted a simplistic representation of the post-diagnosis phase of the disease, though this was partly due to data inadequacies.

The model analysis indicates that these structural limitations had only a minor impact on the cost-effectiveness results relative to the impact of uncertainties around key input parameter values.

Evidence from the Seattle cohort study showed an increased RR of high-grade AIN for men engaging in receptive anal intercourse more than three times per month (mean 2.2, 95% CI 0.9–5.5).[16] This indicates that screening is likely to be more cost-effective if an eligible population of high-frequency MSM could de defined. Such information might usefully inform an awareness campaign for an anal cancer screening programme, but restricting screening eligibility on the basis of frequency of intercourse was assumed to be neither practical nor appropriate.

A screening programme might offer the opportunity for additional benefits that were not represented, such as education regarding safer sexual practices that could be promoted during screening attendance. Screening might also impact on disease progression more indirectly, for example, transmission of HPV may be reduced following the detection of AIN as a result of modified sexual activity. The model did not consider these potential benefits because there is no evidence of effect in the reviewed literature, and the link between sexual activity and anal cancer and HIV risk would add significantly to the complexity of the model.

Conclusions

The current evidence base does not provide sufficient evidence to justify a screening programme for anal cancer, even for identifiable high-risk groups. Analyses of existing primary data to specifically inform the anal cancer screening model might reduce the uncertainty to a significant degree.

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Appendix

The Appendix provides additional details on the estimation of the screening model input parameters.

MSM and HIV parameters

Prevalence rates for MSMs were informed by the National Survey of Sexual Attitudes and Lifestyles (NATSAL) II.[8] Rates in 46–55, 56–65, 66–75 and 76+ age ranges were not included in the NATSAL and so were assumed to be 95, 75, 5 and 0% of the rates estimated for the 35–44 age range.

To allocate the estimated aggregate number of undiagnosed HIV-positive MSM by age and stage, relative likelihoods of remaining undiagnosed were assigned to the individuals of different ages based on clinical opinion. Individuals in the youngest age groups (15–25 and 26–35 year olds) were assigned a relative value of 1, 36–45 and 46–55 year olds a value of 0.5 and 56–65 year olds 0.25. For 5000 iterations, an aggregate undiagnosed HIV-positive MSM population and a set of age-specific diagnosed HIV-positive MSM populations were sampled from relevant Poisson distributions. For each iteration, the non-adjusted numbers of undiagnosed HIV-positive MSM (aggregate undiagnosed cases multiplied by the proportion of diagnosed cases) in each age group were multiplied by the relative likelihood weights, which were then adjusted proportionately so that the aggregate number of undiagnosed individuals equalled the sampled value. The stage distribution was estimated by applying clinical opinion-based relative likelihoods that individuals in each of the three CD4 stages would remain undiagnosed (<200 CD4–0.05; 200–500 CD4–0.1; >500 CD4–1), and then adjusting to equal the estimated aggregate number of undiagnosed HIV cases. Finally, ranges for the prevalence rates were estimated by dividing the lower and upper estimates of the numbers by the upper and lower estimates of the relevant age-specific numbers of MSM in the general population, respectively.

Age-specific HIV population incidence rates by CD4 count were estimated using a sub-Markov model, which assumed:

- All individuals developing an HIV infection start in the '>500' CD4 count category.
- All individuals who developed HIV prior to 1990 died in 2005.
- Age-specific incidence rates of HIV have remained constant since 1990.

The estimation process involves the following stages:

Individuals may leave the '>500' state due to transition to another CD4 state (using the main model transition probabilities) or death (informed by UK male life tables as a CD4 count >500 has been shown to have little effect on mortality[11]). Transition probabilities were not assumed to be affected by treatment so the model does not distinguish between diagnosed and undiagnosed individuals.

The model estimates the numbers of individuals remaining in the '>500' state at each age in 2005 as the sum of

the product of the incidence rate at each age and the probability that patients remain in the '>500' state in 2005. This informed the absolute numbers of individuals in the '>500' state in 2005 in each of seven age categories (15–25, 26–35, 36–45, 46–55, 56–65, 66–75 and >75 years). A simulation exercise was then undertaken to identify the combinations of input parameter values that best predicted the observed prevalence of diagnosed and undiagnosed HIV-infected MSM with a CD4 count of >500.

The number of MSM at risk of HIV infection within each age range was estimated as the prevalence estimate of all MSM (in each age range) minus prevalent HIV infected MSMs at the start of each age range and half of all incident cases in the age range being analysed. The 10-year rates were converted to annual rates using the established equation.[45] The estimates for age groups >66 years were unstable due to small numbers, as the incident numbers were so small for these age groups, incidence rates of zero were assumed.

Risks of AIDS-related mortality and other cause deaths for HIV-positive MSM combined the RRs for death compared with patients with a CD4 count of <200, and the specified distribution of CD4 counts, the Solver function in Excel was used to fit the RR of death in patients with a CD4 count of <200 to a sampled value for the overall RR of death for HIV patients. This process was repeated 1000 times to obtain a joint distribution of the RRs for the three CD4 count categories.

Anal cancer natural history parameters

Two sets of analyses using published data from the two main cohort studies were undertaken.[16–18] The complex analysis used literature-based sources to control for false negative and false positive results in cytology-alone detected cases, the unobserved development of low-grade disease prior to high-grade disease, the timing of events and incomplete follow-up. These analyses were found to be sensitive to the assumptions around follow-up times and the proportions of cases receiving a histological diagnosis. As a result, the calibration inputs were informed by simpler analyses that did not adjust for test sensitivity and specificity, and estimated person years at risk assuming individuals experiencing an AIN event had half the follow-up of those not experiencing an event. It was also assumed that half of the observed cases of high-grade AIN (in individuals with no AIN at baseline) experienced low-grade AIN prior to high-grade AIN.

In addition to increased progression in HIV-positive MSM, the San Francisco study showed that CD4 count is a significant predictor of AIN progression (*P*-test for trend, <0.0005),[17] and the presented RRs were used to adjust AIN-transition probabilities by CD4 count.

Model calibration

The calibration model commences in 1990. The probability of having high-grade AIN in 1990 was estimated using a simple sub-model that estimated the progression of HIV negative MSM from normal to high-grade AIN, assuming a mean age of becoming a MSM of 26 years.

The following stages were involved in the assignment of sampling probabilities to each of the eligible input parameter sets:

(i) The sum of differences between each age- and HIV status-specific incidence estimate and the bounds of the respective observed 95% confidence intervals were calculated for each iteration.
(ii) The proportions of the sum of differences contributed by each input parameter set were estimated.
(iii) The reciprocals of the proportions of the sum of differences contributed by each iteration were estimated (no iterations had a sum of differences of zero).
(iv) The reciprocals were divided by the sum of the reciprocals to estimate the probability that each of the 4515 parameter sets was the most relevant set.

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