Appendix 1. Sources for parameters used in the model.

Proportion of non-cervical cancers caused by infection with HPV 16, HPV 18 and non-vaccine HPV types

We conducted a brief survey of published literature on the prevalence of HPV within cancers in non-cervical sites, and HPV 16/18 prevalence in cancers associated with HPV. The most recent and/or complete meta-analyses were selected for parameterising the model. For cancers of penis the meta-analysis by Miralles-Guri *et al.* [1] was selected; another meta-analysis had very similar results but a smaller sample size [2]. For vulva and vaginal cancer the meta-analysis by de Vuyst *et al.* was selected [3] was selected over another meta-analysis from the same year [4], again due to having a larger sample size. Separate figures for vulvar and vaginal cancers were combined for the purposes of our analysis. The same meta-analysis was used to provide the estimate of anal cancer prevalences; this was the only meta-analysis we found regarding cancers in this site.

There is less clarity with regards to oropharyngeal (including tonsilar) cancers. A meta-analysis by Kreimer *et al.* [5] was chosen over other studies identified [6-8] because this analysis provides estimates specific to the oropharynx, only included studies where HPV detection is performed by high quality PCR, and provides prevalence of both HPV overall and of type-specific HPV prevalence. The study found HPV DNA present in 28.2% of such cancers in Europe, from studies published up to February 2004. Across studies in all regions, 89% of HPV-related cancers involved type 16 or 18 DNA. European specific figures could not be extracted for the latter parameter; however, the authors state that figures are similar across geographical locations.

Other more recent studies have found the involvement of E6 or E7 oncogenes for HPV 16 in up to 60% of cancer cases [9;10], but evidence for a causal link is debated [10]. There is some suggestion, yet to be firmly proven, of an increasing number and proportion of oropharyngeal cancers due to HPV over time, which may be due to increasing frequency of oral sex [11]. Due to the uncertainty, we used the figures given in the meta-analysis, and assumed that they would remain stable over time (in the absence of vaccination). HPV has also been detected in other head and neck cancers, although a causal link has not been established [5], so we did not assume any vaccine protection against non- oropharyngeal head and neck cancers.

The mean and standard error around each of these estimates is shown in Tables A1-1 and A1-2. For the proportion of HPV-related cancers that were due to HPV 16/18 (where this

was not explicitly given in the text), we used the overall number of HPV-related cancers as the denominator to calculate binomial standard errors. The point estimate and uncertainty around it was then used to generate Beta distributions represent the uncertainty around the proportions; parameters of the Beta distributions are given in Tables A1-1 and A1-2 below.

Site	Mean	Standard error	Beta p	Beta q
Penis	47%	1.3%	690	780
Vulva and vagina	42%	4.3%	55	77
Anus	84%	1.2%	800	150
Oropharynx	28%	1.3%	350	890

Table A1-1. Uncertainty distribution used for proportion of cancers in different sites attributable to HPV.

Site	Mean	Standard error	Beta p	Beta q
Penis	74%	4.3%	77	27
Vulva and vagina	90%	2.9%	95	11
Anus	93%	0.88%	760	56
Oropharynx	89%	1.7%	300	37

Table A1-2. Uncertainty distribution used for proportion of HPV-related cancers in different sites attributable to HPV 16 or 18.

The number of cancers in non-cervical sites in England was obtained from the Office for National Statistics (series MB1 number 37, 2007) and is given in the Table A1-3 below:

	Vulva-vagina	Anus	Oropharynx	Penis
20-24	2	1	0	0
25-29	5	4	2	1
30-34	17	7	9	6
35-39	31	15	19	10
40-44	43	25	43	36
45-49	58	26	46	46
50-54	62	44	82	72
55-59	87	62	92	72
60-64	93	52	89	92
65-69	109	60	86	69
70-74	113	59	76	55
75-79	152	46	79	62
80-84	137	40	77	60
85 and over	227	57	91	63

Table A1-3. Number of cancers in non-cervical sites in England in 2007 (no such cancers were reported in individuals under 20 years old).

These data were used to estimate the reduction in the number of non-cervical cancers following vaccination, for a particular scenario, using the following formula:

$$N(a,t) = n(a) \times [\, x \times y \times r_1(a,t) + x \times (1 - y) \times r_2(a,t) + (1 - x) \,]$$

In the above formula:
$N(a,t)$ = annual cancer incidence for a particular site S (vulva/vagina, anus, oropharynx or penis) in individuals at age a and time t after vaccination
$n(a,t)$ = annual cancer incidence for site S in individuals at age a prior to vaccination (from Office for National Statistics data)
x = proportion of cancers in site S attributed to HPV infection
y = proportion of cancers in site S attributed to HPV infection, which are attributed to HPV 16/18
$r_1(a,t)$ = % reduction in HPV 16/18-related cervical cancer incidence in individuals at age a and time t after vaccination (from the transmission dynamic model)
$r_2(a,t)$ = % reduction in non-HPV 16/18-related cervical cancer incidence in individuals at age a and time t after vaccination (from the transmission dynamic model)

Correction for under-estimation of the number of cancers and pre-cancerous lesions due to non-vaccine HPV types as a result of unmasking

To correct for under-estimation of the number of cancers and pre-cancerous lesions due to non-vaccine HPV types as a result of unmasking, a stochastic individual-based model allowing co-infection with multiple HPV types was constructed to represent HPV infection and natural history. Hence in the model, individuals moved between health states (for each HPV type) representing cervical HPV infection in the absence of dysplasia, CIN1-3, carcinoma in situ, invasive cervical cancer, having had a benign hysterectomy and being dead.

The size of the population was set to 100,000. The sampling age for each individual was selected randomly from a uniform distribution between 12 and 75 years old. At that age, each individual's hypothetical screening status is recorded (based on UK screening rates). The model was simulated to generate 1,000 duplicate runs, and the average over all runs taken. Progression rates between different health states were obtained from our previous (compartmental) natural history model of HPV [12]. We picked a particular scenario for this purpose (acquisition of infection from age 14 years, 100% specificity of HPV DNA testing, regression of lesions to the previous health state and high screening accuracy). Hence the results are indicative since they do not capture the full range of uncertainty in the parameter values; however, they given an indication of the magnitude of "unmasked" disease for typical parameter values. The force of infection was assumed to remain static and natural immunity was not considered, since we were not explicitly modelling the effect of vaccination (only the

proportion of HPV 16/18 disease which was actually due to other HPV types and hence may potentially be "unmasked" by vaccination).

The model was run for two scenarios: once without HPV 16/18 infection included in the model, and the second time with HPV 16/18 infection possible (including co-infection between several types). In the second simulation, an "oncogenic hierarchy" [13] was imposed , where a woman with cervical disease infected by several HPV types (HPV 16, 18 and/or other high-risk types) had her disease attributed to HPV 16/18 rather than the other types. The difference between the amount of HPV-related cervical disease in both simulations hence gives the amount of unmasking, i.e. disease due to non-HPV 16/18 which is "masked" by the presence of vaccine-type HPV, but will be "unmasked" (emerge) if vaccine-type HPV decreases as a result of vaccination. Results are summarised in Table A1-4. Using these results, we concluded that if all HPV 16/18 infection is removed, then number of individuals with various cytological states caused by other HPV types will appear to increase by 10.9%, 10.2%, 5.6%, 6.0%, 5.2% and 1.2% for those without lesions, with CIN1 lesions, with CIN2 lesions, with CIN3 lesions, with carcinoma in situ and with invasive cancer respectively.

	HPV infected	**CIN1**	**CIN2**	**CIN3**	**Carcinoma in situ**	**Invasive cancer**
(a) Without HPV 16/18	7,310	1,140	317	271	392	78
(b) With HPV 16/18	6,600	1,030	300	256	373	77
(c) Difference	718	105	17	15	19	1
(d) % increase of (a) over (b)	10.9%	10.2%	5.6%	6.0%	5.2%	1.2%

Table A1-4. Number of individuals (average over 1000 runs) in various cytological states caused by HPV types other than HPV 16/18, in a model (a) with HPV 16/18 infection and (b) without HPV 16/18 infection.

Comparison of quality of life parameters for anogenital warts from the Woodhall study used in this model with those from other studies

Parameters used to represent the quality of life impact of anogenital warts were obtained from the only multi-centre UK-based study that meets NICE guidelines for quality of life measurements (eg. measuring quality of life directly from patients rather than from clinicians). The table below compares the values obtained from this study to those estimated in other similar studies.

Reference	Country	QALY detriment	Reason(s) for not using
Woodhall et al. [14]	UK	0.018 (EQ-5D detriment)	Used in model.
Sénécal et al. [15]	Canada	9.9 (EQ-5D weight)	Not UK based; no information on duration of episode.
Wang et al. [16]	China	Not available	Did not use a generic quality of life measure; not UK based.
Woodhall et al. [17]	Finland	QoL weight 1.9 (EQ-VAS score, for both warts and cytological abnormalities)	Combined warts and cytological abnormalities; not UK based; no information on duration of episode.
Woodhall et al. [18]	UK	0.0045 – 0.023 (EQ-5D)	Single centre study.
Myers et al. [19]	USA	0.02 (Time trade off)	Sample of volunteers rather than patients; not UK based.

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Appendix 2. Detailed numerical results

Estimated annual number of cases of cervical cancer, other HPV-related cancers and vaccine-type warts in the year 2109 under the scenarios 1-12 described in Table 1 of the main text, given use of no vaccine, the quadrivalent vaccine or the bivalent vaccine. Median and interquartile range of 10,000 Monte Carlo samples per scenario are shown.

Cervical cancer

	Prior to vaccination			Quadrivalent vaccination			Bivalent vaccination		
Strategy	**Median**	**Upper**	**Lower**	**Median**	**Upper**	**Lower**	**Median**	**Upper**	**Lower**
1	1,300	1,200	1,300	530	420	620	490	370	580
2	1,300	1,200	1,300	230	160	280	170	100	230
3	1,300	1,200	1,300	240	170	300	170	100	230
4	1,300	1,200	1,300	560	450	640	530	420	620
5	1,300	1,200	1,300	280	220	320	240	180	290
6	1,300	1,200	1,300	290	230	340	240	180	290
7	1,300	1,200	1,300	530	420	620	490	370	580
8	1,300	1,200	1,300	230	160	280	170	100	230
9	1,300	1,200	1,300	240	170	300	170	100	230
10	1,300	1,200	1,300	560	450	640	530	420	620
11	1,300	1,200	1,300	280	220	320	240	180	290
12	1,300	1,200	1,300	290	230	340	240	180	290

Non-cervical cancer

	Prior to vaccination			Quadrivalent vaccination			Bivalent vaccination		
Strategy	**Median**	**Upper**	**Lower**	**Median**	**Upper**	**Lower**	**Median**	**Upper**	**Lower**
1	2,300	2,300	2,300	1,800	1,700	1,900	2,300	2,300	2,300
2	2,300	2,300	2,300	1,600	1,600	1,700	2,300	2,300	2,300
3	2,300	2,300	2,300	1,600	1,600	1,700	2,300	2,300	2,300
4	2,300	2,300	2,300	1,800	1,800	1,900	2,300	2,300	2,300
5	2,300	2,300	2,300	1,700	1,600	1,700	2,300	2,300	2,300
6	2,300	2,300	2,300	1,700	1,600	1,700	2,300	2,300	2,300
7	2,300	2,300	2,300	1,600	1,500	1,700	1,600	1,500	1,700
8	2,300	2,300	2,300	1,300	1,300	1,400	1,300	1,200	1,400
9	2,300	2,300	2,300	1,300	1,300	1,400	1,300	1,300	1,400
10	2,300	2,300	2,300	1,600	1,500	1,700	1,600	1,500	1,700
11	2,300	2,300	2,300	1,400	1,300	1,400	1,400	1,300	1,400
12	2,300	2,300	2,300	1,400	1,300	1,400	1,400	1,300	1,400

Anogenital warts

Strategy	Prior to vaccination			Quadrivalent vaccination			Bivalent vaccination		
	Median	Upper	Lower	Median	Upper	Lower	Median	Upper	Lower
1	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
2	120,000	110,000	130,000	7,400	0	16,000	110,000	100,000	120,000
3	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
4	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
5	120,000	110,000	130,000	7,400	0	16,000	110,000	100,000	120,000
6	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
7	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
8	120,000	110,000	130,000	7,400	0	16,000	110,000	100,000	120,000
9	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
10	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000
11	120,000	110,000	130,000	7,400	0	16,000	110,000	100,000	120,000
12	120,000	110,000	130,000	45,000	32,000	59,000	74,000	58,000	90,000

Discounted health care costs and QALYs saved over 97 years (2012 – 2109) of a quadrivalent (figure (a) and (c)) or bivalent (figure (b) and (d)) HPV vaccination programme (2012 onwards) under the different scenarios described in Table 1 of the main text. The median and interquartile range of 10,000 samples are shown.

Quadrivalent vaccine: median

Strategy	Costs saved (£m)					
	Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers	Warts	HPV 6/11 lesions + RRPs
1	53	110	60	0	160	9
2	79	150	77	0	240	13
3	78	140	76	0	160	9
4	41	110	57	0	160	9
5	59	140	73	0	240	13
6	59	140	72	0	160	9
7	53	110	60	30	160	9
8	79	150	77	39	240	13
9	78	140	76	39	160	9
10	41	110	57	28	160	9
11	59	140	73	36	240	13
12	59	140	72	35	160	9

Strategy	QALYs saved ('000s) Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers	Warts	HPV 6/11 lesions + RRPs
1	22	45	26	0	26	1
2	32	61	34	0	38	1
3	32	60	34	0	26	1
4	17	44	25	0	26	1
5	24	58	33	0	38	1
6	24	57	32	0	26	1
7	22	45	26	13	26	1
8	32	61	34	17	38	1
9	32	60	34	17	26	1
10	17	44	25	12	26	1
11	24	58	33	16	38	1
12	24	57	32	16	26	1

Quadrivalent vaccine: upper quartile

Strategy	Costs saved (£m) Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers	Warts	HPV 6/11 lesions + RRPs
1	70	170	96	0	200	17
2	100	220	120	0	260	24
3	100	220	120	0	200	17
4	55	170	92	0	200	17
5	78	210	120	0	260	24
6	78	210	110	0	200	17
7	70	170	96	47	200	17
8	100	220	120	60	260	24
9	100	220	120	60	200	17
10	55	170	92	43	200	17
11	78	210	120	55	260	24
12	78	210	110	54	200	17

Strategy	QALYs saved ('000s) Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers	Warts	HPV 6/11 lesions + RRPs
1	28	28	50	29	0	33
2	41	41	64	37	0	47
3	41	41	63	36	0	33
4	22	22	48	28	0	33
5	31	31	61	35	0	47

6	31	31	61	35	0	33
7	28	28	50	29	15	33
8	41	41	64	37	19	47
9	41	41	63	36	18	33
10	22	22	48	28	14	33
11	31	31	61	35	17	47
12	31	31	61	35	17	33

Quadrivalent vaccine: lower quartile

	Costs saved (£m)					
Strategy	**Screening**	**Cervical cancer**	**Vulvar/vaginal/anal cancer**	**Other cancers**	**Warts**	**HPV 6/11 lesions + RRPs**
1	38	74	37	0	130	5
2	56	93	47	0	220	8
3	56	92	46	0	130	5
4	30	71	36	0	130	5
5	42	90	45	0	220	8
6	42	89	44	0	130	5
7	38	74	37	19	130	5
8	56	93	47	24	220	8
9	56	92	46	24	130	5
10	30	71	36	18	130	5
11	42	90	45	22	220	8
12	42	89	44	22	130	5

	QALYs saved ('000s)					
Strategy	**Screening**	**Cervical cancer**	**Vulvar/vaginal/anal cancer**	**Other cancers**	**Warts**	**HPV 6/11 lesions + RRPs**
1	16	41	23	0	19	1
2	23	56	32	0	30	1
3	23	55	32	0	19	1
4	12	40	22	0	19	1
5	17	54	30	0	30	1
6	17	53	30	0	19	1
7	16	41	23	12	19	1
8	23	56	32	16	30	1
9	23	55	32	16	19	1
10	12	40	22	11	19	1
11	17	54	30	15	30	1
12	17	53	30	14	19	1

Bivalent vaccine: median

	Costs saved (£m)			
Strategy	Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers
1	65	120	0	0
2	95	150	0	0
3	95	150	0	0
4	50	110	0	0
5	71	150	0	0
6	71	150	0	0
7	65	120	61	31
8	95	150	78	40
9	95	150	78	40
10	50	110	57	28
11	71	150	73	36
12	71	150	73	36

	QALYs saved ('000s)			
Strategy	Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers
1	27	47	0	0
2	39	63	0	0
3	39	63	0	0
4	20	45	0	0
5	29	60	0	0
6	29	60	0	0
7	27	47	26	13
8	39	63	35	18
9	39	63	35	18
10	20	45	25	12
11	29	60	33	16
12	29	60	33	16

Bivalent vaccine: upper quartile

	Costs saved (£m)			
Strategy	Screening	Cervical cancer	Vulvar/vaginal/anal cancer	Other cancers
1	86	180	0	0
2	120	230	0	0
3	120	230	0	0
4	66	170	0	0

5	94	220	0	0
6	94	220	0	0
7	86	180	97	48
8	120	230	120	62
9	120	230	120	62
10	66	170	92	43
11	94	220	120	55
12	94	220	120	55

	QALYs saved ('000s)			
Strategy	**Screening**	**Cervical cancer**	**Vulvar/vaginal/anal cancer**	**Other cancers**
1	35	52	0	0
2	50	67	0	0
3	50	67	0	0
4	27	50	0	0
5	37	63	0	0
6	37	63	0	0
7	35	52	30	15
8	50	67	37	19
9	50	67	37	19
10	27	50	28	14
11	37	63	35	17
12	37	63	35	17

Bivalent vaccine: lower quartile

	Costs saved (£m)			
Strategy	**Screening**	**Cervical cancer**	**Vulvar/vaginal/anal cancer**	**Other cancers**
1	47	77	0	0
2	69	98	0	0
3	69	98	0	0
4	36	74	0	0
5	51	94	0	0
6	51	94	0	0
7	47	77	38	20
8	69	98	48	25
9	69	98	48	25
10	36	74	36	18
11	51	94	45	22
12	51	94	45	22

	QALYs saved ('000s)			
Strategy	**Screening**	**Cervical cancer**	**Vulvar/vaginal/anal cancer**	**Other cancers**
1	19	43	0	0
2	29	58	0	0
3	29	58	0	0
4	15	41	0	0
5	21	56	0	0
6	21	56	0	0
7	19	43	24	12
8	29	58	32	17
9	29	58	32	17
10	15	41	22	11
f11	21	56	30	15
12	21	56	30	15

Benefits of the quadrivalent and bivalent vaccine that contribute towards the difference in price for the two vaccines to be equally cost-effective (median of 10,000 samples). One QALY is assumed to be valued at £30,000. The two benefits of the bivalent vaccine (additional cross-protection and in some scenarios longer duration) contribute negatively towards the price difference (i.e. they make an equally cost-effective quadrivalent vaccine cost less).

Quadrivalent vaccine advantages (value in £ per dose)

	Vulvar/vaginal/anal cancer			Warts			RRPs + HPV 6/11 lesions		
Scenario	**Median**	**Lower**	**Upper**	**Median**	**Lower**	**Upper**	**Median**	**Lower**	**Upper**
1	26	23	30	29	23	37	1.3	0.87	1.9
2	35	32	37	43	35	51	1.8	1.3	2.6
3	34	32	37	29	23	37	1.3	0.87	1.9
4	25	22	29	29	23	37	1.3	0.87	1.9
5	33	31	36	43	35	51	1.8	1.3	2.6
6	33	30	35	29	23	37	1.3	0.87	1.9
7	0	0	0	29	23	37	1.3	0.87	1.9
8	0	0	0	43	35	51	1.8	1.3	2.6
9	0	0	0	29	23	37	1.3	0.87	1.9
10	0	0	0	29	23	37	1.3	0.87	1.9
11	0	0	0	43	35	51	1.8	1.3	2.6
12	0	0	0	29	23	37	1.3	0.87	1.9

Bivalent vaccine advantages (value in £ per dose)

	Cross-protection			Extended duration		
Scenario	**Median**	**Lower**	**Upper**	**Median**	**Lower**	**Upper**
1	7.1	8.5	5.8	0	0	0
2	9.4	11	7.8	0	0	0
3	9.4	11	7.8	0.87	0.95	0.65
4	5.1	6.2	4.2	0	0	0
5	7.1	8.5	5.8	0	0	0
6	7.1	8.5	5.8	0.88	0.85	0.81
7	7.8	9.2	6.5	0	0	0
8	10	12	8.6	0	0	0
9	10	12	8.6	1.6	1.8	1.2
10	5.1	6.2	4.2	0	0	0
11	7.1	8.5	5.8	0	0	0
12	7.1	8.5	5.8	1.6	1.6	1.4