

Health economic evaluation of an mRNA high-risk human papillomavirus (HR-HPV) assay versus a DNA HR-HPV assay for the proposed French cervical screening programme

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Abstract

Objective: Population screening programmes must make good use of resources for the health system and users. To evaluate impacts of the type of diagnostic test in the new French cervical screening programme, an messenger ribonucleic acid (mRNA) high-risk human papillomavirus assay was compared to a deoxyribonucleic acid (DNA) high-risk human papillomavirus assay for a hypothetical cohort of women aged 25 to 65years.

Perspective: This evaluation takes the perspective of the French healthcare system.

Setting: France

Methods: A decision tree model reflecting the French cervical screening algorithms was parametrised using French cost and population data and the Danish Horizon study. The outcomes were total costs, and number of colposcopies, HPV tests and cytology tests for the cohort. One-way and probabilistic sensitivity analyses and scenarios analyses were conducted to test the robustness of results to parameter and structural uncertainty.

Results: Adopting an mRNA versus DNA assay as part of national cervical screening in France is estimated to save €6.5 million (95% credibility intervals €-1.3 - €13.5 million) and prevent 47,795 (95% credibility intervals 35,309 - 60,139) unnecessary colposcopies, 38,666 unnecessary HPV tests and 121,670 cytology tests over two years for a cohort of 2,168,806 million women aged 25 to 65years. Sensitivity analyses indicated robust results across a range of inputs.

Conclusion: The choice of high-risk human papillomavirus assay makes a significant difference to resource use and costs and is important to consider when implementing cervical screening in France. Using an mRNA versus DNA assay can result in cost savings and reductions in unnecessary testing and procedures, which in turn benefits women and the health care system.

Abbreviations: CI = credibility interval, CIN = cervical intraepithelial neoplasia, DNA = deoxyribonucleic acid, FASE = French Aptima Screening Evaluation, HC2 = Qiagen Hybrid Capture 2, HR-HPV = high-risk human papillomavirus, HSIL = high grade squamous intraepithelial lesion, LSIL = low-grade squamous intraepithelial lesion, mRNA = messenger ribonucleic acid, PSA = probabilistic sensitivity analysis.

Keywords: papillomavirus infections, early detection of cancer/methods, models, economic

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Cervical cancer is the fourth most common cancer in women aged 15 to 44years in France.^[1] While cervical cancer incidence and mortality have decreased over time with the implementation of cervical screening, cervical cancer continues to be a concern with 3067 cervical cancer cases and 1472 deaths estimated in France in 2018.^[1]

Human papillomavirus (HPV) infections are common in sexually active women.^[2] While the majority of HPV infections clear spontaneously within twelve months,^[3] in three to ten % of infected women, the HPV infection is not cleared.^[2] Persistent infection with high-risk human papillomavirus (HR-HPV) has been linked to development of precancerous lesions called cervical intraepithelial neoplasia (CIN) and may develop into cervical cancer.^[4]

Since 1990, French guidelines recommended a cervical sample be collected for cytology testing by a gynaecologist or midwife every three years for women aged 25 to 65years.^[5] Cervical screening in France was initiated by a woman or her care provider.^[6] In 2018, guidelines for a national population-based cervical cancer screening program were introduced in France.^[7] The Haute Autorité Santé updated cervical screening guidelines in 2019 to include HPV triage after abnormal primary liquid-based cytology for women aged 25 to 29years, and primary HR-HPV testing for women aged 30 to 65years.^[8] A decree issued in 2020 by the ministry of health^[9] includes the use of the HR-HPV test in cervical screening. Two types of HR-HPV tests, deoxyribonucleic acid (DNA) and messenger ribonucleic acid (mRNA), have been clinically validated for use in cervical screening programmes. There is now a need to evaluate the type of HR-HPV assay used in cervical screening in France, to ensure that resources are being used most efficiently and women do not have to undergo unnecessary testing.

HR-HPV DNA assays identify the presence of HR-HPV viral DNA in cell samples taken from the cervix, but not necessarily an actively replicating infection.^[10] An mRNA assay detects the presence of HR-HPV E6 and E7 oncogenic mRNA in cervical cells, which signal a persistent active infection.^[11] Targeting the actively replicating E6/E7 mRNA means that the mRNA assay is more specific than DNA assays, with fewer false positive results.^[12]

Numerous comparative studies have demonstrated this increased specificity for an mRNA assay with non-inferior sensitivity for detecting (CIN 2+/CIN 3+) that may progress to cervical cancer compared to DNA assays including Qiagen

Hybrid Capture 2 (HC2). Genomica CLART HPV2 and the Roche cobas 4800 HPV at baseline screen through 6year follow up^[4,13-17] The mRNA assay (Aptima HR-HPV assay) has been validated for cervical screening according to the Meijer criteria for non-inferior sensitivity^[18-20] with a pooled relative sensitivity for CIN2+ of 0.98 (90% credibility interval (CI) 0.95-1.01) and higher specificity with a pooled relative specificity of 1.04 (CI 1.02-1.07) compared to HC2.^[21]

Given the higher specificity of an mRNA assay compared to DNA assays, using the mRNA assay as part of the cervical screening programme in France may lead to a reduction in false positive HPV test results. This, in turn, can reduce unnecessary follow up HPV tests, cytology tests and colposcopies in the screened population and reduce overall screening costs, as has been observed in an analysis from England.^[22]

2. Methods

2.1. Aims

This study uses a decision tree model to evaluate the impact on the costs, number of HPV and cytology tests, and colposcopies of using an mRNA HR-HPV assay (Aptima HR-HPV assay) compared to a DNA HR-HPV test (cobas 4800 HPV assay) in a hypothetical cohort of women in France in the proposed cervical screening algorithm in France.

2.2. Screening algorithm in France

In France, the national cervical screening programme is based on published guidelines.^[8,23] Asymptomatic women aged 25 to 29 undergo primary cytology testing (Fig. 1). A normal cytology result is followed up by a second cytology test twelve months later. After two normal results one year apart, women return for cytology screening every three years. Women with atypical squamous cells of undetermined significance or atypical glandular cells have reflex HPV testing. Women with positive HPV results are referred to colposcopy. Women with a negative HPV result return to routine recall. Women with low-grade squamous intraepithelial lesion, atypical squamous cells without being able to exclude HSIL, high grade squamous intraepithelial lesion (HSIL), adenocarcinoma *in situ* or carcinoma cytology results are referred directly to colposcopy.

Asymptomatic women aged 30 to 65years undergo HPV primary screening every 5years with reflex cytology testing

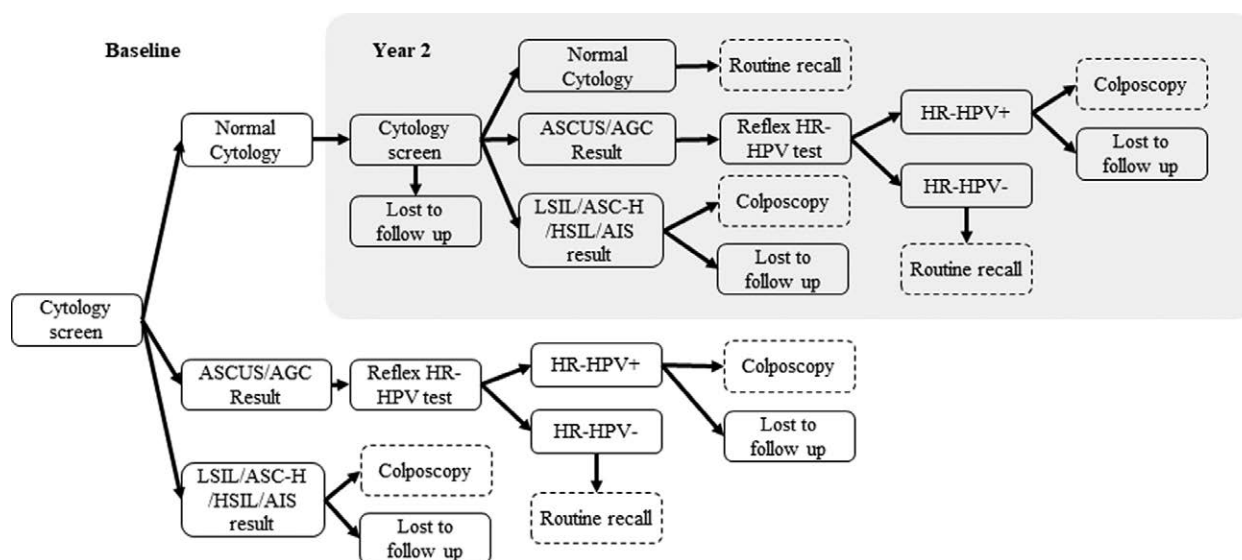


Figure 1. Cytology primary cervical screening algorithm for women aged 25-29^[23].

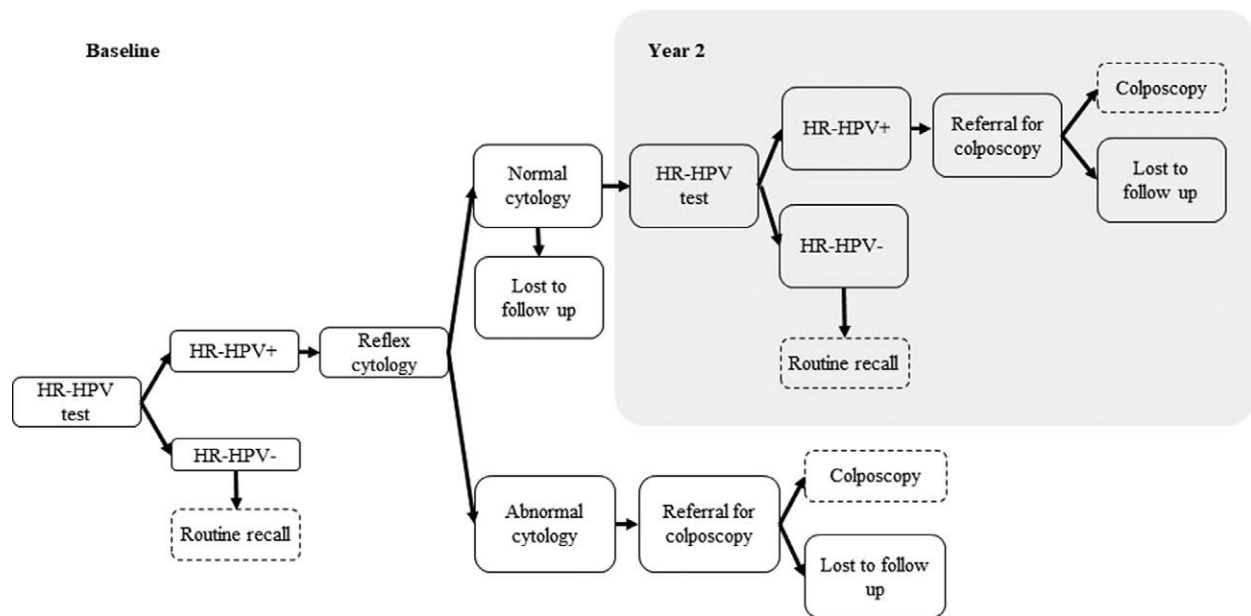


Figure 2. HPV primary cervical screening algorithm in France for women aged 30–65^[8].

following a positive HPV test result (Fig. 2). Women with abnormal reflex cytology results (atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, atypical squamous cells cannot exclude HSIL, atypical glandular cells, HSIL, or adenocarcinoma in situ) are referred to colposcopy. Women with normal reflex cytology results are recalled in one year for follow up HPV testing. Women return to routine recall after normal HPV test results, or normal cytology results at the one-year HPV test follow up.

2.3. Model structure

A cost-consequence analysis was performed using a decision tree model built in Microsoft Excel. The decision tree models the screening algorithms for France and shows the potential short-term impact on costs and resource use. Adapted from an analysis of HPV primary screening in England,^[22] the model follows one cohort of women from baseline screen for two years, through recall visits and exits at discharge to routine recall, colposcopy or loss to follow up. The same structure is used in the model for the mRNA and DNA arms (Figs. 1 and 2).

Arbyn reported pooled relative sensitivity of the Aptima mRNA test compared to the HC2 DNA test for CIN2+ (0.98 for CIN2+ and CIN3+).^[21] According to the Meijer criteria, mRNA and DNA assays have equivalent sensitivity.^[18] Therefore, the number of true positives correctly identified and requiring treatment after colposcopy would be similar in both the DNA and mRNA arms. Correspondingly, the number of false negatives who progress to longer-term disease outcomes would be similar in both arms. Therefore, the costs of treatment, follow up and long-term outcomes are assumed to be the same and are excluded from the model. Model assumptions and rationale are reported in detail.^[22]

Outcomes are total costs and total number of colposcopies, HPV and cytology tests in the DNA and mRNA arms. These outcomes were deemed important to decision makers as the key drivers of resource use and costs.

2.4. Model inputs

France does not currently report the screening population and outcomes from the cervical screening programme in a national

database. To estimate the cohort of women screened in one year, the population of women aged 25–65 years was taken from the Institut national de la statistique et des études économiques 2020 Annual Data report.^[24]

Each year, a percentage of the total population of women aged 25 to 65 years will enter the screening algorithm at age 25 years, or they are invited to return for recall screening after their last screen. Date of prior screening is assumed to be evenly distributed over time. Therefore, the number of women invited to screen is estimated by distributing the age-eligible population equally into the number of years between routine recall appointments.

As there is not yet published information on screening uptake rates in the screening programme,^[7] individual screening coverage rate of 59% (Table 1) for triennial cervical smears was used.^[25]

HPV positivity is needed to calculate the number of women going through the screening algorithm. The French Aptima Screening Evaluation (FASE) study in France compared the HC2 DNA assay to mRNA assay at baseline screen, and found that HPV positivity using HC2 was 23.5% and 13.0% for ages 20 to 29 and 30 to 65, respectively, and 15.6% and 8.5% for Aptima for ages 20 to 29 and 30 to 65, respectively.^[16] However, the FASE study did not provide the head-to-head assay results for follow-up after year one required for the decision trees. Other comparative head-to-head studies (FOCAL,^[10] German AHPV Screening Trial^[4]) reported lower HPV positivity, did not include follow-up, or did not include the younger age range and therefore were not appropriate to use for the French population; more information is given in.^[22]

The Horizon study,^[26,27] a head-to-head comparison of mRNA and DNA tests in a simulated cervical screening algorithm in Copenhagen, reported baseline and follow up results for cytology, and mRNA and DNA tests. The Horizon data most closely resembled the HPV positivity found in France in the FASE study and was selected as the source for the probability inputs for the model. The FASE study reported results from the HC2 DNA test only. The FASE HC2 baseline positivity (23.5% aged 20–29 and 13.0% aged 30–65) was comparable to the Horizon HC2 baseline positivity (31.8% aged 23–29 and 11.7% aged 30–65). FASE mRNA baseline positivity (15.6% aged 20–29 and 8.5% aged 30–65) was comparable to Horizon mRNA baseline positivity (16.1% aged 23–29 and 9.45% aged

Table 1

Baseline model input parameters and deterministic sensitivity analysis high and low parameter values.

Parameter	Pathway (Arm)	Base case value	DSA value (Low)	DSA value (High)	Note/ Reference
Discount rate	Both pathways (Both Arms)	0.04	0.03	0.06	Choix méthodologiques pour l'évaluation économique à la HAS ^[28]
Total number of women in French cohort					
Women aged 25–29 yr	Cytology primary (mRNA and DNA Arms)	1,878,646	–	–	Insee, estimations de population ^[24]
Women aged 30–65 yr	HPV primary (mRNA and DNA Arms)	15,248,637	–	–	Insee, estimations de population ^[24]
Women aged 25–29 yr invited to screening	Cytology primary (mRNA and DNA Arms)	626,215	–	–	Calculated
Women aged 30–65 yr invited to screening	HPV primary (mRNA and DNA Arms)	3,049,727	–	–	Calculated
Routine recall period aged 25–29 yr	HPV primary (mRNA and DNA Arms)	3 yr	–	–	Public Health Guideline for evaluation of HPV tests for primary screening ^[8]
Routine recall period aged 30–65 yr	Cytology primary (mRNA and DNA Arms)	5 yr	–	–	Public Health Guideline for evaluation of HPV tests for primary screening ^[8]
Screening coverage	Both pathways (mRNA and DNA)	59%	38%	80%	Santé Publique France: Coverage of cervical cancer screening in France, 2012–2017 ^[25]
Total women in screened cohort aged 25 to 29 yr	Cytology primary (mRNA and DNA)	369,467	–	–	Calculated
Total women in screened cohort aged 30 to 65 yr	HPV primary (mRNA and DNA)	1,799,339	–	–	Calculated
Cost inputs (€)					
Cost of colposcopy	Both pathways (mRNA and DNA)	49.82	–	–	CCAM Online: JLQE002 ^[29]
Cost of consultation	Both pathways (mRNA and DNA)	30.00	–	–	Federation of Doctors in France: New rates in gynaecology ^[30]
Cost of primary cytology	Both pathways (mRNA and DNA)	17.00	–	–	CCAM Online: JKQX426 and JKQX147 ^[29]
Cost of reflex cytology	Both pathways (mRNA and DNA)	17.00	–	–	CCAM Online: JKQX426 and JKQX147 ^[29] Cytology only.
Cost of primary HR-HPV test	Both pathways (mRNA and DNA)	27.00	–	–	CCAM Online: ZZQX628 and ZZQX603 ^[29]
Cost of reflex HR-HPV test	Both pathways (mRNA and DNA)	27.00	–	–	CCAM Online: ZZQX628 and ZZQX603 ^[29]
Infection and disease probabilities					
Probability of positive HR-HPV test at year one	HPV primary (DNA)	0.1621	0.1216	0.2026	Rebojij ^[26,27]
	HPV primary (mRNA)	0.0945	0.0708	0.1181	Rebojij ^[26,27]
	HPV primary (DNA)	0.2544	0.1908	0.3180	Rebojij ^[26,27]
Probability of positive cytology year one (for women with positive HR-HPV test in year one)	HPV primary (mRNA)	0.2368	0.1776	0.2961	Rebojij ^[26,27]
	HPV primary (DNA)	0.6179	0.4634	0.7724	Rebojij ^[26,27]
Probability of positive HR-HPV test at year two (for women with normal reflex cytology year one)	HPV primary (mRNA)	0.5147	0.3860	0.6433	Rebojij ^[26,27]
	Cytology primary (mRNA and DNA)	0.0132	0.0165	0.0099	Hamers ^[7] , Rebojij ^[26,27]
Probability of ASCUS or AGC cytology at year one (for women with normal cytology at baseline)	Cytology primary (mRNA and DNA)	0.0612	0.0459	0.0765	Hamers ^[7] , Rebojij ^[26,27]
Probability of LSIL, ASC-H, AIS, HSIL, or carcinoma cytology at year one (for women with normal cytology at baseline)	Cytology primary (mRNA and DNA)	0.0037	0.0028	0.0046	Hamers ^[7] , Rebojij ^[26,27] , Ogilvie ^[31]
Probability of ASCUS or AGC cytology at year two (for women with normal cytology at baseline)	Cytology primary (mRNA and DNA)	0.0171	0.0128	0.0214	Hamers ^[7] , Rebojij ^[26,27] , Ogilvie ^[31]
Probability of LSIL, ASC-H, AIS, HSIL, or carcinoma cytology at year two (for women with normal cytology at baseline)	Cytology primary (DNA)	0.9158	0.6868	1.0	Hamers ^[7] , Rebojij ^[26,27] , Ogilvie ^[31]
Probability of positive reflex HR-HPV test	Cytology primary (mRNA)	0.8526	0.6395	1.0	Hamers ^[7] , Rebojij ^[26,27] , Ogilvie ^[31]

AGC = atypical glandular cells, AIS = adenocarcinoma in situ, ASC-H = atypical squamous cells of undetermined significance, CCAM = Classification Commune des Actes Médicaux, cytology primary = cervical screening algorithm in which the primary test is cytology followed by reflex HPV testing, DSA= deterministic sensitivity analysis, DNA = deoxyribonucleic acid, HPV primary = cervical screening algorithm in which the primary test is HPV followed by reflex cytology testing, HR-HPV = high-risk human papillomavirus, HSIL = high grade squamous intraepithelial lesion, Insee = Institut national de la statistique et des études économiques, LSIL = low-grade squamous intraepithelial lesion, mRNA = messenger ribonucleic acid.

Table 2
Baseline results for the primary model outcomes and total costs for colposcopy, human papilloma virus tests and cytology tests.

	Number of tests/procedures			Costs (€)			
	Total colpo-scopies	Total HPV Tests	Total Cytology Tests	Cost of colpo-scopies	Cost of HPV tests	Cost of cytology tests	Total Costs
mRNA arm (Cytology primary)	22,231	5423	520,188	1,103,184	145,850	24,176,363	25,425,397
mRNA arm (HPV Primary)	51,977	1,856,501	169,962	2,547,432	105,695,263	2,889,354	111,132,048
DNA arm. (Cytology primary)	22,487	5423	520,188	1,115,864	145,850	24,176,363	25,438,077
DNA arm. (HPV Primary)	99,516	1,895,167	291,632	4,873,251	107,814,446	4,957,747	117,645,443
Total mRNA arm	74,208	1,861,925	690,150	3,650,616	105,841,112	27,065,717	136,557,446
Total DNA arm	122,003	1,900,590	811,820	5,989,115	107,960,295	29,134,110	143,083,521
Difference (DNA – mRNA)	47,795	38,666	121,670	2,338,499	2,119,183	2,068,393	6,526,075
% increase with DNA versus mRNA	64.4%	2.1%	17.6%	64.1%	2.0%	7.6%	4.8%

Colpo-scopies = colposcopies, cytology primary = cervical screening algorithm in which the primary test is cytology followed by reflex HPV testing, DNA = Deoxyribonucleic acid, HPV primary = cervical screening algorithm in which the primary test is HPV followed by reflex cytology testing, HPV tests = Human Papilloma virus tests, mRNA = messenger ribonucleic acid.

30–65) (see Supplemental Digital Content, <http://links.lww.com/MD2/B97> which describes the probability inputs and assumptions).

Costs were taken from published sources (Table 1) and confirmed in discussion with multi-disciplinary experts. Costs are from the perspective of the French healthcare system. The cost of the primary test (HPV or cytology) includes the cost of sample collection and cost of running the test. The cost of reflex testing includes only the cost of running the cytology or HPV test, as no further sample collection is required.

Costs are reported in 2020 Euros (Table 1). A discount rate of 4.0% was applied in line with French guidelines.^[28] Future costs in year two are discounted to reflect their present value.

2.5. Uncertainty analyses

A deterministic sensitivity analysis was carried out to explore the robustness of the model results to variations in input

parameters. The minimum and maximum values are shown in Table 1. Maximum screening coverage was varied up to 80% to represent French screening coverage goals. Probabilities were varied by 25% from their base case values (with a maximum of 100%).

A probabilistic sensitivity analysis (PSA) was also conducted to assess the robustness of the results (see Supplemental Digital Content Table 1, <http://links.lww.com/MD2/B103> and 2, <http://links.lww.com/MD2/B104> Supplemental Digital Content, <http://links.lww.com/MD2/B97> which provide PSA distributions). A broader range of probabilities were explored in this PSA compared with previous publications.^[22,32] This did not impact the interpretation of the outcomes. Model parameters were independently sampled from appropriate distributions, and 1000 iterations of the model were run to generate results. The distribution in differences in costs and number of colposcopies, HPV and cytology tests between the DNA and mRNA arms was calculated for each set of inputs and the 95% CI.

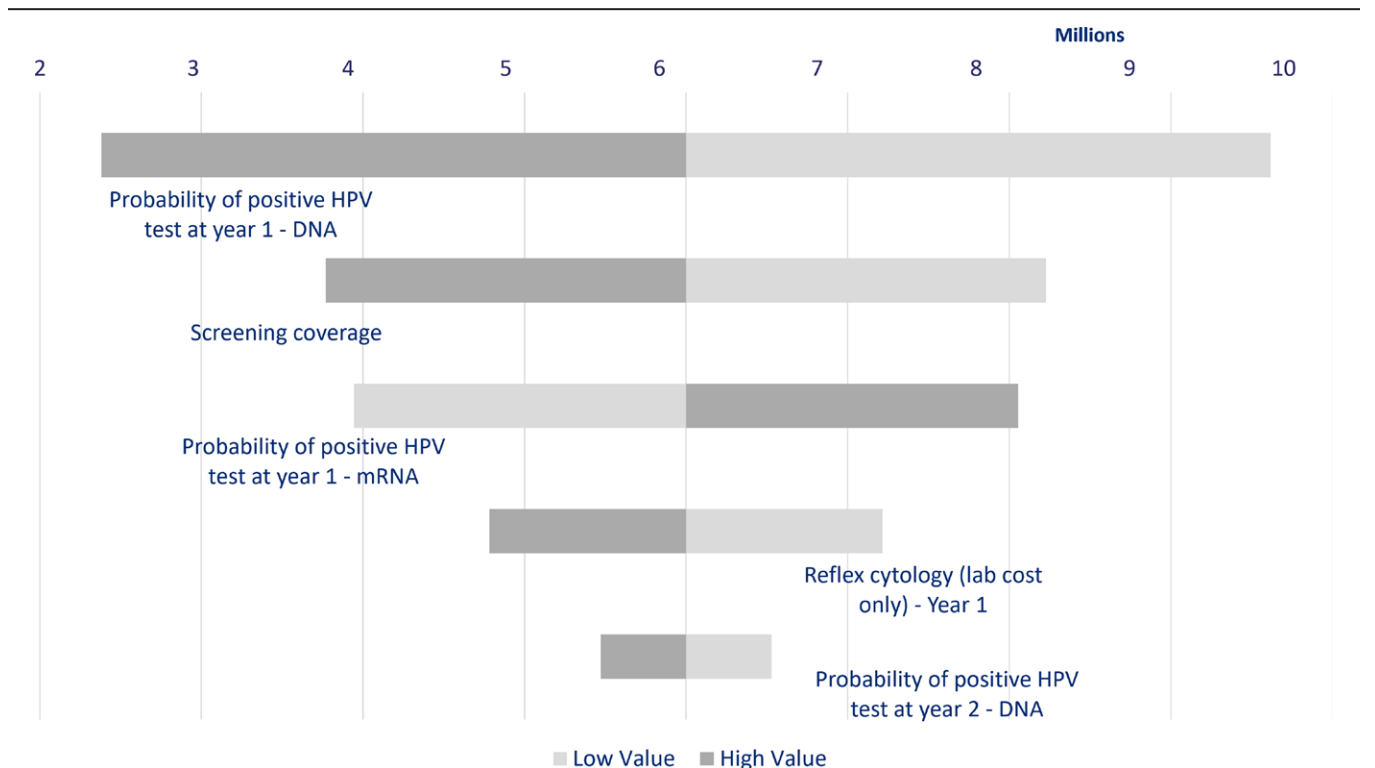


Figure 3. Deterministic sensitivity analysis results: Total cost difference between DNA and mRNA arms.

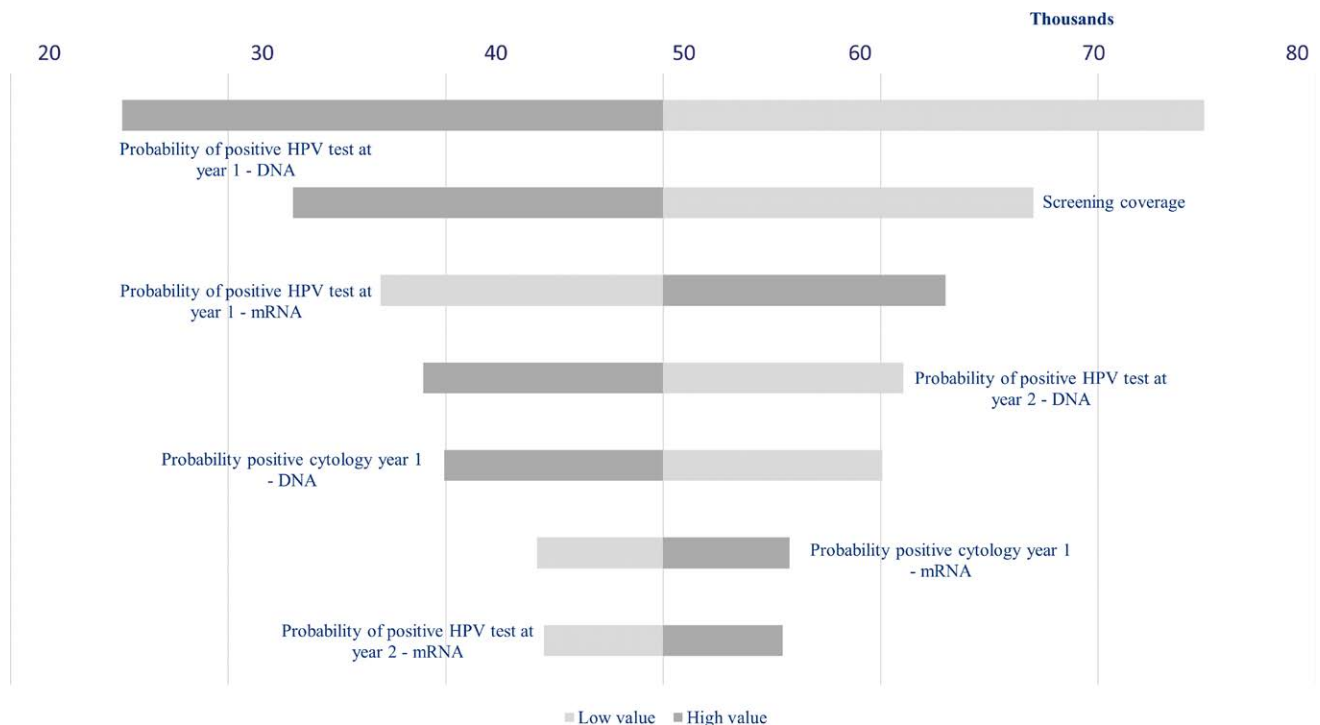


Figure 4. Deterministic sensitivity analysis results: Number of colposcopies difference between DNA and mRNA arms.

2.6. Ethics

Ethical approval was not necessary as this was a theoretical health economic evaluation of the use of a type of HPV test in cervical screening and patients were not involved in the evaluation.

3. Results

Using an mRNA HR-HPV test instead of a DNA test is estimated to save €6.5 million over two years for a cohort of 2,168,806 million women aged 25 to 65 participating in cervical screening in France. The total cost of using mRNA testing was €137 million compared to €143 million for DNA testing. 18.6% of costs of mRNA testing were in the cytology primary screening pathway and 81.4% of costs were in the HPV primary screening pathway. Unnecessary tests and procedures could be eliminated by using an mRNA versus DNA assay: 47,795 colposcopies, 38,666 HPV tests and 121,670 cytology tests (Table 2).

The cost of the HPV tests was the largest component of the total cost of screening in all women in both arms. Costs were higher in the DNA arm than in the mRNA arm (Table 2) (see Supplemental Digital Content Table 3, <http://links.lww.com/MD2/B105> and Supplemental Digital Content Figures 2–5, <http://links.lww.com/MD2/B99>, <http://links.lww.com/MD2/B100>, <http://links.lww.com/MD2/B101>, <http://links.lww.com/MD2/B102>, Supplemental Digital Content, <http://links.lww.com/MD2/B97> which provide the number of procedures and tests by year).

Figure 3 and Figure 4 show the difference in outcomes between the DNA and mRNA arms when inputs are changed in the deterministic sensitivity analysis. The centre line shows the base case difference between the two arms and the bars shows the difference when the minimum or maximum value of the input parameter is used. Values with the largest difference from the base case indicate a larger difference in costs and colposcopies between the use of mRNA and DNA assays. The total cost was most sensitive to the variation in the probability of a positive DNA HR-HPV test in year one with €10.2 million

increased costs in the DNA arm compared to the mRNA arm with the high probability parameter value (Fig. 3). Similarly, the number of colposcopies was most sensitive to variation in the probability of a positive HPV DNA in year one with 72,674 more colposcopies with the high probability parameter value (Fig. 4). When increasing screening coverage to 80%, 64,806 fewer colposcopies are estimated with the use of mRNA assays compared to DNA assay.

The 95% CI calculated from the PSA for the difference in the total costs for mRNA compared to DNA ranged from €-13,480,139 to €1,342,275 where a negative number indicates costs savings with mRNA (see Supplemental Figure 1, <http://links.lww.com/MD2/B98> Supplemental Digital Content, <http://links.lww.com/MD2/B97> which shows the distribution of costs and number of procedures and tests from the PSA).

4. Discussion

4.1. Principal findings

Adopting the use of the Aptima mRNA assay versus the use of a DNA assay in the proposed cervical screening algorithms in France could result in over €6.5 million in total cost savings, 47,795 fewer unnecessary colposcopies, 38,666 fewer HPV tests, and 121,670 fewer cytology tests annually. As test sensitivity between mRNA and DNA tests is similar,^[4,14–17] true positives will not be missed and the reduction in total costs is made by eliminating unnecessary referrals to colposcopy and unnecessary HR-HPV and cytology tests. Uncertainty analyses indicate robust results across a range of inputs.

4.2. Strengths and limitations

While prior publications have considered cervical primary screening^[33] or compared screening strategies^[5] for French women, this is the first evaluation of the use of mRNA compared to DNA assays in a national cervical screening programme in France. This is the first analysis to incorporate both cytology

primary and HPV primary algorithms to mirror the proposed French cervical programme, and French costs and population to best represent reimbursement.

Head-to-head comparative data for mRNA and DNA assays in cervical screening with follow-up screening are not available for people living in France. Therefore, data from the Horizon study from Denmark were used^[26,27] as HPV positivity was similar in both populations, although the other characteristics of women in the study may be dissimilar from France. Data were unavailable for French screening coverage as no national screening registry exists.

Screening more women in a national programme would change the outcomes in the model; additional cost savings and reduced unnecessary tests and procedures are anticipated using mRNA versus DNA testing. As France rolls out a population-based cervical screening programme nationally, publication of French data will allow the calibration of the model to the French population.

This model was adapted from a previous publication^[22] which describes in detail the strengths and limitations of the model structure.

4.3. Comparison to other studies

The UK model, which considered an HPV primary pathway only, found that using the Aptima mRNA assay resulted in cost savings while reducing unnecessary tests.^[22] A related study comparing mRNA and DNA tests in cervical screening in Canada found reduced overall costs and fewer unnecessary tests and procedures when an mRNA test is used.^[32]

Results from an English HPV primary cervical screening pilot found an 80% increase in colposcopies with HPV primary testing and cytology triage compared to screening with cytology alone.^[34] In this analysis in the French population, the use of DNA testing compared to mRNA testing resulted in 64% more colposcopies (Table 2).

Although the screening algorithms and the input data are different, there is a consistent trend towards the use of an mRNA test reducing the number of unnecessary tests and procedures benefiting for women and health services.

4.4. Interpretation and implications

When it is fully implemented, the French cervical screening program may include self-sampling for some women, with the goal of increasing cervical screening coverage.^[25] Due to a lack of data, self-sampling was not included in this study. However, if self-sampling is recommended, this model can be updated to include self-sampling.

The current level of vaccination coverage in France is 23.7% for 16-year-old women.^[35] Haute Autorité Santé guidelines recommend expanding vaccination coverage in France.^[8] A reduced rate in HPV positivity has been seen in countries that have achieved higher levels of vaccination such as Australia.^[36] However, it is unclear how the choice of HR-HPV assay would be impacted by these changes. As head-to-head data in a vaccinated population becomes available, this model should be updated.

Women going through cervical screening may face a negative impact to their psychological health. Women receiving abnormal cytology results or a positive HPV test results may experience stigma, fear, powerlessness, anger, anxiety, distress, or guilt.^[37] 39% of women experience significant psychological distress after follow up cytology 6 months after initial abnormal cytology results.^[38] Given the negative burden on women's mental health and wellbeing, a more specific mRNA test that can reduce unnecessary HPV and cytology follow-up testing and referrals to colposcopy could also significantly alleviate stress, fear and distress associated with further testing.

An anticipated increase in colposcopies when switching to HPV primary screening can be mitigated by eliminating unnecessary procedures associated with false positive results. Implementing the use of the more specific, yet similarly sensitive, mRNA test can result in fewer false positives, reduce unnecessary reflex cytology and referrals to colposcopy, and reduce anxiety and stress experienced while waiting for unneeded appointments and test results. Colposcopist and laboratory time spent on unnecessary testing and procedures will be reduced, thereby freeing up resources in the health care system to address health care needs of women and improve patient management.

5. Conclusion

Results indicate that choice of HR-HPV test can make a significant difference to resource use and costs. Choosing an mRNA rather than DNA test could yield an estimated annual cost savings of €6.5 million and significantly fewer colposcopies, HPV, and cytology tests. These results can inform the implementation of the national screening programme in France.

Author contributions

Conceptualization: Elisabeth Adams, Georgie Weston.

Data curation: Caroline Dombrowski.

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References

- [1] Bruni L, Albero G, Serrano B, et al. Human papillomavirus and related diseases in France. Summary Report ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre) 2019.
- [2] Monsonego J, Bosch FX, Coursaget P, et al. Cervical cancer control, priorities and new directions. *Int J Cancer* 2004;108:329–33.
- [3] Rodríguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst* 2008;100:513–7.
- [4] Iftner T, Becker S, Neis K-J, et al. Head-to-head comparison of the RNA-based aptima human papillomavirus (HPV) assay and the DNA-based hybrid capture 2 HPV test in a routine screening population of women aged 30 to 60 years in Germany. *Tang Y-W, ed. J Clin Microbiol* 2015;53:2509–16.
- [5] Barré S, Massetti M, Leleu H, De Bels F. Organised screening for cervical cancer in France: a cost-effectiveness assessment. *BMJ Open* 2017;7:e014626.
- [6] Chrysostomou CA, Stylianou CD, Constantinidou A, Kostrikis GL. Cervical cancer screening programs in Europe: the transition towards HPV vaccination and population-based HPV testing. *Viruses* 2018;10:
- [7] Hamers FF, Duport N, Beltzer N. Population-based organized cervical cancer screening pilot program in France. *Eur J Cancer Prev* 2018;27:486–92.
- [8] Haute Autorité de Santé HAS. Évaluation de la recherche des papillomavirus humains (HPV) en dépistage primaire des lésions précancéreuses et cancéreuses du col de l'utérus et de la place du double immuno-marquage p16/Ki67. 2019. Available at: https://www.has-sante.fr/jcms/c_2806160/en/evaluation-de-la-recherche-des-papillomavirus-humains-hpv-en-depistage-primaire-des-lesions-precancereuses-et-cancereuses-du-col-de-l-uterus-et-de-la-place-du-double-immuno-marquage-p16-ki67.
- [9] Légifrance. Arrêté du 30 juillet 2020 modifiant l'arrêté du 29 septembre 2006 relatif aux programmes de dépistage organisé des cancers et relatif à l'organisation du dépistage organisé du cancer du col de l'utérus. Vol JORF n(0200). 2020. Available at: <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000042238343>. [Accessed September 8, 2020].

- [10] Cook DA, Smith LW, Law JH, et al. Comparative performance of human papillomavirus messenger RNA versus DNA screening tests at baseline and 48 months in the HPV FOCAL trial. *J Clin Virol* 2018;108:32–7.
- [11] Monsonego J, Hudgens MG, Zerat L, Zerat J-C, Syrjänen K, Smith JS. Risk assessment and clinical impact of liquid-based cytology, oncogenic human papillomavirus (HPV) DNA and mRNA testing in primary cervical cancer screening (The FASE Study). *Gynecol Oncol* 2012;125:175–80.
- [12] Haedicke J, Iftner T. A review of the clinical performance of the Aptima HPV assay. *Recent Adv Mol Detect Hum Papillomavirus Cerv Cancer Screen* 2016;76:S40–8.
- [13] Iftner T, Neis K-J, Castanon A, et al. Longitudinal Clinical Performance of the RNA-Based Aptima Human Papillomavirus (AHPV) Assay in Comparison to the DNA-Based Hybrid Capture 2 HPV Test in Two Consecutive Screening Rounds with a 6-Year Interval in Germany. *J Clin Microbiol* 2019;57:
- [14] Arbyn M, Roelens J, Cuschieri K, et al. The APTIMA HPV assay versus the hybrid capture 2 test in triage of women with ASC-US or LSIL cervical cytology: a meta-analysis of the diagnostic accuracy. *Int J Cancer* 2013;132:101–8.
- [15] Cook DA, Smith LW, Law J, et al. Aptima HPV Assay versus Hybrid Capture® 2 HPV test for primary cervical cancer screening in the HPV FOCAL trial. *J Clin Virol* 2017;87:23–9.
- [16] Monsonego J, Hudgens MG, Zerat L, et al. Evaluation of oncogenic human papillomavirus RNA and DNA tests with liquid-based cytology in primary cervical cancer screening: the FASE study. *Int J Cancer* 2010;129:691–701.
- [17] Cuzick J, Cadman L, Mesher D, et al. Comparing the performance of six human papillomavirus tests in a screening population. *Br J Cancer* 2013;108:908.
- [18] Meijer CJLM, Berkhof J, Castle PE, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer* 2009;124:516–20.
- [19] Heideman DAM, Hesselink AT, van Kemenade FJ, et al. The aptima HPV assay fulfills the cross-sectional clinical and reproducibility criteria of international guidelines for human papillomavirus test requirements for cervical screening. *J Clin Microbiol* 2013;51:3653–7.
- [20] Forslund O, Elfström KM, Lamin H, Dillner J. HPV-mRNA and HPV-DNA detection in samples taken up to seven years before severe dysplasia of cervix uteri. *Int J Cancer* 2019;144:1073–81.
- [21] Arbyn M, Snijders PJF, Meijer CJLM, et al. Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening? *Clin Microbiol Infect* 2015;21:817–26.
- [22] Weston G, Dombrowski C, Harvey MJ, et al. Use of the Aptima mRNA high-risk human papillomavirus (HR-HPV) assay compared to a DNA HR-HPV assay in the English cervical screening programme: a decision tree model based economic evaluation. *BMJ Open* 2020;10:e031303.
- [23] Institut National du Cancer. Conduite à tenir devant une femme ayant une cytologie cervico-utérine anormale - Thésaurus. Institut National du Cancer; 2017. Available at: <https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Conduite-a-tenir-devant-une-femme-ayant-une-cytologie-cervico-uterine-anormale-Thesaurus>.
- [24] Insee. Population par sexe et groupe d'âges: Données annuelles 2020. Institut national de la statistique et des études économiques. Published January 14, 2020. Available at: <https://www.insee.fr/fr/statistiques/2381474>. [Accessed March 12, 2020].
- [25] Hamers F, Jezewski-Serra D. Couverture du dépistage du cancer du col de l'utérus en France, 2012-2017. Published online 2019. Available at: http://beh.santepubliquefrance.fr/beh/2019/22-23/2019_22-23_2.html. [Accessed February 27, 2020].
- [26] Rebolj M, Bonde J, Preisler S, Ejegod D, Rygaard C, Lynge E. Human papillomavirus assays and cytology in primary cervical screening of women aged 30 years and above. *Plos One* 2016;11:e0147326.
- [27] Rebolj M, Bonde J, Ejegod D, Preisler S, Rygaard C, Lynge E. A daunting challenge: human papillomavirus assays and cytology in primary cervical screening of women below age 30 years. *Eur J Cancer* 2015;51:1456–66.
- [28] Haute Autorité de Santé HAS. Choix méthodologiques pour l'évaluation économique à la HAS. 2011. Available at: https://www.has-sante.fr/jcms/r_1499251/en/choices-in-methods-for-economic-evaluation.
- [29] l'Assurance Maladie. Classification Commune des Actes Médicaux. CCAM en ligne. Published 2020. Available at: <https://www.ameli.fr/accueil-de-la-ccam/index.php>. [Accessed March 12, 2020].
- [30] l'Assurance Maladie. Consultations en métropole: vos remboursements. ameli.fr pour les assurés. Published décembre 2019. Available at: <https://www.ameli.fr/paris/assure/remboursements/rembourse/consultations/metropole>. [Accessed March 31, 2020].
- [31] Ogilvie GS, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA* 2018;320:43–52.
- [32] Weston G, Dombrowski C, Steben M, Popadiuk C, Bentley J, Adams EJ. A health economic model to estimate the costs and benefits of an mRNA vs DNA high-risk HPV assay in a hypothetical HPV primary screening algorithm in Ontario, Canada. *Prev Med Rep* 2021;23:101448.
- [33] Beltzer N, Hamers F, Dupont N. Final results of the evaluation of organized screening for cervical cancer in 13 departments in France, 2010-2014. *Bull Epidémiol Hebd*. Published online January 1, 2017;26–31.
- [34] Rebolj M, Rimmer J, Denton K, et al. Primary cervical screening with high risk human papillomavirus testing: observational study. *BMJ* 2019;364:l240.
- [35] Fonteneau L, Barret A, Lévy-Bruhl D. Evolution of the vaccination coverage of the papillomavirus vaccine in France - 2008-2018. *Bull Epidémiol Hebd* 2019;424–30.
- [36] Garland SM. The Australian experience with the human papillomavirus vaccine. *Clin Ther* 2014;36:17–23.
- [37] Daley EM, Perrin KM, (Kay), McDermott RJ, et al. The psychosocial burden of HPV: a mixed-method study of knowledge, attitudes and behaviors among HPV+ women. *J Health Psychol* 2010;15:279–90.
- [38] Sharp L, Cotton S, Cruickshank M, et al. The unintended consequences of cervical screening: distress in women undergoing cytological surveillance. *J Low Genit Tract Dis* 2014;18:142–50.