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Organized screening for cervical cancer in France: a Cost-effectiveness assessment

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French National Cancer Institute

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ABSTRACT

OBJECTIVE: Accordingly to the third Cancer plan, organized screening (OS) of cervical cancer (CC) among women aged 25-65 should be implemented in the forthcoming years in France. The most cost-effective way to implement OS in the French health care system in regard of this objective is yet to be determined.

METHODS: A microsimulation model was developed by the French National Institute of Cancer (INCa) alongside clinical experts and stakeholder representatives. A closed cohort of women eligible to CC screening and representative in terms of age and participation to individual screening (IndScr) was modelled on a lifetime horizon. Different OS strategies, additive to the existing IndScr and based on mailed invitations and recalls to perform OS with different screening tests (Pap, HPV, p16/Ki67) and OS periodicity were assessed. The analysis was conducted from the collective perspective.

RESULTS: Compared to the current situation, all OS strategies are associated with decreased cancer incidence/mortality (from -14.2%/-13.5% to -22.9%/-25.8%, respectively). Most strategies generate extra costs ranging from €37.9 to €1,607 per eligible woman. HPV-testing every 10 and 5 years are cost-saving.

HPV-test every 10 years is the less expensive, non-dominated strategy and represents the reference, being more effective and cost-saving than Pap-based strategies including the current situation. It is the dominating alternative, alongside HPV-test every 5 years. p16Ki67 as primary and HPV+ confirmation tests are more effective strategies with ICERs of €6,541,250 and €101,391 per life year, respectively. Pap-based strategies generate intermediary results.

CONCLUSION: OS strategies based on HPV-test appear highly efficient although those results rely on the assumption that OS periodicity will be respected. Implementing such OS modalities will require major adaptations to the current CC screening organization. Pap-test based strategies might constitute simpler modalities to set-up OS while preparing the field to secure appropriate implementation of other OS screening modalities.

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Strengths and limitations of the study

- A microsimulation model was developed to assess the efficiency of various strategies of cervical cancer organized screening in France.
- The model operates individual women eligible to screening and representative of the current French population on a lifetime horizon.
- Real-life practices and data were used, allowing fine modelling of the screening processes and validation against observed French data.
- The lack of precision of transition probabilities in the context of low incidence of cervical cancer as well as the assumptions required to model screening practices after primary HPV-tests are the main limitations of the study.

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BACKGROUND

Cervical cancer (CC) is the second cancer for incidence and the first for mortality in women worldwide. CC natural history is related to persistent HPV infection of the cervix that lead to squamous intraepithelial lesions that can evolve into cancerous lesions. CC prevention is based on screening, to detect and remove lesions at early stages to prevent invasive cancer, and anti-HPV vaccination to reduce cancer-associated HPV infection.[1]

In France, CC prevention is based on individual voluntary screening (IndScr) of CC for women aged 25 to 65 and vaccination. IndScr is based on a Papanicolaou test (Pap-test) every 3 years, after two negative annual Pap-tests. About 90% of Pap-smears are done by gynaecologists, although general practitioners (GP) and midwifes are authorized to perform it. IndScr has led to a significant decrease of its incidence and associated mortality in the last 20 years. In 2012, CC was the 11th most frequent and 12th most lethal form of cancer in women.[2] However many women still do not participate in CC screening. Participation to IndScr was found to be around 61% of eligible women, with low access to healthcare, comorbidities and poverty as risk factors for non-participation. Furthermore, vaccination has had a slow adoption in the French population.[3] In 2015, it was estimated that only 17% of women eligible to vaccination were vaccinated.[4] Thus, screening remains the main prevention tool to reduce CC. In 2014, the third French Cancer Plan has been launched to rise to both human and societal challenges issued by cancer. Indeed, its first operational objective is to implement CC OS among women aged 25-65 with a participation rate objective of 80% and a 30% reduction in CC-related mortality.[5]

Several OS experimentations have been performed in France to assess the efficacy of several modalities of screening including invitation and positive test follow-up, self-sampling and HPV-testing. The experimentations showed to improve participation by 13.2%, reduced lost to follow-up (LtFU) rate and demonstrated that primary HPV-testing and self-sampling are feasible alternative to Pap-smear in France.[6] Additionally, primary screening by HPV-testing has been evaluated as an alternative to Pap-smear.[7] Finally, innovative testing such as p16/Ki67 double-staining was shown to be a performant alternative for CC screening compared to HPV or Pap-test.[8]

Consequently, many alternative strategies can be considered for the implementation of OS for CC in France. In this context, a medico-economic evaluation of several OS strategies was performed by the French national cancer institute (INCa) which relied on a scientific steering committee involving clinical experts and stakeholder representatives (social security, ministry of health, patients and professionals) to provide advice on methodological choices and best OS implementation modality in the French context.

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METHODS

Seven strategies were compared to the current IndScr-only situation (Table 1). These strategies were all based on adding to the current IndScr layer an invitation to be screened followed by one recall for woman who did not spontaneously participate in the last 3 years (non-participant). The strategies also included an improvement in follow-up resulting in a reduction in LtFU women. Different screening tests were considered for primary screening or confirmation after a positive primary test, including Pap-test (analysed with liquid-based or regular cytology), HPV DNA detection and p16/Ki67 double-staining. Women tested positivize for both primary and confirmation tests went through colposcopy and conisation if a high grade (grade 2 or worse [CIN2+]) cervical intraepithelial neoplasia (CIN) lesion was identified. Women with CIN1 were retested at 12, 18 and 24 months if the initial lesion was ASC-US or LSIL on Pap, or went through colposcopy. Women tested positive for primary and negative for confirmation were retested at one year. A small fraction of participant was LtFU. Women could only be invited once per cycle. Detailed algorithms are available as supplementary material.

The population was limited to woman aged 25-65 currently eligible to IndScr.

Table 1 Strategies compared

Strategy	IR + Improved Follow-up	Primary test	Confirmation test after positive primary test
Current	No	Pap-test / 3 years	Pap-test or HPV
Pap/Pap-HPV	Yes	Pap-test / 3 years	Pap-test
Pap/p16Ki67	Yes	Pap-test / 3 years	p16/Ki67
HPV/Pap-5y†	Yes	HPV / 5 years	Pap-test
HPV/Pap-3y†	Yes	HPV / 3 years	Pap-test
HPV/Pap-10y†	Yes	HPV / 10 years	Pap-test
HPV/p16Ki67-5y†	Yes	HPV / 5 years	p16/Ki67
HPV/p16Ki67-10y†	Yes	HPV / 10 years	p16/Ki67
p16Ki67/p16Ki67	Yes	HPV / 3 years	p16/Ki67

IR: invitation + recall for woman who did not participate in IndScr in the last 3 years (non-participant)

† : women 25-35 are not eligible to HPV screening and receive a Pap-test every 3y instead. Woman tested HPV+/confirmation- go through double testing (HPV + Pap) the following year.

model structure

Given the complexity of screening algorithms (different testing/retesting frequencies) and interactions between participation rates and individual characteristics (age, social), a Markov state microsimulation model was developed. Considering the relatively slow progression of intraepithelial lesions and that the benefits of screening are usually seen on the long term, a 1-year cycle-length was used. The model was adapted from a previously published Markov cohort-based model.[9] A cohort of 100,000 women was simulated. Due to the long term development of the disease and its consequences, a lifetime horizon was applied.

For each woman entering the model, age, IndScr participation and periodicity, health state (HPV-, HPV+, CIN lesions or cancer) and vaccination are randomly attributed at the simulation initiation. At each cycle, non-HPV-infected women can become infected with a risk depending on age and vaccination status. The infection can progress to CIN1 and subsequently to CIN2/3 and FIGO (Federation of Gynecology and Obstetrics) 1 non-invasive cancer. HPV infection and CIN lesions can regress spontaneously until CIN2/3 lesions have become persistent (pCIN2/3). Patients then systematically progress to cancer with an age-dependant rate. FIGO1 lesions can progress to FIGO2, 3 and 4 and become symptomatic. Once symptomatic, the lesion is treated and the woman remains in

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the corresponding treated state with an associated cancer mortality rate. Age-specific general mortality applies at any state.

Each year, the model determines whether the simulated woman undergoes screening either spontaneously (IndScr) or after invitation based on her participation periodicity, time since last screening and participation rates after invitation/recall. Simulated results for screening included positivity and lesion type for Pap-tests and positivity for HPV and p16Ki67 testing. Positivity was based on tests' specific sensitivity and specificity and woman's current state. Screening affects the natural progression of the disease: women with non-cancerous lesions return to HPV- state after conisation, undiagnosed cancerous lesions are treated. Structure of the modelled natural history is presented in Figure 1.

input data

The input data used in the simulation is presented in table 2.

Population characteristics were based on available epidemiologic and demographic data representative of the French population. Vaccination was limited to women aged 30 or less as it was only recently available in France. IndScr participation periodicity depended on age and social status and was obtained from the analysis of the national health insurance database (Supplementary data). About 61.9 % of eligible women were found to participate in IndScr at a ≤4 years frequency.[3] Distribution of each modelled health state by age was not available in France and was estimated by simulating a cohort of non-vaccinated 14 years old women undergoing current IndScr-only screening over life-time.

Transition probabilities (TP) were based on a previously published model.[9] HPV infection rates and pCIN2/3 to cancer progression rate were calibrated using the model to reproduce observed HPV and cancer prevalence by age.[1, 10] High risk HPV annual infection rate was estimated to be 3.5% to 14%, depending on age.[11] The impact of vaccination is simulated by applying a relative risk reduction of infection.[1]

Probabilities of cancer progression and symptoms emergence were obtained from the CC natural history simulation model developed by Myers *et al*.[12] Cancer specific-mortality by grade and time since diagnosis was estimated from SEER using data for white women under 50 as it was assumed that non-specific mortality was low in this group.[13] General mortality is modelled accordingly to French national statistics office (INSEE) data.

Participation rates after invitation and recall, LtFU rate in the current screening, OS impact on LtFU rate, observed lesions on Pap-smear and associated care were all based on observational data from French OS experimentations.[1]

Screening tests' sensitivity and specificity were based on clinical studies for detecting CIN2/3 lesions and took into account the test sequence (eg. HPV after Pap or primary HPV).[8, 14-16] One percent of Pap-tests were non-interpretable and led to retest.[17] Colposcopy was assumed to have 100% sensitivity and specificity. A 95% efficacy was considered for conisation.

The model estimated OS and direct medical costs from a collective perspective. OS costs covered invitations, recall as well as database management related to invitations dispatch, women's participation tracking and follow-up management. All costs were obtained or updated to 2016€ using consumer price index. Cost data for consultations and medical care are based on national tariffs. It was considered that women participating in IndScr do so during a routine follow-up consultation, with no extra-consultation cost. Cost for HPV-analysis was decreased by 60% in strategies with

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primary HPV-testing, assuming a substantial cost reduction in case of wide generalization of HPV-testing. This assumption was validated by health insurance and health ministry representatives. Accordingly to public-health law, no extra co-payment is applied to OS participants. Cancer states were associated with costs accounting for care and follow-up by FIGO stage [11] when entering the corresponding diagnosed state. All costs were updated to 2016, using national consumer price index for healthcare goods and services.

Table 2 Input data

Parameter	Value	Distribution	Source
Demographic			
Age	25 - 65 Based on distribution	NA	National Statistics (INSEE)
CMU-c Eligibility (social status)	12.2 % (9.8% - 14.6%)	Normal	National Health Insurance Data
IndScr participation periodicity	Based on frequency distribution, age and social	Uniform	National Health Insurance Data
Initial Health State	Based on distribution	NA	Based on model prediction for a cohort of 14-years women
Transition probabilities			
HR-HPV infection	0.03 – 0.15 (0.03 – 0.18) Based on distribution	Beta	Estimated to reproduce known prevalence by age [11]
HPV-infection regression	0.50 (0.40 – 0.60)	Beta	Riethmuller et al. (1999)[18], Clavel et al. (2001)[19], Boulanger et al. (2004)[20], Beby-Defaux et al. (2004)[21], Dalstein et al. (2004)[22]
HR-HPV Infection → CIN 1	0.05 (0.04 – 0.06)	Beta	Moscicki et coll. (2001)[23]
CIN1 Regression	0.50 (0.40 – 0.60)	Beta	Melnikow et coll. (1998)[24], Nobbenhuis et coll. (2001)[25], Sanders and Taira (2003)[26], Van De Velde et coll. (2007)[27]
CIN1 → CIN 2/3	0.12 (0.10 – 0.14)	Beta	Melnikow et coll. (1998)[24], Sanders and Taira (2003)[26], Van De Velde et coll. (2007)[27]
CIN2/3 Regression	0.28 (0.22 – 0.33)	Beta	Melnikow et coll. (1998)[24]
CIN2/3 → pCIN 2/3	0.13 (0.10 – 0.15)	Beta	Melnikow et coll. (1998)[24]
Persistent CIN 2/3 → FIGO I	0.01 – 0.05 (0.01 – 0.06) Based on distribution	Beta	Estimated to reproduce known prevalence by age[1, 10]
FIGO I → FIGO II	0.20 (0.16 – 0.24)	Beta	Myers *et al.* 2000[12]
FIGO II → FIGO III	0.26 (0.21 – 0.31)	Beta	Myers *et al.* 2000[12]
FIGO III → FIGO IV	0.36 (0.29 – 0.43)	Beta	Myers *et al.* 2000[12]
FIGO I → Symptomatic FIGO I	0.15 (0.12 – 0.18)	Beta	Myers *et al.* 2000[12]
FIGO II → Symptomatic FIGO II	0.23 (0.18 – 0.27)	Beta	Myers *et al.* 2000[12]
FIGO III → Symptomatic FIGO III	0.60 (0.48 – 0.71)	Beta	Myers *et al.* 2000[12]
FIGO VI → Symptomatic FIGO IV	0.90 (0.67 - 1.00)	Beta	Myers *et al.* 2000[12]
1-year Cancer Survival	0.43 – 0.98 (0.23 – 0.99) By stage	Beta	SEER[13]
5-year Cancer Survival	0.14 – 0.94 (0.06 – 0.97) By stage	Beta	SEER[13]
10-year Cancer Survival	0.05 – 0.93 (0.01 – 0.96) By stage	Beta	SEER[13]
Screening			
Participation after invitation	17.3% (10.0% - 24.0%)	Uniform	Duport *et al.* 2014[17]
Participation after recall	12.1% (5.0% - 18.0%)	Uniform	Duport *et al.* 2014[17]
Lost to follow-up with IndScr	Based on lesion on Pap. Average 27.7%	NA	Duport *et al.* 2014[17]
Reduction in lost to follow-up with OS	0.77 (0.08 – 0.77)	Uniform	OS experimentations, INCA personal communication
Lesions on PAP	Distribution	NA	Duport *et al.* 2014[17]
Care per lesions	Distribution	NA	Duport *et al.* 2014[17]

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Primary Pap-test (Se)	70.0 % (57.0 % - 80.0 %)	Beta	Mustafa *et al.* (2015)[14]
Confirmation Pap-test after HPV+ (Se)	85.9 % (76.6 % - 92.1 %)	Beta	Bergeron *et al.* (2015)[8]
Primary HPV-test (Se)	94.0 % (89.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[14]
Confirmation HPV-test after Pap+ (Se)	100.0 % (NR)	NA	Mayrand *et al.* (2007)[16]
p16/KI67 (Se)	86.7 % (81.1 % - 90.9 %)	Beta	Ikenberg *et al.* (2013)[15]
Colposcopy (Se)	100.0% (NA)	NA	Assumption
Primary Pap-test (Sp)	95.0 % (92.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[14]
Confirmation Pap-test after HPV+ (Sp)	65.9 % (63.1 % - 68.6 %)	Beta	Bergeron *et al.* (2015)[8]
Primary HPV-test (Sp)	90.0 % (86.0 % - 93.0 %)	Beta	Mustafa *et al.* (2015)[14]
Confirmation HPV-test after Pap+ (Sp)	61.1 % (NR)	NA	Mayrand *et al.* (2007)[16]
p16/KI67 (Sp)	95.2 % (94.9 % - 95.4 %)	Beta	Ikenberg *et al.* (2013)[15]
Colposcopy (Sp)	100.0% (NA)	NA	Assumption
Conisation efficacy	95.0%	NA	Assumption
Non-interpretable tests	1.0% (1.0% - 3.0%)	Uniform	Duport *et al.* 2014[17]
Costs (€)			
Pap-test (IndScr)	47.78 (38.88 – 57.59)	Gamma	National tarrifs
Pap-test (OS)	49.62 (40.37 – 59.81)	Gamma	National tarrifs
p16/Ki67 (IndScr)	86.77 (70.60 - 104.58)	Gamma	National tarrifs
p16/Ki67 (OS)	88.61 (72.09 - 106.80)	Gamma	National tarrifs
HPV-test (IndScr)	47.70 (75.48 - 97.17)	Gamma	National tarrifs
HPV-test (OS)	49.54 (49.54 - 71.24)	Gamma	National tarrifs
Confirmation Pap-test (IndScr)	78.17 (63.60 - 94.21)	Gamma	National tarrifs
Confirmation Pap-test (OS)	49.63 (40.38 - 59.82)	Gamma	National tarrifs
Confirmation p16/Ki67 (IndScr)	116.77 (78.09 - 99.57)	Gamma	National tarrifs
Confirmation p16/Ki67 (OS)	88.23 (71.79 - 106.34)	Gamma	National tarrifs
Confirmation HPV-test (IndScr)	78.09 (63.53 - 94.12)	Gamma	National tarrifs
Confirmation HPV-test (OS)	49.55 (49.55 - 71.03)	Gamma	National tarrifs
Colposcopy	49.82 (40.54 - 60.05)	Gamma	National tarrifs
Conization	93.42 (76.01 - 112.60)	Gamma	National tarrifs
FIGO I CC treatment	1041.95 (847.77 - 1255.85)	Gamma	Dervaux *et al.* 2007[11]
FIGO II CC treatment	1818.86 (1479.90 - 2192.25)	Gamma	Dervaux *et al.* 2007[11]
FIGO III CC treatment	25817.84 (21006.43 - 31117.97)	Gamma	Dervaux *et al.* 2007[11]
FIGO IV CC treatment	30582.83 (24883.41 - 36861.16)	Gamma	Dervaux *et al.* 2007[11]
Database management + Invitation dispatch	7.00 (4.00 – 11.00)	Gamma	Cost of invitation to colorectal OS (Heath Ministry data, personal communication)
Recall dispatch	0.40 (0.40 – 3.25)	Gamma	50% postal charges

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validation

Model results were compared to observed epidemiological data for validation. The model faithfully reproduces cancer incidence and CC mortality in France.[11] Results of model validation are available as supplementary material.

analyses

Incremental cost–effectiveness ratios (ICER) were calculated for the life expectancy (QALE). Costs and QALE were discounted at 4% per year, according to existing French guidelines for cost-effectiveness studies.[28]

Several alternative scenarios were tested, including: not taking into account the efficacy of OS on LtFU rate, not taking into account a reduction in HPV cost, taking into account a 60% reduction in p16Ki67 cost.

The robustness of the model was tested using deterministic sensitivity analysis (DSA). In the DSA, all the parameters were tested at their confidence intervals (or at ±20% of baseline value when not available). The ten parameters with the greatest influence on the results are presented with tornado graphs for costs and health outcomes.

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RESULTS

Compared with the current situation, invitation and recall led to an increase in the 4-years participation rate from 61.9% to 65.5%. Every tested strategies was also associated with a reduction in cancer incidence/mortality ranging from -14.2%/-13.5% for the Pap/Pap strategy to -22.9%/-25.8% for the HPV/p16Ki67-5y strategy.

Undiscounted results are presented in table 3.

Table 3 Undiscounted results

	Outcomes		Costs (€) per woman			
Scénario	Cancer	Cancer mortality	OS organisation	Screening	CC care & conizations	Total
IndScr only*	34	13	0	294.2	30.9	325.0
Pap/Pap-HPV	-14.2%	-13.5%	+19.57	+13.32	-3.92	+28.97
Pap/p16Ki67	-16.6%	-15.9%	+19.57	+18.46	-4.57	+33.46
HPV/Pap-5y	-18.9%	-22.5%	+15.12	-29.79	-7.24	-21.91
HPV/Pap-3y	-21.1%	-22.4%	+15.16	+99.87	-7.31	+107.73
HPV/Pap-10y	-8.0%	-13.6%	+14.94	-14.42	-0.48	-134.04
HPV/p16Ki67-5y	-22.9%	-25.8%	+15.10	+1.57	-0.81	+8.55
HPV/p16Ki67-10y	-11.9%	-17.0%	+14.93	-129.7	-5.87	-120.63
p16Ki67/p16Ki67	-24.3%	-24.4%	+19.57	+233.30	-6.87	+246.00

*Reference for other scenarios. Cumulated incidence and mortality for 10,000 women eligible to OS on a lifetime horizon.

Average undiscounted cost of screening for the current eligible French population over lifetime was estimated to be €325 per eligible woman, most of which resulted from screening (€294). Strategies based on HPV-testing with 5 and 10-years frequencies were cost-saving (-€22 and -134 per woman, respectively) despite the additional cost incurred by the OS (€15). Other strategies were responsible of an increased cost ranging from €29 to €33 for Pap based screening to €108 to €246 for HPV/Pap-3y and p16Ki67/p16Ki67.

Although it was the cheapest strategy (€191 per eligible woman), HPV/Pap-10y was the strategy with the smallest cancer reduction (-11.9%), as opposed to p16Ki67/p16Ki67 that led to a 25% reduction in CC with the highest cost (€571 per eligible woman). Figure 2 presents the mean cost per woman and cancer reduction rate for each strategy.

Discounted survival is consistent with incidence and mortality (table 4). Compared to the current situation (19.4 LY survival), included strategies led to increased survival ranging from 10 years/10,000 eligible women for the Pap/Pap and HPV/Pap-10y strategies to 18 years for HPV/p16Ki67 and p16Ki67/ p16Ki67 strategies. Discounted extra costs per 10,000 eligible women ranged from €38K (HPV/Pap-5y confirmation test) to €1,608K (p16Ki67/p16Ki67). HPV-test every 5 and 10 years remained cost-saving after discounting. Thus, those strategies were more effective and cost-saving than Pap-based strategies, including current situation, and were the dominating alternatives. HPV/p16Ki67-5y and p16Ki67/p16Ki67 were more effective than HPV-test every 5 and 10 years and were associated with ICERs of €101,391 and €6,541,250 per LY respectively. HPV/Pap-3y was a dominated alternative, being as effective as HPV/Pap-5y and less effective than HPV/p16Ki67-5y at a much higher cost.

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Table 4 Discounted results

Scénario	Survival (LY)	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	19.4	122.6	Reference	Dominated
Pap/Pap-HPV	+10.04	+22.3	22,234	Dominated
Pap/p16Ki67	+11.68	+25.5	21,918	Dominated
HPV/Pap-5y	+15.89	-13.3	Dominant	Ext. Dominated
HPV/Pap-3y	+15.93	+55.8	35,095	Dominated
HPV/Pap-10y	+10.51	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+18.13	+3.79	2,091	101,389
HPV/p16Ki67-10y	+13.00	-64.6	Dominant	35,846
p16Ki67/p16Ki67	+18.37	+160.7	87,546	6,592,441

*Reference for other scenarios. Extra-survival per 10,000 women eligible to OS on a lifetime horizon. LY: Life Years

sensitivity and scenario analyses

Deterministic sensitivity analysis and scenario results of HPV/Pap-10y versus current situation for LY and costs are shown in tables 5 and 6, respectively.

Table 5 Results of DSA and scenario analyses with the biggest impact on survival for organised screening by invitation and recall of non-participant eligible women to perform a HPV-test every 10 years (Pap-test confirmation) versus current situation

Parameter	Variation of LY		Variation of cost (€)	
	Lower bound	Upper bound	Lower bound	Upper bound
Discounting	19.0431	-5.2955	512.0	-237.34
Age	2.3455	-2.2651	298.3	-525.3
TP pCIN2/3 → FIGOI	0.0013	-0.0024	0.0	-0.03
1-year survival FIGOI	-0.0015	0.0020	0.0	0.0
Pap-test sensitivity	-0.0005	0.0014	-0.1	0.11
TP CIN1 → HPV-	-0.0010	0.0007	-0.2	0.15
TP CIN1 → CIN2/3	-0.0008	-0.0004	0.1	-0.14
TP HPV+ → CIN1	0.0005	-0.0005	-0.1	0.22
TP HPV+ → HPV-	0.0004	-0.0004	-0.2	0.23
TP FIGOI → FIGOII	-0.0003	0.0005	0.1	-0.1

Table 6 Results of DSA and scenario analyses with the biggest impact on costs for organised screening by invitation and recall of non-participant eligible women to perform a HPV-test every 10 years (Pap-test confirmation) versus current situation

Parameter	Variation of LY		Variation of cost (€)	
	Lower bound	Upper bound	Lower bound	Upper bound
Age	2.3455	-2.2651	298.3	-525.3
Discounting	19.0431	-5.2955	512.0	-237.34
Cost treatment FIGOI	0.0	0. 000	-193.9	213.57
Cost primary Pap-test	0.0	0.0000	-32.6	35.96
CMU-c beneficiaries rate	0.0001	0.0001	18.4	18.36
Pap-test specificity	-0.0010	0.0007	-0.2	0.15
Non-readable Pap-tests	-0.0008	-0.0004	0.1	-0.14
Cost confirmation Pap	0.0005	-0.0005	-0.1	0.22
Probability yearly IndScr	0.0004	-0.0004	-0.2	0.23
Cost colposcopy	-0.0003	0.0005	0.1	-0.1

The parameters with the biggest impact were cost of testing (HPV and Pap) and impact of OS on LtFU rate after a positive result. However, HPV/Pap-10y systematically remained the most cost-effective alternative. Age at cohort generation led to drastic impact on results, despite HPV screening being less beneficial in both women <30 and >50 than in the rest of the eligible population. Vaccination rates (up to 80%) had a negligible impact. Similar results were seen for HPV/Pap-5y and

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HPV/p16Ki67-5y. Not taking into account the efficacy of OS on LtFU rate did not change the conclusion although it significantly reduced the LY gains vs. current situation. Similarly not taking into account a reduction in HPV-testing cost led to similar conclusions: HPV/Pap-10y and HPV/Pap-5y remaining less costly than alternative strategies. Finally, 60% reduction in p16Ki67 cost led to a decreased total cost of €41.05 (-75%) for the p16Ki67/p16Ki67 scenario.

DISCUSSION

Using a comprehensive, validated microsimulation model, we showed that regardless of the modality, implementing an OS program for cervical cancer in France leads to an overall improvement in the screening rate and a reduction of CC incidence and mortality. Reducing LtFU rates and improving screening rates with invitations/recall as with the Pap/Pap scenario is a cost-effective strategy compared to current practices with an associated ICER of €22,231 per LY and an average gain of 10 LY per 10,000 eligible women.

Switching primary screening Pap-test to HPV-testing led to similar LY gains for the 10 years frequency. The 5-year frequency had yet better LY gains (15.89 vs. 10.51 per 10,000 eligible women). Furthermore, reducing the frequency of primary testing was cost-saving, even at the current cost of HPV-testing. Despite the longer interval between two screenings, HPV-test strategies remained effective because of their superior sensitivity vs. Pap-test.

Because of its very good sensitivity and specificity, introducing p16/Ki67 double-staining as the primary screening test yielded significant survival gains compared to current situation and HPV-testing (+18.37 and +2.48 per 10,000 eligible women, respectively). However, its very high price made it inefficient with an ICER of €6,592,441/LY.

Switching Pap-test for p16/Ki67 double-staining as confirmation test after positive Pap and HPV primary testing increased efficacy with moderate extra-cost. For HPV every 10 years, LY gains increased from +10.51 to +13.0 and costs from -€734,000 to -€646,000 per 10,000 eligible women. Thus, the HPV/p16Ki67-10y scenario was associated with an ICER of €35,846/LY.

These results were obtained with a microsimulation model that allows fine modelling of CC natural history and screening modalities. Additionally, many inputs were based on observed “real-life” data instead of simple screening guidelines. This enables us to faithfully simulate women’s screening behaviour by taking into account that many women do not strictly follow the screening interval leading to efficiency loss for the current situation, and that women have a tendency to quit screening with age.[3] This also enables us to integrate current professional practices that significantly diverge from recommended screening algorithms: in the current screening context, after a positive Pap-test, not all women proceed to confirmation (Pap or HPV-test) as some directly perform colposcopy or conisation, depending on the initially identified lesion. This has a significant impact on the efficiency of screening. Finally, our model allowed to incorporate LtFU rates which proved to be a key factor in screening efficacy, particularly when screening frequency is superior to 5 years.[17]

The model’s main limitations come from the estimation of the TP. An initial literature review showed important variations between sources with some TP not available. Additionally, the precision of their estimation were usually not sufficient enough given the low incidence of lesions in the general women population (1 in 10,000). Thus, we favoured sources that were previously used in French models to allow comparability with previously published results.[9, 11] Additionally, we calibrated the model on available prevalence data for France and externally validated the model. Furthermore, the sensitivity analyses showed that despite the uncertainty, TP had a limited impact on the results reinforcing our confidence in the ICER estimations. Finally, our results are comparable to previously

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published European studies: Accetta *et al.* have found HPV-test every 5 years to be a dominant strategy over triennial Pap-tests in Italy.[29] The decreased efficiency of HPV-test based CC screening with smaller frequencies was shown by Berkhof *et al.* in the Netherlands.[30] In Norway, Burger *et al.* found results comparable to the Pap/Pap-HPV scenario.[31]

Our results showed that the HPV/Pap-10y was the most efficient strategy with HPV/p16Ki67-10y being a cost-effective alternative. However, the final modality choice for OS-implementation will need to take into consideration several factors. First, the HPV/Pap-10y strategy, albeit the most efficient, is the less effective alternative on cancer incidence and prevalence, conflicting with the primary aim of the Cancer Plan to further reduce CC burden in France [5], potentially leading to consider the HPV/Pap-5y as a more suitable cost-saving modality. Second, current screening behaviour in France results in an over-participation with numerous women undergoing a Pap-test at a higher frequency than recommended. This phenomenon is likely to be related to the yearly recommended consultation with a gynaecologist. Our results showed that going from a 5-year frequency to 3 years implies a huge increase in screening cost (from -€133,000 to +€558,000 per 10,000 eligible women) for a very small increase in survival (from 15.89 to 15.93). Indeed, HPV-testing is sensitive but has a low specificity and cervical lesions evolution is slow, with a majority regressing spontaneously. Women's over-participation will thus be a challenge to HPV-based testing if it is implemented and needs to be address beforehand, or an apparent efficient strategy will turn into a poorly efficient one with a high number of false-positive leading to unnecessary, potentially harmful testing. Third, HPV-testing is not recommended for women under 35, making it necessary to maintain a complex double screening system. Fourth, current screening organization in France is based on Pap-test which implies a different infrastructure. Switching to HPV will require to negotiate HPV tariffs, to develop quality control to ensure similar sensitivity than found during clinical studies and to develop the required infrastructure and equipment. Thus, although primary HPV-testing appears more cost-effective, many challenges will need to be addressed before it can be implemented. In the meantime, switching to a Pap-test based OS remains a cost-effective alternative, and could lead the way to implementing HPV-testing.

As for p16/KI67 double-staining, our results showed that it was a cost-effective opportunity when used as a confirmation test or as a primary test if the tariffs can be negotiated. However, the sensitivity and specificity were based on a single study with centralized reading. It will required additional studies, in different context in France to confirm that the results are reproducible before generalizing it use.

In summary, this modelling study enables the INCa to provide robust information to support public decision on both efficient intermediate modalities for implementation of the CC OS programme but also on optimal screening strategies in a medium term and anticipate the integration of promising technological innovations.

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Declaration of interests

The authors have no conflict of interest to declare concerning this study.

Authorship Statement

All authors participated in the study. Barré S, Leleu H and Massetti M participated in model development, data analysis and redaction of the draft of the manuscript. Barré S and De Bels F made critical review of the manuscript and approved its final version.

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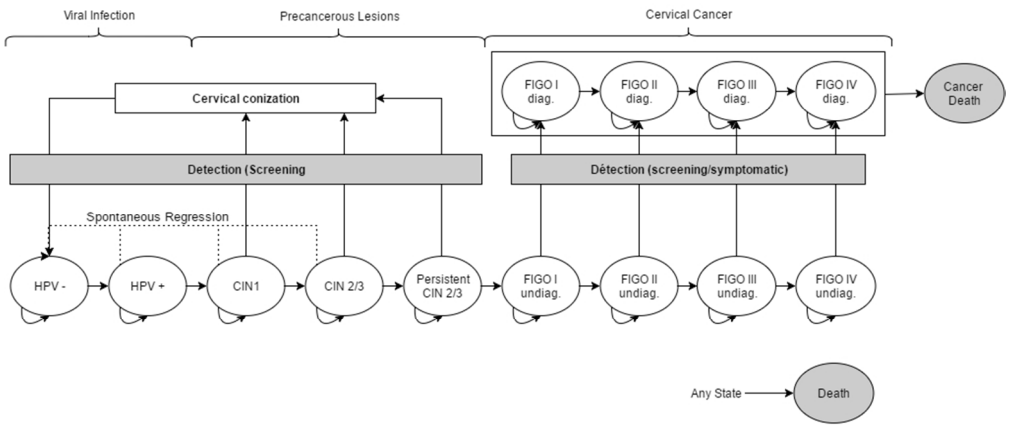

Structure of the model for the natural history of cervical cancer

269x113mm (96 x 96 DPI)

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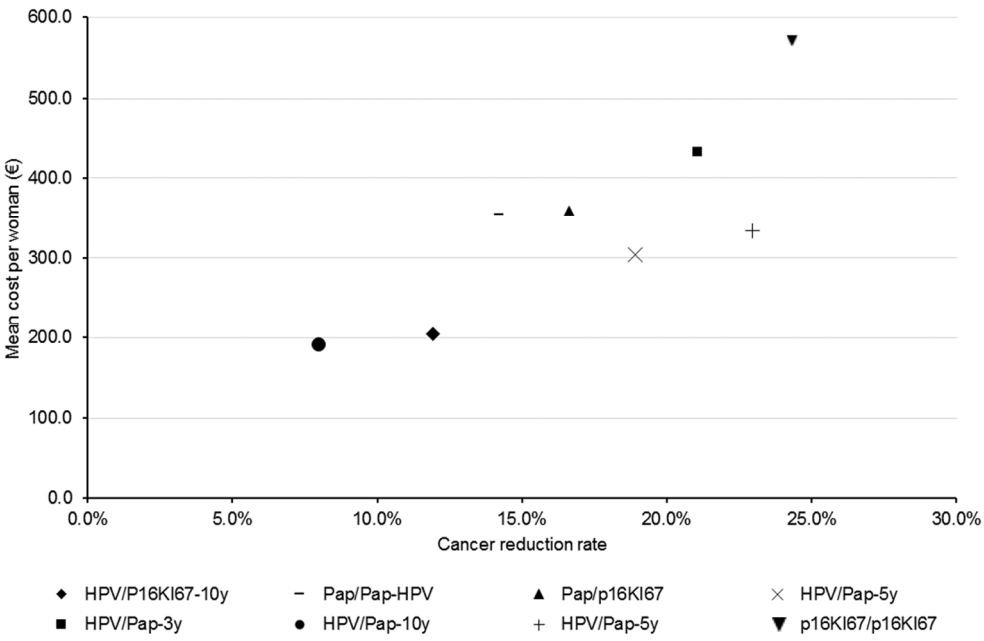

Impact of OS strategies assessed on cancer reduction rate and associated mean cost

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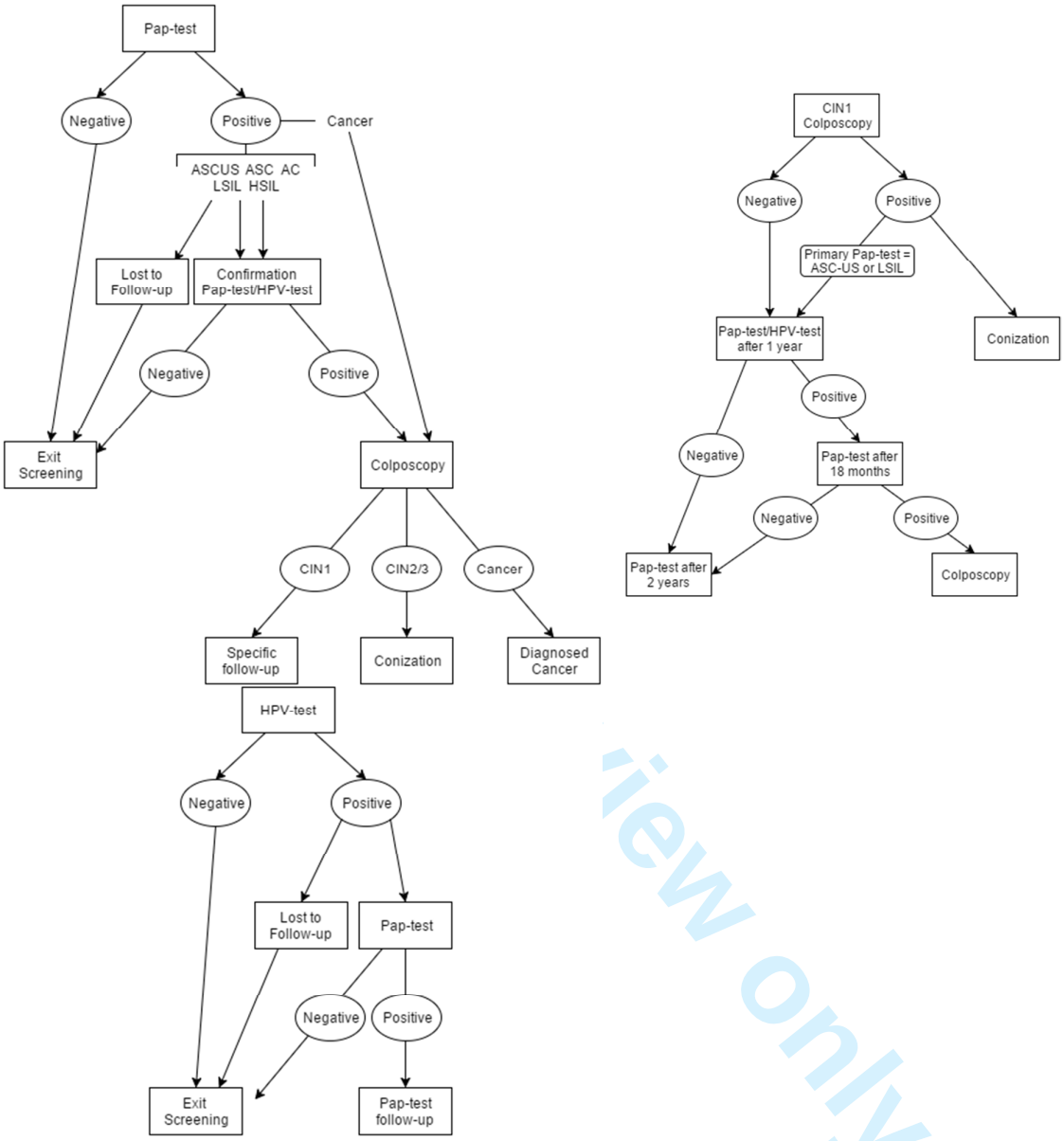
Supplementary

File 1 Screening algorithms



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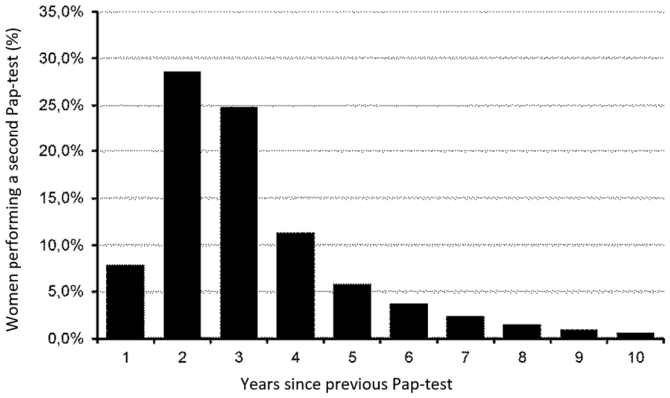
File 2 Individual screening participation and periodicity data

IS period	Distribution
Annual	5,9%
2 years	21,5%
3 years	18,7%
4 years	8,6%
5 years	4,3%
6 years	2,8%
7 years	1,8%
8 years	1,1%
9 years	0,7%
10 years	0,5%



Population	RR	Source
Age		
25 – 30	1,06	National health insurance database [3]
30 – 35	1,08	National health insurance database [3]
35 – 40	1,07	National health insurance database [3]
40 – 45	1,04	National health insurance database [3]
50 – 55	0,92	National health insurance database [3]
55 – 60	0,82	National health insurance database [3]
60 – 65	0,77	National health insurance database [3]
Universal complementary health insurance registration		
Yes	0,80	National health insurance database [3]
No	1,03	National health insurance database [3]

Each woman is associated to a SI participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation in older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} / RR_{current\ age-group})/5$$

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File 3 Pap-test results depending on HPV infection or lesion type

	ASCUS	ASC	AC	LSIL	HSIL	Cancer
HPV-	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
HPV+	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
CIN1	53.5 %	1.5 %	2.7 %	40.1 %	2.3 %	0.0 %
CIN2/3	26.2 %	6.0 %	9.6 %	32.4 %	23.2 %	2.6 %
Cancer (all stages)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

File 4 Follow-up of positive Pap-test, by Pap-test result

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

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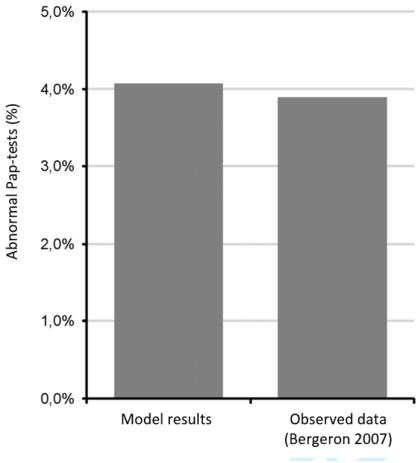
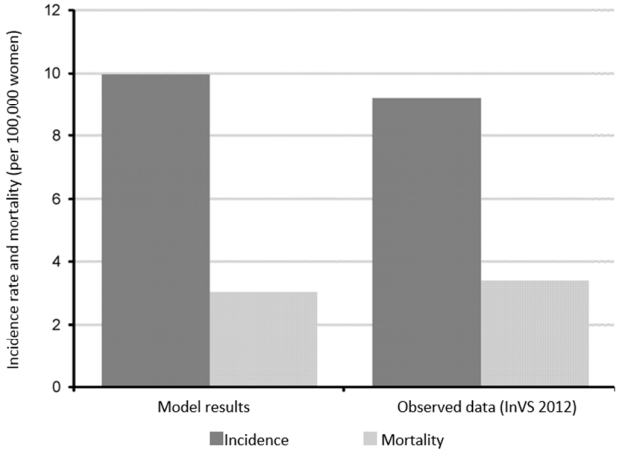
File 5 Model validation results

The model faithfully reproduces cancer incidence, however the modelled CC mortality was slightly higher than observed data, although differences were systematically inferior to 4 per 100,000.





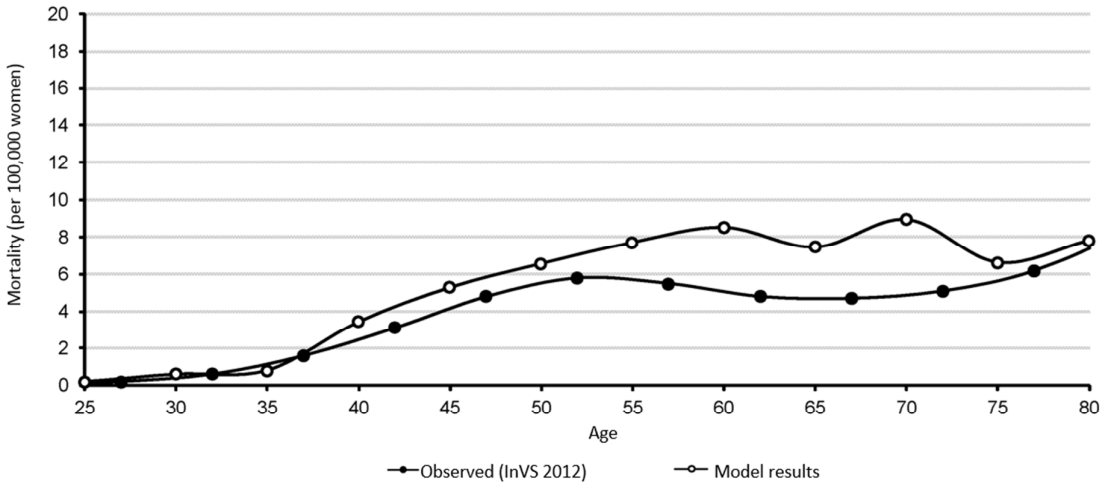


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Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1/1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2/1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	3/2-27
		Present the study question and its relevance for health policy or practice decisions.	3/28-33
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5/14 6/13-20
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6/13-15
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6/38
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	5/2-13
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5/26-27
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9/6-10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	9/6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6/38 - 7/6
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	6/40-41
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	5/21-23
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 2; 6/26 - 7/6
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	7/6-15
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 3 & 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Tables 5 & 6

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(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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French National Cancer Institute

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ABSTRACT

OBJECTIVE: According to the third cancer plan, organized screening (OS) of cervical cancer (CC) among women aged 25-65 years should be implemented in France in the forthcoming years. The most efficient way to implement OS in the French health care system is yet to be determined.

METHODS: A microsimulation model was developed by the French National Institute of Cancer (INCa) alongside clinical experts and stakeholder representatives. A closed cohort of women eligible for CC screening and representative in terms of age and participation in individual screening (IndScr) was modelled on a lifetime horizon. Different OS strategies, additive to IndScr and based on mailed invitations to perform OS with different screening tests (Papanicolaou (Pap) test, HPV test, and p16/Ki67 double-staining) and OS periodicity, were assessed, adopting a collective "all payers" perspective.

RESULTS: Compared to the current IndScr only situation, all OS strategies were associated with decreased cancer incidence/mortality (from -14.2%/-13.5% to -22.9%/-25.8%). Most strategies generated extra costs ranging from €37.9 to €1,607 per eligible woman. HPV testing every 10 and 5 years were cost-saving.

HPV tests every 10 and 5 years were the most efficient strategies, generating more survival at lower costs than Pap-based strategies. Compared to IndScr only, an HPV test every 10 years was cost-saving. The most effective strategies were p16/Ki67 as primary or HPV positive confirmation tests, with respective ICERs of €6,541,250 and €101,391 per life year. Pap-based strategies generated intermediary results.

CONCLUSION: OS strategies based on the HPV test appear highly efficient. However, our results rely on the assumption that women and practitioners comply with the recommended OS periodicities (3, 5, 10 years). Implementing these OS modalities will require major adaptations to the current CC screening organization. Pap-test based strategies might be simpler to set-up while preparing an appropriate implementation of more efficient OS screening modalities.

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Strengths and limitations of the study

- A microsimulation model was developed to assess the efficiency of possible cervical cancer organized screening strategies in France.
- The model operates on individual women who are eligible for screening and representative of the current French population on a lifetime horizon.
- Real-life practices and data were used, allowing for the fine modelling of the screening and validation against observed data.
- The lack of precision of transition probabilities in the context of a low incidence of cervical cancer, as well as the assumptions required to model screening practices after primary HPV tests, are the main limitations of the study.

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BACKGROUND

The natural history of cervical cancer (CC) is related to a persistent HPV infection of the cervix leading to squamous intraepithelial lesions that can evolve into cancerous lesions. CC prevention is based on screening to detect and remove lesions at the early stages to prevent invasive cancer and an anti-HPV vaccination to reduce cancer-associated HPV infection.[1]

In France, CC prevention is based on individual voluntary screening (IndScr) for CC of women aged 25 to 65 years and vaccination. IndScr is based on a Papanicolaou test (Pap test) every 3 years, after two annual Pap tests that are negative. Approximately 90% of Pap smears are done by gynaecologists, although general practitioners (GP) and midwives are also authorized to perform it. IndScr has led to a significant decrease in the incidence and associated mortality of CC in the past 20 years. In 2012, CC was the 11th most frequent and 12th most lethal form of cancer in women.[2] However, many women still do not participate in CC screening. Participation in IndScr was found to be approximately 61% of eligible women, with low access to healthcare, comorbidities and poverty being risk factors for non-participation.

Screening remains the main prevention tool in France, as anti-HPV vaccination is restricted to younger age groups and was only recently made available. Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated.[3;4] In 2014, the third French Cancer Plan has been presented to address both the human and the societal challenges of cancer. CC organized screening (OS) implementation among women aged 25-65 years is part of its first operational objective and aims at a participation rate of 80% and a 30% reduction in CC-related mortality by 2019.[5]

Several OS experimentations have been performed in France to assess the efficacy of different screening modalities, including invitation and positive tests follow-up (FU), self-sampling and HPV-testing. Experimentations that consisted of an invitation of non-participants to perform a Pap test allowed to catch up with 13.2% of all eligible women after 3 years and reduced the lost to follow-up (LtFU) rates of women after a positive result.[6] Additionally, primary HPV-testing and self-sampling were shown to be a feasible alternative to the Pap smear in France.[7;8] Finally, innovative testing, such as p16/Ki67 double-staining, was shown to be a performant alternative for CC screening compared to HPV screening or the Pap test.[9]

Consequently, many alternative strategies can be considered for the implementation of OS for CC in France. Thus, a medico-economic evaluation of several OS strategies based on a cost-effectiveness analysis was performed by the French national cancer institute (INCa), which relied on a scientific steering committee that involved clinical experts and stakeholder representatives (social security, ministry of health, patients and professionals) providing advice on the methodological choices and best OS implementation modality in the French context.

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METHODS

Seven strategies were compared to the current IndScr-only situation (table 1). These strategies were all based on adding to the current IndScr with the dispatch of screening invitations (followed by a single recall) to women who did not spontaneously participate in the last 3 years (non-participants). Hence, women who did not participate in regular screening are the only ones targeted by the interventions. OS strategies also included improved FU, resulting in a reduction in LtFU women.

Different screening tests were considered for primary screening or confirmation after a positive primary test, including Pap test, HPV DNA detection and p16/Ki67 double-staining. The women who tested positive for both primary and confirmation tests went through colposcopy and conization if a high-grade (grade 2 or worse [CIN2+]) cervical intraepithelial neoplasia (CIN) lesion was identified. Women with CIN1 were retested at 12, 18 and 24 months if the initial lesion was atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) on Pap, or went through colposcopy. The women who tested positive for a primary test and negative for confirmation were retested after one year. A fraction of the participants was LtFU. Women could only be invited once per cycle. Detailed screening algorithms are available as supplementary material.

The population was limited to women aged 25-65 years who are currently eligible for IndScr.

Table 1 Strategies compared

Strategy	IR + Improved Follow-up	Primary test	Confirmation test after positive primary test
Current	No	Pap-test / 3 years	Pap-test or HPV
Pap/Pap	Yes	Pap-test / 3 years	Pap-test
Pap/p16Ki67	Yes	Pap-test / 3 years	p16/Ki67
HPV/Pap-5y†	Yes	HPV / 5 years	Pap-test
HPV/Pap-3y†	Yes	HPV / 3 years	Pap-test
HPV/Pap-10y†	Yes	HPV / 10 years	Pap-test
HPV/p16Ki67-5y†	Yes	HPV / 5 years	p16/Ki67
HPV/p16Ki67-10y†	Yes	HPV / 10 years	p16/Ki67
p16Ki67/p16Ki67	Yes	HPV / 3 years	p16/Ki67

IR: invitation + recall for woman who did not participate in IndScr in the last 3 years (non-participant)

†: women 25-35 are not eligible for HPV screening and receive a Pap-test every 3y instead. Women who tested HPV+/confirmation- go through double testing (HPV + Pap) the following year.

model structure

Given the complexity of screening algorithms (different testing/retesting frequencies) and interactions between participation rates and individual characteristics (age and social), a Markov state microsimulation model was developed. Considering the relatively slow progression of intraepithelial lesions and the long-term benefits of screening, a 1-year cycle-length was used. The model was adapted from a previously published cohort-based Markov model.[10] A cohort of 100,000 women was simulated. Due to the long-term development of the disease and its consequences, a lifetime horizon was applied.

The model first generates a woman with a randomly attributed age, IndScr participation and frequency, health state (HPV-, HPV+, CIN lesions or cancer) and vaccination attributes. At each cycle, women can progress through states that correspond to CC natural history: non-infected women can get an HPV infection according to an age- and vaccination-dependent risk. The infection can progress to CIN1, then CIN2/3 and finally FIGO 1 (Federation of Gynecology and Obstetrics) classified non-invasive cancer. HPV infection and CIN lesions can regress spontaneously until CIN2/3 lesions have

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become persistent (pCIN2/3). Women in the pCIN2/3 state systematically progress to cancer at an age-dependant rate. FIGO1 lesions can progress to FIGO 2, 3 and 4 and become symptomatic. Once symptomatic, the lesion is treated and the woman remains in the corresponding treated state with an associated cancer mortality rate. An age-specific general mortality applies at any state.

Each year, the model determines whether the woman undergoes screening individually or after invitation based on her participation periodicity, time since last screening and participation rates after invitation. Screening test results (positivity and lesion type for Pap tests and positivity for HPV and p16/Ki67) are determined based on the current state and type of test performed (supplementary file). After diagnosis, women with a non-cancerous lesion return to the non-infected state after conization and cancerous lesions are treated. The structure of the modelled natural history is presented in figure 1. More details on the model structure are given in the supplementary data.

input data

The input data used in the simulation are presented in table 2.

The population characteristics are based on available epidemiologic and demographic data that are representative of the French population. Vaccination status is only determined in women ≤30 years old, as it was only recently available in France. IndScr participation and frequency depend on age and social status, and based on the national health insurance database (supplementary data), approximately 61.9 % of eligible women were found to participate in IndScr at a frequency ≤4 years.[3] Distribution of each modelled health state by age was not available in France and was estimated by simulating a cohort of non-vaccinated 14-year-old women undergoing current IndScr-only screening over their lifetime (supplementary file).

Transition probabilities (TP) were based on a previously published model.[10] The HPV infection and pCIN2/3 to cancer progression probabilities were calibrated using the model to reproduce observed HPV and cancer prevalence by age.[1;11] The high-risk HPV annual infection rate was estimated to be 3.5% to 14%, depending on age.[12] The impact of vaccination is simulated by applying a relative risk (RR) of infection.[1]

Probabilities of cancer progression and emergence of symptoms were obtained from the CC natural history simulation model developed by Myers *et al*.[13] The cancer specific-mortality by grade and time since diagnosis was estimated from SEER using data for white women under 50, as it was assumed that non-specific mortality was low in this group.[14] General mortality was modelled according to the French national statistics office (INSEE) data.

The participation rates after invitation and recall, LtFU rate associated with IndScr, OS effect on LtFU, observed lesions on Pap smear and associated care were all based on observational data from French OS experimentations.[1]

The sensitivity and specificity of screening tests were based on clinical studies for detecting CIN2/3 lesions and took into account the test sequence (i.e., HPV after Pap or primary HPV).[9;15-17] One percent of Pap tests were non-interpretable, which led to a retest.[18] Colposcopy was assumed to have 100% sensitivity and specificity. A 95% efficacy was considered for conization.

The model estimated OS cost and direct medical costs from a collective, “all payers” perspective, as recommended for France.[19] The OS costs covered invitations and recalls, as well as database management, tracking of women’s participation and FU management. Cost data for consultations and medical care were based on national tariffs. No extra-consultation costs were added, as it was considered that IndScr participants did so during a routine consultation. The HPV-analysis tariff was

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decreased by 60% in strategies with primary HPV-testing, assuming a substantial cost reduction in cases of an adoption of HPV-testing based OS. This assumption was validated by health insurance and health ministry representatives. According to public-health law, no extra co-payment is applied to OS participants. Cancer states were associated with costs accounting for care and FU by FIGO stage [12] when entering the corresponding diagnosed state. All costs were updated to 2016, using the national consumer price index for healthcare goods and services.

Table 2 Input data

Parameter	Value	Distribution	Source
Demographic			
Age	25 - 65 Based on distribution	NA	National Statistics (INSEE)
CMU-c Eligibility (social status)	12.2 % (9.8% - 14.6%)	Normal	National Health Insurance Data
IndScr participation periodicity	Based on frequency distribution, age and social	Uniform	National Health Insurance Data
Initial Health State	Based on distribution	NA	Based on model prediction for a cohort of 14-year-old women
Transition probabilities			
HR-HPV infection	0.03 – 0.15 (0.03 – 0.18) Based on distribution	Beta	Estimated to reproduce known prevalence by age [12]
HPV-infection regression	0.50 (0.40 – 0.60)	Beta	Riethmuller et al. (1999)[19], Clavel et al. (2001)[20], Boulanger et al. (2004)[21], Beby-Defaux et al. (2004)[22], Dalstein et al. (2004)[23]
HR-HPV Infection → CIN 1	0.05 (0.04 – 0.06)	Beta	Moscicki et coll. (2001)[24]
CIN1 Regression	0.50 (0.40 – 0.60)	Beta	Melnikow et coll. (1998)[25], Nobbenhuis et coll. (2001)[26], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN1 → CIN 2/3	0.12 (0.10 – 0.14)	Beta	Melnikow et coll. (1998)[25], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN2/3 Regression	0.28 (0.22 – 0.33)	Beta	Melnikow et coll. (1998)[25]
CIN2/3 → pCIN 2/3	0.13 (0.10 – 0.15)	Beta	Melnikow et coll. (1998)[25]
Persistent CIN 2/3 → FIGO I	0.01 – 0.05 (0.01 – 0.06) Based on distribution	Beta	Estimated to reproduce known prevalence by age[1.11]
FIGO I → FIGO II	0.20 (0.16 – 0.24)	Beta	Myers *et al.* 2000[13]
FIGO II → FIGO III	0.26 (0.21 – 0.31)	Beta	Myers *et al.* 2000[13]
FIGO III → FIGO IV	0.36 (0.29 – 0.43)	Beta	Myers *et al.* 2000[13]
FIGO I → Symptomatic FIGO I	0.15 (0.12 – 0.18)	Beta	Myers *et al.* 2000[13]
FIGO II → Symptomatic FIGO II	0.23 (0.18 – 0.27)	Beta	Myers *et al.* 2000[13]
FIGO III → Symptomatic FIGO III	0.60 (0.48 – 0.71)	Beta	Myers *et al.* 2000[13]
FIGO VI → Symptomatic FIGO IV	0.90 (0.67 - 1.00)	Beta	Myers *et al.* 2000[13]
1-year Cancer Survival	0.43 – 0.98 (0.23 – 0.99) By stage	Beta	SEER[14]
5-year Cancer Survival	0.14 – 0.94 (0.06 – 0.97) By stage	Beta	SEER[14]
10-year Cancer Survival	0.05 – 0.93 (0.01 – 0.96) By stage	Beta	SEER[14]
Screening			
Participation after invitation	17.3% (10.0% - 24.0%)	Uniform	Hamers *et al.* 2014[6]
Participation after recall	12.1% (5.0% - 18.0%)	Uniform	Hamers *et al.* 2014[6]
Lost to follow-up with IndScr	Based on lesion on Pap. Average 27.7%	NA	Hamers *et al.* 2014[6]
Reduction in lost to follow-up with OS	0.77 (0.08 – 0.77)	Uniform	OS experimentations, INCA personal communication
Lesions on PAP	Distribution	NA	Hamers *et al.* 2014[6]
Care per lesion	Distribution	NA	Hamers *et al.* 2014[6]

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Primary Pap-test (Se)	70.0 % (57.0 % - 80.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Se)	85.9 % (76.6 % - 92.1 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Se)	94.0 % (89.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Se)	100.0 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Se)	86.7 % (81.1 % - 90.9 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Se)	100.0% (NA)	NA	Assumption
Primary Pap-test (Sp)	95.0 % (92.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Sp)	65.9 % (63.1 % - 68.6 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Sp)	90.0 % (86.0 % - 93.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Sp)	61.1 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Sp)	95.2 % (94.9 % - 95.4 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Sp)	100.0% (NA)	NA	Assumption
Conisation efficacy	95.0%	NA	Assumption
Non-interpretable tests	1.0% (1.0% - 3.0%)	Uniform	Hamers *et al.* 2014[6]
Costs (€)			
Pap-test (IndScr)	47.78 (38.88 – 57.59)	Gamma	National tarrifs
Pap-test (OS)	49.62 (40.37 – 59.81)	Gamma	National tarrifs
p16/Ki67 (IndScr)	86.77 (70.60 - 104.58)	Gamma	National tarrifs
p16/Ki67 (OS)	88.61 (72.09 - 106.80)	Gamma	National tarrifs
HPV-test (IndScr)	47.70 (75.48 - 97.17)	Gamma	National tarrifs
HPV-test (OS)	49.54 (49.54 - 71.24)	Gamma	National tarrifs
Confirmation Pap-test (IndScr)	78.17 (63.60 - 94.21)	Gamma	National tarrifs
Confirmation Pap-test (OS)	49.63 (40.38 - 59.82)	Gamma	National tarrifs
Confirmation p16/Ki67 (IndScr)	116.77 (78.09 - 99.57)	Gamma	National tarrifs
Confirmation p16/Ki67 (OS)	88.23 (71.79 - 106.34)	Gamma	National tarrifs
Confirmation HPV-test (IndScr)	78.09 (63.53 - 94.12)	Gamma	National tarrifs
Confirmation HPV-test (OS)	49.55 (49.55 - 71.03)	Gamma	National tarrifs
Colposcopy	49.82 (40.54 - 60.05)	Gamma	National tarrifs
Conization	93.42 (76.01 - 112.60)	Gamma	National tarrifs
FIGO I CC treatment	1041.95 (847.77 - 1255.85)	Gamma	Dervaux *et al.* 2007[12]
FIGO II CC treatment	1818.86 (1479.90 - 2192.25)	Gamma	Dervaux *et al.* 2007[12]
FIGO III CC treatment	25817.84 (21006.43 - 31117.97)	Gamma	Dervaux *et al.* 2007[12]
FIGO IV CC treatment	30582.83 (24883.41 - 36861.16)	Gamma	Dervaux *et al.* 2007[12]
Database management + Invitation dispatch	7.00 (4.00 – 11.00)	Gamma	Cost of invitation to colorectal OS (Heath Ministry data, personal communication)
Recall dispatch	0.40 (0.40 – 3.25)	Gamma	50% postal charges

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validation

The model results were compared to observed epidemiological data for validation. The model faithfully reproduces cancer incidence and CC mortality in France.[12] Results of the model validation are available in a supplementary appendix.

analyses

Incremental cost–effectiveness ratios (ICER) were calculated for the life expectancy. Costs and survival were discounted at 4% per year, according to French guidelines for cost-effectiveness studies.[18]

Several alternative scenarios were tested, including not applying the efficacy of OS on LtFU rate, not considering a reduction in HPV cost, and assuming a 60% reduction in p16/Ki67 cost.

The robustness of the model was tested using deterministic sensitivity analysis (DSA). In the DSA, all of the parameters were tested at their confidence intervals (or at ±20% of the baseline value when the confidence intervals were not available).

RESULTS

Compared with the current situation, invitation and recall (Pap/Pap) led to an increase from 61.9% to 65.5% in the 4-year participation rate. Every strategy that was tested was associated with a reduction in cancer incidence/mortality, ranging from -14.2%/-13.5% for the Pap/Pap strategy to -22.9%/-25.8% for the HPV/p16Ki67-5y strategy. The undiscounted results are presented in table 3.

Table 3 Undiscounted results

	Outcomes		Costs (€) per woman			
Scenario	Cancer	Cancer mortality	OS organisation	Screening	CC care & conizations	Total
IndScr only*	34	13	0	294.2	30.9	325.0
Pap/Pap	-14.2%	-13.5%	+19.57	+13.32	-3.92	+28.97
Pap/p16Ki67	-16.6%	-15.9%	+19.57	+18.46	-4.57	+33.46
HPV/Pap-3y	-21.1%	-22.4%	+15.16	+99.87	-7.31	+107.73
HPV/Pap-5y	-18.9%	-22.5%	+15.12	-29.79	-7.24	-21.91
HPV/Pap-10y	-8.0%	-13.6%	+14.94	-14.42	-0.48	-134.04
HPV/p16Ki67-5y	-22.9%	-25.8%	+15.10	+1.57	-0.81	+8.55
HPV/p16Ki67-10y	-11.9%	-17.0%	+14.93	-129.7	-5.87	-120.63
p16Ki67/p16Ki67	-24.3%	-24.4%	+19.57	+233.30	-6.87	+246.00

*Reference for other scenarios. Cumulated incidence and mortality for 10,000 women eligible for OS on a lifetime horizon.

The average undiscounted cost of screening for the modelled population over a lifetime was €325 per eligible woman, most of which was imputable to screening (€294). Strategies based on HPV-testing with 5-year and 10-year frequencies were cost-saving (-€22 and -€134 per woman, respectively), despite the additional cost of OS (€15). Other strategies were responsible for extra costs, ranging from €29 to €33 for Pap-based screening to €108 for HPV/Pap-3y and €246 for p16Ki67/p16Ki67.

Although it was the cheapest strategy (€191 per eligible woman), HPV/Pap-10y was the strategy with the smallest cancer reduction (-11.9%), as opposed to p16Ki67/p16Ki67, which led to a 25% reduction in CC while being the most expensive strategy (€571 per eligible woman). Figure 2 presents the mean cost per woman and cancer reduction rate for each strategy.

Discounted survival is consistent with CC incidence and mortality (table 4). Compared to the current situation (19.4 LY survival), OS strategies led to an increase in survival, ranging from 10 years per

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10,000 women for the Pap/Pap and HPV/Pap-10y strategies to 18 years per 10,000 women for the HPV/p16Ki67 and p16Ki67/p16Ki67 strategies. Discounted extra costs per 10,000 eligible women ranged from €38,000 (HPV/Pap-5y) to €1,608,000 (p16Ki67/p16Ki67). HPV/Pap-5y and HPV/Pap-10y remained cost-saving after discounting. Hence, these strategies were more effective and more cost-saving than Pap-based strategies, including the current situation, and were the dominant OS strategies. HPV/p16Ki67-5y and p16Ki67/p16Ki67 were more effective than HPV/Pap-5y and HPV/Pap-10y with ICERs of €101,391 and €6,541,250 per LY, respectively. HPV/Pap-3y was as effective as HPV/Pap-5y but less effective than HPV/p16Ki67-5y while generating much more expenses.

Table 4 Discounted results

Scenario	Survival (LY)	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	19.4	122.6	Reference	Dominated
Pap/Pap-HPV	+10.04	+22.3	22,234	Dominated
Pap/p16Ki67	+11.68	+25.5	21,918	Dominated
HPV/Pap-3y	+15.93	+55.8	35,095	Dominated
HPV/Pap-5y	+15.89	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+10.51	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+18.13	+3.79	2,091	101,389
HPV/p16Ki67-10y	+13.00	-64.6	Dominant	35,846
p16Ki67/p16Ki67	+18.37	+160.7	87,546	6,592,441

*Reference for other scenarios. Extra-survival per 10,000 women eligible for OS on a lifetime horizon. LY: Life Years

Regardless of the modality, implementing an OS programme for cervical cancer in France led to an overall improvement in the CC screening rate and a reduction in CC incidence and mortality. Reducing LtFU rates and improving screening rates with invitations/recall as in the Pap/Pap scenario results in an ICER of €22,231 per LY and an average extra survival of 10 LY per 10,000 eligible women.

Switching primary screening from the Pap-test to HPV-testing led to similar LY gains with a 10-year screening frequency, yet the 5-year frequency led to a longer survival (15.89 vs. 10.51 LY per 10,000 eligible women). Furthermore, reducing the frequency of primary testing was cost-saving, even at the current cost of HPV-testing. Despite the longer interval between the two screening tests, HPV-based strategies remained effective because of their superior sensitivity compared to the Pap-test.

The very good sensitivity/specificity of p16/Ki67 double-staining used as a primary screening test led to significant survival gains compared to the current situation and HPV-testing (+18.37 and +2.48 per 10,000 eligible women, respectively). However, its high cost made it inefficient, with an ICER of €6,592,441/LY.

Switching the Pap test with p16/Ki67 double-staining in the confirmation of positive Pap and HPV primary tests increased efficacy and led to moderate additional costs. The confirmation of HPV tests every 10 years increased the survival from +10.51 to +13.0 LY and the costs from -€734,000 to -€646,000 per 10,000 eligible women. Thus, the HPV/p16Ki67-10y scenario was associated with an ICER of €35,846/LY. The cost-utility results do not lead to different conclusions. A cost-utility analysis was performed by applying specific health utilities to the health states and utility decrements to non-cancerous and cancerous states. Its results and the utility values used are available in a supplementary appendix.

sensitivity and scenario analyses

Deterministic sensitivity analysis and scenario analyses for HPV/Pap-10y versus the current situation for LY and costs are shown in figures 3 and 4, respectively.

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The parameters with the biggest impact were the cost of testing (HPV and Pap) and OS effect on LtFU rate after a positive result. However, HPV/Pap-10y systematically remained the most cost-effective alternative. The mean age of the cohort impacted results drastically, despite HPV screening being less beneficial in women under 30 years old and over 50 years old than in the rest of the eligible population. Vaccination rates up to 80% had a negligible impact. Similar results were seen for HPV/Pap-5y and HPV/p16Ki67-5y scenarios. Not taking into account the effect of OS on LtFU rate did not change the conclusion, although it significantly reduced the LY gains compared to in the IndScr only. Similarly, not considering a reduction in the cost of the HPV test led to similar conclusions: HPV/Pap-10y and HPV/Pap-5y remained less costly than the alternative strategies. Finally, a 60% reduction in p16/Ki67 cost led to a decreased total cost of €41.05 (-75%) for the p16Ki67/p16Ki67 scenario.

DISCUSSION

Using a comprehensive, validated microsimulation model that allows for the fine modelling of CC natural history and screening modalities, we showed that the OS programme for cervical cancer in France leads to a reduction of CC incidence and mortality. HPV-based screening with 5- or 10-year frequencies would be cost-saving, and other modalities would generate extra costs ranging between €37.9 and €1,607 per woman.

Most model inputs were based on observed “real-life” data instead of simple screening guidelines. This allows for an accurate simulation of women’s screening behaviour by considering that many women do not comply with the recommended screening frequency and that older women tend to drop out of screening.[3] This also allowed for the implementation of current professional practices that significantly differ from recommended screening algorithms: in the current IndScr only situation, after a positive Pap test, not all women proceed to confirmation (Pap or HPV test), as some directly undergo colposcopy or conization, depending on the identified lesion with a significant impact on IndScr efficiency. Finally, the model incorporates LtFU rates, which proved to be a key factor in OS efficacy, particularly when screening frequency was superior to 5 years.[6]

The model’s main limitations stem from the estimation of the TP. An initial literature review showed important variations between sources with some TP being not available. Additionally, the identified TP were not precise enough given the low incidence of lesions in the general population of women (1 in 10,000). Thus, we favoured sources that had previously been used in French models to allow comparability with previously published results.[10.12] Additionally, the model was calibrated on available prevalence data in France and externally validated. Furthermore, the sensitivity analyses showed that, despite the uncertainty, TP variations had a limited impact on the results, which reinforces our confidence in the estimations. Finally, our results are comparable to previously published European studies: Accetta *et al.* have found that an HPV test every 5 years is more effective and less costly than triennial Pap-tests in Italy.[29] The decreased efficiency of CC screening based on the HPVtest at lower frequencies was shown by Berkhof *et al.* in the Netherlands.[30] In Norway, Burger *et al.* found results comparable to ours for the Pap/Pap strategy.[31]

In our analysis, HPV/Pap-10y was the most efficient strategy, with HPV/p16Ki67-10y being a more cost-effective alternative. However, the final modality choice for OS-implementation will need to consider several factors. First, the HPV/Pap-10y strategy, albeit the most efficient, is the less effective strategy in terms of cancer incidence and prevalence reduction, conflicting with the primary aim of the Cancer Plan to further reduce the CC burden in France [5] and thus making the HPV/Pap-5y a more suitable, cost-saving modality. Second, current screening behaviours in France result in over-participation, with numerous women performing Pap-tests more often than is recommended. This phenomenon is likely to be related to the yearly recommended consultation with a

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gynaecologist. Our results showed that going from a 5-year frequency to a 3-year frequency implies a huge increase in screening cost (from -€133,000 to +€558,000 per 10,000 eligible women) for a very small increase in survival (from 15.89 to 15.93). Indeed, HPV-testing is sensitive, but it has a low specificity and cervical lesion evolution is slow, with most lesions regressing spontaneously. Women's over-participation will thus be a challenge in the case of HPV-based OS implementation. This should be addressed beforehand, or these apparent efficient strategies would be poorly efficient, leading to frequent false-positive results and related unnecessary and potentially harmful testing. Third, HPV-testing is not recommended in women under 35 years of age, which would require a complex double screening system. Finally, the current screening organization in France is based on the Pap-test, which implies a different infrastructure. Switching to HPV would require the negotiation of HPV-test tariffs, the development of a quality assurance protocol to ensure a sensitivity that is consistent with those found during clinical studies, as well as the development of the required infrastructure and equipment. Thus, although primary HPV-testing produces results with a better efficiency, many challenges will need to be addressed before its implementation. In the meantime, switching to a Pap-test based OS remains an acceptable alternative and could lead the way to HPV-testing deployment.

As for p16/KI67 double-staining, our results show that it would be an efficient confirmation test or primary test with negotiated tariffs. However, the sensitivity and specificity of the test were based on a single study with centralized reading. Additional studies in different French settings would be required to confirm that the results are reproducible before generalization.

In summary, this modelling study enabled the INCa to provide robust information to support a public decision on both efficient intermediate modalities for implementation of the CC OS programme and also on optimal screening strategies in a longer term and to anticipate the integration of promising technological innovations.

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Declaration of interests

The authors have no conflict of interest to declare concerning this study.

Authorship Statement

All authors participated in the study. Barré S, Leleu H and Massetti M participated in model development, data analysis and drafting of the manuscript. Barré S and De Bels F made critical review of the manuscript and approved its final version.

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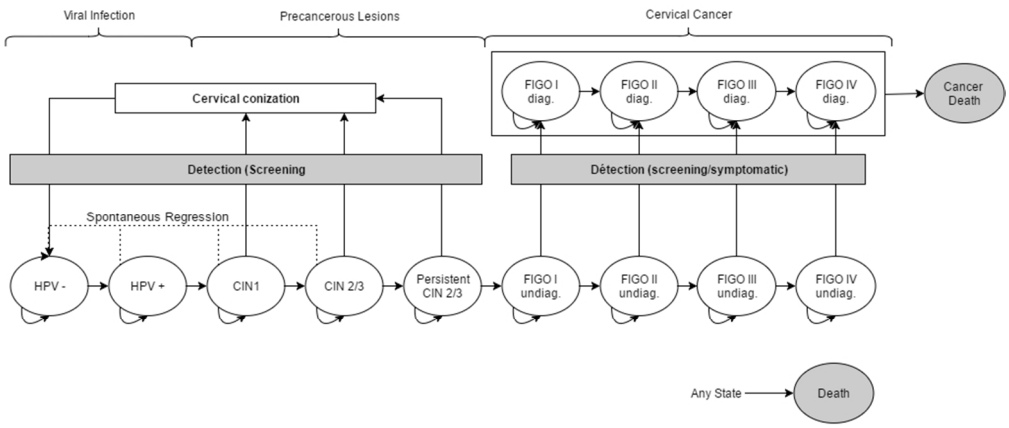

Structure of the model for the natural history of cervical cancer

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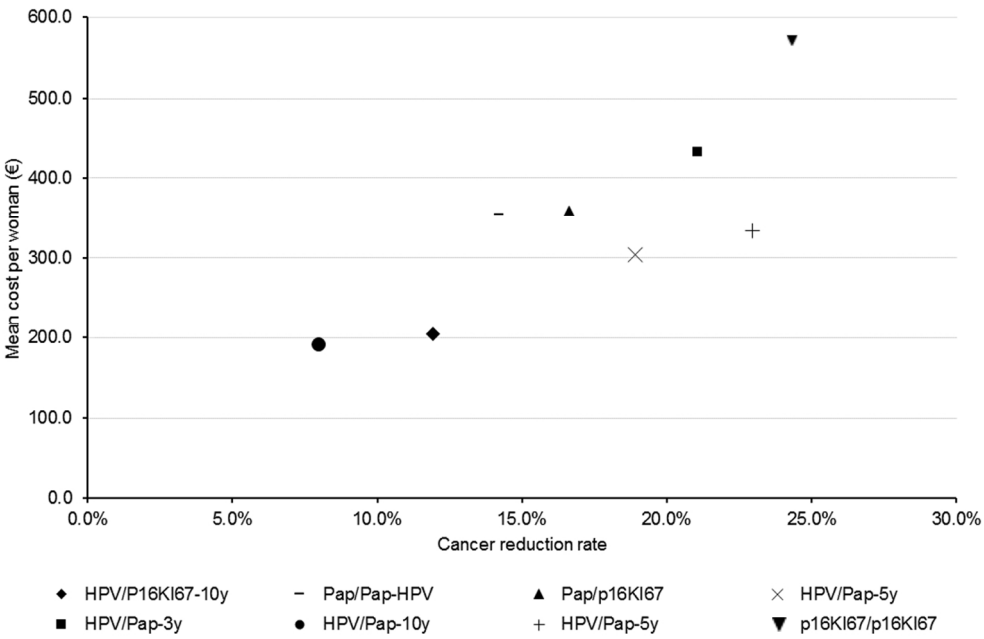

Impact of OS strategies assessed on cancer reduction rate and associated mean cost

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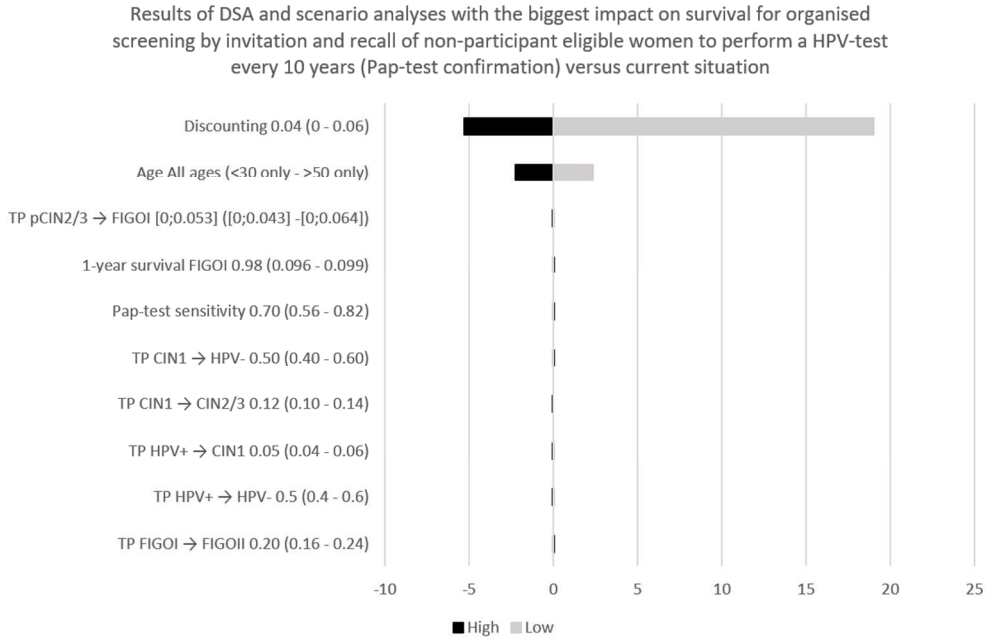

Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

320x211mm (96 x 96 DPI)

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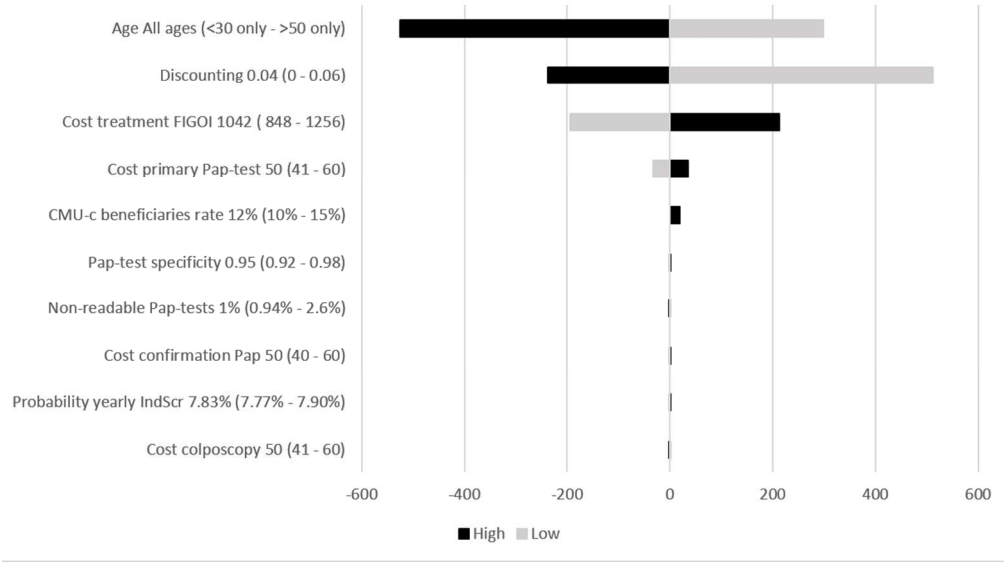

Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

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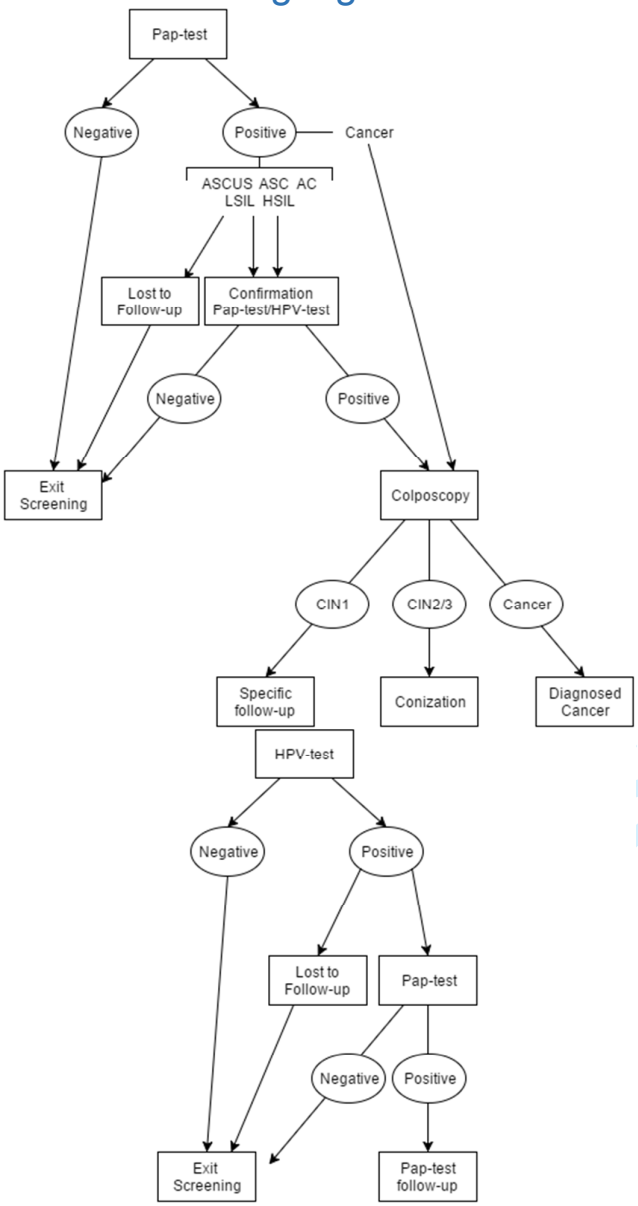
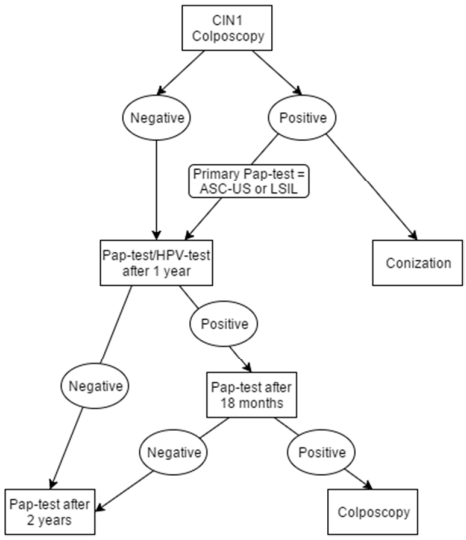
Supplementary

File 1 Screening algorithms





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File 2 Extended model presentation

Due to the complexity of screening algorithms and screening pace depending on the women's history and interactions that exist between screening and individual characteristics, a stochastic microsimulation model based on a Markov methodology and a 1-year cycle length was adapted based on a previously published Markov cohort-based model that has been updated.

Given the importance of individual characteristics, the analysis is based on the simulation of closed cohorts of women eligible for CC screening and representative in terms of age, HPV infection and precancerous and cancerous lesions in order to assess the actual cost-effectiveness of SO implementation in eligible women. Therefore, the results of the model specifically address the efficiency of the various OS strategies assessed and do not allow for epidemiological prediction.

According to the French national health authority (HAS), the model perspective is the collective perspective, meaning that costs borne by all payers are taken into consideration. Costs and survival results are discounted at a 4% annual rate.

The model is programmed in C++. Input data and scenario definition are entered through a Microsoft Excel interface. Model results are then exported to Excel to generate the figures and tables.

Women generation

The model first generates women with the following characteristics: age (25-56), participant in IndScr, period between carrying out two voluntary IndScr, health state at model initiation and vaccination status. Due to the recent introduction of vaccination, only women aged under 30 can be vaccinated.

Natural history of CC

Women then initiate the simulation of CC's natural history. At each cycle, non-HPV-infected women can become infected. This infection can spontaneously regress or progress and lead to grade 1 cervical intraepithelial neoplasia (CIN 1). CIN1 lesions can become pre-cancerous (grades 2 and 3 cervical intraepithelial neoplasia, CIN2/3). Once CIN 2/3 lesions have become persistent, they cannot regress spontaneously any longer and can only progress to cancerous lesions of first grade, based on the International Federation of Gynecology and Obstetrics (FIGO) classification. FIGO I CC can progress to grades 2, 3 and 4 and/or become symptomatic, leading to diagnosis of the CC and treatment initiation. Cancer mortality based on cancer severity grade and time since diagnosis is applied to women with symptomatic/diagnosed cancer. Women can die of age-specific general mortality at any state. See figure 1 for the structure of the model.

Considering the age distribution of the cohort and its low adoption in France (17% of women under 30), the effect of vaccination is simulated by applying a relative risk of infection by oncogenic HPV to vaccinated women (i.e. herd immunity is not considered).

Screening

Each year, the model determines whether the simulated woman performs IndScr based on her status (participant in IndScr or not) and her specific IndScr frequency, both parameters generated at the initiation and updated throughout the simulation. If the woman has not performed a CC screening or received an OS invitation/recall for a period that exceeds the OS periodicity, she receives an invitation to participate. Women that are still NP receive a recall during the same cycle.

Invitation and recall modalities determine different participation probabilities upon receiving. During the screening cycle, IndScr and OS participants perform the screening test determined by the OS

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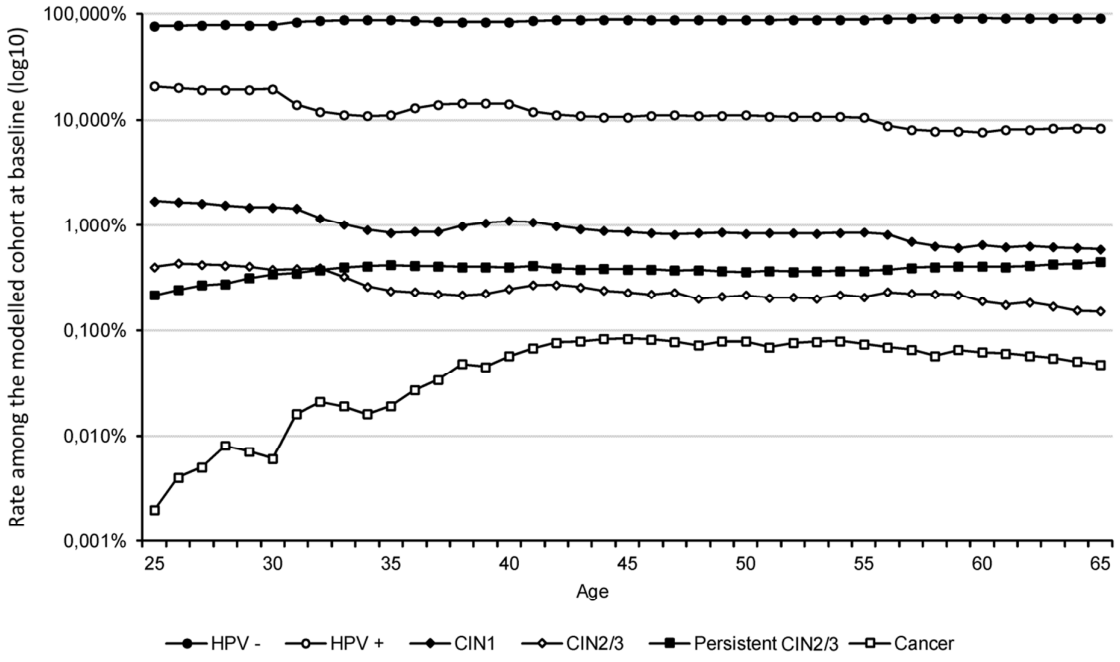
strategy assessed. Test characteristics (sensitivity/specificity) and the screening algorithm determine the result of the primary screening test based on the actual health state of the woman as well as the follow-up actions in case of positive results. Follow-up includes confirmation tests, colposcopy and conizations. Some women become lost to follow-up. Women diagnosed with CC switch to the corresponding diagnosed state.

Women's characteristics

The modelled population corresponds to all women aged 25 to 65, that is, all women eligible for IndScr according to current recommendations. Age distribution within the population is based on the national statistics office (INSEE) data.

Twelve percent (12.2%) of the eligible women were found to benefit from the universal complementary health insurance (CMU-c) in an analysis of a representative sample of the French SHI general regimen (employees). Vaccination rate among women aged 25 was based on the last available data which found a 17% uptake among young women since the vaccine became available. Distribution of each modelled health state by age within the population was based on the results of the simulation of a cohort of 14-year-old women. Health-state distribution in the generated cohort at each age is presented in the figure below.



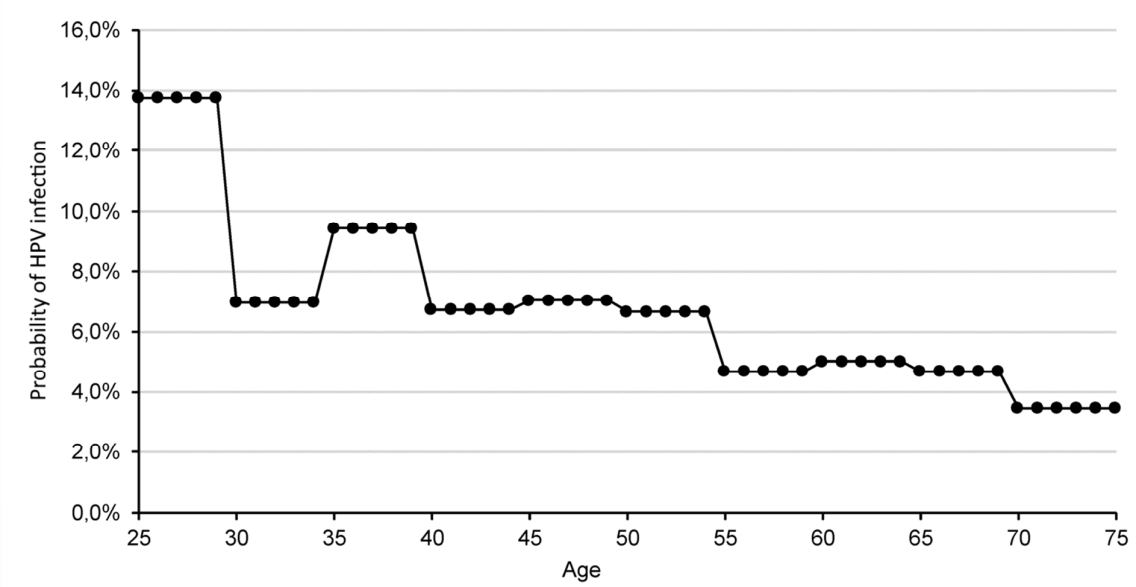
In scenarios based on Pap-test and p16/Ki67, IndScr participation is determined based on the analysis of a sample of the SHI general regimen: at 4 years, 61.9 % of eligible women were found to be participants. At patient generation, a relative risk (RR) of participation is applied to account for the impact of age and universal complementary health insurance (CMU-c). Another analysis of the same dataset provided the observed period between two IndScr (annual to every 10 years, see Supplementary file 3).

Each woman is associated with a SI participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} / RR_{current\ age-group})/5$$

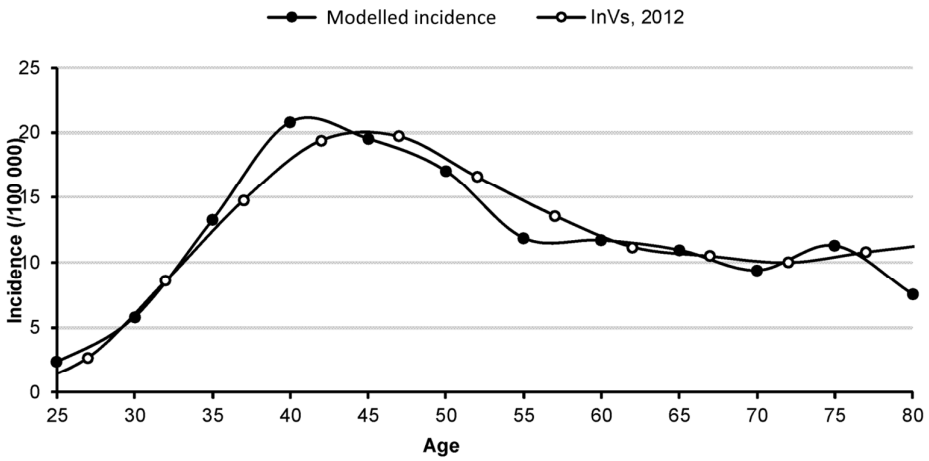
Transition probabilities

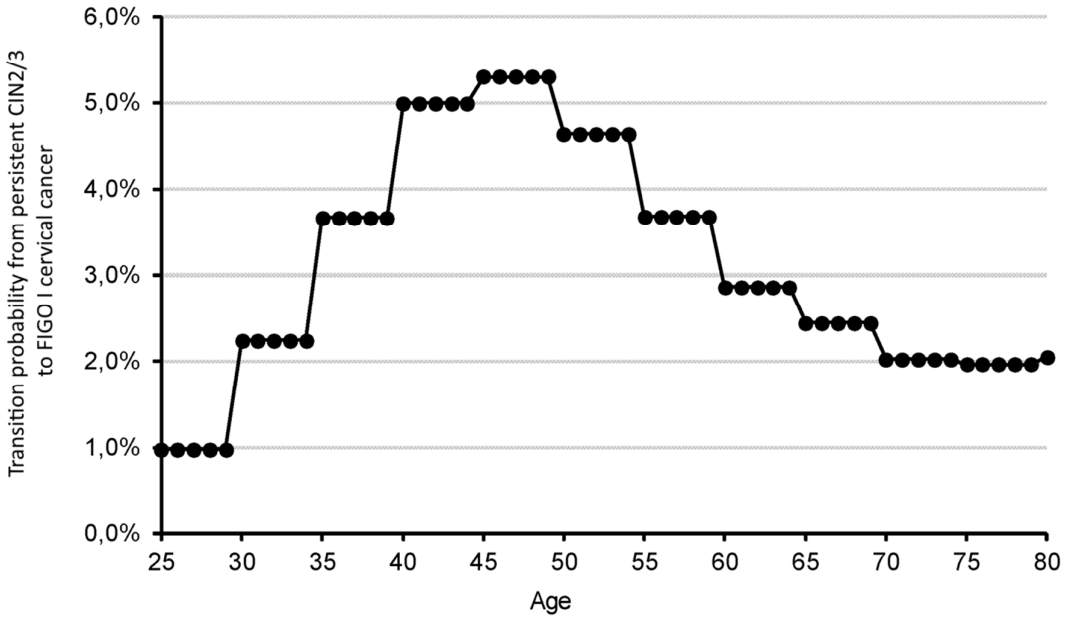
High risk (HR) HPV annual infection rate was estimated to vary from 3.5% and 14% depending on age, in order to fit with the observed HR-HPV prevalence, considering a 50% annual viral clearance rate, according to the model developed by Demarteau *et al.* In younger women, vaccination is modelled through the application of a relative risk of infection taking into account the vaccination rate and decreased infection risk among vaccinated women.



Annual transition probabilities that determine the odds of progression from HPV infection to persistent CIN2/3 precancerous lesion are replicated from the model developed by Demarteau *et al.* and presented in table 2.

Considering the lack of appropriate data, the age-specific progression transition probability of persistent CIN2/3 to FIGO I CC was estimated by calibrating the model to the CC incidence data available. The calibration process consisted in the simulation of a cohort of 14-year-old women, taking the observed IndScr participation rate into account. Transition probabilities were adjusted within a plausible interval in order to duplicate the observed incidence of CC by age. The following figures respectively present the results of the calibration process and the resulting persistent CIN 2/3 to FIGO I CC transition probabilities by age.





Probabilities of cancer progression and symptom emergence were obtained from the natural history of CC simulation model developed by Myers *et al*.

Cancer mortality by cancer grade and time since diagnosis were obtained from the study by Wright *et al.* based on the estimation of survival among 46,932 women with CC diagnosed from 1983-2009 and recorded in the Surveillance, Epidemiology, and End Results (SEER) database. Survival data for white women under 50 were selected, as mortality by causes other than CC seems unlikely in women under 50. General mortality is modelled according to French national statistics office (INSEE) data.

Screening

OS participation rates after receiving an invitation or recall are based on the results of local OS experimentations carried out in different regions. The weighted averages of the participation rate upon receiving a mailed invitation or recall letter by the number of Pap-tests performed during each experimentation were respectively found to be 17.3% and 12.1%. Screening test sensitivity and specificity are given in the following table.

Screening test	Sensitivity	Specificity	Source
Primary Pap-test	70.0 % (57.0 % - 80.0 %)	95.0 % (92.0 % - 97.0 %)	Mustafa (2015)
Confirmation Pap-test after HPV+	85.9 % (76.6 % - 92.1 %)	65.9 % (63.1 % - 68.6 %)	Bergeron (2015)
Primary HPV-test	94.0 % (89.0 % - 97.0 %)	90.0 % (86.0 % - 93.0 %)	Mustafa (2015)
Confirmation HPV-test after Pap+	100.0 % (NR)	61.1 % (NR)	Mayrand (2007)
P16/KI67	86.7 % (81.1 % - 90.9 %)	95.2 % (94.9 % - 95.4 %)	Ikenberg (2013)
Colposcopy	100.0% (NA)	100.0% (NA)	Assumption

At each screening cycle, test performances determine whether women with lesions are screened positive or not depending on their current health state.

Pap-test and p16/Ki67 specificity and specificity are relative to the detection of CIN2/3 and more severe lesions. Women with negative results exit screening, positive results lead to the random draw of an observed lesion type based on the results of the OS experimentation led in the Alsace region (Supplementary file 4).

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The action that follows each type of result is then randomly drawn according to the screening algorithms and the results of the OS experimentation led in Alsace. Based on the probabilities reported in Supplementary file 5, the different types of results can lead to further confirmation tests or conisation. Some women become lost to follow-up and exit screening.

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

In order to take the impact of the screening organization structures into account, OS implementation leads to reduced odds of becoming lost to follow-up after a positive result for both OS and IndScr participants. Based on the Alsace and Indre-et-Loire regional OS experimentation results, a 0.77 RR of becoming lost to follow-up is applied.

Colpscopy is associated with 100% sensitivity and specificity. Therefore, colposcopy results are negative in HPV- and HPV+ women and positive in women with CIN1, CIN2/3 and persistent CIN2/3 lesions. Women with CIN1 proceed to a particular screening algorithm based on recommendations by the French national scientific society of obstetricians and gynaecologists (CNGOF).

HPV-tests and specificity are relative to the detection of HPV+ and more severe lesions. Women with negative results exit screening, positive results lead to a confirmation Pap-test (or p16/Ki67) followed by a colposcopy in case of a new positive result. If negative, a new round of HPV and Pap-tests are performed concomitantly after one year: a positive result for either of them (or both) leads to colposcopy; women with negative-only results exit screening.

Rates of lost to follow-up observed during the START-HPV experimentation (Ardennes region) were used. The lost to follow-up rate after positive confirmation Pap-tests was estimated by subtracting the latter from the average rate of lost to follow-up in HPV+ women observed in the Alsace region OS experimentation (27.7%). Similarly to Pap-based screening, a 0.77 RR of being lost to follow-up is applied in OS-participant women.

Lost to follow-up after	Probability	Source
Positive HPV-test	19,4 %	START-HPV, Ardennes
Positive confirmation pap-test	8,3 %	START-HPV, Ardennes, Alsace OS experimentation

All samples have odds of being unreadable, depending on the nature of the sample. Women with unreadable samples perform a new test.

A 95% efficacy was considered for conisation. Women with successful conisation go back to the HPV- state. In case of failure, women leave screening in their current state.

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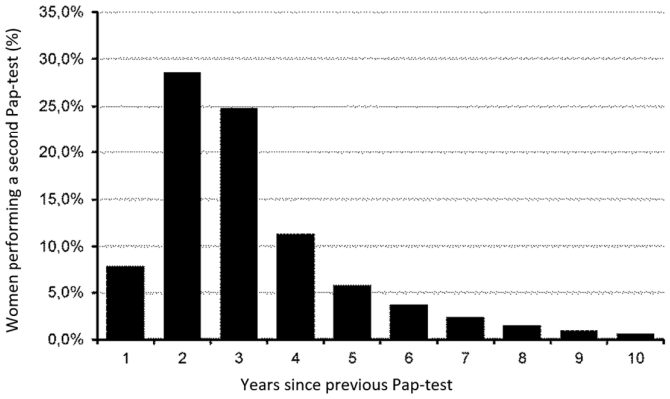
File 3 Individual screening participation and periodicity data

Individual screening frequency	Distribution
Annual	5,9%
2 years	21,5%
3 years	18,7%
4 years	8,6%
5 years	4,3%
6 years	2,8%
7 years	1,8%
8 years	1,1%
9 years	0,7%
10 years	0,5%



Population	RR of participating vs. average	Source
Age		
25 – 30	1,06	National health insurance database [3]
30 – 35	1,08	National health insurance database [3]
35 – 40	1,07	National health insurance database [3]
40 – 45	1,04	National health insurance database [3]
50 – 55	0,92	National health insurance database [3]
55 – 60	0,82	National health insurance database [3]
60 – 65	0,77	National health insurance database [3]
Universal complementary health insurance registration		
Yes	0,80	National health insurance database [3]
No	1,03	National health insurance database [3]

Each woman is associated with an IndScr participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} / RR_{current\ age-group})/5$$

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File 4 Pap-test results depending on HPV infection or lesion type

	ASCUS	ASC	AC	LSIL	HSIL	Cancer
HPV-	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
HPV+	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
CIN1	53.5 %	1.5 %	2.7 %	40.1 %	2.3 %	0.0 %
CIN2/3	26.2 %	6.0 %	9.6 %	32.4 %	23.2 %	2.6 %
Cancer (all stages)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

File 5 Follow-up of positive Pap-test, by Pap-test result

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

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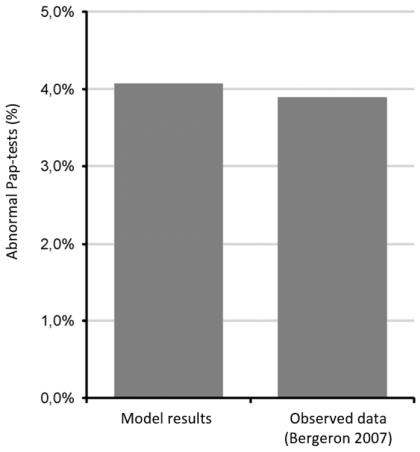
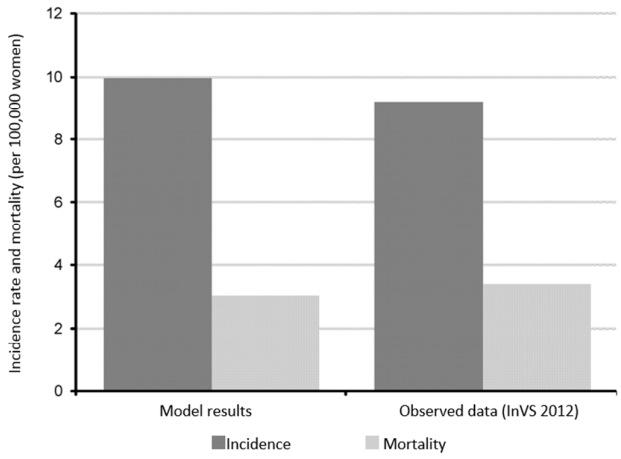
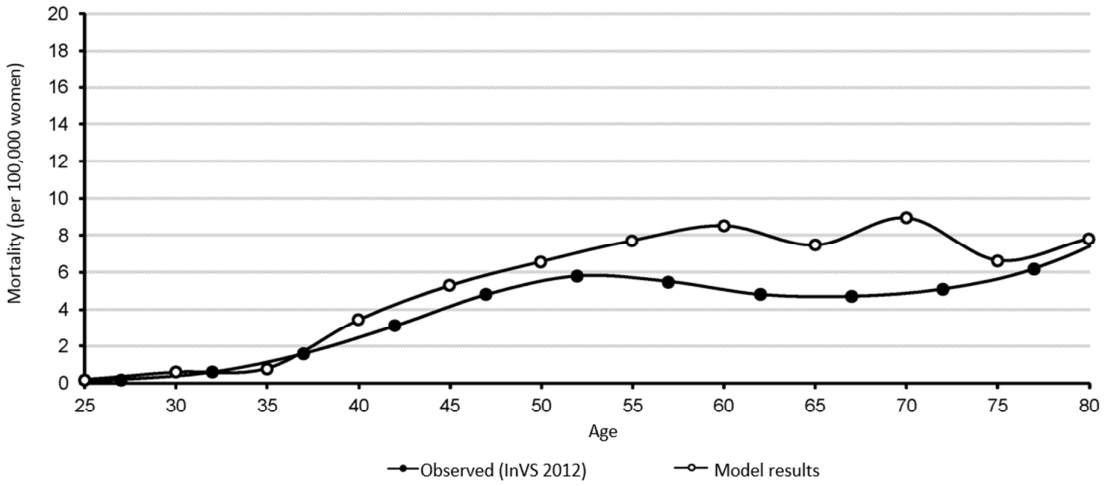
File 6 Model validation results

The model faithfully reproduces cancer incidence, however the modelled CC mortality was slightly higher than observed data, although differences were systematically inferior to 4 per 100,000.







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File 7 Cost-utility analysis - specific inputs and results

State	Utility/Utility decrement	Source
Age 18-29	0.86	Perneger, 2010
Age 30-39	0.86	
Age 40-49	0.84	
Age 50-59	0.81	
Age 60-69	0.8	
Age 70-79	0.76	
Age 80+	0.74	
Diagnosed CIN1	-0.01	Demarteau, 2011
Diagnosed CIN2/3	-0.01	
Cervical Cancer (1st year)	-0.27	
Cervical Cancer (thereafter)	-0.06	Korfage, 2009

Scénario	QALY	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	16.4	122.6	Reference	Dominated
Pap/Pap-HPV	+9.54	+22.3	23,392	Dominated
Pap/p16Ki67	+11.18	+25.5	22,891	Dominated
HPV/Pap-3y	+14.99	+55.8	37,290	Dominated
HPV/Pap-5y	+14.76	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+9.44	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+17.06	+3.79	2,222	131,965
HPV/p16Ki67-10y	+11.88	-64.6	Dominant	36,468
p16Ki67/p16Ki67	+17.53	+160.7	91,703	3,302,932

*Reference for other scenarios. Extra-QALY per 10,000 women eligible for OS on a lifetime horizon. QALY: Quality Adjusted Life Years

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Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	3
		Present the study question and its relevance for health policy or practice decisions.	3/28 - 29
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Table 2, 6/12 - 18
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6/36 - 37
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Table 1, 4/2 - 20
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5/27 - 28
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9/6 - 7
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	9/6 - 7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6/36 - 7/3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7/2 - 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Figure 1, 5/23 - 26
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 2, 5/29 - 7/3
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	8/6 - 12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2, 6/11 - 7/3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 3 & 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	

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(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Figures 3 & 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Figures 3 & 4; 11/24 - 35
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12 & 13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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French National Cancer Institute

The French National Cancer Institute was established under the Public Health Act of 9 August 2004 as the government health and science agency specialised in cancer control. It is a Public Interest Grouping which brings together State representatives, charities, health insurance funds, hospital federations and research organisations. It is responsible for rolling out the 2014-2019 Cancer Control Plan and reports to the Ministries for Health and for Research.

The Institute provides an integrated approach encompassing all cancer-control dimensions (health, scientific, social and economic) and areas of intervention (prevention, screening, care and research), for the benefit of patients and their relatives.

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ABSTRACT

OBJECTIVE: According to the third cancer plan, organized screening (OS) of cervical cancer (CC) among women aged 25-65 years should be implemented in France in the forthcoming years. The most efficient way to implement OS in the French health care system is yet to be determined.

METHODS: A microsimulation model was developed adopting a collective "all payers" perspective. A closed cohort of women eligible for CC screening and representative in terms of age and participation in individual screening (IndScr) was modelled on a lifetime horizon. Different OS strategies, additive to IndScr with a 61.9% participation rate and based on mailed invitations to perform OS were assessed. 17.3% and 12.1% of women performed a primary test after invitation and recall, respectively. Strategies implied different screening tests (Papanicolaou (Pap) test, HPV test, and p16/Ki67 double-staining) and OS periodicity.

RESULTS: Compared to the current IndScr only situation, all OS strategies were associated with decreased cancer incidence/mortality (from -14.2%/-13.5% to -22.9%/-25.8%). Most strategies generated extra costs ranging from €37.9 to €1,607 per eligible woman. HPV testing every 10 and 5 years were cost-saving.

HPV tests every 10 and 5 years were the most efficient strategies, generating more survival at lower costs than Pap-based strategies. Compared to IndScr only, an HPV test every 10 years was cost-saving. The most effective strategies were p16/Ki67 as primary or HPV positive confirmation tests, with respective ICERs of €6,541,250 and €101,391 per life year. Pap-based strategies generated intermediary results.

CONCLUSION: OS strategies based on the HPV test appear highly efficient. However, our results rely on the assumption that women and practitioners comply with the recommended OS periodicities (3, 5, 10 years). Implementing these OS modalities will require major adaptations to the current CC screening organization. Pap-test based strategies might be simpler to set-up while preparing an appropriate implementation of more efficient OS screening modalities.

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Strengths and limitations of the study

- A microsimulation model was developed to assess the efficiency of possible cervical cancer organized screening strategies in France.
- The model operates on individual women who are eligible for screening and representative of the current French population on a lifetime horizon.
- Real-life practices and data were used, allowing for the fine modelling of the screening and validation against observed data.
- The lack of precision of transition probabilities in the context of a low incidence of cervical cancer, as well as the assumptions required to model screening practices after primary HPV tests, are the main limitations of the study.

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BACKGROUND

The natural history of cervical cancer (CC) is related to a persistent HPV infection of the cervix leading to squamous intraepithelial lesions that can evolve into cancerous lesions. CC prevention is based on screening to detect and remove lesions at the early stages to prevent invasive cancer and an anti-HPV vaccination to reduce cancer-associated HPV infection.[1]

In France, CC prevention is based on individual voluntary screening (IndScr) for CC of women aged 25 to 65 years and vaccination. IndScr is based on a Papanicolaou test (Pap test) every 3 years, after two annual Pap tests that are negative. Approximately 90% of Pap smears are done by gynaecologists, although general practitioners (GP) and midwives are also authorized to perform it. IndScr has led to a significant decrease in the incidence and associated mortality of CC in the past 20 years. In 2012, CC was the 11th most frequent and 12th most lethal form of cancer in women.[2] However, many women still do not participate in CC screening. Participation in IndScr was found to be approximately 61% of eligible women, with low access to healthcare, comorbidities and poverty being risk factors for non-participation.

Screening remains the main prevention tool in France, as anti-HPV vaccination is restricted to younger age groups and was only recently made available. Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated.[3;4] In 2014, the third French Cancer Plan has been presented to address both the human and the societal challenges of cancer. CC organized screening (OS) implementation among women aged 25-65 years is part of its first operational objective and aims at a participation rate of 80% and a 30% reduction in CC-related mortality by 2019.[5]

Several OS experimentations have been performed in France to assess the efficacy of different screening modalities, including invitation and positive tests follow-up (FU), self-sampling and HPV-testing. Experimentations that consisted of an invitation of non-participants to perform a Pap test allowed to catch up with 13.2% of all eligible women after 3 years and reduced the lost to follow-up (LtFU) rates of women after a positive result.[6] Additionally, primary HPV-testing and self-sampling were shown to be a feasible alternative to the Pap smear in France.[7;8] Finally, innovative testing, such as p16/Ki67 double-staining, was shown to be a performant alternative for CC screening compared to HPV screening or the Pap test.[9]

Consequently, many alternative strategies can be considered for the implementation of OS for CC in France. Thus, a medico-economic evaluation of several OS strategies based on a cost-effectiveness analysis was performed by the French national cancer institute (INCa), which relied on a scientific steering committee that involved clinical experts and stakeholder representatives (social security, ministry of health, patients and professionals) providing advice on the methodological choices and best OS implementation modality in the French context.

In order to assist decision-making regarding the implementation of CC OS, our study's main outcomes correspond to the objectives of CC OS implementation: participation rate, survival and avoided CC. A cost-utility analysis was performed as well.

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METHODS

Seven strategies were compared to the current IndScr-only situation (table 1). These strategies were all based on adding to the current IndScr with the dispatch of screening invitations (followed by a single recall) to women who did not spontaneously participate in the last 3 years (non-participants). Hence, women who did not participate in regular screening are the only ones targeted by the interventions. OS strategies also included improved FU, resulting in a reduction in LtFU women.

Different screening tests were considered for primary screening or confirmation after a positive primary test, including Pap test, HPV DNA detection and p16/Ki67 double-staining. The women who tested positive for both primary and confirmation tests went through colposcopy and conization if a high-grade (grade 2 or worse [CIN2+]) cervical intraepithelial neoplasia (CIN) lesion was identified. Women with CIN1 were retested at 12, 18 and 24 months if the initial lesion was atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) on Pap, or went through colposcopy. The women who tested positive for a primary test and negative for confirmation were retested after one year. A fraction of the participants was LtFU. Women could only be invited once per cycle. Detailed screening algorithms are available in supplementary file 1.

The population was limited to women aged 25-65 years who are currently eligible for IndScr.

Table 1 Strategies compared

Strategy	IR + Improved Follow-up	Primary test	Confirmation test after positive primary test
Current	No	Pap-test / 3 years	Pap-test or HPV
Pap/Pap	Yes	Pap-test / 3 years	Pap-test
Pap/p16Ki67	Yes	Pap-test / 3 years	p16/Ki67
HPV/Pap-5y†	Yes	HPV / 5 years	Pap-test
HPV/Pap-3y†	Yes	HPV / 3 years	Pap-test
HPV/Pap-10y†	Yes	HPV / 10 years	Pap-test
HPV/p16Ki67-5y†	Yes	HPV / 5 years	p16/Ki67
HPV/p16Ki67-10y†	Yes	HPV / 10 years	p16/Ki67
p16Ki67/p16Ki67	Yes	HPV / 3 years	p16/Ki67

IR: invitation + recall for woman who did not participate in IndScr in the last 3 years (non-participant)

†: women 25-35 are not eligible for HPV screening and receive a Pap-test every 3y instead. Women who tested HPV+/confirmation- go through double testing (HPV + Pap) the following year.

model structure

Given the complexity of screening algorithms (different testing/retesting frequencies) and interactions between participation rates and individual characteristics (age and social), a Markov state microsimulation model was developed. Considering the relatively slow progression of intraepithelial lesions and the long-term benefits of screening, a 1-year cycle-length was used. The model was adapted from a previously published cohort-based Markov model.[10] A cohort of 100,000 women was simulated. Due to the long-term development of the disease and its consequences, a lifetime horizon was applied.

The model first generates a woman with a randomly attributed age, IndScr participation and frequency, health state (HPV-, HPV+, CIN lesions or cancer) and vaccination attributes. At each cycle, women can progress through states that correspond to CC natural history: non-infected women can get an HPV infection according to an age- and vaccination-dependent risk. The infection can progress to CIN1, then CIN2/3 and finally FIGO 1 (Federation of Gynecology and Obstetrics) classified non-invasive cancer. HPV infection and CIN lesions can regress spontaneously until CIN2/3 lesions have become persistent (pCIN2/3). Women in the pCIN2/3 state systematically progress to cancer at an

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age-dependant rate. FIGO1 lesions can progress to FIGO 2, 3 and 4 and become symptomatic. Once symptomatic, the lesion is treated and the woman remains in the corresponding treated state with an associated cancer mortality rate. An age-specific general mortality applies at any state.

Each year, the model determines whether the woman undergoes screening individually or after invitation based on her participation periodicity, time since last screening and participation rates after invitation. The same primary screening modality is applied to OS and IndScr participants. Screening test results (positivity and lesion type for Pap tests and positivity for HPV and p16/Ki67) are determined based on the current state and type of test performed (supplementary file 2). After diagnosis, women with a non-cancerous lesion return to the non-infected state after conization and cancerous lesions are treated. The structure of the modelled natural history is presented in figure 1. More details on the model structure are given in the supplementary file 3.

input data

The input data used in the simulation are presented in table 2.

The population characteristics are based on available epidemiologic and demographic data that are representative of the French population. Vaccination status is only determined in women ≤30 years old, as it was only recently available in France. IndScr participation and frequency depend on age and social status, and based on the national health insurance database (supplementary file 4), approximately 61.9 % of eligible women were found to participate in IndScr at a frequency ≤4 years.[3] Distribution of each modelled health state by age was not available in France and was estimated by simulating a cohort of non-vaccinated 14-year-old women undergoing current IndScr-only screening over their lifetime (supplementary file 3).

Transition probabilities (TP) were based on a previously published model.[10] The HPV infection and pCIN2/3 to cancer progression probabilities were calibrated using the model to reproduce observed HPV and cancer prevalence by age.[1;11] The high-risk HPV annual infection rate was estimated to be 3.5% to 14%, depending on age.[12] The impact of vaccination is simulated by applying a relative risk (RR) of infection.[1]

Probabilities of cancer progression and emergence of symptoms were obtained from the CC natural history simulation model developed by Myers *et al*.[13] The cancer specific-mortality by grade and time since diagnosis was estimated from SEER using data for white women under 50, as it was assumed that non-specific mortality was low in this group.[14] General mortality was modelled according to the French national statistics office (INSEE) data.

The participation rates after invitation and recall, LtFU rate associated with IndScr, OS effect on LtFU (RR=0.88), observed lesions on Pap smear and associated care were all based on observational data from French OS experimentations.[1]

The sensitivity and specificity of screening tests were based on clinical studies for detecting CIN2/3 lesions and took into account the test sequence (i.e., HPV after Pap or primary HPV).[9;15-17] One percent of Pap tests were non-interpretable, which led to a retest.[18] Colposcopy was assumed to have 100% sensitivity and specificity. A 95% efficacy was considered for conization.

The model estimated OS cost and direct medical costs from a collective, “all payers” perspective, as recommended for France.[19] The OS costs covered invitations and recalls, as well as database management, tracking of women’s participation and FU management. Cost data for consultations and medical care were based on national tariffs. No extra-consultation costs were added, as it was considered that IndScr participants did so during a routine consultation. The HPV-analysis tariff was

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decreased by 60% in strategies with primary HPV-testing, assuming a substantial cost reduction in cases of an adoption of HPV-testing based OS. This assumption was validated by health insurance and health ministry representatives. According to public-health law, no extra co-payment is applied to OS participants. Cancer states were associated with costs accounting for care and FU by FIGO stage [12] when entering the corresponding diagnosed state. All costs were updated to 2016, using the national consumer price index for healthcare goods and services.

Table 2 Input data

Parameter	Value	Distribution	Source
Demographic			
Age	25 - 65 Based on distribution	NA	National Statistics (INSEE)
CMU-c Eligibility (social status)	12.2 % (9.8% - 14.6%)	Normal	National Health Insurance Data
IndScr participation periodicity	Based on frequency distribution, age and social	Uniform	National Health Insurance Data
Initial Health State	Based on distribution	NA	Based on model prediction for a cohort of 14-year-old women
Transition probabilities			
HR-HPV infection	0.03 – 0.15 (0.03 – 0.18) Based on distribution	Beta	Estimated to reproduce known prevalence by age [12]
HPV-infection regression	0.50 (0.40 – 0.60)	Beta	Riethmuller et al. (1999)[19], Clavel et al. (2001)[20], Boulanger et al. (2004)[21], Beby-Defaux et al. (2004)[22], Dalstein et al. (2004)[23]
HR-HPV Infection → CIN 1	0.05 (0.04 – 0.06)	Beta	Moscicki et coll. (2001)[24]
CIN1 Regression	0.50 (0.40 – 0.60)	Beta	Melnikow et coll. (1998)[25], Nobbenhuis et coll. (2001)[26], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN1 → CIN 2/3	0.12 (0.10 – 0.14)	Beta	Melnikow et coll. (1998)[25], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN2/3 Regression	0.28 (0.22 – 0.33)	Beta	Melnikow et coll. (1998)[25]
CIN2/3 → pCIN 2/3	0.13 (0.10 – 0.15)	Beta	Melnikow et coll. (1998)[25]
Persistent CIN 2/3 → FIGO I	0.01 – 0.05 (0.01 – 0.06) Based on distribution	Beta	Estimated to reproduce known prevalence by age[1.11]
FIGO I → FIGO II	0.20 (0.16 – 0.24)	Beta	Myers *et al.* 2000[13]
FIGO II → FIGO III	0.26 (0.21 – 0.31)	Beta	Myers *et al.* 2000[13]
FIGO III → FIGO IV	0.36 (0.29 – 0.43)	Beta	Myers *et al.* 2000[13]
FIGO I → Symptomatic FIGO I	0.15 (0.12 – 0.18)	Beta	Myers *et al.* 2000[13]
FIGO II → Symptomatic FIGO II	0.23 (0.18 – 0.27)	Beta	Myers *et al.* 2000[13]
FIGO III → Symptomatic FIGO III	0.60 (0.48 – 0.71)	Beta	Myers *et al.* 2000[13]
FIGO VI → Symptomatic FIGO IV	0.90 (0.67 - 1.00)	Beta	Myers *et al.* 2000[13]
1-year Cancer Survival	0.43 – 0.98 (0.23 – 0.99) By stage	Beta	SEER[14]
5-year Cancer Survival	0.14 – 0.94 (0.06 – 0.97) By stage	Beta	SEER[14]
10-year Cancer Survival	0.05 – 0.93 (0.01 – 0.96) By stage	Beta	SEER[14]
Screening			
Participation after invitation	17.3% (10.0% - 24.0%)	Uniform	Hamers *et al.* 2014[6]
Participation after recall	12.1% (5.0% - 18.0%)	Uniform	Hamers *et al.* 2014[6]
Lost to follow-up with IndScr	Based on lesion on Pap. Average 27.7%	NA	Hamers *et al.* 2014[6]
Reduction in lost to follow-up with OS	0.77 (0.08 – 0.77)	Uniform	OS experimentations, INCA personal communication
Lesions on PAP	Distribution	NA	Hamers *et al.* 2014[6]
Care per lesion	Distribution	NA	Hamers *et al.* 2014[6]

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Primary Pap-test (Se)	70.0 % (57.0 % - 80.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Se)	85.9 % (76.6 % - 92.1 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Se)	94.0 % (89.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Se)	100.0 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Se)	86.7 % (81.1 % - 90.9 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Se)	100.0% (NA)	NA	Assumption
Primary Pap-test (Sp)	95.0 % (92.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Sp)	65.9 % (63.1 % - 68.6 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Sp)	90.0 % (86.0 % - 93.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Sp)	61.1 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Sp)	95.2 % (94.9 % - 95.4 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Sp)	100.0% (NA)	NA	Assumption
Conisation efficacy	95.0%	NA	Assumption
Non-interpretable tests	1.0% (1.0% - 3.0%)	Uniform	Hamers *et al.* 2014[6]
Costs (€)			
Pap-test (IndScr)	47.78 (38.88 – 57.59)	Gamma	National tariffs
Pap-test (OS)	49.62 (40.37 – 59.81)	Gamma	National tariffs
p16/Ki67 (IndScr)	86.77 (70.60 - 104.58)	Gamma	National tariffs
p16/Ki67 (OS)	88.61 (72.09 - 106.80)	Gamma	National tariffs
HPV-test (IndScr)	47.70 (75.48 - 97.17)	Gamma	National tariffs
HPV-test (OS)	49.54 (49.54 - 71.24)	Gamma	National tariffs
Confirmation Pap-test (IndScr)	78.17 (63.60 - 94.21)	Gamma	National tariffs
Confirmation Pap-test (OS)	49.63 (40.38 - 59.82)	Gamma	National tariffs
Confirmation p16/Ki67 (IndScr)	116.77 (78.09 - 99.57)	Gamma	National tariffs
Confirmation p16/Ki67 (OS)	88.23 (71.79 - 106.34)	Gamma	National tariffs
Confirmation HPV-test (IndScr)	78.09 (63.53 - 94.12)	Gamma	National tariffs
Confirmation HPV-test (OS)	49.55 (49.55 - 71.03)	Gamma	National tariffs
Colposcopy	49.82 (40.54 - 60.05)	Gamma	National tariffs
Conization	93.42 (76.01 - 112.60)	Gamma	National tariffs
FIGO I CC treatment	1041.95 (847.77 - 1255.85)	Gamma	Dervaux *et al.* 2007[12]
FIGO II CC treatment	1818.86 (1479.90 - 2192.25)	Gamma	Dervaux *et al.* 2007[12]
FIGO III CC treatment	25817.84 (21006.43 - 31117.97)	Gamma	Dervaux *et al.* 2007[12]
FIGO IV CC treatment	30582.83 (24883.41 - 36861.16)	Gamma	Dervaux *et al.* 2007[12]
Database management + Invitation dispatch	7.00 (4.00 – 11.00)	Gamma	Cost of invitation to colorectal OS (Heath Ministry data, personal communication)
Recall dispatch	0.40 (0.40 – 3.25)	Gamma	50% postal charges

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validation

The model results were compared to observed epidemiological data for validation. The model faithfully reproduces cancer incidence and CC mortality in France.[12] Results of the model validation are available in supplementary file 5.

analyses

Incremental cost–effectiveness ratios (ICER) were calculated for the life expectancy. Costs and survival were discounted at 4% per year, according to French guidelines for cost-effectiveness studies.[18]

Several alternative scenarios were tested, including not applying the efficacy of OS on LtFU rate, not considering a reduction in HPV cost, and assuming a 60% reduction in p16/Ki67 cost.

The robustness of the model was tested using deterministic sensitivity analysis (DSA). In the DSA, all of the parameters were tested at their confidence intervals (or at ±20% of the baseline value when the confidence intervals were not available).

RESULTS

Compared with the current situation, invitation and recall (Pap/Pap) led to an increase from 61.9% to 65.5% in the 4-year participation rate. Every strategy that was tested was associated with a reduction in cancer incidence/mortality, ranging from -14.2%/-13.5% for the Pap/Pap strategy to -22.9%/-25.8% for the HPV/p16Ki67-5y strategy. The undiscounted results are presented in table 3.

Table 3 Undiscounted results

	Outcomes		Costs (€) per woman			
Scenario	Cancer	Cancer mortality	OS organisation	Screening	CC care & conizations	Total
IndScr only*	34	13	0	294.2	30.9	325.0
Pap/Pap	-14.2%	-13.5%	+19.57	+13.32	-3.92	+28.97
Pap/p16Ki67	-16.6%	-15.9%	+19.57	+18.46	-4.57	+33.46
HPV/Pap-3y	-21.1%	-22.4%	+15.16	+99.87	-7.31	+107.73
HPV/Pap-5y	-18.9%	-22.5%	+15.12	-29.79	-7.24	-21.91
HPV/Pap-10y	-8.0%	-13.6%	+14.94	-14.42	-0.48	-134.04
HPV/p16Ki67-5y	-22.9%	-25.8%	+15.10	+1.57	-0.81	+8.55
HPV/p16Ki67-10y	-11.9%	-17.0%	+14.93	-129.7	-5.87	-120.63
p16Ki67/p16Ki67	-24.3%	-24.4%	+19.57	+233.30	-6.87	+246.00

*Reference for other scenarios. Cumulated incidence and mortality for 10,000 women eligible for OS on a lifetime horizon.

The average undiscounted cost of screening for the modelled population over a lifetime was €325 per eligible woman, most of which was imputable to screening (€294). Strategies based on HPV-testing with 5-year and 10-year frequencies were cost-saving (-€22 and -€134 per woman, respectively), despite the additional cost of OS (€15). Other strategies were responsible for extra costs, ranging from €29 to €33 for Pap-based screening to €108 for HPV/Pap-3y and €246 for p16Ki67/p16Ki67.

Although it was the cheapest strategy (€191 per eligible woman), HPV/Pap-10y was the strategy with the smallest cancer reduction (-11.9%), as opposed to p16Ki67/p16Ki67, which led to a 25% reduction in CC while being the most expensive strategy (€571 per eligible woman). Figure 2 presents the mean cost per woman and cancer reduction rate for each strategy.

Discounted survival is consistent with CC incidence and mortality (table 4). Compared to the current situation (19.4 LY survival), OS strategies led to an increase in survival, ranging from 10 years per

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10,000 women for the Pap/Pap and HPV/Pap-10y strategies to 18 years per 10,000 women for the HPV/p16Ki67 and p16Ki67/p16Ki67 strategies. Discounted extra costs per 10,000 eligible women ranged from €38,000 (HPV/Pap-5y) to €1,608,000 (p16Ki67/p16Ki67). HPV/Pap-5y and HPV/Pap-10y remained cost-saving after discounting. Hence, these strategies were more effective and more cost-saving than Pap-based strategies, including the current situation, and were the dominant OS strategies. HPV/p16Ki67-5y and p16Ki67/p16Ki67 were more effective than HPV/Pap-5y and HPV/Pap-10y with ICERs of €101,391 and €6,541,250 per LY, respectively. HPV/Pap-3y was as effective as HPV/Pap-5y but less effective than HPV/p16Ki67-5y while generating much more expenses.

Table 4 Discounted results

Scenario	Survival (LY)	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	19.4	122.6	Reference	Dominated
Pap/Pap-HPV	+10.04	+22.3	22,234	Dominated
Pap/p16Ki67	+11.68	+25.5	21,918	Dominated
HPV/Pap-3y	+15.93	+55.8	35,095	Dominated
HPV/Pap-5y	+15.89	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+10.51	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+18.13	+3.79	2,091	101,389
HPV/p16Ki67-10y	+13.00	-64.6	Dominant	35,846
p16Ki67/p16Ki67	+18.37	+160.7	87,546	6,592,441

*Reference for other scenarios. Extra-survival per 10,000 women eligible for OS on a lifetime horizon. LY: Life Years

Regardless of the modality, implementing an OS programme for cervical cancer in France led to an overall improvement in the CC screening rate and a reduction in CC incidence and mortality. Reducing LtFU rates and improving screening rates with invitations/recall as in the Pap/Pap scenario results in an ICER of €22,231 per LY and an average extra survival of 10 LY per 10,000 eligible women.

Switching primary screening from the Pap-test to HPV-testing led to similar LY gains with a 10-year screening frequency, yet the 5-year frequency led to a longer survival (15.89 vs. 10.51 LY per 10,000 eligible women). Furthermore, reducing the frequency of primary testing was cost-saving, even at the current cost of HPV-testing. Despite the longer interval between the two screening tests, HPV-based strategies remained effective because of their superior sensitivity compared to the Pap-test.

The very good sensitivity/specificity of p16/Ki67 double-staining used as a primary screening test led to significant survival gains compared to the current situation and HPV-testing (+18.37 and +2.48 per 10,000 eligible women, respectively). However, its high cost made it inefficient, with an ICER of €6,592,441/LY.

Switching the Pap test with p16/Ki67 double-staining in the confirmation of positive Pap and HPV primary tests increased efficacy and led to moderate additional costs. The confirmation of HPV tests every 10 years increased the survival from +10.51 to +13.0 LY and the costs from -€734,000 to -€646,000 per 10,000 eligible women. Thus, the HPV/p16Ki67-10y scenario was associated with an ICER of €35,846/LY. The cost-utility results do not lead to different conclusions. A cost-utility analysis was performed by applying specific health utilities to the health states and utility decrements to non-cancerous and cancerous states. Its results and the utility values used are available in a supplementary file 6.

sensitivity and scenario analyses

Deterministic sensitivity analysis and scenario analyses for HPV/Pap-10y versus the current situation for LY and costs are shown in figures 3 and 4, respectively.

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The parameters with the biggest impact were the cost of testing (HPV and Pap) and OS effect on LtFU rate after a positive result. However, HPV/Pap-10y systematically remained the most cost-effective alternative. The mean age of the cohort impacted results drastically, despite HPV screening being less beneficial in women under 30 years old and over 50 years old than in the rest of the eligible population. Vaccination rates up to 80% had a negligible impact. Similar results were seen for HPV/Pap-5y and HPV/p16Ki67-5y scenarios. Not taking into account the effect of OS on LtFU rate did not change the conclusion, although it significantly reduced the LY gains compared to in the IndScr only. Similarly, not considering a reduction in the cost of the HPV test led to similar conclusions: HPV/Pap-10y and HPV/Pap-5y remained less costly than the alternative strategies. Finally, a 60% reduction in p16/Ki67 cost led to a decreased total cost of €41.05 (-75%) for the p16Ki67/p16Ki67 scenario.

DISCUSSION

Using a comprehensive, validated microsimulation model that allows for the fine modelling of CC natural history and screening modalities, we showed that the OS programme for cervical cancer in France leads to a reduction of CC incidence and mortality. HPV-based screening with 5- or 10-year frequencies would be cost-saving, and other modalities would generate extra costs ranging between €37.9 and €1,607 per woman.

Most model inputs were based on observed “real-life” data instead of simple screening guidelines. This allows for an accurate simulation of women’s screening behaviour by considering that many women do not comply with the recommended screening frequency and that older women tend to drop out of screening.[3] This also allowed for the implementation of current professional practices that significantly differ from recommended screening algorithms: in the current IndScr only situation, after a positive Pap test, not all women proceed to confirmation (Pap or HPV test), as some directly undergo colposcopy or conization, depending on the identified lesion with a significant impact on IndScr efficiency. Finally, the model incorporates LtFU rates, which proved to be a key factor in OS efficacy, particularly when screening frequency was superior to 5 years.[6]

The model’s main limitations stem from the estimation of the transition probabilities (TP). An initial literature review showed important variations between sources with some TP being not available. Additionally, the identified TP were not precise enough given the low incidence of lesions in the general population of women (1 in 10,000). Thus, we favoured sources that had previously been used in French models to allow comparability with previously published results.[10.12] Additionally, the model was calibrated on available prevalence data in France and externally validated. Furthermore, the sensitivity analyses showed that, despite the uncertainty, TP variations had a limited impact on the results, which reinforces our confidence in the estimations. Finally, our results are comparable to previously published European studies: Accetta *et al.* have found that an HPV test every 5 years is more effective and less costly than triennial Pap-tests in Italy.[29] The decreased efficiency of CC screening based on the HPVtest at lower frequencies was shown by Berkhof *et al.* in the Netherlands.[30] In Norway, Burger *et al.* found results comparable to ours for the Pap/Pap strategy.[31]

In our analysis, HPV/Pap-10y was the most efficient strategy, with HPV/p16Ki67-10y being a more cost-effective alternative. However, the final modality choice for OS-implementation will need to consider several factors. First, the HPV/Pap-10y strategy, albeit the most efficient, is the less effective strategy in terms of cancer incidence and prevalence reduction, conflicting with the primary aim of the Cancer Plan to further reduce the CC burden in France [5] and thus making the HPV/Pap-5y a more suitable, cost-saving modality. Second, current screening behaviours in France result in over-participation, with numerous women performing Pap-tests more often than is recommended.

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This phenomenon is likely to be related to the yearly recommended consultation with a gynaecologist. Our results showed that going from a 5-year frequency to a 3-year frequency implies a huge increase in screening cost (from -€133,000 to +€558,000 per 10,000 eligible women) for a very small increase in survival (from 15.89 to 15.93). Indeed, HPV-testing is sensitive, but it has a low specificity and cervical lesion evolution is slow, with most lesions regressing spontaneously. Women's over-participation will thus be a challenge in the case of HPV-based OS implementation. This should be addressed beforehand, or these apparent efficient strategies would be poorly efficient, leading to frequent false-positive results and related unnecessary and potentially harmful testing. Third, HPV-testing is not recommended in women under 35 years of age, which would require a complex double screening system. Finally, the current screening organization in France is based on the Pap-test, which implies a different infrastructure. Switching to HPV would require the negotiation of HPV-test tariffs, the development of a quality assurance protocol to ensure a sensitivity that is consistent with those found during clinical studies, as well as the development of the required infrastructure and equipment. Thus, although primary HPV-testing produces results with a better efficiency, many challenges will need to be addressed before its implementation. In the meantime, switching to a Pap-test based OS remains an acceptable alternative and could lead the way to HPV-testing deployment.

As for p16/KI67 double-staining, our results show that it would be an efficient confirmation test or primary test with negotiated tariffs. However, the sensitivity and specificity of the test were based on a single study with centralized reading. Additional studies in different French settings would be required to confirm that the results are reproducible before generalization.

Lastly, we do not present our results relatively to a willingness-to-pay threshold. This choice results from the fact that no cost-effectiveness threshold is relevant in France, since the national agency in charge of health technology assessment, including pharmacoeconomic evaluation (HAS) does not wish cost-effectiveness results to be compared to a threshold. Indeed, cost-effectiveness analyses are not used as a resource allocation tool for health technologies in France. Furthermore, since implementation of CC OS was decided, we did not aim to assess whether and how OS was efficient, but to determine which screening modality was the most efficient, keeping in mind practical issues. We feel that this choice is further reinforced by our results that confirm the legislator's decision to implement OS. In summary, this modelling study enabled the INCa to provide robust information to support a public decision on both efficient intermediate modalities for implementation of the CC OS programme and also on optimal screening strategies in a longer term and to anticipate the integration of promising technological innovations.

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Declaration of interests

The authors have no conflict of interest to declare concerning this study.

Authorship Statement

All authors participated in the study. Barré S, Leleu H and Massetti M participated in model development, data analysis and drafting of the manuscript. Barré S and De Bels F made critical review of the manuscript and approved its final version.

Data Sharing

No additional data available.

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Figure Legends

Figure 1: Structure of the model for the natural history of cervical cancer

Figure 2: Results of OS strategies assessed on cancer reduction rate and associated mean cost

Figure 3: Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

Figure 4: Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

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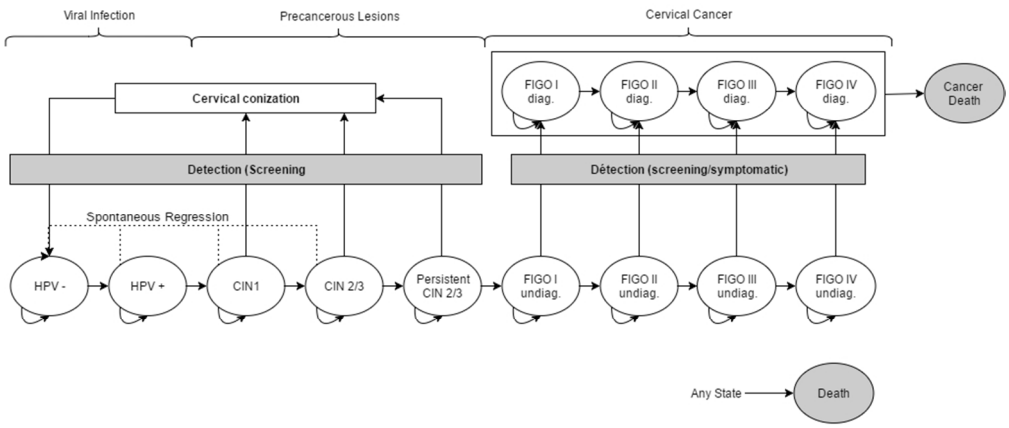

Structure of the model for the natural history of cervical cancer

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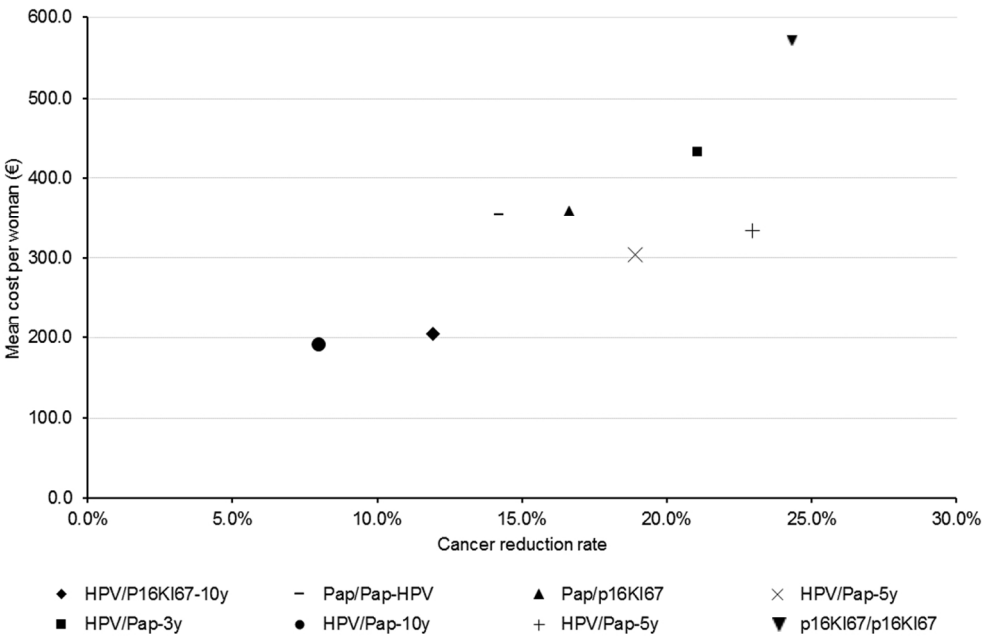

Results of OS strategies assessed on cancer reduction rate and associated mean cost

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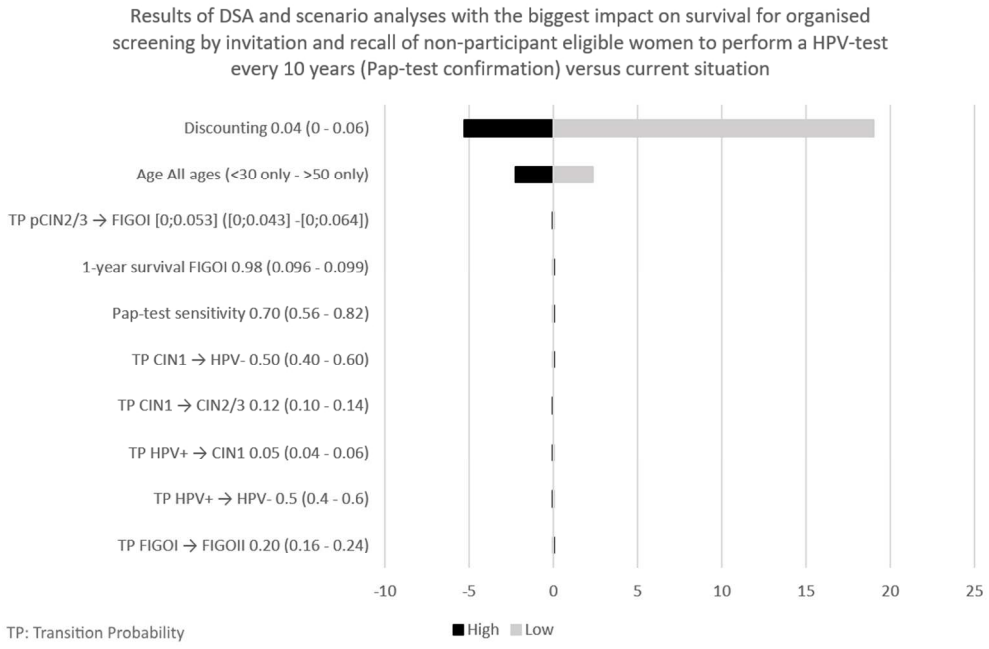
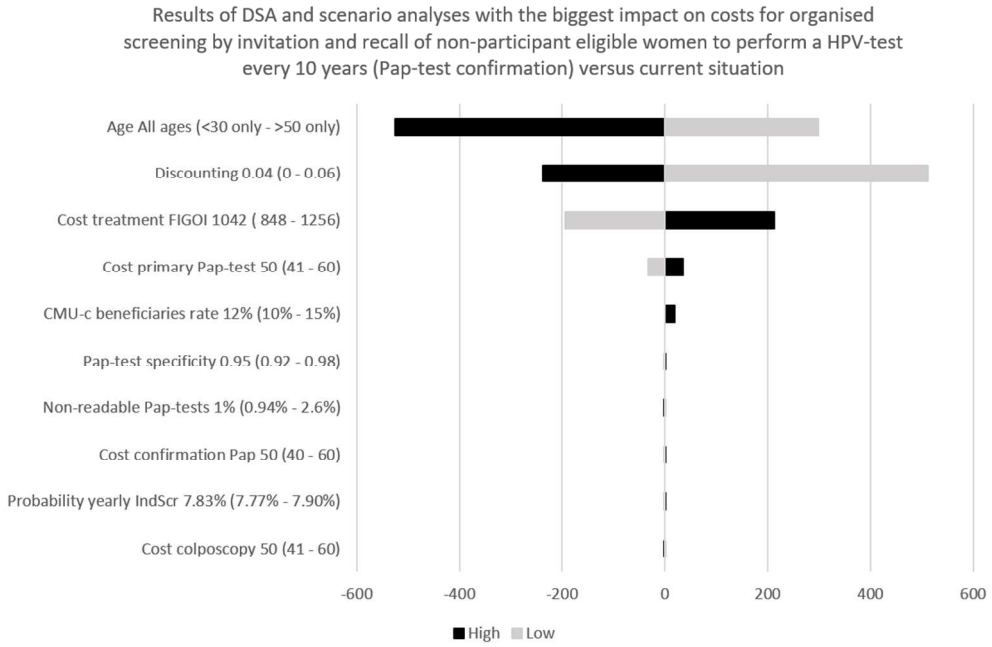


Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

102x67mm (300 x 300 DPI)

View only

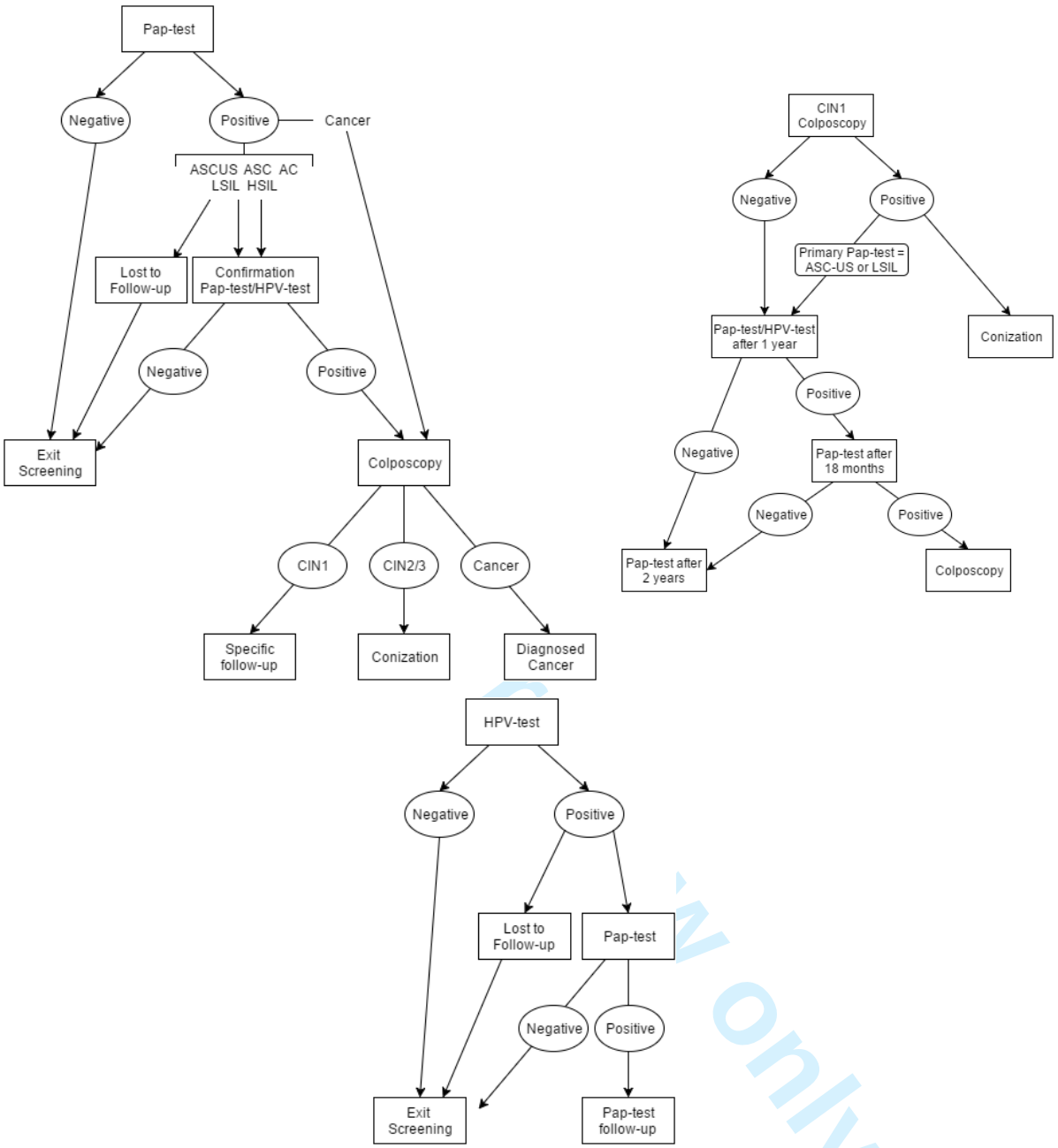


Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

102x67mm (300 x 300 DPI)

View only

Supplementary File 1 Screening algorithms



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Supplementary File 2 Pap-test results depending on HPV infection or lesion type

	ASCUS	ASC	AC	LSIL	HSIL	Cancer
HPV-	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
HPV+	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
CIN1	53.5 %	1.5 %	2.7 %	40.1 %	2.3 %	0.0 %
CIN2/3	26.2 %	6.0 %	9.6 %	32.4 %	23.2 %	2.6 %
Cancer (all stages)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Follow-up of positive Pap-test, by Pap-test result

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

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Supplementary File 3 Extended model presentation

Due to the complexity of screening algorithms and screening pace depending on the women's history and interactions that exist between screening and individual characteristics, a stochastic microsimulation model based on a Markov methodology and a 1-year cycle length was adapted based on a previously published Markov cohort-based model that has been updated.

Given the importance of individual characteristics, the analysis is based on the simulation of closed cohorts of women eligible for CC screening and representative in terms of age, HPV infection and precancerous and cancerous lesions in order to assess the actual cost-effectiveness of SO implementation in eligible women. Therefore, the results of the model specifically address the efficiency of the various OS strategies assessed and do not allow for epidemiological prediction.

According to the French national health authority (HAS), the model perspective is the collective perspective, meaning that costs borne by all payers are taken into consideration. Costs and survival results are discounted at a 4% annual rate.

The model is programmed in C++. Input data and scenario definition are entered through a Microsoft Excel interface. Model results are then exported to Excel to generate the figures and tables.

Women generation

The model first generates women with the following characteristics: age (25-56), participant in IndScr, period between carrying out two voluntary IndScr, health state at model initiation and vaccination status. Due to the recent introduction of vaccination, only women aged under 30 can be vaccinated.

Natural history of CC

Women then initiate the simulation of CC's natural history. At each cycle, non-HPV-infected women can become infected. This infection can spontaneously regress or progress and lead to grade 1 cervical intraepithelial neoplasia (CIN 1). CIN1 lesions can become pre-cancerous (grades 2 and 3 cervical intraepithelial neoplasia, CIN2/3). Once CIN 2/3 lesions have become persistent, they cannot regress spontaneously any longer and can only progress to cancerous lesions of first grade, based on the International Federation of Gynecology and Obstetrics (FIGO) classification. FIGO I CC can progress to grades 2, 3 and 4 and/or become symptomatic, leading to diagnosis of the CC and treatment initiation. Cancer mortality based on cancer severity grade and time since diagnosis is applied to women with symptomatic/diagnosed cancer. Women can die of age-specific general mortality at any state. See figure 1 for the structure of the model.

Considering the age distribution of the cohort and its low adoption in France (17% of women under 30), the effect of vaccination is simulated by applying a relative risk of infection by oncogenic HPV to vaccinated women (i.e. herd immunity is not considered).

Screening

Each year, the model determines whether the simulated woman performs IndScr based on her status (participant in IndScr or not) and her specific IndScr frequency, both parameters generated at the initiation and updated throughout the simulation. If the woman has not performed a CC screening or received an OS invitation/recall for a period that exceeds the OS periodicity, she receives an invitation to participate. Women that are still NP receive a recall during the same cycle.

Invitation and recall modalities determine different participation probabilities upon receiving. During the screening cycle, IndScr and OS participants perform the screening test determined by the OS

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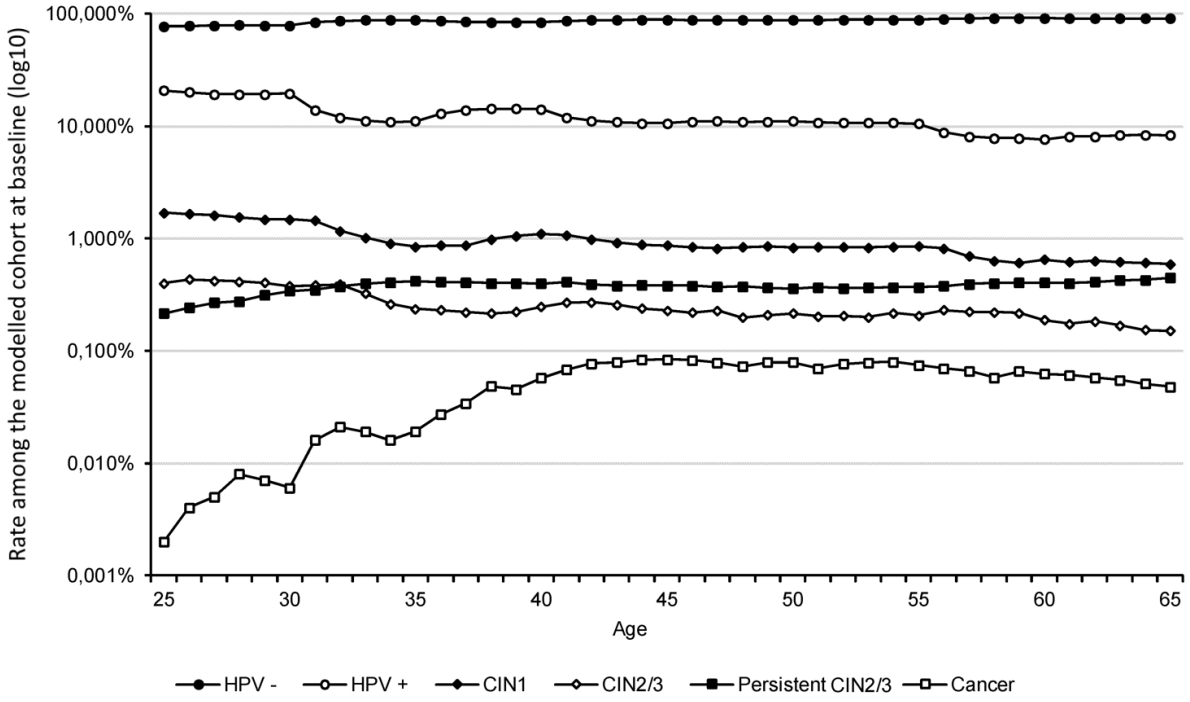
strategy assessed. Test characteristics (sensitivity/specificity) and the screening algorithm determine the result of the primary screening test based on the actual health state of the woman as well as the follow-up actions in case of positive results. Follow-up includes confirmation tests, colposcopy and conizations. Some women become lost to follow-up. Women diagnosed with CC switch to the corresponding diagnosed state.

Women's characteristics

The modelled population corresponds to all women aged 25 to 65, that is, all women eligible for IndScr according to current recommendations. Age distribution within the population is based on the national statistics office (INSEE) data.

Twelve percent (12.2%) of the eligible women were found to benefit from the universal complementary health insurance (CMU-c) in an analysis of a representative sample of the French SHI general regimen (employees). Vaccination rate among women aged 25 was based on the last available data which found a 17% uptake among young women since the vaccine became available. Distribution of each modelled health state by age within the population was based on the results of the simulation of a cohort of 14-year-old women. Health-state distribution in the generated cohort at each age is presented in the figure below.



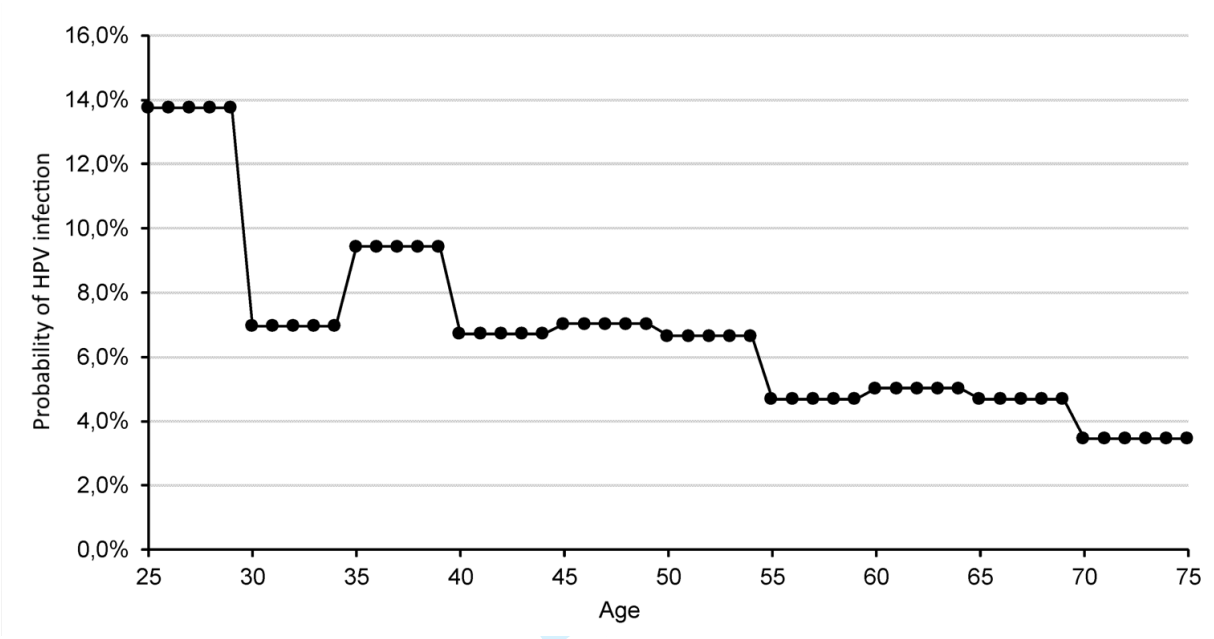
In scenarios based on Pap-test and p16/Ki67, IndScr participation is determined based on the analysis of a sample of the SHI general regimen: at 4 years, 61.9 % of eligible women were found to be participants. At patient generation, a relative risk (RR) of participation is applied to account for the impact of age and universal complementary health insurance (CMU-c). Another analysis of the same dataset provided the observed period between two IndScr (annual to every 10 years, see Supplementary file 3).

Each woman is associated with a SI participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} / RR_{current\ age-group})/5$$

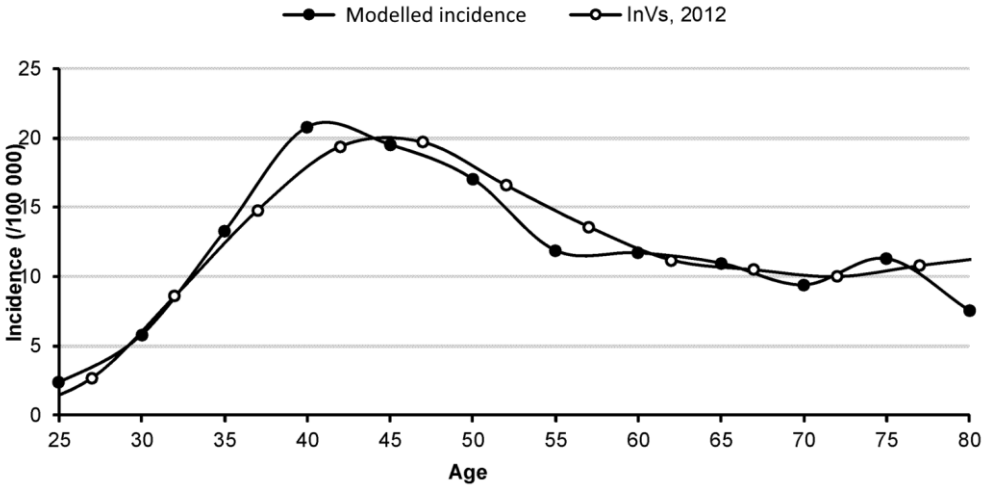
Transition probabilities

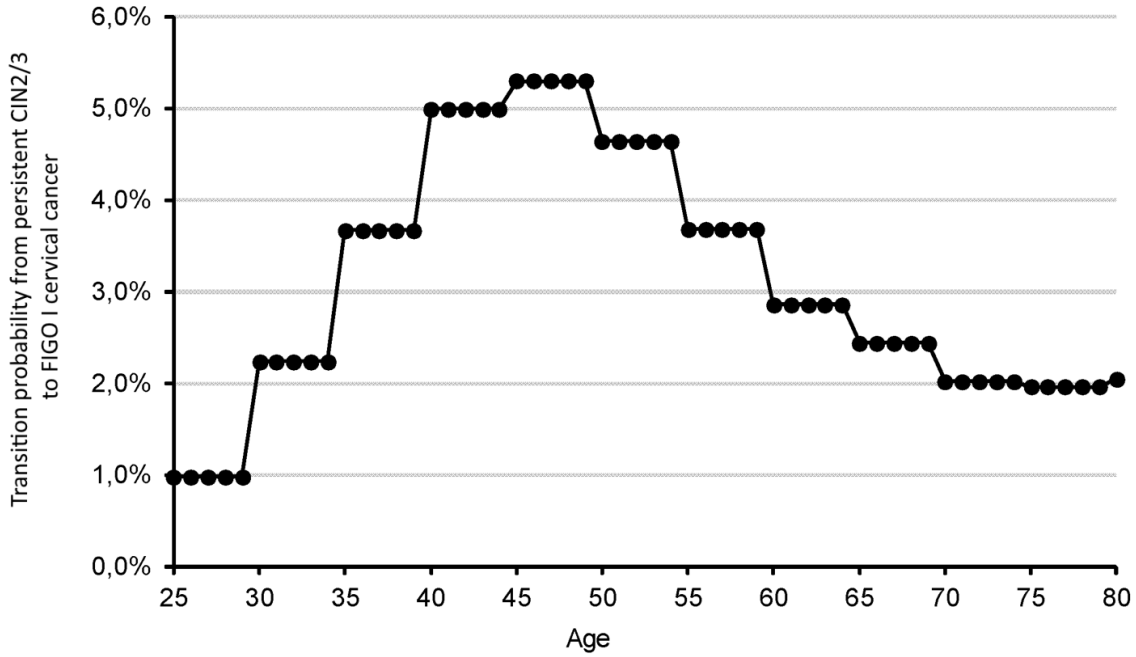
High risk (HR) HPV annual infection rate was estimated to vary from 3.5% and 14% depending on age, in order to fit with the observed HR-HPV prevalence, considering a 50% annual viral clearance rate, according to the model developed by Demarteau *et al.* In younger women, vaccination is modelled through the application of a relative risk of infection taking into account the vaccination rate and decreased infection risk among vaccinated women.



Annual transition probabilities that determine the odds of progression from HPV infection to persistent CIN2/3 precancerous lesion are replicated from the model developed by Demarteau *et al.* and presented in table 2.

Considering the lack of appropriate data, the age-specific progression transition probability of persistent CIN2/3 to FIGO I CC was estimated by calibrating the model to the CC incidence data available. The calibration process consisted in the simulation of a cohort of 14-year-old women, taking the observed IndScr participation rate into account. Transition probabilities were adjusted within a plausible interval in order to duplicate the observed incidence of CC by age. The following figures respectively present the results of the calibration process and the resulting persistent CIN 2/3 to FIGO I CC transition probabilities by age.





Probabilities of cancer progression and symptom emergence were obtained from the natural history of CC simulation model developed by Myers *et al*.

Cancer mortality by cancer grade and time since diagnosis were obtained from the study by Wright *et al.* based on the estimation of survival among 46,932 women with CC diagnosed from 1983-2009 and recorded in the Surveillance, Epidemiology, and End Results (SEER) database. Survival data for white women under 50 were selected, as mortality by causes other than CC seems unlikely in women under 50. General mortality is modelled according to French national statistics office (INSEE) data.

Screening

OS participation rates after receiving an invitation or recall are based on the results of local OS experimentations carried out in different regions. The weighted averages of the participation rate upon receiving a mailed invitation or recall letter by the number of Pap-tests performed during each experimentation were respectively found to be 17.3% and 12.1%. Screening test sensitivity and specificity are given in the following table.

Screening test	Sensitivity	Specificity	Source
Primary Pap-test	70.0 % (57.0 % - 80.0 %)	95.0 % (92.0 % - 97.0 %)	Mustafa (2015)
Confirmation Pap-test after HPV+	85.9 % (76.6 % - 92.1 %)	65.9 % (63.1 % - 68.6 %)	Bergeron (2015)
Primary HPV-test	94.0 % (89.0 % - 97.0 %)	90.0 % (86.0 % - 93.0 %)	Mustafa (2015)
Confirmation HPV-test after Pap+	100.0 % (NR)	61.1 % (NR)	Mayrand (2007)
P16/KI67	86.7 % (81.1 % - 90.9 %)	95.2 % (94.9 % - 95.4 %)	Ikenberg (2013)
Colposcopy	100.0% (NA)	100.0% (NA)	Assumption

At each screening cycle, test performances determine whether women with lesions are screened positive or not depending on their current health state.

Pap-test and p16/Ki67 specificity and specificity are relative to the detection of CIN2/3 and more severe lesions. Women with negative results exit screening, positive results lead to the random draw of an observed lesion type based on the results of the OS experimentation led in the Alsace region (Supplementary file 4).

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The action that follows each type of result is then randomly drawn according to the screening algorithms and the results of the OS experimentation led in Alsace. Based on the probabilities reported in Supplementary file 5, the different types of results can lead to further confirmation tests or conisation. Some women become lost to follow-up and exit screening.

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

In order to take the impact of the screening organization structures into account, OS implementation leads to reduced odds of becoming lost to follow-up after a positive result for both OS and IndScr participants. Based on the Alsace and Indre-et-Loire regional OS experimentation results, a 0.77 RR of becoming lost to follow-up is applied.

Colpscopy is associated with 100% sensitivity and specificity. Therefore, colposcopy results are negative in HPV- and HPV+ women and positive in women with CIN1, CIN2/3 and persistent CIN2/3 lesions. Women with CIN1 proceed to a particular screening algorithm based on recommendations by the French national scientific society of obstetricians and gynaecologists (CNGOF).

HPV-tests and specificity are relative to the detection of HPV+ and more severe lesions. Women with negative results exit screening, positive results lead to a confirmation Pap-test (or p16/Ki67) followed by a colposcopy in case of a new positive result. If negative, a new round of HPV and Pap-tests are performed concomitantly after one year: a positive result for either of them (or both) leads to colposcopy; women with negative-only results exit screening.

Rates of lost to follow-up observed during the START-HPV experimentation (Ardennes region) were used. The lost to follow-up rate after positive confirmation Pap-tests was estimated by subtracting the latter from the average rate of lost to follow-up in HPV+ women observed in the Alsace region OS experimentation (27.7%). Similarly to Pap-based screening, a 0.77 RR of being lost to follow-up is applied in OS-participant women.

Lost to follow-up after	Probability	Source
Positive HPV-test	19,4 %	START-HPV, Ardennes
Positive confirmation pap-test	8,3 %	START-HPV, Ardennes, Alsace OS experimentation

All samples have odds of being unreadable, depending on the nature of the sample. Women with unreadable samples perform a new test.

A 95% efficacy was considered for conisation. Women with successful conisation go back to the HPV- state. In case of failure, women leave screening in their current state.

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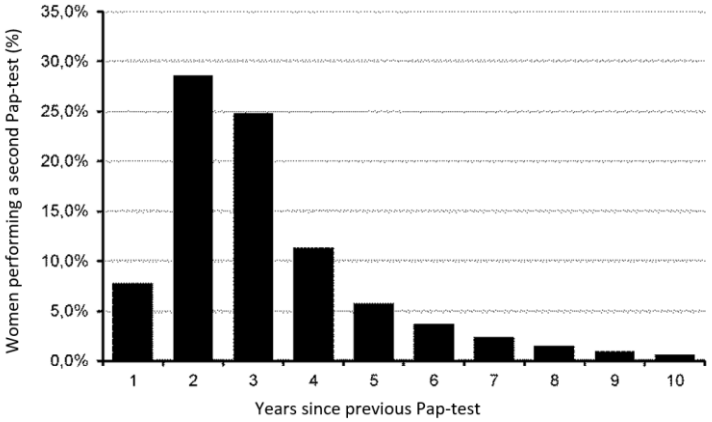
Supplementary File 4 Individual screening participation and periodicity data

Individual screening frequency	Distribution
Annual	5,9%
2 years	21,5%
3 years	18,7%
4 years	8,6%
5 years	4,3%
6 years	2,8%
7 years	1,8%
8 years	1,1%
9 years	0,7%
10 years	0,5%



Population	RR of participating vs. average	Source
Age		
25 – 30	1,06	National health insurance database [3]
30 – 35	1,08	National health insurance database [3]
35 – 40	1,07	National health insurance database [3]
40 – 45	1,04	National health insurance database [3]
50 – 55	0,92	National health insurance database [3]
55 – 60	0,82	National health insurance database [3]
60 – 65	0,77	National health insurance database [3]
Universal complementary health insurance registration		
Yes	0,80	National health insurance database [3]
No	1,03	National health insurance database [3]

Each woman is associated with an IndScr participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} \,/\, RR_{current\ age-group})/5$$

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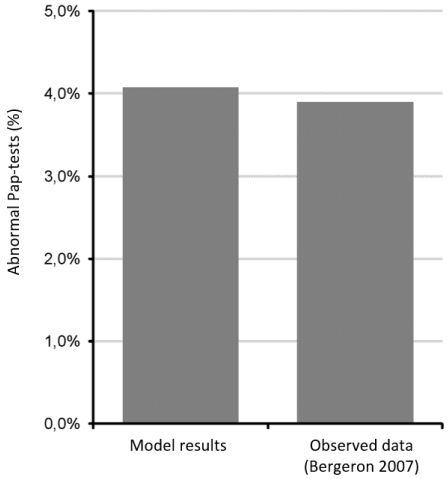
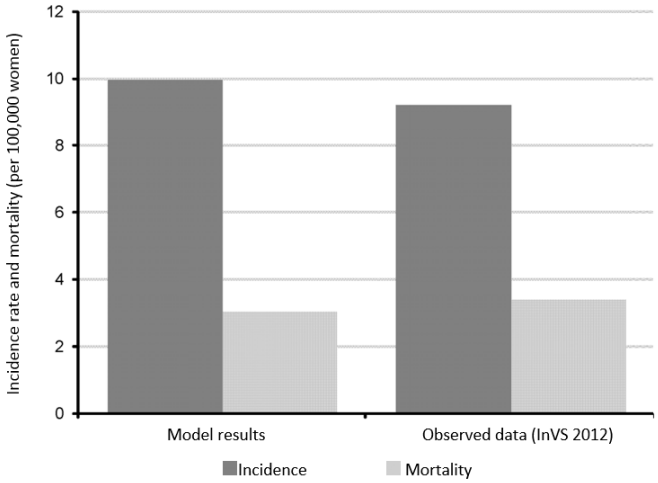
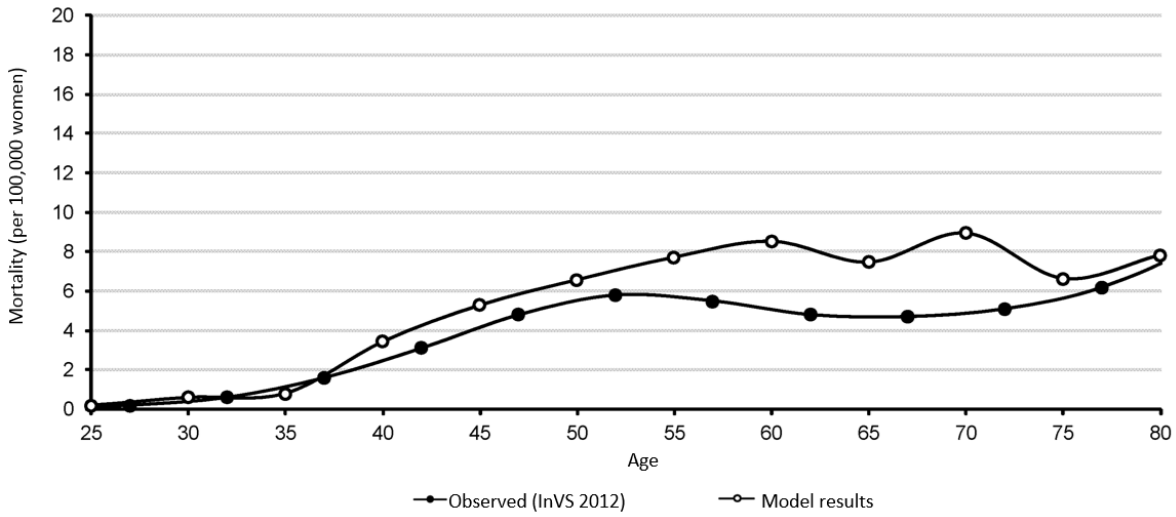
Supplementary File 5 Model validation results

The model faithfully reproduces cancer incidence, however the modelled CC mortality was slightly higher than observed data, although differences were systematically inferior to 4 per 100,000.







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Supplementary File 6 Cost-utility analysis - specific inputs and results

State	Utility/Utility decrement	Source
Age 18-29	0.86	Perneger, 2010
Age 30-39	0.86	
Age 40-49	0.84	
Age 50-59	0.81	
Age 60-69	0.8	
Age 70-79	0.76	
Age 80+	0.74	
Diagnosed CIN1	-0.01	Demarteau, 2011
Diagnosed CIN2/3	-0.01	
Cervical Cancer (1st year)	-0.27	
Cervical Cancer (thereafter)	-0.06	Korfage, 2009

Scénario	QALY	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	16.4	122.6	Reference	Dominated
Pap/Pap-HPV	+9.54	+22.3	23,392	Dominated
Pap/p16Ki67	+11.18	+25.5	22,891	Dominated
HPV/Pap-3y	+14.99	+55.8	37,290	Dominated
HPV/Pap-5y	+14.76	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+9.44	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+17.06	+3.79	2,222	131,965
HPV/p16Ki67-10y	+11.88	-64.6	Dominant	36,468
p16Ki67/p16Ki67	+17.53	+160.7	91,703	3,302,932

*Reference for other scenarios. Extra-QALY per 10,000 women eligible for OS on a lifetime horizon. QALY: Quality Adjusted Life Years

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Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	3
		Present the study question and its relevance for health policy or practice decisions.	3/28 - 29
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Table 2, 6/12 - 18
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6/36 - 37
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Table 1, 4/2 - 20
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5/27 - 28
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9/6 - 7
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	9/6 - 7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6/36 - 7/3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7/2 - 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Figure 1, 5/23 - 26
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 2, 5/29 - 7/3
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	8/6 - 12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2, 6/11 - 7/3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 3 & 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	

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(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Figures 3 & 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Figures 3 & 4; 11/24 - 35
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12 & 13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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Secondary Subject Heading:	Oncology, Public health, Diagnostics
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Gynaecological oncology < GYNAECOLOGY, PUBLIC HEALTH

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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French National Cancer Institute

The French National Cancer Institute was established under the Public Health Act of 9 August 2004 as the government health and science agency specialised in cancer control. It is a Public Interest Grouping which brings together State representatives, charities, health insurance funds, hospital federations and research organisations. It is responsible for rolling out the 2014-2019 Cancer Control Plan and reports to the Ministries for Health and for Research.

The Institute provides an integrated approach encompassing all cancer-control dimensions (health, scientific, social and economic) and areas of intervention (prevention, screening, care and research), for the benefit of patients and their relatives.

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ABSTRACT

OBJECTIVE: According to the third cancer plan, organized screening (OS) of cervical cancer (CC) among women aged 25-65 years should be implemented in France in the forthcoming years. The most efficient way to implement OS in the French health care system is yet to be determined.

METHODS: A microsimulation model was developed adopting a collective "all payers" perspective. A closed cohort of women eligible for CC screening and representative in terms of age and participation in individual screening (IndScr) was modelled on a lifetime horizon. Different OS strategies, additive to IndScr with a 61.9% participation rate and based on mailed invitations to non-participant women to perform OS were assessed. Similar modalities were applied to OS and IndScr participants. Strategies implied different screening tests (Papanicolaou (Pap) test, HPV test, and p16/Ki67 double-staining) and OS periodicity.

RESULTS: Compared to the current IndScr only situation, all OS strategies were associated with decreased cancer incidence/mortality (from 14.2%/13.5% to 22.9%/25.8%). Most strategies generated extra costs ranging from €37.9 to €1,607 per eligible woman. HPV testing every 10 and 5 years were cost-saving.

HPV tests every 10 and 5 years were the most efficient strategies, generating more survival at lower costs than Pap-based strategies. Compared to IndScr only, an HPV test every 10 years was cost-saving. The most effective strategies were p16/Ki67 as primary or HPV positive confirmation tests, with respective ICERs of €6,541,250 and €101,391 per life year. Pap-based strategies generated intermediary results.

CONCLUSION: OS strategies based on the HPV test appear highly efficient. However, our results rely on the assumption that women and practitioners comply with the recommended OS periodicities (3, 5, 10 years). Implementing these OS modalities will require major adaptations to the current CC screening organization. Pap-test based strategies might be simpler to set-up while preparing an appropriate implementation of more efficient OS screening modalities.

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STRENGTHS AND LIMITATIONS OF THE STUDY

- A microsimulation model was developed to assess the efficiency of possible cervical cancer organized screening strategies in France.
- The model operates on individual women who are eligible for screening and representative of the current French population on a lifetime horizon.
- Real-life practices and data were used, allowing for the fine modelling of the screening and validation against observed data.
- The lack of precision of transition probabilities in the context of a low incidence of cervical cancer, as well as the assumptions required to model screening practices after primary HPV tests, are the main limitations of the study.

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BACKGROUND

The natural history of cervical cancer (CC) is related to a persistent HPV infection of the cervix leading to squamous intraepithelial lesions that can evolve into cancerous lesions. CC prevention is based on screening to detect and remove lesions at the early stages to prevent invasive cancer and an anti-HPV vaccination to reduce cancer-associated HPV infection.[1]

In France, CC prevention is based on individual voluntary screening (IndScr) for CC of women aged 25 to 65 years and vaccination. IndScr is based on a Papanicolaou test (Pap test) every 3 years, after two annual Pap tests that are negative. Approximately 90% of Pap smears are done by gynaecologists, although general practitioners (GP) and midwives are also authorized to perform it. IndScr has led to a significant decrease in the incidence and associated mortality of CC in the past 20 years. In 2012, CC was the 11th most frequent and 12th most lethal form of cancer in women.[2] However, many women still do not participate in CC screening. Participation in IndScr was found to be approximately 61% of eligible women, with low access to healthcare, comorbidities and poverty being risk factors for non-participation.

Screening remains the main prevention tool in France, as anti-HPV vaccination is restricted to younger age groups and was only recently made available. Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated.[3;4] In 2014, the third French Cancer Plan has been presented to address both the human and the societal challenges of cancer. CC organized screening (OS) implementation among women aged 25-65 years is part of its first operational objective and aims at a participation rate of 80% and a 30% reduction in CC-related mortality by 2019.[5]

Several OS experimentations have been performed in France to assess the efficacy of different screening modalities, including invitation and positive tests follow-up (FU), self-sampling and HPV-testing. Experimentations that consisted of an invitation of non-participants to perform a Pap test allowed to catch up with 13.2% of all eligible women after 3 years and reduced the lost to follow-up (LtFU) rates of women after a positive result.[6] Additionally, primary HPV-testing and self-sampling were shown to be a feasible alternative to the Pap smear in France.[7;8] Finally, innovative testing, such as p16/Ki67 double-staining, was shown to be a performant alternative for CC screening compared to HPV screening or the Pap test.[9]

Consequently, many alternative strategies can be considered for the implementation of OS for CC in France. Thus, a medico-economic evaluation of several OS strategies based on a cost-effectiveness analysis was performed by the French national cancer institute (INCa), which relied on a scientific steering committee that involved clinical experts and stakeholder representatives (social security, ministry of health, patients and professionals) providing advice on the methodological choices and best OS implementation modality in the French context.

In order to assist decision-making regarding the implementation of CC OS, our study's main outcomes correspond to the objectives of CC OS implementation: participation rate, survival and avoided CC. A cost-utility analysis was performed as well.

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METHODS

Seven strategies were compared to the current IndScr-only situation (table 1). These strategies were all based on adding to the current IndScr with the dispatch of screening invitations (followed by a single recall) to women who did not spontaneously participate in the last 3 years (non-participants). Hence, women who did not participate in regular screening are the only ones targeted by the interventions. OS strategies also included improved FU, resulting in a reduction in LtFU women.

Different screening tests were considered for primary screening or confirmation after a positive primary test, including Pap test, HPV DNA detection and p16/Ki67 double-staining. The women who tested positive for both primary and confirmation tests went through colposcopy and conization if a high-grade (grade 2 or worse [CIN2+]) cervical intraepithelial neoplasia (CIN) lesion was identified. Women with CIN1 were retested at 12, 18 and 24 months if the initial lesion was atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) on Pap, or went through colposcopy. The women who tested positive for a primary test and negative for confirmation were retested after one year. A fraction of the participants was LtFU. Women could only be invited once per cycle. Detailed screening algorithms are available in supplementary file 1.

The population was limited to women aged 25-65 years who are currently eligible for IndScr.

Table 1 Strategies compared

Strategy	IR + Improved Follow-up	Primary test	Confirmation test after positive primary test
Current	No	Pap-test / 3 years	Pap-test or HPV
Pap/Pap	Yes	Pap-test / 3 years	Pap-test
Pap/p16Ki67	Yes	Pap-test / 3 years	p16/Ki67
HPV/Pap-5y†	Yes	HPV / 5 years	Pap-test
HPV/Pap-3y†	Yes	HPV / 3 years	Pap-test
HPV/Pap-10y†	Yes	HPV / 10 years	Pap-test
HPV/p16Ki67-5y†	Yes	HPV / 5 years	p16/Ki67
HPV/p16Ki67-10y†	Yes	HPV / 10 years	p16/Ki67
p16Ki67/p16Ki67	Yes	HPV / 3 years	p16/Ki67

IR: invitation + recall for woman who did not participate in IndScr in the last 3 years (non-participant)

†: women 25-35 are not eligible for HPV screening and receive a Pap-test every 3y instead. Women who tested HPV+/confirmation- go through double testing (HPV + Pap) the following year.

MODEL STRUCTURE

Given the complexity of screening algorithms (different testing/retesting frequencies) and interactions between participation rates and individual characteristics (age and social), a Markov state microsimulation model was developed. Considering the relatively slow progression of intraepithelial lesions and the long-term benefits of screening, a 1-year cycle-length was used. The model was adapted from a previously published cohort-based Markov model.[10] A cohort of 100,000 women was simulated. Due to the long-term development of the disease and its consequences, a lifetime horizon was applied.

The model first generates a woman with a randomly attributed age, IndScr participation and frequency, health state (HPV-, HPV+, CIN lesions or cancer) and vaccination attributes. At each cycle, women can progress through states that correspond to CC natural history: non-infected women can get an HPV infection according to an age- and vaccination-dependent risk. The infection can progress to CIN1, then CIN2/3 and finally FIGO 1 (Federation of Gynecology and Obstetrics) classified non-invasive cancer. HPV infection and CIN lesions can regress spontaneously until CIN2/3 lesions have become persistent (pCIN2/3). Women in the pCIN2/3 state systematically progress to cancer at an

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age-dependant rate. FIGO1 lesions can progress to FIGO 2, 3 and 4 and become symptomatic. Once symptomatic, the lesion is treated and the woman remains in the corresponding treated state with an associated cancer mortality rate. An age-specific general mortality applies at any state.

Each year, the model determines whether the woman undergoes screening individually or after invitation based on her participation periodicity, time since last screening and participation rates after invitation. Invitations are sent to non-participant women in the manner of prevention campaigns, following the screening recommended frequency (i.e. 3 years in the case of Pap/Pap). Therefore, only a fraction of non-participant women are invited every year. The same primary screening modality is applied to OS and IndScr participants. Screening test results (positivity and lesion type for Pap tests and positivity for HPV and p16/Ki67) are determined based on the current state and type of test performed (supplementary file 2). After diagnosis, women with a non-cancerous lesion return to the non-infected state after conization and cancerous lesions are treated. The structure of the modelled natural history is presented in figure 1. More details on the model structure are given in the supplementary file 3.

INPUT DATA

The input data used in the simulation are presented in table 2.

The population characteristics are based on available epidemiologic and demographic data that are representative of the French population. Vaccination status is only determined in women ≤30 years old, as it was only recently available in France. IndScr participation and frequency depend on age and social status, and based on the national health insurance database (supplementary file 4), approximately 61.9 % of eligible women were found to participate in IndScr at a frequency ≤4 years.[3] Distribution of each modelled health state by age was not available in France and was estimated by simulating a cohort of non-vaccinated 14-year-old women undergoing current IndScr-only screening over their lifetime (supplementary file 3).

Transition probabilities (TP) were based on a previously published model.[10] The HPV infection and pCIN2/3 to cancer progression probabilities were calibrated using the model to reproduce observed HPV and cancer prevalence by age.[1;11] The high-risk HPV annual infection rate was estimated to be 3.5% to 14%, depending on age.[12] The impact of vaccination is simulated by applying a relative risk (RR) of infection.[1]

Probabilities of cancer progression and emergence of symptoms were obtained from the CC natural history simulation model developed by Myers *et al*.[13] The cancer specific-mortality by grade and time since diagnosis was estimated from SEER using data for white women under 50, as it was assumed that non-specific mortality was low in this group.[14] General mortality was modelled according to the French national statistics office (INSEE) data.

The participation rates after invitation and recall, LtFU rate associated with IndScr, OS effect on LtFU (RR=0.88), observed lesions on Pap smear and associated care were all based on observational data from French OS experimentations.[1]

The sensitivity and specificity of screening tests were based on clinical studies for detecting CIN2/3 lesions and took into account the test sequence (i.e., HPV after Pap or primary HPV).[9;15-17] One percent of Pap tests were non-interpretable, which led to a retest.[18] Colposcopy was assumed to have 100% sensitivity and specificity. A 95% efficacy was considered for conization.

The model estimated OS cost and direct medical costs from a collective, “all payers” perspective, as recommended for France.[19] The OS costs covered invitations and recalls, as well as database

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management, tracking of women's participation and FU management. Cost data for consultations and medical care were based on national tariffs. No extra-consultation costs were added, as it was considered that IndScr participants did so during a routine consultation. The HPV-analysis tariff was decreased by 60% in strategies with primary HPV-testing, assuming a substantial cost reduction in cases of an adoption of HPV-testing based OS. This assumption was validated by health insurance and health ministry representatives. According to public-health law, no extra co-payment is applied to OS participants. Cancer states were associated with costs accounting for care and FU by FIGO stage [12] when entering the corresponding diagnosed state. All costs were updated to 2016, using the national consumer price index for healthcare goods and services.

Table 2 Input data

Parameter	Value	Distribution	Source
Demographic			
Age	25 - 65 Based on distribution	NA	National Statistics (INSEE)
CMU-c Eligibility (social status)	12.2 % (9.8% - 14.6%)	Normal	National Health Insurance Data
IndScr participation periodicity	Based on frequency distribution, age and social	Uniform	National Health Insurance Data
Initial Health State	Based on distribution	NA	Based on model prediction for a cohort of 14-year-old women
Transition probabilities			
HR-HPV infection	0.03 – 0.15 (0.03 – 0.18) Based on distribution	Beta	Estimated to reproduce known prevalence by age [12]
HPV-infection regression	0.50 (0.40 – 0.60)	Beta	Riethmuller et al. (1999)[19], Clavel et al. (2001)[20], Boulanger et al. (2004)[21], Beby-Defaux et al. (2004)[22], Dalstein et al. (2004)[23]
HR-HPV Infection → CIN 1	0.05 (0.04 – 0.06)	Beta	Moscicki et coll. (2001)[24]
CIN1 Regression	0.50 (0.40 – 0.60)	Beta	Melnikow et coll. (1998)[25], Nobbenhuis et coll. (2001)[26], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN1 → CIN 2/3	0.12 (0.10 – 0.14)	Beta	Melnikow et coll. (1998)[25], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN2/3 Regression	0.28 (0.22 – 0.33)	Beta	Melnikow et coll. (1998)[25]
CIN2/3 → pCIN 2/3	0.13 (0.10 – 0.15)	Beta	Melnikow et coll. (1998)[25]
Persistent CIN 2/3 → FIGO I	0.01 – 0.05 (0.01 – 0.06) Based on distribution	Beta	Estimated to reproduce known prevalence by age[1.11]
FIGO I → FIGO II	0.20 (0.16 – 0.24)	Beta	Myers *et al.* 2000[13]
FIGO II → FIGO III	0.26 (0.21 – 0.31)	Beta	Myers *et al.* 2000[13]
FIGO III → FIGO IV	0.36 (0.29 – 0.43)	Beta	Myers *et al.* 2000[13]
FIGO I → Symptomatic FIGO I	0.15 (0.12 – 0.18)	Beta	Myers *et al.* 2000[13]
FIGO II → Symptomatic FIGO II	0.23 (0.18 – 0.27)	Beta	Myers *et al.* 2000[13]
FIGO III → Symptomatic FIGO III	0.60 (0.48 – 0.71)	Beta	Myers *et al.* 2000[13]
FIGO VI → Symptomatic FIGO IV	0.90 (0.67 - 1.00)	Beta	Myers *et al.* 2000[13]
1-year Cancer Survival	0.43 – 0.98 (0.23 – 0.99) By stage	Beta	SEER[14]
5-year Cancer Survival	0.14 – 0.94 (0.06 – 0.97) By stage	Beta	SEER[14]
10-year Cancer Survival	0.05 – 0.93 (0.01 – 0.96) By stage	Beta	SEER[14]
Screening			
Participation after invitation	17.3% (10.0% - 24.0%)	Uniform	Hamers *et al.* 2014[6]
Participation after recall	12.1% (5.0% - 18.0%)	Uniform	Hamers *et al.* 2014[6]
Lost to follow-up with IndScr	Based on lesion on Pap. Average 27.7%	NA	Hamers *et al.* 2014[6]

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Reduction in lost to follow-up with OS	0.77 (0.08 – 0.77)	Uniform	OS experimentations, INCA personal communication
Lesions on PAP	Distribution	NA	Hamers *et al.* 2014[6]
Care per lesion	Distribution	NA	Hamers *et al.* 2014[6]
Primary Pap-test (Se)	70.0 % (57.0 % - 80.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Se)	85.9 % (76.6 % - 92.1 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Se)	94.0 % (89.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Se)	100.0 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Se)	86.7 % (81.1 % - 90.9 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Se)	100.0% (NA)	NA	Assumption
Primary Pap-test (Sp)	95.0 % (92.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Sp)	65.9 % (63.1 % - 68.6 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Sp)	90.0 % (86.0 % - 93.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Sp)	61.1 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Sp)	95.2 % (94.9 % - 95.4 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Sp)	100.0% (NA)	NA	Assumption
Conisation efficacy	95.0%	NA	Assumption
Non-interpretable tests	1.0% (1.0% - 3.0%)	Uniform	Hamers *et al.* 2014[6]
Costs (€)			
Pap-test (IndScr)	47.78 (38.88 – 57.59)	Gamma	National tariffs
Pap-test (OS)	49.62 (40.37 – 59.81)	Gamma	National tariffs
p16/Ki67 (IndScr)	86.77 (70.60 - 104.58)	Gamma	National tariffs
p16/Ki67 (OS)	88.61 (72.09 - 106.80)	Gamma	National tariffs
HPV-test (IndScr)	47.70 (75.48 - 97.17)	Gamma	National tariffs
HPV-test (OS)	49.54 (49.54 - 71.24)	Gamma	National tariffs
Confirmation Pap-test (IndScr)	78.17 (63.60 - 94.21)	Gamma	National tariffs
Confirmation Pap-test (OS)	49.63 (40.38 - 59.82)	Gamma	National tariffs
Confirmation p16/Ki67 (IndScr)	116.77 (78.09 - 99.57)	Gamma	National tariffs
Confirmation p16/Ki67 (OS)	88.23 (71.79 - 106.34)	Gamma	National tariffs
Confirmation HPV-test (IndScr)	78.09 (63.53 - 94.12)	Gamma	National tariffs
Confirmation HPV-test (OS)	49.55 (49.55 - 71.03)	Gamma	National tariffs
Colposcopy	49.82 (40.54 - 60.05)	Gamma	National tariffs
Conization	93.42 (76.01 - 112.60)	Gamma	National tariffs
FIGO I CC treatment	1041.95 (847.77 - 1255.85)	Gamma	Dervaux *et al.* 2007[12]
FIGO II CC treatment	1818.86 (1479.90 - 2192.25)	Gamma	Dervaux *et al.* 2007[12]
FIGO III CC treatment	25817.84 (21006.43 - 31117.97)	Gamma	Dervaux *et al.* 2007[12]
FIGO IV CC treatment	30582.83 (24883.41 - 36861.16)	Gamma	Dervaux *et al.* 2007[12]
Database management + Invitation dispatch	7.00 (4.00 – 11.00)	Gamma	Cost of invitation to colorectal OS (Heath Ministry data, personal communication)
Recall dispatch	0.40 (0.40 – 3.25)	Gamma	50% postal charges

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VALIDATION

The model results were compared to observed epidemiological data for validation. The model faithfully reproduces cancer incidence and CC mortality in France.[12] Results of the model validation are available in supplementary file 5.

COST-EFFECTIVENESS ANALYSES

Incremental cost–effectiveness ratios (ICER) were calculated for the life expectancy. Costs and survival were discounted at 4% per year, according to French guidelines for cost-effectiveness studies.[18]

Several alternative scenarios were tested, including not applying the efficacy of OS on LtFU rate, not considering a reduction in HPV cost, and assuming a 60% reduction in p16/Ki67 cost.

The robustness of the model was tested using deterministic sensitivity analysis (DSA). In the DSA, all of the parameters were tested at their confidence intervals (or at ±20% of the baseline value when the confidence intervals were not available).

RESULTS

Compared with the current situation, invitation and recall of non-participant women led to an increase from 61.9% to 65.5% in the 4-year participation rate. Every strategy that was tested was associated with a reduction in cancer incidence/mortality, ranging from -14.2%/-13.5% for the Pap/Pap strategy to -22.9%/-25.8% for the HPV/p16Ki67-5y strategy. The undiscounted results are presented in table 3.

Table 3 Undiscounted results

	Outcomes		Costs (€) per woman			
Scenario	Cancer	Cancer mortality	OS organisation	Screening	CC care & conizations	Total
IndScr only*	34	13	0	294.2	30.9	325.0
Pap/Pap	-14.2%	-13.5%	+19.57	+13.32	-3.92	+28.97
Pap/p16Ki67	-16.6%	-15.9%	+19.57	+18.46	-4.57	+33.46
HPV/Pap-3y	-21.1%	-22.4%	+15.16	+99.87	-7.31	+107.73
HPV/Pap-5y	-18.9%	-22.5%	+15.12	-29.79	-7.24	-21.91
HPV/Pap-10y	-8.0%	-13.6%	+14.94	-14.42	-0.48	-134.04
HPV/p16Ki67-5y	-22.9%	-25.8%	+15.10	+1.57	-0.81	+8.55
HPV/p16Ki67-10y	-11.9%	-17.0%	+14.93	-129.7	-5.87	-120.63
p16Ki67/p16Ki67	-24.3%	-24.4%	+19.57	+233.30	-6.87	+246.00

*Reference for other scenarios. Cumulated incidence and mortality for 10,000 women eligible for OS on a lifetime horizon.

The average undiscounted cost of screening for the modelled population over a lifetime was €325 per eligible woman, most of which was imputable to screening (€294). Strategies based on HPV-testing with 5-year and 10-year frequencies were cost-saving (-€22 and -€134 per woman, respectively), despite the additional cost of OS (€15). Other strategies were responsible for extra costs, ranging from €29 to €33 for Pap-based screening to €108 for HPV/Pap-3y and €246 for p16Ki67/p16Ki67.

Although it was the cheapest strategy (€191 per eligible woman), HPV/Pap-10y was the strategy with the smallest cancer reduction (-11.9%), as opposed to p16Ki67/p16Ki67, which led to a 25% reduction in CC while being the most expensive strategy (€571 per eligible woman). Figure 2 presents the mean cost per woman and cancer reduction rate for each strategy.

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Discounted survival is consistent with CC incidence and mortality (table 4). Compared to the current situation (19.4 LY survival), OS strategies led to an increase in survival, ranging from 10 years per 10,000 women for the Pap/Pap and HPV/Pap-10y strategies to 18 years per 10,000 women for the HPV/p16Ki67 and p16Ki67/p16Ki67 strategies. Discounted extra costs per 10,000 eligible women ranged from €38,000 (HPV/Pap-5y) to €1,608,000 (p16Ki67/p16Ki67). HPV/Pap-5y and HPV/Pap-10y remained cost-saving after discounting. Hence, these strategies were more effective and more cost-saving than Pap-based strategies, including the current situation, and were the dominant OS strategies. HPV/p16Ki67-5y and p16Ki67/p16Ki67 were more effective than HPV/Pap-5y and HPV/Pap-10y with ICERs of €101,391 and €6,541,250 per LY, respectively. HPV/Pap-3y was as effective as HPV/Pap-5y but less effective than HPV/p16Ki67-5y while generating much more expenses.

Table 4 Discounted results

Scenario	Survival (LY)	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	19.4	122.6	Reference	Dominated
Pap/Pap-HPV	+10.04	+22.3	22,234	Dominated
Pap/p16Ki67	+11.68	+25.5	21,918	Dominated
HPV/Pap-3y	+15.93	+55.8	35,095	Dominated
HPV/Pap-5y	+15.89	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+10.51	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+18.13	+3.79	2,091	101,389
HPV/p16Ki67-10y	+13.00	-64.6	Dominant	35,846
p16Ki67/p16Ki67	+18.37	+160.7	87,546	6,592,441

*Reference for other scenarios. Extra-survival per 10,000 women eligible for OS on a lifetime horizon. LY: Life Years

Regardless of the modality, implementing an OS programme for cervical cancer in France led to an overall improvement in the CC screening rate and a reduction in CC incidence and mortality. Reducing LtFU rates and improving screening rates with invitations/recall as in the Pap/Pap scenario results in an ICER of €22,231 per LY and an average extra survival of 10 LY per 10,000 eligible women.

Switching primary screening from the Pap-test to HPV-testing led to similar LY gains with a 10-year screening frequency, yet the 5-year frequency led to a longer survival (15.89 vs. 10.51 LY per 10,000 eligible women). Furthermore, reducing the frequency of primary testing was cost-saving, even at the current cost of HPV-testing. Despite the longer interval between the two screening tests, HPV-based strategies remained effective because of their superior sensitivity compared to the Pap-test.

The very good sensitivity/specificity of p16/Ki67 double-staining used as a primary screening test led to significant survival gains compared to the current situation and HPV-testing (+18.37 and +2.48 per 10,000 eligible women, respectively). However, its high cost made it inefficient, with an ICER of €6,592,441/LY.

Switching the Pap test with p16/Ki67 double-staining in the confirmation of positive Pap and HPV primary tests increased efficacy and led to moderate additional costs. The confirmation of HPV tests every 10 years increased the survival from +10.51 to +13.0 LY and the costs from -€734,000 to -€646,000 per 10,000 eligible women. Thus, the HPV/p16Ki67-10y scenario was associated with an ICER of €35,846/LY. The cost-utility results do not lead to different conclusions. A cost-utility analysis was performed by applying specific health utilities to the health states and utility decrements to non-cancerous and cancerous states. Its results and the utility values used are available in a supplementary file 6.

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SENSITIVITY AND SCENARIO ANALYSES

Deterministic sensitivity analysis and scenario analyses for HPV/Pap-10y versus the current situation for LY and costs are shown in figures 3 and 4, respectively.

The parameters with the biggest impact were the cost of testing (HPV and Pap) and OS effect on LtFU rate after a positive result. However, HPV/Pap-10y systematically remained the most cost-effective alternative. The mean age of the cohort impacted results drastically, despite HPV screening being less beneficial in women under 30 years old and over 50 years old than in the rest of the eligible population. Vaccination rates up to 80% had a negligible impact. Similar results were seen for HPV/Pap-5y and HPV/p16Ki67-5y scenarios. Not taking into account the effect of OS on LtFU rate did not change the conclusion, although it significantly reduced the LY gains compared to in the IndScr only. Similarly, not considering a reduction in the cost of the HPV test led to similar conclusions: HPV/Pap-10y and HPV/Pap-5y remained less costly than the alternative strategies. Finally, a 60% reduction in p16/Ki67 cost led to a decreased total cost of €41.05 (-75%) for the p16Ki67/p16Ki67 scenario.

DISCUSSION

Using a validated microsimulation model that allows for the fine modelling of screening modalities, we showed that the OS programme for cervical cancer in France leads to a reduction of CC incidence and mortality. HPV-based screening with 5- or 10-year frequencies would be cost-saving, and other modalities would generate extra costs ranging between €37.9 and €1,607 per woman.

Most model inputs were based on observed “real-life” data instead of simple screening guidelines. This allows for an accurate simulation of women’s screening behaviour by considering that many women do not comply with the recommended screening frequency and that older women tend to drop out of screening.[3] This also allowed for the implementation of current professional practices that significantly differ from recommended screening algorithms: in the current IndScr only situation, after a positive Pap test, not all women proceed to confirmation (Pap or HPV test), as some directly undergo colposcopy or conization, depending on the identified lesion with a significant impact on IndScr efficiency. Finally, the model incorporates LtFU rates, which proved to be a key factor in OS efficacy, particularly when screening frequency was superior to 5 years.[6]

The model’s main limitations stem from the estimation of the transition probabilities (TP). An initial literature review showed important variations between sources with some TP being not available. Additionally, the identified TP were not precise enough given the low incidence of lesions in the general population of women (1 in 10,000). Thus, we favoured sources that had previously been used in French models to allow comparability with previously published results.[10.12] Additionally, the model was calibrated on available prevalence data in France and externally validated. Furthermore, the sensitivity analyses showed that, despite the uncertainty, TP variations had a limited impact on the results, which reinforces our confidence in the estimations. Finally, our results are comparable to previously published European studies: Accetta *et al.* have found that an HPV test every 5 years is more effective and less costly than triennial Pap-tests in Italy.[29] The decreased efficiency of CC screening based on the HPVtest at lower frequencies was shown by Berkhof *et al.* in the Netherlands.[30] In Norway, Burger *et al.* found results comparable to ours for the Pap/Pap strategy.[31]

In our analysis, HPV/Pap-10y was the most efficient strategy, with HPV/p16Ki67-10y being a more cost-effective alternative. However, the final modality choice for OS-implementation will need to consider several factors. First, the HPV/Pap-10y strategy, albeit the most efficient, is the less effective strategy in terms of cancer incidence and prevalence reduction, conflicting with the primary

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aim of the Cancer Plan to further reduce the CC burden in France [5] and thus making the HPV/Pap-5y a more suitable, cost-saving modality. Second, current screening behaviours in France result in over-participation, with numerous women performing Pap-tests more often than is recommended. This phenomenon is likely to be related to the yearly recommended consultation with a gynaecologist. Our results showed that going from a 5-year frequency to a 3-year frequency implies a huge increase in screening cost (from -€133,000 to +€558,000 per 10,000 eligible women) for a very small increase in survival (from 15.89 to 15.93). Indeed, HPV-testing is sensitive, but it has a low specificity and cervical lesion evolution is slow, with most lesions regressing spontaneously. Women's over-participation will thus be a challenge in the case of HPV-based OS implementation. This should be addressed beforehand, or these apparent efficient strategies would be poorly efficient, leading to frequent false-positive results and related unnecessary and potentially harmful testing. Third, HPV-testing is not recommended in women under 35 years of age, which would require a complex double screening system. Finally, the current screening organization in France is based on the Pap-test, which implies a different infrastructure. Switching to HPV would require the negotiation of HPV-test tariffs, the development of a quality assurance protocol to ensure a sensitivity that is consistent with those found during clinical studies, as well as the development of the required infrastructure and equipment. Thus, although primary HPV-testing produces results with a better efficiency, many challenges will need to be addressed before its implementation. In the meantime, switching to a Pap-test based OS remains an acceptable alternative and could lead the way to HPV-testing deployment.

As for p16/KI67 double-staining, our results show that it would be an efficient confirmation test or primary test with negotiated tariffs. However, the sensitivity and specificity of the test were based on a single study with centralized reading. Additional studies in different French settings would be required to confirm that the results are reproducible before generalization.

Lastly, we do not present our results relatively to a willingness-to-pay threshold. This choice results from the fact that no cost-effectiveness threshold is relevant in France, since the national agency in charge of health technology assessment, including pharmacoeconomic evaluation (HAS) does not wish cost-effectiveness results to be compared to a threshold. Indeed, cost-effectiveness analyses are not used as a resource allocation tool for health technologies in France. Furthermore, since implementation of CC OS was decided, we did not aim to assess whether and how OS was efficient, but to determine which screening modality was the most efficient, keeping in mind practical issues. We feel that this choice is further reinforced by our results that confirm the legislator's decision to implement OS. In summary, this modelling study enabled the INCa to provide robust information to support a public decision on both efficient intermediate modalities for implementation of the CC OS programme and also on optimal screening strategies in a longer term and to anticipate the integration of promising technological innovations.

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Declaration of interests

The authors have no conflict of interest to declare concerning this study.

Authorship Statement

All authors participated in the study. Barré S, Leleu H and Massetti M participated in model development, data analysis and drafting of the manuscript. Barré S and De Bels F made critical review of the manuscript and approved its final version.

Data Sharing

No additional data available.

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Figure Legends

Figure 1: Structure of the model for the natural history of cervical cancer

Figure 2: Results of OS strategies assessed on cancer reduction rate and associated mean cost

Figure 3: Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

Figure 4: Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

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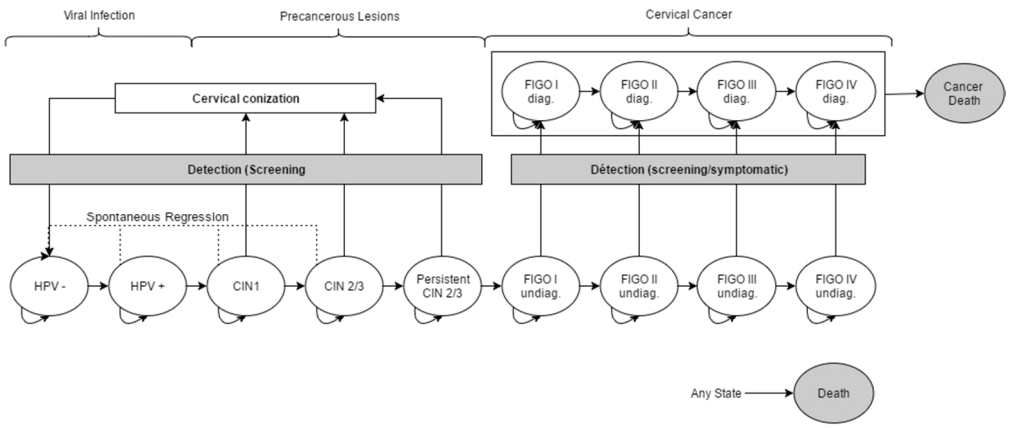

Structure of the model for the natural history of cervical cancer

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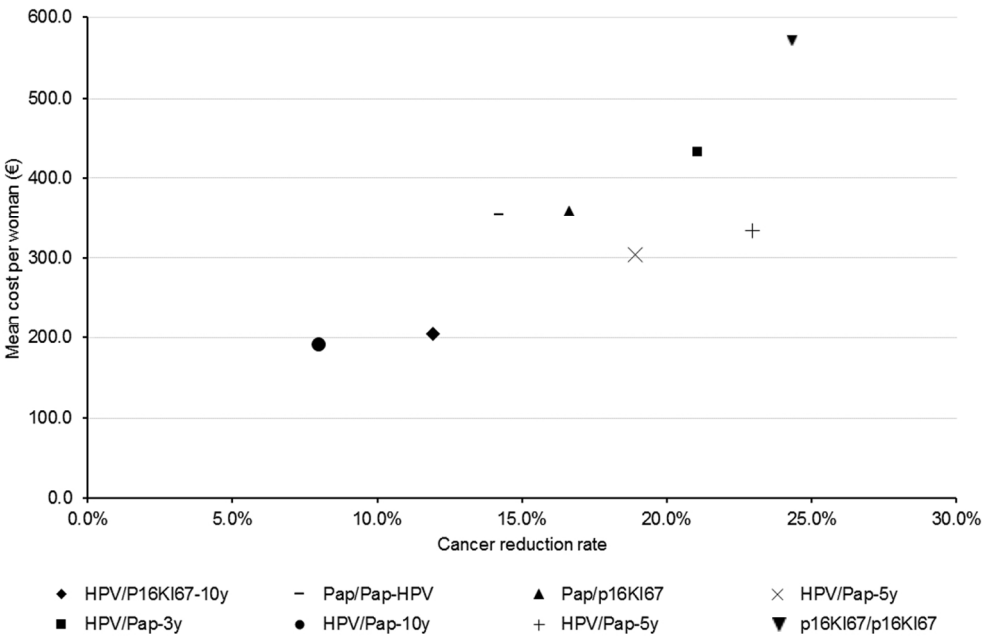

Results of OS strategies assessed on cancer reduction rate and associated mean cost

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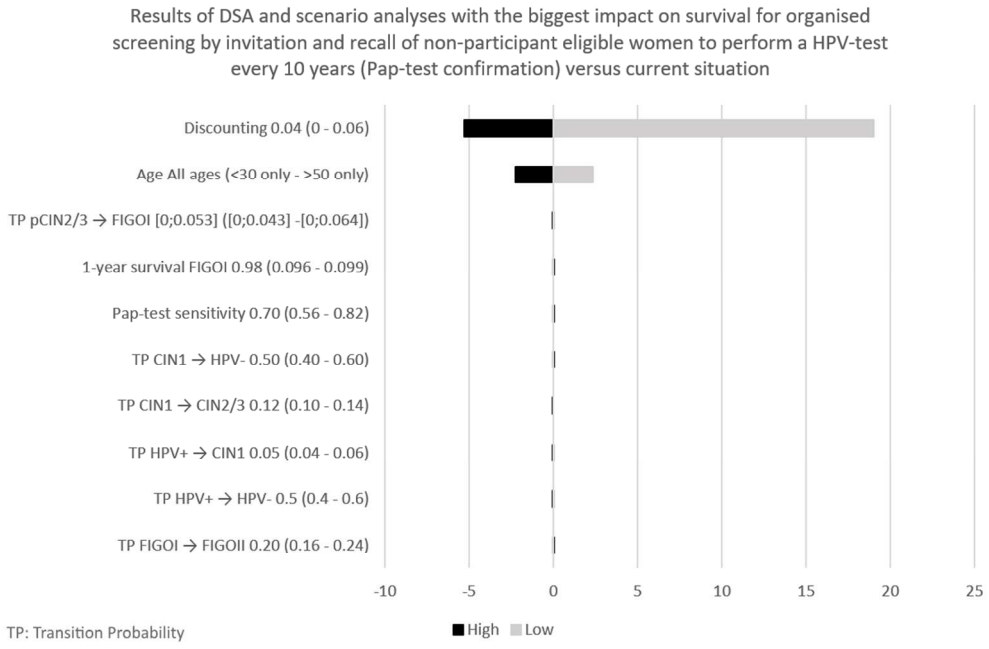

Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

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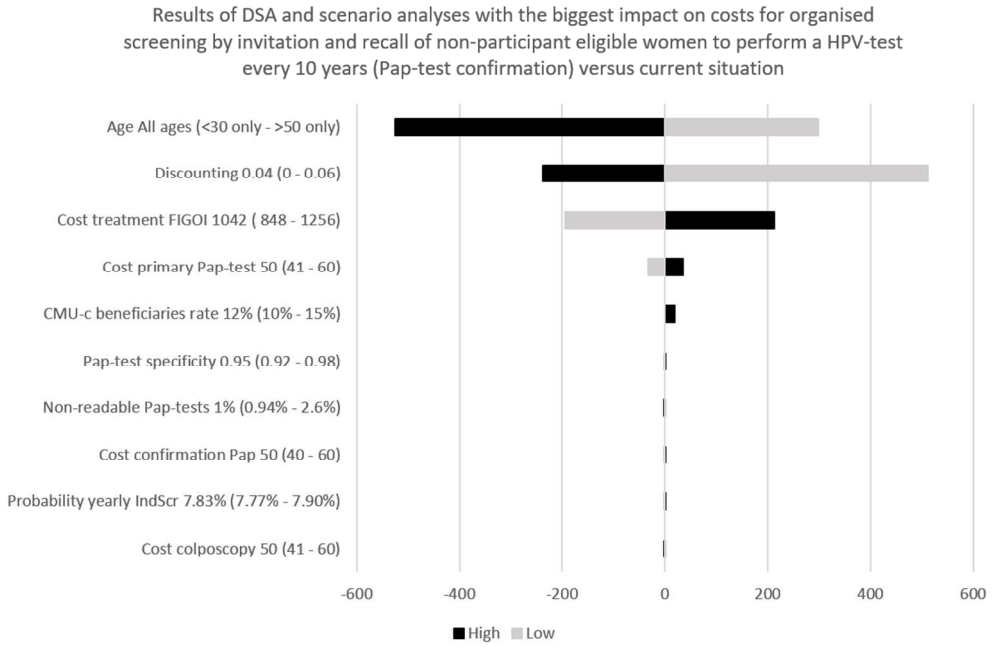

Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

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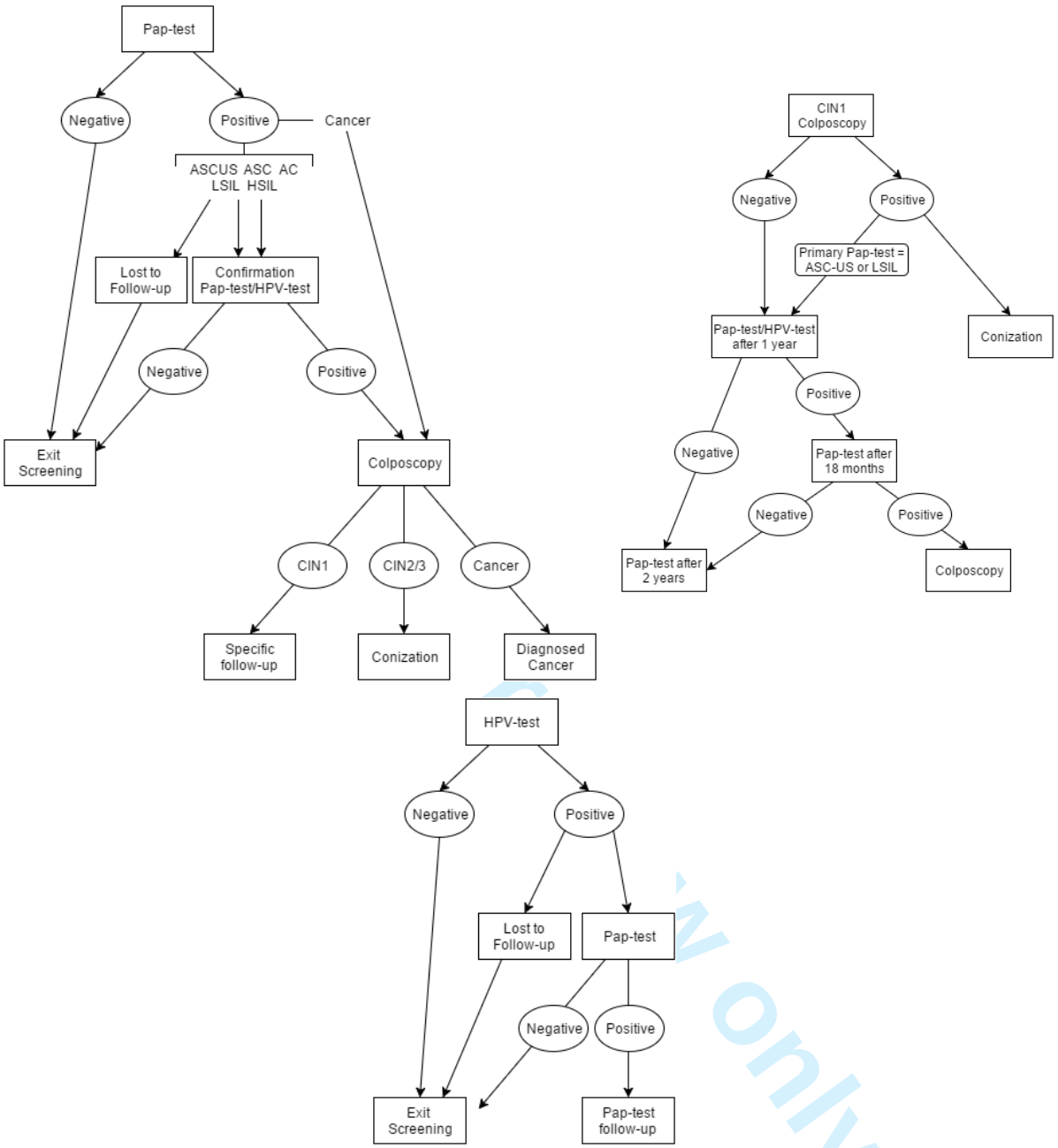
Supplementary File 1 Screening algorithms



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Supplementary File 2 Pap-test results depending on HPV infection or lesion type

	ASCUS	ASC	AC	LSIL	HSIL	Cancer
HPV-	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
HPV+	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
CIN1	53.5 %	1.5 %	2.7 %	40.1 %	2.3 %	0.0 %
CIN2/3	26.2 %	6.0 %	9.6 %	32.4 %	23.2 %	2.6 %
Cancer (all stages)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Follow-up of positive Pap-test, by Pap-test result

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

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Supplementary File 3 Extended model presentation

Due to the complexity of screening algorithms and screening pace depending on the women's history and interactions that exist between screening and individual characteristics, a stochastic microsimulation model based on a Markov methodology and a 1-year cycle length was adapted based on a previously published Markov cohort-based model that has been updated.

Given the importance of individual characteristics, the analysis is based on the simulation of closed cohorts of women eligible for CC screening and representative in terms of age, HPV infection and precancerous and cancerous lesions in order to assess the actual cost-effectiveness of SO implementation in eligible women. Therefore, the results of the model specifically address the efficiency of the various OS strategies assessed and do not allow for epidemiological prediction.

According to the French national health authority (HAS), the model perspective is the collective perspective, meaning that costs borne by all payers are taken into consideration. Costs and survival results are discounted at a 4% annual rate.

The model is programmed in C++. Input data and scenario definition are entered through a Microsoft Excel interface. Model results are then exported to Excel to generate the figures and tables.

Women generation

The model first generates women with the following characteristics: age (25-56), participant in IndScr, period between carrying out two voluntary IndScr, health state at model initiation and vaccination status. Due to the recent introduction of vaccination, only women aged under 30 can be vaccinated.

Natural history of CC

Women then initiate the simulation of CC's natural history. At each cycle, non-HPV-infected women can become infected. This infection can spontaneously regress or progress and lead to grade 1 cervical intraepithelial neoplasia (CIN 1). CIN1 lesions can become pre-cancerous (grades 2 and 3 cervical intraepithelial neoplasia, CIN2/3). Once CIN 2/3 lesions have become persistent, they cannot regress spontaneously any longer and can only progress to cancerous lesions of first grade, based on the International Federation of Gynecology and Obstetrics (FIGO) classification. FIGO I CC can progress to grades 2, 3 and 4 and/or become symptomatic, leading to diagnosis of the CC and treatment initiation. Cancer mortality based on cancer severity grade and time since diagnosis is applied to women with symptomatic/diagnosed cancer. Women can die of age-specific general mortality at any state. See figure 1 for the structure of the model.

Considering the age distribution of the cohort and its low adoption in France (17% of women under 30), the effect of vaccination is simulated by applying a relative risk of infection by oncogenic HPV to vaccinated women (i.e. herd immunity is not considered).

Screening

Each year, the model determines whether the simulated woman performs IndScr based on her status (participant in IndScr or not) and her specific IndScr frequency, both parameters generated at the initiation and updated throughout the simulation. If the woman has not performed a CC screening or received an OS invitation/recall for a period that exceeds the OS periodicity, she receives an invitation to participate. Women that are still NP receive a recall during the same cycle.

Invitation and recall modalities determine different participation probabilities upon receiving. During the screening cycle, IndScr and OS participants perform the screening test determined by the OS

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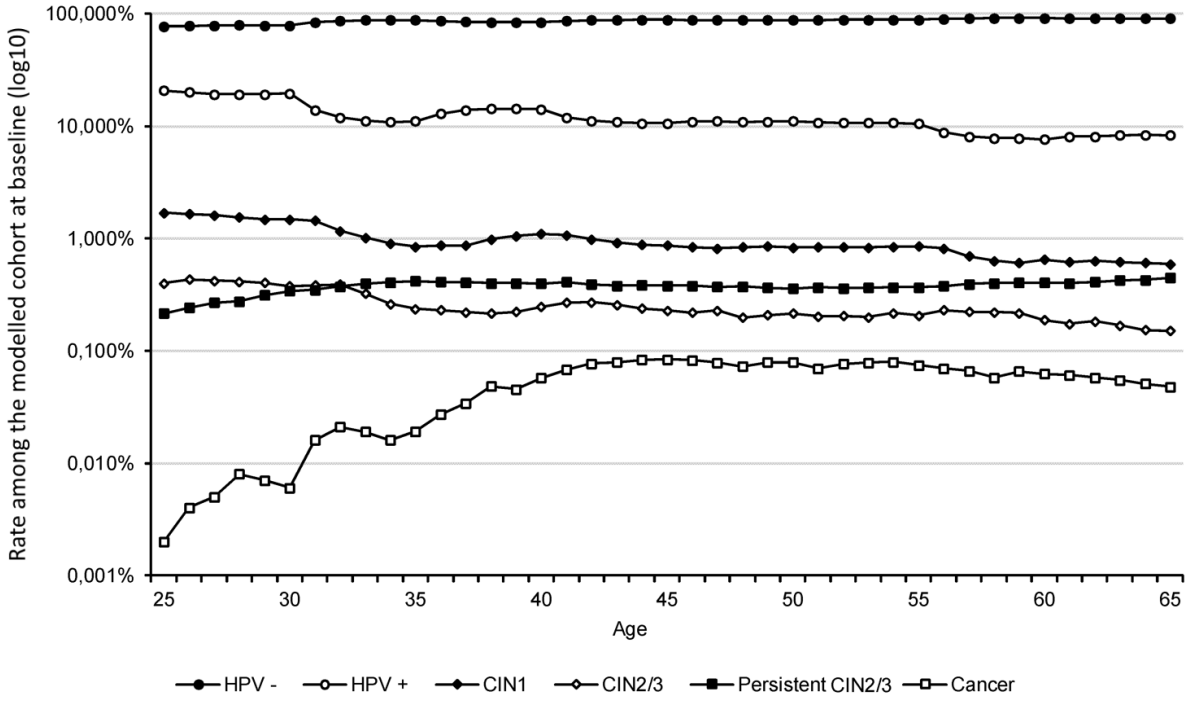
strategy assessed. Test characteristics (sensitivity/specificity) and the screening algorithm determine the result of the primary screening test based on the actual health state of the woman as well as the follow-up actions in case of positive results. Follow-up includes confirmation tests, colposcopy and conizations. Some women become lost to follow-up. Women diagnosed with CC switch to the corresponding diagnosed state.

Women's characteristics

The modelled population corresponds to all women aged 25 to 65, that is, all women eligible for IndScr according to current recommendations. Age distribution within the population is based on the national statistics office (INSEE) data.

Twelve percent (12.2%) of the eligible women were found to benefit from the universal complementary health insurance (CMU-c) in an analysis of a representative sample of the French SHI general regimen (employees). Vaccination rate among women aged 25 was based on the last available data which found a 17% uptake among young women since the vaccine became available. Distribution of each modelled health state by age within the population was based on the results of the simulation of a cohort of 14-year-old women. Health-state distribution in the generated cohort at each age is presented in the figure below.



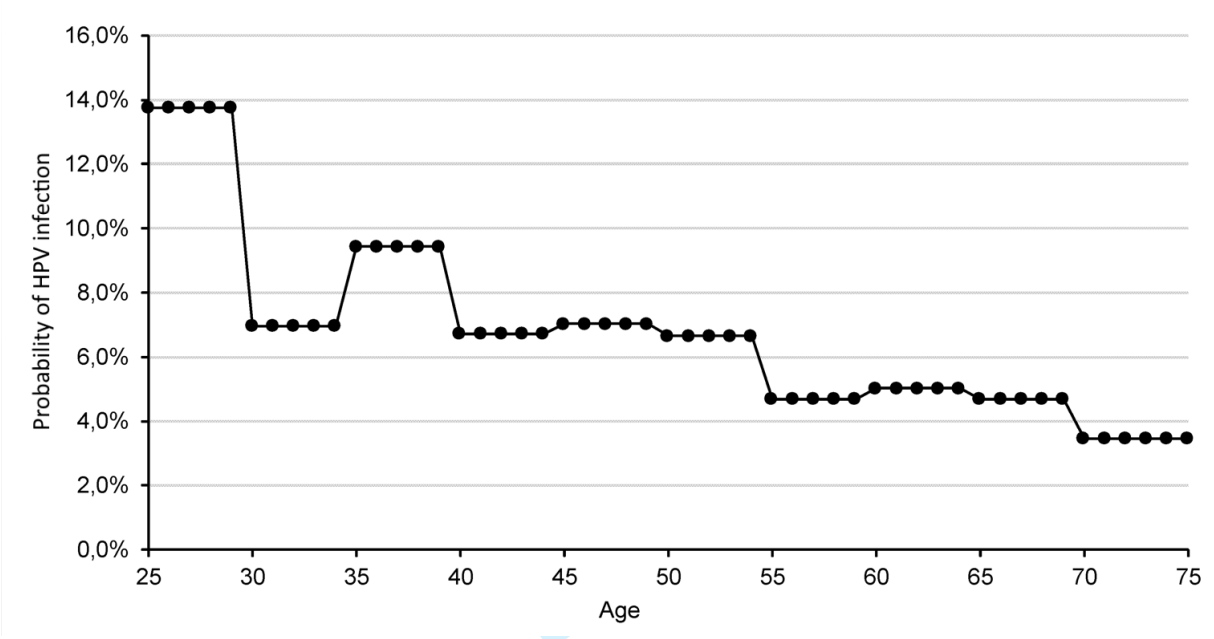
In scenarios based on Pap-test and p16/Ki67, IndScr participation is determined based on the analysis of a sample of the SHI general regimen: at 4 years, 61.9 % of eligible women were found to be participants. At patient generation, a relative risk (RR) of participation is applied to account for the impact of age and universal complementary health insurance (CMU-c). Another analysis of the same dataset provided the observed period between two IndScr (annual to every 10 years, see Supplementary file 3).

Each woman is associated with a SI participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} / RR_{current\ age-group})/5$$

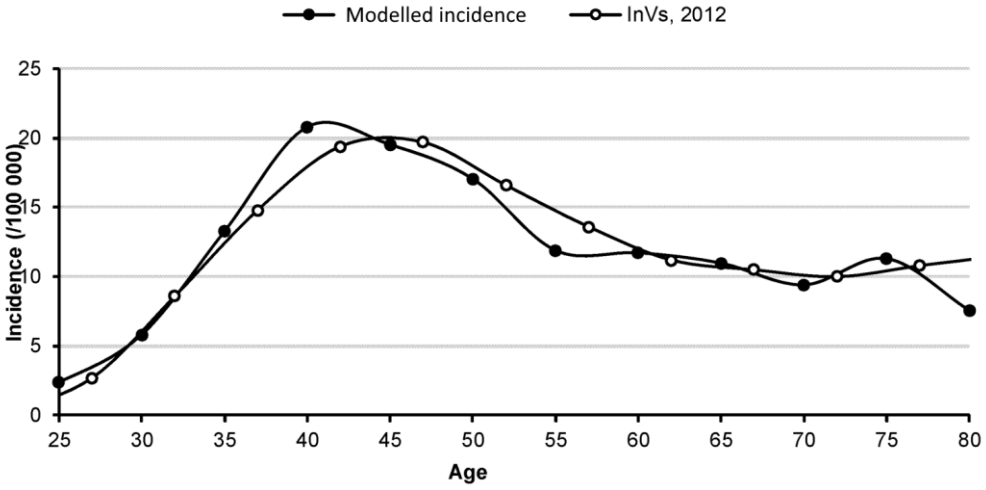
Transition probabilities

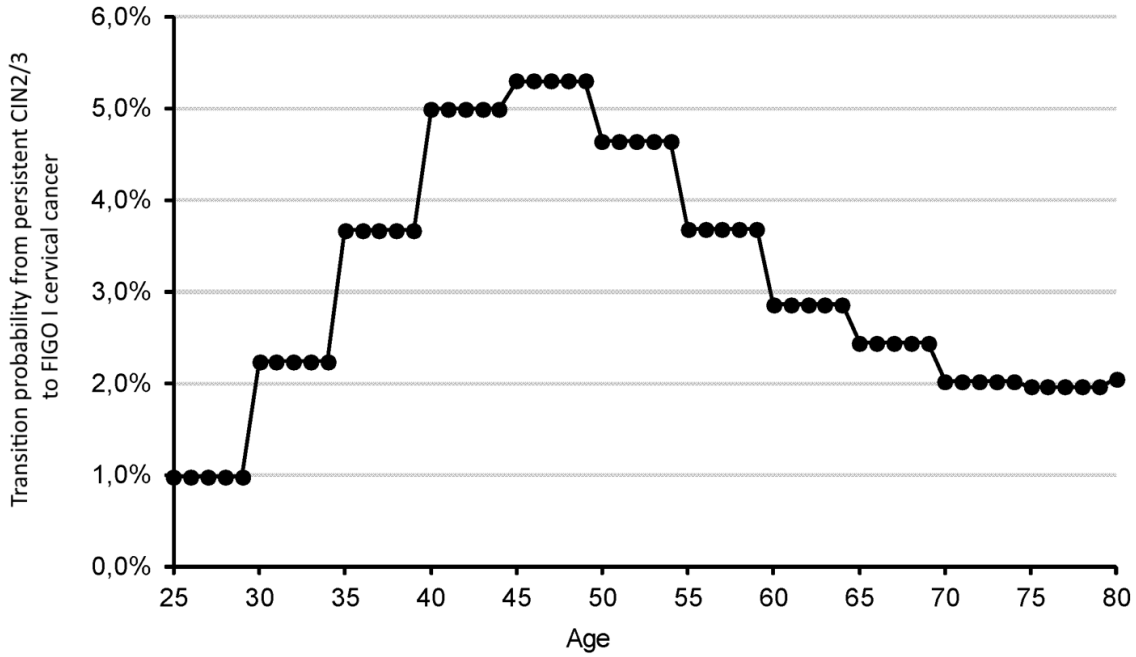
High risk (HR) HPV annual infection rate was estimated to vary from 3.5% and 14% depending on age, in order to fit with the observed HR-HPV prevalence, considering a 50% annual viral clearance rate, according to the model developed by Demarteau *et al.* In younger women, vaccination is modelled through the application of a relative risk of infection taking into account the vaccination rate and decreased infection risk among vaccinated women.



Annual transition probabilities that determine the odds of progression from HPV infection to persistent CIN2/3 precancerous lesion are replicated from the model developed by Demarteau *et al.* and presented in table 2.

Considering the lack of appropriate data, the age-specific progression transition probability of persistent CIN2/3 to FIGO I CC was estimated by calibrating the model to the CC incidence data available. The calibration process consisted in the simulation of a cohort of 14-year-old women, taking the observed IndScr participation rate into account. Transition probabilities were adjusted within a plausible interval in order to duplicate the observed incidence of CC by age. The following figures respectively present the results of the calibration process and the resulting persistent CIN 2/3 to FIGO I CC transition probabilities by age.





Probabilities of cancer progression and symptom emergence were obtained from the natural history of CC simulation model developed by Myers *et al*.

Cancer mortality by cancer grade and time since diagnosis were obtained from the study by Wright *et al.* based on the estimation of survival among 46,932 women with CC diagnosed from 1983-2009 and recorded in the Surveillance, Epidemiology, and End Results (SEER) database. Survival data for white women under 50 were selected, as mortality by causes other than CC seems unlikely in women under 50. General mortality is modelled according to French national statistics office (INSEE) data.

Screening

OS participation rates after receiving an invitation or recall are based on the results of local OS experimentations carried out in different regions. The weighted averages of the participation rate upon receiving a mailed invitation or recall letter by the number of Pap-tests performed during each experimentation were respectively found to be 17.3% and 12.1%. Screening test sensitivity and specificity are given in the following table.

Screening test	Sensitivity	Specificity	Source
Primary Pap-test	70.0 % (57.0 % - 80.0 %)	95.0 % (92.0 % - 97.0 %)	Mustafa (2015)
Confirmation Pap-test after HPV+	85.9 % (76.6 % - 92.1 %)	65.9 % (63.1 % - 68.6 %)	Bergeron (2015)
Primary HPV-test	94.0 % (89.0 % - 97.0 %)	90.0 % (86.0 % - 93.0 %)	Mustafa (2015)
Confirmation HPV-test after Pap+	100.0 % (NR)	61.1 % (NR)	Mayrand (2007)
P16/KI67	86.7 % (81.1 % - 90.9 %)	95.2 % (94.9 % - 95.4 %)	Ikenberg (2013)
Colposcopy	100.0% (NA)	100.0% (NA)	Assumption

At each screening cycle, test performances determine whether women with lesions are screened positive or not depending on their current health state.

Pap-test and p16/Ki67 specificity and specificity are relative to the detection of CIN2/3 and more severe lesions. Women with negative results exit screening, positive results lead to the random draw of an observed lesion type based on the results of the OS experimentation led in the Alsace region (Supplementary file 4).

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The action that follows each type of result is then randomly drawn according to the screening algorithms and the results of the OS experimentation led in Alsace. Based on the probabilities reported in Supplementary file 5, the different types of results can lead to further confirmation tests or conisation. Some women become lost to follow-up and exit screening.

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

In order to take the impact of the screening organization structures into account, OS implementation leads to reduced odds of becoming lost to follow-up after a positive result for both OS and IndScr participants. Based on the Alsace and Indre-et-Loire regional OS experimentation results, a 0.77 RR of becoming lost to follow-up is applied.

Colpscopy is associated with 100% sensitivity and specificity. Therefore, colposcopy results are negative in HPV- and HPV+ women and positive in women with CIN1, CIN2/3 and persistent CIN2/3 lesions. Women with CIN1 proceed to a particular screening algorithm based on recommendations by the French national scientific society of obstetricians and gynaecologists (CNGOF).

HPV-tests and specificity are relative to the detection of HPV+ and more severe lesions. Women with negative results exit screening, positive results lead to a confirmation Pap-test (or p16/Ki67) followed by a colposcopy in case of a new positive result. If negative, a new round of HPV and Pap-tests are performed concomitantly after one year: a positive result for either of them (or both) leads to colposcopy; women with negative-only results exit screening.

Rates of lost to follow-up observed during the START-HPV experimentation (Ardennes region) were used. The lost to follow-up rate after positive confirmation Pap-tests was estimated by subtracting the latter from the average rate of lost to follow-up in HPV+ women observed in the Alsace region OS experimentation (27.7%). Similarly to Pap-based screening, a 0.77 RR of being lost to follow-up is applied in OS-participant women.

Lost to follow-up after	Probability	Source
Positive HPV-test	19,4 %	START-HPV, Ardennes
Positive confirmation pap-test	8,3 %	START-HPV, Ardennes, Alsace OS experimentation

All samples have odds of being unreadable, depending on the nature of the sample. Women with unreadable samples perform a new test.

A 95% efficacy was considered for conisation. Women with successful conisation go back to the HPV- state. In case of failure, women leave screening in their current state.

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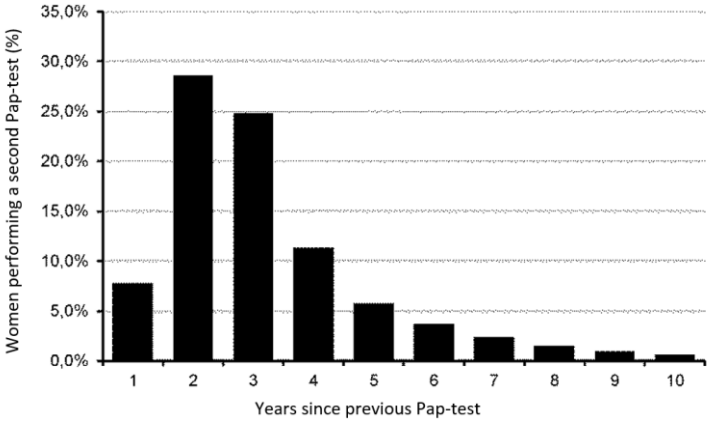
Supplementary File 4 Individual screening participation and periodicity data

Individual screening frequency	Distribution
Annual	5,9%
2 years	21,5%
3 years	18,7%
4 years	8,6%
5 years	4,3%
6 years	2,8%
7 years	1,8%
8 years	1,1%
9 years	0,7%
10 years	0,5%



Population	RR of participating vs. average	Source
Age		
25 – 30	1,06	National health insurance database [3]
30 – 35	1,08	National health insurance database [3]
35 – 40	1,07	National health insurance database [3]
40 – 45	1,04	National health insurance database [3]
50 – 55	0,92	National health insurance database [3]
55 – 60	0,82	National health insurance database [3]
60 – 65	0,77	National health insurance database [3]
Universal complementary health insurance registration		
Yes	0,80	National health insurance database [3]
No	1,03	National health insurance database [3]

Each woman is associated with an IndScr participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} \,/\, RR_{current\ age-group})/5$$

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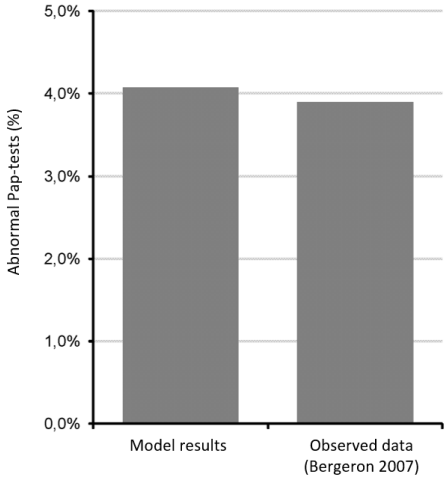
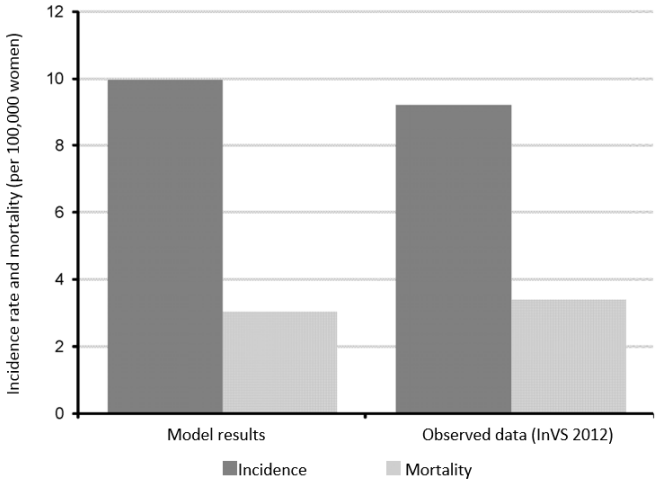
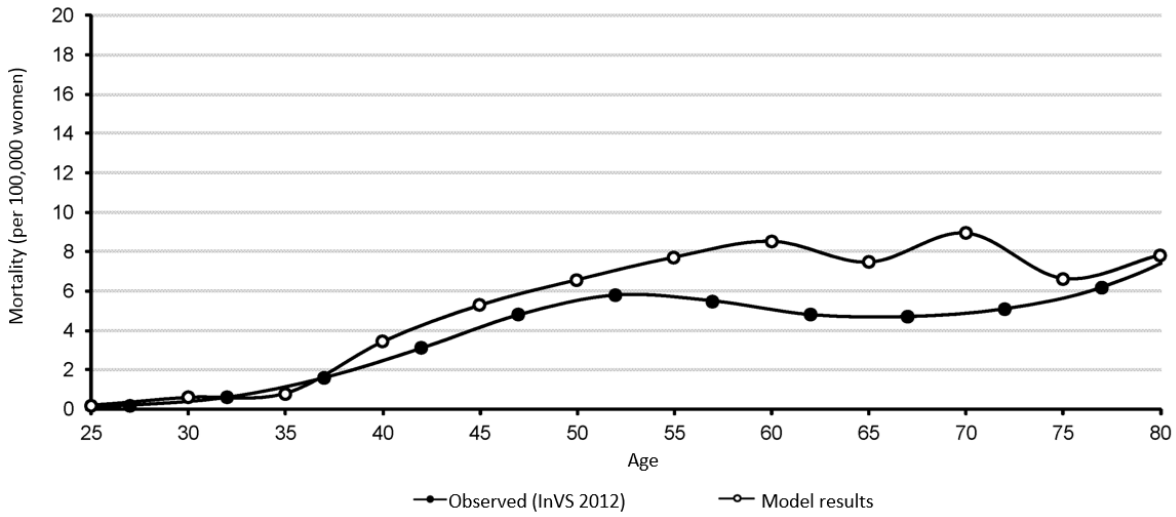
Supplementary File 5 Model validation results

The model faithfully reproduces cancer incidence, however the modelled CC mortality was slightly higher than observed data, although differences were systematically inferior to 4 per 100,000.







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Supplementary File 6 Cost-utility analysis - specific inputs and results

State	Utility/Utility decrement	Source
Age 18-29	0.86	Perneger, 2010
Age 30-39	0.86	
Age 40-49	0.84	
Age 50-59	0.81	
Age 60-69	0.8	
Age 70-79	0.76	
Age 80+	0.74	
Diagnosed CIN1	-0.01	Demarteau, 2011
Diagnosed CIN2/3	-0.01	
Cervical Cancer (1st year)	-0.27	
Cervical Cancer (thereafter)	-0.06	Korfage, 2009

Scénario	QALY	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	16.4	122.6	Reference	Dominated
Pap/Pap-HPV	+9.54	+22.3	23,392	Dominated
Pap/p16Ki67	+11.18	+25.5	22,891	Dominated
HPV/Pap-3y	+14.99	+55.8	37,290	Dominated
HPV/Pap-5y	+14.76	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+9.44	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+17.06	+3.79	2,222	131,965
HPV/p16Ki67-10y	+11.88	-64.6	Dominant	36,468
p16Ki67/p16Ki67	+17.53	+160.7	91,703	3,302,932

*Reference for other scenarios. Extra-QALY per 10,000 women eligible for OS on a lifetime horizon. QALY: Quality Adjusted Life Years

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Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	3
		Present the study question and its relevance for health policy or practice decisions.	3/28 - 29
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Table 2, 6/12 - 18
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6/36 - 37
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Table 1, 4/2 - 20
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5/27 - 28
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9/6 - 7
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	9/6 - 7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6/36 - 7/3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7/2 - 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Figure 1, 5/23 - 26
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 2, 5/29 - 7/3
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	8/6 - 12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2, 6/11 - 7/3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 3 & 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	

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(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Figures 3 & 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Figures 3 & 4; 11/24 - 35
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12 & 13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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Organized screening for cervical cancer in France: a cost-effectiveness assessment

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Word count: 3680

French National Cancer Institute

The French National Cancer Institute was established under the Public Health Act of 9 August 2004 as the government health and science agency specialised in cancer control. It is a Public Interest Grouping which brings together State representatives, charities, health insurance funds, hospital federations and research organisations. It is responsible for rolling out the 2014-2019 Cancer Control Plan and reports to the Ministries for Health and for Research.

The Institute provides an integrated approach encompassing all cancer-control dimensions (health, scientific, social and economic) and areas of intervention (prevention, screening, care and research), for the benefit of patients and their relatives.

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ABSTRACT

OBJECTIVE: According to the third cancer plan, organized screening (OS) of cervical cancer (CC) among women aged 25-65 years should be implemented in France in the forthcoming years. The most efficient way to implement OS in the French health care system is yet to be determined.

METHODS: A microsimulation model was developed adopting a collective "all payers" perspective. A closed cohort of women eligible for CC screening and representative in terms of age and participation in individual screening (IndScr) by annual Papanicolaou (Pap) testing every 3 years was modelled on a lifetime horizon. Different OS strategies, additive to IndScr with a 61.9% participation rate based on mailed invitations to non-participant women to perform OS were assessed. Similar modalities were applied to OS and IndScr participants. Strategies implied different screening tests (Pap-test, HPV-test, and p16/Ki67 double-staining) and OS periodicity.

RESULTS: Compared to IndScr only, all OS strategies were associated with decreased cancer incidence/mortality (from 14.2%/13.5% to 22.9%/25.8%). Most strategies generated extra costs ranging from €37.9 to €1,607 per eligible woman. HPV testing every 10 and 5 years were cost-saving.

HPV tests every 10 and 5 years were the most efficient strategies, generating more survival at lower costs than Pap-based strategies. Compared to IndScr only, an HPV test every 10 years was cost-saving. The most effective strategies were p16/Ki67 as primary or HPV positive confirmation tests, with respective ICERs of €6,541,250 and €101,391 per life year. Pap-based strategies generated intermediary results.

CONCLUSION: OS strategies based on the HPV test appear highly efficient. However, our results rely on the assumption that women and practitioners comply with the recommended OS periodicities (3, 5, 10 years). Implementing these OS modalities will require major adaptations to the current CC screening organization. Pap-test based strategies might be simpler to set-up while preparing an appropriate implementation of more efficient OS screening modalities.

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STRENGTHS AND LIMITATIONS OF THE STUDY

- A microsimulation model was developed to assess the efficiency of possible cervical cancer organized screening strategies in France.
- The model operates on individual women who are eligible for screening and representative of the current French population on a lifetime horizon.
- Real-life practices and data were used, allowing for the fine modelling of the screening and validation against observed data.
- The lack of precision of transition probabilities in the context of a low incidence of cervical cancer, as well as the assumptions required to model screening practices after primary HPV tests, are the main limitations of the study.

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BACKGROUND

The natural history of cervical cancer (CC) is related to a persistent HPV infection of the cervix leading to squamous intraepithelial lesions that can evolve into cancerous lesions. CC prevention is based on screening to detect and remove lesions at the early stages to prevent invasive cancer and an anti-HPV vaccination to reduce cancer-associated HPV infection.[1]

In France, CC prevention is based on individual voluntary screening (IndScr) for CC of women aged 25 to 65 years and vaccination. IndScr is based on a Papanicolaou test (Pap test) every 3 years, after two annual Pap tests that are negative. Approximately 90% of Pap smears are done by gynaecologists, although general practitioners (GP) and midwives are also authorized to perform it. IndScr has led to a significant decrease in the incidence and associated mortality of CC in the past 20 years. In 2012, CC was the 11th most frequent and 12th most lethal form of cancer in women.[2] However, many women still do not participate in CC screening. Participation in IndScr was found to be approximately 61% of eligible women, with low access to healthcare, comorbidities and poverty being risk factors for non-participation.

Screening remains the main prevention tool in France, as anti-HPV vaccination is restricted to younger age groups and was only recently made available. Furthermore, vaccination has had a slow adoption in the French population. In 2015, it was estimated that only 17% of women eligible for vaccination were vaccinated.[3;4] In 2014, the third French Cancer Plan has been presented to address both the human and the societal challenges of cancer. CC organized screening (OS) implementation among women aged 25-65 years is part of its first operational objective and aims at a participation rate of 80% and a 30% reduction in CC-related mortality by 2019.[5]

Several OS experimentations have been performed in France to assess the efficacy of different screening modalities, including invitation and positive tests follow-up (FU), self-sampling and HPV-testing. Experimentations that consisted of an invitation of non-participants to perform a Pap test allowed to catch up with 13.2% of all eligible women after 3 years and reduced the lost to follow-up (LtFU) rates of women after a positive result.[6] Additionally, primary HPV-testing and self-sampling were shown to be a feasible alternative to the Pap smear in France.[7;8] Finally, innovative testing, such as p16/Ki67 double-staining, was shown to be a performant alternative for CC screening compared to HPV screening or the Pap test.[9]

Consequently, many alternative strategies can be considered for the implementation of OS for CC in France. Thus, a medico-economic evaluation of several OS strategies based on a cost-effectiveness analysis was performed by the French national cancer institute (INCa), which relied on a scientific steering committee that involved clinical experts and stakeholder representatives (social security, ministry of health, patients and professionals) providing advice on the methodological choices and best OS implementation modality in the French context.

In order to assist decision-making regarding the implementation of CC OS, our study's main outcomes correspond to the objectives of CC OS implementation: participation rate, survival and avoided CC. A cost-utility analysis was performed as well.

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METHODS

Seven strategies were compared to the current IndScr-only situation (table 1). These strategies were all based on adding to the current IndScr with the dispatch of screening invitations (followed by a single recall) to women who did not spontaneously participate in the last 3 years (non-participants). Hence, women who did not participate in regular screening are the only ones targeted by the interventions. OS strategies also included improved FU, resulting in a reduction in LtFU women.

Different screening tests were considered for primary screening or confirmation after a positive primary test, including Pap test, HPV DNA detection and p16/Ki67 double-staining. The women who tested positive for both primary and confirmation tests went through colposcopy and conization if a high-grade (grade 2 or worse [CIN2+]) cervical intraepithelial neoplasia (CIN) lesion was identified. Women with CIN1 were retested at 12, 18 and 24 months if the initial lesion was atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) on Pap, or went through colposcopy. The women who tested positive for a primary test and negative for confirmation were retested after one year. A fraction of the participants was LtFU. Women could only be invited once per cycle. Detailed screening algorithms are available in supplementary file 1.

The population was limited to women aged 25-65 years who are currently eligible for IndScr.

Table 1 Strategies compared

Strategy	IR + Improved Follow-up	Primary test	Confirmation test after positive primary test
Current	No	Pap-test / 3 years	Pap-test or HPV
Pap/Pap	Yes	Pap-test / 3 years	Pap-test
Pap/p16Ki67	Yes	Pap-test / 3 years	p16/Ki67
HPV/Pap-5y†	Yes	HPV / 5 years	Pap-test
HPV/Pap-3y†	Yes	HPV / 3 years	Pap-test
HPV/Pap-10y†	Yes	HPV / 10 years	Pap-test
HPV/p16Ki67-5y†	Yes	HPV / 5 years	p16/Ki67
HPV/p16Ki67-10y†	Yes	HPV / 10 years	p16/Ki67
p16Ki67/p16Ki67	Yes	HPV / 3 years	p16/Ki67

IR: invitation + recall for woman who did not participate in IndScr in the last 3 years (non-participant)

†: women 25-35 are not eligible for HPV screening and receive a Pap-test every 3y instead. Women who tested HPV+/confirmation- go through double testing (HPV + Pap) the following year.

MODEL STRUCTURE

Given the complexity of screening algorithms (different testing/retesting frequencies) and interactions between participation rates and individual characteristics (age and social), a Markov state microsimulation model was developed. Considering the relatively slow progression of intraepithelial lesions and the long-term benefits of screening, a 1-year cycle-length was used. The model was adapted from a previously published cohort-based Markov model.[10] A cohort of 100,000 women was simulated. Due to the long-term development of the disease and its consequences, a lifetime horizon was applied.

The model first generates a woman with a randomly attributed age, IndScr participation and frequency, health state (HPV-, HPV+, CIN lesions or cancer) and vaccination attributes. At each cycle, women can progress through states that correspond to CC natural history: non-infected women can get an HPV infection according to an age- and vaccination-dependent risk. The infection can progress to CIN1, then CIN2/3 and finally FIGO 1 (Federation of Gynecology and Obstetrics) classified non-invasive cancer. HPV infection and CIN lesions can regress spontaneously until CIN2/3 lesions have become persistent (pCIN2/3). Women in the pCIN2/3 state systematically progress to cancer at an

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age-dependant rate. FIGO1 lesions can progress to FIGO 2, 3 and 4 and become symptomatic. Once symptomatic, the lesion is treated and the woman remains in the corresponding treated state with an associated cancer mortality rate. An age-specific general mortality applies at any state.

Each year, the model determines whether the woman undergoes screening individually or after invitation based on her participation periodicity, time since last screening and participation rates after invitation. Invitations are sent to non-participant women in the manner of prevention campaigns, following the screening recommended frequency (i.e. 3 years in the case of Pap/Pap). Therefore, only a fraction of non-participant women are invited every year. The same primary screening modality is applied to OS and IndScr participants. Screening test results (positivity and lesion type for Pap tests and positivity for HPV and p16/Ki67) are determined based on the current state and type of test performed (supplementary file 2). After diagnosis, women with a non-cancerous lesion return to the non-infected state after conization and cancerous lesions are treated. The structure of the modelled natural history is presented in figure 1. More details on the model structure are given in the supplementary file 3.

INPUT DATA

The input data used in the simulation are presented in table 2.

The population characteristics are based on available epidemiologic and demographic data that are representative of the French population. Vaccination status is only determined in women ≤30 years old, as it was only recently available in France. IndScr participation and frequency depend on age and social status, and based on the national health insurance database (supplementary file 4), approximately 61.9 % of eligible women were found to participate in IndScr at a frequency ≤4 years.[3] Distribution of each modelled health state by age was not available in France and was estimated by simulating a cohort of non-vaccinated 14-year-old women undergoing current IndScr-only screening over their lifetime (supplementary file 3).

Transition probabilities (TP) were based on a previously published model.[10] The HPV infection and pCIN2/3 to cancer progression probabilities were calibrated using the model to reproduce observed HPV and cancer prevalence by age.[1;11] The high-risk HPV annual infection rate was estimated to be 3.5% to 14%, depending on age.[12] The impact of vaccination is simulated by applying a relative risk (RR) of infection.[1]

Probabilities of cancer progression and emergence of symptoms were obtained from the CC natural history simulation model developed by Myers *et al*.[13] The cancer specific-mortality by grade and time since diagnosis was estimated from SEER using data for white women under 50, as it was assumed that non-specific mortality was low in this group.[14] General mortality was modelled according to the French national statistics office (INSEE) data.

The participation rates after invitation and recall, LtFU rate associated with IndScr, OS effect on LtFU (RR=0.88), observed lesions on Pap smear and associated care were all based on observational data from French OS experimentations.[1]

The sensitivity and specificity of screening tests were based on clinical studies for detecting CIN2/3 lesions and took into account the test sequence (i.e., HPV after Pap or primary HPV).[9;15-17] One percent of Pap tests were non-interpretable, which led to a retest.[18] Colposcopy was assumed to have 100% sensitivity and specificity. A 95% efficacy was considered for conization.

The model estimated OS cost and direct medical costs from a collective, “all payers” perspective, as recommended for France.[19] The OS costs covered invitations and recalls, as well as database

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management, tracking of women's participation and FU management. Cost data for consultations and medical care were based on national tariffs. No extra-consultation costs were added, as it was considered that IndScr participants did so during a routine consultation. The HPV-analysis tariff was decreased by 60% in strategies with primary HPV-testing, assuming a substantial cost reduction in cases of an adoption of HPV-testing based OS. This assumption was validated by health insurance and health ministry representatives. According to public-health law, no extra co-payment is applied to OS participants. Cancer states were associated with costs accounting for care and FU by FIGO stage [12] when entering the corresponding diagnosed state. All costs were updated to 2016, using the national consumer price index for healthcare goods and services.

Table 2 Input data

Parameter	Value	Distribution	Source
Demographic			
Age	25 - 65 Based on distribution	NA	National Statistics (INSEE)
CMU-c Eligibility (social status)	12.2 % (9.8% - 14.6%)	Normal	National Health Insurance Data
IndScr participation periodicity	Based on frequency distribution, age and social	Uniform	National Health Insurance Data
Initial Health State	Based on distribution	NA	Based on model prediction for a cohort of 14-year-old women
Transition probabilities			
HR-HPV infection	0.03 – 0.15 (0.03 – 0.18) Based on distribution	Beta	Estimated to reproduce known prevalence by age [12]
HPV-infection regression	0.50 (0.40 – 0.60)	Beta	Riethmuller et al. (1999)[19], Clavel et al. (2001)[20], Boulanger et al. (2004)[21], Beby-Defaux et al. (2004)[22], Dalstein et al. (2004)[23]
HR-HPV Infection → CIN 1	0.05 (0.04 – 0.06)	Beta	Moscicki et coll. (2001)[24]
CIN1 Regression	0.50 (0.40 – 0.60)	Beta	Melnikow et coll. (1998)[25], Nobbenhuis et coll. (2001)[26], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN1 → CIN 2/3	0.12 (0.10 – 0.14)	Beta	Melnikow et coll. (1998)[25], Sanders and Taira (2003)[27], Van De Velde et coll. (2007)[28]
CIN2/3 Regression	0.28 (0.22 – 0.33)	Beta	Melnikow et coll. (1998)[25]
CIN2/3 → pCIN 2/3	0.13 (0.10 – 0.15)	Beta	Melnikow et coll. (1998)[25]
Persistent CIN 2/3 → FIGO I	0.01 – 0.05 (0.01 – 0.06) Based on distribution	Beta	Estimated to reproduce known prevalence by age[1.11]
FIGO I → FIGO II	0.20 (0.16 – 0.24)	Beta	Myers *et al.* 2000[13]
FIGO II → FIGO III	0.26 (0.21 – 0.31)	Beta	Myers *et al.* 2000[13]
FIGO III → FIGO IV	0.36 (0.29 – 0.43)	Beta	Myers *et al.* 2000[13]
FIGO I → Symptomatic FIGO I	0.15 (0.12 – 0.18)	Beta	Myers *et al.* 2000[13]
FIGO II → Symptomatic FIGO II	0.23 (0.18 – 0.27)	Beta	Myers *et al.* 2000[13]
FIGO III → Symptomatic FIGO III	0.60 (0.48 – 0.71)	Beta	Myers *et al.* 2000[13]
FIGO VI → Symptomatic FIGO IV	0.90 (0.67 - 1.00)	Beta	Myers *et al.* 2000[13]
1-year Cancer Survival	0.43 – 0.98 (0.23 – 0.99) By stage	Beta	SEER[14]
5-year Cancer Survival	0.14 – 0.94 (0.06 – 0.97) By stage	Beta	SEER[14]
10-year Cancer Survival	0.05 – 0.93 (0.01 – 0.96) By stage	Beta	SEER[14]
Screening			
Participation after invitation	17.3% (10.0% - 24.0%)	Uniform	Hamers *et al.* 2014[6]
Participation after recall	12.1% (5.0% - 18.0%)	Uniform	Hamers *et al.* 2014[6]
Lost to follow-up with IndScr	Based on lesion on Pap. Average 27.7%	NA	Hamers *et al.* 2014[6]

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Reduction in lost to follow-up with OS	0.77 (0.08 – 0.77)	Uniform	OS experimentations, INCA personal communication
Lesions on PAP	Distribution	NA	Hamers *et al.* 2014[6]
Care per lesion	Distribution	NA	Hamers *et al.* 2014[6]
Primary Pap-test (Se)	70.0 % (57.0 % - 80.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Se)	85.9 % (76.6 % - 92.1 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Se)	94.0 % (89.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Se)	100.0 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Se)	86.7 % (81.1 % - 90.9 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Se)	100.0% (NA)	NA	Assumption
Primary Pap-test (Sp)	95.0 % (92.0 % - 97.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation Pap-test after HPV+ (Sp)	65.9 % (63.1 % - 68.6 %)	Beta	Bergeron *et al.* (2015)[9]
Primary HPV-test (Sp)	90.0 % (86.0 % - 93.0 %)	Beta	Mustafa *et al.* (2015)[15]
Confirmation HPV-test after Pap+ (Sp)	61.1 % (NR)	NA	Mayrand *et al.* (2007)[17]
p16/KI67 (Sp)	95.2 % (94.9 % - 95.4 %)	Beta	Ikenberg *et al.* (2013)[16]
Colposcopy (Sp)	100.0% (NA)	NA	Assumption
Conisation efficacy	95.0%	NA	Assumption
Non-interpretable tests	1.0% (1.0% - 3.0%)	Uniform	Hamers *et al.* 2014[6]
Costs (€)			
Pap-test (IndScr)	47.78 (38.88 – 57.59)	Gamma	National tariffs
Pap-test (OS)	49.62 (40.37 – 59.81)	Gamma	National tariffs
p16/Ki67 (IndScr)	86.77 (70.60 - 104.58)	Gamma	National tariffs
p16/Ki67 (OS)	88.61 (72.09 - 106.80)	Gamma	National tariffs
HPV-test (IndScr)	47.70 (75.48 - 97.17)	Gamma	National tariffs
HPV-test (OS)	49.54 (49.54 - 71.24)	Gamma	National tariffs
Confirmation Pap-test (IndScr)	78.17 (63.60 - 94.21)	Gamma	National tariffs
Confirmation Pap-test (OS)	49.63 (40.38 - 59.82)	Gamma	National tariffs
Confirmation p16/Ki67 (IndScr)	116.77 (78.09 - 99.57)	Gamma	National tariffs
Confirmation p16/Ki67 (OS)	88.23 (71.79 - 106.34)	Gamma	National tariffs
Confirmation HPV-test (IndScr)	78.09 (63.53 - 94.12)	Gamma	National tariffs
Confirmation HPV-test (OS)	49.55 (49.55 - 71.03)	Gamma	National tariffs
Colposcopy	49.82 (40.54 - 60.05)	Gamma	National tariffs
Conization	93.42 (76.01 - 112.60)	Gamma	National tariffs
FIGO I CC treatment	1041.95 (847.77 - 1255.85)	Gamma	Dervaux *et al.* 2007[12]
FIGO II CC treatment	1818.86 (1479.90 - 2192.25)	Gamma	Dervaux *et al.* 2007[12]
FIGO III CC treatment	25817.84 (21006.43 - 31117.97)	Gamma	Dervaux *et al.* 2007[12]
FIGO IV CC treatment	30582.83 (24883.41 - 36861.16)	Gamma	Dervaux *et al.* 2007[12]
Database management + Invitation dispatch	7.00 (4.00 – 11.00)	Gamma	Cost of invitation to colorectal OS (Heath Ministry data, personal communication)
Recall dispatch	0.40 (0.40 – 3.25)	Gamma	50% postal charges

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VALIDATION

The model results were compared to observed epidemiological data for validation. The model faithfully reproduces cancer incidence and CC mortality in France.[12] Results of the model validation are available in supplementary file 5.

COST-EFFECTIVENESS ANALYSES

Incremental cost–effectiveness ratios (ICER) were calculated for the life expectancy. Costs and survival were discounted at 4% per year, according to French guidelines for cost-effectiveness studies.[18]

Several alternative scenarios were tested, including not applying the efficacy of OS on LtFU rate, not considering a reduction in HPV cost, and assuming a 60% reduction in p16/Ki67 cost.

The robustness of the model was tested using deterministic sensitivity analysis (DSA). In the DSA, all of the parameters were tested at their confidence intervals (or at ±20% of the baseline value when the confidence intervals were not available).

RESULTS

Compared with the current situation, invitation and recall of non-participant women led to an increase from 61.9% to 65.5% in the 4-year participation rate. Every strategy that was tested was associated with a reduction in cancer incidence/mortality, ranging from -14.2%/-13.5% for the Pap/Pap strategy to -22.9%/-25.8% for the HPV/p16Ki67-5y strategy. The undiscounted results are presented in table 3.

Table 3 Undiscounted results

	Outcomes		Costs (€) per woman			
Scenario	Cancer	Cancer mortality	OS organisation	Screening	CC care & conizations	Total
IndScr only*	34	13	0	294.2	30.9	325.0
Pap/Pap	-14.2%	-13.5%	+19.57	+13.32	-3.92	+28.97
Pap/p16Ki67	-16.6%	-15.9%	+19.57	+18.46	-4.57	+33.46
HPV/Pap-3y	-21.1%	-22.4%	+15.16	+99.87	-7.31	+107.73
HPV/Pap-5y	-18.9%	-22.5%	+15.12	-29.79	-7.24	-21.91
HPV/Pap-10y	-8.0%	-13.6%	+14.94	-14.42	-0.48	-134.04
HPV/p16Ki67-5y	-22.9%	-25.8%	+15.10	+1.57	-0.81	+8.55
HPV/p16Ki67-10y	-11.9%	-17.0%	+14.93	-129.7	-5.87	-120.63
p16Ki67/p16Ki67	-24.3%	-24.4%	+19.57	+233.30	-6.87	+246.00

*Reference for other scenarios. Cumulated incidence and mortality for 10,000 women eligible for OS on a lifetime horizon.

The average undiscounted cost of screening for the modelled population over a lifetime was €325 per eligible woman, most of which was imputable to screening (€294). Strategies based on HPV-testing with 5-year and 10-year frequencies were cost-saving (-€22 and -€134 per woman, respectively), despite the additional cost of OS (€15). Other strategies were responsible for extra costs, ranging from €29 to €33 for Pap-based screening to €108 for HPV/Pap-3y and €246 for p16Ki67/p16Ki67.

Although it was the cheapest strategy (€191 per eligible woman), HPV/Pap-10y was the strategy with the smallest cancer reduction (-11.9%), as opposed to p16Ki67/p16Ki67, which led to a 25% reduction in CC while being the most expensive strategy (€571 per eligible woman). Figure 2 presents the mean cost per woman and cancer reduction rate for each strategy.

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Discounted survival is consistent with CC incidence and mortality (table 4). Compared to the current situation (19.4 LY survival), OS strategies led to an increase in survival, ranging from 10 years per 10,000 women for the Pap/Pap and HPV/Pap-10y strategies to 18 years per 10,000 women for the HPV/p16Ki67 and p16Ki67/p16Ki67 strategies. Discounted extra costs per 10,000 eligible women ranged from €38,000 (HPV/Pap-5y) to €1,608,000 (p16Ki67/p16Ki67). HPV/Pap-5y and HPV/Pap-10y remained cost-saving after discounting. Hence, these strategies were more effective and more cost-saving than Pap-based strategies, including the current situation, and were the dominant OS strategies. HPV/p16Ki67-5y and p16Ki67/p16Ki67 were more effective than HPV/Pap-5y and HPV/Pap-10y with ICERs of €101,391 and €6,541,250 per LY, respectively. HPV/Pap-3y was as effective as HPV/Pap-5y but less effective than HPV/p16Ki67-5y while generating much more expenses.

Table 4 Discounted results

Scenario	Survival (LY)	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	19.4	122.6	Reference	Dominated
Pap/Pap-HPV	+10.04	+22.3	22,234	Dominated
Pap/p16Ki67	+11.68	+25.5	21,918	Dominated
HPV/Pap-3y	+15.93	+55.8	35,095	Dominated
HPV/Pap-5y	+15.89	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+10.51	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+18.13	+3.79	2,091	101,389
HPV/p16Ki67-10y	+13.00	-64.6	Dominant	35,846
p16Ki67/p16Ki67	+18.37	+160.7	87,546	6,592,441

*Reference for other scenarios. Extra-survival per 10,000 women eligible for OS on a lifetime horizon. LY: Life Years

Regardless of the modality, implementing an OS programme for cervical cancer in France led to an overall improvement in the CC screening rate and a reduction in CC incidence and mortality. Reducing LtFU rates and improving screening rates with invitations/recall as in the Pap/Pap scenario results in an ICER of €22,231 per LY and an average extra survival of 10 LY per 10,000 eligible women.

Switching primary screening from the Pap-test to HPV-testing led to similar LY gains with a 10-year screening frequency, yet the 5-year frequency led to a longer survival (15.89 vs. 10.51 LY per 10,000 eligible women). Furthermore, reducing the frequency of primary testing was cost-saving, even at the current cost of HPV-testing. Despite the longer interval between the two screening tests, HPV-based strategies remained effective because of their superior sensitivity compared to the Pap-test.

The very good sensitivity/specificity of p16/Ki67 double-staining used as a primary screening test led to significant survival gains compared to the current situation and HPV-testing (+18.37 and +2.48 per 10,000 eligible women, respectively). However, its high cost made it inefficient, with an ICER of €6,592,441/LY.

Switching the Pap test with p16/Ki67 double-staining in the confirmation of positive Pap and HPV primary tests increased efficacy and led to moderate additional costs. The confirmation of HPV tests every 10 years increased the survival from +10.51 to +13.0 LY and the costs from -€734,000 to -€646,000 per 10,000 eligible women. Thus, the HPV/p16Ki67-10y scenario was associated with an ICER of €35,846/LY. The cost-utility results do not lead to different conclusions. A cost-utility analysis was performed by applying specific health utilities to the health states and utility decrements to non-cancerous and cancerous states. Its results and the utility values used are available in a supplementary file 6.

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SENSITIVITY AND SCENARIO ANALYSES

Deterministic sensitivity analysis and scenario analyses for HPV/Pap-10y versus the current situation for LY and costs are shown in figure 3 and figure 4, respectively.

The parameters with the biggest impact were the cost of testing (HPV and Pap) and OS effect on LtFU rate after a positive result. However, HPV/Pap-10y systematically remained the most cost-effective alternative. The mean age of the cohort impacted results drastically, despite HPV screening being less beneficial in women under 30 years old and over 50 years old than in the rest of the eligible population. Vaccination rates up to 80% had a negligible impact. Similar results were seen for HPV/Pap-5y and HPV/p16Ki67-5y scenarios. Not taking into account the effect of OS on LtFU rate did not change the conclusion, although it significantly reduced the LY gains compared to in the IndScr only. Similarly, not considering a reduction in the cost of the HPV test led to similar conclusions: HPV/Pap-10y and HPV/Pap-5y remained less costly than the alternative strategies. Finally, a 60% reduction in p16/Ki67 cost led to a decreased total cost of €41.05 (-75%) for the p16Ki67/p16Ki67 scenario.

DISCUSSION

Using a validated microsimulation model that allows for the fine modelling of screening modalities, we showed that the OS programme for cervical cancer in France leads to a reduction of CC incidence and mortality. HPV-based screening with 5- or 10-year frequencies would be cost-saving, and other modalities would generate extra costs ranging between €37.9 and €1,607 per woman.

Most model inputs were based on observed “real-life” data instead of simple screening guidelines. This allows for an accurate simulation of women’s screening behaviour by considering that many women do not comply with the recommended screening frequency and that older women tend to drop out of screening.[3] This also allowed for the implementation of current professional practices that significantly differ from recommended screening algorithms: in the current IndScr only situation, after a positive Pap test, not all women proceed to confirmation (Pap or HPV test), as some directly undergo colposcopy or conization, depending on the identified lesion with a significant impact on IndScr efficiency. Finally, the model incorporates LtFU rates, which proved to be a key factor in OS efficacy, particularly when screening frequency was superior to 5 years.[6]

The model’s main limitations stem from the estimation of the transition probabilities (TP). An initial literature review showed important variations between sources with some TP being not available. Additionally, the identified TP were not precise enough given the low incidence of lesions in the general population of women (1 in 10,000). Thus, we favoured sources that had previously been used in French models to allow comparability with previously published results.[10.12] Additionally, the model was calibrated on available prevalence data in France and externally validated. Furthermore, the sensitivity analyses showed that, despite the uncertainty, TP variations had a limited impact on the results, which reinforces our confidence in the estimations. Finally, our results are comparable to previously published European studies: Accetta *et al.* have found that an HPV test every 5 years is more effective and less costly than triennial Pap-tests in Italy.[29] The decreased efficiency of CC screening based on the HPVtest at lower frequencies was shown by Berkhof *et al.* in the Netherlands.[30] In Norway, Burger *et al.* found results comparable to ours for the Pap/Pap strategy.[31]

In our analysis, HPV/Pap-10y was the most efficient strategy, with HPV/p16Ki67-10y being a more cost-effective alternative. However, the final modality choice for OS-implementation will need to consider several factors. First, the HPV/Pap-10y strategy, albeit the most efficient, is the less effective strategy in terms of cancer incidence and prevalence reduction, conflicting with the primary

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aim of the Cancer Plan to further reduce the CC burden in France [5] and thus making the HPV/Pap-5y a more suitable, cost-saving modality. Second, current screening behaviours in France result in over-participation, with numerous women performing Pap-tests more often than is recommended. This phenomenon is likely to be related to the yearly recommended consultation with a gynaecologist. Our results showed that going from a 5-year frequency to a 3-year frequency implies a huge increase in screening cost (from -€133,000 to +€558,000 per 10,000 eligible women) for a very small increase in survival (from 15.89 to 15.93). Indeed, HPV-testing is sensitive, but it has a low specificity and cervical lesion evolution is slow, with most lesions regressing spontaneously. Women's over-participation will thus be a challenge in the case of HPV-based OS implementation. This should be addressed beforehand, or these apparent efficient strategies would be poorly efficient, leading to frequent false-positive results and related unnecessary and potentially harmful testing. Third, HPV-testing is not recommended in women under 35 years of age, which would require a complex double screening system. Finally, the current screening organization in France is based on the Pap-test, which implies a different infrastructure. Switching to HPV would require the negotiation of HPV-test tariffs, the development of a quality assurance protocol to ensure a sensitivity that is consistent with those found during clinical studies, as well as the development of the required infrastructure and equipment. Thus, although primary HPV-testing produces results with a better efficiency, many challenges will need to be addressed before its implementation. In the meantime, switching to a Pap-test based OS remains an acceptable alternative and could lead the way to HPV-testing deployment.

As for p16/KI67 double-staining, our results show that it would be an efficient confirmation test or primary test with negotiated tariffs. However, the sensitivity and specificity of the test were based on a single study with centralized reading. Additional studies in different French settings would be required to confirm that the results are reproducible before generalization.

Lastly, we do not present our results relatively to a willingness-to-pay threshold. This choice results from the fact that no cost-effectiveness threshold is relevant in France, since the national agency in charge of health technology assessment, including pharmacoeconomic evaluation (HAS) does not wish cost-effectiveness results to be compared to a threshold. Indeed, cost-effectiveness analyses are not used as a resource allocation tool for health technologies in France. Furthermore, since implementation of CC OS was decided, we did not aim to assess whether and how OS was efficient, but to determine which screening modality was the most efficient, keeping in mind practical issues. We feel that this choice is further reinforced by our results that confirm the legislator's decision to implement OS. In summary, this modelling study enabled the INCa to provide robust information to support a public decision on both efficient intermediate modalities for implementation of the CC OS programme and also on optimal screening strategies in a longer term and to anticipate the integration of promising technological innovations.

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Declaration of interests

The authors have no conflict of interest to declare concerning this study.

Authorship Statement

All authors participated in the study. Barré S, Leleu H and Massetti M participated in model development, data analysis and drafting of the manuscript. Barré S and De Bels F made critical review of the manuscript and approved its final version.

Data Sharing

No additional data available.

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Figure Legends

Figure 1: Structure of the model for the natural history of cervical cancer

Figure 2: Results of OS strategies assessed on cancer reduction rate and associated mean cost

Figure 3: Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

Figure 4: Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

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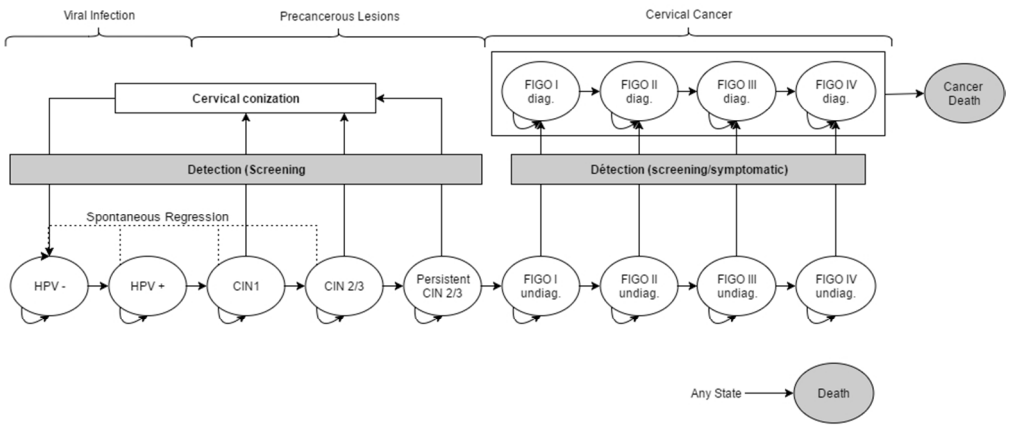

Structure of the model for the natural history of cervical cancer

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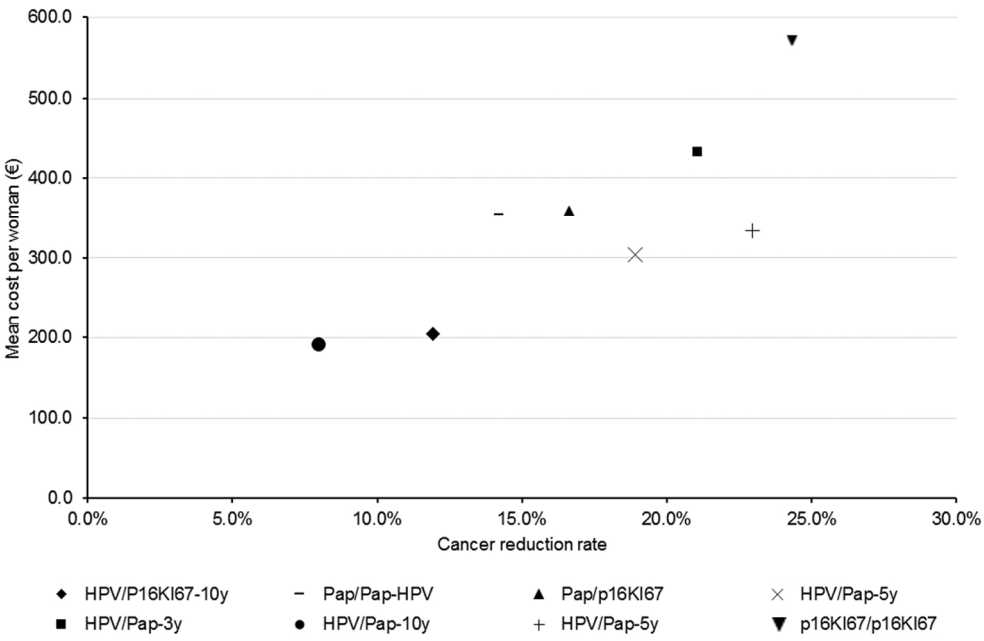

Results of OS strategies assessed on cancer reduction rate and associated mean cost

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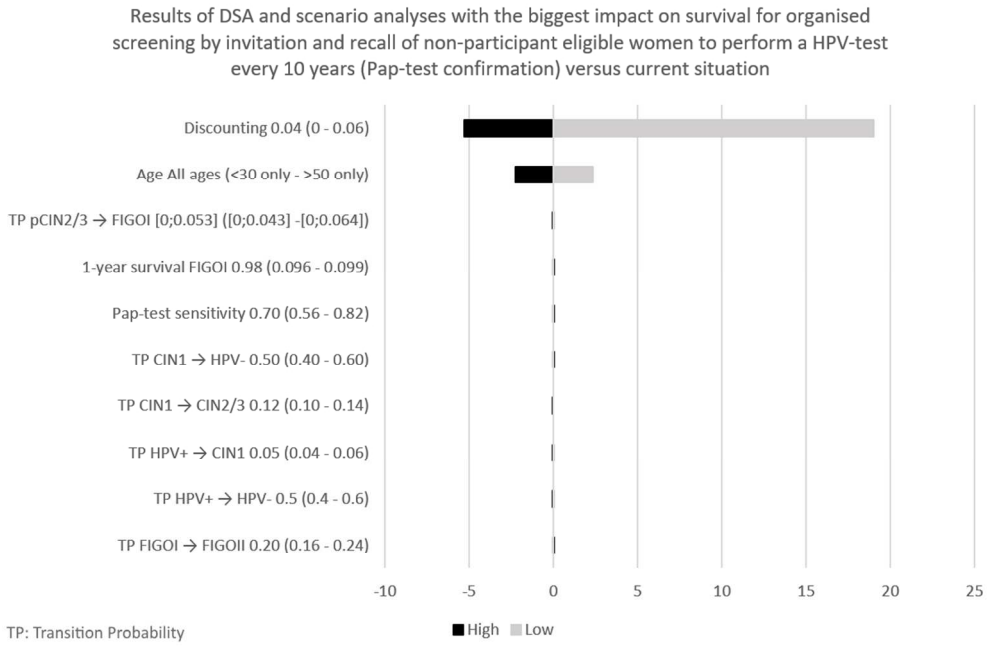

Tornado diagram of DSA and scenario analyses with the biggest impact on survival for HPV/Pap-10y versus current situation

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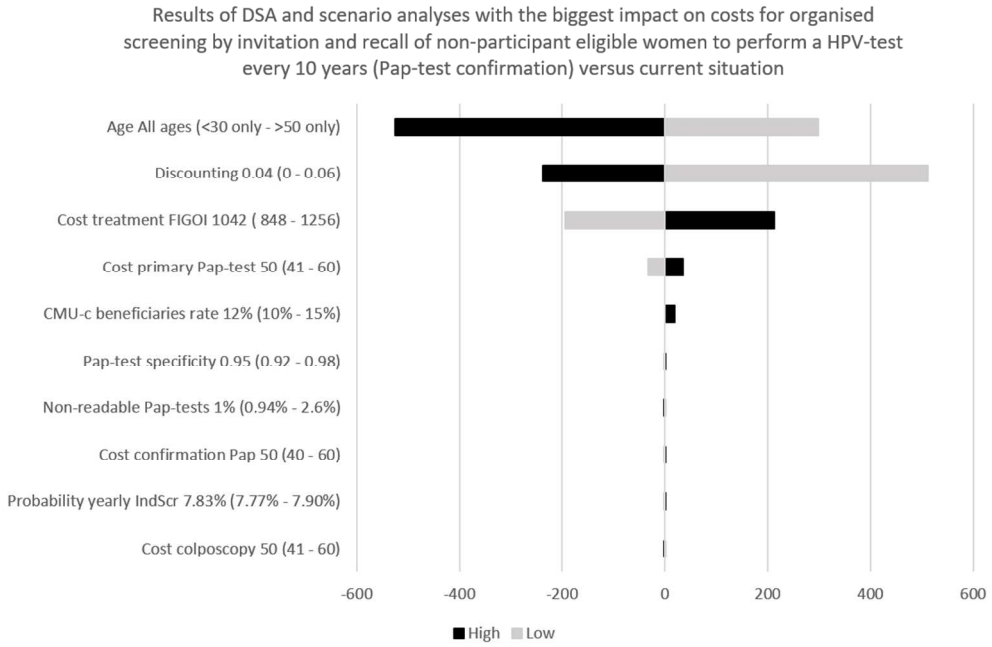

Tornado diagram of DSA and scenario analyses with the biggest impact on costs for HPV/Pap-10y versus current situation

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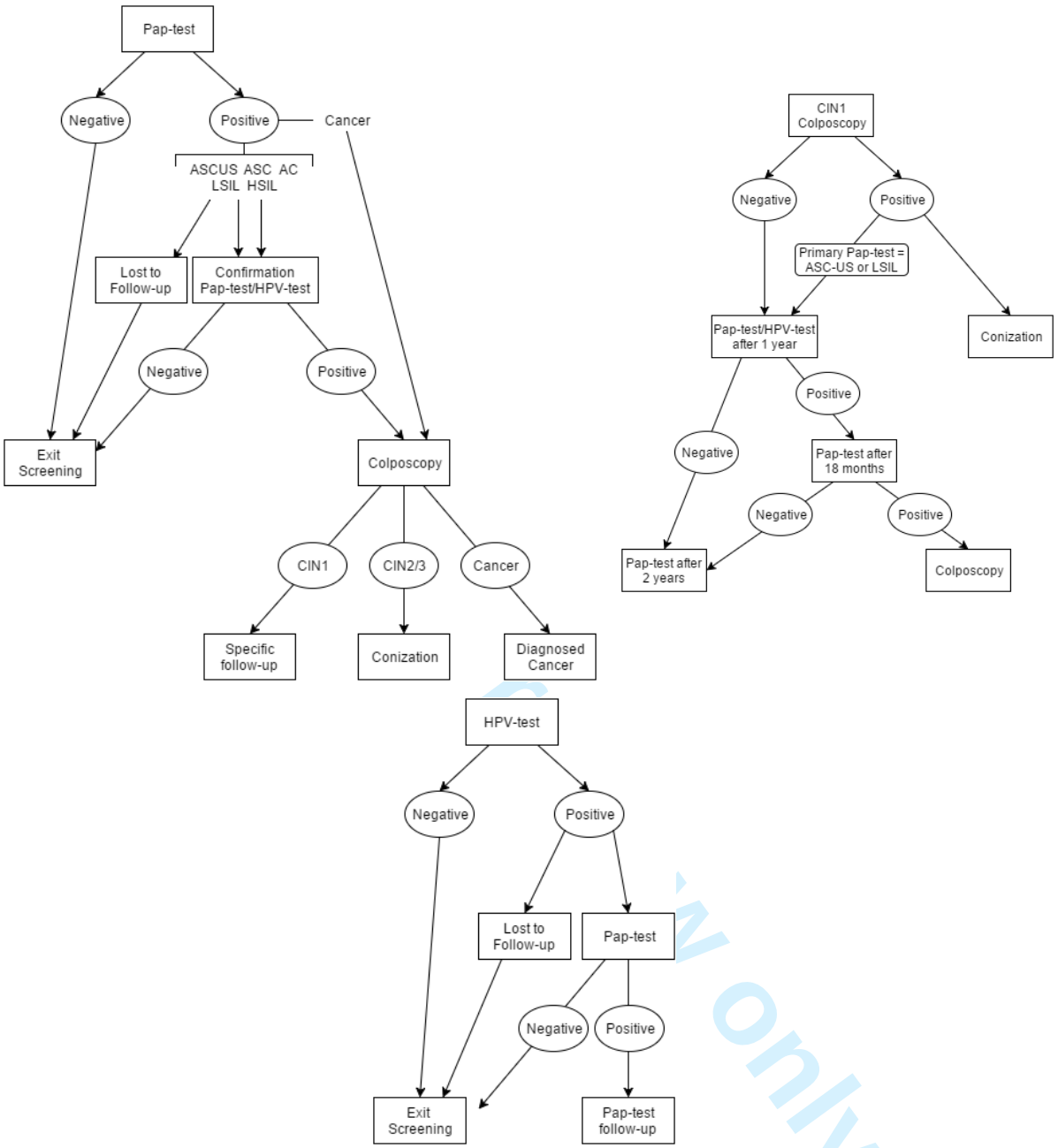
Supplementary File 1 Screening algorithms



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Supplementary File 2 Pap-test results depending on HPV infection or lesion type

	ASCUS	ASC	AC	LSIL	HSIL	Cancer
HPV-	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
HPV+	53.5%	1.5%	2.7%	40.1%	2.3%	0.0%
CIN1	53.5 %	1.5 %	2.7 %	40.1 %	2.3 %	0.0 %
CIN2/3	26.2 %	6.0 %	9.6 %	32.4 %	23.2 %	2.6 %
Cancer (all stages)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Follow-up of positive Pap-test, by Pap-test result

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

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Supplementary File 3 Extended model presentation

Due to the complexity of screening algorithms and screening pace depending on the women's history and interactions that exist between screening and individual characteristics, a stochastic microsimulation model based on a Markov methodology and a 1-year cycle length was adapted based on a previously published Markov cohort-based model that has been updated.

Given the importance of individual characteristics, the analysis is based on the simulation of closed cohorts of women eligible for CC screening and representative in terms of age, HPV infection and precancerous and cancerous lesions in order to assess the actual cost-effectiveness of SO implementation in eligible women. Therefore, the results of the model specifically address the efficiency of the various OS strategies assessed and do not allow for epidemiological prediction.

According to the French national health authority (HAS), the model perspective is the collective perspective, meaning that costs borne by all payers are taken into consideration. Costs and survival results are discounted at a 4% annual rate.

The model is programmed in C++. Input data and scenario definition are entered through a Microsoft Excel interface. Model results are then exported to Excel to generate the figures and tables.

Women generation

The model first generates women with the following characteristics: age (25-56), participant in IndScr, period between carrying out two voluntary IndScr, health state at model initiation and vaccination status. Due to the recent introduction of vaccination, only women aged under 30 can be vaccinated.

Natural history of CC

Women then initiate the simulation of CC's natural history. At each cycle, non-HPV-infected women can become infected. This infection can spontaneously regress or progress and lead to grade 1 cervical intraepithelial neoplasia (CIN 1). CIN1 lesions can become pre-cancerous (grades 2 and 3 cervical intraepithelial neoplasia, CIN2/3). Once CIN 2/3 lesions have become persistent, they cannot regress spontaneously any longer and can only progress to cancerous lesions of first grade, based on the International Federation of Gynecology and Obstetrics (FIGO) classification. FIGO I CC can progress to grades 2, 3 and 4 and/or become symptomatic, leading to diagnosis of the CC and treatment initiation. Cancer mortality based on cancer severity grade and time since diagnosis is applied to women with symptomatic/diagnosed cancer. Women can die of age-specific general mortality at any state. See figure 1 for the structure of the model.

Considering the age distribution of the cohort and its low adoption in France (17% of women under 30), the effect of vaccination is simulated by applying a relative risk of infection by oncogenic HPV to vaccinated women (i.e. herd immunity is not considered).

Screening

Each year, the model determines whether the simulated woman performs IndScr based on her status (participant in IndScr or not) and her specific IndScr frequency, both parameters generated at the initiation and updated throughout the simulation. If the woman has not performed a CC screening or received an OS invitation/recall for a period that exceeds the OS periodicity, she receives an invitation to participate. Women that are still NP receive a recall during the same cycle.

Invitation and recall modalities determine different participation probabilities upon receiving. During the screening cycle, IndScr and OS participants perform the screening test determined by the OS

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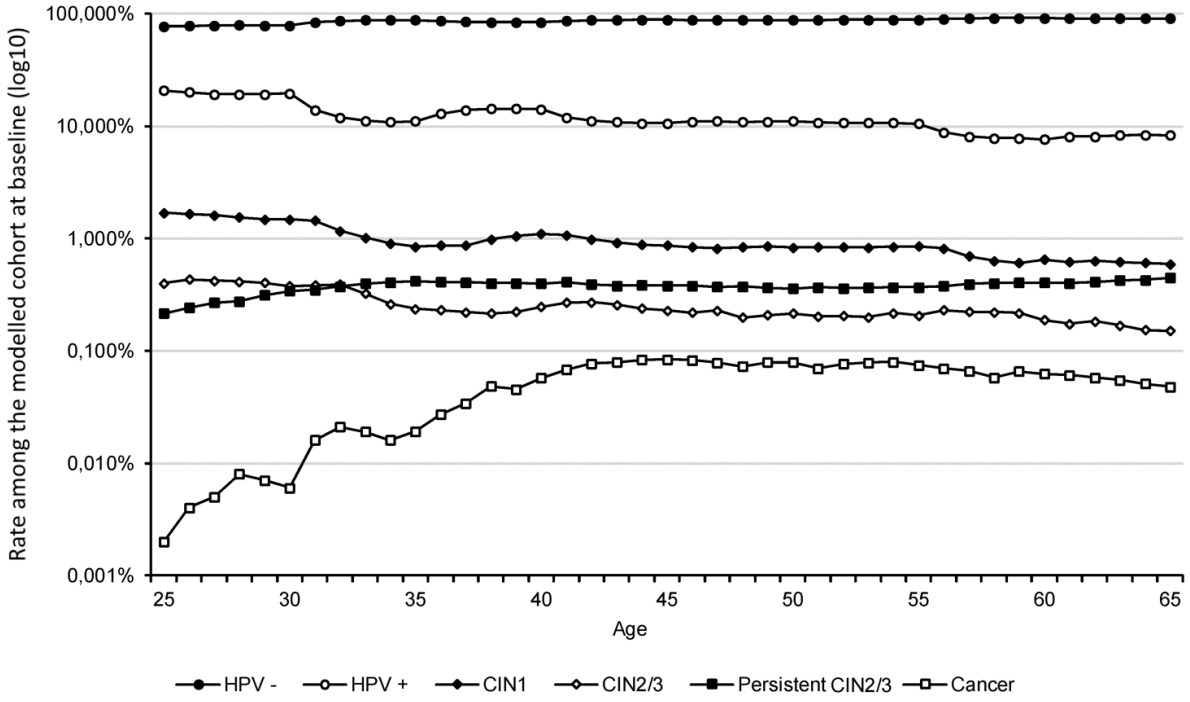
strategy assessed. Test characteristics (sensitivity/specificity) and the screening algorithm determine the result of the primary screening test based on the actual health state of the woman as well as the follow-up actions in case of positive results. Follow-up includes confirmation tests, colposcopy and conizations. Some women become lost to follow-up. Women diagnosed with CC switch to the corresponding diagnosed state.

Women's characteristics

The modelled population corresponds to all women aged 25 to 65, that is, all women eligible for IndScr according to current recommendations. Age distribution within the population is based on the national statistics office (INSEE) data.

Twelve percent (12.2%) of the eligible women were found to benefit from the universal complementary health insurance (CMU-c) in an analysis of a representative sample of the French SHI general regimen (employees). Vaccination rate among women aged 25 was based on the last available data which found a 17% uptake among young women since the vaccine became available. Distribution of each modelled health state by age within the population was based on the results of the simulation of a cohort of 14-year-old women. Health-state distribution in the generated cohort at each age is presented in the figure below.



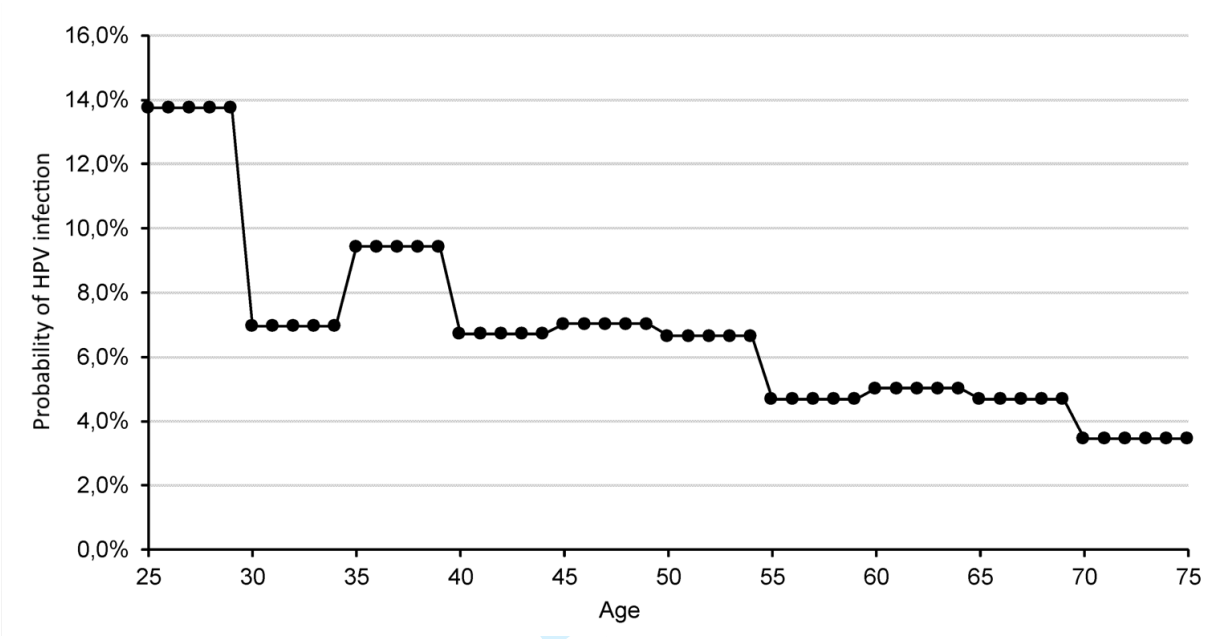
In scenarios based on Pap-test and p16/Ki67, IndScr participation is determined based on the analysis of a sample of the SHI general regimen: at 4 years, 61.9 % of eligible women were found to be participants. At patient generation, a relative risk (RR) of participation is applied to account for the impact of age and universal complementary health insurance (CMU-c). Another analysis of the same dataset provided the observed period between two IndScr (annual to every 10 years, see Supplementary file 3).

Each woman is associated with a SI participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} / RR_{current\ age-group})/5$$

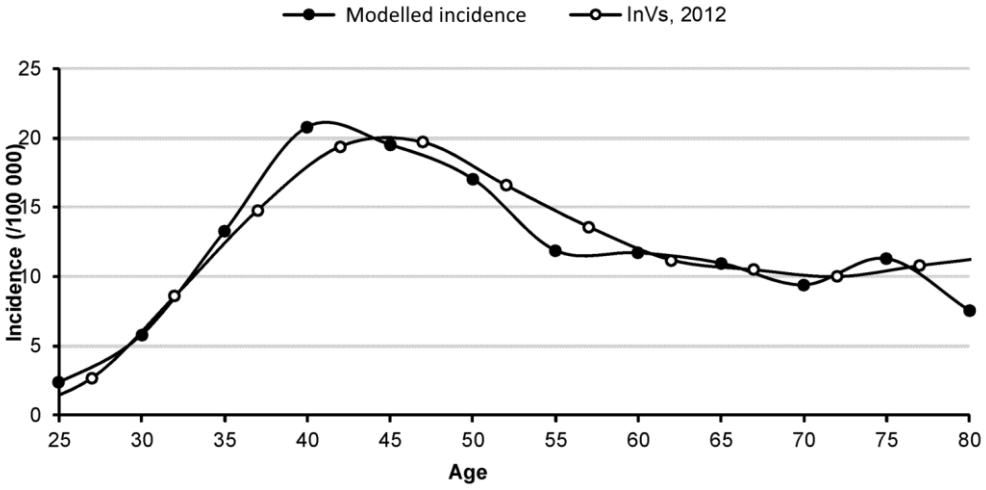
Transition probabilities

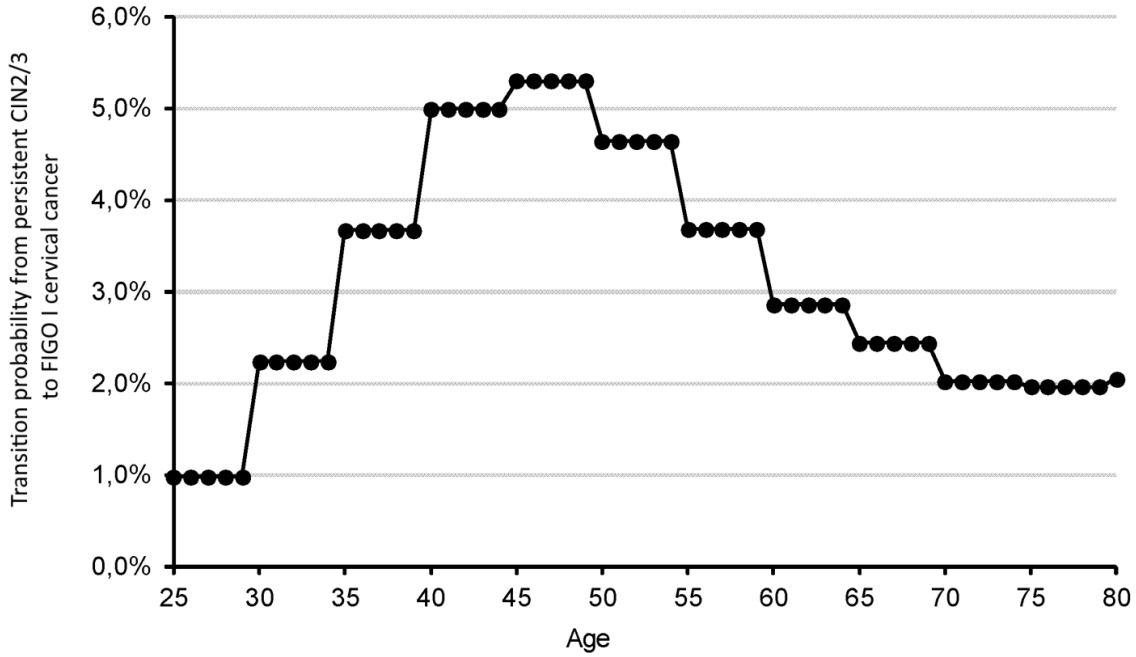
High risk (HR) HPV annual infection rate was estimated to vary from 3.5% and 14% depending on age, in order to fit with the observed HR-HPV prevalence, considering a 50% annual viral clearance rate, according to the model developed by Demarteau *et al.* In younger women, vaccination is modelled through the application of a relative risk of infection taking into account the vaccination rate and decreased infection risk among vaccinated women.



Annual transition probabilities that determine the odds of progression from HPV infection to persistent CIN2/3 precancerous lesion are replicated from the model developed by Demarteau *et al.* and presented in table 2.

Considering the lack of appropriate data, the age-specific progression transition probability of persistent CIN2/3 to FIGO I CC was estimated by calibrating the model to the CC incidence data available. The calibration process consisted in the simulation of a cohort of 14-year-old women, taking the observed IndScr participation rate into account. Transition probabilities were adjusted within a plausible interval in order to duplicate the observed incidence of CC by age. The following figures respectively present the results of the calibration process and the resulting persistent CIN 2/3 to FIGO I CC transition probabilities by age.





Probabilities of cancer progression and symptom emergence were obtained from the natural history of CC simulation model developed by Myers *et al*.

Cancer mortality by cancer grade and time since diagnosis were obtained from the study by Wright *et al.* based on the estimation of survival among 46,932 women with CC diagnosed from 1983-2009 and recorded in the Surveillance, Epidemiology, and End Results (SEER) database. Survival data for white women under 50 were selected, as mortality by causes other than CC seems unlikely in women under 50. General mortality is modelled according to French national statistics office (INSEE) data.

Screening

OS participation rates after receiving an invitation or recall are based on the results of local OS experimentations carried out in different regions. The weighted averages of the participation rate upon receiving a mailed invitation or recall letter by the number of Pap-tests performed during each experimentation were respectively found to be 17.3% and 12.1%. Screening test sensitivity and specificity are given in the following table.

Screening test	Sensitivity	Specificity	Source
Primary Pap-test	70.0 % (57.0 % - 80.0 %)	95.0 % (92.0 % - 97.0 %)	Mustafa (2015)
Confirmation Pap-test after HPV+	85.9 % (76.6 % - 92.1 %)	65.9 % (63.1 % - 68.6 %)	Bergeron (2015)
Primary HPV-test	94.0 % (89.0 % - 97.0 %)	90.0 % (86.0 % - 93.0 %)	Mustafa (2015)
Confirmation HPV-test after Pap+	100.0 % (NR)	61.1 % (NR)	Mayrand (2007)
P16/KI67	86.7 % (81.1 % - 90.9 %)	95.2 % (94.9 % - 95.4 %)	Ikenberg (2013)
Colposcopy	100.0% (NA)	100.0% (NA)	Assumption

At each screening cycle, test performances determine whether women with lesions are screened positive or not depending on their current health state.

Pap-test and p16/Ki67 specificity and specificity are relative to the detection of CIN2/3 and more severe lesions. Women with negative results exit screening, positive results lead to the random draw of an observed lesion type based on the results of the OS experimentation led in the Alsace region (Supplementary file 4).

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The action that follows each type of result is then randomly drawn according to the screening algorithms and the results of the OS experimentation led in Alsace. Based on the probabilities reported in Supplementary file 5, the different types of results can lead to further confirmation tests or conisation. Some women become lost to follow-up and exit screening.

	Confirmation Pap-test	Confirmation HPV-test	Colposcopy	Conization	Lost to follow-up
ASCUS	36,9 %	10,8 %	23,9 %	1,3 %	27,1 %
ASC	36,3 %	0,0 %	48,8 %	7,1 %	7,8 %
AC	6,5 %	0,0 %	30,7 %	7,0 %	55,9 %
LSIL	36,2 %	0,0 %	32,0 %	3,5 %	28,3 %
HSIL	21,4 %	0,0 %	50,1 %	19,1 %	9,4 %
Cancer	10,0 %	0,0 %	85,0 %	5,0 %	0,0 %

In order to take the impact of the screening organization structures into account, OS implementation leads to reduced odds of becoming lost to follow-up after a positive result for both OS and IndScr participants. Based on the Alsace and Indre-et-Loire regional OS experimentation results, a 0.77 RR of becoming lost to follow-up is applied.

Colpscopy is associated with 100% sensitivity and specificity. Therefore, colposcopy results are negative in HPV- and HPV+ women and positive in women with CIN1, CIN2/3 and persistent CIN2/3 lesions. Women with CIN1 proceed to a particular screening algorithm based on recommendations by the French national scientific society of obstetricians and gynaecologists (CNGOF).

HPV-tests and specificity are relative to the detection of HPV+ and more severe lesions. Women with negative results exit screening, positive results lead to a confirmation Pap-test (or p16/Ki67) followed by a colposcopy in case of a new positive result. If negative, a new round of HPV and Pap-tests are performed concomitantly after one year: a positive result for either of them (or both) leads to colposcopy; women with negative-only results exit screening.

Rates of lost to follow-up observed during the START-HPV experimentation (Ardennes region) were used. The lost to follow-up rate after positive confirmation Pap-tests was estimated by subtracting the latter from the average rate of lost to follow-up in HPV+ women observed in the Alsace region OS experimentation (27.7%). Similarly to Pap-based screening, a 0.77 RR of being lost to follow-up is applied in OS-participant women.

Lost to follow-up after	Probability	Source
Positive HPV-test	19,4 %	START-HPV, Ardennes
Positive confirmation pap-test	8,3 %	START-HPV, Ardennes, Alsace OS experimentation

All samples have odds of being unreadable, depending on the nature of the sample. Women with unreadable samples perform a new test.

A 95% efficacy was considered for conisation. Women with successful conisation go back to the HPV- state. In case of failure, women leave screening in their current state.

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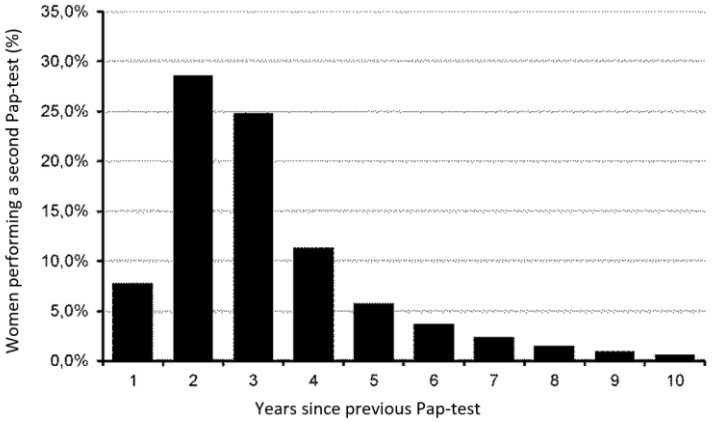
Supplementary File 4 Individual screening participation and periodicity data

Individual screening frequency	Distribution
Annual	5,9%
2 years	21,5%
3 years	18,7%
4 years	8,6%
5 years	4,3%
6 years	2,8%
7 years	1,8%
8 years	1,1%
9 years	0,7%
10 years	0,5%



Population	RR of participating vs. average	Source
Age		
25 – 30	1,06	National health insurance database [3]
30 – 35	1,08	National health insurance database [3]
35 – 40	1,07	National health insurance database [3]
40 – 45	1,04	National health insurance database [3]
50 – 55	0,92	National health insurance database [3]
55 – 60	0,82	National health insurance database [3]
60 – 65	0,77	National health insurance database [3]
Universal complementary health insurance registration		
Yes	0,80	National health insurance database [3]
No	1,03	National health insurance database [3]

Each woman is associated with an IndScr participation status (Yes/No) and a screening period. Age-dependent probabilities of becoming NP are applied throughout the simulation to account for the lesser participation among older women. These probabilities are determined as follows:

$$P_{become\ non-participant} = (RR_{next\ age-group} \,/\, RR_{current\ age-group})/5$$

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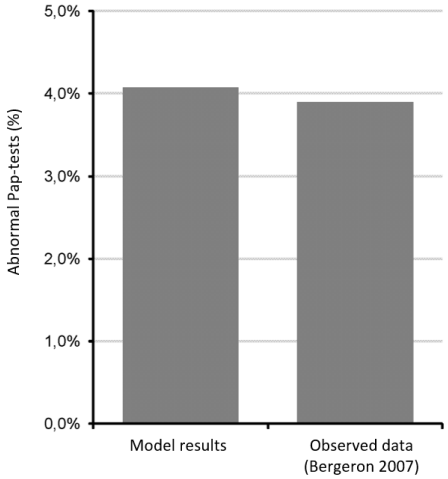
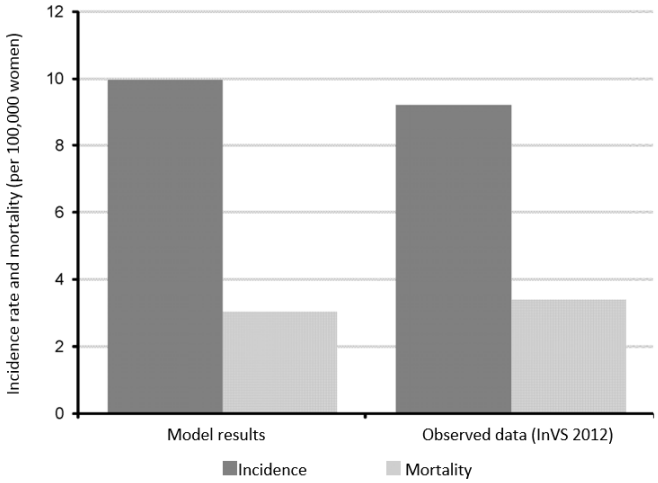
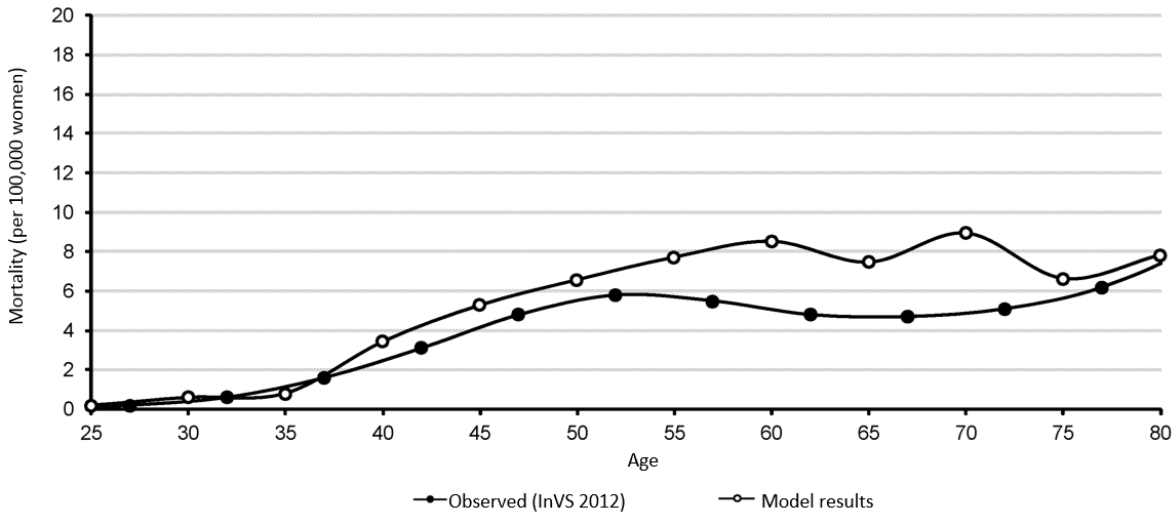
Supplementary File 5 Model validation results

The model faithfully reproduces cancer incidence, however the modelled CC mortality was slightly higher than observed data, although differences were systematically inferior to 4 per 100,000.







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Supplementary File 6 Cost-utility analysis - specific inputs and results

State	Utility/Utility decrement	Source
Age 18-29	0.86	Perneger, 2010
Age 30-39	0.86	
Age 40-49	0.84	
Age 50-59	0.81	
Age 60-69	0.8	
Age 70-79	0.76	
Age 80+	0.74	
Diagnosed CIN1	-0.01	Demarteau, 2011
Diagnosed CIN2/3	-0.01	
Cervical Cancer (1st year)	-0.27	
Cervical Cancer (thereafter)	-0.06	Korfage, 2009

Scénario	QALY	Total cost (K€)	ICER (€/LY) vs current	Frontier
IndScr only*	16.4	122.6	Reference	Dominated
Pap/Pap-HPV	+9.54	+22.3	23,392	Dominated
Pap/p16Ki67	+11.18	+25.5	22,891	Dominated
HPV/Pap-3y	+14.99	+55.8	37,290	Dominated
HPV/Pap-5y	+14.76	-13.3	Dominant	Ext. Dominated
HPV/Pap-10y	+9.44	-73.4	Dominant	Reference
HPV/p16Ki67-5y	+17.06	+3.79	2,222	131,965
HPV/p16Ki67-10y	+11.88	-64.6	Dominant	36,468
p16Ki67/p16Ki67	+17.53	+160.7	91,703	3,302,932

*Reference for other scenarios. Extra-QALY per 10,000 women eligible for OS on a lifetime horizon. QALY: Quality Adjusted Life Years

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Table

Table 1| CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	3
		Present the study question and its relevance for health policy or practice decisions.	3/28 - 29
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Table 2, 6/12 - 18
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6/36 - 37
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Table 1, 4/2 - 20
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5/27 - 28
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9/6 - 7
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	9/6 - 7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6/36 - 7/3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7/2 - 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Figure 1, 5/23 - 26
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 2, 5/29 - 7/3
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	8/6 - 12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2, 6/11 - 7/3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 3 & 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	

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(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Figures 3 & 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Figures 3 & 4; 11/24 - 35
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12 & 13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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