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.

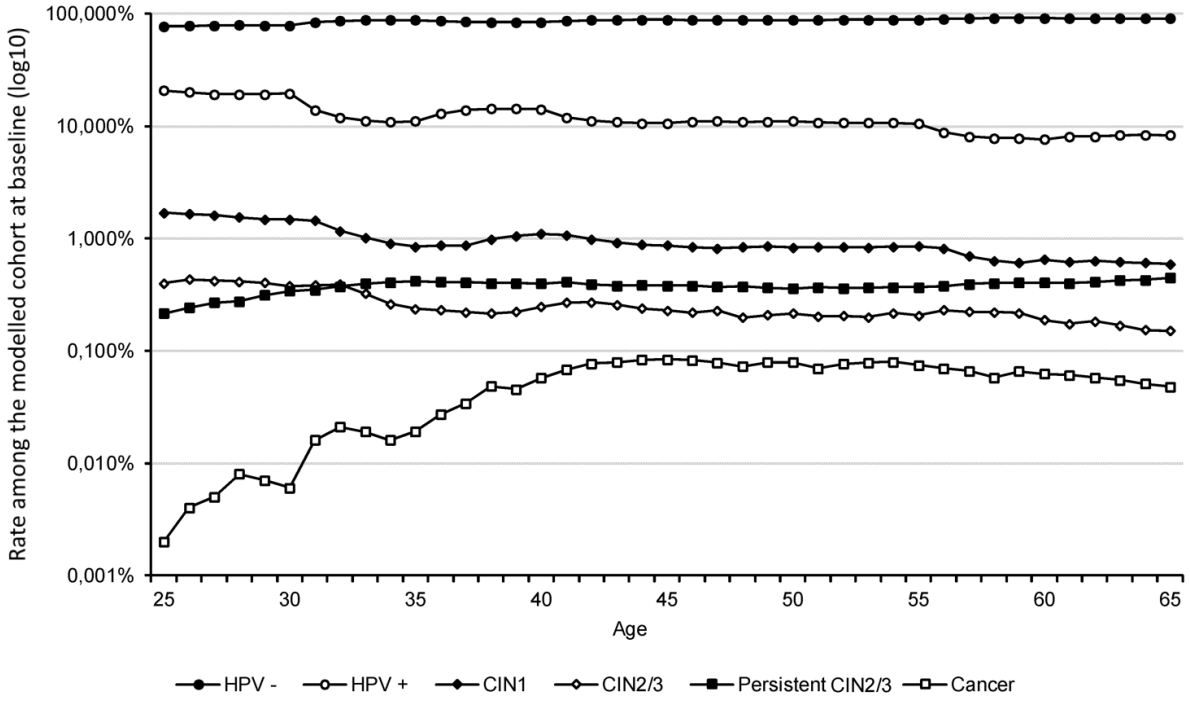
Invitation and recall modalities determine different participation probabilities upon receiving. During the screening cycle, IndScr and OS participants perform the screening test determined by the OS

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.



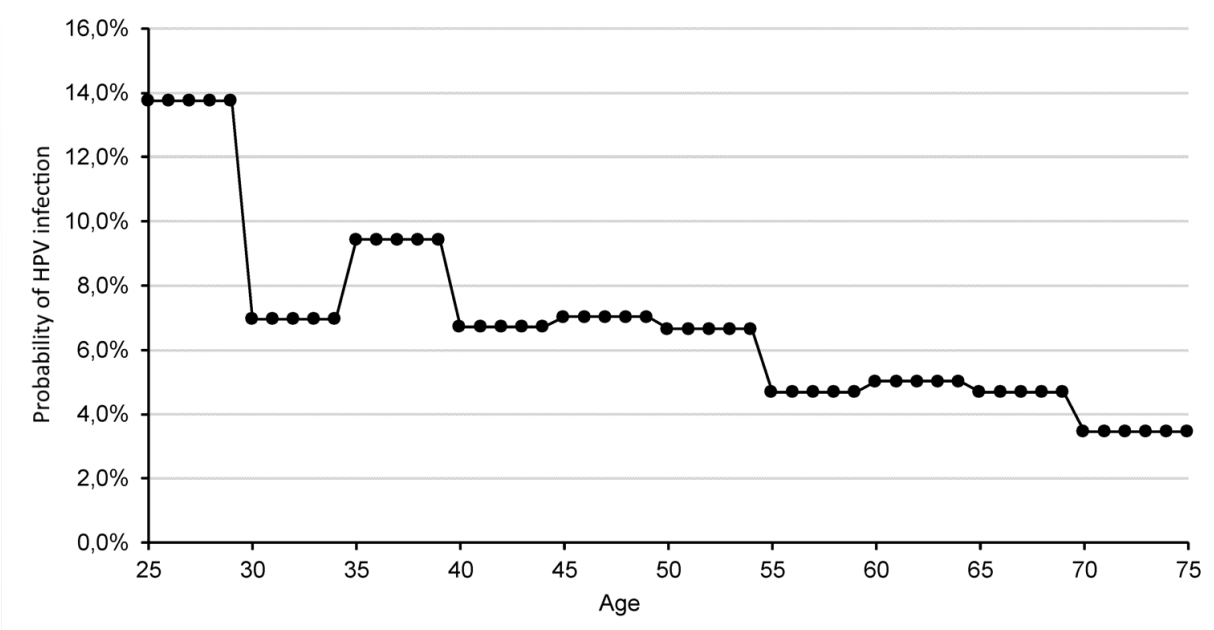
In scenarios based on Pap-test and p16/Ki67, IndScr participation is determined based on the analysis of a sample of the SHI general regimen: at 4 years, 61.9 % of eligible women were found to be participants. At patient generation, a relative risk (RR) of participation is applied to account for the 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:

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

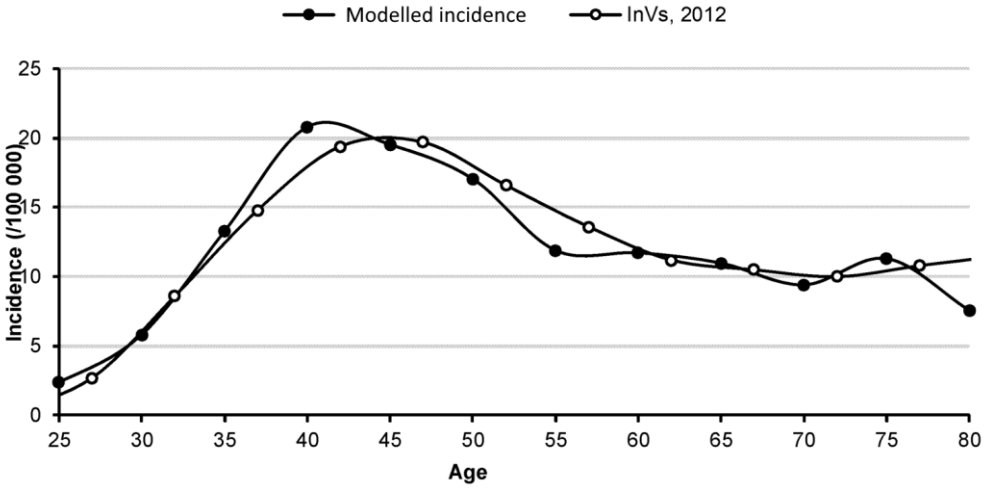
Transition probabilities

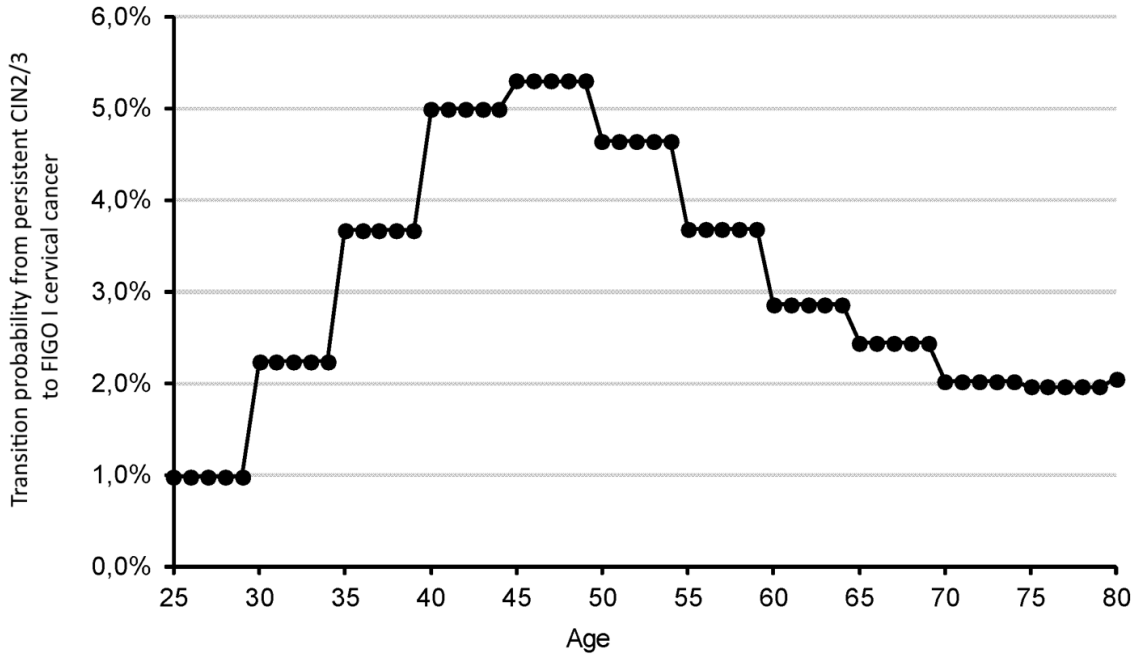
High risk (HR) HPV annual infection rate was estimated to vary from 3.5% and 14% depending on age, in order to fit with the observed HR-HPV prevalence, considering a 50% annual viral clearance rate, according to the model developed by Demarteau *et al.* In younger women, vaccination is modelled through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

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.