



## Experience with HPV self-sampling and clinician-based sampling in women attending routine cervical screening in the Netherlands

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### ABSTRACT

Several countries offer HPV self-sampling for screening non-attendees. It is assumed that screening attendees also prefer self-sampling to clinician-based sampling, however, little research has been conducted with respect to this. Women participating in the IMPROVE-study were randomised (1:1) to self- or clinician-collected HPV testing, and HPV-positive women were retested using the other collection method. Three different questionnaires were sent out among a subset of participating women: Q1) HPV-positive women from both study groups were asked about their experiences with self-sampling and clinician-based sampling ( $n = 497$ ); Q2) HPV-negative women from the self-sampling group were asked about their experiences with self-sampling ( $n = 2366$ ); and Q3) HPV-negative women in the clinician-collection group were asked about their experiences with clinician-based sampling ( $n = 2092$ ). Response rates ranged from 71.6 to 79.4%. Women reported significantly lower levels of shame, nervousness, discomfort and pain during self-sampling compared to clinician-based sampling. However, trust in correct sampling was significantly higher during clinician-based sampling. The majority of women in group Q1 preferred self-sampling (76.5%) to clinician-based sampling (11.9%) in future screening, while 11.6% of women reported to have no preference for either method. To conclude, women from a regular screening population have a positive attitude towards self-sampling but express some concerns with respect to accuracy. The majority prefers self-sampling to clinician-based sampling in future screening. Based on these results, a screening approach where women can choose for either self-sampling or clinician-based sampling seems highly justifiable.

### 1. Introduction

Testing for the presence of high-risk human papillomavirus (HPV) provides better protection against cervical cancer and high-grade cervical intraepithelial neoplasia (CIN) than cytology testing (Arbyn et al., 2012; Ronco et al., 2014). Therefore, several countries have replaced cytology by HPV testing as the primary screening method (Wentzensen et al., 2017). While cytology cannot be performed on a self-collected cervicovaginal sample due to the lack of a sufficient number of intact cervical cells (indicator cells), HPV testing can be performed reliably on self-sampled specimen (HPV self-sampling) (Garcia et al., 2003). Hence, the introduction of HPV-based screening opens up the possibility of offering self-sampling to women.

Studies have shown that offering HPV self-sampling to screening non-attendees increases participation rates (Virtanen et al., 2011a; Virtanen et al., 2011b; Wikstrom et al., 2011; Giorgi Rossi et al., 2011; Szarewski et al., 2011). Self-sampling participation rates up to 34.2% were found among screening non-attendees in the Netherlands (Bais et al., 2007; Gok et al., 2010; Gok et al., 2012; Bosgraaf et al., 2015; Verhoef et al., 2014). Surveys evaluating women's experiences with self-sampling, showed that most non-attendees would prefer self-sampling to clinician-based sampling in the next screening round (Bosgraaf et al., 2015; Huynh et al., 2010; Nelson et al., 2017). Besides, a meta-analysis indicated that the sensitivity of HPV testing on self-collected and clinician-collected specimens for detection of cervical intraepithelial grade 2 or worse (CIN2+) are similar when HPV testing is

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conducted with a clinically validated PCR-based assay (Arbyn et al., 2014). Based on these results, several countries, including the Netherlands, have implemented HPV self-sampling for screening non-attendees (Dutch Health Council, 2016; Lew et al., 2013; Danish Health Council, 2017).

HPV self-sampling may also be considered as a primary screening instrument in the screening population as a whole. Implementation of self-sampling as a primary screening option would reduce the costs of cervical screening as it obviates the need of smear taking at the physician's office. The accuracy of HPV self-sampling as compared to HPV testing on physician-collected specimens in women invited for routine screening has recently been evaluated in the IMPROVE study (Polman et al., 2019). The IMPROVE study, a randomised non-inferiority trial among 16,410 women from a routine screening population in the Netherlands, showed that HPV self-sampling has similar sensitivity and specificity as clinician-based HPV testing for detection of CIN2+ and CIN3+, further supporting the implementation of HPV self-sampling as a primary screening option. It is generally hypothesized that screening attendees, alike most non-attendees, would prefer self-sampling to clinician-based sampling. However, little research has yet been conducted with respect to experiences and preferences of regular screening attendees.

The aim of this study was to evaluate experiences and preferences with HPV self-sampling and clinician-based sampling among women participating in routine screening. In order to evaluate this, we did a survey among a subset of women who participated in the IMPROVE study.

## 2. Methods

### 2.1. Study population

The IMPROVE study (Polman et al., 2019) was designed to assess the non-inferiority of HPV self-sampling as compared to clinician-based HPV testing. Women were invited to participate in the IMPROVE study in 2015 and 2016. At that time, routine cervical screening in the Netherlands was cytology-based and women aged 30–60 years were invited every 5 years for sample collection for cervical cytology at a general practitioner's practice. A total of 16,410 women provided informed consent to participate. These women were randomised (1:1) to the intervention group (HPV self-sampling using the Evalyn Brush, Rovers Medical Devices B.V., Oss, The Netherlands) and the control group (clinician-based HPV testing using the Cervex Brush, Rovers Medical Devices B.V., Oss, The Netherlands). Both self-sampling and clinician-based sampling were offered free of charge, as is participation in routine screening in the Netherlands. Both within the IMPROVE study and within routine screening, women were informed that possible additional research in case of a positive screening test result could entail costs. The IMPROVE study was approved by the Ministry of Public Health (no. 2014/32) and is registered in the Dutch Trial Register (NTR5078).

To assess the relative sensitivity of self-collected compared to clinician-based HPV testing in the IMPROVE study, HPV-positive women in the intervention group were also tested for HPV on a clinician-collected sample, and HPV-positive women in the control group were requested to send in a self-sample for HPV testing. This second test (i.e. cross-test) was also free of charge.

For this survey, three different questionnaires were developed (see Fig. 1): questionnaire 1 (Q1): HPV-positive women from both study groups were asked about their experiences with both self-sampling and clinician-based sampling; questionnaire 2 (Q2): HPV-negative women from the intervention group were asked about their experiences with self-sampling; and questionnaire 3 (Q3): HPV-negative women from the control group were asked about their experiences with clinician-based sampling.

Invitations to participate in the questionnaire study were sent out in

January 2017. Because of privacy and ethical reasons, questionnaires were completely anonymous and therefore could not be linked to the IMPROVE study on the individual level. To minimize the risk of recall bias, women who tested HPV positive between June and November 2016 ( $n = 497$  HPV-positive women [Q1]) and women who tested HPV negative between September and November 2016 ( $n = 4458$ ; 2366 women in the intervention group [Q2] and 2092 in the control group [Q3]) were invited to participate.

### 2.2. Questionnaire

The questionnaires (see supplementary material) were developed based on previous studies evaluating experiences with HPV self-sampling (Bosgraaf et al., 2015; Sultana et al., 2015; Virtanen et al., 2014; Karjalainen et al., 2016; Berner et al., 2013; Waller et al., 2006). The questionnaires were tested in an external pilot group of ten women within the screening age in order to make sure that the questions were clear and understandable.

The questionnaires contained three to five components. The first component contained questions about age, level of education and screening history and was included in Q1, Q2, and Q3. The second component contained questions about the intelligibility of the given instructions and the usability of the self-sampling device and was included in Q1 and Q2. The third component contained questions about experiences with self-sampling and/or clinician-based sampling (discomfort, pain, nervousness, shame, privacy and trust in correct execution of the sampling procedure) and was included in Q1, Q2 and Q3. In addition, Q2 and Q3 had one extra question regarding trust in accuracy of the HPV result. HPV-positive women in the IMPROVE study were advised to undergo follow-up testing and had often already received additional test results, making this question unsuitable for HPV-positives. The fourth component contained questions about preference for participation in future screening (self-sampling, clinician-based sampling, or no preference) and was included in Q1 and Q2. The fifth component contained questions about knowledge with respect to HPV and cervical cancer, feelings of concern after receiving the HPV-positive test result, and whether the provided information after receiving the HPV-positive test result was reassuring. Since we aimed to evaluate what information HPV-positive women wanted to receive and how they could best be reassured after receiving the test result, this part of the questionnaire was only included in Q1. Women could either fill in the questionnaire on paper and sent it back using the provided return envelope, or log in and fill in the questionnaire online. Formatted responses were either binary (yes/no) or on a five point Likert-type scale.

### 2.3. Statistical analysis

Differences in age between women who participated in Q2 versus Q3 were analysed with the Mann-Whitney *U* test, while differences in level of education and time to previous cervical smear were analysed with the Chi-square test.

Scores were filled in on a five-point scale and are presented with mean and median scores. Differences in scores between self-sampling and clinician-based sampling among HPV-positive women (Q1) were analysed using the Wilcoxon Signed-Rank test, while differences in scores between HPV-negative women from the self-sampling and clinician-based sampling group (Q2 vs. Q3) were analysed using the Chi-square test. The presented *p*-values are Bonferroni corrected (multiplied by the number of hypotheses tested, i.e. multiplied by 13).

Preference in future screening was only analysed for women who had experience with both self-sampling and clinician-based sampling and therefore were able to make an informed decision regarding their preference for the next screening round. Therefore, only HPV-positive women (Q1) and HPV-negative women from the intervention group (Q2) who indicated that they had participated in cervical screening before were included in this analysis. The effect of age on preference in

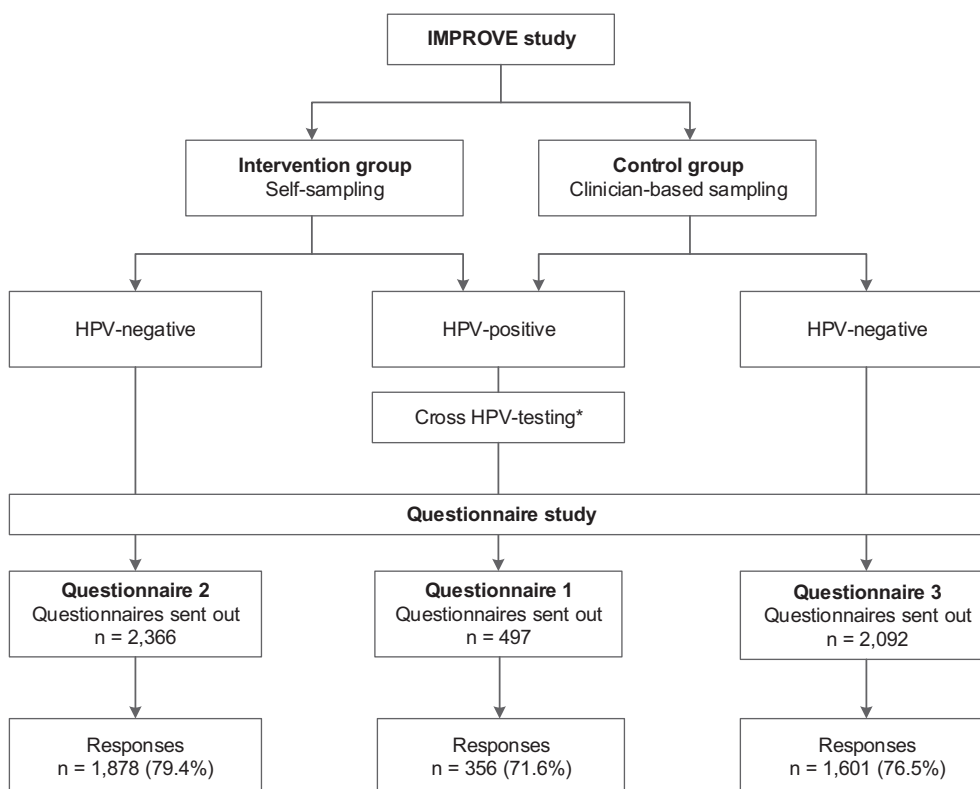


Fig. 1. Flowchart of the IMPROVE study design, including information on participation in the questionnaire study.

\* Cross-testing: HPV-positive women in the intervention group were also tested for HPV on a clinician-collected sample, and HPV-positive women in the control group were also tested for HPV on a self-sample.

future screening was evaluated with the Kruskal Wallis test, while differences between lower and higher educated women on preference in future screening were evaluated with the Chi-square test. As there was a small percentage of missing data, these were excluded for analysis. Data analysis was performed with IBM SPSS Statistics version 22.0.

### 3. Results

#### 3.1. Response rate and study cohort characteristics

Response rates of the Q1, Q2, and Q3 group ranged from 71.6% to 79.4% (see Fig. 1). Overall, 68.0% of women (n = 2608) completed the questionnaire on paper and 32.0% (n = 1227) completed the questionnaire online. Demographic characteristics of the questionnaire responders are shown in Table 1. There were no differences with respect to age, educational level, and time to previous cervical smear between women filling out Q2 and Q3 (p = 0.886, p = 0.916, and p = 0.083, respectively).

#### 3.2. Self-sampling instructions and usability

Results regarding intelligibility of the self-sampling instructions and usability of the self-sampling device, both for HPV-positive women in the Q1 group and HPV-negative women in the self-sampling group Q2, are shown in Table 2. Overall, > 95% of women reported a very to extremely good intelligibility of the self-sampling instructions (95.5% in Q1 and 96.5% in Q3). Moreover, 77.7% of women in Q1 group and 84.6% of women in Q3 group reported a very to extremely good usability of the self-sampling device.

#### 3.3. Experience of self-sampling versus clinician-based sampling

Results among HPV-positive women (Q1) who performed both self-

sampling and clinician-based sampling are shown in Table 3. Women reported significantly less discomfort during self-sampling as compared to clinician-based sampling: 68.7% reported no discomfort at all during self-sampling, compared to 19.2% during clinician-based sampling (p = 0.002). Additionally, 80.8% of women reported no pain at all during self-sampling, compared to 33.0% of women during clinician-based sampling (p < 0.001). Women reported significantly lower levels of nervousness and shame during self-sampling than during clinician-based sampling: 62.0% vs. 27.6% reported no nervousness at all (p = 0.018) and 92.1% vs. 37.3% reported no shame at all (p < 0.001). The vast majority of women experienced a high degree of privacy during self-sampling (93.2%), while only 31.4% reported this during clinician-based sampling (p < 0.001). Finally, 53.7% of women reported maximal trust in correct execution of the self-sampling procedure, compared to 73.3% that reported extreme trust in correct execution of the clinician-based sampling procedure (p < 0.001).

Results of HPV-negative women from the self-sampling group versus HPV-negative women from the clinician-based sampling group (Q2 vs. Q3) are shown in Table 4. The majority (76.9%) of women from the self-sampling group reported no discomfort at all while performing self-sampling, while only 28.3% of women from the control group reported no discomfort during clinician-based sampling (p < 0.001). Moreover, 81.9% of women in the self-sampling group reported no pain, compared to 40.1% of women in the clinician-based sampling group (p < 0.001). Women from the self-sampling group reported significantly lower levels of nervousness and shame as compared to women from the clinician-based sampling group: 63.7% vs. 43.0% reported no nervousness at all (p < 0.001) and 91.4% vs. 47.9% reported no shame at all (p < 0.001). With regard to privacy, 95.5% of women in the self-sampling group reported extremely high privacy compared to 61.8% of women in the clinician-based sampling group (p < 0.001). The percentage of women who reported extreme trust in correct execution of the sampling procedure was 53.3% in the self-sampling group and

**Table 1**

Demographic characteristics of responders to questionnaire 1 (HPV-positive women from both study groups), questionnaire 2 (HPV-negative women from the intervention group), and questionnaire 3 (HPV-negative women from the control group).

Characteristics	Questionnaire 1		Questionnaire 2		Questionnaire 3	
	n	%	n	%	n	%
Mean age in years (range)	43.7	(30–60)	48.4	(30–63)	48.4	(30–61)
Age cohorts						
30–33	74	20.9%	105	5.6%	82	5.1%
34–38	46	13.0%	129	6.9%	130	8.1%
39–43	35	9.9%	246	13.2%	207	13.0%
44–48	51	14.4%	361	19.3%	266	16.7%
49–53	67	18.9%	316	16.9%	295	18.5%
54–58	53	15.0%	376	20.1%	344	21.5%
59–63	28	7.9%	337	18.0%	273	17.1%
Missing	2	–	8	–	4	–
Level of education						
No or primary education	1	0.3%	13	0.7%	12	0.8%
Secondary education	48	13.6%	396	21.1%	321	20.2%
Intermediate/Higher vocational education	212	59.9%	1116	59.6%	951	59.7%
University	93	26.3%	348	18.6%	309	19.4%
Missing	2	–	5	–	8	–
Time to previous cervical smear						
Women aged < 34 years (first invitation for cervical screening)	74	21.1%	104	5.6%	82	5.2%
Women aged ≥ 34 years						
< 7 years	243	69.2%	1545	83.7%	1353	86.6%
7–12 years	16	4.6%	107	5.8%	79	5.1%
≥ 13 years ago	6	1.7%	22	1.2%	11	0.7%
Never	12	3.4%	68	3.7%	38	2.4%
Missing	5	–	32	–	38	–
Total	356		1878		1601	

64.4% in the clinician-based sampling group ( $p < 0.001$ ). Finally, 54.1% of women in the self-sampling group reported extreme trust towards the test result, as compared to 59.4% of women in the clinician-based sampling group ( $p = 0.002$ ).

### 3.4. Preference in future screening

Among 356 HPV-positive women who participated in both self-sampling and clinician-based sampling within the IMPROVE trial (Q1), 353 filled in the question about a preference for future screening. The vast majority of these women (76.5%) reported to prefer self-sampling in future screening, 11.9% reported to prefer clinician-based sampling and 11.6% reported to have no preference for either method. The preferred screening method in future screening was not influenced by age, level of education, or screening history ( $p = 0.502$ ,  $p = 0.811$ , and  $p = 0.550$ , respectively).

A total of 1674 (89.1%) of 1878 HPV-negative women in the self-sampling group (Q2) reported that they had previously participated in screening. Of these, 1662 filled in the question about preference in future screening. The vast majority of these women (89.4%;  $n = 1486$ ) reported to prefer self-sampling to clinician-based sampling in future screening. In contrast, 2.8% ( $n = 47$ ) of women reported to prefer clinician-based sampling for future screening and 7.8% ( $n = 129$ ) of

women reported that they had no preference for either method. The preferred screening method in future screening was not influenced by age, level of education, or screening history ( $p = 0.894$ ,  $p = 0.086$ , and  $p = 0.434$ , respectively). When we analysed preference for future screening among all HPV-negative women (Q2 and Q3), irrespective of whether they have experience with both sampling methods, 2420 (70.1%) reported to prefer self-sampling to clinician-based sampling in future screening, while 439 (12.7%) reported to prefer clinician-based sampling and 595 (17.2%) reported to have no preference.

### 3.5. Knowledge and attitudes

A total of 157 (44.5%) of 353 HPV-positive women reported to be fully familiar with the relation between HPV and cervical (pre)cancer. However, also a substantial proportion of women (28.3%, 100 of 353) reported not to be familiar at all with this causal relationship (mean score: 3.4). Among HPV-positive women, 17.0% (60 of 353) reported not to be concerned or only slightly concerned, after being informed about the HPV-positive test result, while 51.8% of women reported to be very or extremely concerned. Most women (49.7%; 175 of 352) reported that the information provided in the result letter, via the website and/or via the information line was very to extremely reassuring, while 15.9% (56 of 352) reported that the provided

**Table 2**

Experiences regarding instructions and intelligibility of self-sampling in HPV-positive women (questionnaire 1) and HPV-negative women from the intervention group (questionnaire 2).

	Mean	(95% CI)	Median	(Range)	1- not at all		2-slightly		3-moderately		4-very		5-extremely		Total	Missing
					n	%	n	%	n	%	n	%	n	n		
Intelligibility of self-sampling instructions																
Questionnaire 1	4.7	(4.61–4.73)	5	(2–5)	0	0.0%	2	0.6%	14	3.9%	83	23.3%	257	72.2%	356	0
Questionnaire 2	4.7	(4.67–4.72)	5	(1–5)	4	0.2%	14	0.7%	47	2.5%	413	22.0%	1397	74.5%	1875	3
Usability of self-sampling device																
Questionnaire 1	3.1	(2.99–3.27)	5	(1–5)	28	7.9%	38	10.7%	13	3.7%	55	15.5%	220	62.1%	354	2
Questionnaire 2	3.4	(3.32–3.42)	5	(1–5)	92	4.9%	131	7.0%	66	3.5%	287	15.3%	1296	69.2%	1872	6

**Table 3**  
Experiences with self-sampling and clinician-based sampling (Q1).

	Mean (95% CI)		Median (Range)	P-value*	1-not at all		2-slightly		3-moderately		4-very		5-extremely		Total	Missing	
					n	%	n	%	n	%	n	%	n	%	n	n	
<b>Discomfort</b>																	
Self-sampling	1.4	(1.35–1.49)	1	(1–5)	< 0.001	244	68.7%	84	23.7%	19	5.4%	6	1.7%	2	0.6%	355	1
Clinician-based sampling	2.8	(2.70–2.96)	3	(1–5)		68	19.2%	71	20.0%	103	29.0%	80	22.5%	33	9.3%	355	1
<b>Pain</b>																	
Self-sampling	1.3	(1.22–1.36)	1	(1–5)	< 0.001	286	80.8%	45	12.7%	14	4.0%	6	1.7%	3	0.8%	354	2
Clinician-based sampling	2.4	(2.25–2.51)	2	(1–5)		116	33.0%	86	24.4%	72	20.5%	57	16.2%	21	6.0%	352	4
<b>Nervousness</b>																	
Self-sampling	1.6	(1.46–1.64)	1	(1–5)	< 0.001	220	62.0%	95	26.8%	24	6.8%	13	3.7%	3	0.8%	355	1
Clinician-based sampling	2.6	(2.50–2.77)	3	(1–5)		98	27.6%	68	19.2%	84	23.7%	73	20.6%	32	9.0%	355	1
<b>Shame</b>																	
Self-sampling	1.1	(1.05–1.13)	1	(1–4)	< 0.001	327	92.1%	24	6.8%	3	0.8%	1	0.3%	0	0.0%	355	1
Clinician-based sampling	2.2	(2.09–2.35)	2	(1–5)		132	37.3%	88	24.9%	76	21.5%	41	11.6%	17	4.8%	354	2
<b>Privacy</b>																	
Self-sampling	4.8	(4.71–4.89)	5	(1–5)	< 0.001	15	4.2%	1	0.3%	1	0.3%	7	2.0%	329	93.2%	353	3
Clinician-based sampling	3.6	(3.44–3.71)	4	(1–5)		31	8.8%	50	14.1%	65	18.4%	97	27.4%	111	31.4%	354	2
<b>Trust in correct execution of sampling procedure</b>																	
Self-sampling	4.3	(4.25–4.43)	5	(1–5)	< 0.001	6	1.7%	12	3.4%	28	7.9%	119	33.4%	191	53.7%	356	0
Clinician-based sampling	4.7	(4.61–4.73)	5	(1–5)		1	0.3%	3	0.8%	13	3.7%	78	21.9%	261	73.3%	356	0

\* Bonferroni corrected p-value.

information was not or only slightly reassuring.

**4. Discussion**

We aimed to evaluate experiences with HPV self-sampling as compared to clinician-based sampling among women from a routine Dutch screening cohort. Overall, results show that experiences with self-sampling were rated more positive than experiences with clinician-based sampling. Intelligibility of the self-sampling instructions was rated good and usability of the self-sampling device was rated moderately good. Women experienced significantly lower levels of

discomfort, pain, nervousness and shame with self-sampling, and significantly higher levels of privacy. Trust in correct execution of sampling method and trust in accuracy of the HPV result were slightly lower with self-sampling as compared to clinician-based sampling. Nonetheless, the majority of women reported to prefer self-sampling in future screening.

Previous studies among non-attendees who were offered self-sampling showed that women found self-sampling to be more convenient, less embarrassing, less uncomfortable and less painful as compared to clinician-based sampling (Sultana et al., 2015). In addition, women indicated that they would prefer self-sampling to clinician-based

**Table 4**  
Experiences with self-sampling in the intervention group (Q2) versus experiences with clinician-based sampling in the control group (Q3).

	Mean (95% CI)		Median (Range)	P-value*	1-not at all		2-slightly		3-moderately		4-very		5-extremely		Total	Missing	
					n	%	n	%	n	%	n	%	n	%	n	n	
<b>Discomfort</b>																	
Self-sampling	1.3	(1.31–1.37)	1	(1–5)	< 0.001	1441	76.9%	285	15.2%	96	5.1%	42	2.2%	10	0.5%	1874	4
Clinician-based sampling	2.4	(2.34–2.46)	2	(1–5)		451	28.3%	474	29.7%	355	22.3%	218	13.7%	97	6.1%	1595	6
<b>Pain</b>																	
Self-sampling	1.3	(1.25–1.59)	1	(1–5)	< 0.001	1534	81.9%	224	12.0%	58	3.1%	44	2.3%	13	0.7%	1873	5
Clinician-based sampling	2.1	(2.08–2.20)	2	(1–5)		639	40.1%	427	26.8%	264	16.6%	190	11.9%	75	4.7%	1595	6
<b>Nervousness</b>																	
Self-sampling	1.6	(1.52–1.61)	1	(1–5)	< 0.001	1194	63.7%	401	21.4%	182	9.7%	80	4.3%	16	0.9%	1873	5
Clinician-based sampling	2.1	(2.00–2.10)	2	(1–5)		687	43.0%	403	25.2%	304	19.0%	154	9.6%	49	3.1%	1597	4
<b>Shame</b>																	
Self-sampling	1.1	(1.09–1.13)	1	(1–5)	< 0.001	1712	91.4%	126	6.7%	23	1.2%	6	0.3%	6	0.3%	1873	5
Clinician-based sampling	1.9	(1.87–1.97)	2	(1–5)		764	47.9%	414	26.0%	233	14.6%	145	9.1%	39	2.4%	1595	6
<b>Privacy</b>																	
Self-sampling	4.9	(4.84–4.90)	5	(1–5)	< 0.001	51	2.7%	3	0.2%	7	0.4%	24	1.3%	1788	95.5%	1873	5
Clinician-based sampling	4.3	(4.29–4.39)	5	(1–5)		67	4.2%	58	3.6%	130	8.1%	354	22.2%	987	61.8%	1596	5
<b>Trust in correct execution of sampling procedure</b>																	
Self-sampling	4.4	(4.33–4.41)	5	(1–5)	< 0.001	7	0.4%	42	2.2%	194	10.4%	631	33.7%	998	53.3%	1872	6
Clinician-based sampling	4.5	(4.48–4.56)	5	(1–5)		13	0.8%	29	1.8%	107	6.7%	420	26.3%	1030	64.4%	1599	2
<b>Trust in test result</b>																	
Self-sampling	4.4	(4.41–4.47)	5	(1–5)	0.005	4	0.2%	11	0.6%	157	8.4%	687	36.7%	1011	54.1%	1870	8
Clinician-based sampling	4.5	(4.47–4.53)	5	(1–5)		10	0.6%	12	0.8%	88	5.5%	538	33.7%	947	59.4%	1595	6

\* Bonferroni corrected p-value.

sampling for future screening (Bosgraaf et al., 2015; Sultana et al., 2015; Virtanen et al., 2014; Karjalainen et al., 2016). Results of the current study are in line with previous studies and show that experiences and preferences regarding self-sampling do also apply to a routine screening population. Previous studies that evaluated self-sampling experiences in a routine screening population showed, as in the current study, that women reported self-sampling to be convenient and user-friendly (Waller et al., 2006; Ketelaars et al., 2017). Moreover, 63% of women reported to prefer self-sampling over clinician-based sampling for future screening, as compared to about 80% in the current study (Ketelaars et al., 2017).

As in several previous studies (Sultana et al., 2015; Waller et al., 2006), women in the current study performing self-sampling reported significantly lower levels of trust in correct execution of the sampling procedure and in the test result as compared to clinician-based sampling. Trust in correct execution of sampling procedure and in the test result are likely to increase when additional evidence about the clinical accuracy of HPV self-sampling in a routine screening population becomes available to women. In this regard, the results of the IMPROVE study, showing that HPV self-sampling is non-inferior to clinician-based HPV testing with respect to detection of CIN2+ and CIN3+, are encouraging and may help to reduce uncertainties about HPV self-sampling. If women become informed that self-sampling is a reliable and safe method for participation in cervical screening, it is to be expected that an even higher proportion of women would prefer self-sampling. Here, the authorities responsible for screening programs, as well as general practitioners, physician assistants and gynaecologists, play an important role in informing and educating women, and are likely to have major impact on the acceptability of HPV self-sampling.

A majority of HPV-negative women (89%) indicated to prefer self-sampling to clinician-based sampling in future screening. HPV-positives also reported a preference towards self-sampling, however, slightly less pronounced: 77% preferred self-sampling. A possible explanation for the difference in preference between HPV-negative and HPV-positive women is that self-sampling HPV-positives in the IMPROVE study still had to undergo clinician-based sampling for cytology triage (Polman et al., 2019). This second step may be experienced as burdensome and may have decreased HPV-positive women's preference regarding self-sampling as compared to HPV-negative women. Direct triage tests for HPV-positive samples that are applicable on self-collected samples may overcome this problem. Cytology testing cannot be accurately performed on self-collected samples, but molecular triage testing may provide a solution in the future (Luttmer et al., 2016; Ebisch et al., 2016; Verlaet et al., 2018; Snoek et al., 2019).

In this study, all women performing self-sampling used the Evalyn brush. Consequently, results with regard to usability, discomfort, pain, nervousness, shame, privacy, trust in correct execution of sampling procedure, and trust in accuracy of the HPV result were reported specifically for this brush-based self-sampling device. However, previous studies reported similar acceptability and experiences between brush- and lavage-based self-sampling devices (Bosgraaf et al., 2015; Karjalainen et al., 2016).

Important strengths of this study are its large sample size and its setting within the nationwide screening programme in the Netherlands. However, there are also some limitations. The IMPROVE study was an opt-in study with a fairly low response rate: only 16,000 out of 185,000 invited women participated in the IMPROVE study. Moreover, among participating women, there was a higher percentage of withdrawal among women randomised to clinician-based sampling as compared to self-sampling, which may indicate a pre-existing preference for self-sampling among study participants. This may raise questions about the representativeness of the IMPROVE study for a routine screening setting. However, women in the IMPROVE cohort had a similar screening history and CIN2+ rate as women participating in the national screening programme, indicating that the IMPROVE study population does not represent a subset of underscreened women. The IMPROVE

population may still be a cohort in which the attitude towards HPV self-sampling is more positive than in the routine screening population, although results observed in our study are consistent with other preference studies. Another limitation of this study is that women received the questionnaire a few months after participation in the IMPROVE trial. Therefore, results may be subject to recall bias. However, in order to minimize this type of bias, questionnaires were only sent to women who had participated in the IMPROVE study within six months prior to the start of the questionnaire study. Another limitation is that, because of privacy and ethical regulations in the Netherlands, questionnaires were completely anonymous and therefore could not be linked to the IMPROVE study on the individual level.

Future research should focus on the clinical accuracy of other self-sampling devices in combination with HPV assays, and on the experiences and preferences of women, and the participation rate of self-sampling as a primary screening method in routine screening. Depending on results of these studies self-sampling might be offered as a primary method in the future. Arguments that are expected to play a role in the discussion about how to screen women in the future are cost-effectiveness, maximisation of screening coverage, and women their preferences.

In conclusion, results of this study show that women from a routine screening population have a positive attitude towards self-sampling but do express some concerns with respect to accuracy. Moreover, the majority of these women prefer self-sampling to clinician-based sampling in future screening. These results are supportive of self-sampling as a female-friendly primary screening method. Given that there are some concerns about the reliability of self-sampling and a minority of women prefer clinician-based sampling, a screening approach where women can choose for either method seems highly justifiable.

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## Conflict of interest

NJP, YH, NJV, HCWV, LFAGM and FJK have no conflict of interest. DAMH has minority stake in Self-screen B.V., a spin-off company of Amsterdam UMC (formerly known as VU University Medical Center Amsterdam), which owns patents related to this work. DAMH has been on the speaker's bureau of Qiagen, serves occasionally on the scientific advisory boards of Pfizer and Bristol-Meyer Squibb.

CJLMM served occasionally on the scientific advisory board (expert meeting) of Qiagen and SPMSD/Merck, and served by occasion as a consultant for Qiagen. He also served occasionally on the scientific board of GSK, and has received speakers' fee from SPMSD/Merck. CJLMM has been co-investigator on a Sanofi Pasteur MSD sponsored trial, of which his institute received research funding. CJLMM is minority shareholder and part-time CEO of Self-Screen B.V., which holds patents on hrHPV test and methylation marker tests in cervical screening. CJLMM has very small number of shares of Qiagen.

JB received fees for attending expert meetings organized by Merck and GSK and travel support by DDL. Fees were collected by JB's employer.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpmed.2019.04.025>.

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