



## **Danish method study on cervical screening in women offered HPV vaccination as girls (Trial23) a study protocol**

Thamsborg, Lise Holst; Andersen, Berit; Larsen, Lise Grupe; Christensen, Jette; Johansen, Tonje; Hariri, Jalil; Christiansen, Sanne; Rygaard, Carsten; Lyng, Elsebeth

*Published in:*  
BMJ Open

*DOI:*  
[10.1136/bmjopen-2017-020294](https://doi.org/10.1136/bmjopen-2017-020294)

*Publication date:*  
2018

*Document version*  
Publisher's PDF, also known as Version of record

*Document license:*  
[CC BY](https://creativecommons.org/licenses/by/4.0/)

*Citation for published version (APA):*  
Thamsborg, L. H., Andersen, B., Larsen, L. G., Christensen, J., Johansen, T., Hariri, J., ... Lyng, E. (2018). Danish method study on cervical screening in women offered HPV vaccination as girls (Trial23): a study protocol. *BMJ Open*, 8(5), [e020294]. <https://doi.org/10.1136/bmjopen-2017-020294>

# BMJ Open Danish method study on cervical screening in women offered HPV vaccination as girls (Trial23): a study protocol

Lise Holst Thamsborg,<sup>1</sup> Berit Andersen,<sup>2</sup> Lise Grupe Larsen,<sup>3</sup> Jette Christensen,<sup>4</sup> Tonje Johansen,<sup>5</sup> Jalil Hariri,<sup>6</sup> Sanne Christiansen,<sup>7</sup> Carsten Rygaard,<sup>1</sup> Elsebeth Lynge<sup>8</sup>

**To cite:** Thamsborg LH, Andersen B, Larsen LG, *et al.* Danish method study on cervical screening in women offered HPV vaccination as girls (Trial23): a study protocol. *BMJ Open* 2018;0:e020294. doi:10.1136/bmjopen-2017-020294

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-020294>).

Received 27 October 2017  
Revised 8 April 2018  
Accepted 13 April 2018

## ABSTRACT

**Introduction** The first birth cohorts of women offered human papillomavirus (HPV) vaccination as girls are now entering cervical screening. However, there is no international consensus on how to screen HPV vaccinated women. These women are better protected against cervical cancer and could therefore be offered less intensive screening. Primary HPV testing is more sensitive than cytology, allowing for a longer screening interval. The aim of Trial23 is to investigate if primary HPV testing with cytology triage of HPV positive samples is a reasonable screening scheme for women offered HPV vaccination as girls.

**Methods** Trial23 is a method study embedded in the existing cervical screening programme in four out of five Danish regions. Without affecting the screening programme, women born in 1994 are randomised to present screening with liquid-based cytology every third year (present programme arm) or present screening plus an HPV test (HPV arm). The study started 1 February 2017 and will run over three screening rounds corresponding to 7–8 years.

**Analyses** The primary endpoint is cervical intraepithelial neoplasia grade 3 or above. The trial is undertaken as a non-inferiority study including intention-to-treat and per-protocol analyses. The potential effect of primary HPV screening with a 6-year interval will be calculated from the observed data.

**Ethics and dissemination** The study protocol has been submitted to the ethical committee and deemed a method study. All women are screened according to routine guidelines. The study will contribute new evidence on the future screening of HPV vaccinated birth cohorts of women. All results will be published in open-access journal.

**Trial registration** NCT03049553; Pre-results.

## INTRODUCTION

There are two preventive measures against cervical cancer: the long-time practised cervical cancer screening aiming to find precancerous lesions before they develop into invasive cancer and the newer vaccination

## Strengths and limitations of this study

- Embedded in the existing cervical screening programme.
- Cross-regional study including large number of women.
- Six-year screening interval in human papillomavirus arm estimated based on observed data.

against human papillomavirus (HPV), a necessary cause of cervical cancer.<sup>1</sup> In Denmark, as well as in many other countries, both measures are used. However, there is no international consensus on the best way to combine the two. Trial23 aims to contribute in answering this question.

In 2016, the first birth cohort of Danish women offered HPV vaccination as girls entered the cervical screening programme. So far, the national recommendations for cervical screening have not changed. Denmark was among the first countries to introduce HPV vaccination and is consequently one of the first countries to face the challenge of how to screen HPV vaccinated women. Trial23 aims to optimise screening for women offered HPV vaccination as girls.

In 2008, Danish girls born in 1993–1995 were offered free HPV vaccination with the quadrivalent Gardasil (Merck). They were 13–15 years old at the time. Since 2009, HPV vaccination has been part of the Danish child vaccination programme for 12-year-old girls.<sup>2</sup> The vaccine high risk (HR) HPV types 16 and 18 are present in 70% of cervical cancers.<sup>3</sup> Vaccine studies have shown a protection of almost 100% against vaccine type (HPV 16 and 18) related cervical intraepithelial neoplasia (CIN) 2+ in women HPV naive at the time of vaccination<sup>4,5</sup> and a protection of 43% against all CIN2+.<sup>6</sup> As HPV



For numbered affiliations see end of article.

### Correspondence to

MD Lise Holst Thamsborg;  
lith@sund.ku.dk

is a sexually transmitted infection, vaccination should preferably take place before sexual debut.

Cervical screening in Denmark targets women aged 23–64 years. From ages 23– to 49 years, women are offered cytology-based screening every third year, and for 50 years and above, every fifth year. Liquid-based cytology is used nationwide. Women above age 60 years are offered an HPV-DNA ‘exit-test’.<sup>7</sup> Most of the samples are taken in general practice. Coverage is about 75% for all age groups<sup>8</sup> and around 60% for women aged 23–24 years.<sup>9</sup>

Several countries are implementing primary HPV testing, such as Australia, New Zealand, Sweden and the Netherlands.<sup>10–13</sup> Primary HPV testing has been compared with cytology in large randomised controlled trials (RCTs) showing that HPV testing provides a better protection against cervical cancer.<sup>14</sup> Indeed, the 6-year protection against CIN3+ after a negative HPV test was higher than the 3-year protection after a negative cytology test.<sup>15</sup> For young women, data from A Randomised Trial In Screening To Improve Cytology (ARTISTIC) trial show similar results.<sup>16</sup> However, the European Guidelines recommend against primary HPV screening in women younger than 30 years because of a risk of increased overdiagnosis and referral for colposcopy.<sup>17</sup> This is due to a high HPV prevalence combined with a high regression rate of lesions in young women.<sup>18</sup> A Danish study estimated that 46% of unvaccinated Danish women aged 20–23 years have an HR HPV infection.<sup>19</sup> This underlines the need for triage in primary HPV testing of young women.

### Objective

Women HPV vaccinated as girls are better protected against cervical cancer than previous birth cohorts. HPV vaccination is expected to prevent 70% of cervical cancers. So even in these women, some screening may still be beneficial. It is therefore pertinent to find less intensive screening schemes for women HPV vaccinated as girls.

The objective of this study is to investigate if primary HPV testing with cytology triage every 6 years protects women offered HPV vaccination as girls against CIN3+ to the same extent as the current cytology-based screening every 3 years. The longer screening interval would reduce the burden of screening in HPV-negative women by reducing the number of screening rounds. In this way the screening programme could take into account that the optimal balance between screening-related harms and gains differs between HPV-vaccinated women and previous birth cohorts.

### Hypothesis

No difference between cumulative risk of CIN3+ after two rounds of primary HPV screening with cytology triage and three rounds of cytology-based screening (present screening programme).

### METHODS AND ANALYSIS

Trial23 is a method study embedded in the Danish cervical screening programme.

Originally, the intention was to compare the present screening method (cytology) to primary HPV testing with cytology triage with different time intervals. However, the Danish Ethical Committee required informed consent for permission to randomise screening scheme. Collection of informed consent was not feasible due to the large number of participants and decentralised sampling procedure. For this reason, the trial is undertaken as a method study as defined by the Danish Ethical Committees. However, although the design has changed, the objective of the trial is unchanged, and the comparison between the two envisioned schemes will be calculated from the collected data. We therefore operate with the terms ‘HPV’ and ‘present program arm’.

In the method study, the HPV test is made as a cotest on the cytology sample material without affecting the screening programme. The HPV test does not affect the clinical management of the woman.

### Study design

Women are randomly allocated 1:1 for HPV or present programme arm:

- ▶ HPV arm: cytology and HPV-test every third year.
- ▶ Present programme arm: cytology every third year

There are four possible scenarios for women in the HPV-arm (see [figure 1](#)):

- ▶ HPV-negative, cytology normal.
- ▶ HPV-negative, cytology abnormal.
- ▶ HPV-positive, cytology normal.
- ▶ HPV-positive, cytology abnormal.

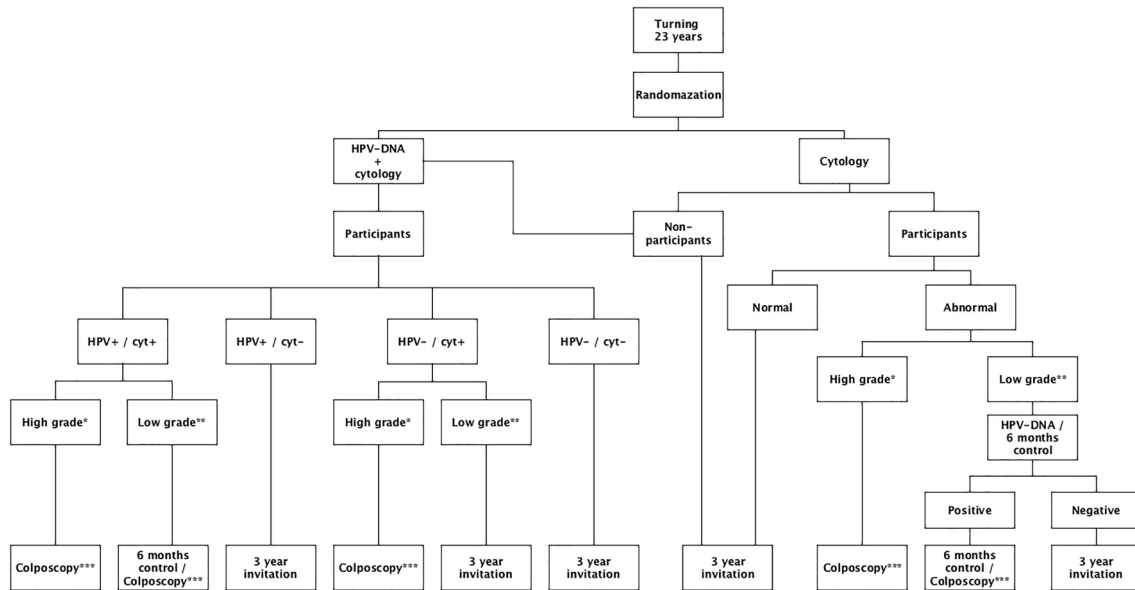
Among these scenarios only the HPV-negative/cytology abnormal differs from primary HPV screening with cytology triage. In this case, cytology triage would not have been performed and abnormal cytology would not have been found.

In the present screening programme, all regions refer women with high-grade cytology changes to colposcopy and biopsy. In case of low-grade cytology changes, some regions use HPV triage, while others recommend cytology control after 6 months. These regional practices are incorporated into the HPV arm (see [figure 1](#)).

In order to avoid increased referral for colposcopy and overdiagnosis when young women are screened with HPV tests, the cytology determines the course of action. A woman with a positive HPV test and normal cells at baseline is retested for both HPV and cytology in the next round 3 years later, as in the new Swedish cervical screening programme.<sup>11</sup>

### Setting

The study is set in four out of five Danish regions: Central Denmark Region, North Denmark Region, Region Zealand and part of Region of Southern Denmark (see [figure 2](#)). Cervical screening is centralised to one or a few pathology departments in each region.



**Figure 1** Trial flow for participation in cervical screening. \*Abnormal cytology, high grade: HSIL, ASCH and AIS (Bethesda classification). \*\*Abnormal cytology, low grade: ASCUS, AGC and LSIL (Bethesda classification). \*\*\*Colposcopy with biopsy. AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASCH, atypical squamous cells cannot exclude; ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high grade squamous intraepithelial lesions; LSIL, low grade squamous intraepithelial lesions.

### Timeline

Trial23 commenced on 1 February 2017 and will run over three screening rounds, that is, 7–8 years (see [table 1](#)). The final results will be analysed when follow-up is completed. Results of the baseline screening round will be analysed after 1 October 2018 allowing for at least 3 months from invitation to screening and 6 months for follow-up in case of abnormal screening result.

### Target population

Women born in 1994 turning 23 years in 2017 and living in the geographical areas covered by the trial form the target population (see [table 2](#)). These women were 14 years old when they were offered HPV vaccination, and more than 80% of them had at least one dose.<sup>20</sup> According to a Danish school survey, 76% had not had their sexual debut and are therefore expected to have been HPV naïve at the time of vaccination.<sup>21</sup>

### Eligibility criteria

#### Inclusion criteria

Women born in 1994 and living in the geographical areas covered by the trial are automatically included.

#### Exclusion criteria

None.<sup>22</sup>

### Randomisation

All persons ever living in Denmark have a personal identification number (PIN) and are included in the Danish Central Person Register (CPR). The PIN is registered at all contacts to the healthcare system. PINs for women born in 1994 and living in Denmark in January 2017 were obtained from the CPR.

These women were individually randomised to HPV or present programme arm, and this allocation was loaded onto the pathology IT systems of the participating pathology departments.

Randomisation is based on birth year instead of participation in screening, because we want to include all women to allow for intention-to-treat analysis. Women are not randomised by region in spite of the small regional differences in management and follow-up ([figure 1](#)). Young women tend to be mobile, and we therefore prefer to stratify the results by region afterwards.

When a cytology sample from a randomised woman is received at a laboratory and scanned into the IT system, a ‘pop-up’ message appears on the screen. The ‘pop-up’ message shows that the woman is included in Trial23 and informs if an HPV test should be performed. A specific project code is assigned at registration.

### Blinding

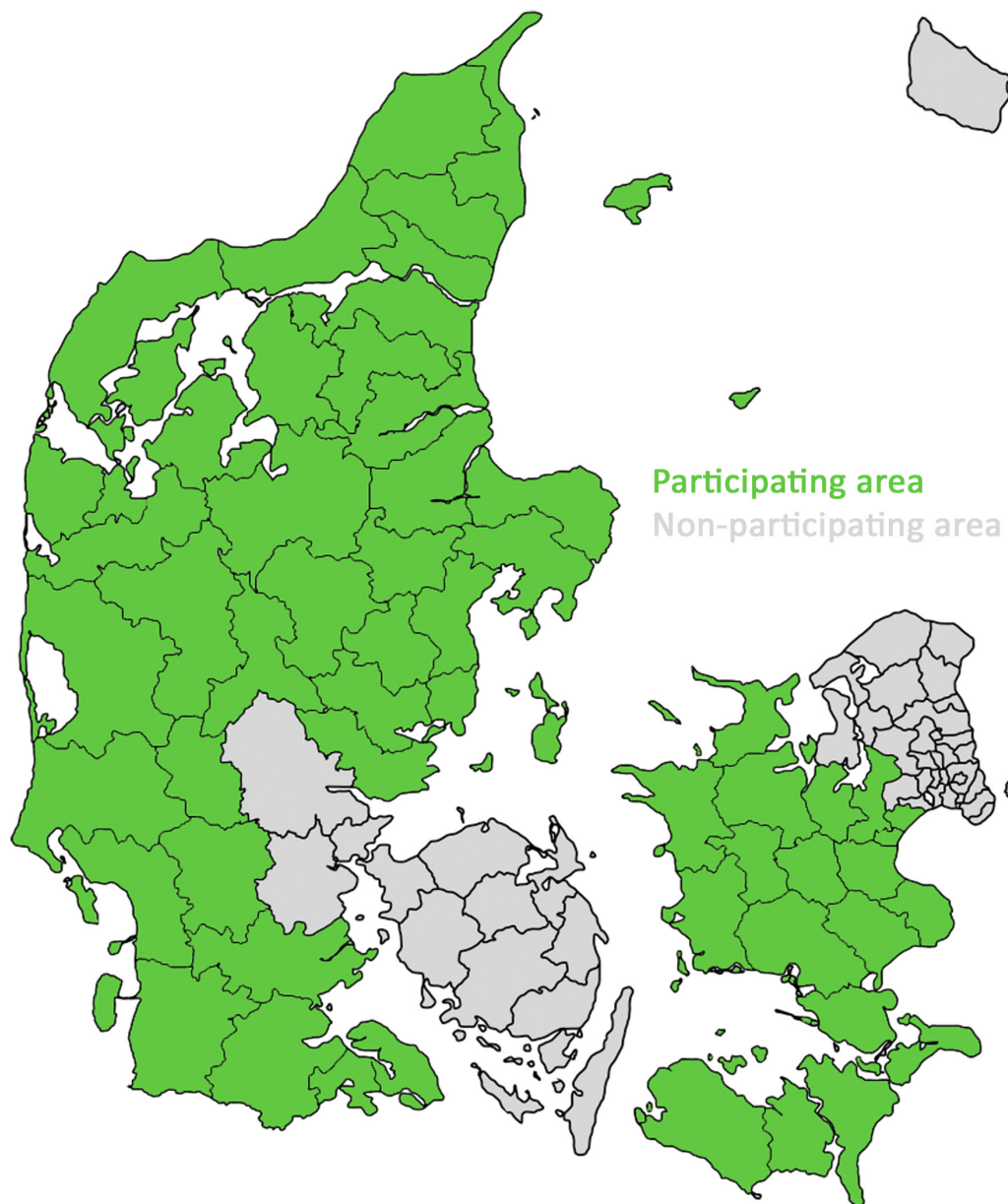
The trial is unblinded.

### Outcome measures

#### Primary outcome

How many cases of CIN3+ seen over two rounds of HPV screening with cytology triage with a 6 years interval, including follow-up after 3 years of women HPV-positive and cytology normal at baseline, would have been seen over three rounds of cytology screening with a 3-year interval.

CIN3+ is chosen as primary outcome because the Danish Society of Gynecology and Obstetrics<sup>23</sup> at this stage always recommends Large Loop Excision of the Transformation Zone (LLETZ).



**Figure 2** Map over the geographical areas covered by Trial23.

#### Secondary outcomes

Number of colposcopies and number of LLETZs observed over three rounds of cytology screening and estimated over two rounds of HPV screening with cytology triage.

#### Other outcomes

Baseline screening results.

#### Intervention

There is no real intervention in this study as it is a method study, and the result of the HPV test does not affect the clinical management of the woman. However, in the intervention arm, an HPV test is performed in addition to routine cytology screening. Cobas 4800 HPV-DNA test (Roche) is used in the trial, because it was already in routine use in the participating pathology departments. There was therefore no need for special training or extra equipment.

Roche sponsors test kits for the trial. Cobas is a PCR test and detects 14HR HPV types. It operates with three signals: HPV-16, HPV-18 and 'HPV-other' covering the remaining 12HR HPV-types (31,33,35,39,45,51,52,56,58,59,66, 68).<sup>24</sup> Standard laboratory requirements from the manufacturer are followed. As part of the trial, cervical biopsies are analysed with CINtec p16 Histology (Roche)<sup>25</sup> in addition to the routine pathology reading. Roche sponsors the p16 test kits.

#### Data analysis plan

The trial is undertaken as a non-inferiority study. If non-inferiority is proved, analysis for superiority will be carried out. Incidence rate ratios for outcomes will be calculated using Poisson regression analysis and SAS statistical software. We plan two types of analysis. First, an intention-to-treat analysis (ITT) including all randomised

**Table 1** SPIRIT flow chart for Trial23

Study period	Enrolment/ allocation	Postallocation			Close-out
		Baseline screen	Second screen	Third screen	
Timepoint	January 2017*	February 2017– September 2018	January 2020– September 2021	January 2023– September 2024	1 October 2025†
<b>Enrolment</b>					
Eligibility	X				
Allocation	X				
<b>Intervention</b>					
HPV arm (CYT+HPV)		<-->	<-->‡	<-->	
Present programme arm (CYT)		<-->	<-->	<-->	
<b>Assessment</b>					
Baseline screen		X			
Second screen			X		
Third screen				X	
Final					X

\*All women born in 1994 living in Denmark in January 2017 were randomly allocated to HPV or present programme arm.

†End-of-study allowing for 1 year extra for women followed up due to abnormal cytology in former screening rounds.

‡Women with positive HPV test and normal cytology at baseline are retested after 3 years for both HPV and cytology.

CYT, cytology; HPV, human papillomavirus; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

women followed from study start on 1 February 2017 until censoring due to death, emigration, event or end-of-study. Second, a per-protocol analysis including only screened women. Follow-up of this group will start on the date of their first cytology sample and end at censoring due to death, emigration, event or end-of-study as in the ITT population. The analyses will be stratified by HPV vaccination status and region of residence. The expected outcome of primary HPV screening with cytology triage will be estimated by including CIN3+ lesions found over the 7 years of follow-up. For the envisioned primary HPV screening with cytology triage, we will include CIN3+ lesions in women HPV-positive/cytology abnormal at baseline; HPV-positive/cytology normal at baseline, but HPV-positive/cytology abnormal at re-testing after 3 years; or HPV-positive/cytology abnormal at re-screening after 6 years. For the routine cytology screening, we will include

CIN3+ lesions in women cytology abnormal, at either the baseline screen, at second screen after 3 years or at third screen after 6 years.

### Power calculation

The power calculation was based on the number of 23-year-old women residing in the geographic areas covered by the trial. We expect 60% of 23-year-old girls to participate in the screening programme.<sup>9</sup> Based on experience from women born in 1983, we expect 1% of the screened women to be diagnosed with CIN3+ at the first screening,<sup>26</sup> and we expect 80% of the women to be HPV vaccinated.<sup>20</sup> Furthermore, we expect the HPV vaccine efficacy for all CIN3+ to be 43%.<sup>6</sup> If there truly is no difference between the intervention and the present programme in our trial population, the upper limit of a one-sided 95% CI will exclude a difference of more than 0.35% with a power of 80% and a difference of 0.4% with a power of 90%. We expect approximately 12000 women born in 1994 to be included in the trial, with 6000 women in each arm.

### Data sources

Data on the screening tests (cervical cytologies and HPV tests) and other screening-related outcomes for women assigned a project code will be retrieved from the Danish Pathology register and other national health registers. Use of PINs ensures that there is almost no loss to follow-up and makes it possible to merge data from different registers for the study population.

**Table 2** Number of eligible women residing in the geographical areas covered by Trial23

Participating region	Number of 23-year-old women
Central Denmark	9242
North Denmark	3895
Zealand	3705
Southern Denmark (Soenderborg and Esbjerg)	2082
Total	18924

## Patient and public involvement

The research question was developed in response to discussions in Denmark about future screening of HPV-vaccinated women. No representative of patient organisations participated in the design of the study. The results will be disseminated to women and healthcare authorities.

## ETHICS AND DISSEMINATION

### Ethics

The study is a method study and therefore not notifiable to the ethical committees, and informed consent is not required. In this study, all women are screened according to routine practice with cytology every 3 years as in the present screening programme and all receive usual care. The two screening schedules are compared without affecting the screening programme, and there will be no change for the individual woman. In order to avoid confusion, general practitioners and women are, therefore, not informed about the HPV test. Handling and storage of data were approved by the Danish Data Inspective Agency (SUND-2016–22).

### Dissemination

The study protocol is registered at ClinicalTrials.gov (NCT03049553) and is made public in this protocol paper. Final and baseline results will be published in peer-reviewed, international open-access journals, listing authors according to authorship guidelines. Publication will be independent of results. Trial data will be deposited in the Danish Data Archive after end of study. Access to the data will follow the rules of the archive.<sup>27</sup>

## DISCUSSION

In Denmark, the first birth cohorts of women offered HPV vaccination as girls are currently entering the cervical screening programme. The purpose of Trial23 is to test a new, less intensive screening scheme for these women than the one currently offered in Denmark. The intention is to guide decision makers on future screening of HPV-vaccinated birth cohorts.

In Trial23, the focus is on the HPV-negative women who can benefit from a longer screening interval. Cytology is chosen as triage method, because it is in routine use in the pathology departments and of good diagnostic quality in Denmark.

Trial23 is undertaken as a method study. Originally, we planned for a public health trial with randomisation to either the new or the current screening scheme. Such public health trials have been undertaken in the other Nordic countries. In a Swedish trial, women aged 56–60 years were randomly invited to the present cytology-based screening or a new HPV-based screening scheme. The study was approved by the ethical committee who regarded participation in screening as consent.<sup>28</sup> Likewise, in Finland women aged 25–65 years were randomly

invited for the present cytology-based screening or a new HPV-based screening. The local ethical committees and national authorities deemed that informed consent was not necessary because the trial was part of the routine screening programme.<sup>29</sup> In Denmark, it was not possible to get permission for such a trial.

## Strengths and limitations

The major limitation of the method study design is that a 6-year screening interval in the HPV arm has to be estimated and that we have to account for the HPV-negative/cytology positive samples that would not have been found by primary HPV screening with cytology triage.

However, this design gives us the opportunity to evaluate a new screening scheme without changing the screening programme. Moreover, informed consent is not required, which is expected to ensure routine screening coverage and limited selection. It is also a strength that the study is undertaken within the existing screening programme, because the results reflect implementation directly.

As there is no real intervention, randomisation would not have been needed. However, the decision from the Ethical Committee not to allow randomisation of the screening test without informed consent came at a late stage, where the organisation and resource allocation were already in place. At that time, we could not double the number of needed HPV tests neither could we exclude participating laboratories. Therefore, we kept randomisation of the supplementary HPV test. The randomisation will furthermore allow for check of a possible difference in the cytology reading between the HPV and the cytology arms. All women are from the same birth cohort and examined in the same calendar period. However, we are not able to adjust for HPV status at the time of vaccination and risk factors such as number of sexual partners and smoking habits. Misclassification of codes in the national registers are of course present, but there is no reason to believe that it will introduce bias. In primary HPV screening with cytology triage, the HPV status is known before the cytology is read. However, our study is embedded in the routine procedure in five pathology laboratories with primary cytology screening involving many laboratory technicians and pathologists. In some laboratories, the HPV status is known before the cytology reading, while in other laboratories, cytology is read prior to the HPV testing.

## Perspectives

There is no international consensus on how to screen HPV-vaccinated women, and Denmark is one of the first countries to face this challenge. However, Australia implemented HPV vaccination already in 2007 and will in 2017 implement primary HPV screening with partial genotyping and cytology triage every 5 years for HPV-vaccinated and unvaccinated women aged 25–69 years. COMPASS (a Randomised Controlled Trial of Primary HPV Testing for

Cervical Screening in Australia) running in parallel aims to compare the new screening programme to cytology every two and a half years.<sup>10</sup> In addition, a consensus on cervical screening in HPV-vaccinated women has been reached in Italy,<sup>30</sup> where HPV vaccination started in 2008. Italy will change to primary HPV screening in 2021, when the first birth cohorts of women HPV vaccinated at age 12 years enter the screening programme. Age at start of screening will change from the current 25 to 30 years, and the new screening protocol will be used only for vaccinated women until herd immunity is sufficient for all women to receive the same screening regardless of vaccination status.

In Denmark, the next seven birth cohorts of women entering the cervical screening programme were offered HPV vaccination at age 12–13 years with high coverage around 90% for first dose.<sup>20</sup> However, recently HPV vaccination coverage has dropped in Denmark due to public concern about possible side effects.<sup>31</sup> Coverage is now 46% for first dose for girls born in 2004.<sup>20</sup> Japan has abandoned HPV vaccination because of attention to possible side effects,<sup>32</sup> and decreasing coverage is at present also observed in the Netherlands<sup>33</sup> and Ireland.<sup>34</sup> If HPV-vaccination coverage regains its former high level in Denmark, the same screening scheme would be applicable for all women because of high herd immunity. However, if coverage stays low, a similar approach as the Italian with different screening schemes for vaccinated and unvaccinated women may be considered.

## TRIAL STATUS

Ongoing.

### Author affiliations

<sup>1</sup>Centre for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

<sup>2</sup>Department of Public Health Programs, Randers Regional Hospital, Randers, Denmark

<sup>3</sup>Department of Pathology, Naestved Hospital, Naestved, Denmark

<sup>4</sup>Department of Pathology, Aalborg University Hospital, Aalborg, Denmark

<sup>5</sup>Department of Pathology, Randers Regional Hospital, Randers, Denmark

<sup>6</sup>Department of Pathology, Soenderjylland Hospital, Soenderborg, Denmark

<sup>7</sup>Department of Pathology, Sydvestjysk Hospital, Esbjerg, Denmark

<sup>8</sup>Nykøbing Falster Hospital, University of Copenhagen, Copenhagen, Denmark

**Acknowledgements** We would like to thank all employees at the pathology departments for their efforts and commitment in implementing and running Trial23. We are very grateful for your participation. Also we would like to thank Bjarne Andersen from CGL, who is responsible for the technical aspects of the trial in relation to the IT system Patobank. Your help and knowledge is indispensable.

**Contributors** LHT is the project manager, and EL is primary investigator. LHT, BA, LGL, JC, CR and EL have contributed to the design of the study. LHT, LGL, JC, TJ, JH and SC have contributed to collection of data. LHT is first author, but BA, LGL, JC, TJ, JH, CR and EL have all contributed to the preparation of the protocol and this protocol paper. All authors have approved the final version of the manuscript.

**Funding** The trial is funded by the Independent Research Fund Denmark (public funding) and smaller grants from private funds. Roche sponsors Cobas HPV-DNA test kits and CINtec p16 test kits for the trial. Roche has commented on the study protocol, but all decisions have been made by the research group.

**Competing interests** Roche has sponsored test kits for the trial. BA had participation in a scientific conference sponsored by Roche and participated in other studies with test kits sponsored by Roche and self-sampling devices sponsored by Axlabs. EL and CR participated in meetings with Roche with fees paid to the University of Copenhagen. The remaining authors have no other conflicts of interest.

**Patient consent** Not required.

**Ethics approval** The study protocol was submitted to the ethical committees of the Capital Region and deemed a method study (H-16022292).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19.
2. EPI-NEWS. Statens Serum Institut [in Danish]. 2008 <http://www.ssi.dk/~media/Indhold/EN%20-%20engelsk/EPI-NEWS/2008/pdf/EPI-NEWS%20-%202008%20-%20No%2035.ashx>
3. de Sanjose S, Quint WG, Alemany L, *et al.* Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010;11:1048–56.
4. Garland SM, Hernandez-Avila M, Wheeler CM, *et al.* Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356:1928–43.
5. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915–27.
6. Muñoz N, Kjaer SK, Sigurdsson K, *et al.* Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst* 2010;102:325–39.
7. National recommendations for cervical screening. (Sundhedsstyrelsens anbefalinger) [summary in English]. 2012 <http://www.sst.dk/~media/B1211EAFEDFB47C5822E883205F99B79.ashx> (accessed 20 Dec 2015).
8. Quality report on the Danish cervical cancer screening program (DKLS årsrapport). 2015 [https://www.sundhed.dk/content/cms/82/4682\\_dkls-%C3%A5rsrapport-2015.pdf](https://www.sundhed.dk/content/cms/82/4682_dkls-%C3%A5rsrapport-2015.pdf).
9. Lam JU, Lyng E, Njor SH, *et al.* Hysterectomy and its impact on the calculated incidence of cervical cancer and screening coverage in Denmark. *Acta Oncol* 2015;54:1136–43.
10. Saville AM. Cervical cancer prevention in Australia: Planning for the future. *Cancer Cytopathol* 2016;124:235–40.
11. Swedish recommendations for cervical Screening. 2015 <https://www.socialstyrelsen.se/riktlinjer/nationellascreeningprogram/livmoderhalscancer-screeningme> (accessed 20 Dec 2015).
12. National Screening Unit. *Planned changes to cervical screening test in 2018*. New Zealand, 2018. <https://www.nsu.govt.nz/news/planned-changes-cervical-screening-test-2018>. (accessed 10 May 2018).
13. National Institute of Public Health and Environment. Cervical cancer screening in the Netherlands. [http://www.rivm.nl/en/Documents\\_and\\_publications/Common\\_and\\_Present/Newsmessages/2014/Cervical\\_cancer\\_screening\\_in\\_the\\_Netherlands](http://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2014/Cervical_cancer_screening_in_the_Netherlands) (accessed 10 May 2017).
14. Ronco G, Dillner J, Elfström KM, *et al.* Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014;383:524–32.
15. Dillner J, Rebolj M, Birembaut P, *et al.* Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ* 2008;337:a1754.
16. Kitchener HC, Gilham C, Sargent A, *et al.* A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. *Eur J Cancer* 2011;47:864–71.



17. European Commission. European guidelines for quality assurance in cervical cancer screening. <http://www.ispo.toscana.it/sites/default/files/Documenti/raccomandazioni/supplemento%202015.pdf> (accessed 20 Dec 2015).
18. van Oortmarsen GJ, Habbema JD. Epidemiological evidence for age-dependent regression of pre-invasive cervical cancer. *Br J Cancer* 1991;64:559–65.
19. Kjær SK, Munk C, Junge J, *et al*. Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention? *Cancer Causes Control* 2014;25:179–89.
20. Statens Serum Institut. Vaccine coverage [in Danish]. <http://www.ssi.dk/Smitteberedskab/Sygdomsovervaagning/VaccinationSurveillance.aspx?xaxis=Cohort&vaccination=5&sex=0&landsdel=100&show=&datatype=Vaccination&extendedfilters=True#HeaderText> (accessed 10 Jul 2017).
21. Statens Institut for Folkesundhed. School Survey 2010 (Skolebørnsundersøgelsen) [in Danish]. <http://www.hbsc.dk/downcount/HBSC-Rapport-2010.pdf> (accessed 20 Dec 2015).
22. Statistics Denmark. Population count. <http://www.statistikbanken.dk/statbank5a/selectvarval/define.asp?PLanguage=0&subword=tabel&MainTable=FOLK1A&PXSI=199113&tablestyle=&ST=SD&buttons=0> (accessed 10 Jul 2017).
23. Guidelines Danish society of gynecology and obstetrics [in Danish]. <http://gynobsguideline.dk/hindsgavl/Cervixdysplasi2012.pdf>
24. Roche Molecular Diagnostics. Cobas HPV-test. <https://molecular.roche.com/assays/cobas-hpv-test/> (accessed 3 Jul 2017).
25. Roche. PKG INS, CINtec p16 Histology, English. [http://productlibrary.ventana.com/ventana\\_portal](http://productlibrary.ventana.com/ventana_portal) (accessed 3 Jul 2017).
26. Hestbech MS, Lynge E, Kragstrup J, *et al*. The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark. *BMJ Open* 2015;5:e007921.
27. Rigsarkivat. Danish data archive [in Danish]. <https://www.sa.dk/da/brug-arkivet/dda/> (accessed 6 Oct 2017).
28. Lamin H, Eklund C, Elfström KM, *et al*. Randomised healthcare policy evaluation of organised primary human papillomavirus screening of women aged 56–60. *BMJ Open* 2017;7:e014788.
29. Leinonen M, Nieminen P, Kotaniemi-Talonen L, *et al*. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. *J Natl Cancer Inst* 2009;101:1612–23.
30. Giorgi Rossi P, Carozzi F, Federici A, *et al*. Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference. *Prev Med* 2017;98:21–30.
31. Mølbak K, Hansen ND, Valentiner-Branth P. Pre-vaccination care-seeking in females reporting severe adverse reactions to hpv vaccine. a registry based case-control study. *PLoS One* 2016;11:e0162520.
32. Hanley SJB, Yoshioka E, Ito Y, *et al*. HPV vaccination crisis in Japan. *The Lancet* 2015;385:2571.
33. National Institute for Public Health and Environment. *Risk of measles outbreaks increases with decreasing vaccination coverage*. The Netherlands, 2017. [http://www.rivm.nl/en/Documents\\_and\\_publications/Common\\_and\\_Present/Newsmessages/2017/Risk\\_of\\_measles\\_outbreaks\\_increases\\_with\\_decreasing\\_vaccination\\_coverage](http://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2017/Risk_of_measles_outbreaks_increases_with_decreasing_vaccination_coverage) (accessed 3 Jul 2017).
34. thejournal.ie. News article: Irish parents are stopping their children from getting a cervical cancer vaccine - but why? <http://www.thejournal.ie/hpv-vaccine-4-2697247-Apr2016/>