BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009875
Article Type:	Research
Date Submitted by the Author:	01-Sep-2015
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Paediatrics
Keywords:	adolescents, HPV, prevention, randomised control trial, school-based

School-based intervention for the prevention of HPV among adolescents: a randomised controlled study

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Keywords: adolescents, HPV, prevention, randomised control trial, school-based
Word count: 4534

Abstract

Objective To improve primary prevention of human papillomavirus (HPV) infection by promoting vaccination and increased condom use among upper secondary school students.

Design Randomised controlled trial.

Setting 18 upper secondary schools in Sweden.

Participants Schools were first randomised to the intervention or the control group, after which individual classes were randomised to be included or not. 832 students aged 16 were invited to participate during the regular individual health interview with the school nurse. In the end, 741 (89.1%) students completed the study.

Interventions The intervention was based on the Health Belief Model (HBM). According to HBM a person's health behaviour can be explained by individual beliefs regarding health actions. School nurses delivered 30 minute face-to-face structured information about HPV, including cancer risks and HPV prevention, i.e. condom use and HPV vaccination. Students in both the intervention and the control groups completed questionnaires at baseline and after three months.

Main outcome measures Intention to use condom with a new partner and beliefs about primary prevention of HPV; and also specifically vaccination status and increased condom use.

Results The intervention had significant effect on the intention to use condom (p=0.004). There was also a significant effect on HBM total score (p=0.003), with a 2.559 points higher score for the intervention group compared to the controls. The influence on the HBM parameters *susceptibility* and *severity* was also significant (p<0.001 for both variables).The intervention also influenced behaviour: girls in the intervention group chose to have themselves vaccinated to a significantly higher degree than the controls (p=0.02).

Conclusions The school-based intervention had favourable effects on the beliefs about primary prevention of HPV and increased HPV vaccination rates in a diverse population of adolescents. These results provide the scientific support for the implication of nation-wide educational interventions that will, in the long run, save lives.

Trial registration - ClinicalTrials.gov Identifier: NCT02280967

Strengths and limitations of this study

- This is the first school-based educational randomised controlled trial targeting a diverse and representative population of adolescents of both sexes, with the aim to improve primary prevention of HPV.
- The rigorously tested and validated intervention was found to have significant favourable effects on both the behaviour and beliefs of the participants.
- Although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.
- For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. Consequently, the groups differed somewhat at baseline.

Introduction

Infection with human papillomavirus (HPV) is one of the major causes of infection-related cancer worldwide. HPV is related to cancer in the cervix uteri, penis, vulva, vagina, anus and the oropharynx.[1 2] These malignancies can be effectively prevented by the prophylactic vaccination against HPV and by safe sex, i.e. condom use, in addition to regular screening.[3-7] Many countries have implemented national HPV immunization programmes.[8] In Sweden girls aged 10-12 years are since 2012 offered the quadrivalent vaccine as part of the school-based vaccination programme administered by the school nurse, while older girls and young women are offered the vaccine in the catch-up programme administered in the primary care setting. The coverage among young women is substantially lower (58%) than in the lower age group (82%).[9]

HPV infections and HPV related diseases have increased in recent decades due to increased sexual risk-taking, i.e. lower condom use and multiple partners.[10 11] The highest prevalence of HPV is found among teenagers and young adults.[12 13] Therefore, preventive strategies, such as the implementation of effective educational interventions among adolescents, are very much needed.

Adolescents do not receive education regarding HPV on a regular basis. We have found that the school nurses play a key role in providing such information.[14-16] Adolescents have low awareness and low knowledge about the virus, especially regarding the cancer risks.[17] Educational school-based interventions can increase adolescents' awareness and knowledge about HPV prevention,[18 19] enhance preventive behaviours for sexually transmitted infections in general [20] and reduce sexual risk-taking.[21 22] Interventions can also have a beneficial effect on beliefs about HPV vaccination among girls.[23] So far, very few randomised controlled trials have been conducted among adolescents with the aim to promote primary HPV prevention.[24-26] And as far as we know, no such trial has been performed in a diverse population of both adolescent boys and girls.

Aim and hypothesis

The overall aim of the project was to improve primary prevention of HPV by promoting HPV vaccination and increased condom use among upper secondary school students. The hypothesis was that at follow-up the intervention group would have more favourable beliefs

towards HPV prevention than the control group and that this would influence their actual behaviour.

Methods

Study design

A randomised controlled trial with measurements at baseline and at follow-up after three months.

Setting

Sweden is a multicultural country: almost a third of all children under age 18 have an immigrant background (at least one parent born outside Sweden).[27] The Swedish upper secondary school, which the vast majority of students attend, comprises both theoretical and vocational programs and reaches adolescents aged 16-19 years. According to Swedish law all students should have access to school health. The school health work is mainly preventive and involves at least a school nurse and a school doctor. The school nurse works in the school on a regular basis, while the school doctor is only intermittently available. In Sweden sexual education is mandatory since 1955, and includes topics such as anatomy, sexuality, prevention of sexually transmitted infections and reproductive health. The education is age-adjusted and given repeatedly in primary and secondary school.

All first year upper secondary school students are offered a health interview with the school nurse, who provides a dialogue regarding psychosocial health, eating habits, sleep, physical activity, tobacco, alcohol and drugs as well as sexual health and relationships. Like most healthcare interventions in Sweden, the general health interview is optional, although usually all students do participate. The interview is scheduled for approximately one hour and conducted in an empathic atmosphere based on Motivational Interviewing, [28] with focus on the individual student's health and well-being. Thus, the health interviews differ somewhat depending on the individual's situation and needs.

Population and sample

First year upper secondary school students attending the regular health interview with the school nurse in the autumn semester of 2014 were eligible for participation. We excluded students who were not able to speak or write Swedish (i.e. recently arrived immigrants) and adolescents with learning disabilities (i.e. studying at special schools). Upper secondary

schools (n=18) in nine municipalities in central Sweden with a total of about 600 000 rural and urban inhabitants, and with different socio-economic levels represented, were included. The participating schools included those both municipally and privately managed, offered vocationally as well as theoretically oriented education, and had a varying number of students.

Recruitment and randomisation

School nurses were recruited to the project via the school heads and through direct contact at a national school health conference. For logistical reasons, those working in the far north or south of Sweden were not invited. Initially 59 schools were approached and eventually 18 schools were included, for details see the flow chart in Fig 1. A total of 23 school nurses working in 20 schools in nine municipalities agreed to participate in the study. Three nurses in two schools dropped out at the start of the intervention due to heavy workload as a result of reorganisation in the school health. This resulted in a total of 20 school nurses working in 18 schools. All the recruited nurses happened to be females.

Randomisation was performed in two steps. Firstly, in order to avoid the possibility of contamination, the schools were randomised into either the intervention group or the control group (the school names were randomly drawn by a person not involved in the project). Secondly, 113 school classes within these schools were randomly selected to be included in the study; this number was chosen in order to achieve the desired number of students according to power calculations (described below). The school nurses provided basic details about the classes (for example Social science 14A), and number of students in each class. If the class consisted of less than 25 students, an additional class was allocated. The students were recruited by the school nurses as described below. The end result was an intervention group of 392 students from 60 classes and a control group of 358 students from 53 classes (Fig 1).

Two school nurses in two schools dropped out during the intervention, due to termination of employment and personal reasons, and did not complete the health interviews with their allotted students. In order to compensate for these losses, which were all from the intervention group, all school nurses in the intervention group were offered to perform health interviews with an additional class. Consequently, similar classes were included in the study.

The students (n=832) were invited to participate in the study when they met the school nurse for the general health interview. Those who agreed to participate (n=751), gave informed written consent. Before the health interview started all students were asked to complete a baseline questionnaire. A follow-up questionnaire was completed after three months (n=741). The baseline questionnaire was completed individually at the school nurse's office while the follow-up questionnaire was given to the whole class. Students not present at this time could complete the follow-up questionnaire afterwards at the school nurse's office. School nurses were provided with checklists regarding the procedure and used log lists (protocols completed after each health interview) to assure that the intervention was performed in a uniform fashion.

Theoretical framework

The Health Belief Model (HBM) was used as a theoretical framework. This model has previously been used in studies about HPV and HPV vaccination[29 30] and in interventions with the aim to increase prevention of sexually transmitted infections.[18 31] According to the HBM framework, a person's health behaviour can be explained by the individual beliefs regarding health actions. HBM includes the following central constructs: perceived *susceptibility*, perceived *severity*, perceived *benefit* and perceived *barriers*. Furthermore, socio-demographic factors such as age, sex, ethnicity and parental education level, as well as knowledge, are recognised as factors that indirectly can influence the individual's behaviour. The main limitation of the model is that it does not consider emotional or relational aspects involved in decisions regarding health behaviour.[32]

Intervention

The intervention consisted of face-to-face education about HPV guided by HBM and following a pre-designed structure. The school nurse used a specially designed flipchart with pictures and brief information facing the students. On the other side of the flip chart, facing the school nurse, she had the information she was asked to provide (see example in Table 1). She also handed out a specially designed leaflet. The educational intervention was included in the regular health interview, which is normally scheduled for approximately one hour. The intervention took about 30 minutes and included the following information:

- general facts about the virus
- transmission
- what HPV can cause

- risk factors
- prevention, i.e. safe sex with condom use and HPV vaccination
- locations where the girls could receive the vaccine free of charge in the municipality
- facts about the HPV vaccine
- the importance for girls of attending future cervical cancer screening controls

The leaflet consisted of 12 pages and included similar information and also an HPV quiz as well as links to the national online youth clinic, the homepage of the university where the researchers worked and contact information to the authors. At the time for the follow-up questionnaire, students in the intervention group were provided with condoms. Students in the control group received standard treatment, i.e. the regular health interview, as described above (in Setting).

Outcome measures

Primary outcomes: Intention to use condom with a new partner and beliefs towards primary prevention about HPV.

Secondary outcomes: Increased HPV vaccination and increased condom use.

Pilot study

In early 2014 the intervention procedure, including the educational material and questionnaire, was tested by three school nurses among 45 students aged 16 years. The nurses were asked to take notes of any difficulties and provide suggestions for improvements. The nurses' experiences and suggestions were discussed in a feed-back session with MG and CS. This resulted in minor revisions: the educational material was shortened, some statements were simplified and the additional response alternative "do not know" was added to the block of questions regarding beliefs about HPV. A few of the questions were clarified and two were considered redundant and thus removed. In parallel, the questionnaire was tested among adolescents aged 17 (n=230),[33] who confirmed the school nurses' observations.

Instrument

The questionnaire was based on previous research and clinical experience. The questions about beliefs, awareness and knowledge about HPV (n=24) were adapted from our previous studies[14] and had multiple choice alternatives and six-point verbal rating scales from "Totally agree" to" Totally disagree", including "Do not know". The demographic background questions (n=14) were taken from the national questionnaire for adolescents [34] and the

questions regarding sexual behaviour (n=17) were based on a project among university students which has been used repeatedly since 1989.[10] The questions about beliefs towards primary prevention of HPV according to the HBM constructs on *susceptibility* comprised questions regarding the risk for contracting HPV; while *severity* included how serious it would be to receive an HPV infection or cancer. In addition, questions about *benefits* comprised confidence in vaccine effectiveness and intention to vaccinate; while *barriers* embraced the individual's perceived barriers for HPV vaccination, such as fear of needles and difficulties booking an appointment for vaccination.

Validity and reliability of the intervention including the questionnaire

The validity and reliability were rigorously tested with both qualitative and quantitative methods. Two focus group interviews were undertaken with adolescents (n=8) aged 16-17 years (both boys and girls) who were asked what they considered important to include in an intervention regarding prevention of HPV. Cognitive interviews (n=5) and discussion sessions (n=8) regarding the questionnaire were performed with adolescents aged 15-18 years. We also consulted other experts, such as a specialist in adolescent cognitive psychology, the head of the school health in a municipality and school nurses working with upper secondary school students. In addition, we had discussions in the interdisciplinary research group consisting of specialists in public health, biostatistics, school health, adolescents' sexual health, social medicine, virology, cervical cancer screening, and paediatrics.

To test the stability and reliability over time a test-retest evaluation was undertaken with first year upper secondary school students (n=29) randomly selected from a school situated in a city of 200 000 habitants in mid Sweden in 2014. The questionnaire was distributed on two occasions with a time interval of two weeks. Analysis was based on Cronbach's alpha and showed high reliability scores for the questions regarding the decision-making process about HPV vaccination (0.800-0.998), except for the single question "Do you want to be vaccinated later" (0.436). Statements regarding beliefs about HPV ranged from low to high (scores 0.331-0.918), consequently, two statements were removed.

Ethical considerations

The study was conducted according to the Declaration of Helsinki. All participants received oral and written information before giving their written consent. The participants were informed that participation was voluntary, that they could withdraw participation at any time without providing a motivation or incurring any negative consequences for themselves. They were also informed that only the researchers would have access to the data and that all data would be presented on a group level. Contact details to the researchers were provided in case of further questions. According to the Swedish law children above 15 years of age who understand what participation means have the right to give informed consent regarding participation in research studies.[35] Therefore, informed consent was not obtained from the parents. We asked permission to conduct the study from the head of the school health in each municipality and from the principals of the schools. The project was approved by the Regional Ethical Review Board of Uppsala University (D.nr.2013/324).

Education to school nurses

All participating school nurses (n=20) received written and verbal instructions and participated in educational sessions (with MG and CS) scheduled for about two hours. We provided the education in each municipality for groups of two to five nurses, while three nurses were educated individually due to the location of their schools. The education comprised factual information about HPV and the HPV vaccine. The flipchart educational material was presented and the nurses were encouraged to give comments if anything was unclear or if anything considered important was missing. Furthermore, each school nurse received a minimum of one hour additional education at the time for the start of the intervention at the school where she worked. During the intervention the nurses were contacted on a weekly basis.

Sample size calculation

The power calculation was based on a previous study among the research group[36] and clinical experience. The sample size of 400 participants per study arm were based on assumptions of baseline *intention to use condom if new partner* of 60%, with a power of 80% to detect differences of 10 percentage points between intervention and control group at a significance level of 5% (356/study arm IG/CG, a dropout of 10% and missing values=400).

Statistical analysis

For descriptive statistics, categorical data are presented as frequencies and percentages, n (%), ordinal data as medians, means and standard deviations (SD), while discrete and continuous data are given as mean and SD. Differences between the intervention and control groups at baseline and follow-up, respectively, are tested with Pearsons' Chi-square test for categorical data, Mann-Whitney test for ordinal and discrete data, and Student's independent samples *t*-test for continuous data. The effects of the intervention were measured from baseline at follow-up. First, the HBM scores were calculated by measuring the differences between baseline and at follow-up for each HBM question. Then the questions were grouped together according to the HBM constructs *susceptibility*, *severity*, *benefits* and *barriers*. Finally the total HBM index was calculated by adding all HBM constructs together. The McNemar test was used to determine differences in HPV vaccinations and condom use from baseline to follow-up.

In order to take into account the dependence between students who were informed by the same school nurse, Generalized Estimating Equations models were used for examining the results of the intervention on the outcome measures. The differences between the outcome variables at baseline and follow-up were used as dependent variables in the Generalized Estimating Equations models, while treatment group (intervention or control) was used as a predictor together with the socioeconomic and demographic variables sex and immigrant background, which differed significantly between the two groups at baseline. In all analyses, a two-sided p-value <0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics 22.0.

Results

Participants and sample

As mentioned above, a flow chart with details of the participants and samples is presented in Fig 1. A total of 2883 adolescents in 113 classes were allocated to either intervention group or control group. We excluded 496 adolescents not meeting the inclusion criteria. Of the 832 adolescents invited to participate, 81 declined, resulting in a total of 751 participants (i.e. the response rate was 90.2%); 394 in the intervention and 357 in the control group. At follow-up after three months 741 (98.7%) adolescents participated and were analysed (intervention group n=390 and control group n=351).

Baseline characteristics of participants by randomised group are presented in Table 2. The mean age was 16.1 years, 46.8% attended theoretical and 53.2% vocational programmes. More than a quarter (27.8%) had an immigrant background and over half of the girls (56.1%) were already vaccinated against HPV. There were significant differences between the groups at baseline regarding sex and immigrant background (Table 2). The reason for this is discussed in the Discussion section below. The effects of the intervention, unadjusted as well as adjusted for treatment group (intervention or control), sex and immigrant background, are presented in Tables 3 and 4. The adjusted analyses are further elaborated below. The validity of the Generalized Estimating Equations model fit for the HBM construct *benefits* was not certain, thus this result is not presented.

The mean time from baseline to follow-up was 3.26 months, with no differences between intervention and control groups. In some classes the health interviews were delayed due to the fact that some students participated in practical training, national examinations or other mandatory school activities. Consequently, the follow-up questionnaire was sometimes delayed for a maximum of two months.

Effect of the intervention

Condom use

The intervention had an effect on intention to use a condom with a new partner, with 1.751 higher points score for the intervention than the control group (p=0.004). Looking at subgroups, there were significant effects among boys (p=0.045), with a 1.355 points higher score after the intervention, while there were no significant differences among participants with an immigrant background (p=0.717) (Table 3). Still, there were no significant differences between the intervention and the control groups regarding their reports of the actual condom use during their latest intercourse (p=0.377).

HBM total score

The intervention had a significant effect on HBM total score (p=0.003), with a 2.559 points higher score for the intervention compared to the control group. For further details see Table 4. There were also differences between the groups regarding the two predictors, sex and immigrant background. Notably, boys in the intervention group had significantly lower scores (p=0.003) compared to the controls. Students with immigrant background in the intervention

group, however, had a 3.291 higher score compared to immigrant students in the control group (p=0.003).

Susceptibility

The intervention group reported higher scores for susceptibility (p<0.001) with a 1.675 points higher score compared to the control group; for details see Table 4. On the other hand, boys in the intervention group had again significantly lower scores for this outcome parameter as compared to boys in the control group (p<0.001). In contrast, the intervention had a significant effect among adolescents with an immigrant background, who had a 1.770 higher score (p<0.001), compared to the control group.

Severity

The intervention also had significant effect on severity (p<0.001), with a 0.409 higher score for the intervention group compared to the control group, for details see Table 4. Boys had again significant lower scores (p<0.001), while there were no differences between the groups for participants with immigrant background (p=0.330).

Barriers

There were no significant differences between the intervention and the control group for this parameter (p=0.262), for further details see Table 4. Notably, the intervention had significant positive effect (p=0.015) for boys, with a 0.469 higher score in the intervention group compared to the controls. The effect for individuals with an immigrant background, on the other hand, was the opposite (p=0.014).

HPV vaccination

The intervention increased the likelihood that the students actually became vaccinated. The proportion of vaccinated girls in the intervention group was 52.5% before and 59.0% after the intervention, whereas no difference over time was seen in the control group. This difference was significant (p=0.02). In actual numbers, 15 girls and one boy received the vaccine between the intervention and completion of the follow-up questionnaire. In addition, one girl wanted to be vaccinated, but her parents did not consent.

Discussion

Principal findings

This randomised controlled trial of a school-based educational session showed that adolescents' beliefs and behaviour regarding HPV prevention can successfully be improved. After the intervention the students who had received the intervention had significantly more favourable beliefs towards HPV prevention and were more inclined to use condom during sex with a new partner. In addition, the intervention increased actual HPV vaccination rates.

It is encouraging that the intervention's effect on the intention to use condom was substantial among boys, since they are neither included in the national HPV vaccination programme nor do they receive any organised information about HPV. Our finding gives support for the speculation that boys – when provided with adequate information – also want to protect themselves, and their partners, against the virus.

It was frustrating that the effects on the students' intentions did not result in clear differences in actual reported condom use. But it should be kept in mind that this is a small group – not all of them were sexually active, and those who were may not have had a new opportunity, with a new partner, between the intervention and the follow-up questionnaire. Consequently, too much weight should not be given to this finding. More important is the finding that several girls (and one boy) chose to have themselves vaccinated shortly after the intervention. Since the older girls are offered the vaccine in the catch-up programme and the families have to contact the primary care centre themselves to book an appointment, it is encouraging that the intervention had effects on vaccination rates.

There were significant effects on the HBM total score, which includes the parameters perceived *susceptibility*, perceived *severity*, perceived *benefits* and perceived *barriers*. The intervention was especially effective regarding beliefs about HPV prevention among adolescents with an immigrant background. This is an important finding, since Sweden is a multicultural country with many immigrants from countries with limited access to healthcare and health education. It was also encouraging that these students reported higher scores for perceived *susceptibility*, i.e. they had become aware of the risks. Immigrant background is associated with increased risk for cervical cancer [37] and lower attendance in cervical cancer screening programmes.[38 39]

We also found significant differences between the groups regarding perceived severity. According to HBM the combination of *susceptibility* and *severity* are labelled as perceived *threat*.[32] Since adolescence is a time in life when the perception of being at risk of contracting an sexually transmitted infection is generally low, especially among boys,[40] and

the sexual risk-taking is increasing,[11] we are happy to note that the intervention increased the adolescents' perception of HPV as a serious threat. This is beneficial for their future sexual health behaviour.

Strengths

The educational intervention was carefully developed, standardised, validated and monitored and had high response rate; 89.1% completed the study. Further major strengths are the randomised control trial design and the fact that various kinds of schools with a representative sample of both boys and girls were included. The percentage of adolescents with an immigrant background, as well as the number of HPV vaccinated girls at baseline, are representative for the Swedish population in general. This means that the findings can, with a fair degree of certainty, be extrapolated to the population at large. The target group, adolescents aged 16 years, is adequate since this is a time in life when many become sexually active. The school nurses, with their professional role and experience of discussing sensitive issues, are the proper persons to deliver the intervention. Finally, a school-based intervention reaches all adolescents regardless of socio-economic status, ethnicity or cultural background.

Weaknesses

For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. Consequently, the groups differed somewhat at baseline with, for example, more girls in the intervention group and more boys in the control group. We took this into account in the Generalized Estimating Equations model and adjusted for the demographic differences at baseline.

It is possible that the participating school nurses are more committed to HPV prevention and sexual health issues than their colleagues. These nurses' commitment and personal communication skills might have affected the outcome of the intervention in a favourable direction. To compensate for this and ensure uniformity the intervention was highly structured, the school nurses were provided with exhaustive instructions and the researchers regularly contacted them, asking questions systematically about *how does it work for you?* Also, as in all studies including self-reported questionnaires, there is a risk of participant over- or under-reporting or recall bias, although we consider this risk small in the present study.

Finally, although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.

Strengths and weaknesses in relation to other studies

To our knowledge this is the first randomised, educational, school-based face-to-face intervention study among a diverse population of adolescents with the aim to improve primary prevention of HPV. Previous studies have mainly been undertaken among young adult women.[25 29] As discussed in the systematic review by Sheperd et al[41] there is a need for interventions with greater focus on HPV and especially the link between HPV and cancer. Previous interventions have tended to focus on prevention of cervical cancer only.[41] It is also an advantage to use a theoretical framework such as HBM when developing an educational intervention with preventive aims. HBM is a systematic way to explain a person's health behaviour, which clarifies the key concepts on which the intervention is based.[32]

Our results stand in contrast to previous school-based interventions delivered in class in which no significant effects on beliefs[18] neither about condom use nor HPV vaccination, were found.[18 19] This discrepancy indicates that it is beneficial with a face-to-face intervention delivered by school nurses.

Implications

The results indicate that an educational intervention delivered by health care providers, school nurses, is a highly feasible and effective way to increase adolescents' beliefs and behaviour towards primary prevention of HPV, regardless of socio-economic status, ethnicity or cultural background.

Unanswered questions and future research

Larger studies with more participants may help understand if there are also further differences between girls and boys, and between students with or without an immigrant background. Some of our conclusions remain speculative, awaiting such studies. In addition, studies with longer follow-up are needed, in order to find out if school-based educational interventions are effective in the long term, and if the participants' actual behaviour changes in the desired direction.

Acknowledgements

We thank all the participants; especially the school nurses and the adolescents. We also thank the heads of the school health in each municipality and the principals of the schools. A special thanks to the Swedish Association of School nurses for support, and for allowing us to present the project at the national conference. In addition we thank Åke Pålshammar for valuable discussions about the project, especially about adolescents' psychosocial and cognitive development.

Contributors: MG conceptualised and designed the study, recruited participants, managed the data collection, completed data analysis and interpretation, wrote the draft manuscript, and obtained funding. AR assisted in design, data analysis and interpretation, funding and manuscript preparation. CS assisted in design, participant recruitment, data collection, data interpretation, manuscript preparation and funding. ML, MO, RW and TT assisted in design, data collection, data interpretation, manuscript preparations and funding. BA and TD assisted in design, data interpretation, funding, and were available for clinical consultation. TN assisted in all activities including design, data interpretation, data collection, manuscript preparation and funding. All authors made critical comments on drafts of the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding statement: This work was supported by [the Swedish Cancer Society] grant number [130744], [Uppsala-Örebro Regional Research Council] grant number [RFR-387561/476021] and [Uppsala County Council] grant number [LUL-347931], [the Swedish Government Funds for Clinical Research] grant number [19049/470102/44957] and the [Medical Faculty at Uppsala University] grant number [2012/278]. In addition, MG and CS received a scholarship from [the Gillbergska Foundation]. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests statement: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Uppsala University, Department of Public health and Caring Sciences and the Regional Ethical Committee in Uppsala, Sweden, D.nr. 2013/324 approved this study. All participants gave informed consent.

Data sharing: No additional data are available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table1. Example of the Flip chart

Student information	School nurses' work material "chat script"
Prevention of HPV 1. Vaccination HPV vaccine protects against the most common HPV types that causes cervical cancer och condyloma (genital warts). The vaccine is offered free of charge to young girls in school and to older girls at the primary care centres. The vaccine gives best protection before exposure to HPV. Therefore it is recommended to vaccinate before sexual debut.	How can HPV be prevented? The HPV vaccine is highly efficient against the most common HPV types that can cause cervical cancer and condyloma (genital warts). The vaccine is offered free of charge to 11 year old girls in the school and to older girls at the primary care centres. Note! You, as school nurse, shall inform where (at what primary care centre) the student can be vaccinated free of charge in your area. The vaccine gives best protection before exposure to HPV, therefore it is best to vaccinate before sexual debut, but you can also be vaccinated later on.

Table 2 Baseline characteristics of participants by randomised group (n=741)

	Intervention n =390 (52.6%)		Control n=351 (47.4%)		*p*-value
Characteristic					
Age (years) mean (Md) (Sd)	16.15 (16)	(0.77)	16.06 (16)	(0.73)	0.800[†]
Sex					<0.001[††]
Female	239	(61.4)	146	(41.6)	
Male	150	(38.6)	205	(58.4)	
Education					0.117[††]
Theoretical programme	172	(44.1)	176	(50.1)	
Vocational programme	218	(55.9)	175	(49.9)	
Immigrant background[¶]					0.017[††]
Yes	123	(31.5)	83	(23.6)	
No	267	(68.5)	268	(76.4)	
Educational level, mother[*]					0.799[†††]
University	167	(54.9)	158	(53.7)	
Upper secondary school	118	(38.8)	118	(40.1)	
Elementary school	19	(6.3)	18	(6.1)	
Educational level, father [*]					0.334[†††]
University	100	(36.2)	112	(39.9)	
Upper secondary school	145	(52.5)	142	(50.5)	
Elementary school	31	(11.2)	27	(9.6)	
Main occupation, mother					0.148[††]
Employed[¶¶]	339	(87.1)	315	(90.5)	
Unemployed[¶¶¶]	50	(12.9)	33	(9.5)	
Main occupation, father					0.095[††]
Employed[¶¶]	331	(92.5)	318	(92.5)	
Unemployed[¶¶¶]	27	(7.5)	15	(4.5)	
Tobacco use (smoking)					0.197[††]
Never	316	(81.0)	297	(84.6)	
Occassionally/Daily	74	(19.0)	54	(15.4)	
Tobacco use (snuff)					0.767[††]
Never	359	(92.1)	321	(91.5)	
Occassionally/Daily	31	(7.9)	30	(8.5)	
Alcohol consumption					0.284[††]
Never	257	(66.1)	218	(62.3)	
Occasionally/Monthly/Weekly	132	(33.9)	132	(37.7)	
HPV vaccinated (only girls[a])					0.103[††]
Yes	126	(52.9)	89	(61.4)	
No	83	(34.9)	47	(32.4)	
Do not know	29	(12.2)	9	(6.2)	

[†]Independent Samples T-test[††]Chi-Square Tests, [†††]Mann-Whitney Test, [¶]Immigrant background: born outside Sweden or one or two parents born outside Sweden[¶¶]Employed includes studying and/or parental leave, [¶¶¶]Unemployed includes sick leave and similar.**Total amount do not add up to n=751 (100%) due do not know not presented and/or missing answer.*, [a] Not included in the numbers: One boy in CG HPV vaccinated at baseline

Table 3. Results of the Generalized Estimating Equations analyses. Effect of the intervention for the main outcome - intention to use condom if new partner.

Outcome	Predictors	Unadjusted Slope coefficient (95% CI)	P-value	Adjusted¶ Slope coefficient (95% CI)	P-value
Intention to use condom if new partner	Intervention	0.449 (0.150 to 0.749)	0.003	1.751	0.004
	Boys	N/A		1.355 (0.031 to 2.679)	0.045
	Immigrant	N/A		0.132 (-0.580 to 0.844)	0.717

¶ Adjusted for treatment group (intervention or control group), sex and immigrant background

Table 4. Results of the Generalized Estimating Equations analyses. Effect of the intervention according to the Health Belief Model (HBM).

Outcome	Predictors	Unadjusted Slope coefficient (95% CI)	P-value	Adjusted¶ Slope coefficient (95% CI)	P-value
HBM total score	Intervention	0.666 (-0.065 to 1.398)	0.074	2.559 (0.875 to 4.324)	0.003
	Boys	N/A		-2.244 (-3.729 to -0.759)	0.003
	Immigrant	N/A		3.291 (1.107 to 5.474)	0.003
Susceptibility	Intervention	0.444 (0.099-0.790)	0.012	1.675 (0.850 to 2.500)	<0.001
	Boys	N/A		-1.544 (-2.172 to -0.916)	<0.001
	Immigrant	N/A		1.770 (0.953 to 2.587)	<0.001
Severity	Intervention	0.307 (0.011-0.603)	0.042	0.409 (0.183 to 0.634)	<0.001
	Boys	N/A		-0.339 (-0.490 to -0.187)	<0.001
	Immigrant	N/A		0.131 (-0.133 to 0.395)	0.330
Barriers	Intervention	-0.047 (-0.509 to 0.315)	0.799	-0.172 (-0.473 to 0.129)	0.262
	Boys	N/A		0.469 (0.091 to 0.845)	0.015
	Immigrant	N/A		-0.505 (-0.910 to -1.00)	0.014

¶ Adjusted for treatment group (intervention or control group), sex and immigrant background

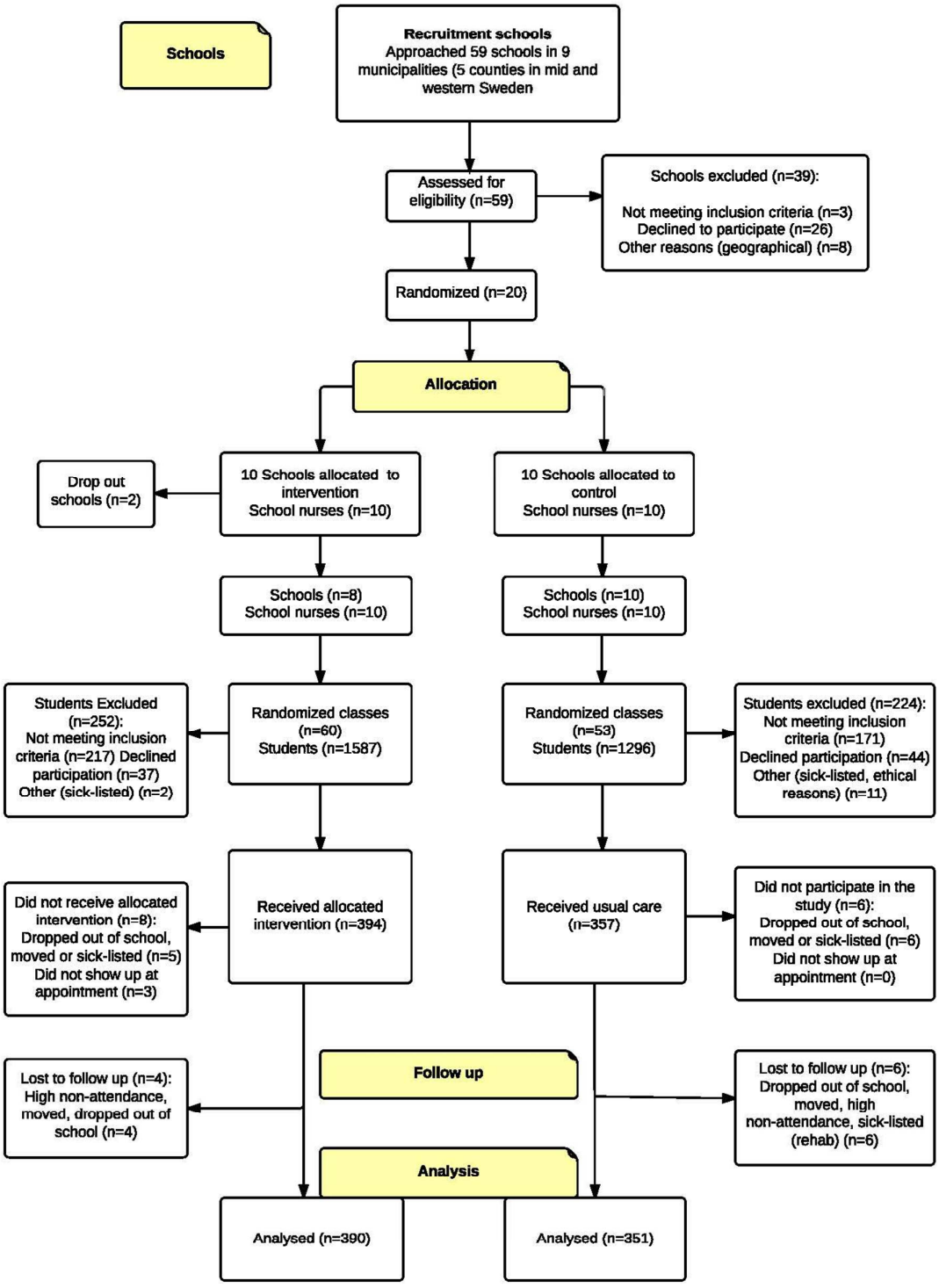

Fig 1. Flow of schools and students through trial

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5-6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8 and 5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11 and figure page 25
	13b	For each group, losses and exclusions after randomisation, together with reasons	12 and figure page 25
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5-7
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2 page 22
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 3 and Table 4 page 22 and 23.
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-15 and ethics page 10
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009875.R1
Article Type:	Research
Date Submitted by the Author:	04-Nov-2015
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Paediatrics
Keywords:	adolescents, HPV, prevention, randomised control trial, school-based

School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study

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Keywords: adolescents, HPV, prevention, randomised control trial, school-based
Word count: 4649

Abstract

Objective To improve primary prevention of human papillomavirus (HPV) infection by promoting vaccination and increased condom use among upper secondary school students.

Design Cluster randomised controlled trial.

Setting 18 upper secondary schools in Sweden.

Participants Schools were first randomised to the intervention or the control group, after which individual classes were randomised to be included or not. 832 students aged 16 were invited to participate during the regular individual health interview with the school nurse, 751 (90.2%) agreed to participate, and 741 (89.1%) students completed the study.

Interventions The intervention was based on the Health Belief Model (HBM). According to HBM a person's health behaviour can be explained by individual beliefs regarding health actions. School nurses delivered 30 minute face-to-face structured information about HPV, including cancer risks and HPV prevention, i.e. condom use and HPV vaccination. Students in both the intervention and the control groups completed questionnaires at baseline and after three months.

Main outcome measures Intention to use condom with a new partner and beliefs about primary prevention of HPV; and also specifically vaccination status and increased condom use.

Results All statistical analyses were performed on individual level. The intervention had a significant effect on the intention to use condom ($p=0.004$). There was also a significant effect on HBM total score ($p=0.003$), with a 2.559 points higher score for the intervention group compared to the controls. The influence on the HBM parameters *susceptibility* and *severity* was also significant ($p<0.001$ for both variables). The intervention also influenced behaviour: girls in the intervention group chose to have themselves vaccinated to a significantly higher degree than the controls ($p=0.02$). No harms were reported.

Conclusions The school-based intervention had favourable effects on the beliefs about primary prevention of HPV and increased HPV vaccination rates in a diverse population of adolescents.

Trial registration - ClinicalTrials.gov Identifier: NCT02280967

Strengths and limitations of this study

- This is the first school-based educational cluster randomised controlled trial targeting a diverse and representative population of adolescents of both sexes, with the aim to improve primary prevention of HPV.
- The rigorously tested and validated intervention was found to have significant favourable effects on both the behaviour and beliefs of the participants.
- Although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.
- For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. Consequently, the groups differed somewhat at baseline.

Introduction

Infection with human papillomavirus (HPV) is one of the major causes of infection-related cancer worldwide. HPV is related to cancer in the cervix uteri, penis, vulva, vagina, anus and the oropharynx.[1 2] These malignancies can be effectively prevented by the prophylactic vaccination against HPV and by safe sex, i.e. condom use, in addition to regular screening.[3-7] Many countries have implemented national HPV immunization programmes.[8] In Sweden girls aged 10-12 years are since 2012 offered the quadrivalent vaccine as part of the school-based vaccination programme administered by the school nurse, while older girls and young women are offered the vaccine in the catch-up programme administered in the primary care setting. The coverage among young women is substantially lower (58%) than in the lower age group (82%).[9]

HPV infections and HPV related diseases have increased in recent decades due to increased sexual risk-taking.[10-12] The highest prevalence of HPV is found among teenagers and young adults.[13 14] Therefore, preventive strategies, such as the implementation of effective educational interventions among adolescents, are very much needed.

Adolescents do not receive education regarding HPV on a regular basis. The school nurses play a key role in providing such information.[15-17] Adolescents have low awareness and knowledge about the virus, especially regarding the cancer risks.[18] Educational school-based interventions can increase adolescents' awareness and knowledge about HPV prevention,[19 20] enhance preventive behaviours for sexually transmitted infections in general [21] and reduce sexual risk-taking.[22 23] Interventions can also have a beneficial effect on beliefs about HPV vaccination among girls.[24] So far, very few randomised controlled trials have been conducted among adolescents with the aim to promote primary HPV prevention.[25-27] And as far as we know, no such trial has been performed in a diverse population of both adolescent boys and girls.

Aim and hypothesis

The overall aim was to improve primary prevention of HPV by promoting HPV vaccination and increased condom use among upper secondary school students. The hypothesis was that intervention was associated with favourable beliefs (positive attitude) towards HPV prevention at follow-up and that this influenced the actual behaviour.

Methods

Study design

A cluster randomised controlled trial with measurements at baseline and at follow-up after three months. Cluster randomisation was used since randomisation first was conducted on school level and thereafter classes were randomised to be included. Follow up after 12 and 24 month are not presented in this paper.

Setting

Sweden is a multicultural country: almost a third of all children under age 18 have an immigrant background.[28] The Swedish upper secondary school, which the vast majority of students attend, comprises both theoretical and vocational programs and reaches adolescents aged 16-19 years. According to Swedish law all students should have access to school health. The school health work is mainly preventive and involves at least a school nurse and a school physician, but only the nurse works in the school on a regular basis. In Sweden sexual education is mandatory in primary and secondary school, and includes topics such as anatomy, sexuality, prevention of sexually transmitted infections and reproductive health. .

All first year upper secondary school students (aged 16) are offered a health interview with the school nurse, who provides a dialogue regarding psychosocial health, eating habits, sleep, physical activity, tobacco, alcohol and drugs as well as sexual health and relationships. This intervention is optional, although usually all students do participate. The interview is scheduled for approximately one hour and conducted in an empathic atmosphere based on Motivational Interviewing,[29] with focus on the individual student's health and well-being..

Population and sample

First year upper secondary school students attending the regular health interview with the school nurse in the autumn semester of 2014 were eligible for participation. We excluded students who were not able to speak or write Swedish (i.e. recently arrived immigrants) and adolescents with severe learning disabilities and development disorders (i.e. studying at special schools). Upper secondary schools (n=18) in nine municipalities in central Sweden with a total of about 600 000 rural and urban inhabitants, and with different socio-economic levels represented, were included. The participating schools included those both municipally and privately managed, offered vocationally as well as theoretically oriented education, and had a varying number of students.

Recruitment and randomisation

School nurses were recruited to the project via the school heads and through direct contact at a national school health conference. For logistical reasons, those working in the far north or south of Sweden were not invited. Initially 59 upper secondary schools were approached and eventually 18 of them were included, for details see the flow chart in Fig 1. A total of 23 school nurses working in 20 schools in nine municipalities agreed to participate in the study. Three nurses in two schools dropped out at the start of the intervention due to heavy workload. This opportunistic selection resulted in a total of 20 school nurses working in 18 schools.

Randomisation was performed in two steps. First, in order to avoid contamination, the schools were randomised into either the intervention group or the control group. The schools were randomly drawn, by administrative personnel not involved in the project. Second, 113 school classes within these schools were randomly selected to be included in the study; this number was chosen in order to achieve the desired number of students according to power calculations (described below). The school nurses provided basic details about the classes (for example Social science 14A), and number of students in each class. If the class consisted of less than 25 students, an additional class was allocated. The students were recruited by the school nurses as described below. The end result was an intervention group of 394 students from 60 classes and a control group of 357 students from 53 classes (Fig 1). Recruitment did not begin until registration was public.

Two school nurses in two schools dropped out during the intervention, due to termination of employment and personal reasons, and did not complete the health interviews with their allotted students. In order to compensate for these losses, which were all from the intervention group, all school nurses in the intervention group were offered to perform health interviews with an additional class. Consequently, similar classes were included in the study.

The students (n=832) were invited to participate in the study when they met the school nurse for the general health interview. Those who agreed to participate (n=751), gave informed written consent. Before the health interview started all students were asked to complete a baseline questionnaire. A follow-up questionnaire was completed after three months (n=741). The baseline questionnaire was completed individually at the school nurse's office while the follow-up questionnaire was given to the whole class. Students not present at this time could

complete the follow-up questionnaire afterwards at the school nurse's office. School nurses were provided with checklists regarding the procedure and used log lists (protocols completed after each health interview) to assure that the intervention was performed in a uniform fashion. For obvious reasons, the school nurse could not be blinded to whether the student belonged to the intervention or control group, but the research assistant who recorded the data from the participants did not possess this knowledge.

Theoretical framework

The Health Belief Model (HBM) was used as a theoretical framework. This model has previously been used in studies about HPV and HPV vaccination[30 31] and in interventions with the aim to increase prevention of sexually transmitted infections.[19 32] According to the HBM framework, a person's health behaviour can be explained by the individual beliefs regarding health actions. HBM includes the following central constructs: perceived *susceptibility*, perceived *severity*, perceived *benefit* and perceived *barriers*. Furthermore, socio-demographic factors such as age, sex, ethnicity and parental education level, as well as knowledge, are recognised as factors that indirectly can influence the individual's behaviour. The main limitation of the model is that it does not consider emotional or relational aspects involved in decisions regarding health behaviour.[33]

Intervention

The intervention was included in the general one hour face-to-face health interview.. Thus, whereas the controls received general information, including sexual health, the intervention group received specific HPV education guided by HBM and following a pre-designed structure.. The school nurse used a specially designed flipchart with pictures and brief information facing the students (see example in Table 1). She also handed out a specially designed leaflet. The intervention took about 30 minutes and included the following information:

- general facts about the virus
- viral transmission
- what HPV can cause
- risk factors
- prevention, i.e. safe sex with condom use and HPV vaccination
- locations where the girls could receive the vaccine free of charge in the municipality
- facts about the HPV vaccine

- the importance for girls of attending future cervical cancer screening controls

The leaflet consisted of 12 pages and included similar information and also an HPV quiz as well as links to the national online youth clinic, the homepage of the university where the researchers worked and contact information to the authors. After the follow-up questionnaire was completed, students in the intervention group were provided with condoms. Students in the control group only received standard treatment, i.e. the regular health interview, as described above.

Outcome measures

The outcomes pertain to the individual student. Primary outcomes: Intention to use condom with a new partner and beliefs towards primary prevention about HPV, five point Likert scale (strongly agree to strongly disagree).

Secondary outcomes: Increased HPV vaccination (yes/no/do not know) and increased condom use (yes/no).

Pilot study

In early 2014 the intervention procedure, including the educational material and questionnaire, was tested by three school nurses among 45 students aged 16 years. The nurses' experiences resulted in minor revisions: for logistic reasons the methods was changed from individual follow-up at the school nurses office to follow-up in class, the educational material was shortened, some statements were simplified and the additional response alternative "do not know" was added to the block of questions regarding beliefs about HPV. A few of the questions were clarified and two were considered redundant and thus removed. In parallel, the questionnaire was tested among adolescents aged 17 (n=230),[34] who confirmed the school nurses' observations.

Instrument

The questionnaire was based on previous research and clinical experience. The questions about beliefs, awareness and knowledge about HPV (n=24) were adapted from our previous study[15] and had multiple choice alternatives and six-point verbal rating scales from "Totally agree" to" Totally disagree", including "Do not know". The demographic background questions (n=14) were taken from the national questionnaire for adolescents[35] and the questions regarding sexual behaviour (n=17) were based on a project among university students which has been used repeatedly since 1989.[10] The questions about beliefs towards

primary prevention of HPV according to the HBM constructs on *susceptibility* comprised questions regarding the risk for contracting HPV; while *severity* included how serious it would be to receive an HPV infection or cancer. In addition, questions about *benefits* comprised confidence in vaccine effectiveness and intention to vaccinate; while *barriers* embraced the individual's perceived barriers for HPV vaccination, such as fear of needles and difficulties booking an appointment for vaccination.

Validity and reliability of the intervention including the questionnaire

The validity and reliability were rigorously tested with both qualitative and quantitative methods. Two focus group interviews were undertaken with adolescents (n=8) aged 16-17 years (both boys and girls) who were asked what they considered important to include in an intervention regarding prevention of HPV. Cognitive interviews (n=5) and discussion sessions (n=8) regarding the questionnaire were performed with adolescents aged 15-18 years.

To test the stability and reliability over time a test-retest evaluation was undertaken with first year upper secondary school students (n=29) randomly selected from a school situated in a city of 200 000 habitants in mid Sweden in 2014. The questionnaire was distributed on two occasions with a time interval of two weeks. Analysis was based on Cronbach's alpha and showed high reliability scores for the questions regarding the decision-making process about HPV vaccination (0.800-0.998), except for the single question "Do you want to be vaccinated later" (0.436). Statements regarding beliefs about HPV ranged from low to high (scores 0.331-0.918), consequently, two statements were removed.

Ethical considerations

The study was conducted according to the Declaration of Helsinki. All participants received oral and written information before giving their written consent. The participants were informed that participation was voluntary, that they could withdraw participation at any time without providing a motivation or incurring any negative consequences for themselves. They were also informed that only the researchers would have access to the data and that all data would be presented on a group level. Contact details to the researchers were provided in case of further questions. According to the Swedish law children above 15 years of age who understand what participation means have the right to give informed consent regarding participation in research studies.[36] Therefore, informed consent was not obtained from the parents. We asked permission to conduct the study from the head of the school health in each

municipality and from the principals of the schools. The project was approved by the Regional Ethical Review Board of Uppsala University (D.nr.2013/324).

Education to school nurses

All participating school nurses (n=20) received written and verbal instructions and participated in educational sessions (with MG and CS) scheduled for about two hours. The education comprised factual information about HPV and the HPV vaccine. The flipchart educational material was presented and the nurses were encouraged to give comments if anything was unclear or if anything considered important was missing. Furthermore, each school nurse received a minimum of one hour additional education at the time for the start of the intervention at the school where she worked. During the intervention the nurses were contacted on a weekly basis.

Sample size calculation

The power calculation was based on a previous study among the research group[37] and clinical experience. The sample size of 400 participants per study arm were based on assumptions of baseline *intention to use condom if new partner* of 60%, with a power of 80% to detect differences of 10 percentage points between intervention and control group at a significance level of 5% (356/study arm IG/CG, a dropout of 10% and missing values=400).

Statistical analysis

For descriptive statistics, categorical data are presented as frequencies and percentages, n (%), ordinal data as medians, means and standard deviations (SD), while continuous data are given as mean and SD. Differences between the intervention and control groups are tested with Pearsons' Chi-square test for categorical data, Mann-Whitney test for ordinal data, and Student's independent samples *t*-test for continuous data.

The effects of the intervention were measured from baseline at follow-up. First, the HBM scores were calculated by measuring the differences between baseline and at follow-up for each HBM question. Then the questions were grouped together according to the HBM constructs *susceptibility*, *severity*, *benefits* and *barriers*. Finally the total HBM index was calculated by adding all HBM constructs together. For each individual item in the HBM index, the answers on the five-point Likert scale (Strongly agree to Strongly disagree) where given scores 0-4 for negative questions, i.e., "strongly disagree" would imply higher health

belief and 4-0 for reversed questions. "Do not know" was classified as answering the neutral option. Finally, scores from all included individuals were summarized to give a total score. The McNemar test was used to determine differences in actual HPV vaccinations and actual condom use from baseline to follow-up. The analyses are conducted on an individual level, analysed according to intention to treat principle, comprising all 741 students completing the follow up questionnaire.

In order to take into account the dependence between students who were informed by the same school nurse, Generalized Estimating Equations models were used for examining the results of the intervention on the outcome measures. The differences between the outcome variables at baseline and follow-up were used as dependent variables in the Generalized Estimating Equations models, while treatment group (intervention or control) was used as a predictor together with the socioeconomic and demographic variables sex and immigrant background, which differed significantly between the two groups at baseline. These variables were only included as main effects in the regression models, with no interaction used. In all analyses, a two-sided p-value <0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics 22.0.

Results

Participants and sample

As mentioned above, a flow chart with details of the participants and samples is presented in Fig 1. A total of 2883 adolescents in 113 classes were allocated to either intervention group or control group. We excluded 496 adolescents not meeting the inclusion criteria. Of the 832 adolescents invited to participate, 81 declined, resulting in a total of 751 participants (i.e. the response rate was 90.2%); 394 in the intervention and 357 in the control group. At follow-up after three months 741 (89.1%) adolescents participated and were analysed (intervention group n=390 and control group n=351).

Baseline characteristics of participants by randomised group are presented in Table 2. The mean age was 16.1 years, 46.8% attended theoretical and 53.2% vocational programmes. More than a quarter (27.8%) had an immigrant background and over half of the girls (56.1%) were already vaccinated against HPV. There were significant differences between the groups at baseline regarding sex and immigrant background (Table 2). The reason for this is discussed in the Discussion section below. The effects of the intervention, adjusted for treatment group (intervention or control), sex and immigrant background, are presented in

Tables 3 and 4. The adjusted analyses are further elaborated below. Since the Generalized Estimating Equations model did not converge for the HBM construct *benefits*, results for this construct are not presented.

The mean time from baseline to follow-up was 3.26 months, with no differences between intervention and control groups. In some classes the health interviews were delayed due to the fact that some students participated in practical training, national examinations or other mandatory school activities. Consequently, the follow-up questionnaire was sometimes delayed for a maximum of two months.

Effect of the intervention

Condom use

The intervention resulted in increased intention to use a condom with a new partner, with 1.751 higher points score for the intervention than the control group (p=0.004).,There were significant effects among boys (p=0.045), with a 1.355 points higher score after the intervention compared to baseline, while there were no significant differences among participants with an immigrant background (p=0.717) (Table 3). Still, there were no significant differences between the intervention and the control groups regarding their reports of the actual condom use during their latest intercourse (p=0.377).

HBM total score

The intervention had a significant effect on HBM total score (p=0.003), (i.e. the students perceived more benefits of vaccination, perceived themselves to be at increased risk for an HPV infection or HPV-related disease, considered HPV-related disease a severe threat and perceived fewer barriers against HPV vaccination), with a 2.559 points higher score for the intervention compared to the control group. For further details see Table 4. There were also differences between the groups regarding the two predictors, sex and immigrant background. Notably, boys in the intervention group had significantly lower scores (p=0.003) compared to the controls. Students with immigrant background in the intervention group, however, had a 3.291 higher score compared to immigrant students in the control group (p=0.003).

Susceptibility

The intervention group reported higher scores for susceptibility (p<0.001) (i.e. they perceived increased risk for HPV infection and HPV related disease) with a 1.675 points higher score

compared to the control group; for details see Table 4. On the other hand, boys in the intervention group had again significantly lower scores for this outcome parameter as compared to boys in the control group ($p<0.001$). In contrast, the intervention had a significant effect among adolescents with an immigrant background, who had a 1.770 higher score ($p<0.001$), and thus perceived increased risk, compared to the control group.

Severity

The intervention also had significant effect on severity ($p<0.001$), with a 0.409 higher score (i.e. higher perceived HPV severity) for the intervention group compared to the control group, for details see Table 4. Boys had again significant lower scores ($p<0.001$), while there were no differences between the groups for participants with immigrant background ($p=0.330$).

Barriers

There were no significant differences between the intervention and the control group for this parameter ($p=0.262$), for further details see Table 4. Notably, the intervention had significant positive effect ($p=0.015$) for boys, with a 0.469 higher score (i.e. boys perceived lower barriers against HPV vaccination) in the intervention group compared to the controls. The effect for individuals with an immigrant background, on the other hand, was the opposite ($p=0.014$).

HPV vaccination

The intervention increased the likelihood that the students actually became vaccinated. The proportion of vaccinated girls in the intervention group was 52.5% before and 59.0% after the intervention, whereas no difference over time was seen in the control group (60.9%). This difference was significant ($p=0.02$). In actual numbers, 15 girls and one boy received the vaccine between the intervention and completion of the follow-up questionnaire. In addition, one girl wanted to be vaccinated, but her parents did not consent.

No harmful effects of the intervention were reported.

Discussion

Principal findings

This randomised controlled trial of a school-based educational session showed that adolescents' beliefs and behaviour regarding HPV prevention can successfully be improved.

After the intervention the students had significantly more favourable beliefs towards HPV prevention and were more inclined to use condom during sex with a new partner. In addition, the intervention increased actual HPV vaccination rates.

It is encouraging that the intervention's effect on the intention to use condom was substantial among boys, since they are neither included in the national HPV vaccination programme nor do they receive any organised information about HPV. Our finding gives support for the speculation that boys – when provided with adequate information – also want to protect themselves, and their partners, against the virus.

It was frustrating that the effects on the students' intentions did not result in clear differences in actual reported condom use. But it should be kept in mind that this is a small group and follow-up was short. The results might have been different with a longer follow up – not all of them were sexually active, and those who were may not have had a new opportunity, with a new partner, between the intervention and the follow-up questionnaire. Consequently, too much weight should not be given to this finding. More important is the finding that several girls (and one boy) chose to have themselves vaccinated shortly after the intervention. Since the older girls are offered the vaccine in the catch-up programme and the families have to contact the primary care centre themselves to book an appointment, it is encouraging that the intervention had effects on vaccination rates.

There were significant effects on the HBM total score, which includes the parameters perceived *susceptibility*, perceived *severity*, perceived *benefits* and perceived *barriers*. The intervention was especially effective regarding beliefs about HPV prevention among adolescents with an immigrant background. This is an important finding, since Sweden is a multicultural country with many immigrants from countries with limited access to healthcare and health education. It was also encouraging that these students reported higher scores for perceived *susceptibility*, i.e. they had become aware of the risks. Immigrant background is associated with increased risk for cervical cancer [38] and lower attendance in cervical cancer screening programmes.[39 40]

We also found significant differences between the groups regarding perceived severity. According to HBM the combination of *susceptibility* and *severity* are labelled as perceived *threat*.[33] Since adolescence is a time in life when the perception of being at risk of contracting an sexually transmitted infection is generally low, especially among boys,[41] and the sexual risk-taking is increasing,[11] we are happy to note that the intervention increased the adolescents' perception of HPV as a serious threat. This is beneficial for their future sexual health behaviour.

Strengths

This complex educational intervention was carefully developed, standardised, validated and monitored and had high response rate; 89.1% completed the study. Further major strengths are the randomised control trial design and the fact that various kinds of schools with a representative sample of both boys and girls were included. The percentage of adolescents with an immigrant background, as well as the number of HPV vaccinated girls at baseline, are representative for the Swedish population in general. This means that the findings can, with a fair degree of certainty, be extrapolated to the population at large. The target group, adolescents aged 16 years, is adequate since this is a time in life when many become sexually active. The school nurses, with their professional role and experience of discussing sensitive issues, are the proper persons to deliver the intervention. Finally, a school-based intervention reaches all adolescents regardless of socio-economic status, ethnicity or cultural background.

Weaknesses

For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. This became clear during the evaluation of the pilot study. Consequently, the groups differed somewhat at baseline with, for example, more girls in the intervention group and more boys in the control group. We took this into account in the Generalized Estimating Equations model and adjusted for the demographic differences at baseline.

It is possible that the participating school nurses are more committed to HPV prevention and sexual health issues than their colleagues. These nurses' commitment and personal communication skills might have affected the outcome of the intervention in a favourable direction. To compensate for this and ensure uniformity the intervention was highly structured, the school nurses were provided with exhaustive instructions and the researchers regularly contacted them, asking questions systematically about *how does it work for you?* The initial process evaluation and log lists indicate that the fidelity was very high; all school nurses performed the intervention according to the given guidelines. Also, as in all studies including self-reported questionnaires, there is a risk of participant over- or under-reporting or recall bias, although we consider this risk small in the present study.

Finally, although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.

Strengths and weaknesses in relation to other studies

To our knowledge this is the first randomised, educational, school-based face-to-face intervention study among a diverse population of adolescents with the aim to improve primary prevention of HPV. Previous studies have mainly been undertaken among young adult women.[26 30] As discussed in the systematic review by Sheperd et al[42] there is a need for interventions with greater focus on HPV and especially the link between HPV and cancer. Previous interventions have tended to focus on prevention of cervical cancer only.[42] It is also an advantage to use a theoretical framework such as HBM when developing an educational intervention with preventive aims. HBM is a systematic way to explain a person's health behaviour, which clarifies the key concepts on which the intervention is based.[33]

Our results stand in contrast to previous school-based interventions delivered in class in which no significant effects on beliefs[19] neither about condom use nor HPV vaccination, were found.[19 20] This discrepancy indicates that it is beneficial with a face-to-face intervention delivered by school nurses.

Implications

The results indicate that an educational intervention delivered by health care providers, school nurses, is a highly feasible and effective way to increase adolescents' beliefs and behaviour towards primary prevention of HPV, regardless of socio-economic status, ethnicity or cultural background.

Unanswered questions and future research

Larger studies with more participants may help understand if there are also further differences between girls and boys, and between students with or without an immigrant background. Some of our conclusions remain speculative, awaiting such studies. In addition, studies with longer follow-up are needed, in order to find out if school-based educational interventions are effective in the long term, and if the participants' actual behaviour changes in the desired direction.

Acknowledgements

We thank all the participants; especially the school nurses and the adolescents. We also thank the heads of the school health in each municipality and the principals of the schools. A special thanks to the Swedish Association of School nurses for support, and for allowing us to present the project at the national conference. In addition we thank Åke Pålshammar for valuable

discussions about the project, especially about adolescents' psychosocial and cognitive development.

Contributors: MG conceptualised and designed the study, recruited participants, managed the data collection, completed data analysis and interpretation, wrote the draft manuscript, and obtained funding. AR assisted in design, data analysis and interpretation, funding and manuscript preparation. CS assisted in design, participant recruitment, data collection, data interpretation, manuscript preparation and funding. ML, MO, RW and TT assisted in design, data collection, data interpretation, manuscript preparations and funding. BA and TD assisted in design, data interpretation, funding, and were available for clinical consultation. TN assisted in all activities including design, data interpretation, data collection, manuscript preparation and funding. All authors made critical comments on drafts of the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding statement: This work was supported by [the Swedish Cancer Society] grant number [130744], [Uppsala-Örebro Regional Research Council] grant number [RFR-387561/476021] and [Uppsala County Council] grant number [LUL-347931], [the Swedish Government Funds for Clinical Research] grant number [19049/470102/44957] and the [Medical Faculty at Uppsala University] grant number [2012/278]. In addition, MG and CS received a scholarship from [the Gillbergska Foundation]. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests statement: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Uppsala University, Department of Public health and Caring Sciences and the Regional Ethical Committee in Uppsala, Sweden, D.nr. 2013/324 approved this study. All participants gave informed consent.

Data sharing: No additional data are available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Example of the Flip chart

Student information	School nurses' work material "chat script"
Prevention of HPV 1. Vaccination HPV vaccine protects against the most common HPV types that causes cervical cancer och condyloma (genital warts). The vaccine is offered free of charge to young girls in school and to older girls at the primary care centres. The vaccine gives best protection before exposure to HPV. Therefore it is recommended to vaccinate before sexual debut.	How can HPV be prevented? The HPV vaccine is highly efficient against the most common HPV types that can cause cervical cancer and condyloma (genital warts). The vaccine is offered free of charge to 11 year old girls in the school and to older girls at the primary care centres. Note! You, as school nurse, shall inform where (at what primary care centre) the student can be vaccinated free of charge in your area. The vaccine gives best protection before exposure to HPV, therefore it is best to vaccinate before sexual debut, but you can also be vaccinated later on.

Table 2. Baseline characteristics of participants by randomised group (n=741)

	Intervention n =390 (52.6%)		Control n=351 (47.4%)		*p*-value
Characteristic					
Age (years) mean (Md) (Sd)	16.15 (16)	(0.77)	16.06 (16)	(0.73)	0.800†
Sex					<0.001††
Female	239	(61.4)	146	(41.6)	
Male	150	(38.6)	205	(58.4)	
Education					0.117††
Theoretical programme	172	(44.1)	176	(50.1)	
Vocational programme	218	(55.9)	175	(49.9)	
Immigrant background¶					0.017††
Yes	123	(31.5)	83	(23.6)	
No	267	(68.5)	268	(76.4)	
Educational level, mother*					0.799†††
University	167	(54.9)	158	(53.7)	
Upper secondary school	118	(38.8)	118	(40.1)	
Elementary school	19	(6.3)	18	(6.1)	
Educational level, father *					0.334†††
University	100	(36.2)	112	(39.9)	
Upper secondary school	145	(52.5)	142	(50.5)	
Elementary school	31	(11.2)	27	(9.6)	
Main occupation, mother					0.148††
Employed¶¶	339	(87.1)	315	(90.5)	
Unemployed¶¶¶	50	(12.9)	33	(9.5)	
Main occupation, father					0.095††
Employed¶¶	331	(92.5)	318	(92.5)	
Unemployed¶¶¶	27	(7.5)	15	(4.5)	
Tobacco use (smoking)					0.197††
Never	316	(81.0)	297	(84.6)	
Occassionally/Daily	74	(19.0)	54	(15.4)	
Tobacco use (snuff)					0.767††
Never	359	(92.1)	321	(91.5)	
Occassionally/Daily	31	(7.9)	30	(8.5)	
Alcohol consumption					0.284††
Never	257	(66.1)	218	(62.3)	
Occasionally/Monthly/Weekly	132	(33.9)	132	(37.7)	
HPV vaccinated (only girls[a])					0.103††
Yes	126	(52.7)	89	(60.9)	
No	83	(34.9)	47	(32.4)	
Do not know	29	(12.2)	9	(6.2)	

†Independent Samples T-test††Chi-Square Tests, †††Mann-Whitney Test, ¶Immigrant background: born outside Sweden or one or two parents born outside Sweden¶¶Employed includes studying and/or parental leave, ¶¶¶Unemployed includes sick leave and similar.**Total amount do not add up to n=751 (100%) due do not know not presented and/or missing answer.*, [a] Not included in the numbers: One boy in CG HPV vaccinated at baseline

Table 3. Results of the Generalized Estimating Equations analyses. Effect of the intervention for the main outcome - intention to use condom if new partner.

Outcome	Predictors	Adjusted[¶] Slope coefficient (95% CI)	P-value
Intention to use condom if new partner	Intervention	1.751	0.004
	Boys	1.355 (0.031 to 2.679)	0.045
	Immigrant	0.132 (-0.580 to 0.844)	0.717

¶ Adjusted for treatment group (intervention or control group), sex and immigrant background

Table 4. Results of the Generalized Estimating Equations analyses. Effect of the intervention according to the Health Belief Model (HBM).

Outcome	Predictors	Adjusted¶ Slope coefficient (95% CI)	P-value
HBM total score	Intervention	2.559 (0.875 to 4.324)	0.003
	Boys	-2.244 (-3.729 to -0.759)	0.003
	Immigrant	3.291 (1.107 to 5.474)	0.003
Susceptibility	Intervention	1.675 (0.850 to 2.500)	<0.001
	Boys	-1.544 (-2.172 to -0.916)	<0.001
	Immigrant	1.770 (0.953 to 2.587)	<0.001
Severity	Intervention	0.409 (0.183 to 0.634)	<0.001
	Boys	-0.339 (-0.490 to -0.187)	<0.001
	Immigrant	0.131 (-0.133 to 0.395)	0.330
Barriers	Intervention	-0.172 (-0.473 to 0.129)	0.262
	Boys	0.469 (0.091 to 0.845)	0.015
	Immigrant	-0.505 (-0.910 to -1.00)	0.014

¶ Adjusted for treatment group (intervention or control group), sex and immigrant background

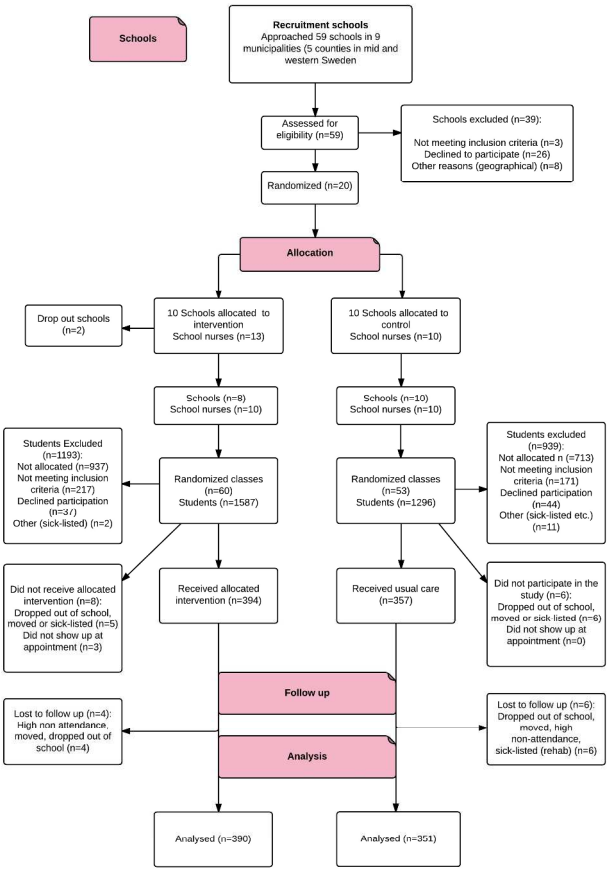

Fig 1. Flow of schools and students through trial
270x354mm (300 x 300 DPI)

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	5
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	5
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		No changes were made
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	6
	4b	Settings and locations where the data were collected		6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	8

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		No changes were made
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	The second author, Dr Rosenblad, biostatistician and associate professor has been involved in this project since the design of the study. The paper was not reported as a cluster RCT since we had to recruit school nurses willing to participate before we could randomize schools and classes on cluster level. In addition, all analyses are performed on individual level. The power (sample size) is adequate for these analyses. However, as we discuss on page 16 it would have been even better with a larger sample size in order to be able to conduct more subgroups analyses. Nevertheless, this was not feasible due to logistic reasons. We have now revised the paper as a cluster randomised study Considering the inherent

				uncertainties in and approximations of all power calculations, our statistician deemed these power calculations to be appropriate.
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	No stratification or matching was used
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	6
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	6
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	6
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or	10

			both), and whether consent was sought before or after randomisation	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		The study was not blinded 7
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	By using GEE 11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11-12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	6 + Flowchart
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	6 + Flowchart
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5-6
	14b	Why the trial ended or was stopped		The study ended after the spring semester, 2015, due to the schools summer holiday.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 2

		group		
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	The analyses are conducted on individual level as described on page 11.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	The results are analysed on individual level, page 11. The clusters are too small to produce reliable ICC results.
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		None of the primary outcomes were binary.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		The analyses were undertaken as reported on page 11. No additional subgroup analyses etc. were performed due to not enough power as discussed on page 16.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		No harms were reported.
Discussion				14-17
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		15-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant		16

		evidence	
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	No protocol is available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

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1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

BMJ Open

School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009875.R2
Article Type:	Research
Date Submitted by the Author:	20-Nov-2015
Complete List of Authors:	Grandahl, Maria; Uppsala University, Department of Public Health and Caring Sciences Rosenblad, Andreas; Uppsala University, Center for Clinical Research Västerås Stenhammar, Christina; Uppsala University, Department of Public Health and Caring Sciences Tydén, Tanja; Uppsala University, Department of Public Health and Caring Sciences Westerling, Ragnar; Uppsala University, Department of Public Health and Caring Sciences Larsson, Margareta; Uppsala University, Department of Women's and Children's Health Oscarsson, Marie; Linnaeus University, Department of Health and Caring Sciences; Uppsala University, Department of Public Health and Caring Sciences Andrae, Bengt; Centre for Research and Development, Uppsala University/Region of Gävleborg, Gävle, Sweden, Dalianis, Tina; Karolinska Institute, Department of Oncology-Pathology Nevéus, Tryggve; Uppsala University, Department of Women's and Children's Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Paediatrics
Keywords:	adolescents, HPV, prevention, randomised control trial, school-based

School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study

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Keywords: adolescents, HPV, prevention, randomised control trial, school-based

Word count: 4644

Abstract

Objective To improve primary prevention of human papillomavirus (HPV) infection by promoting vaccination and increased condom use among upper secondary school students.

Design Cluster randomised controlled trial.

Setting 18 upper secondary schools in Sweden.

Participants Schools were first randomised to the intervention or the control group, after which individual classes were randomised to be included or not. 832 students aged 16 were invited to participate during the regular individual health interview with the school nurse, 751 (90.2%) agreed to participate, and 741 (89.1%) students completed the study.

Interventions The intervention was based on the Health Belief Model (HBM). According to HBM a person's health behaviour can be explained by individual beliefs regarding health actions. School nurses delivered 30 minute face-to-face structured information about HPV, including cancer risks and HPV prevention, i.e. condom use and HPV vaccination. Students in both the intervention and the control groups completed questionnaires at baseline and after three months.

Main outcome measures Intention to use condom with a new partner and beliefs about primary prevention of HPV; and also specifically vaccination status and increased condom use.

Results All statistical analyses were performed on individual level. The intervention had a significant effect on the intention to use condom (p=0.004). There was also a significant effect on HBM total score (p=0.003), with a 2.559 points higher score for the intervention group compared to the controls. The influence on the HBM parameters *susceptibility* and *severity* was also significant (p<0.001 for both variables). The intervention also influenced behaviour: girls in the intervention group chose to have themselves vaccinated to a significantly higher degree than the controls (p=0.02). No harms were reported.

Conclusions The school-based intervention had favourable effects on the beliefs about primary prevention of HPV and increased HPV vaccination rates in a diverse population of adolescents.

Trial registration - ClinicalTrials.gov Identifier: NCT02280967

Strengths and limitations of this study

- This is the first school-based educational cluster randomised controlled trial targeting a diverse and representative population of adolescents of both sexes, with the aim to improve primary prevention of HPV.
- The rigorously tested and validated intervention was found to have significant favourable effects on both the behaviour and beliefs of the participants.
- Although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.
- For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. Consequently, the groups differed somewhat at baseline.

Introduction

Infection with human papillomavirus (HPV) is one of the major causes of infection-related cancer worldwide. HPV is related to cancer in the cervix uteri, penis, vulva, vagina, anus and the oropharynx.[1 2] These malignancies can be effectively prevented by the prophylactic vaccination against HPV and by safe sex, i.e. condom use, in addition to regular screening.[3-7] Many countries have implemented national HPV immunization programmes.[8] In Sweden girls aged 10-12 years are since 2012 offered the quadrivalent vaccine as part of the school-based vaccination programme administered by the school nurse, while older girls and young women are offered the vaccine in the catch-up programme administered in the primary care setting. The coverage among young women is substantially lower (59%) than in the lower age group (83%).[9]

HPV infections and HPV related diseases have increased in recent decades due to increased sexual risk-taking.[10-12] The highest prevalence of HPV is found among teenagers and young adults.[13 14] Therefore, preventive strategies, such as the implementation of effective educational interventions among adolescents, are very much needed.

Adolescents do not receive education regarding HPV on a regular basis. The school nurses play a key role in providing such information.[15-17] Adolescents have low awareness and knowledge about the virus, especially regarding the cancer risks.[18] Educational school-based interventions can increase adolescents' awareness and knowledge about HPV prevention,[19 20] enhance preventive behaviours for sexually transmitted infections in general [21] and reduce sexual risk-taking.[22 23] Interventions can also have a beneficial effect on beliefs about HPV vaccination among girls.[24] So far, very few randomised controlled trials have been conducted among adolescents with the aim to promote primary HPV prevention.[25-27] And as far as we know, no such trial has been performed in a diverse population of both adolescent boys and girls.

Aim and hypothesis

The overall aim was to improve primary prevention of HPV by promoting HPV vaccination and increased condom use among upper secondary school students. The hypothesis was that intervention was associated with different beliefs (different attitude) towards HPV prevention at follow-up and that this influenced the actual behaviour.

Methods

Study design

A cluster randomised controlled trial with measurements at baseline and at follow-up after three months. Cluster randomisation was used since randomisation first was conducted on school level and thereafter classes were randomised to be included. Follow up after 12 and 24 month are not presented in this paper.

Setting

Sweden is a multicultural country: almost a third of all children under age 18 have an immigrant background.[28] The Swedish upper secondary school, which the vast majority of students attend, comprises both theoretical and vocational programs and reaches adolescents aged 16-19 years. According to Swedish law all students should have access to school health. The school health work is mainly preventive and involves at least a school nurse and a school physician, but only the nurse works in the school on a regular basis. In Sweden sexual education is mandatory in primary and secondary school, and includes topics such as anatomy, sexuality, prevention of sexually transmitted infections and reproductive health.

All first year upper secondary school students (aged 16) are offered a health interview with the school nurse, who provides a dialogue regarding psychosocial health, eating habits, sleep, physical activity, tobacco, alcohol and drugs as well as sexual health and relationships. This intervention is optional, although usually all students do participate. The interview is scheduled for approximately one hour and conducted in an empathic atmosphere based on Motivational Interviewing,[29] with focus on the individual student's health and well-being..

Population and sample

First year upper secondary school students attending the regular health interview with the school nurse in the autumn semester of 2014 were eligible for participation. We excluded students who were not able to speak or write Swedish (i.e. recently arrived immigrants) and adolescents with severe learning disabilities and development disorders (i.e. studying at special schools). Upper secondary schools (n=18) in nine municipalities in central Sweden with a total of about 600 000 rural and urban inhabitants, and with different socio-economic levels represented, were included. The participating schools included those both municipally and privately managed, offered vocationally as well as theoretically oriented education, and had a varying number of students.

Recruitment and randomisation

School nurses were recruited to the project via the school heads and through direct contact at a national school health conference. For logistical reasons, those working in the far north or south of Sweden were not invited. Initially 59 upper secondary schools were approached and eventually 18 of them were included, for details see the flow chart in Fig 1. A total of 23 school nurses working in 20 schools in nine municipalities agreed to participate in the study. Three nurses in two schools dropped out at the start of the intervention due to heavy workload. This opportunistic selection resulted in a total of 20 school nurses working in 18 schools.

Randomisation was performed in two steps. First, in order to avoid contamination, the schools were randomised into either the intervention group or the control group. The schools were randomly drawn, by administrative personnel not involved in the project. Second, 113 school classes within these schools were randomly selected to be included in the study; this number was chosen in order to achieve the desired number of students according to power calculations (described below). The school nurses provided basic details about the classes (for example Social science 14A), and number of students in each class. If the class consisted of less than 25 students, an additional class was allocated. The students were recruited by the school nurses as described below. The end result was an intervention group of 394 students from 60 classes and a control group of 357 students from 53 classes (Fig 1). Recruitment did not begin until registration was public.

Two school nurses in two schools dropped out during the intervention, due to termination of employment and personal reasons, and did not complete the health interviews with their allotted students. In order to compensate for these losses, which were all from the intervention group, all school nurses in the intervention group were offered to perform health interviews with an additional class. Consequently, similar classes were included in the study.

The students (n=832) were invited to participate in the study when they met the school nurse for the general health interview. Those who agreed to participate (n=751), gave informed written consent. Before the health interview started all students were asked to complete a baseline questionnaire. A follow-up questionnaire was completed after three months (n=741). The baseline questionnaire was completed individually at the school nurse's office while the follow-up questionnaire was given to the whole class. Students not present at this time could

complete the follow-up questionnaire afterwards at the school nurse's office. School nurses were provided with checklists regarding the procedure and used log lists (protocols completed after each health interview) to assure that the intervention was performed in a uniform fashion. For obvious reasons, the school nurse could not be blinded to whether the student belonged to the intervention or control group, but the research assistant who recorded the data from the participants did not possess this knowledge.

Theoretical framework

The Health Belief Model (HBM) was used as a theoretical framework. This model has previously been used in studies about HPV and HPV vaccination[30 31] and in interventions with the aim to increase prevention of sexually transmitted infections.[19 32] According to the HBM framework, a person's health behaviour can be explained by the individual beliefs regarding health actions. HBM includes the following central constructs: perceived *susceptibility*, perceived *severity*, perceived *benefit* and perceived *barriers*. Furthermore, socio-demographic factors such as age, sex, ethnicity and parental education level, as well as knowledge, are recognised as factors that indirectly can influence the individual's behaviour. The main limitation of the model is that it does not consider emotional or relational aspects involved in decisions regarding health behaviour.[33]

Intervention

The intervention was included in the general one hour face-to-face health interview. Thus, whereas the controls received general information, including sexual health, the intervention group received specific HPV education guided by HBM and following a pre-designed structure. The school nurse used a specially designed flipchart with pictures and brief information facing the students (see example in Table 1). She also handed out a specially designed leaflet. The intervention took about 30 minutes and included the following information:

- general facts about the virus
- viral transmission
- what HPV can cause
- risk factors
- prevention, i.e. safe sex with condom use and HPV vaccination
- locations where the girls could receive the vaccine free of charge in the municipality
- facts about the HPV vaccine
- the importance for girls of attending future cervical cancer screening controls

The leaflet consisted of 12 pages and included similar information and also an HPV quiz as well as links to the national online youth clinic, the homepage of the university where the researchers worked and contact information to the authors. After the follow-up questionnaire was completed, students in the intervention group were provided with condoms. Students in the control group only received standard treatment, i.e. the regular health interview, as described above.

Outcome measures

The outcomes pertain to the individual student. Primary outcomes: Intention to use condom with a new partner and beliefs towards primary prevention about HPV, (strongly agree to strongly disagree, see Appendix).

Secondary outcomes: Increased HPV vaccination (yes/no/do not know) and increased condom use (yes/no).

Pilot study

In early 2014 the intervention procedure, including the educational material and questionnaire, was tested by three school nurses among 45 students aged 16 years. The nurses' experiences resulted in minor revisions: for logistic reasons the methods was changed from individual follow-up at the school nurses office to follow-up in class, the educational material was shortened, some statements were simplified and the additional response alternative "do not know" was added to the block of questions regarding beliefs about HPV. A few of the questions were clarified and two were considered redundant and thus removed. In parallel, the questionnaire was tested among adolescents aged 17 (n=230),[34] who confirmed the school nurses' observations.

Instrument

The questionnaire was based on previous research and clinical experience. The questions about beliefs, awareness and knowledge about HPV (n=24) were adapted from our previous study[15] and had multiple choice alternatives and six-point verbal rating scales (Likert scale) from "Totally agree" to" Totally disagree", including "Do not know". The demographic background questions (n=14) were taken from the national questionnaire for adolescents[35] and the questions regarding sexual behaviour (n=17) were based on a project among university students which has been used repeatedly since 1989.[10] The questions about beliefs towards primary prevention of HPV according to the HBM constructs on *susceptibility* comprised questions regarding the risk for contracting HPV; while *severity* included how serious it would be to receive an HPV infection or cancer. In addition, questions about *benefits*

comprised confidence in vaccine effectiveness and intention to vaccinate; while *barriers* embraced the individual's perceived barriers for HPV vaccination, such as fear of needles and difficulties booking an appointment for vaccination.

Validity and reliability of the intervention including the questionnaire

The validity and reliability were rigorously tested with both qualitative and quantitative methods. Two focus group interviews were undertaken with adolescents (n=8) aged 16-17 years (both boys and girls) who were asked what they considered important to include in an intervention regarding prevention of HPV. Cognitive interviews (n=5) and discussion sessions (n=8) regarding the questionnaire were performed with adolescents aged 15-18 years.

To test the stability and reliability over time a test-retest evaluation was undertaken with first year upper secondary school students (n=29) randomly selected from a school situated in a city of 200 000 habitants in mid Sweden in 2014. The questionnaire was distributed on two occasions with a time interval of two weeks. Analysis was based on Cronbach's alpha and showed high reliability scores for the questions regarding the decision-making process about HPV vaccination (0.800-0.998), except for the single question "Do you want to be vaccinated later" (0.436). Statements regarding beliefs about HPV ranged from low to high (scores 0.331-0.918), consequently, two statements were removed.

Ethical considerations

The study was conducted according to the Declaration of Helsinki. All participants received oral and written information before giving their written consent. The participants were informed that participation was voluntary, that they could withdraw participation at any time without providing a motivation or incurring any negative consequences for themselves. They were also informed that only the researchers would have access to the data and that all data would be presented on a group level. Contact details to the researchers were provided in case of further questions. According to the Swedish law children above 15 years of age who understand what participation means have the right to give informed consent regarding participation in research studies.[36] Therefore, informed consent was not obtained from the parents. We asked permission to conduct the study from the head of the school health in each municipality and from the principals of the schools. The project was approved by the Regional Ethical Review Board of Uppsala University (D.nr.2013/324).

Education to school nurses

All participating school nurses (n=20) received written and verbal instructions and participated in educational sessions (with MG and CS) scheduled for about two hours. The education comprised factual information about HPV and the HPV vaccine. The flipchart educational material was presented and the nurses were encouraged to give comments if anything was unclear or if anything considered important was missing. Furthermore, each school nurse received a minimum of one hour additional education at the time for the start of the intervention at the school where she worked. During the intervention the nurses were contacted on a weekly basis.

Sample size calculation

The power calculation was based on a previous study among the research group[37] and clinical experience. The sample size of 400 participants per study arm were based on assumptions of baseline *intention to use condom if new partner* of 60%, with a power of 80% to detect differences of 10 percentage points between intervention and control group at a significance level of 5% (356/study arm IG/CG, a dropout of 10% and missing values=400).

Statistical analysis

For descriptive statistics, categorical data are presented as frequencies and percentages, n (%), ordinal data as medians, means and standard deviations (SD), while continuous data are given as mean and SD. Differences between the intervention and control groups are tested with Pearsons' Chi-square test for categorical data, Mann-Whitney test for ordinal data, and Student's independent samples *t*-test for continuous data.

The effects of the intervention were measured from baseline at follow-up. First, the HBM scores were calculated by measuring the differences between baseline and at follow-up for each HBM question. Then the questions were grouped together according to the HBM constructs *susceptibility*, *severity*, *benefits* and *barriers*. Finally the total HBM index was calculated by adding all HBM constructs together. For each individual item in the HBM index, the answers on the five-point Likert scale (Strongly agree to Strongly disagree) where given scores 0-4 for negative questions, i.e., "strongly disagree" would imply higher health belief and 4-0 for reversed questions. "Do not know" was classified as answering the neutral option. Finally, scores from all included individuals were summarized to give a total score. The McNemar test was used to determine differences in actual HPV vaccinations and actual condom use from baseline to follow-up, we have excluded the "do not know" group for vaccination in the analysis. The analyses are conducted on an individual level, analysed

according to intention to treat principle, comprising all 741 students completing the follow up questionnaire.

In order to take into account the dependence between students who were informed by the same school nurse, Generalized Estimating Equations models were used for examining the results of the intervention on the outcome measures. The differences between the outcome variables at baseline and follow-up were used as dependent variables in the Generalized Estimating Equations models, while treatment group (intervention or control) was used as a predictor together with the socioeconomic and demographic variables sex and immigrant background, which differed significantly between the two groups at baseline. These variables were only included as main effects in the regression models, with no interaction used. In all analyses, a two-sided p-value <0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics 22.0.

Results

Participants and sample

As mentioned above, a flow chart with details of the participants and samples is presented in Fig 1. A total of 2883 adolescents in 113 classes were allocated to either intervention group or control group. We excluded 496 adolescents not meeting the inclusion criteria. Of the 832 adolescents invited to participate, 81 declined, resulting in a total of 751 participants (i.e. the response rate was 90.2%); 394 in the intervention and 357 in the control group. At follow-up after three months 741 (89.1%) adolescents participated and were analysed (intervention group n=390 and control group n=351).

Baseline characteristics of participants by randomised group are presented in Table 2. The mean age was 16.1 years, 46.8% attended theoretical and 53.2% vocational programmes. More than a quarter (27.8%) had an immigrant background and over half of the girls (56.1%) were already vaccinated against HPV. There were significant differences between the groups at baseline regarding sex and immigrant background (Table 2). The reason for this is discussed in the Discussion section below. The effects of the intervention, adjusted for treatment group (intervention or control), sex and immigrant background, are presented in Tables 3 and 4. The adjusted analyses are further elaborated below. Since the Generalized Estimating Equations model did not converge for the HBM construct *benefits*, results for this construct are not presented.

The mean time from baseline to follow-up was 3.26 months, with no differences between intervention and control groups. In some classes the health interviews were delayed due to the fact that some students participated in practical training, national examinations or other mandatory school activities. Consequently, the follow-up questionnaire was sometimes delayed for a maximum of two months.

Effect of the intervention

Condom use

The intervention resulted in increased intention to use a condom with a new partner, with 1.751 higher points score for the intervention than the control group (p=0.004).There were significant changes from baseline to follow-up due to gender (p=0.045), with boys having 1.355 points higher scores than girls, while there were no significant differences due to immigrant background (p=0.717) (Table 3). Still, there were no significant differences between the intervention and the control groups regarding their reports of the actual condom use during their latest intercourse (p=0.377).

HBM total score

The intervention had a significant effect on HBM total score (p=0.003), (i.e. the students perceived more benefits of vaccination, perceived themselves to be at increased risk for an HPV infection or HPV-related disease, considered HPV-related disease a severe threat and perceived fewer barriers against HPV vaccination), with a 2.559 points higher score for the intervention compared to the control group. For further details see Table 4. There were also differences in changes from baseline to follow-up due to gender and immigrant background. Notably, boys had significantly lower scores (p=0.003) compared to girls. Students with immigrant background, however, had a 3.291 higher score compared to non-immigrant students (p=0.003).

Susceptibility

The intervention group reported higher scores for susceptibility (p<0.001) (i.e. they perceived increased risk for HPV infection and HPV related disease) with a 1.675 points higher score compared to the control group; for details see Table 4. On the other hand, boys had again significantly lower scores for this outcome parameter compared to girls (p<0.001). In contrast, adolescents with an immigrant background had a 1.770 higher score (p<0.001), and thus perceived increased risk, compared to non-immigrants.

Severity

The intervention also had significant effect on severity (p<0.001), with a 0.409 higher score (i.e. higher perceived HPV severity) for the intervention group compared to the control group, for details see Table 4. Boys had again significantly lower scores than girls (p<0.001), while there were no significant changes from baseline to follow-up due to immigrant background (p=0.330).

Barriers

There were no significant differences between the intervention and the control group for this parameter (p=0.262), for further details see Table 4. Notably, there were a significant change from baseline to follow-up due to gender (p=0.015), with a 0.469 higher score for boys (i.e. boys perceived lower barriers against HPV vaccination) compared to girls. The observed change for individuals with an immigrant background, on the other hand, was the opposite (p=0.014).

HPV vaccination

The intervention increased the likelihood that the students actually became vaccinated. The proportion of vaccinated girls in the intervention group was 52.5% before and 59.0% after the intervention, whereas no difference over time was seen in the control group (60.9%). This difference was significant (p=0.02). In actual numbers, 15 girls and one boy received the vaccine between the intervention and completion of the follow-up questionnaire. In addition, one girl wanted to be vaccinated, but her parents did not consent.

No harmful effects of the intervention were reported.

Discussion

Principal findings

This randomised controlled trial of a school-based educational session showed that adolescents' beliefs and behaviour regarding HPV prevention can successfully be improved. After the intervention the students had significantly more favourable beliefs towards HPV prevention and were more inclined to use condom during sex with a new partner. In addition, the intervention increased actual HPV vaccination rates.

It is encouraging that the intervention's effect on the intention to use condom was substantial among boys, since they are neither included in the national HPV vaccination programme nor do they receive any organised information about HPV. Our finding gives

support for the speculation that boys – when provided with adequate information – also want to protect themselves, and their partners, against the virus.

It was frustrating that the effects on the students' intentions did not result in clear differences in actual reported condom use. But it should be kept in mind that this is a small group and follow-up was short. The results might have been different with a longer follow up – not all of them were sexually active, and those who were may not have had a new opportunity, with a new partner, between the intervention and the follow-up questionnaire. Consequently, too much weight should not be given to this finding. More important is the finding that several girls (and one boy) chose to have themselves vaccinated shortly after the intervention. Since the older girls are offered the vaccine in the catch-up programme and the families have to contact the primary care centre themselves to book an appointment, it is encouraging that the intervention had effects on vaccination rates.

There were significant effects on the HBM total score, which includes the parameters perceived *susceptibility*, perceived *severity*, perceived *benefits* and perceived *barriers*. The intervention was especially effective regarding beliefs about HPV prevention among adolescents with an immigrant background. This is an important finding, since Sweden is a multicultural country with many immigrants from countries with limited access to healthcare and health education. It was also encouraging that these students reported higher scores for perceived *susceptibility*, i.e. they had become aware of the risks. Immigrant background is associated with increased risk for cervical cancer [38] and lower attendance in cervical cancer screening programmes.[39 40]

We also found significant differences between the groups regarding perceived severity. According to HBM the combination of *susceptibility* and *severity* are labelled as perceived *threat*.[33] Since adolescence is a time in life when the perception of being at risk of contracting an sexually transmitted infection is generally low, especially among boys,[41] and the sexual risk-taking is increasing,[11] we are happy to note that the intervention increased the adolescents' perception of HPV as a serious threat. This is beneficial for their future sexual health behaviour.

Strengths

This complex educational intervention was carefully developed, standardised, validated and monitored and had high response rate; 89.1% completed the study. Further major strengths are the randomised control trial design and the fact that various kinds of schools with a representative sample of both boys and girls were included. The percentage of adolescents with an immigrant background, as well as the number of HPV vaccinated girls at baseline, are

representative for the Swedish population in general. This means that the findings can, with a fair degree of certainty, be extrapolated to the population at large. The target group, adolescents aged 16 years, is adequate since this is a time in life when many become sexually active. The school nurses, with their professional role and experience of discussing sensitive issues, are the proper persons to deliver the intervention. Finally, a school-based intervention reaches all adolescents regardless of socio-economic status, ethnicity or cultural background.

Weaknesses

For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. This became clear during the evaluation of the pilot study. Consequently, the groups differed somewhat at baseline with, for example, more girls in the intervention group and more boys in the control group. We took this into account in the Generalized Estimating Equations model and adjusted for the demographic differences at baseline.

It is possible that the participating school nurses are more committed to HPV prevention and sexual health issues than their colleagues. These nurses' commitment and personal communication skills might have affected the outcome of the intervention in a favourable direction. To compensate for this and ensure uniformity the intervention was highly structured, the school nurses were provided with exhaustive instructions and the researchers regularly contacted them, asking questions systematically about *how does it work for you?* The initial process evaluation and log lists indicate that the fidelity was very high; all school nurses performed the intervention according to the given guidelines. Also, as in all studies including self-reported questionnaires, there is a risk of participant over- or under-reporting or recall bias, although we consider this risk small in the present study.

Finally, although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.

Strengths and weaknesses in relation to other studies

To our knowledge this is the first randomised, educational, school-based face-to-face intervention study among a diverse population of adolescents with the aim to improve primary prevention of HPV. Previous studies have mainly been undertaken among young adult women.[26 30] As discussed in the systematic review by Sheperd et al[42] there is a need for interventions with greater focus on HPV and especially the link between HPV and cancer. Previous interventions have tended to focus on prevention of cervical cancer only.[42] It is also an advantage to use a theoretical framework such as HBM when developing an educational

intervention with preventive aims. HBM is a systematic way to explain a person's health behaviour, which clarifies the key concepts on which the intervention is based.[33]

Our results stand in contrast to previous school-based interventions delivered in class in which no significant effects on beliefs[19] neither about condom use nor HPV vaccination, were found.[19 20] This discrepancy indicates that it is beneficial with a face-to-face intervention delivered by school nurses, similar interventions have previously been delivered by the researchers.[19 20 24]

Implications

The results indicate that an educational intervention delivered by health care providers, school nurses, is a highly feasible and effective way to increase adolescents' beliefs and behaviour towards primary prevention of HPV, regardless of socio-economic status, ethnicity or cultural background.

Unanswered questions and future research

Larger studies with more participants may help understand if there are also further differences between girls and boys, and between students with or without an immigrant background. Some of our conclusions remain speculative, awaiting such studies. In addition, studies with longer follow-up are needed, in order to find out if school-based educational interventions are effective in the long term, and if the participants' actual behaviour changes in the desired direction.

Acknowledgements

We thank all the participants; especially the school nurses and the adolescents. We also thank the heads of the school health in each municipality and the principals of the schools. A special thanks to the Swedish Association of School nurses for support, and for allowing us to present the project at the national conference. In addition we thank Åke Pålshammar for valuable discussions about the project, especially about adolescents' psychosocial and cognitive development.

Contributors: MG conceptualised and designed the study, recruited participants, managed the data collection, completed data analysis and interpretation, wrote the draft manuscript, and obtained funding. AR assisted in design, data analysis and interpretation, funding and manuscript preparation. CS assisted in design, participant recruitment, data collection, data interpretation, manuscript preparation and funding. ML, MO, RW and TT assisted in design, data collection, data interpretation, manuscript preparations and funding. BA and TD assisted

in design, data interpretation, funding, and were available for clinical consultation. TN assisted in all activities including design, data interpretation, data collection, manuscript preparation and funding. All authors made critical comments on drafts of the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding statement: This work was supported by [the Swedish Cancer Society] grant number [130744], [Uppsala-Örebro Regional Research Council] grant number [RFR-387561/476021] and [Uppsala County Council] grant number [LUL-347931], [the Swedish Government Funds for Clinical Research] grant number [19049/470102/44957] and the [Medical Faculty at Uppsala University] grant number [2012/278]. In addition, MG and CS received a scholarship from [the Gillbergska Foundation]. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests statement: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Uppsala University, Department of Public health and Caring Sciences and the Regional Ethical Committee in Uppsala, Sweden, D.nr. 2013/324 approved this study. All participants gave informed consent.

Data sharing: No additional data are available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Example of the Flip chart

Student information	School nurses' work material "chat script"
Prevention of HPV 1. Vaccination HPV vaccine protects against the most common HPV types that causes cervical cancer och condyloma (genital warts). The vaccine is offered free of charge to young girls in school and to older girls at the primary care centres. The vaccine gives best protection before exposure to HPV. Therefore it is recommended to vaccinate before sexual debut.	How can HPV be prevented? The HPV vaccine is highly efficient against the most common HPV types that can cause cervical cancer and condyloma (genital warts). The vaccine is offered free of charge to 11 year old girls in the school and to older girls at the primary care centres. Note! You, as school nurse, shall inform where (at what primary care centre) the student can be vaccinated free of charge in your area. The vaccine gives best protection before exposure to HPV, therefore it is best to vaccinate before sexual debut, but you can also be vaccinated later on.

Table 2. Baseline characteristics of participants by randomised group (n=741)

	Intervention n =390 (52.6%)		Control n=351 (47.4%)		*p*-value
Characteristic					
Age (years) mean (Md) (Sd)	16.15 (16)	(0.77)	16.06 (16)	(0.73)	0.800[†]
Sex					<0.001[††]
Female	239	(61.4)	146	(41.6)	
Male	150	(38.6)	205	(58.4)	
Education					0.117[††]
Theoretical programme	172	(44.1)	176	(50.1)	
Vocational programme	218	(55.9)	175	(49.9)	
Immigrant background[¶]					0.017[††]
Yes	123	(31.5)	83	(23.6)	
No	267	(68.5)	268	(76.4)	
Educational level, mother[*]					0.799[†††]
University	167	(54.9)	158	(53.7)	
Upper secondary school	118	(38.8)	118	(40.1)	
Elementary school	19	(6.3)	18	(6.1)	
Educational level, father [*]					0.334[†††]
University	100	(36.2)	112	(39.9)	
Upper secondary school	145	(52.5)	142	(50.5)	
Elementary school	31	(11.2)	27	(9.6)	
Main occupation, mother					0.148[††]
Employed[¶¶]	339	(87.1)	315	(90.5)	
Unemployed[¶¶¶]	50	(12.9)	33	(9.5)	
Main occupation, father					0.095[††]
Employed[¶¶]	331	(92.5)	318	(92.5)	
Unemployed[¶¶¶]	27	(7.5)	15	(4.5)	
Tobacco use (smoking)					0.197[††]
Never	316	(81.0)	297	(84.6)	
Occassionally/Daily	74	(19.0)	54	(15.4)	
Tobacco use (snuff)					0.767[††]
Never	359	(92.1)	321	(91.5)	
Occassionally/Daily	31	(7.9)	30	(8.5)	
Alcohol consumption					0.284[††]
Never	257	(66.1)	218	(62.3)	
Occasionally/Monthly/Weekly	132	(33.9)	132	(37.7)	
HPV vaccinated (only girls[a])					0.103[††]
Yes	126	(52.7)	89	(60.9)	
No	83	(34.9)	47	(32.4)	
Do not know	29	(12.2)	9	(6.2)	

[†]Independent Samples T-test[††]Chi-Square Tests, [†††]Mann-Whitney Test, [¶]Immigrant background: born outside Sweden or one or two parents born outside Sweden[¶¶]Employed includes studying and/or parental leave, [¶¶¶]Unemployed includes sick leave and similar.**Total amount do not add up to n=751 (100%) due do not know not presented and/or missing answer.*, [a] Not included in the numbers: One boy in CG HPV vaccinated at baseline

Table 3. Results of the Generalized Estimating Equations analyses. Effect of the intervention for the main outcome - intention to use condom if new partner.

Outcome	Predictors	Adjusted[¶] Slope coefficient (95% CI)	P-value
Intention to use condom if new partner	Intervention	1.751	0.004
	Boys	1.355 (0.031 to 2.679)	0.045
	Immigrant	0.132 (-0.580 to 0.844)	0.717

[¶]Adjusted for treatment group (intervention or control group), sex and immigrant background

Table 4. Results of the Generalized Estimating Equations analyses. Effect of the intervention according to the Health Belief Model (HBM).

Outcome	Predictors	Adjusted[¶] Slope coefficient (95% CI)	P-value
HBM total score	Intervention	2.559 (0.875 to 4.324)	0.003
	Boys	-2.244 (-3.729 to -0.759)	0.003
	Immigrant	3.291 (1.107 to 5.474)	0.003
Susceptibility	Intervention	1.675 (0.850 to 2.500)	<0.001
	Boys	-1.544 (-2.172 to -0.916)	<0.001
	Immigrant	1.770 (0.953 to 2.587)	<0.001
Severity	Intervention	0.409 (0.183 to 0.634)	<0.001
	Boys	-0.339 (-0.490 to -0.187)	<0.001
	Immigrant	0.131 (-0.133 to 0.395)	0.330
Barriers	Intervention	-0.172 (-0.473 to 0.129)	0.262
	Boys	0.469 (0.091 to 0.845)	0.015
	Immigrant	-0.505 (-0.910 to -1.00)	0.014

[¶]Adjusted for treatment group (intervention or control group), sex and immigrant background

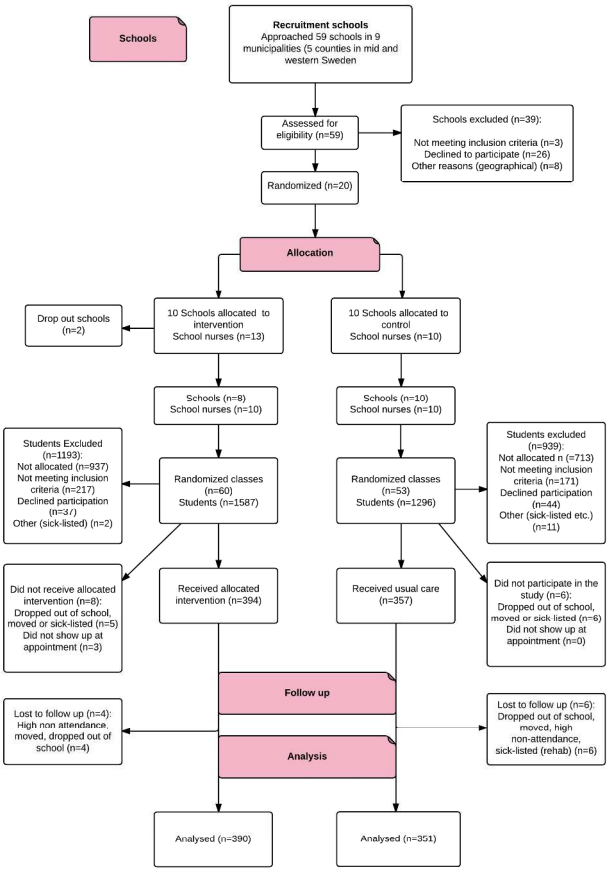

Fig 1. Flow of schools and students through trial
270x354mm (300 x 300 DPI)

Appendix - Questions used for primary outcome

Six point Likert scale: Totally agree to totally disagree and Do not know (Do not know grouped together with neither agree nor disagree in the analysis)

HBM Benefits
The HPV vaccine is effective in preventing condyloma
The HPV vaccine is effective in preventing cervical cancer
I will vaccinate against HPV

HBM Barriers
The HPV vaccine can cause adverse effects
It is problematic to book an appointment for HPV vaccination
I am afraid of needles

HBM Severity
The HPV infection is a serious health concern
Cervical cancer is a serious disease

HBM Susceptibility
Young women are at risk of contracting HPV
Young men are at risk of contracting HPV

Condom use
I intend to use condom if I have sex with a new partner

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	5
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	5
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		No changes were made
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	6
	4b	Settings and locations where the data were collected		6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	8

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		No changes were made
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	The second author, Dr Rosenblad, biostatistician and associate professor has been involved in this project since the design of the study. The paper was not reported as a cluster RCT since we had to recruit school nurses willing to participate before we could randomize schools and classes on cluster level. In addition, all analyses are performed on individual level. The power (sample size) is adequate for these analyses. However, as we discuss on page 16 it would have been even better with a larger sample size in order to be able to conduct more subgroups analyses. Nevertheless, this was not feasible due to logistic reasons. We have now revised the paper as a cluster randomised study Considering the inherent

				uncertainties in and approximations of all power calculations, our statistician deemed these power calculations to be appropriate.
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	No stratification or matching was used
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	6
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	6
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	6
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or	10

			both), and whether consent was sought before or after randomisation	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		The study was not blinded 7
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	By using GEE 11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11-12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	6 + Flowchart
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	6 + Flowchart
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5-6
	14b	Why the trial ended or was stopped		The study ended after the spring semester, 2015, due to the schools summer holiday.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 2

		group		
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	The analyses are conducted on individual level as described on page 11.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	The results are analysed on individual level, page 11. The clusters are too small to produce reliable ICC results.
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		None of the primary outcomes were binary.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		The analyses were undertaken as reported on page 11. No additional subgroup analyses etc. were performed due to not enough power as discussed on page 16.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		No harms were reported.
Discussion				14-17
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		15-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant		16

		evidence	
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	No protocol is available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

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BMJ Open

School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009875.R3
Article Type:	Research
Date Submitted by the Author:	08-Dec-2015
Complete List of Authors:	Grandahl, Maria; Uppsala University, Department of Public Health and Caring Sciences Rosenblad, Andreas; Uppsala University, Center for Clinical Research Västerås Stenhammar, Christina; Uppsala University, Department of Public Health and Caring Sciences Tydén, Tanja; Uppsala University, Department of Public Health and Caring Sciences Westerling, Ragnar; Uppsala University, Department of Public Health and Caring Sciences Larsson, Margareta; Uppsala University, Department of Women's and Children's Health Oscarsson, Marie; Linnaeus University, Department of Health and Caring Sciences; Uppsala University, Department of Public Health and Caring Sciences Andrae, Bengt; Centre for Research and Development, Uppsala University/Region of Gävleborg, Gävle, Sweden, Dalianis, Tina; Karolinska Institute, Department of Oncology-Pathology Nevéus, Tryggve; Uppsala University, Department of Women's and Children's Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Paediatrics
Keywords:	adolescents, HPV, prevention, randomised control trial, school-based

School-based intervention for the prevention of HPV among adolescents: a cluster randomised controlled study

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Keywords: adolescents, HPV, prevention, randomised control trial, school-based

Word count: 4661

Abstract

Objective To improve primary prevention of human papillomavirus (HPV) infection by promoting vaccination and increased condom use among upper secondary school students.

Design Cluster randomised controlled trial.

Setting 18 upper secondary schools in Sweden.

Participants Schools were first randomised to the intervention or the control group, after which individual classes were randomised to be included or not. 832 students aged 16 were invited to participate during the regular individual health interview with the school nurse, 751 (90.2%) agreed to participate, and 741 (89.1%) students completed the study.

Interventions The intervention was based on the Health Belief Model (HBM). According to HBM a person's health behaviour can be explained by individual beliefs regarding health actions. School nurses delivered 30 minute face-to-face structured information about HPV, including cancer risks and HPV prevention, i.e. condom use and HPV vaccination. Students in both the intervention and the control groups completed questionnaires at baseline and after three months.

Main outcome measures Intention to use condom with a new partner and beliefs about primary prevention of HPV; and also specifically vaccination status and increased condom use.

Results All statistical analyses were performed on individual level. The intervention had a significant effect on the intention to use condom ($p=0.004$). There was also a significant effect on HBM total score ($p=0.003$), with a 2.559 points higher score for the intervention group compared to the controls. The influence on the HBM parameters *susceptibility* and *severity* was also significant ($p<0.001$ for both variables). The intervention also influenced behaviour: girls in the intervention group chose to have themselves vaccinated to a significantly higher degree than the controls ($p=0.02$). No harms were reported.

Conclusions The school-based intervention had favourable effects on the beliefs about primary prevention of HPV and increased HPV vaccination rates in a diverse population of adolescents.

Trial registration - ClinicalTrials.gov Identifier: NCT02280967

Strengths and limitations of this study

- This is the first school-based educational cluster randomised controlled trial targeting a diverse and representative population of adolescents of both sexes, with the aim to improve primary prevention of HPV.
- The rigorously tested and validated intervention was found to have significant favourable effects on both the behaviour and beliefs of the participants.
- Although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.
- For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. Consequently, the groups differed somewhat at baseline.

Introduction

Infection with human papillomavirus (HPV) is one of the major causes of infection-related cancer worldwide. HPV is related to cancer in the cervix uteri, penis, vulva, vagina, anus and the oropharynx.[1 2] These malignancies can be effectively prevented by the prophylactic vaccination against HPV and by safe sex, i.e. condom use, in addition to regular screening.[3-7] Many countries have implemented national HPV immunization programmes.[8] In Sweden girls aged 10-12 years are since 2012 offered the quadrivalent vaccine as part of the school-based vaccination programme administered by the school nurse, while older girls and young women are offered the vaccine in the catch-up programme administered in the primary care setting. The coverage among young women is substantially lower (59%) than in the lower age group (83%).[9]

HPV infections and HPV related diseases have increased in recent decades due to increased sexual risk-taking.[10-12] The highest prevalence of HPV is found among teenagers and young adults.[13 14] Therefore, preventive strategies, such as the implementation of effective educational interventions among adolescents, are very much needed.

Adolescents do not receive education regarding HPV on a regular basis. The school nurses play a key role in providing such information.[15-17] Adolescents have low awareness and knowledge about the virus, especially regarding the cancer risks.[18] Educational school-based interventions can increase adolescents' awareness and knowledge about HPV prevention,[19 20] enhance preventive behaviours for sexually transmitted infections in general [21] and reduce sexual risk-taking.[22 23] Interventions can also have a beneficial effect on beliefs about HPV vaccination among girls.[24] So far, very few randomised controlled trials have been conducted among adolescents with the aim to promote primary HPV prevention.[25-27] And as far as we know, no such trial has been performed in a diverse population of both adolescent boys and girls.

Aim and hypothesis

The overall aim was to improve primary prevention of HPV by promoting HPV vaccination and increased condom use among upper secondary school students. The hypothesis was that intervention was associated with different beliefs (different attitude) towards HPV prevention at follow-up and that this influenced the actual behaviour.

Methods

Study design

A cluster randomised controlled trial with measurements at baseline and at follow-up after three months. Cluster randomisation was used since randomisation first was conducted on school level and thereafter classes were randomised to be included. Follow up after 12 and 24 month are not presented in this paper.

Setting

Sweden is a multicultural country: almost a third of all children under age 18 have an immigrant background.[28] The Swedish upper secondary school, which the vast majority of students attend, comprises both theoretical and vocational programs and reaches adolescents aged 16-19 years. According to Swedish law all students should have access to school health. The school health work is mainly preventive and involves at least a school nurse and a school physician, but only the nurse works in the school on a regular basis. In Sweden sexual education is mandatory in primary and secondary school, and includes topics such as anatomy, sexuality, prevention of sexually transmitted infections and reproductive health.

All first year upper secondary school students (aged 16) are offered a health interview with the school nurse, who provides a dialogue regarding psychosocial health, eating habits, sleep, physical activity, tobacco, alcohol and drugs as well as sexual health and relationships. This intervention is optional, although usually all students do participate. The interview is scheduled for approximately one hour and conducted in an empathic atmosphere based on Motivational Interviewing,[29] with focus on the individual student's health and well-being..

Population and sample

First year upper secondary school students attending the regular health interview with the school nurse in the autumn semester of 2014 were eligible for participation. We excluded students who were not able to speak or write Swedish (i.e. recently arrived immigrants) and adolescents with severe learning disabilities and development disorders (i.e. studying at special schools). Upper secondary schools (n=18) in nine municipalities in central Sweden with a total of about 600 000 rural and urban inhabitants, and with different socio-economic levels represented, were included. The participating schools included those both municipally and privately managed, offered vocationally as well as theoretically oriented education, and had a varying number of students.

Recruitment and randomisation

School nurses were recruited to the project via the school heads and through direct contact at a national school health conference. For logistical reasons, those working in the far north or south of Sweden were not invited. Initially 59 upper secondary schools were approached and eventually 18 of them were included, for details see the flow chart in Fig 1. A total of 23 school nurses working in 20 schools in nine municipalities agreed to participate in the study. Three nurses in two schools dropped out at the start of the intervention due to heavy workload. This opportunistic selection resulted in a total of 20 school nurses working in 18 schools.

Randomisation was performed in two steps. First, in order to avoid contamination, the schools were randomised into either the intervention group or the control group. The schools were randomly drawn, by administrative personnel not involved in the project. Second, 113 school classes within these schools were randomly selected to be included in the study; this number was chosen in order to achieve the desired number of students according to power calculations (described below). The school nurses provided basic details about the classes (for example Social science 14A), and number of students in each class. If the class consisted of less than 25 students, an additional class was allocated. The students were recruited by the school nurses as described below. The end result was an intervention group of 394 students from 60 classes and a control group of 357 students from 53 classes (Fig 1). Recruitment did not begin until registration was public.

Two school nurses in two schools dropped out during the intervention, due to termination of employment and personal reasons, and did not complete the health interviews with their allotted students. In order to compensate for these losses, which were all from the intervention group, all school nurses in the intervention group were offered to perform health interviews with an additional class. Consequently, similar classes were included in the study.

The students (n=832) were invited to participate in the study when they met the school nurse for the general health interview. Those who agreed to participate (n=751), gave informed written consent. Before the health interview started all students were asked to complete a baseline questionnaire. A follow-up questionnaire was completed after three months (n=741). The baseline questionnaire was completed individually at the school nurse's office while the follow-up questionnaire was given to the whole class. Students not present at this time could

complete the follow-up questionnaire afterwards at the school nurse's office. School nurses were provided with checklists regarding the procedure and used log lists (protocols completed after each health interview) to assure that the intervention was performed in a uniform fashion. For obvious reasons, the school nurse could not be blinded to whether the student belonged to the intervention or control group, but the research assistant who recorded the data from the participants did not possess this knowledge.

Theoretical framework

The Health Belief Model (HBM) was used as a theoretical framework. This model has previously been used in studies about HPV and HPV vaccination[30 31] and in interventions with the aim to increase prevention of sexually transmitted infections.[19 32] According to the HBM framework, a person's health behaviour can be explained by the individual beliefs regarding health actions. HBM includes the following central constructs: perceived *susceptibility*, perceived *severity*, perceived *benefit* and perceived *barriers*. Furthermore, socio-demographic factors such as age, sex, ethnicity and parental education level, as well as knowledge, are recognised as factors that indirectly can influence the individual's behaviour. The main limitation of the model is that it does not consider emotional or relational aspects involved in decisions regarding health behaviour.[33]

Intervention

The intervention was included in the general one hour face-to-face health interview. Thus, whereas the controls received general information, including sexual health, the intervention group received specific HPV education guided by HBM and following a pre-designed structure. The school nurse used a specially designed flipchart with pictures and brief information facing the students (see example in Table 1). She also handed out a specially designed leaflet. The intervention took about 30 minutes and included the following information:

- general facts about the virus
- viral transmission
- what HPV can cause
- risk factors
- prevention, i.e. safe sex with condom use and HPV vaccination
- locations where the girls could receive the vaccine free of charge in the municipality
- facts about the HPV vaccine
- the importance for girls of attending future cervical cancer screening controls

The leaflet consisted of 12 pages and included similar information and also an HPV quiz as well as links to the national online youth clinic, the homepage of the university where the researchers worked and contact information to the authors. After the follow-up questionnaire was completed, students in the intervention group were provided with condoms. Students in the control group only received standard treatment, i.e. the regular health interview, as described above.

Outcome measures

The outcomes pertain to the individual student. Primary outcomes: Intention to use condom with a new partner and beliefs towards primary prevention about HPV, (strongly agree to strongly disagree, see Appendix).

Secondary outcomes: Increased HPV vaccination (yes/no/do not know) and increased condom use (yes/no).

Pilot study

In early 2014 the intervention procedure, including the educational material and questionnaire, was tested by three school nurses among 45 students aged 16 years. The nurses' experiences resulted in minor revisions: for logistic reasons the methods was changed from individual follow-up at the school nurses office to follow-up in class, the educational material was shortened, some statements were simplified and the additional response alternative "do not know" was added to the block of questions regarding beliefs about HPV. A few of the questions were clarified and two were considered redundant and thus removed. In parallel, the questionnaire was tested among adolescents aged 17 (n=230),[34] who confirmed the school nurses' observations.

Instrument

The questionnaire was based on previous research and clinical experience. The questions about beliefs, awareness and knowledge about HPV (n=24) were adapted from our previous study[15] and had multiple choice alternatives and six-point verbal rating scales (Likert scale) from "Totally agree" to" Totally disagree", including "Do not know". The demographic background questions (n=14) were taken from the national questionnaire for adolescents[35] and the questions regarding sexual behaviour (n=17) were based on a project among university students which has been used repeatedly since 1989.[10] The questions about beliefs towards primary prevention of HPV according to the HBM constructs on *susceptibility* comprised questions regarding the risk for contracting HPV; while *severity* included how serious it would be to receive an HPV infection or cancer. In addition, questions about *benefits*

comprised confidence in vaccine effectiveness and intention to vaccinate; while *barriers* embraced the individual's perceived barriers for HPV vaccination, such as fear of needles and difficulties booking an appointment for vaccination.

Validity and reliability of the intervention including the questionnaire

The validity and reliability were rigorously tested with both qualitative and quantitative methods. Two focus group interviews were undertaken with adolescents (n=8) aged 16-17 years (both boys and girls) who were asked what they considered important to include in an intervention regarding prevention of HPV. Cognitive interviews (n=5) and discussion sessions (n=8) regarding the questionnaire were performed with adolescents aged 15-18 years.

To test the stability and reliability over time a test-retest evaluation was undertaken with first year upper secondary school students (n=29) randomly selected from a school situated in a city of 200 000 habitants in mid Sweden in 2014. The questionnaire was distributed on two occasions with a time interval of two weeks. Analysis was based on Cronbach's alpha and showed high reliability scores for the questions regarding the decision-making process about HPV vaccination (0.800-0.998), except for the single question "Do you want to be vaccinated later" (0.436). Statements regarding beliefs about HPV ranged from low to high (scores 0.331-0.918), consequently, two statements were removed.

Ethical considerations

The study was conducted according to the Declaration of Helsinki. All participants received oral and written information before giving their written consent. The participants were informed that participation was voluntary, that they could withdraw participation at any time without providing a motivation or incurring any negative consequences for themselves. They were also informed that only the researchers would have access to the data and that all data would be presented on a group level. Contact details to the researchers were provided in case of further questions. According to the Swedish law children above 15 years of age who understand what participation means have the right to give informed consent regarding participation in research studies.[36] Therefore, informed consent was not obtained from the parents. We asked permission to conduct the study from the head of the school health in each municipality and from the principals of the schools. The project was approved by the Regional Ethical Review Board of Uppsala University (D.nr.2013/324).

Education to school nurses

All participating school nurses (n=20) received written and verbal instructions and participated in educational sessions (with MG and CS) scheduled for about two hours. The education comprised factual information about HPV and the HPV vaccine. The flipchart educational material was presented and the nurses were encouraged to give comments if anything was unclear or if anything considered important was missing. Furthermore, each school nurse received a minimum of one hour additional education at the time for the start of the intervention at the school where she worked. During the intervention the nurses were contacted on a weekly basis.

Sample size calculation

The power calculation was based on a previous study among the research group[37] and clinical experience. The sample size of 400 participants per study arm were based on assumptions of baseline *intention to use condom if new partner* of 60%, with a power of 80% to detect differences of 10 percentage points between intervention and control group at a significance level of 5% (356/study arm IG/CG, a dropout of 10% and missing values=400).

Statistical analysis

For descriptive statistics, categorical data are presented as frequencies and percentages, n (%), ordinal data as medians, means and standard deviations (SD), while continuous data are given as mean and SD. Differences between the intervention and control groups are tested with Pearsons' Chi-square test for categorical data, Mann-Whitney test for ordinal data, and Student's independent samples *t*-test for continuous data.

The effects of the intervention were measured from baseline at follow-up. First, the HBM scores were calculated by measuring the differences between baseline and at follow-up for each HBM question. Then the questions were grouped together according to the HBM constructs *susceptibility*, *severity*, *benefits* and *barriers*. Finally the total HBM index was calculated by adding all HBM constructs together. For each individual item in the HBM index, the answers on the five-point Likert scale (Strongly agree to Strongly disagree) where given scores 0-4 for negative questions, i.e., "strongly disagree" would imply higher health belief and 4-0 for reversed questions. "Do not know" was classified as answering the neutral option. Finally, scores from all included individuals were summarized to give a total score. The McNemar test was used to determine differences in actual HPV vaccinations and actual condom use from baseline to follow-up, we have excluded the "do not know" group for vaccination in the analysis. The analyses are conducted on an individual level, analysed

according to intention to treat principle, comprising all 741 students completing the follow up questionnaire.

In order to take into account the dependence between students who were informed by the same school nurse, Generalized Estimating Equations models were used for examining the results of the intervention on the outcome measures. The differences between the outcome variables at baseline and follow-up were used as dependent variables in the Generalized Estimating Equations models, while treatment group (intervention or control) was used as a predictor together with the socioeconomic and demographic variables sex and immigrant background, which differed significantly between the two groups at baseline. These variables were only included as main effects in the regression models, with no interaction used. In all analyses, a two-sided p-value <0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics 22.0.

Results

Participants and sample

As mentioned above, a flow chart with details of the participants and samples is presented in Fig 1. A total of 2883 adolescents in 113 classes were allocated to either intervention group or control group. We excluded 496 adolescents not meeting the inclusion criteria. Of the 832 adolescents invited to participate, 81 declined, resulting in a total of 751 participants (i.e. the response rate was 90.2%); 394 in the intervention and 357 in the control group. At follow-up after three months 741 (89.1%) adolescents participated and were analysed (intervention group n=390 and control group n=351).

Baseline characteristics of participants by randomised group are presented in Table 2. The mean age was 16.1 years, 46.8% attended theoretical and 53.2% vocational programmes. More than a quarter (27.8%) had an immigrant background and over half of the girls (56.1%) were already vaccinated against HPV. There were significant differences between the groups at baseline regarding sex and immigrant background (Table 2). The reason for this is discussed in the Discussion section below. The effects of the intervention, adjusted for treatment group (intervention or control), sex and immigrant background, are presented in Tables 3 and 4. The adjusted analyses are further elaborated below. Since the Generalized Estimating Equations model did not converge for the HBM construct *benefits*, results for this construct are not presented.

The mean time from baseline to follow-up was 3.26 months, with no differences between intervention and control groups. In some classes the health interviews were delayed due to the fact that some students participated in practical training, national examinations or other mandatory school activities. Consequently, the follow-up questionnaire was sometimes delayed for a maximum of two months.

Effect of the intervention

Condom use

The intervention resulted in increased intention to use a condom with a new partner, with 1.751 higher points score for the intervention than the control group (p=0.004).There were significant changes from baseline to follow-up due to gender (p=0.045), with boys having 1.355 points higher scores than girls, while there were no significant differences due to immigrant background (p=0.717) (Table 3). Still, there were no significant differences between the intervention and the control groups regarding their reports of the actual condom use during their latest intercourse (p=0.377).

HBM total score

The intervention had a significant effect on HBM total score (p=0.003), (i.e. the students perceived more benefits of vaccination, perceived themselves to be at increased risk for an HPV infection or HPV-related disease, considered HPV-related disease a severe threat and perceived fewer barriers against HPV vaccination), with a 2.559 points higher score for the intervention compared to the control group. For further details see Table 4. There were also differences in changes from baseline to follow-up due to gender and immigrant background. Notably, boys had significantly lower scores (p=0.003) compared to girls. Students with immigrant background, however, had a 3.291 higher score compared to non-immigrant students (p=0.003).

Susceptibility

The intervention group reported higher scores for susceptibility (p<0.001) (i.e. they perceived increased risk for HPV infection and HPV related disease) with a 1.675 points higher score compared to the control group; for details see Table 4. On the other hand, boys had again significantly lower scores for this outcome parameter compared to girls (p<0.001). In contrast, adolescents with an immigrant background had a 1.770 points higher score (p<0.001), and thus perceived increased risk, compared to non-immigrants.

Severity

The intervention also had significant effect on severity (p<0.001), with a 0.409 higher score (i.e. higher perceived HPV severity) for the intervention group compared to the control group, for details see Table 4. Boys had again significantly lower scores than girls (p<0.001), while there were no significant changes from baseline to follow-up due to immigrant background (p=0.330).

Barriers

There were no significant differences between the intervention and the control group for this parameter (p=0.262), for further details see Table 4. Notably, there were a significant change from baseline to follow-up due to gender (p=0.015), with a 0.469 higher score for boys (i.e. boys perceived lower barriers against HPV vaccination) compared to girls. The observed change for individuals with an immigrant background, on the other hand, was the opposite (p=0.014).

HPV vaccination

The intervention increased the likelihood that the students actually became vaccinated. The proportion of vaccinated girls in the intervention group was 52.5% before and 59.0% after the intervention, whereas no difference over time was seen in the control group (60.9%). This difference was significant (p=0.02). In actual numbers, 15 girls and one boy received the vaccine between the intervention and completion of the follow-up questionnaire. In addition, one girl wanted to be vaccinated, but her parents did not consent.

No harmful effects of the intervention were reported.

Discussion

Principal findings

This randomised controlled trial of a school-based educational session showed that adolescents' beliefs and behaviour regarding HPV prevention can successfully be improved. After the intervention the students had significantly more favourable beliefs towards HPV prevention and were more inclined to use condom during sex with a new partner. In addition, the intervention increased actual HPV vaccination rates.

It is encouraging that the changes from baseline to follow-up on the intention to use condom was higher among boys than among girls, since they are neither included in the national HPV vaccination programme nor do they receive any organised information about

HPV. Our finding gives support for the speculation that boys also want to protect themselves, and their partners, against the virus.

It was frustrating that the effects on the students' intentions did not result in clear differences in actual reported condom use. But it should be kept in mind that this is a small group and follow-up was short. The results might have been different with a longer follow up – not all of them were sexually active, and those who were may not have had a new opportunity to use a condom, with a new partner, between the intervention and the follow-up questionnaire. Consequently, too much weight should not be given to this finding. More important is the finding that several girls (and one boy) chose to have themselves vaccinated shortly after the intervention. Since the older girls are offered the vaccine in the catch-up programme and the families have to contact the primary care centre themselves to book an appointment, it is encouraging that the intervention had effects on vaccination rates.

There were significant effects on the HBM total score, which includes the parameters perceived *susceptibility*, perceived *severity*, perceived *benefits* and perceived *barriers*. Interestingly, the increase in beliefs about HPV prevention from baseline to follow-up was higher among adolescents with an immigrant background. This is an important finding, since Sweden is a multicultural country with many immigrants from countries with limited access to healthcare and health education. It was also encouraging that these students reported higher scores for perceived *susceptibility*, i.e. they were aware of the risks. Immigrant background is known to be associated with increased risk for cervical cancer[38] and lower attendance in cervical cancer screening programmes.[39 40]

We also found significant differences between the intervention and control groups regarding perceived severity. According to HBM the combination of *susceptibility* and *severity* are labelled as perceived *threat*.[33] Since adolescence is a time in life when the perception of being at risk of contracting an sexually transmitted infection is generally low, especially among boys,[41] and the sexual risk-taking is increasing,[11] we are happy to note that the intervention increased the adolescents' perception of HPV as a serious threat. This is beneficial for their future sexual health behaviour.

Strengths

This complex educational intervention was carefully developed, standardised, validated and monitored and had high response rate; 89.1% completed the study. Further major strengths are the randomised control trial design and the fact that various kinds of schools with a representative sample of both boys and girls were included. The percentage of adolescents with an immigrant background, as well as the number of HPV vaccinated girls at baseline, are

representative for the Swedish population in general. This means that the findings can, with a fair degree of certainty, be extrapolated to the population at large. The target group, adolescents aged 16 years, is adequate since this is a time in life when many become sexually active. The school nurses, with their professional role and experience of discussing sensitive issues, are the proper persons to deliver the intervention. Finally, a school-based intervention reaches all adolescents regardless of socio-economic status, ethnicity or cultural background.

Weaknesses

For logistic reasons, we could not randomise the students one by one, since the school nurses could not perform the follow-up on an individual level. This became clear during the evaluation of the pilot study. Consequently, the groups differed somewhat at baseline with, for example, more girls in the intervention group and more boys in the control group. We took this into account in the Generalized Estimating Equations model and adjusted for the demographic differences at baseline.

It is possible that the participating school nurses are more committed to HPV prevention and sexual health issues than their colleagues. These nurses' commitment and personal communication skills might have affected the outcome of the intervention in a favourable direction. To compensate for this and ensure uniformity the intervention was highly structured, the school nurses were provided with exhaustive instructions and the researchers regularly contacted them, asking questions systematically about *how does it work for you?* The initial process evaluation and log lists indicate that the fidelity was very high; all school nurses performed the intervention according to the given guidelines. Also, as in all studies including self-reported questionnaires, there is a risk of participant over- or under-reporting or recall bias, although we consider this risk small in the present study.

Finally, although our study was fairly large, it would have been even better if we had been able to include more participants in order to be able to go into further detail and perform more subgroup analyses.

Strengths and weaknesses in relation to other studies

To our knowledge this is the first randomised, educational, school-based face-to-face intervention study among a diverse population of adolescents with the aim to improve primary prevention of HPV. Previous studies have mainly been undertaken among young adult women.[26 30] As discussed in the systematic review by Sheperd et al[42] there is a need for interventions with greater focus on HPV and especially the link between HPV and cancer. Previous interventions have tended to focus on prevention of cervical cancer only.[42] It is also an advantage to use a theoretical framework such as HBM when developing an educational

intervention with preventive aims. HBM is a systematic way to explain a person's health behaviour, which clarifies the key concepts on which the intervention is based.[33]

Our results stand in contrast to previous school-based interventions delivered in class in which no significant effects on beliefs[19] neither about condom use nor HPV vaccination, were found.[19 20] This discrepancy indicates that it is beneficial with a face-to-face intervention delivered by school nurses, similar interventions have previously been delivered by the researchers.[19 20 24]

Implications

The results indicate that an educational intervention delivered by health care providers, school nurses, is a highly feasible and effective way to increase adolescents' beliefs and behaviour towards primary prevention of HPV, regardless of socio-economic status, ethnicity or cultural background.

Unanswered questions and future research

Larger studies with more participants may help understand if there are also further differences between girls and boys, and between students with or without an immigrant background. Some of our conclusions remain speculative, awaiting such studies. In addition, studies with longer follow-up are needed, in order to find out if school-based educational interventions are effective in the long term, and if the participants' actual behaviour changes in the desired direction.

Acknowledgements

We thank all the participants; especially the school nurses and the adolescents. We also thank the heads of the school health in each municipality and the principals of the schools. A special thanks to the Swedish Association of School nurses for support, and for allowing us to present the project at the national conference. In addition we thank Åke Pålshammar for valuable discussions about the project, especially about adolescents' psychosocial and cognitive development.

Contributors: MG conceptualised and designed the study, recruited participants, managed the data collection, completed data analysis and interpretation, wrote the draft manuscript, and obtained funding. AR assisted in design, data analysis and interpretation, funding and manuscript preparation. CS assisted in design, participant recruitment, data collection, data interpretation, manuscript preparation and funding. ML, MO, RW and TT assisted in design, data collection, data interpretation, manuscript preparations and funding. BA and TD assisted

in design, data interpretation, funding, and were available for clinical consultation. TN assisted in all activities including design, data interpretation, data collection, manuscript preparation and funding. All authors made critical comments on drafts of the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding statement: This work was supported by [the Swedish Cancer Society] grant number [130744], [Uppsala-Örebro Regional Research Council] grant number [RFR-387561/476021] and [Uppsala County Council] grant number [LUL-347931], [the Swedish Government Funds for Clinical Research] grant number [19049/470102/44957] and the [Medical Faculty at Uppsala University] grant number [2012/278]. In addition, MG and CS received a scholarship from [the Gillbergska Foundation]. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests statement: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Uppsala University, Department of Public health and Caring Sciences and the Regional Ethical Committee in Uppsala, Sweden, D.nr. 2013/324 approved this study. All participants gave informed consent.

Data sharing: No additional data are available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Example of the Flip chart

Student information	School nurses' work material "chat script"
Prevention of HPV 1. Vaccination HPV vaccine protects against the most common HPV types that causes cervical cancer and condyloma (genital warts). The vaccine is offered free of charge to young girls in school and to older girls at the primary care centres. The vaccine gives best protection before exposure to HPV. Therefore it is recommended to vaccinate before sexual debut.	How can HPV be prevented? The HPV vaccine is highly efficient against the most common HPV types that can cause cervical cancer and condyloma (genital warts). The vaccine is offered free of charge to 11 year old girls in the school and to older girls at the primary care centres. Note! You, as school nurse, shall inform where (at what primary care centre) the student can be vaccinated free of charge in your area. The vaccine gives best protection before exposure to HPV, therefore it is best to vaccinate before sexual debut, but you can also be vaccinated later on.

Table 2. Baseline characteristics of participants by randomised group (n=741)

	Intervention n =390 (52.6%)		Control n=351 (47.4%)		*p*-value
Characteristic					
Age (years) mean (Md) (Sd)	16.15 (16)	(0.77)	16.06 (16)	(0.73)	0.800[†]
Sex					<0.001[††]
Female	239	(61.4)	146	(41.6)	
Male	150	(38.6)	205	(58.4)	
Education					0.117[††]
Theoretical programme	172	(44.1)	176	(50.1)	
Vocational programme	218	(55.9)	175	(49.9)	
Immigrant background[¶]					0.017[††]
Yes	123	(31.5)	83	(23.6)	
No	267	(68.5)	268	(76.4)	
Educational level, mother[*]					0.799[†††]
University	167	(54.9)	158	(53.7)	
Upper secondary school	118	(38.8)	118	(40.1)	
Elementary school	19	(6.3)	18	(6.1)	
Educational level, father [*]					0.334[†††]
University	100	(36.2)	112	(39.9)	
Upper secondary school	145	(52.5)	142	(50.5)	
Elementary school	31	(11.2)	27	(9.6)	
Main occupation, mother					0.148[††]
Employed[¶¶]	339	(87.1)	315	(90.5)	
Unemployed[¶¶¶]	50	(12.9)	33	(9.5)	
Main occupation, father					0.095[††]
Employed[¶¶]	331	(92.5)	318	(92.5)	
Unemployed[¶¶¶]	27	(7.5)	15	(4.5)	
Tobacco use (smoking)					0.197[††]
Never	316	(81.0)	297	(84.6)	
Occassionally/Daily	74	(19.0)	54	(15.4)	
Tobacco use (snuff)					0.767[††]
Never	359	(92.1)	321	(91.5)	
Occassionally/Daily	31	(7.9)	30	(8.5)	
Alcohol consumption					0.284[††]
Never	257	(66.1)	218	(62.3)	
Occasionally/Monthly/Weekly	132	(33.9)	132	(37.7)	
HPV vaccinated (only girls[a])					0.103[††]
Yes	126	(52.7)	89	(60.9)	
No	83	(34.9)	47	(32.4)	
Do not know	29	(12.2)	9	(6.2)	

[†]Independent Samples T-test[††]Chi-Square Tests, [†††]Mann-Whitney Test, [¶]Immigrant background: born outside Sweden or one or two parents born outside Sweden[¶¶]Employed includes studying and/or parental leave, [¶¶¶]Unemployed includes sick leave and similar.**Total amount do not add up to n=751 (100%) due do not know not presented and/or missing answer.*, [a] Not included in the numbers: One boy in CG HPV vaccinated at baseline

Table 3. Results of the Generalized Estimating Equations analyses. Effect of the intervention for the main outcome - intention to use condom if new partner.

Outcome	Predictors	Adjusted[¶] Slope coefficient (95% CI)	P-value
Intention to use condom if new partner	Intervention	1.751	0.004
	Boys	1.355 (0.031 to 2.679)	0.045
	Immigrant	0.132 (-0.580 to 0.844)	0.717

[¶]Adjusted for treatment group (intervention or control group), sex and immigrant background

Table 4. Results of the Generalized Estimating Equations analyses. Effect of the intervention according to the Health Belief Model (HBM).

Outcome	Predictors	Adjusted[¶] Slope coefficient (95% CI)	P-value
HBM total score	Intervention	2.559 (0.875 to 4.324)	0.003
	Boys	-2.244 (-3.729 to -0.759)	0.003
	Immigrant	3.291 (1.107 to 5.474)	0.003
Susceptibility	Intervention	1.675 (0.850 to 2.500)	<0.001
	Boys	-1.544 (-2.172 to -0.916)	<0.001
	Immigrant	1.770 (0.953 to 2.587)	<0.001
Severity	Intervention	0.409 (0.183 to 0.634)	<0.001
	Boys	-0.339 (-0.490 to -0.187)	<0.001
	Immigrant	0.131 (-0.133 to 0.395)	0.330
Barriers	Intervention	-0.172 (-0.473 to 0.129)	0.262
	Boys	0.469 (0.091 to 0.845)	0.015
	Immigrant	-0.505 (-0.910 to -1.00)	0.014

[¶]Adjusted for treatment group (intervention or control group), sex and immigrant background

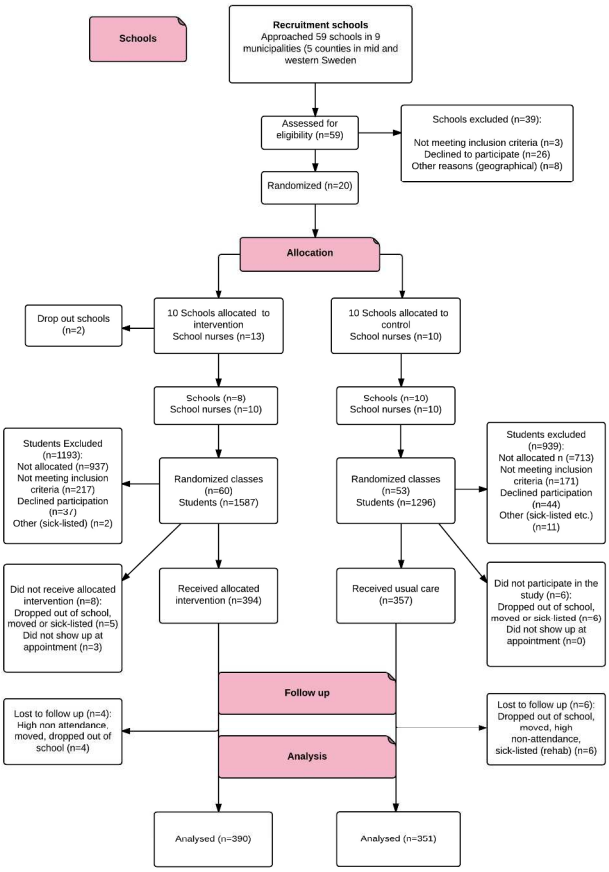

Fig 1. Flow of schools and students through trial
270x354mm (300 x 300 DPI)

Appendix - Questions used for primary outcome

Six point Likert scale: Totally agree to totally disagree and Do not know (Do not know grouped together with neither agree nor disagree in the analysis)

HBM Benefits
The HPV vaccine is effective in preventing condyloma
The HPV vaccine is effective in preventing cervical cancer
I will vaccinate against HPV

HBM Barriers
The HPV vaccine can cause adverse effects
It is problematic to book an appointment for HPV vaccination
I am afraid of needles

HBM Severity
The HPV infection is a serious health concern
Cervical cancer is a serious disease

HBM Susceptibility
Young women are at risk of contracting HPV
Young men are at risk of contracting HPV

Condom use
I intend to use condom if I have sex with a new partner

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	5
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	5
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		No changes were made
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	6
	4b	Settings and locations where the data were collected		6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	8

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		No changes were made
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	The second author, Dr Rosenblad, biostatistician and associate professor has been involved in this project since the design of the study. The paper was not reported as a cluster RCT since we had to recruit school nurses willing to participate before we could randomize schools and classes on cluster level. In addition, all analyses are performed on individual level. The power (sample size) is adequate for these analyses. However, as we discuss on page 16 it would have been even better with a larger sample size in order to be able to conduct more subgroups analyses. Nevertheless, this was not feasible due to logistic reasons. We have now revised the paper as a cluster randomised study Considering the inherent

				uncertainties in and approximations of all power calculations, our statistician deemed these power calculations to be appropriate.
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	No stratification or matching was used
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	6
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	6
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	6
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or	10

			both), and whether consent was sought before or after randomisation	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		The study was not blinded 7
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	By using GEE 11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		11-12
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	6 + Flowchart
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	6 + Flowchart
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5-6
	14b	Why the trial ended or was stopped		The study ended after the spring semester, 2015, due to the schools summer holiday.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 2

		group		
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	The analyses are conducted on individual level as described on page 11.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	The results are analysed on individual level, page 11. The clusters are too small to produce reliable ICC results.
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		None of the primary outcomes were binary.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		The analyses were undertaken as reported on page 11. No additional subgroup analyses etc. were performed due to not enough power as discussed on page 16.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		No harms were reported.
Discussion				14-17
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		15-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant		16

		evidence	
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	No protocol is available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.