Girls' and Parents' Decision-Making About HPV Vaccination Uptake

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Girls' and Parents' Decision-Making About HPV Vaccination Uptake

Besluitvorming van meisjes en ouders ten aanzien van HPV vaccinatie

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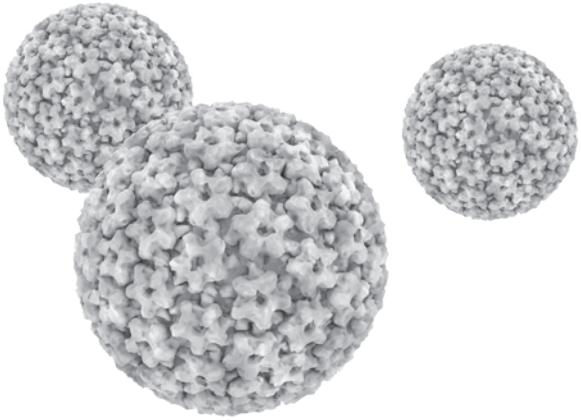
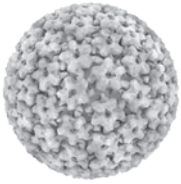


Chapter 1

General introduction



1. CERVICAL CANCER

In Europe 60,000 women are diagnosed with cervical cancer every year [1]. In the Netherlands, about 700 women are diagnosed with cervical cancer annually and about 200 to 250 women die from the disease [www.rivm.nl]. Cervical cancer can only develop in the presence of infection with a high-risk type of human papillomavirus (HPV) [2-3]. There are two types of HPVs: high-risk (oncogenic) and low-risk. HPV 16 and 18, both high-risk strains, cause approximately 70% of cervical cancers [4]. HPV 16 and 18 can also cause cancer of the vulva, vagina, penis, or anus; and oropharyngeal cancer (cancer in the back of throat). The low-risk strains HPV 6 and 11 cause approximately 90% of genital warts. HPV infections are sexually transmitted, most often during vaginal or anal sex. Condoms may lower the risk of HPV infection, but do not provide complete protection. The estimated lifetime risk of HPV infection is 75% to 80% in Europe and in the US [5-6], so it is very common. Most HPV infections are cleared rapidly by the immune system and do not progress into cervical cancer. When the infection persists there is a risk of developing precancerous lesions of the cervix. The precancerous lesions are called cervical intraepithelial neoplasia (CIN) and are graded into three categories: mild (CIN1), moderate (CIN2), and severe dysplasia (CIN3) [7-9]. Precancerous lesions can progress to invasive cervical cancer. One percent of CIN1 cases, 5% of CIN2 cases and 12% of CIN3 cases will progress to invasive cervical cancer. Progression to cervical cancer typically takes about 12-15 years.

Routine screenings to detect precancerous tissue changes in the cervix help lower the risk of cervical cancer. In the Netherlands, such screenings are available to women aged 30-60 years (once every 5 years). Diagnosing and treating precancerous conditions often makes it possible to prevent cervical cancer. In 2016 the screening program will be changed. Instead of cytological screening to look for neoplastic abnormalities, screening for the presence of high-risk HPV will take place first. If high-risk HPV is detected, the smear will also be screened for cytological abnormalities. If both high-risk HPV and cytological abnormalities are present, a woman will be referred to a gynecologist for follow-up examination. If no cytological abnormalities are found, a cytological follow-up test will be performed six months later. The advantage of screening for high-risk HPV is that cervical cancer can be prevented in an earlier stage. Such screening would prevent 75 extra cases of cervical cancer and 18 deaths each year [10].

2. VACCINATION

Since 2006 a quadrivalent vaccine which protects against HPV 6, 11, 16 and 18 has been available; since 2007 a bivalent vaccine is available which protects against HPV 16 and 18 has been available. Since HPV 16 and 18 cause about 70% of all cervical cancer cases, these vaccines have the potential to reduce the number of new cervical cancer cases by up to 70%. Screening is therefore still necessary. Preferably, the HPV vaccine is given prior to the initiation of sexual activity, because the degree of protection is reduced after HPV infection and the incidence of HPV infections is highest in the first months after onset of sexual activity [11-12]. The vaccine is administered in a 3-dose schedule, with the second dose administered 1 to 2 months after the first dose and the third dose 6 months after the first dose. In 2014, a 2-dose scheme was introduced, because two doses have been found to provide as much protection as 3 doses as long as the vaccination is given before girls turn 15 years of age [13-14]. The second dose is given 6 months after the first dose. To date, follow-up data on HPV vaccinated young women are available for 9.4 years and show a high sustained efficacy against HPV 16 and 18 [15]. Statistical modeling predicts a slow decay of the vaccine-induced antibodies for at least 20 years with the assumption that if the long-term persistence of antibodies has a similar relevance for protection to that observed with some other vaccines, then a booster may not be needed until considerable time has passed after vaccination [16].

In 2010 the Netherlands' National Immunization Program (NIP), which is free of charge and voluntary, was extended to include the bivalent HPV vaccine for 12-year-old girls. These girls receive an information leaflet and invitation to be vaccinated at their home address. In the Netherlands, 12-year-old girls do not need parental permission to make a decision about uptake.

In 2009 a catch-up campaign was organized for 13- to 16-year-old girls (birth cohorts 1993-1996). The uptake rate of this campaign was 52% [17]. In 2011 58% of all 12-year-old girls were vaccinated against HPV (birth cohort 1998) [18]. In 2012, uptake increased to 61% (birth cohort 1999) [19]. In some regions uptake is much lower, such as in areas where relatively more conservative Protestants live. For instance, in the municipality of Staphorst uptake was 13% in 2012, while in the municipality of Beuningen uptake was much higher (78%) [20].

3. DECISION-MAKING

Although 12-year-old Dutch girls are legally entitled to make their own decision about uptake, in practice parents play a considerable role in decision-making about the uptake of HPV vaccinations [21-22]. Consequently, research into the decision-making process

regarding the acceptance of HPV vaccination should include both girls and parents. Various models have been used to explain health-related behavior, for example HPV vaccination uptake, such as the Theory of Planned Behavior (TPB) [23] and the Health Belief Model (HBM) [24]. The TPB proposes that the most proximal determinant of behavior is intention, which is an indication of how hard people are willing to try to perform a behavior. The stronger the intention to engage in a behavior, the more likely it is that the behavior will be carried out. Intention, in turn, is guided by three constructs: attitudes towards the behavior (i.e. evaluation of the advantages and disadvantages of a behavior), social norms (perceived approval or support of the behavior by others), and perceived behavioral control (perceived ease or difficulty of performing a behavior). In general, the more favorable the attitude and social norm with respect to a behavior, and the greater the perceived behavioral control, the stronger the intention to perform the behavior should be.

In accordance with the TPB, the HBM suggests that behavior is the result of the evaluation of its advantages and disadvantages. However, the HBM suggests that an important prerequisite of such an evaluation is a person's subjective perception of their risk of acquiring a disease (perceived susceptibility) and their perception of its seriousness (perceived severity). The HBM has been widely used to understand and predict vaccination uptake.

It is important that parents and girls make an informed choice about uptake, i.e. a choice based on relevant knowledge, consistent with the decision-maker's values and one that is actually implemented [25]. In the case of HPV vaccination, an informed choice to have one's daughter vaccinated is characterized by having sufficient decision-relevant knowledge, a positive attitude towards HPV vaccination, and results in having one's daughter vaccinated. An informed choice not to have one's daughter vaccinated is characterized by having sufficient decision-relevant knowledge, a negative attitude towards HPV vaccination, and results in not having one's daughter vaccinated.

Overall, many factors play a role in the decision-making of parents and girls about whether or not to have HPV vaccinations. It is difficult to assess the influence of each of these factors on the choice that is eventually made. One way to quantify the influence of these factors and the trade-offs that people make between these factors is to conduct a Discrete Choice Experiment (DCE).

4. DISCRETE CHOICE EXPERIMENTS

The willingness to accept HPV vaccination may be largely influenced by general preferences toward healthcare interventions [26]. A way to assess preferences is to conduct a DCE, in which people trade off the risks and benefits among competing programs [27]. In the design of DCEs it is assumed that a healthcare intervention or treatment can be

described by its characteristics (attributes) and that levels of those attributes determine preferences for an intervention or treatment [28]. In a DCE questionnaire respondents make a number of selections; in this case, between two alternative vaccination strategies and an opt-out (no vaccination). Each vaccination strategy is characterized by predefined attributes (e.g. degree of protection). Each attribute is defined by a specific level (e.g. 50%, 70% or 90%). By analyzing parents' and girls' choices, the underlying utility function can be estimated. The relative regression coefficients (betas) represent the importance of the attributes for acceptance of the vaccination [29]. The ratios of betas represent the trade-offs parents and girls are willing to make, e.g. between the degree of protection against cervical cancer and the age at which the vaccinations will be given.

5. CONTENTS OF THIS THESIS

This thesis addresses the following research questions:

1. Which decisional strategies do parents use to develop an intention towards HPV vaccination and which factors direct uptake intentions prior to the introduction of the vaccine program?
2. Which parental determinants predict uptake of HPV vaccination by their daughters?
3. How are various aspects of HPV vaccination associated with parents' preferences for uptake by their daughters, and which trade-offs are parents willing to make between these aspects?
4. What are girls' preferences for HPV vaccination and are they willing to trade off between protection against cervical cancer and other characteristics of HPV vaccination?
5. To what extent have girls' preferences changed almost three years after the much-debated start of the HPV vaccination program?
6. To what extent does an official information leaflet about HPV contribute to girls' knowledge levels?

6. STRUCTURE OF THIS THESIS

Part 1 of this thesis (Chapters 2-4) focuses on parents and part 2 concentrates on girls (Chapters 5-7). **Chapter 2** describes the results of focus-group discussions about decisional strategies that parents use to develop an intention towards HPV vaccination prior to the introduction of the vaccine program. **Chapter 3** describes the parental predictors influencing HPV vaccination uptake by their daughters. **Chapter 4** describes parental preferences for vaccinating daughters against HPV and the trade-offs parents are willing to make. In part 2, **Chapter 5** concerns the preferences of girls for HPV vaccination and

their trade-offs as registered during the media debate about the vaccine. **Chapter 6** also concerns girls' preferences for HPV vaccination, but the preferences are measured three years after the media debate. **Chapter 7** focuses on the extent to which an information leaflet about HPV increases girls' knowledge about HPV. In **Chapter 8**, results of the studies are integrated in a general discussion and recommendations for practice are provided.

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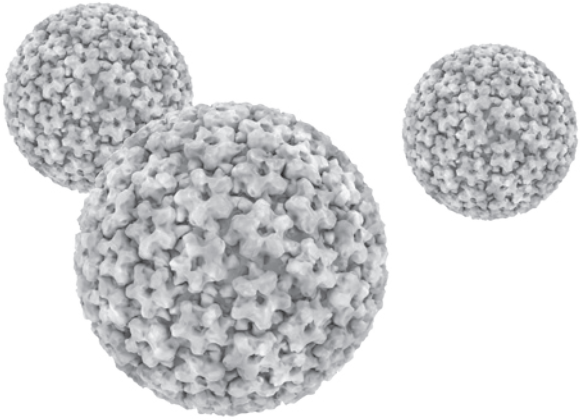
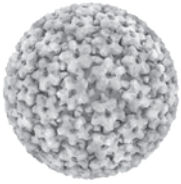
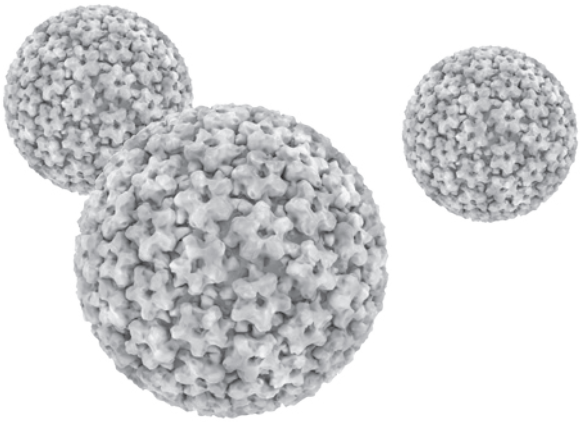


Part 1

Parents





Chapter 2

Parental decisional strategies regarding HPV vaccination prior to media debates: a focus-group study

Robine Hofman, Pepijn van Empelen, Ineke Vogel, Hein Raat, Marjolijn van Ballegooijen, Ida J. Korfage

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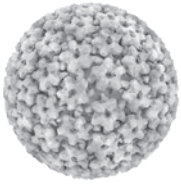

ABSTRACT

Prior to the introduction of the human papillomavirus (HPV) vaccine, decisional strategies and factors that could guide HPV vaccination intentions were explored. We conducted four focus-group discussions with 36 parents of children aged 8-15 years. Three groups consisted primarily of Dutch parents and one group of only Turkish parents. Discussions followed a semi-structured question route. Results showed that some parents used an approach of systematically seeking information as a way to prepare a decision, while others merely relied on trust in the message source. Generally, parents believed it was important to protect their child against negative outcomes that could result from vaccinating or not, and felt it their responsibility to decide about uptake. Perceived susceptibility, vaccine effectiveness and the possibility of serious side-effects were most important in the HPV vaccination decision-making process. In conclusion, parents perceived a lack of information and felt insecure about the vaccine's safety and effectiveness. This may result in ambivalent feelings towards HPV vaccination which, in turn, may lead to postponing decisions about uptake. To facilitate informed decision-making, which requires central processing, personally relevant messages about the knowns and unknowns regarding the effects of HPV vaccination should be provided.

INTRODUCTION

Cervical cancer can only develop in the presence of infection with high-risk human papillomavirus (HPV) [1-2]. Prophylactic vaccines against HPV 16 and 18, which cause approximately 70% of cervical cancers [3], have been licensed in the European Union and the USA. Preferably, the HPV vaccine is given prior to the initiation of sexual activity, because the degree of protection is reduced after HPV infection and the incidence of HPV infections is highest in the first months after sexual debut [4-5]. For public health activities, such as screening or vaccinations, it is considered important that people make an informed choice to participate or not [6-7], i.e. one that is based on relevant knowledge, consistent with the decision maker's values and behaviorally implemented [8].

Since November 2008 the Dutch National Immunization Program (NIP), which is free of charge and voluntary, offers HPV vaccinations to 12-year-old girls. The effectiveness of the NIP depends on the availability of high-quality vaccines and acceptance by parents [9]. Although childhood vaccination is well-accepted among parents in the Netherlands, with a 95% vaccination rate [10], general parental acceptance of new vaccinations such as the one against HPV cannot be taken for granted [11]. Moreover, it was generally found that the decision to vaccinate was not the result of thorough information processing [12]. This is crucial, because if parental decisions about vaccination are not based on thorough deliberation, such decisions are likely to be unstable [13].

Furthermore, HPV vaccination differs from other childhood vaccinations: the HPV vaccine is the first against a cause of cancer; its long-term effectiveness and potential side-effects are unknown; it is a vaccine against a sexually transmittable virus; the vaccine is offered to pre-adolescents who (in the Netherlands) do not need their parents' permission to get vaccinated, though in practice they will make a shared decision [14-15]; it targets an adult disease; HPV is behaviorally induced; and, finally, another method of (secondary) prevention against cervical cancer is available through Pap smears, which are offered via screening programs in many Western countries.

A review on predictors of HPV vaccine acceptability [16] showed that higher acceptability was associated with its recommendation by a physician [17-22], a higher perceived likelihood of HPV exposure or infection [17, 22-23], and a higher perceived effectiveness against HPV infection [20]. Barriers were low perceived vaccine safety [18-19, 24] and anticipated side-effects [18-19, 25].

Although many studies focused on predictors of HPV vaccination acceptability, less is known about decisional strategies parents use to decide about their daughters' uptake. Different theories about decision-making [26-27] suggest that, when information is centrally processed, decisions are more likely to be based on information content and therefore more likely to be stable, i.e. attitude-behavior consistency is more likely.

In the present study we mainly examined information-processing strategies. This information may be important with regard to preferred delivery of information. According to the Elaboration Likelihood Model there are two types of information processes, referred to as central or peripheral processing [26]. Both processing systems probably play a role but, depending on the ability to elaborate on a message and the perceived relevance (and hence motivation) of a message, one of the processing systems is likely to play a more prominent role. When motivation and processing ability are high, centrally-driven processing is more likely. When the ability or motivation is low, peripheral processing is more likely. In central processing, an approach of systematically seeking information is used, i.e. comprehensive analysis of judgment-relevant information. This usually results in stable attitudes that are more likely to guide actual behavior. In contrast, a peripheral processing strategy (in which, e.g., reliance on trust or distrust in the message source is used) is more likely when people are not motivated or are unable to engage in thorough processing; this results in weak attitudes that may easily be changed by means of counter-attitudinal information.

Generally speaking, participation in the Dutch NIP is not based on thorough decision-making [12]. Moreover, parents often seem to base their decision on trust in the message source, such as an expert, institute or public figure. Trust or mistrust in the government and pharmaceutical companies was found to be associated with vaccination behavior [28-29]. Within the context of HPV, little is known about decisional strategies, although this is important to better understand potential HPV vaccination behavior, to understand how to increase informed (central) decision-making, and to reduce potential dissatisfaction with the decisions made.

Thus, although predictors of HPV vaccination have been examined, less is known about how parents make a decision. Therefore, this study explores decisional strategies that parents used to develop an intention towards HPV vaccination and the factors that may guide uptake intentions at a unique point in time *prior* to the introduction of the vaccine.

METHODS

Participants

Four focus-group discussions were conducted in three different areas (1 urban, 2 rural) in the Netherlands. Each parent had at least one daughter aged 8-15 years. We choose this range because the exact age target was not yet known but was likely to fall within the range 8-15, because vaccination against HPV is most effective before sexual activity. Three groups consisted primarily of native Dutch parents and one group consisted of Turkish parents only (the largest ethnic minority group in the Netherlands. Turkish

parents were included because, having a different cultural background, they might have other considerations regarding the vaccination of their daughter.

Procedure

Approval for the focus-group discussions was obtained from the Medical Ethics Committee, Erasmus MC, University Medical Center Rotterdam. Parents were recruited from four primary schools and four secondary schools. All were public (state funded) schools, three of which had a religious affiliation. The schools handed out information letters to 833 children aged 8-15 years to give to their parents. If parents were interested to participate, they could contact the researchers. All participating parents gave written informed consent.

The focus-group discussions were held between June and November 2008, which was prior to the introduction of the HPV vaccine in the NIP. Discussions were conducted by a discussion leader and an assistant, both researchers of the Erasmus MC. After conducting the four focus-group discussions, no new themes emerged and all themes were covered in all focus groups. Discussion with the Turkish parents was conducted in the Turkish language by a native speaker. All discussions followed a semi-structured question route (Appendix A), which was based on relevant literature.

During the first focus-group discussion, parents asked for more information about HPV because they considered their knowledge level to be too low. To enable the discussion to progress, information was given and the same information was provided to the participants of all subsequent sessions (Appendix A). This information was neither positive nor negative regarding HPV vaccination. The length of the discussion sessions ranged from 73-110 (mean 95) min. After the discussion, parents received a gift coupon of 20 euros (ca. 28 US dollars).

Analyses

The discussions were transcribed verbatim. The discussion with Turkish parents was translated into Dutch by the research assistant that led that discussion. Four authors (RH; PvE; IV; IJK) read all the transcripts in-depth and examined the content. Second, a thematic analysis [30] was performed by one author (RH) on one transcript by identifying and coding text passages relevant to the study objectives. These codes were: knowledge, arguments pro vaccination (trust and prevention), arguments con vaccination (distrust and lack of information in general and of long-term effects), anticipated regret, and difference between vaccination in general and HPV vaccination. This first coding scheme was extensively scrutinized and validated by examining the other focus groups. Based on these analyses, adaptations in coding took place until general themes could be identified.

The first codes were based on the content of making a decision, in which similarities could be seen between the codes. These codes were then regrouped into larger themes about the decision-making process and key themes were identified that appeared throughout all discussions. Representative quotations for each theme were selected to illustrate the results.

The identification and validation of common themes was the result of 12 two-hour sessions with the four authors (RH; PvE; IV; IJK). The final coding was the result of a consensus between all four authors.

RESULTS

Respondent's characteristics

Overall, 36 parents (34 female and 2 male) participated in the focus-group discussions (Table 1). More than half (61%) had an intermediate or high educational level. Most of the children (88.9%) had been vaccinated against all childhood diseases available in the Dutch NIP.

Overview of results

Below, we first describe the decisional strategies parents used, followed by the (partly overlapping) themes that emerged relating to parents' intention about uptake of HPV vaccination: i.e. perceived parental responsibility, relevance of having one's daughter vaccinated against HPV, and insecurity about long-term side-effects.

Decisional strategy

Two types of decisional strategies to prepare a decision emerged. First, some parents used an approach of systematically seeking information to arrive at an informed decision. For example, at the start of the session when discussing decision-making related to uptake, one parent stated:

I went to check websites to see what it is. It's a virus - I've heard something about it. But first you have to get into it. I don't only rely on what I can find on websites. I think I have to find more information. So if I have to say: I'll do it now, or I will not do it - then I would say 'not now'. (session 1).

Table 1 Characteristics of the respondents.

	Total (n=36)
Age in years: mean (SD)	43.7 (4.7)
Range	33 – 53
Sex (n, %)	
Female	34 (94.4)
Having a daughter (n, %)	36 (100)
Age of daughter[a] (years) (n, %)	33 (91.7)
8-9	8 (22.2)
10-11	9 (25.0)
12-13	14 (38.9)
14-15	4 (11.1)
Children of respondents vaccinated against childhood diseases[a] (n, %)	
Yes	33 (91.7)
No	1 (2.9)
Partly	2 (5.7)
Educational level (n, %)	
Lowest (primary education)	8 (22.2)
Low	6 (16.7)
Intermediate	10 (27.8)
High	12 (33.3)
Country of birth of respondents (n, %)	
The Netherlands	26 (72.2)
Turkey	8 (22.2)
Other (Senegal, Surinam)	2 (5.6)
Country of birth of parents of the respondents (n, %)	
Both parents in the Netherlands	23 (63.9)
One parent outside the Netherlands	4 (11.1)
Both parents outside the Netherlands	9 (25.0)

[a] *These columns do not add up to the total number of respondents (n=36) because the data of one respondent are missing.*

Other parents seemed to use trust or distrust in the message source as a strategy to prepare a decision about uptake. Parents who trusted the NIP and the government thought that the vaccine would not have been introduced into the NIP if it was not safe: "*I think a lot of research has been done by the time we'll receive an invitation, right? That won't happen just like that if there are big risks attached to it. So I'll just trust that it'll be all right*." (session 3). However, there was some distrust towards the pharmaceutical industry related to profit making:

I have two sisters on DES [diethylstilboestrol. And I hold something against the pharmaceutical industries… not against doctors, but against the pharmaceutical industries. I don't know what it [HPV vaccine] is or how long it works. I know far too little about the vaccine. (session 1).

Perceived parental responsibility

The major factor within this theme was 'child-protection' motivation, i.e. parents feel responsible to protect the health of their child at all times and to do what they consider best for their child's benefit. Although this underlying motive appeared to be similar, some parents expressed a positive and others a negative attitude towards HPV vaccination. Parents with a positive attitude wanted their daughter to be vaccinated against cervical cancer: *"As a parent I'll do everything I can do to protect my child."* (session 1).

Those expressing a negative attitude wanted to protect their daughter against possible side-effects on the long term, as was expressed during the discussion on fear of anticipated regret if one's daughter was not vaccinated:

What have I done to my child? She might end up with something else. Then I'll be feeling guilty. So I'd rather wait longer and get the right information: what is this substance that's being injected? And what are the disadvantages and the advantages? (session 1).

The second factor was related to the attribution of responsibility of the decision-making about uptake. Three types of responsibilities emerged: a sole responsibility of the parent; a shared responsibility; and a sole responsibility of the daughter. Most parents thought they should decide about their daughter's uptake, either with or without discussion with their daughter. Some parents saw it as their responsibility because they considered a 12-year-old girl incapable of making such a decision: "*Because she's not of an age to make such decisions, I would try to convince her in a good way. An 11 or 12 year old girl is too young to make decisions on her own. That's my opinion*." (session 4). Other parents preferred a shared decision and thought that children can be involved in the decision:

I've already had my daughter vaccinated. We had discussions like: '*Mom, cervical cancer, you wouldn't want me [daughter] to get it, would you?' We discussed it for an hour and looked at the pros and cons together. So even children can be involved in the decision-making at a very early age, if you inform them honestly and use understandable language*. (session 3).

Finally, some parents thought that their daughter could make her own decision about the uptake of HPV vaccinations, even if she did not share her parents' opinion. This was mentioned during the discussions about their daughter wanting to be vaccinated, whilst the parents did not want her to:

In that case she'll go [to get the vaccination]. I'll leave that decision with her. I'll inform her and tell her about the pros and cons. I always try to be as neutral as possible and then I really think it's up to her. It's her body and her life. (session 3).

Relevance of having one's daughter vaccinated against HPV

Some parents thought it was irrelevant to have their daughter vaccinated. First, the availability of alternatives for HPV vaccinations was discussed:

I think that besides this [vaccination] many other possibilities are available to prevent cervical cancer, by having an HPV test or by regularly having a smear taken. That way I think you'll cover it for a large part. That's not the case with other vaccinations. I mean, you can't do anything else to prevent mumps, measles or rubella. I think that's a big difference [compared to HPV]. In my view there's a good alternative in this case. (session 3).

Second, vaccinating was considered irrelevant because of its unknown length of protection. For example, it was considered useless to have the vaccination if its effectiveness lasts only 5 years:

And with a 12-year-old child, imagine that such a thing will work for five years, it will have worn off by the time she*'s 17. My oldest is 16 and she's not yet sexually active. Imagine she had got it [the HPV vaccination] when she was 12, then it would had worn off by the time she turned 16. Well, then it would have been useless*. (session 3).

Most Turkish parents considered HPV vaccination as irrelevant because their daughters are supposed to have sexual contact only with their husband and only after marriage:

With us, in our [Turkish] community it's unusual to have sex before marriage ... let's hope that they really will not have it. That's the way it is in our culture, you marry only once and only have sexual contact with each other once you're married. So that's another reason not to do it [vaccination]. (session 4).

On the other hand, HPV vaccinations were considered relevant by some parents who expected their daughters to become sexually active (although not at age of 12 years) and thus become vulnerable for HPV infections. Parents also related the relevance of vaccinating their daughter to the perceived severity of cervical cancer: "*I read somewhere that 200-250 women die of cervical cancer every year. Of course those are 200-250 too many.*" (session 1). To most parents knowing someone who had cancer was a reason to

consider vaccinating as relevant and to be positive about HPV vaccination. One mother explained why she would find it difficult if her daughter refused to be vaccinated:

For me that would really tilt the scales [if daughter refuses to be vaccinated]. I'm from a family of six children, of whom three have different kinds of cancer. So that's what I grew up with. If she would say 'no' [to the HPV vaccination], I'd find that very difficult. Then I'd still try to persuade her: please have them. (session 2).

Insecurity about long-term side-effects

Some parents felt insecure about the long-term side-effects, because the vaccine is new and long-term research is lacking: "*What I find difficult is to be the first [who is offered this vaccine]. You don't know what the long-term consequences are. Actually you should have vaccinated thousands of girls and should have followed them for 15 years…maybe…"* (session 2). Also it was questioned whether the vaccine could cause infertility:

I wonder if it'll have unwanted consequences for the fertility of my daughter. Can she still become pregnant later on? I have my doubts about that… What if this vaccination has a side-effect and I had her vaccinated? In our [Turkish] community you want to become grandmother and grandfather when your daughter marries. What if she'll not be able to have children … I'm serious. (session 4).

One parent found the lack of research on the target group for HPV vaccination difficult: "*Isn't it true that it [the HPV vaccine] was tested on a very different age category and it is projected on youngsters just like that, without knowing anything about it. I have a big problem with that*." (session 3). Parents' perceived insecurity and responsibility to protect their daughter's health sometimes resulted in ambivalence toward uptake intentions: "*You want the best for your child. So what do I keep my child from - or what do I give to her? You keep on weighing it up …*" (session 3).

DISCUSSION

This focus-group study yields information about parental attitudes and decisional strategies regarding HPV vaccination uptake, prior to the vaccine being extensively discussed in the media. Thus, the study provides insight into how people react when a new vaccine becomes available in a situation with many unknown quantities.

Factors underlying uptake intentions

We identified factors underlying the uptake intentions of HPV vaccination, as well as process factors that might influence HPV vaccination decision-making. Motivation to vaccinate was related to perceiving cervical cancer as a severe disease, perceiving one's daughter as potentially susceptible to an HPV infection, and having experienced significant others with cancer. Motivation not to vaccinate was related to fear of long-term side-effects of the vaccination and doubts about the effectiveness of HPV vaccination. In general, parents felt inadequately informed and lacked factual information about HPV, HPV infection risk and HPV vaccination, as also reported by others [31-32]. This is important because it reflects the state of affairs *prior* to introduction of the vaccine. Parents had insufficient knowledge, and a clear need to receive information. There was a threat of HPV causing cervical cancer, which most were unaware of. As could be observed in the media-debate some months after our data-collection was completed: although parents in the Netherlands received an information leaflet about HPV vaccination, they wanted to know more and searched the internet, sometimes landing on curious websites offering incorrect information. We recommend that parents and girls be supplied with more extensive information. It should be stated what is known and unknown about the vaccine, in this respect openness is important. Also, it should have been acknowledged that parents could not be expected to have proper knowledge before the introduction of such a new issue. Overall, based on our results, we conclude that parents perceived HPV vaccination as being different from other childhood vaccinations. Generally, the view on HPV vaccination was not positive, and there was a perceived lack of information and a feeling of insecurity about the safety and effectiveness of the vaccine. This led to some parents feeling ambivalent towards the HPV vaccination. This is important with regard to informed decision-making, because ambivalent attitudes are easily malleable and are less predictive of actual behavior [33].

Child-protection motivation

Apart from factors that might influence the intention to vaccinate, we identified two mechanisms that are likely to influence the process of HPV vaccination decision-making: these were labeled as 1) child-protection motivation, and 2) decision-making responsibility.

First, our results show that parents were motivated to protect their child, irrespective of whether they did or did not want their daughter to be vaccinated. The need to protect one's daughter from harm was also found in an other focus group study [34].

Although parents differed in the outcome of their decision-making processes, in both cases this could be attributable to anticipated regret of a potential decision (not) to act.

Anticipated regret can be defined as an aversive combination of thoughts and feelings elicited when comparing an event that occurred to another (perhaps more favorable) event that did not [35]. A study among caregivers of girls aged 10-18 years also showed that anticipated regret played an important role in their decision-making [36]. However, in that case vaccination regret concerned the anticipated regret if one's daughter became more sexually active after vaccination, which was not an issue in our focus-group discussions. The anticipated regret we found focused on parents being concerned that their daughter could suffer from serious side-effects after vaccination. This is an important target for public health. Some parents primarily focused on the negative consequences of a decision to vaccinate, and anticipated how they might feel should an unfavorable outcome occur as a result of that decision, e.g. that their daughter suffers from long-term side-effects of the vaccine. Other parents primarily focused on the potential gains that might result from the HPV vaccination, and how they would feel had they decided not to vaccinate and this led to an unfavorable outcome, i.e. their daughter getting cervical cancer. A possible explanation for this difference may be derived from the Regulatory Focus Theory, which suggests that people may differ in self-regulatory orientations: prevention or promotion [37]. A prevention focus is aimed at avoiding losses and a promotion focus on reaching gains. Our findings partly corroborate those of Paulussen et al. (2006) who suggested that the anticipation of regret in the case a child would become ill due to not acting was an important precursor of the decision to vaccinate. However, our findings suggest that this is only likely for parents who are focused on the gains of a decision to vaccinate, rather than on the losses. Acknowledging the difference in foci may have important consequences for information materials, as decisions may depend on how messages are framed [38-39].

Decision-making responsibility

Second, our study suggests differences in the attribution of decision-making responsibility. Most parents indicated that they needed to decide about uptake of HPV vaccinations, either alone or together with their daughter. This is certainly important, given that the parental viewpoint appears at odds with the fact that girls aged 12 years and older officially do not need their parents' permission to get vaccinated, and with the approach taken in the 2009 HPV campaign that was directed towards the girls only. This campaign was organised by the Dutch National Institute of Public Health and the Environment and consisted among other things of a website, and of information letters and leaflets which were sent to all girls who were invited for HPV vaccinations. In the 2010 campaign the parental role was acknowledged to some extent by sending an information letter not only to the daughter, but another letter to the parents as well. In addition, our results may partly explain why the uptake of HPV vaccinations was lower in the first HPV vaccination

round (49%) than originally expected (70%) [40]. They may also explain the inconsistency between earlier study results from women/parents [41-42] which suggested positive intentions towards the vaccination, compared with the actual uptake rates.

Mechanisms of decision-making

Participants prepared a decision regarding uptake of HPV vaccination in various ways [26]. Some parents used a more systematic approach of seeking information, e.g. checking websites and other mediums and thus focused more on content. Others mainly relied on trust in the message source (e.g. the government), or distrusted the message source (e.g. the pharmaceutical industry); attitudes based on such heuristic information are usually weak and prone to counter-attitudinal information. For an informed choice it is important that attitudes are stable, in order to achieve a correspondence between attitude and choice. These types of decision-making processing are described in the Elaboration Likelihood Model [13]. Our findings reflect (at least in part) those of Paulussen et al. (2006) that some parents use decisional strategies that may hamper thorough informed decision-making, and are in line with others reporting that trust is associated with acceptability [43]. Parents who use such heuristic cues as a primary route for HPV vaccination decision-making, may have intentions that can easily be changed or may make decisions that are not well informed. This might be prevented by making messages (more) personally relevant, providing information multiple times, and by stimulating active learning. For public health activities such as screening or vaccinations, people need to make an informed choice [6-8]. Our study provides information that may prove useful to facilitate informed decision-making with regard to HPV vaccination, and to better target HPV information campaigns. The need for informed-decision making was also shown by a study that reported that educational materials improved HPV vaccine knowledge [44].

Strengths and limitations

A strength of this study was that it yields information about parental attitudes and decisional strategies regarding HPV vaccination uptake, prior to the vaccine being extensively discussed in the media. This study has also some limitations. First, although the information letter was addressed to both parents and not to the mother in particular, the majority of responding parents were mothers. This seems common in studies assessing parental attitudes regarding HPV vaccination [19, 45-46]. One study found that among mothers who had a discussion with their daughters about HPV vaccine, almost half reported that doing so led to a discussion with their daughters about sex [47]. However, this was not a topic of discussion in the present study. Second, although participants were informed that everything they said would be treated anonymously, they may not have revealed

their true opinions. Third, too few Turkish parents were included to make a comparison with Dutch parents. We want to acknowledge that this is a qualitative study that cannot be generalized to the larger population, but is still quite valuable because of the level of detail and in-depth understand it provides about this particular set of parents.

Conclusion

In conclusion, parents perceived a lack of information and felt insecure about the safety and effectiveness of this vaccine. This may result in feeling ambivalent towards HPV vaccination, which may lead to postponing decisions about uptake. To facilitate informed decision-making, campaigns should provide clear information on both the advantages and disadvantages of HPV vaccination. If parents use heuristic processing to prepare a decision, this may lead to making uninformed decisions which might result in weak attitudes that can easily be changed by means of counter-attitudinal information. Therefore, it is important that parents and girls make a decision based on the content of balanced arguments, rather than on trust/distrust of the message source. To promote central processing in parents and girls, messages should be made personally relevant, e.g. by giving tailored information or using scenarios. Also, repetition (and active learning) may increase elaboration, e.g. by providing information *before* the girls and parents have to decide about uptake. Furthermore, it should be clearly stated what is known and unknown about the effects of HPV vaccination. When taking these suggestions into account, parents and girls may become less ambivalent. Finally, the campaign should be directed at the girls and their parents, since parents will play a major role (or even the only role) in the decision-making process.

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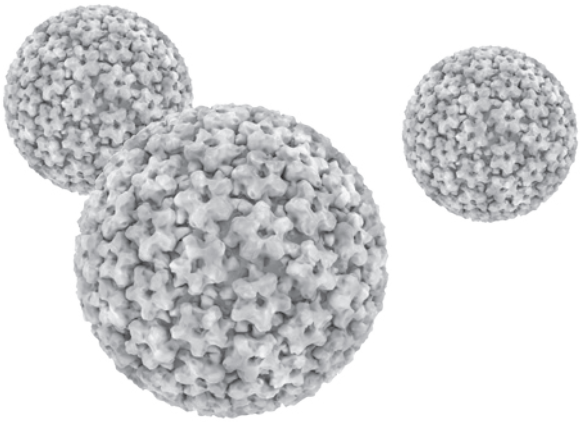

Chapter 3

Predictors of HPV vaccination uptake: a longitudinal study among parents

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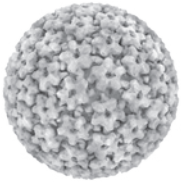

ABSTRACT

To assess among parents longitudinal predictors of human papillomavirus vaccination uptake for their daughters, random samples of parents were identified via municipal services and sent baseline questionnaires in June 2009 and follow-up questionnaires in November 2011 after their uptake decision. Hierarchical logistic regression analysis was used to assess whether demographic characteristics, and affective and social cognitive factors, predicted uptake at follow-up. Response rates of the baseline and follow-up questionnaire were 29.8% (1762/5918) and 74.3% (793/1067), respectively. Uptake was predicted by a later (2011) versus earlier (2010) decision about uptake since HPV vaccination implementation (OR 2.48; 95%CI: 1.11-5.52), anticipated regret about no uptake (OR 1.43; 95%CI: 1.08-1.89), and intention (OR 2.61; 95%CI: 1.47-4.61). There was an interaction between ambivalence and attitude (OR 1.68; 95%CI 1.14-2.47): parents with a positive attitude and a high ambivalence towards vaccination were more likely to have their daughter vaccinated than parents with a positive attitude and a low ambivalence. An informed choice about uptake (5/7 correct items) was made by 44%. In conclusion, uptake was predicted by intention, a later (2011) versus earlier (2010) decision, and by anticipated regret about no uptake. Decisions regarding new vaccines are difficult to make, we recommend a well-balanced implementation process.

INTRODUCTION

In Europe 60,000 women are diagnosed with cervical cancer annually [1]. Cervical cancer can only develop in the presence of infection with high-risk human papillomavirus (HPV) [2-3]. Two vaccines are available which protect against HPV 16 and 18, which together cause about 70% of cervical cancers [4]. Preferably, the HPV vaccine is given prior to the initiation of sexual activity because the degree of protection is reduced after HPV infection and the incidence of HPV infection is highest in the first months after sexIn November 2008 the Dutch National Immunization Program (NIP), which is free of charge and voluntary, was extended with HPV vaccinations for 12-year-old girls. The effectiveness of the NIP depends on the availability of high-quality vaccines and acceptance by parents [7]. Although childhood vaccination is well accepted among parents in the Netherlands, with a 95% vaccination rate [8], uptake rates of the HPV vaccine are much lower (58% in 2010) [9]. In the Netherlands, 12-year-old girls are legally entitled to make their own decision about uptake. In practice, however, parents play a considerable role in the decision-making about the uptake of HPV vaccinations [10-11].

The present study aims to elucidate which psychosocial factors of parents predict intended and actual HPV vaccination uptake. Previous studies examining (HPV) vaccination behavior [12-14] have generally relied on psychosocial concepts derived from the Theory of Planned Behavior (TPB) [15] and the Health Belief Model (HBM) [16]. Both models are useful in explaining HPV vaccination uptake. The TPB proposes that the most proximal determinant of behavior is intention which, in turn, is guided by three constructs: attitudes towards the behavior (i.e., the evaluation of advantages and disadvantages of a behavior), social norms (perceived approval or support of others), and perceived behavioral control (perceived ease of performing a behavior). In accordance with the TPB, the HBM suggests that behavior is the result of the evaluation of advantages and disadvantages of a behavior. However, the HBM suggests that an important prerequisite of such an evaluation is the perceived severity and personal susceptibility of acquiring an illness.

Although these models are useful in explaining behavior towards vaccination, including HPV vaccination, these models generally neglect more affective components that are likely to influence the decision about and actual uptake of HPV vaccination [17]. Such affective factors may explain the vaccination behaviour, beyond the more cognitive predictors [18]. In focus group discussions on decisions to vaccinate against HPV among parents of HPV vaccination eligible girls, factors that played a role were the perceived lack of knowledge about HPV vaccination (risk), the felt ambivalence about the decision to vaccinate (simultaneous positive and negative evaluations of an attitude object) [19-20], (dis)trust in authorities, perceived parental responsibility, and the anticipation of regret of (not) acting [21]. These findings underpin observations that the first HPV vaccination

campaigns were met by (parental) concerns about the reliability of the vaccine. Therefore, in the present study, we assessed whether HPV vaccination uptake was predicted by anticipated regret [22], (dis)trust in health authorities [23], ambivalence, social norm, intention, knowledge and/or perceived severity and risk of cervical cancer. In addition to studying predictors of HPV vaccination uptake, changes in parental knowledge, attitudes and ambivalence were explored both before and after their decision about uptake.

METHODS

Respondents

Questionnaires were sent to parents who had not yet made the decision to have their daughter vaccinated against HPV, but had to decide within 3-15 months when their daughters become 12 years of age. In the Netherlands, all girls receive an invitation to get vaccinated with the bivalent HPV vaccine (free of cost) in the year they turn 12 years of age.

Procedure

Random samples of parents were identified via four municipal health services spread throughout the Netherlands. These municipal services hold the addresses of all girls eligible for HPV vaccination in their region. The Dutch vaccination program offers one opportunity to get vaccinated against HPV, i.e. at age 12. The baseline questionnaire and an information letter were sent by mail to 5918 parents in June 2009 (the information letter was addressed to both parents). Parents could return the completed questionnaire in a self-addressed envelope. The questionnaire was pilot tested to check for face validity and for problems in interpretation (n=10).

In the baseline questionnaire we asked parents if they were willing to complete a follow-up questionnaire after the uptake decision. After the baseline questionnaires were sent, the Mexican flu (H1N1 virus) outbreak in the summer of 2009 led to the implementation of an H1N1 vaccination program. Therefore, the HPV vaccination programs were postponed until March 2010 and March 2011. Those who consented to complete a follow-up questionnaire received this questionnaire in November 2011.

The study was approved by the Medical Ethics Committee, of the Erasmus MC Rotterdam.

Baseline questionnaire

Factors derived from HBM

Perceived risk and severity. One single item assessed parents' perceived risk of their daughter getting cervical cancer if she was vaccinated, and one additional item assessed the perceived severity if their daughter would get cervical cancer. Both risk and severity items (adapted from Weinstein, 2000) were measured on an 11-point Likert scale, with higher scores indicating a higher risk or severity [24].

Factors derived from TPB

Attitudes towards HPV vaccination. Attitude was assessed using 9 items on a 5-point Likert scale phrased as: 'I think having my daughter getting vaccinated against cervical cancer is…', (e.g. bad - good, unimportant - important; unwise – wise, harmful – beneficial, adapted from Marteau et al., 2001 & van den Bergh, 2005) [25-26]. The total score was calculated as the mean of the 9 items (Cronbach's alpha = 0.94).

Intention. Parents' intention to have their daughter vaccinated against cervical cancer was assessed with the question: 'I want to have my daughter vaccinated against cervical cancer' [response options: (definitely not, probably not, not sure (yet), probably, definitely)].

Parental subjective norms. Social norms were examined using 8 items on a 5-point Likert scale measuring the perceived beliefs about and desire to comply with family, partner, general practitioner and friends about vaccinating one's daughter against HPV (Cronbach's alpha = 0.82) (adapted from Tiro et al., 2005) [27]. Parents' normative belief was assessed using a question about what percentage of other parents the respondents thought would want the vaccination for their 12-year-old daughters (11 options ranging from 0-100%) (adapted from Marlow et al., 2007) [28].

Complementary factors

HPV knowledge. We developed a knowledge scale with items about HPV, HPV vaccination and cervical cancer consisting of 4 true/false/don't know items (e.g. 'The HPV vaccination will decrease the risk of cervical cancer') and 3 multiple choice questions with 3 or 4 response options: [e.g. 'What is the protection rate of the HPV vaccine?' (response options: 55%; 70%; 85%; 100%)]. A total score was calculated by summing the correct responses (score range 0-7).

Decisional evaluation. The subscales satisfaction-uncertainty (e.g. 'I am satisfied with my decision', Cronbach's alpha = 0.80) and informed choice (e.g. 'I made a well-informed

choice', Cronbach's alpha = 0.79) from the Decision Evaluation Scales [29] were included to assess how respondents evaluated their decision about having their daughter vaccinated or not. Both scales consisted of 5 items and responses were on a 5-point Likert scale (1=strongly disagree; 5=strongly agree).

Parental responsibility. To asses parental responsibility we used the subscale 'basic needs – health care' of the Perceptions of Parental Role Scales [30], consisting of 7 items (e.g. 'Arrange for child to see dentist for routine checkup') on a 5-point Likert scale (1=not at all important; 5=very important). Cronbach's alpha = 0.73.

Anticipated regret and worry. To measure anticipated regret and worry we adapted 2 items from Korfage et. al., (2011) [31], measured on a 7-point Likert scale: 'If I don't have my daughter vaccinated against cervical cancer, then I would regret this/then I would worry' (1=definitely not; 7=definitely). The total score was calculated as the mean of the 2 items (Cronbach's alpha = 0.82).

Ambivalence. Ambivalence was measured using 2 items regarding positive and negative thoughts about HPV vaccination (adapted from Kaplan, 1972) [19]: 'Considering only the positive things about HPV vaccination, and ignoring the negative things, then what do you think of HPV vaccination?' (response options: not at all positive; slightly positive; quite positive; extremely positive), and vice versa for negative thoughts. Total ambivalence was calculated as half the sum of the positive and negative judgments, minus the absolute difference between the two [32].

Trust. We developed two items to assess trust in the NIP and the HPV vaccine on a 6-point Likert scale (1=none; 6=a lot).

Reasons for vaccinating. Parents' reasons to have or not to have their daughter vaccinated were assessed using 11 predefined items for 'vaccinating', 17 items for 'not vaccinating', and an option to write down additional reasons.

Parental characteristics. We assessed sex, marital status, educational level, job status, ethnicity and religion of the parents. Female respondents were asked about their perceived risk of getting cervical cancer themselves (11-point Likert scale) (adapted from Marlow et al., 2007) [24] and if they had ever had an abnormal pap smear result.

Follow-up questionnaire

In the follow-up questionnaire we again assessed knowledge, attitude towards HPV vaccination, decisional evaluation, social norms (without compliance items, because compliance will logically not change over time), ambivalence, risk perception and severity, and trust. In addition, vaccination uptake was assessed.

An informed choice to participate or not [33-34], i.e. a choice based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented [25], was calculated using knowledge (at follow-up), attitude (at baseline), and uptake.

Since there is no standard cut-off to measure sufficient decision-relevant knowledge, we presented rates of informed decisions for 3, 4, 5 and 6 correct items (out of 7). As an example, results with the cut-off level of 5 correct items are fully displayed. An informed choice to have one's daughter vaccinated is characterized by sufficient decision-relevant knowledge, a positive attitude towards HPV vaccination (score >3), and having one's daughter vaccinated. An informed choice not to have one's daughter vaccinated is characterized by sufficient decision-relevant knowledge, a negative attitude towards HPV vaccination (score <3), and not having one's daughter vaccinated. An attitude score of 3 was defined as neutral.

Data analyses

The significance of mean and frequency differences between the baseline and follow-up group was assessed with the Mann-Whitney U test and Chi-square statistics. Pearson correlations were calculated to analyze associations between parent characteristics and social cognitive factors . To determine significant predictors of uptake (yes/no) measured at follow-up (T2), multiple hierarchical logistic regression analyses were performed with various factors measured at baseline as independent variables . In model 1 demographic characteristics were entered, because these were considered more distal and non-modifiable predictors. In model 2a parent characteristics were added. Model 2b consisted of demographic characteristics and social cognitive factors. In model 3 we entered demographic characteristics, parent characteristics, social cognitive factors, and an interaction term of attitude x ambivalence. Finally, in model 4 intention was added. Intention was added only in the last model because of its high correlation with other predictors. We aimed to show significant predictors with and without intention in the model. The procedure recommended by Aiken and West (1991) was used to determine whether ambivalence moderated the relationship between attitude and uptake, and the unstandardised regression coefficients were examined for attitude at different levels of ambivalence (i.e. the mean ambivalence score, 1 SD above the mean, and 1 SD below the mean) [35]. To compare predictors of uptake and intention, the regression analysis of model 3 was repeated with intention as the dependent variable (ordinal logistic regression analyses).

To assess the impact of the time gap between baseline and follow-up on changes in attitude and ambivalence, two linear regression analyses were performed with change scores between the baseline and follow-up measurement. Variables that showed a significant ($p<0.05$) change over time were included. First, we used attitude as the dependent variable. Independent variables were knowledge, informed choice (subscale of the Decision Evaluation Scales [29]), ambivalence towards HPV vaccination, social norm, and trust in the vaccine. Second, we used ambivalence towards HPV vaccination as

the dependent variable. Independent variables were knowledge, informed choice, social norm, and trust in the vaccine.

McNemar's test was used to assess the significance of the difference in correct responses to the knowledge items between baseline and follow-up .

RESULTS

Respondents

The response rate of the baseline questionnaire was 29.8% (1762/5918). A total of 1067 respondents were willing to complete the follow-up questionnaire, of which 793 responded (74.3%) (Figure 1). At baseline, the mean age of those who completed both questionnaires was 43 years. Most respondents were female (baseline: 93.3%; follow-up: 93.7%), had an intermediate (baseline: 47.9%; follow-up: 46.7%) or high educational level (baseline: 40%; follow-up: 45.0%), and were born in the Netherlands (baseline: 91.0%; follow-up: 93.8%). In the follow-up group, 652 (82.2%) daughters had been vaccinated against HPV. The subgroup that completed the follow-up assessment differed significantly from those who did not, on six characteristics (Table 1).

Predictors of HPV vaccination uptake

Pearson's correlations showed that most associations between the predictors were positive (Table 2). Table 3 presents the results of the hierarchical logistic regression analyses to predict HPV vaccination uptake. The first model in which HPV vaccination uptake was regressed on demographic factors showed that uptake at follow-up was significantly predicted by religion, and the year the decision about uptake was made (2011 vs. 2010) (pseudo R2 = 0.06). Specifically, those respondents without a religious affiliation and those who had to decide in 2011 were more likely to have their daughter vaccinated. In model 2a, parent characteristics were added; this model explained an additional 29% variance. HPV vaccination was more likely for parents with a higher educational level, having no religious affiliation, decision about uptake in 2011, and higher trust in the NIP and the vaccine. In model 2b (demographic characteristics and social cognitive factors) significant predictors were: year of decision about uptake (2011 vs. 2010), a positive attitude towards HPV vaccination, social norm, and anticipated regret and worry about no uptake (pseudo R2 = 0.53). In model 3 (including all predictors except intention), vaccination was more likely for parents who had to decide in 2011, ambivalence towards HPV vaccination (under the condition that attitude is equal to 0), and higher anticipated regret and worry about no uptake. The interaction term of attitude x ambivalence was

also significant (pseudo R2 = 0.57). In model 4 (including all predictors), significant predictors of uptake were the year the decision about uptake was made (2011 vs. 2010), a higher intention, ambivalence towards HPV vaccination (under the condition that attitude is equal to 0), and the interaction term of attitude x ambivalence.

The significant interaction term attitude x ambivalence showed that the predictive validity of attitude improved as scores of ambivalence increased from low (b=0.89, p=0.0238) to moderate (b=1.44, p=0.001), and from moderate (b=1.44, p=0.001) to high (b=1.98,p<0.001).

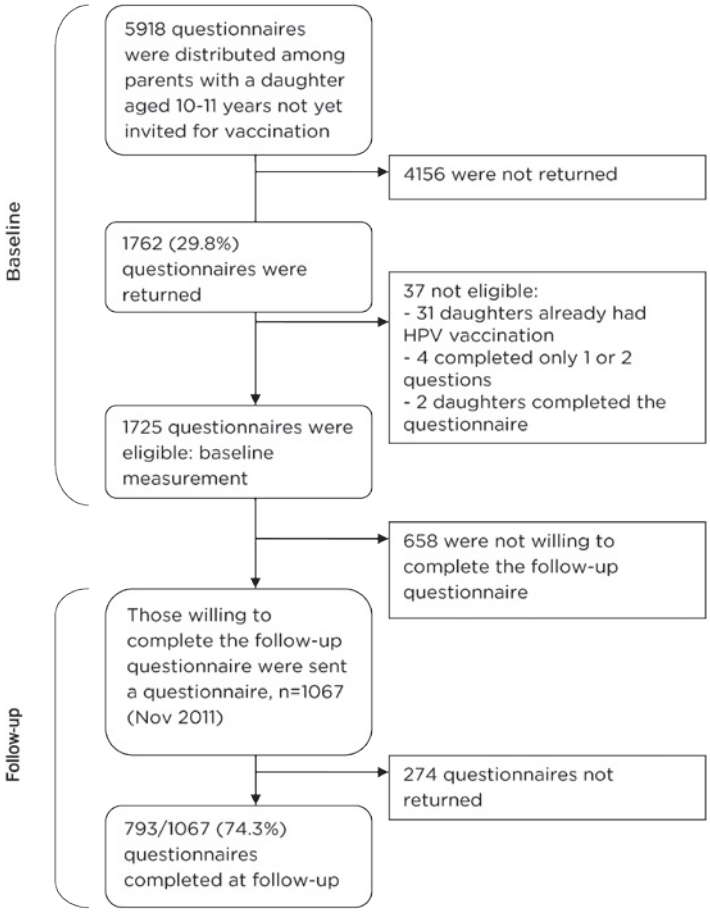

Fig. 1 Flow diagram of numbers of questionnaires at baseline and at follow-up.

Table 1: Characteristics of the respondents (parents).

	Total baseline group (n=1725)		Subgroup that completed follow-up assessment (n=793)		
Characteristics	**Mean**	**(SD)**	**Mean**	**(SD)**	**p-value**
Age at baseline (years)	42.8	4.17	43.0	4.05	0.015
range	29-59		32-58		
Children					
Age (years)	13.3	3.42	13.3	3.21	
Age range	0-34		0-34		
Number of girls	1.7	0.78	1.7	0.74	
Number of boys	0.9	0.77	0.9	0.76	
	n	**%**	**n**	**%**	
Marital status					0.372
Married/cohabiting	1477	87.2	693	89.4	
Partner, but living alone	34	2.0	16	2.1	
No partner	165	9.7	66	8.5	
Sex					0.233
Female	1596	93.3	743	93.7	
Educational level					<0.001
Low	200	12.1	64	8.3	
Intermediate	789	47.9	358	46.7	
High	658	40.0	345	45.0	
Job status					0.270
Paid job	1268	78.6	617	81.6	
Housewife or houseman or unpaid job or student	295	18.3	119	15.7	
No job	51	3.2	20	2.6	
Net income per month (euros)					<0.001
< 1,500	161	10.5	45	6.1	
1,500 – 3,000	584	38.2	267	36.4	
3,000 – 4,500	488	32.0	264	36.0	
> 4,500	294	19.3	157	21.4	
Country of birth					<0.001
The Netherlands	1550	91.0	740	93.8	
Turkey; Morocco	37	2.2	6	0.8	
Suriname; Aruba; Netherlands Antilles	16	0.9	4	0.5	
Other	100	5.9	39	4.9	
Country of birth of both parents					0.002
The Netherlands	1459	88.5	703	89.4	
Turkey; Morocco	44	2.7	9	1.1	
Suriname; Aruba; Netherlands Antilles	19	1.2	5	0.6	
Other	126	7.6	69	8.8	
Religion					0.590
None	960	57.0	450	57.9	
Christian	611	36.3	290	37.3	
Muslim	57	3.4	13	1.7	

Table 1 Continued

	Total baseline group (n=1725)		Subgroup that completed follow-up assessment (n=793)		
Characteristics	**Mean**	**(SD)**	**Mean**	**(SD)**	**p-value**
Other	54	3.2	24	3.1	
Decision about HPV vaccination uptake					
In 2010	-	-	555	71.5	
In 2011	-	-	221	28.5	
If female: abnormal pap smear result					0.103
Yes	185	11.7	98	13.2	
No	1351	85.6	634	85.3	
Never had a pap smear taken	42	2.7	11	1.5	
Daughter vaccinated against DPTP[1] and MMR[2]					0.038
Yes	1654	95.9	778	98.1	
Daughter vaccinated against HPV					
Yes	-	-	652	83.1	

The subgroup that completed the follow-up assessment differed significantly from the baseline group on six characteristics.

[1] DPTP refers to diphtheria, pertussis, tetanus and poliomyelitis.

[2] MMR refers to measles, mumps and rubella.

Table 2. Means, standard deviations (SD) and Pearson's correlation between the predictors at baseline (n=793)

	Mean (SD)	1	2	3	4	5	6	7	8	9	10	11	12
1. Parental responsibility	4.50 (0.46)												
2. Trust in NIP	4.86 (0.67)	0.04											
3. Trust in vaccine	4.31 (0.92)	0.06	0.54*										
4. Perceived susceptibility of mother to cervical cancer	4.97 (1.74)	0.05	0.01	0.02									
5. Intention	3.89 (1.07)	0.03	0.48*	0.73**	0.05								
6. Ambivalence	1.71 (1.07)	-0.07	-0.20**	-0.26**	0.01	-0.29**							
7. Attitude towards HPV vaccination	3.73 (1.44)	0.09**	0.51**	0.77**	0.05	0.84**	-0.33**						
8. Social norm	6.10 (10.31)	0.15**	0.33**	0.51**	0.07	0.61**	-0.18**	0.64**					
9. Normative belief	7.12 (1.57)	0.05	0.19**	0.33**	0.01	0.33**	-0.09*	0.34**	0.37**				
10. Knowledge	4.32 (1.49)	-0.09**	0.10**	0.03	0.03	0.03	-0.07	0.02	0.03	-0.03			
11. Perceived susceptibility of daughter if vaccinated to cervical cancer	3.73 (1.44)	0.06	-0.23**	-0.30**	0.41**	-0.26**	0.03	-0.31**	-0.23**	-0.23**	0.01		
12. Perceived severity of cervical cancer	10.60 (0.93)	0.25**	0.04	0.05	0.03	0.05	0.04	0.06	0.07	0.09*	-0.12**	0.01	
13. Anticipated regret and worry about no uptake	4.92 (1.56)	0.23**	0.38**	0.62**	0.11**	0.69**	-0.19**	0.71**	0.53**	0.36**	-0.06	-0.23**	0.20**

Small effect size: r > 0.10; medium effect size: 0.30 < r < 0.50; large effect size: r > 0.50. * p < 0.05 ** p< 0.01. NIP; Dutch National Immunization Program

Table 3. Hierarchical logistic regression analyses with uptake (yes/no) as dependent variable: all variables are reported by parents at baseline.

	Univariate	Model 1 (n=708)	Model 2a (n=644)	Model 2b (n=617)	Model 3 (n=572)	Model 4 (n=569)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Demographic characteristics						
Age of parents (years)	1.02 (0.98-1.07)	1.01 (0.96-1.06)	1.03 (0.96-1.09)	1.02 (0.95-1.10)	1.02 (0.94-1.11)	1.01 (0.93-1.09)
Educational level	1.15 (1.00-1.34)	1.17 (0.99-1.37)	**1.25 (1.00-1.54)***	1.20 (0.93-1.55)	1.27 (0.96-1.70)	1.33 (0.99-1.78)
No religious affiliation	**1.73 (1.19-2.53)****	**1.63 (1.09-2.42)***	**1.73 (1.07-2.81)***	1.12 (0.63-2.00)	1.19 (0.63-2.25)	1.16 (0.60-2.23)
Decision about uptake: 2011 (vs. 2010)	**2.08 (1.28-3.36)****	**2.68 (1.57-4.53)*****	**2.69 (1.42-5.10)****	**2.45 (1.20-5.01)***	**2.48 (1.11-5.52)***	**2.60 (1.16-5.80)***
Parent characteristics						
No abnormal smear experience	1.02 (0.58-1.78)		0.94 (0.45-1.95)		0.70 (0.26-1.88)	0.68 (0.24-1.95)
Parental responsibility	1.23 (0.83-1.84)		1.53 (0.91-2.59)		1.55 (0.76-3.18)	1.86 (0.90-3.83)
Trust in NIP	**3.54 (2.61-4.81)*****		**1.82 (1.21-2.74)****		1.40 (0.86-2.30)	1.33 (0.79-2.24)
Trust in vaccine	**3.64 (2.85-4.64)*****		**3.41 (2.49-4.68)*****		1.23 (0.69-1.83)	0.99 (0.59-1.67)
Perceived susceptibility of mother to cervical cancer	1.04 (0.93-1.16)		1.03 (0.88-1.21)		0.97 (0.77-1.22)	0.96 (0.76-1.22)
Social cognitive factors						
Intention	**4.59 (3.56-5.92)*****					**2.61 (1.47-4.61)****
Ambivalence towards HPV vaccination	**0.82 (0.69-0.92)***			1.07 (0.79-1.45)	**0.27 (0.08-0.87)***	**0.22 (0.07-0.71)***
Positive attitude towards HPV vaccination	**5.73 (4.26-7.71)*****			**3.43 (2.01-5.84)*****	1.70 (0.69-4.21)	0.89 (0.34-2.36)
Social norm	**1.21 (1.16-1.26)*****			**1.07 (1.01-1.13)***	1.05 (0.99-1.11)	1.03 (0.97-1.09)
Normative belief	**1.44 (1.28-1.63)*****			0.99 (0.81-1.21)	1.03 (0.83-1.29)	1.03 (0.81-1.29)
Knowledge	1.08 (0.95-1.22)			0.95 (0.87-1.04)	0.93 (0.76-1.13)	0.95 (0.78-1.17)
Perceived susceptibility of daughter if vaccinated to cervical cancer	**0.65 (0.57-0.74)*****			0.86 (0.70-1.05)	0.89 (0.69-1.14)	0.88 (0.68-1.14)
Perceived severity of cervical cancer	**1.22 (1.03-1.46)***			1.08 (0.81-1.42)	1.06 (0.78-1.44)	1.08 (0.79-1.48)
Anticipated regret and worry about no uptake	**2.23 (1.93-2.58)*****			**1.43 (1.11-1.84)****	**1.43 (1.08-1.89)***	1.24 (0.92-1.67)
Ambivalence x attitude interaction					**1.68 (1.14-2.47)****	**1.79 (1.22-2.62)****
R^2		0.06	0.35	0.53	0.57	0.59

*$p < 0.05$ **$p < 0.01$ and ***$p < 0.001$

OR, odds ratio. CI, confidence interval. NIP, National Immunization Programme

Associations of HPV vaccination intention

Alternatively, we performed an ordinal logistic regression analysis with intention (instead of uptake) as dependent variable (results not shown). This analysis showed that a higher intention was associated with a positive attitude towards HPV vaccination (OR 19.53; 95%CI: 10.32-36.93) (under the condition that ambivalence is equal to 0), ambivalence towards HPV vaccination (OR 2.39; 95%CI: 1.10-5.18) (under the condition that attitude is equal to 0), trust in the vaccine (OR 1.62; 95%CI: 1.16-2.27), anticipated regret and worry about no uptake (OR 1.59; 95%CI: 1.32-1.92), and social norm (OR 1.07; 95%CI: 1.04-1.10). A lower uptake intention was associated with a higher educational level (OR 0.83; 95%CI: 0.70-0.99) and a higher perceived parental responsibility for their daughter's health (OR 0.48; 95%CI: 0.30-0.75). The interaction term of attitude x ambivalence was significant (OR 0.73; 95%CI: 0.59-0.90).

Impact of time

Favorable changes in attitudes towards HPV uptake over time were significantly related to an increase in trust in the vaccine (OR 1.45; 95%CI: 1.36-1.53) and social norm (OR 1.22; 95%CI: 1.15-1.28) over time, and a decrease in ambivalence towards HPV vaccination (OR 0.94; 95%CI: 0.91-0.98). A decrease in ambivalence towards HPV vaccination over time was significantly related to an increase in feeling informed about HPV vaccination (OR 0.79; 95%CI: 0.69-0.91) and an increase in trust in the vaccine (OR 0.88; 95%CI: 0.77-0.99) over time.

Informed decision-making

Overall, knowledge levels about the degree/duration of protection was low at baseline and at follow-up (33-43% correct answers). Percentages of correct responses to 5 knowledge items increased significantly at follow-up (Table 4). When 5 (out of 7) correct items were defined as sufficient decision-relevant knowledge, then n=338 (43.9%) of the respondents made an informed choice about uptake. When 4 correct items were considered sufficient, then n=437 (65.7%) of the respondents made an informed choice about uptake (Table 5).

Reasons for vaccinating or not

Main reasons as reported by parents at baseline to have their daughter vaccinated include feeling responsible for her health (n=947; 54.9%), a family history of cancer (n=128; 7.4%), anticipating regret in case their daughter gets cervical cancer (n=103; 6.0%), and other

(n=547; 31.7%). Main reasons as reported by parents at baseline not to have their daughter vaccinated include that consequences of vaccinating are unpredictable (497; 28.8%), fear of serious side-effects (n=401; 23.2%), and too little information about the vaccine being available (n=125; 7.2%).

Table 4: Knowledge items as completed by those who responded to the baseline and follow-up questionnaire (n=793)

	Correct responses				
	Baseline measurement		Follow-up measurement		Significance level for difference between baseline and follow-up
Item (true/false)	n	%	n	%	*p-value*
HPV causes cervical cancer (true)	496	62.5	479	60.4	0.336
A condom protects 100% against HPV (false)	464	58.5	518	65.3	0.001
The HPV vaccination will decrease the risk of cervical cancer (true)	673	84.9	726	91.6	<0.001
Vaccination in combination with having a smear taken is more protective than only vaccination (true)	521	65.7	598	75.4	<0.001
Item (multiple choice)					
How is HPV transmitted? (through blood; oxygen; sexual contact)	699	88.1	730	92.1	0.006
What is the protection rate of the HPV vaccine (55%; 70%; 85%; 100%)	286	36.1	337	42.5	0.005
What is the protection duration of a complete vaccination against cervical cancer? (at least 6 [8 at follow-up] years; at least 30 years; lifetime)	289	36.4	262	33.0	0.094

Correct answers are shaded

Table 5: Informed decision at follow-up (n=770)

	Daughter vaccinated (n=640)		Daughter not vaccinated (n=130)	
	n	%	n	%
Positive attitude				
≥5 correct items	280	36.4	14	1.8
<5 correct items	246	31.9	16	2.1
Negative attitude				
≥5 correct items	51	6.6	58	7.5
<5 correct items	32	4.2	34	4.4

Knowledge was measured with 7 items at follow-up. Informed decision rate for cut-off at 3 correct items: 76.1% ([504+82]/770); 4 correct items: 65.7% ([437+69]/770); 5 correct items: 43.9% ([280+58]/770); 6 correct items: 18.7% ([117+27]/770). Due to missing items, analyses were based on n=770 respondents instead of n=793. Informed choice (as defined) is shaded.

DISCUSSION

In this study among parents we assessed longitudinal predictors of HPV vaccination uptake of their daughters. Uptake was predicted by intention, a later (2011) versus earlier (2010) decision about uptake, and anticipated regret and worry in case of abstaining from HPV vaccination. Ambivalence towards HPV vaccination at baseline moderated the attitude (baseline)- uptake (follow-up) relationship, with the attitude-uptake relationship being stronger at higher ambivalence levels.

HPV vaccination was most strongly predicted by intention, which fits the TPB model and was also reported in an earlier study on predictors of HPV vaccination uptake [22]. HPV vaccination intention was positively associated with parental trust in the vaccine, the belief that according to significant others their daughter should be vaccinated, and the motivation to comply with that (social norm), and anticipated regret and worry (which also predicted uptake). Positive intention was negatively associated with educational level and perceived parental responsibility for one's daughter's health. Knowledge did not predict uptake or intention. The relationship found between intention and uptake, and between intention and social norm, is consistent with the TPB model and with another study [22] which also confirms the association we found between anticipated regret/worry and uptake, and anticipated regret/worry and intention. The factors 'perceived susceptibility' and 'severity' of cancer of the HBM were not associated with intention or uptake, which confirms the results of an earlier study [22, 36].

A possible explanation for the positive effect on uptake of having to decide later (2011) versus earlier (2010) might be the amount of time that passed between the baseline questionnaire (2009) when an intensive societal debate involving politics, physicians, media, parents and girls about HPV vaccination was ongoing and the actual decision about uptake of vaccination. In 2011 this debate probably had less impact on the uptake decision than in 2010. Also, after millions of girls worldwide had been vaccinated and no serious side-effects had been reported, parents who had to decide later versus earlier probably felt more reassured about the vaccine's safety.

The present study shows that ambivalence moderated the attitude-uptake relationship. Parents with a positive attitude and a high level of ambivalence towards HPV vaccination were more likely to have their daughter vaccinated than parents with a positive attitude and a low level of ambivalence. This finding might be explained in two ways. First, ambivalence is characterized as being subjectively uncomfortable and people may be motivated to resolve the conflicting evaluations that they hold [37], e.g. by searching for information. Second, earlier studies found that ambivalent people processed pro-attitudinal messages to a greater extent than counter-attitudinal messages, probably because pro-attitudinal messages are more likely to reduce ambivalence [38-39]. Taking these two mechanisms together, it is likely that in our study ambivalent parents with a

positive attitude towards HPV vaccination processed 'positive' messages about HPV vaccination to a greater extent than 'negative' messages, and were therefore more likely to have their daughter vaccinated. In other words, parents who had both positive attitudes and were ambivalent towards HPV vaccination, became even more positive because they elaborated only information in favor of HPV vaccination. This may imply that this 'biased' information processing has a negative impact on informed decision-making, although parents will have gained more knowledge during their efforts to resolve their ambivalence.

Assessing decisional factors related to HPV vaccination both before and after the decision-making process about uptake, provided a unique opportunity to determine changes in those factors over time. Since uptake was predicted by intention, and intention was highly correlated with attitude (r=0.84) (at baseline), we think it is relevant to show which factors are important for changes in attitude over time. Our results show that a more positive attitude towards HPV vaccination over time was associated with an increase in trust in the vaccine and in social norm over time, and a decrease in ambivalence towards HPV vaccination over time. This latter factor was related to an increase in feeling informed about HPV vaccination and an increase in trust in the vaccine over time. In summary, over time parents felt better informed, became less ambivalent and had more trust in the vaccine. These results are in accordance with our finding that girls who had to decide with their parents whether or not to be vaccinated in 2011, were more likely to be vaccinated than those who had to decide in 2010.

An important finding is that knowledge about the duration of protection was low at both baseline and follow-up. For instance, about 65% of the parents thought that protection lasts 30 years or even lifelong. Since the duration of protection is still unknown, it is important that parents and girls know that booster vaccinations might be needed in the future. When we applied a cut-off of 4 or 5 correct knowledge items (out of 7), then the rates of informed choice about uptake were not high, 66% and 44%, respectively. However, this finding should be interpreted with caution because the time period between the assessment of knowledge and the last vaccination out of 3 shots was 1 month (decision in 2011) or 14 months (decision in 2010). In educational material it should be clearly stated what is known and not yet known about HPV vaccination.

Study strengths include: the longitudinal design, as recommended by authors of a cross sectional study [40]; the high (absolute) number of respondents of the baseline (n=1725) and follow-up questionnaires (n=793); and the high response rate of the follow-up questionnaire (74%).

Limitations

A limitation was the low response rate of the baseline questionnaire (30%), which might be due to the length of the questionnaire. Our sample may therefore not be representative of the general population, as few parents had a low educational level. Also, demographic characteristics of the follow-up group were slightly different from those of the baseline group, with more parents being better educated and well-off at follow-up. These parents might possibly be more likely than those in the wider population to seek to reduce high ambivalence by searching information, allowing them to respond positively to the vaccine invitation - rather than do nothing.

Conclusion

In conclusion, this study shows that intention, a later versus earlier decision about uptake, and anticipated regret/worry about abstaining from vaccination were predictors of uptake. Anticipated regret was a common predictor of intention and uptake and thus an important factor in the decision-making process about HPV vaccination. In turn, predictors of intention, like social norm and trust in the vaccine, are also important when deciding about HPV vaccination. Over time, parents felt better informed, became less ambivalent and had more trust in the vaccine.

Practice implications

This study shows the usefulness of including affective factors in studies examining HPV vaccination behaviour, since anticipated regret, trust in the vaccine, and ambivalence were found to play a role in the decision-making about uptake. However, it is also important that parents are enabled to base their decision about HPV vaccination of their daughter on decision-relevant knowledge. Since these results suggest that people need sufficient time to decide about the uptake of a new vaccine, we recommend a well-balanced, stepwise process of implementation, i.e. let parents first become aware of the link between HPV and cervical cancer, then provide them with balanced information about all the knowns and also the unknowns of HPV vaccination, and then finally offer them the opportunity to have their daughter vaccinated. Since two third of parents wrongly thought that protection lasts 30 years or even lifelong, educational material should clearly state that booster vaccinations might be needed in the future.

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Conflict of interest

There is no conflict of interest to declare.

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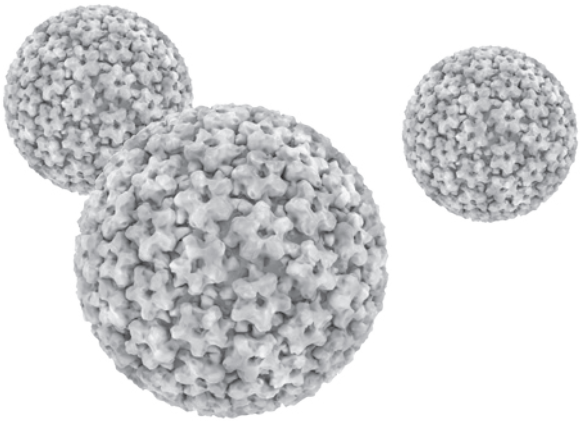

Chapter 4

Parents' preferences for vaccinating daughters against human papillomavirus in the Netherlands: a discrete choice experiment

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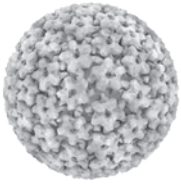

ABSTRACT

Background: To generate knowledge about potential to improvements to human papillomavirus (HPV) vaccination information and organization strategies, we assessed how aspects of HPV vaccination are associated with parents' preferences for their daughters' uptake, and which trade-offs parents are willing to make between these aspects.

Methods: A discrete choice experiment (DCE) was conducted among parents with a daughter aged 10-12 years. Panel mixed logit regression models were used to determine parents' preferences for vaccination. Trade-offs were quantified between four vaccination programme aspects: degree of protection against cervical cancer, duration of protection, risk of serious side-effects, and age of vaccination.

Results: Total response rate was 302/983 (31%). All aspects influenced respondents' preferences for HPV vaccination ($p<0.05$). Respondents preferred vaccination at age 14 years instead of at a younger age. Respondents were willing to trade-off 11% of the degree of protection to obtain life-time protection instead of 25 years. To obtain a vaccination with a risk of serious side-effects of 1/750,000 instead of 1/150,000, respondents were willing to trade-off 21%.

Conclusions: Uptake may rise if the age ranges for free HPV vaccinations are broadened. Based on the trade-offs parents were willing to make, we conclude that uptake would increase if new evidence indicated outcomes are better than are currently understood, particularly for degree and duration of protection.

BACKGROUND

Human Papillomavirus (HPV) infection is a necessary factor in the development of cervical cancer [1]. Vaccines are available against HPV 16 and 18, that are responsible for 71% of all cervical cancers worldwide [2]. Most European countries offer the vaccine to girls aged between 9 to 17 years [3-4]. However, uptake rates vary considerably between countries (range 17-84%) [4]. In 2009, the Dutch National Immunization Programme (NIP) was extended to include the bivalent HPV vaccine for 12-year-old girls. A catch-up campaign was organized in 2009 for 13 to 16 year old girls. The uptake rate of this campaign was 52% [5]. In 2010, 56% of all 12-year-old girls were vaccinated against HPV and in 2011 the uptake was 58% [6]. Vaccination through the NIP is voluntary, is free of costs, and 12-year-olds are legally entitled to make their own decision about uptake.

The attitude of parents and girls towards HPV vaccination and consequently its uptake, may be influenced by their perception of the advantages and disadvantages of the vaccine [7]. An advantage is the (partial) protection against cervical cancer that the vaccine provides. The fact that only partial protection is provided by HPV vaccinations may be considered a disadvantage: in spite of HPV vaccinations, girls are still vulnerable to develop cervical cancer [8]. Furthermore, insecurity about the safety of the vaccine [8-11], anticipated side-effects such as pain or discomfort [10, 12], and cost [11, 13-14] can be considered as disadvantages. Parents and girls may become ambivalent towards HPV vaccination when they weigh these 'pros' and 'cons' [8], and have, e.g., simultaneous positive and negative evaluations of an attitude object [15-16], in this case HPV vaccination. This may lead to postponing decisions about uptake, and hence, low uptake rates, while a proportion of girls (and parents) potentially had decided to have the HPV vaccination if better information had been available to them. Our study aimed to generate knowledge to improve information and organization strategies. We therefore wanted to assess which vaccine characteristics were important for parents and girls when deciding about uptake and which trade-offs they were willing to make between these characteristics. We used a discrete choice experiment (DCE), a quantitative approach that is increasingly used in health care to elicit preferences [17-18]. Although Dutch girls are legally allowed to decide about their own uptake, previous research showed that twelve to thirteen year old girls made a shared decision with their parents regarding uptake [19]. We therefore aimed at assessing preferences for HPV vaccination in both girls [20] and in parents. The current study describes the DCE as conducted among parents.

METHODS

Discrete Choice Experiment

In DCEs, it is assumed that a medical intervention, such as a vaccination programme, can be described by its characteristics (attributes; e.g. duration of protection)[21], and by variants of that characteristic (levels of the attribute; e.g. a duration of protection of 6 years, 25 years and life-time). Furthermore, it is assumed that individual preferences for a medical intervention are determined by the levels of those attributes [21]. The relative importance of attributes and the trade-offs that respondents make between them can be assessed by offering a series of choices between two or more medical intervention alternatives with different combinations of attribute levels (Table 1) [22]. A DCE is a straightforward task, which more closer resembles a real world decision (i.e. trading off health and non-health outcomes) in comparison with other stated preference techniques [23]. We conducted the DCE according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) DCE guideline [24] and Lancsar and Louviere's guide [25].

Table 1: Choice set example

Attributes	Programme A	Programme B	No vaccination
Degree of protection against cervical cancer	70%	90%	0%
Duration of protection	Lifetime	6 years	n.a.
Risk of serious side-effects	1:750,000	1:750,000	No risk
Age at vaccination	14 years	9 years	n.a.
Which vaccination programme do you prefer?	**A**	**B**	**None**

n.a. = not applicable

Attributes and attribute levels

The selection of attributes and their levels was based on data from the literature [7]; focus groups with 36 parents about decisional strategies and factors that could guide HPV vaccination intentions [8]; and interviews with experts in the field of HPV vaccination, such as professors in gynaecology, adolescent public health, and infectious disease control (n=8). This resulted in eight attributes which were ranked by parents (n=10) and the experts (n=8). The attributes identified as most relevant were: 1) the degree of protection against cervical cancer; 2) the duration of protection; 3) the risk of serious side-effects (e.g. hospitalization); and 4) the age of vaccination (Table 2). These were included in the DCE design. Attributes that were considered less relevant were total costs, the risk of mild side-effects, the reduction in required number of pap tests, and the HPV vaccine

being recommended by e.g. one's general practioner/the government/family or friends. Levels of the attributes were selected in such a way that they were plausible and relevant from both the clinical and the policy viewpoint. Levels of risk of serious side-effects were based on a report of the Centers for Disease Control and Prevention (CDC) (2009).

Table 2: Considered attributes and levels for HPV vaccination

Attributes	Levels
Degree of protection against cervical cancer (%)	50, 70, 90
Duration of protection (yrs)	6, 25, lifetime
Risk of serious side-effects (1 out of..)	750,000, 150,000, 30,000
Age at vaccination (yrs)	9, 12, 14

Study design

The combination of four attributes with three levels each resulted in 81 (3^4) hypothetical HPV vaccination alternatives. Using an efficient design by maximizing D-efficiency (SAS software version 9.1, SAS Institute Inc., Cary, NC, USA), 54 choice sets were constructed to be able to estimate all main effects and all two-way interactions between attributes. Choice sets consisted of two HPV vaccination alternatives and a 'no HPV vaccination' option to allow respondents to 'opt out' (Table 1). HPV vaccination is a preventive medical intervention and, as in real life, respondents are not obliged to opt for HPV vaccination. Respondents were asked to consider all three options in a choice set as realistic alternatives and to choose the option that appealed most to them. Presenting a single individual with a large amount of choice sets is expected to result in a lower response rate and/or response reliability [26-27]. We therefore used a blocked design [22], which resulted in dividing the 54 choice sets over six questionnaires containing nine choice sets each.

Study sample

A sample of parents with a daughter aged 10-12 years was approached through five primary school administrations in urban and rural areas in the Netherlands. These school administrations consisted of a total of 57 schools, of which 55 were willing to participate. Calculation of optimal sample sizes for estimating non-linear discrete choice models from DCE data is complicated as it depends on the true values of the unknown parameters estimated in the choice models [25]. One however rarely requires more than 20 respondents per parameter to estimate reliable models [25]. Our DCE contained 8 main-effect parameters (see equation 1). It, therefore, needed to include at least 160 respondents. Taking into account some two-way interactions between attributes, 300 questionnaires was expected to be sufficient based on other studies [24, 28-29].

Questionnaire

The first page of the questionnaire provided information about HPV and its link with cervical cancer, and HPV vaccination. In the DCE section, respondents were asked to choose the option that appealed to them most. A separate sheet showed the percentages of the degree of protection illustrated with bar graphs, and a description of the risk of serious side-effects in words (i.e. the risk of serious side-effects is small, very small or extremely small).

We assessed respondents' understanding of the DCE task by including a dominant choice set as a rationality test. In this choice set the HPV vaccine was given at the age of 12 years in both alternatives, while one alternative was characterized by logically preferable levels on all other attributes. Convergent validity was checked with a ranking task, i.e. ranking the four attributes of HPV vaccination from most important to least important. To gain more insight into respondents' understanding of the DCE task, i.e. comparing risks and percentages, we included the Subjective Numeracy Scale (SNS), a scale that correlates well with objective measures of numeracy skills [30-31]. Higher scores indicate higher numeracy.

The questionnaire was pilot tested to check for face validity and for problems in interpretation (n=16). This resulted in an improved explanation of the risk of serious side-effects. Approval for the study was obtained from the Medical Ethics Committee, Erasmus MC, University Medical Center Rotterdam (MEC 2008-206).

Questionnaires and information letters were sent to primary schools between March and June 2009 to be distributed to 10 to 12-year-old girls to give to their parents. Parents could return the questionnaire in a postage-paid envelope that was included in the mailing package.

Statistical analyses

The DCE was analysed by taking each choice among the three options as an observation, i.e. two 'no' and one 'yes' responses. The observations were analysed by panel mixed logit regression models to take heterogeneity as well as correlation between the choice sets completed by each individual into account [22]. After testing for linear continuous effects of the attributes, we selected the model with the best fit based on the Akaike information criterion (AIC). Doing so, the following utility model was estimated:

$$V = \beta_0 + \beta_1 \text{EFFECTIVENESS} + \beta_2 \text{DURATION\_25Y} + \beta_3 \text{DURATION\_LIFETIME} + \beta_4 \text{SERIOUS\_1/150,000} + \beta_5 \text{SERIOUS\_1/30,000} + \beta_6 \text{AGE\_12Y} + \beta_7 \text{AGE\_14Y}$$

(Eq. 1)

V is the observable utility that is composed of the preference scores (β-coefficients) for the individual and the characteristics of the HPV vaccination alternative. β_1-β_7 are coefficients of the attributes indicating the relative weight individuals place on a certain attribute(level). When considering an HPV vaccination that generates a 50%, 70% or 90% protection rate, the coefficient β_1EFFECTIVENESS should be multiplied five, seven or nine times, respectively. The statistical significance of a coefficient (p-value ≤0.05) indicates that respondents differentiated between one attribute (or attribute level) and another in making stated choices about HPV vaccination programmes. A priori, we expected all attributes to be significant. The sign of a coefficient reflects whether the attribute has a positive or negative effect on the preference score of HPV vaccination. We expected that only the attribute 'risk of serious side-effects' would have a negative effect. The value of each coefficient represents the relative importance respondents assign to an attribute (level).

Sensitivity analyses were conducted to explore the impact of excluding respondents who failed the rationality test by excluding their data from the sample and re-running the analysis [32-33]. Also a number of two-way interactions between attributes were added to the main effects model to test which ones were significant and improved the fit of the model.

The trade-offs respondents were willing to make between the HPV vaccination attributes were calculated by the ratios of the coefficients of the different attributes with the degree of protection as the denominator. Choice probabilities for HPV vaccination uptake were also calculated to provide a way to convey DCE results to decision makers that is easier to interpret. The probability that an individual will say "yes" to an HPV vaccination programme is equal to:

$$P = 1 / (1+e^{-V})$$

(Eq. 2)

where V is defined as in Equation 1. We calculated the choice probability (i.e. the mean uptake) of a base-case compared to no vaccination (V (no vaccination) = 0)). Our base-case represents an HPV vaccination programme at the age of 12 years, a 1/150,000 risk of serious side-effects, a duration of protection of 6 years, and a 70% degree of protection. This base-case was chosen to correspond with i) the Dutch situation (vaccination at the age of 12 years) and ii) an HPV vaccination programme that contained most plausible levels based on literature. Noteworthy, in the calculation of the mean uptake all heterogeneity of the respondents was taken into account as the mean uptake is not just equal to the uptake of someone with average coefficient values of the levels. We presented these results in a "tornado" graph to illustrate the marginal effect on uptake of varying

one attribute level at a time from the base-case, holding all other attributes constant [34] (Figure 1).

RESULTS

Respondents

The response rate was 302/983 (31%). In total, 294 out of these 302 parents (97%) completed the DCE task and were included for further analyses. The mean age of the parents was 42.7 (SD=3.4) years. 90% of the respondents were female and about half had an intermediate educational level (54%) and had a religious affiliation (56%) (Table 3).

DCE results

All vaccine characteristics proved to influence parents' preferences for HPV vaccination ($p<0.05$; Table 4). The directions of the coefficients of the characteristics were in accordance with our priori hypotheses, indicating theoretical validity. The positive directions of the coefficients 'degree of protection' and 'duration of protection' indicated that parents preferred a higher protection rate and a longer duration of protection over a lower protection rate and a shorter duration of protection. The negative direction of serious side-effects indicated that parents preferred an HPV vaccination programme with low levels of serious side-effects. Most estimated standard deviations were significant, which indicated preference heterogeneity among respondents for several characteristics of HPV vaccination. Parents did not prefer vaccination at age 12 years over vaccination at the age of 9 years, but did prefer vaccination at age 14 years over vaccination at age 9 years (Table 4).

Sensitivity analyses showed that excluding the data of five out of 294 parents (1.7%) who 'failed' the rationality test had no relevant impact on the size or relative importance of the attributes. Adding two-way interactions did not significantly improve the fit of the model (data not shown).

Ranking test and numeracy

The results of the ranking task showed that the most important attributes were: the degree of protection (49%; 95% CI: 0.42 to 0.54); the risk of serious side-effects (44%; 95%CI: 0.38 to 0.50); and the duration of protection (5%; 95%CI: 0.03 to 0.09). These results are in accordance with the DCE results (i.e. the order of importance is the same as the order of the coefficients), supporting a convergent validity of the DCE results.

Table 3: Respondent characteristics

	(n=294)	
Characteristics		
Age (years) **Mean (SD)**	42.7	(3.4)
range	32-53	
	n	**(%)**
Sex		
Female	264	(90.1)
Educational level		
Low	26	(9.3)
Intermediate	151	(53.9)
High	103	(36.3)
Religion		
None	128	(43.7)
Christian	156	(53.2)
Muslim	1	(0.3)
Other	8	(2.7)
Country of birth		
The Netherlands	272	(92.5)
Country of birth of parents		
Both parents in the Netherlands	268	(96.8)
One parent outside the Netherlands	3	(1.1)
Both parents outside the Netherlands	6	(2.2)
Daughter HPV vaccinated		
Yes	36	(12.4)
Intention if daughter not vaccinated		
Yes	146	(58.4)
No	54	(21.5)
Don't know	51	(20.3)
Job status		
Paid job	259	(88.4)
Housewife or -man/unpaid job/student	28	(9.6)
No job	6	(2.0)
Marital status		
Married/cohabiting	274	(93.8)
Partner, but living alone	7	(2.4)
No partner	11	(3.8)
Net income per month (euro's)		
< 1.500	13	(5.2)
1.500 – 3.000	113	(45.6)
3.000 – 4.500	86	(34.7)
> 4.500	36	(14.5)

Table 4: Respondents' preferences for HPV vaccination based on a panel mixed logit model [N=294]

Attributes		Coefficient		
		Value		(95% CI)
Constant (vaccination)	Mean	-3.18	***[a]	(-4.50 to -1.86)
	S.D.	9.26	***	(7.62 to 10.9)
Degree of protection against cervical cancer (per 10%)	Mean	1.18[b]	***	(0.99 to 1.36)
	S.D.	0.75	***	(0.60 to 0.90)
Duration of protection 6 years (omitted)[c]	Mean	-2.37	***	(-2.72 to -2.03)
	S.D.	1.46	***	(1.41 to 1.51)
Duration of protection 25 years	Mean	0.56	***	(0.40 to 0.72)
	S.D.	0.36	***	(0.10 to 0.62)
Duration of protection lifetime	Mean	1.81	***	(1.51 to 2.11)
	S.D.	1.42	***	(1.14 to 1.70)
1/750,000 risk of serious side effects (omitted)[c]	Mean	3.04	***	(2.54 to 3.55)
	S.D.	3.18	***	(2.98 to 3.38)
1/150,000 risk of serious side effects	Mean	0.62	***	(0.37 to 0.86)
	S.D.	0.70	***	(0.42 to 0.98)
1/30,000 risk of serious side effects	Mean	-3.66	***	(-3.06 to -4.25)
	S.D.	3.11	***	(2.45 to 3.77)
Vaccination at age 9 years (omitted)[c]	Mean	-0.65	***	(-0.86 to -0.44)
	S.D.	0.32	***	(0.30 to 0.33)
Vaccination at age 12 years	Mean	0.11		(-0.06 to 0.29)
	S.D.	0.29	***	(0.10 to 0.48)
Vaccination at age 14 years	Mean	0.54	***	(0.36 to 0.72)
	S.D.	0.29	***	(0.10 to 0.48)
Model fits				
Log-Likelihood function			-1205.62	
Akaike information criterion			0.93	
Bayesian information criterion			0.96	
Pseudo R-squared			0.58	

Notes: Effects coded variables used for protection duration, serious side effects, and age at vaccination; Normal distribution for random coefficients used on all attributes; Number of observations = 7938 (i.e. 294 respondents completed 9 choice sets containing 3 response options each)
[a] *** Denotes p<.01; [b] When looking at an HPV vaccination that generates a 50%, 70% or 90% protection rate, the coefficient should be multiplied five, seven or nine times; [c] The value of the omitted term equals the negative sum of the coefficients

Parents' scores on the Subjective Numeracy Scale ranged from 1.5 to 6.0 with a median of 4.6 (95% CI: 4.50 to 4.75, calculated with bootstrapping) and inter quartile range (IQR) of 1.2 (data negatively skewed). The Cronbach alpha coefficient was 0.88, suggesting very good internal consistency reliability.

Trade-offs

Parents were willing to trade-off the degree of protection against cervical cancer in order to gain improvement in the levels of the other attributes. They were willing to trade-off 11% of the degree of protection to obtain life-time protection instead of 25 years. To obtain

Table 5: Respondents' trade-offs between degree of protection and different aspects of a vaccination programme

Change in levels	Trade-off in a decreased degree of protection against cervical cancer (%; CI)
A **protection duration** of lifetime instead of 25 years	10.7 (8.6 to 12.7)
A **risk of serious side-effects** of 1/750,000 instead of 1/150,000	20.6 (15.9 to 25.3)
A vaccination at **age** 14 years instead of 9 years	10.1 (8.3 to 11.9)

an HPV vaccination with a risk of serious side-effects of 1/750,000 instead of 1/150,000, parents were willing to trade-off 21%. To get a vaccination at age 14 years instead of 9 years, parents were willing to trade-off 10% (Table 5).

Expected uptake of HPV vaccination

Assuming our base-case HPV vaccination programme (an HPV vaccination programme at the age of 12 years, a 1/150,000 risk of serious side-effects; a duration of protection of 6 years, and a 70% degree of protection), the expected uptake based on parents' preferences was 63.3%. Especially an increase in the duration of protection from 6 years to lifetime would result in a relatively large increase in the expected uptake (12.2%). On the other hand, an increased risk of serious side-effects from 1/150,000 to 1/30,000 would result in a decrease in the expected uptake (13.4%) (Figure 1).

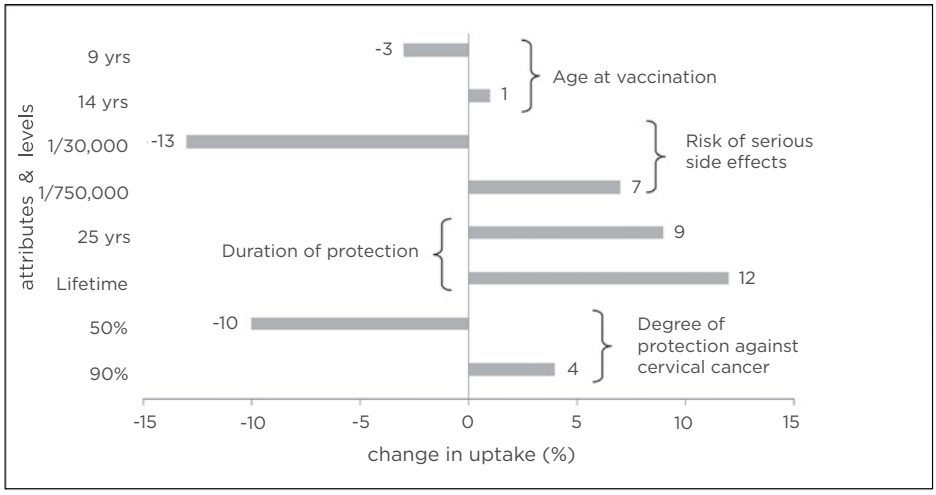

Fig. 1. Univariate marginal estimates for change in predicted probability of participation of parents; highest and lowest value for attributes versus base-case. The base-case is an HPV vaccination at age 12 years, 1/150,000 risk of serious side-effects, duration of protection of 6 years, and 70% degree of protection against cervical cancer. This base-case is indicated as zero change in the probability of the x-axis. Assuming our base-case, the expected uptake was 63.3%

DISCUSSION

This study shows that the degree of protection against cervical cancer, the duration of protection, the risk of serious side-effects, and the age of vaccination, significantly influenced parents' preferences for HPV vaccination. Parents preferred vaccination at age 14 years over age 9 years. Although parents preferred a higher degree of protection against cervical cancer, they were willing to trade-off some degree of protection in order to gain improvement in the levels of the other attributes.

Our finding that the duration and the degree of protection were relevant for parents' preferences for HPV vaccination was also found in a DCE study among mothers [35]. Our study is innovative, in that we used new attributes (risk of serious side-effects and age at vaccination), and that we sampled European parents. Also, our findings were in line with the findings of a DCE study, which investigated girls' preferences for HPV vaccination [20]. With the exception that parents prefer vaccination at age 14 years instead of at a younger age, whereas girls prefer vaccination at age 12 years over age 14 years [20]. Our findings are consistent with the results from the previous studies which

found that vaccine acceptability of parents increases as the proposed age of vaccination increases (infant, preadolescent and older teenagers) [10]. This might have implications for vaccination programmes: uptake may rise if the age ranges within which a girl is entitled to free HPV vaccinations are broadened to e.g. 12 to 16 years.

The expected uptake of our base-case HPV vaccination programme was 63% based on parents' preferences. This rate is higher than the actual uptake of 52% in the Netherlands in 2009 at the time our study was conducted [5] and higher than the 58% of parents in our study who intend to have their daughter vaccinated, but lower than the uptake of other childhood vaccination in the Dutch NIP, which is 95% [36]. A possible explanation might be the current uncertainty considering several aspects of the vaccine. Our results showed that the unknown duration and degree of protection against cervical cancer and the unknown risk of serious side-effects all played an important role in parents' choices about HPV vaccination uptake. If for example the duration of protection was lifetime instead of 6 years, the expected uptake would increase to 76-80%. To date, follow-up data on HPV vaccinated young women are available for 8.4 years [37]. Therefore the effects of HPV vaccination on the long-term are unknown. Furthermore, when the HPV vaccination campaign started in the Netherlands in 2009, an intensive societal debate involving politics, physicians, media, parents and girls was ongoing. Contradictions in this debate could also explain the low uptake. Possibly parents and girls became ambivalent towards HPV vaccination, i.e. they may have held simultaneous positive and negative feelings towards HPV vaccinating, which can have a moderating effect on attitude-intention and attitude-behavior relationships resulting in postponing the decision about uptake [38].

Our study has some limitations. First, the majority of responding parents were mothers, although the questionnaire was addressed to both parents. This seems common in studies assessing parental attitudes regarding HPV vaccination [10, 39-40]. We do not expect this limitation to have biased the results. Second, the response rate of parents was relatively low (31%). However, the rate is similar to other DCE studies [28, 41]. As indicated by the high educational level of most parents, due to the low response rate, our sample may not be representative of the general population. This may limit the external validity of our results. We recommend that in future research ways are sought to include parents with a low educational level in DCE studies. The relatively high score for subjective numeracy score indicates that our sample probably did understand the risks and percentages they had to compare in the DCE task.

Conclusion

In conclusion, this study shows that parents' preferences for HPV vaccination were influenced by the degree of protection against cervical cancer, the duration of protection, the risk of serious side-effects, and the age of vaccination. Uptake may rise if the age ranges within which a girl is entitled to free HPV vaccinations are broadened. Based on the trade-offs parents were willing to make, we conclude that uptake would increase if new evidence indicated outcomes are better than are currently understood, particularly for degree and duration of protection.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

IJK conceived the idea for the study, designed the protocol, and supervised the execution of the study; EWBG, RH, IJK, MB, TJMH, and HR designed the questionnaire; RH performed the retrieval of the sample and was responsible for all mailings; RH and EWBG were responsible for the database design and data entry; EWBG performed the statistical design and analyses; RH drafted the report. All authors revised the article critically and approved the final version to be published.

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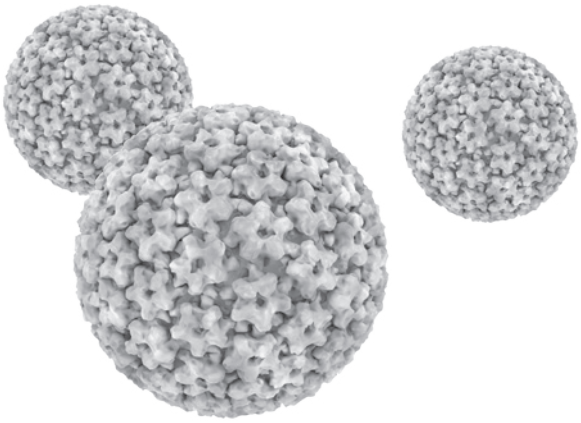
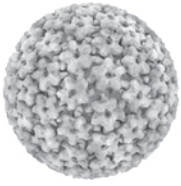
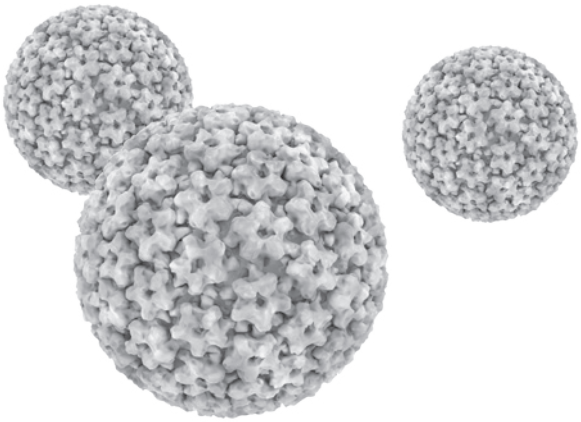


Part 2

Girls



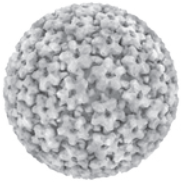


Chapter 5

Girls' preferences for HPV vaccination: a discrete choice experiment

Esther W. De Bekker-Grob, Robine Hofman, Bas Donkers, Marjolijn van Ballegooijen, Theo J. Helmerhorst, Hein Raat, Ida J. Korfage

Vaccine. 2010;28:6692-7



ABSTRACT

A discrete choice experiment was developed to investigate if girls aged 12-16 years make trade-offs between various aspects of human papillomavirus (HPV) vaccination, and to elicit the relative weight that girls' place on these characteristics. Degree of protection against cervical cancer, protection duration, risk of side-effects, and age of vaccination, all proved to influence girls' preferences for HPV vaccination. We found that girls were willing to trade-off 38% protection against cervical cancer to obtain a life-time protection instead of a protection duration of 6 years, or 17% to obtain an HPV vaccination with a 1 per 750,000 instead of 1 per 150,000 risk of serious side-effects. We conclude that girls indeed made a trade-off between degree of protection and other vaccine characteristics, and that uptake of HPV vaccination may change considerably if girls are supplied with new evidence-based information about the degree of protection against cervical cancer, the protection duration, and the risk of serious side-effects.

INTRODUCTION

In countries with cytological screening programmes the mortality of cervical cancer has significantly decreased [1]. Since the discovery of human papillomavirus (HPV) as the cause of cervical cancer [2], new types of cervical cancer prevention, such as HPV screening and HPV vaccination, have been developed [3]. Currently HPV vaccines are available against HPVs 16 en 18, which have been estimated to cause 73-76% of cases of cervical cancer in Europe [4-5]. HPV vaccination is useful for women who have not been previously infected with these HPV types since the protection against cancer for women with existing or previous infections of type 16 or 18 is low. By the end of 2008 fifteen countries of the European Union had decided to introduce HPV vaccination into their national immunisation schedule for adolescent girls, while another six have started the decision-making process with a recommendation favouring introduction [6].

Attitude towards and uptake of the offered HPV vaccine may be influenced by its perceived advantages and drawbacks. Individuals may be willing to undergo an HPV vaccination despite several drawbacks (risk of side effects, injections needed) in order to maximize health benefit or, vice versa, they may accept a lower health benefit in order to avoid side-effects of vaccination. Research has shown that preferences (i.e. individual's valuation) can have a major impact on the willingness to use health care services [7]. Several qualitative studies gave some insights into girls' preferences for HPV vaccination [8-10]. However, quantitative studies investigating girls' preferences for HPV vaccination and their willingness to trade-off between protection against cervical cancer and other characteristics of HPV vaccination are lacking.

Therefore, this study investigates the preferences of girls aged 12-16 years for HPV vaccination through a discrete choice experiment (DCE), a quantitative approach that is increasingly used in health care [11-12].

MATERIALS AND METHODS

HPV vaccination

In the Netherlands, a National Immunisation Programme (NIP) provides vaccinations against diphtheria, pertussis (whooping cough), tetanus, polio, type B Haemophilus influenzae, hepatitis B, mumps, measles, rubella (German measles) and meningococcosis C. In 2009, HPV vaccinations for 12-year-old girls (given as a series of three injections) were added to the NIP. To begin with, a catch-up programme was organised for girls aged 13 to 16 years. In the Netherlands, the HPV vaccine Cervarix is used, which protects against HPV-16 and HPV-18. Parental consent for this vaccination is not needed as teenagers at the age of 12 years or older are officially allowed to decide for themselves whether they want to be vaccinated. All Dutch NIP vaccinations are offered free of charge.

Discrete Choice Experiment

DCEs, with their origin in marketing, are a novel approach to assess preferences for medical interventions. In DCEs it is assumed that a medical intervention, such as a vaccination programme, can be described by its characteristics (attributes; e.g. protection duration) [13]. Those characteristics are further specified by variants of that characteristic (attribute levels; e.g. for protection duration: 6 years, 25 years, and lifetime). A second assumption is that the individual's preference for a medical intervention is determined by the levels of those attributes [13]. The relative importance of attributes and the trade-offs that respondents make between them can be assessed by offering a series of choices between two or more medical intervention alternatives with different combinations of attribute levels (see Table 1 for an example of a choice set) [14]. In comparison to other stated preference techniques, a DCE presents a reasonably straightforward task and one which more closely resembles a real-world decision, i.e. trading-off health and non-health outcomes [15].

Table 1: Example of choice set

Attributes	Programme A	Programme B	No vaccination
Degree of protection against cervical cancer	70%	90%	0%
Duration of protection	Lifetime	6 years	n.a.
Risk of serious side-effects	1:750,000	1:750,000	No risk
Age at vaccination	14 years	9 years	n.a.
Which vaccination programme do you prefer?	**A**	**B**	**None**

n.a. = not applicable

Attributes and attribute levels

We selected the most relevant HPV vaccination attributes and their levels based on the literature, interviews with experts in the field of HPV vaccination (n=8), and focus groups data (n=4; 36 parents participated (34 female and 2 male), aged 33 to 53 years with at least one child in the age of 8 to 14 years. We did not include girls in the focus groups, because at that time it was expected that the target group for HPV vaccination would be 9-year old girls, who are under Dutch law not allowed to decide themselves about the vaccination uptake). In the focus groups we collected data on the attributes that individuals expected to be important or that had been important in their decision to participate in an HPV vaccination programme. Experts were asked to comment on a list of attributes, which were derived from a literature review, and to rank them in order of importance. Based on these data we selected the five most important attributes as identified by both groups: 1) degree of protection against cervical cancer; 2) protection duration; 3) serious side-effects (e.g. hospitalization); 4) mild side-effects (e.g. nausea); and 5) age of vaccination. Attributes that were plausible and relevant both clinically and from a policy viewpoint were determined. A sufficiently wide range of levels was used to avoid respondents ignoring attributes because of too small differences in levels. The attributes and levels are presented in Table 2.

Table 2: Considered attributes and attribute levels for HPV vaccination

	Regression analysis	
Attributes and levels	**Coefficient**	**Attribute name**
Protection against cervical cancer	β_1	EFFECTIVENESS
50%		
70%		
90%		
Protection duration		
6 years (reference level)		
25 years	β_2	DURATION_25Y
Lifetime	β_3	DURATION_LIFETIME
Serious side effects		
1/750,000		
1/150,000	β_4	SERIOUS_1/150,000
1/30,000	β_5	SERIOUS_1/30,000
Mild side effects	β_6	MILD
1/50		
1/30		
1/10		
Age of vaccination		
At age 9 years (reference level)		
At age 12 years	β_7	AGE_12Y
At age 14 years	β_8	AGE_14Y

Study design and questionnaire

The combination of five attributes with three levels each resulted in 243 (3^5) hypothetical HPV vaccination alternatives. Since it is not feasible to present a single individual with all these alternatives (i.e. full factorial design), we generated a sample of alternatives from all these 243 alternatives (i.e., we used a fractional factorial design) by means of a catalogue, which contains a library of orthogonal arrays [16]. Fifty-four HPV vaccination alternatives proved sufficient to estimate all main effects and a number of two-way interactions between attributes in a regression analysis. In this fractional factorial design, attributes were independent of each other, thus guaranteeing orthogonality (i.e. the design was defined in such a way that the attributes could not represent the same facts), and attribute levels occurred with equal frequency, maintaining level balance [17]. Choice sets were designed using the discrete choice experiment software of Street and Burgess [18]. Our design, which contained 54 choice sets, had an efficiency of 82% compared with an optimal choice design. This means that our design was a near optimal design that counterbalanced statistical reasons and practical reasons (a higher amount of choice sets will result in a more precise estimation of the coefficients, however as a consequence (much) more respondents are needed). Choice sets consisted of two HPV vaccination alternatives and a 'no HPV vaccination' option to allow respondents to 'opt out' (Table 1); HPV vaccination is a preventive medical intervention and, as in real life, respondents are not obliged to opt for HPV vaccination. Respondents were asked to consider all three options in a choice set as realistic alternatives and to choose the option that appealed most to them. Presenting a single individual with a large amount of choice sets is expected to result in a lower response rate and/or lower response reliability [19-20]. To avoid this, we used a blocked design [14], which resulted in dividing the 54 choice sets over six types of questionnaires containing nine choice sets each.

Each questionnaire started with a detailed description of the attributes and their levels (the (complete) questionnaire is available from the authors on request). Pictures, graphs and pictograms were included to demonstrate percentages and rates. To assess the understanding of the attributes (protection levels against cervical cancer, levels of serious side effects, and levels of mild side-effects) the questionnaire contained a dominant choice set (rationality test). In this set one of two HPV vaccination alternatives was characterised by equal or logically preferable levels on all attributes.

The main part of each questionnaire comprised nine choice sets. Furthermore, the following data were collected: age at completing the questionnaire, level of education, religious affiliation, country of birth, parents' countries of birth, history of childhood vaccinations, and of vaccinations against HPV. To check the convergent validity of the DCE, respondents were asked to rank the five attributes of HPV vaccination from most impor-

tant to least important. The questionnaire was pilot tested to check for any problems in interpretation and face validity (n=16).

Study sample

A representative sample of 359 girls aged 12 to 16 years were randomly approached at 30 classes from four secondary schools and cities located in the north-east (rural area) and west part (urban area) of the Netherlands. This age range was chosen based on current Dutch policy guideline. Calculation of optimal sample sizes for estimating non-linear discrete choice models from DCE data is complicated as it depends on the true values of the unknown parameters estimated in the choice models [21]. Lancsar and Louviere [21] mentioned that one rarely requires more than 20 respondents per parameter to estimate reliable models; our DCE contained eight parameters in the main effects model (see Equation 1), which meant that we had to include at least 160 respondents. Taking into account a suboptimal response rate, and some two-way interactions between attributes, we aimed at having at least 300 questionnaires completed.

Procedure

Questionnaires were completed in the classroom or auditorium in the presence of a researcher or assistant. First, general information was given about HPV, cervical cancer, the causal link between them, HPV vaccinations, cervical cancer screening and the NIP (± 5 minutes). This was followed by an explanation of DCE questions (± 5 minutes). Subsequently, respondents completed the questionnaire on paper (± 20-30 minutes). The whole procedure lasted at most 45 minutes. Beforehand parents had received an information letter covering the purpose, voluntariness and anonymity of the study and an opt-out form. Approval for the study was obtained from the Medical Ethics Committee, Erasmus MC, University Medical Centre Rotterdam.

Statistical analyses

The DCE was analysed by taking each choice among the three options (two HPV vaccination alternatives, and a 'no HPV vaccination' alternative) as an observation, i.e. two 'no' and one 'yes'. The observations were analysed by a mixed logit regression model to take heterogeneity as well as correlation between the choice task completed by each individual into account [14]. After testing for linear continuous effects of one or more attributes, the following utility model was estimated:

$$V = \beta_0 + \beta_1 EFFECTIVENESS + \beta_2 DURATION\_25Y + \beta_3 DURATION\_LIFETIME + \beta_4 SERIOUS\_1/150{,}000 + \beta_5 SERIOUS\_1/30{,}000 + \beta_6 MILD + \beta_7 AGE\_12Y + \beta_8 AGE\_14Y \quad \text{(Eq. 1)}$$

V is the observable relative utility that is composed of the preference scores for the individual β-coefficients of the model. β_0 is a constant reflecting respondents' preference for receiving HPV vaccination relative to 'no HPV vaccination'. β_1-β_8 are coefficients of the attributes indicating the relative weight individuals place on a certain attribute(level). The statistical significance of a coefficient (p-value ≤0.05) indicates that individuals differentiated between one attribute (or attribute level) and another in making stated choices. A priori, we expected all attributes to be statistically significant. The sign of a coefficient reflects whether the attribute has a positive or negative effect on preference score. We expected that only the attribute 'mild' and the estimated attribute levels of 'serious side-effects' would have a negative effect (i.e., a negative sign).

The value of each coefficient represents the importance respondents assign to an attribute(level). However, different attributes utilise different units of measurement. For example, the coefficient for 'protection against cervical cancer' represents the importance per absolute 10% protection rate. When looking at an HPV vaccination that generates a 70% protection rate, the coefficient should be multiplied seven times (7 * coefficient of 'protection against cervical cancer' of 10% = coefficient of 'protection against cervical cancer' of 70%).

To explore the impact of respondents who failed the rationality test, sensitivity analyses were conducted by excluding such individuals from the sample and rerunning the analysis.[22-23] Also, two-way interactions were added to the main effects model to test which two-way interactions were significant and improved the fit of the modTo investigate the willingness of girls to trade-off protection against cervical cancer to achieve an improvement in one level of the other HPV vaccination attributes, we calculated the ratios between the coefficients of the attributes with protection against cervical cancer as the denominator. For example, $-\beta_6/\beta_1$ indicates how much protection against cervical cancer girls were willing to forego to get an HPV vaccination programme that had a five percent lower risk in mild side-effects.

Finally, choice probabilities were also calculated to provide a way to convey DCE results to decision makers that is more easily understandable.

The probability that an individual says "yes" to an HPV vaccination programme is equal to:

$$P = 1 / (1+e^{-V}) \quad \textit{(Eq. 2)}$$

where V is defined as in Equation 1. We calculated the choice probability (i.e. the mean uptake) for the base case. The base case used in this study represents an HPV vaccination programme at the age of 12 years, a 1/30 risk of mild side-effects, a 1/150,000 risk of serious side-effects; a protection duration of 6 years, and a 70% protection against cervical cancer. We presented these results in a 'tornado' graph [17] to illustrate the marginal effect of varying one attribute level at a time from the base case, holding all other attributes constant. This base was chosen to correspond i) with an HPV vaccination programme that contained most plausible levels based on literature, and ii) with the Dutch situation (HPV vaccination programme at the age of 12 years). The graph shows how each attribute systematically affects choices relative to the base case. Noteworthy, in the calculation of the mean uptake we took all heterogeneity into account as the mean uptake is not just equal to the uptake of someone with average coefficient values. Additionally, we calculated the minimum acceptable efficacy and maximum acceptable risk of mild side-effects, in which the base case HPV vaccination programme is preferred over no HPV vaccination (i.e. relative utility composed of the preference scores for the individual β-coefficients and standard deviations of the model is higher than zero).

RESULTS

Respondents

The response rate was 312/359 (87%). The respondents had a mean age of 13.3 years (SD=1.0). Of all respondents, 58% had at least one dose of HPV-vaccine, 62% had a higher secondary educational level, and 38% considered themselves to be religious (Table 3). Results of direct ranking showed that the protection against cervical cancer, the protection duration, and the risk of serious side-effects of HPV vaccination were considered the most important attributes of an HPV vaccination programme (Figure 1).

Table 3: Respondent characteristics

Characteristics	Respondents (n=312)	
	Mean	**(SD)**
Age (years)	13.3	(1.0)
	n	**(%)**
Educational level		
Lower secondary education	38	(12.2)
Intermediate secondary education	81	(26.0)
Higher secondary education	193	(61.9)
Religion		
None	191	(61.2)
Christian (incl. Catholic, Protestant)	104	(33.3)
Muslim	11	(3.5)
Other	4	(1.3)
Country of birth		
The Netherlands	293	(93.9)
Other (UK, France, Poland, Albania, Mexico, Aruba, Afghanistan, Pakistan, China, India, Iraq, Kazakhstan, Philippines)	15	(4.9)
Country of birth of parents		
Both parents in the Netherlands	256	(82.1)
One parent outside the Netherlands	23	(7.4)
Both parents outside the Netherlands	26	(8.3)
HPV vaccinated		
Yes	181	(58.0)
Vaccinated against childhood diseases		
Yes	259	(83.0)
No	5	(1.6)
Unknown	47	(15.1)

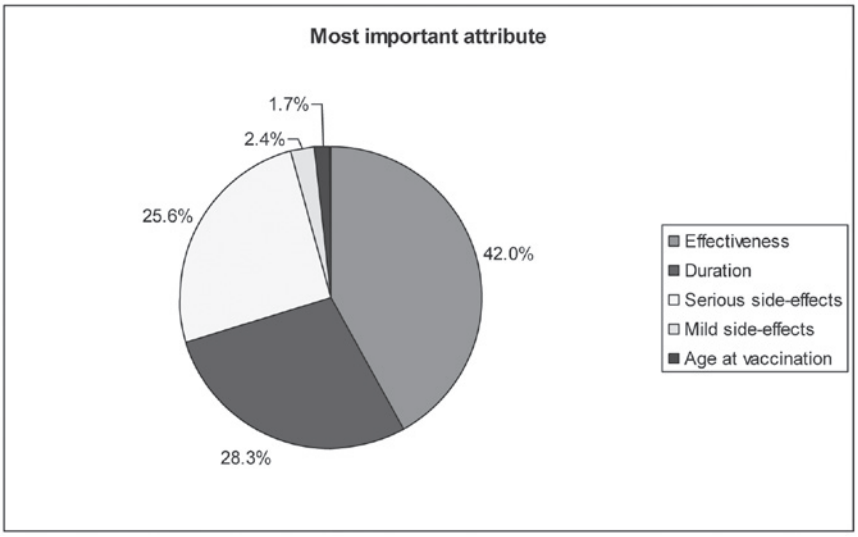


Figure 1: Most important vaccination characteristic based on direct ranking (n=290 respondents).

DCE results

The 'no HPV vaccination' option was chosen in 21.4% of the choice sets. Twenty-one out of 312 girls (6.7%) always chose the 'no HPV vaccination' option. All five vaccination characteristics proved to influence girls' preferences for HPV vaccination ($p<0.05$; Table 4). The positive or negative directions of the coefficients of the characteristics were consistent with our a priori hypotheses and showed, therefore, theoretical validity. The positive sign given to the coefficients 'degree of protection against cervical cancer' and 'protection duration' indicated that respondents preferred an HPV vaccination generating a higher degree of protection and a longer protection duration over an HPV vaccination that generates a lower degree of protection and a shorter protection duration. The negative signs for 'side-effects' indicate that girls preferred an HPV vaccination programme with low serious and low mild side-effects. The non-significant coefficient of the characteristic level 'vaccination at age 14 years' indicated that respondents did not significantly prefer this age of vaccination over a vaccination at age 9 years. However, respondents significantly preferred vaccination at age 12 years over vaccination at age 9 years. Most estimated standard deviations were significant, which indicated preference heterogeneity among girls for several characteristics of HPV vaccination.

The results of the sensitivity analyses indicated that i) excluding respondents who 'failed' the rationality test (2.6% of the respondents) had no relevant impact on the size or relative importance of the attributes, and ii) none of the two-way interactions were significant and improved the fit of the model (data not shown).

Comparing our DCE results with the results of the direct ranking in our questionnaire, both preference methods showed that protection against cervical cancer, protection duration, and risk of serious side-effects of HPV vaccination were considered the most important attributes of an HPV vaccination programme. These results support convergent validity of the DCE results.

Trade-offs

Based on the expressed preferences, girls showed their willingness to trade-off protection against cervical cancer to achieve an improvement in one level of the other HPV vaccination attributes (Table 5). On average, girls were willing to trade-off 38% protection against cervical cancer to obtain an HPV vaccination programme with a life-time protection duration instead of a protection duration of 6 years. Girls were willing to trade-off 17% protection against cervical cancer to obtain a vaccination with a risk of serious side effects of 1/750,000 instead of 1/150,000, 9% protection against cervical cancer to get an HPV vaccination that had a five percent lower risk in mild side-effects, and 7% protection against cervical cancer to get an HPV vaccination at age 12 years instead of age 9

Table 4: Girls' preferences for HPV vaccination

Attributes	Coefficient	Mixed logit		
		Value		(95% CI)
Constant (vaccination)	Mean	-0.28		(-0.92 to 0.36)
	S.D.	3.60	***	(3.03 to 4.17)
Protection against cervical cancer (per 10%)	Mean	0.64	***	(0.55 to 0.72)
	S.D.	0.36	***	(0.30 to 0.42)
Duration of protection 6 years (omitted)	Mean	-1.41	***	(-1.70 to -1.12)
	S.D.	0.88	***	(0.87 to 0.90)
Duration of protection 25 years	Mean	0.20	***	(0.08 to 0.33)
	S.D.	0.07		(-0.22 to 0.35)
Duration of protection lifetime	Mean	1.20	***	(1.03 to 1.37)
	S.D.	0.88	***	(0.71 to 1.05)
1/750,000 risk of serious side effects (omitted)	Mean	2.15	***	(1.89 to 2.40)
	S.D.	0.80	***	(0.78 to 0.83)
1/150,000 risk of serious side effects	Mean	-0.55	***	(-0.68 to -0.43)
	S.D.	0.18	*	(0.04 to 0.40)
1/30,000 risk of serious side effects	Mean	-1.60	***	(-1.78 to -1.42)
	S.D.	0.78	***	(0.56 to 1.01)
Mild side effects (per 5%)	Mean	-0.57	***	(-0.71 to -0.44)
	S.D.	0.50	***	(0.30 to 0.71)
Vaccination at age 9 years (omitted)	Mean	-0.24	***	(-0.37 to -0.11)
	S.D.	0.34	***	(0.32 to 0.35)
Vaccination at age 12 years	Mean	0.21	***	(0.09 to 0.33)
	S.D.	0.04		(-0.36 to 0.27)
Vaccination at age 14 years	Mean	0.03		(-0.08 to 0.14)
	S.D.	0.34	***	(0.18 to 0.49)
Number of responses			8,424	
Number of respondents			312	
Log-Likelihood			-1,735.60	

Notes: (1) Effects coded variables used for protection duration, serious side effects, and age at vaccination; (2) Normal distribution for random coefficients used on all attributes; (3) The value of the omitted term equals the negative sum of the coefficients of the included attributes; (4) *** denotes p<.01, **p<.05, *p<0.10 for statistical significance; (5) S.D. = standard deviation

Table 5: Girls' trade-offs between risk reduction and different aspects of a vaccination programme

	Girls		Interpretation note
	Were willing to forego protection against cervical cancer of ..(%; CI)		
Protection duration	37.8	(32.1 to 44.3)	..to get a vaccination with life-time protection instead of a protection duration of 6 years
Serious side effects	17.4	(13.4 to 22.0)	..to get a vaccination with a risk of serious side effects of 1/750,000 instead of 1/150,000
Mild side effects	9.0	(6.9 to 11.2)	..to get a vaccination with a 5% lower risk of mild side effects
Age of vaccination	6.6	(2.6 to 10.6)	..to get a vaccination at age 12 years instead of age 9 years

years. Considering the relative trade-off between the risk of mild and serious side effects, girls were willing to accept a 9.7% (7.1% to 13.2%) increased risk of mild side effects if the risk of serious side effects decreased from 1/150,000 to 1/750,000.

Expected uptake of HPV-vaccination

We found an expected uptake of the base case HPV vaccination programme (70% protection against cervical cancer, at age 12 years, 1/30 risk of mild side-effects, 1/150,000 risk of serious side-effects, and protection duration of 6 years) of approximately 77% (CI: 74-80%). Especially an increased risk of serious side-effects from 1/150,000 to 1/30,000, a life-time protection instead of a protection duration of 6 years, or a decrease in protection against cervical cancer from 70% to 50% had a relatively large impact on the average expected uptake (a decrease of 14.6%, an increase of 12.0%, and a decrease of 7.3%, respectively) (Figure 2). Assuming an HPV vaccination at age 12 years, a 1/30 risk of mild side-effects, a 1/150,000 risk of serious side-effects, and a protection duration of 6 years, the minimum efficiency of this HPV vaccination should be 15% to be preferred over no vaccination. Or assuming an HPV vaccination at age 12 years, a 1/150,000 risk of serious side-effects, a protection duration of 6 years, and a 70% protection rate against cervical cancer, the maximum risk for mild side effects should be 34% to be preferred over no vaccination.

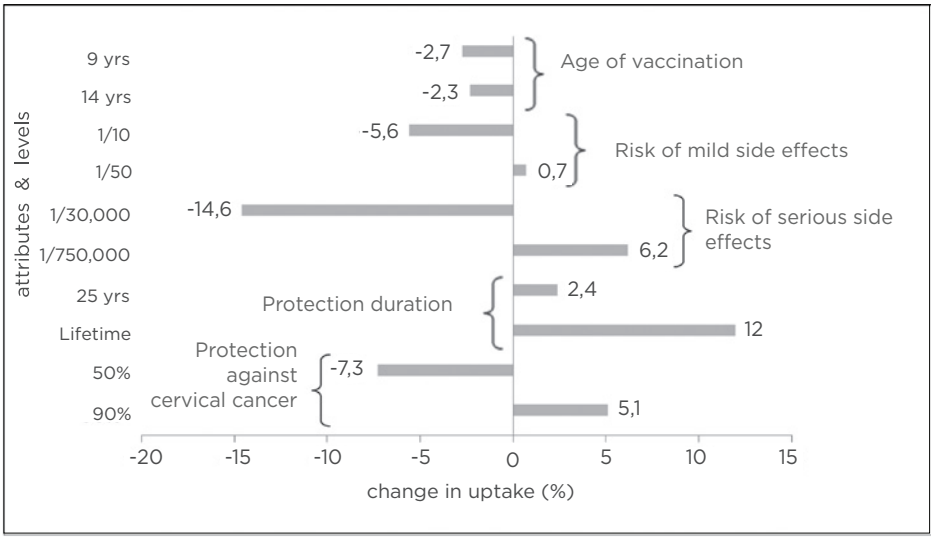


Figure 2: Univariate marginal estimates for predicted probability of participation; highest and lowest values for attributes level changes versus base case. The base case is an HPV vaccination at age 12 years, 1/30 risk of mild side-effects, 1/150,000 risk of serious side-effects; protection duration of 6 years and 70% protection against cervical cancer. This base case is indicated as zero change in the probability of the x-axis.

DISCUSSION

The present study shows that girls made a trade-off between vaccine characteristics. Degree of protection against cervical cancer, duration of protection, risk of serious side-effects (e.g. hospitalization), risk of mild side-effects (e.g. nausea), and age of vaccination, all proved to influence girls' preferences for HPV vaccination. On average, girls were willing to forego protection against cervical cancer if the protection duration of HPV vaccination was longer, or if the risk of serious or mild side-effects of HPV vaccination was lower. An increase in protection duration, an increase in risk of serious side-effects, or a decrease in degree of protection against cervical cancer had a relatively large impact on the average expected uptake.

There are no previous DCEs investigating how characteristics of HPV vaccination determine girls' preferences for participation in HPV vaccination. However, Dahlström et al. [24] investigated the attitudes to HPV vaccination among parents of children aged 12-15 years. They found that beliefs about vaccine safety and efficacy were strong correlates of willingness to vaccinate. Dempsey et al. [25], who investigated the reasons why mothers do or do not have their adolescent daughters vaccinated against HPV, concluded that addressing safety concerns may be one of the most useful targets for future interventions to increase HPV vaccine utilisation. Brown et al. [26], who estimated how features of HPV vaccines affect mothers' perceived benefit for daughters aged 13-17 years, showed that cervical cancer protection and duration of effectiveness were the most important attributes. All these results are in line with the findings of our study, which show that protection against cervical cancer, protection duration, and serious side-effects play an important role in girls' choices for HPV vaccination. In a vaccination context, Hall et al. [27] used a DCE to study the introduction of varicella vaccination. They showed that immunisation rates would increase in case of a lower incidence of mild and severe side-effects, which is similar to our study results.

The possibility to estimate the willingness to forego protection against cervical cancer is an additional advantage of DCE. However, in our opinion this additional advantage is limited. In the context of willingness to pay (WTP), earlier studies showed that the WTP derived from a DCE changed if a wider cost range was chosen [28], or that the WTP derived from an open-ended question differed from the WTP derived from a DCE [29]. This same phenomenon might be possible for the willingness to forego protection against cervical cancer derived from a DCE. Further research in this area is needed and, meanwhile, we recommend the interpretation of these absolute willingness values to forego protection against cervical cancer in a relative manner (i.e. ranking order).

Our results showed that the expected uptake of the base case HPV vaccination programme was much higher (76%) than the attendance rate in the first HPV vaccination round in the Netherlands in 2009 (49%) [30]. This 49% is also relatively low compared to

the Dutch National Immunisation Programme for protection against childhood infectious disease (>95%).[31] Possible clarifications are uncertainty about the degree of protection against cervical cancer, protection duration, and serious side-effects (all of which played the most important role in girls' preferences for HPV vaccination). To date, follow-up data on HPV vaccinated young women are available for 7.3 years [32-33].

The present study had several limitations. First, our sample contained a relatively large number of high educated respondents, which precludes generalisation of the findings to all girls. Second, we selected the most relevant attributes in our DCE using literature, interviews with experts in the field of HPV vaccination, and focus group data; however, this careful procedure does not guarantee that we included all attributes that are relevant to girls' preferences for HPV vaccination. Third, we did not include genital warts protection as an attribute of HPV vaccination as we did not receive signals that genital warts protection would play a role in the decision about HPV vaccination uptake, and as the Dutch vaccination programme offers only Cervarix, which provides no protection against HPV types causing warts. However, girls may well have a preference for HPV vaccines offering warts protection. Fourth, the inclusion of percentages and rates in our discrete choice experiment, especially the inclusions of small risk levels, might have caused difficulties with understanding the choice task. Finally, the current results should preferably be validated by comparing them with the actual behaviour of girls in an HPV vaccination programme.

In conclusion, this study shows that girls made trade-offs between protection against cervical cancer and other characteristics of HPV vaccination. Especially the degree of protection against cervical cancer, protection duration, and risk of serious side-effects influenced HPV vaccination preferences. We conclude that, uptake of HPV vaccination may change considerably if girls are supplied with new evidence-based information about the degree of protection against cervical cancer, the protection duration, and the risk of serious side-effects.

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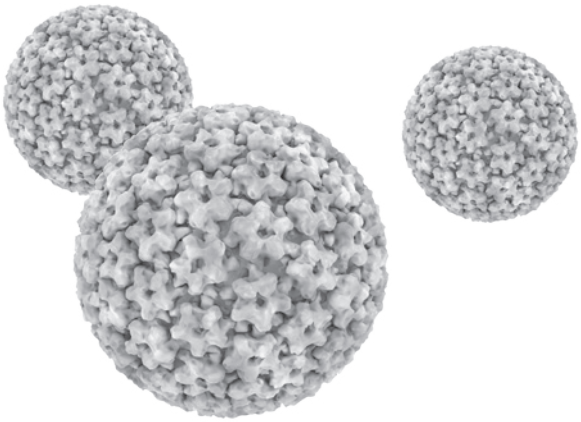

Chapter 6

Have preferences of girls' changed almost 3 years after the much debated start of the HPV vaccination program in the Netherlands? A discrete choice experiment

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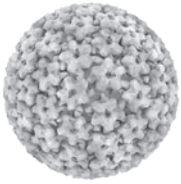

ABSTRACT

Objectives: To assess how girls' preferences have changed almost 3 years after the much debated start of the human papillomavirus (HPV) vaccination program.

Methods: A discrete choice experiment (DCE) was conducted among girls aged 11-15 years who were invited, or were not yet invited, to get vaccinated. A panel latent class model was used to determine girls' preferences for vaccination based on five characteristics: degree of protection against cervical cancer; duration of protection; risk of mild side-effects; age of vaccination; and the number of required doses of the vaccine.

Results: The response rate was 85% (500/592). Most girls preferred vaccination at age 14 years (instead of at age 9 years) and a 2-dose scheme (instead of the current 3-dose scheme). Girls were willing to trade-off 7% (CI: 3.2% to 10.8%) of the degree of protection to have 10% less risk of mild side-effects, and 4% (CI: 1.2% to 5.9%) to receive 2 doses instead of 3 doses. Latent class analyses showed that there was preference heterogeneity among girls, i.e. higher educated girls and HPV vaccinated girls had a higher probability to opt for HPV vaccination at a higher age than lower educated girls or non-vaccinated girls.

Conclusions: Three years after the start of HPV vaccination program the risk of mild side-effects and age at vaccination seem to have become less important. For the Dutch national immunization program, we recommend *not* to lower the current target age of 12 years. A 2-dose scheme may result in a higher uptake and we recommend that if this scheme is introduced, it needs to receive adequate publicity.

INTRODUCTION

Human Papillomavirus (HPV) infection is a necessary factor in the development of cervical cancer [1-2]. HPV types 16 and 18 are responsible for about 70% of all cervical cancers worldwide [3]. Preferably the HPV vaccine (which protects against those two types) is given prior to the initiation of sexual activity, because the degree of protection is reduced after HPV infection [4-6].

Many Western countries have included HPV vaccination in their immunization program. For example, the United Kingdom, Canada, Australia and the Netherlands offer the HPV vaccine to girls at an age between 11 and 14 years; in these countries, the uptake rates range from 50-80%. The willingness to accept HPV vaccination can largely be influenced by general preferences for healthcare interventions [7]. One way to assess preferences is to conduct a discrete choice experiment (DCE), in which people trade off risks and benefits among competing programs [8]. In the design of a DCE it is assumed that a healthcare intervention can be described by its characteristics (attributes) and that the levels of those attributes determine preferences for an intervention [9]. By offering a series of choices between two or more intervention alternatives with different combinations of attribute levels, the relative importance of attributes can be assessed [10]. Previous DCE studies about preferences for HPV vaccination showed that attributes such as the duration and degree of protection against cervical cancer were important among mothers of eligible girls [11], adults from the general public [12], and eligible girls [13].

In the Netherlands, the bivalent HPV vaccine is offered free of costs to 12-year-old girls by sending a personal invitation. These girls do not need their parents' permission when deciding about uptake. Since the introduction of the vaccine in the Netherlands in 2009, uptake rates increased from 52% in 2009 [14] to 59% in 2011 [15]. The introduction of the program coincided with an intensive societal debate involving politics, physicians, media, parents and girls, which may have resulted in uptake rates being lower than expected beforehand. During that period we carried out a DCE to assess girls' preferences for HPV vaccination [13]. We showed how girls made trade-offs between the degree of protection against cervical cancer, the duration of protection, the risk of serious side-effects (e.g. hospitalization), the risk of mild side-effects (e.g. nausea), and age of vaccination. Currently, almost 3 years later, although no serious side-effects have been linked to the vaccine, this has not resulted in a large increase in the vaccination rates.

Therefore, the present study assesses which attributes of HPV vaccination have influenced preferences for HPV vaccination uptake *after* the media debates have ended and in the absence of reports of serious side-effects. To our knowledge, this is the first study to compare preferences for HPV vaccination as expressed in DCEs. We will look at the differences in preferences as measured in 2009 versus 2011. This comparison may provide

insight into girls' motivation to be vaccinated or not, how this motivation can change over time, and how to improve dissemination of information about the vaccine.

METHODS

Attributes and attribute levels

The selection of HPV vaccination attributes and their levels was based on our previous study [13]. However, for the present study we excluded the attribute 'risk of serious side-effects' from the choice sets since no serious side-effects of the vaccine have been reported since its introduction in vaccination campaigns. The Centers for Disease Control and Prevention (CDC) state the following about the bivalent vaccine: the bivalent vaccine is safe, it has been in use around the world for several years and has been very safe. However, any medicine can potentially cause a serious problem, such as a severe allergic reaction. The risk of a vaccine causing a serious injury, or death, is extremely small. Life-threatening allergic reactions from vaccines are very rare [16]. Instead, we mentioned in the questionnaire that the risk of serious side-effects on the long term is unknown. We added the attribute 'number of doses of the vaccine', because less than the currently applied number of 3 doses is also likely to be effective [17].

The final set consisted of the following attributes: 1) the degree of protection against cervical cancer; 2) the duration of protection; 3) the risk of mild side-effects; 4) the age of vaccination; and 5) the number of doses of the vaccine (Table 1). The levels we used for degree of protection were 50%, 70% and 90%. It is assumed that the protection against cervical cancer is 70%, but since it takes 10 to 15 years for cervical cancer to develop it is not sure yet whether the protection indeed will be 70%. It might also be possible that the protection is lower or a new HPV vaccine will be available in the future that has an effectiveness of 90% [18]. Since to date, follow-up data on HPV vaccinated young women are available for 8.4 years, it is known that protection lasts at least 8 years, but it is unknown how long the duration of protection will be [19]. We therefore wanted to know girls' preferences for a duration of 8 years, 25 years and lifelong protection. The levels of the risk of mild side-effects were 1:30, 10:30 and 20:30, which were based on figures from the Centers for Disease Control and Prevention [20]. We choose 30 as the denominator, because many classes consist of 30 students and therefore girls could interpret the risk as 1, 10 or 20 students in their class suffering from mild side-effects. The side-effects were defined as: pain, itch, redness and swelling on the injection area; fever; headache; dizziness; nausea and fainting within 2 hours after vaccination. The risk of mild side-effects is not modifiable, but if for example girls put a lot of weight on this risk, information about the risk may highlight the short duration of the side-effects. Levels of the age of vaccina-

tion were 9, 12 and 14 years. If most girls will have a preference for 9 or 14 years instead of the current 12 years, it might be a possibility to broaden the age range at which girls are offered the vaccine for free. The levels of the number of doses of the vaccine were 2 and 3 doses. If for example most girls have a preference for 2 doses, then uptake may increase if 2 doses are used instead of 3.

Table 1: Attributes and levels for HPV vaccination included in the discrete choice experiment design.

Attributes	Levels
Degree of protection against cervical cancer (%)	50, 70, 90
Duration of protection (years)	8, 25, lifetime
Risk of mild side-effects	1:30, 10:30, 20:30
Age at vaccination (years)	9, 12, 14
Number of doses of the vaccine	2, 3

Study design

The combination of four attributes with three levels each, and one attribute with two levels, resulted in 162 (3^4x2^1) hypothetical HPV vaccination alternatives. We generated a subsample of these alternatives using priors available from De Bekker-Grob et al. [13] and a zero prior for the attribute 'number of doses' to generate an efficient design by maximizing D-efficiency (using Ngene software, version 1.1.1, http://www.choice-metrics.com/) [21]. Sixteen choice sets were constructed to be able to estimate all main effects. Choice sets consisted of two HPV vaccination alternatives and a 'no HPV vaccination' option to allow respondents to 'opt out' (Table 2).

Table 2: Choice set example

Attributes	Program A	Program B	No vaccination
Degree of protection against cervical cancer	70%	90%	0%
Duration of protection	Lifetime	8 years	n.a.
Risk of mild side-effects	10:30	20:30	No risk
Age at vaccination	12 years	12 years	n.a.
Number of doses of the vaccine	3	3	0
Which vaccination program do you prefer?	**A**	**B**	**None**

n.a. = not applicable

Study sample

Calculation of the optimal sample size for estimating discrete choice models from DCE data is complicated, as it depends on the true values of the unknown parameters estimated in the choice models [22]. Earlier studies have shown that sample sizes of 300-400 respondents are sufficient for reliable statistical analyses [23-24]. Therefore, first, we strived to collect at least 400 completed questionnaires. In order to do so, taking

into account an expected response rate of at least 80% [13], we recruited a representative sample of n=592 girls aged 11-15 years through four secondary schools in urban and rural areas in the Netherlands. Second, we checked a posteriori whether our sample size would be sufficient to find significant differences for each attribute (level) at a 5% level using the true values of the estimated parameters and NGene software (http://www.choice-metrics.com/).

Questionnaire

The first page of the questionnaire provided basic information about HPV vaccination. Next, respondents were asked to indicate per choice set which option appealed to them most. Pictographs were used to illustrate the percentages of the degree of protection and the risk of mild side-effects.

To assess respondents' understanding of the DCE task we included a dominant choice set as a rationality test. In this choice set age of vaccine administration was similar in both alternatives, while one alternative was characterized by logically preferable levels on all other attributes. Also we included four items on a 5-point Likert scale to evaluate whether respondents considered the DCE questions 'clear-unclear, 'difficult-easy', 'annoying-pleasant', and the number of questions as 'too many-not too many'. Convergent validity was checked by asking the respondents to rank the five attributes of HPV vaccination from most important to least important. This ranking is compared with the trade-offs respondents were willing to make between the degree of protection and the other attributes.

The questionnaire used in our 2009 study was pilot tested to check for face validity and for problems in interpretation (n = 16). Because the number of attributes are the same as in the present study and only the attribute 'risk of serious side-effects' is replaced with 'number of doses of the vaccine', we did not expect problems in interpretation and therefore did not pilot test the questionnaire of the present study.

Procedure

Respondents completed the questionnaire in the classroom or auditorium during school time. First, general information was given about HPV and vaccination and about the way DCE questions should be completed. Completion of the written questionnaire lasted about 20-30 min. Questionnaires were completed in November and December 2011.

Beforehand, girls' parents had received an information letter covering the purpose, the voluntary nature and anonymity of the study, and an opt-out form. Parents that did not want their daughter to participate could sign the opt-out form. Girls' parents who approved participation did not have to sign an informed consent form. The Medical Ethics

Committee of Erasmus MC, University Medical Center Rotterdam declared that this research (number MEC 2011-059) did not fell under the Medical Research Involving Human Subjects Act, because Participants were not subject to procedures or are required to follow rules of behavior.

Statistical analyses

The DCE was analyzed by taking each choice among the three options (two HPV vaccination options, and a 'no vaccination option') as an observation. The utility for "no vaccination" was normalized to zero: V(no vaccination) = 0. Using NLogit software (http://www.limdep.com/), the observations were analysed by a panel latent class model [25]. This model can be used to identify classes in the population, i.e., identifying different utility (preference) functions across unobserved subgroups. Class membership is latent in that each respondent belongs to each class up to a modelled probability and is not deterministically assigned by the analyst a priori. The model is flexible in that the probability that sampled respondents belong to a particular class can be linked to covariates (such as age, education, etc.), hence allowing for some understanding as to the make-up of the various class segments [26]. *Panel* latent class model means that the model accounts for the pseudo panel nature of the DCE data since each respondent completed 16 choice tasks. To determine the number of classes to impose on the model structure, we selected the model with the best fit based on the Akaike information criterion (AIC) [25].

We tested a number of different specifications for the utility (preference) function. After testing for linear continuous effects of the attributes, the following final specification of the utility model was estimated:

$$V_{|c} = \beta_{0|c} + \beta_{1|c}\,\text{EFFECTIVENESS} + \beta_{2|c}\,\text{DURATION\_25Y} + \beta_{3|c}\,\text{DURATION\_LIFETIME} + \beta_{4|c}\,\text{SIDE-EFFECTS} + \beta_{5|c}\,\text{AGE\_12Y} + \beta_{6|c}\,\text{AGE\_14Y} + \beta_{7|c}\,\text{NUMBER OF DOSES\_3} \quad \text{(Eq. 1)}$$

$V_{|c}$ represents the observable utility (preference score) that respondents belonging to class segment c have for an HPV vaccination. $\beta_{1|c\text{-}7|c}$ are class specific coefficients of the attributes indicating the relative weight individuals place on a certain attribute (level). The unobserved component, ε, is assumed to be independently and identically (IID) extreme value type 1 (EV1) distributed. In addition to the utility function, the final model allowed for several significant covariates ('respondent's history of HPV vaccination' and 'education') to enter into the class assignment model. Effects coded variables were used for protection of duration, age at vaccination, and doses of the vaccine. Degree of protection and risk of mild side-effects were coded as a linear term.

The statistical significance of a coefficient (p-value ≤0.05) indicates that conditional to belonging to a class, respondents differentiated between one attribute (or attribute level) and another in making stated choices about HPV vaccination programs. A priori, we expected all attributes to be significant. The sign of a coefficient reflects whether the attribute has a positive or negative effect on the preference score (utility). We expected that the attributes 'risk of mild-effects' and 'the number of doses of the vaccine' would have a negative effect. The value of each coefficient represents the relative importance respondents assign to an attribute level. Sensitivity analyses were conducted to explore the impact of excluding respondents who failed the rationality test by excluding their data from the sample and re-running the analysis [27-28].

In terms of the class assignment parameters, statistically significant parameter estimates indicate that the associate covariate (i.e. 'respondent's history of HPV vaccination' and 'education') can be used to help in understanding the different segments. For example, if the education parameter associated with a particular class in the assignment model is positive and significant, then this is indicative that people who have a higher educational level are more likely to belong to that particular class and, hence, have preferences associated with the utility function belonging to that class as given in Equation (1).

The trade-offs respondents were willing to make between the attributes were calculated by the ratios of the coefficients of the different attributes with the degree of protection as the denominator. These trade-offs were weighted by the probability that a respondent belongs to a given class. Confidence intervals were calculated in Excel using the Krinsky and Robb method [29]. The number of simulations was 65,000 (i.e., 130 Sobol draws x 500 respondents).

Since our 2009 study is a point of reference for this study, we compared the similarity of the present sample to the 2009 sample. Mann-Whitney U tests were used for continuous variables and Chi-square tests were used for categorical variables.

RESULTS

Respondents

The response rate was 85% (500/592). The mean age of the respondents was 12.9 years; most had a higher level of secondary education (38%) and no religious affiliation (68%). Of the respondents, 63% had already been invited to get vaccinated against HPV of whom 70% had opted for vaccination (Table 3). Compared to the 2009 sample, respondents in the present sample were younger (difference 0.4 years, p-value<0.01); more respondents had a lower or intermediate educational level and less girls had a higher educational level (p-value<0.01); and less respondents were vaccinated against HPV (p-value=0.045)

Table 3: Characteristics of the study respondents (n=500)

Characteristics		
	Mean	**(SD)**
Age (years)	12.9	(0.96)
range	11-15	
	N	**(%)**
Educational level		
Low	145	(29.1)
Intermediate	164	(32.9)
High	189	(38.0)
Religion		
None	338	(68.0)
Christian	124	(24.9)
Muslim	28	(5.6)
Other	7	(1.4)
Country of birth		
The Netherlands	472	(99.0)
Country of birth of parents		
Both parents in the Netherlands	385	(79.9)
One parent outside the Netherlands	42	(8.7)
Both parents outside the Netherlands	55	(11.4)
HPV vaccination		
Invited to get vaccinated against HPV	311	(62.7)
HPV vaccinated	220	(70.7)
Intention if not yet invited:		
Low	20	(10.9)
Neutral	31	(16.8)
High	133	(72.3)

DCE results

Based on the AIC criterion, three classes were identified (Table 4). The average class probabilities within the sampled population were 31.0%, 45.5% and 23.5% for latent class 1, 2 and 3, respectively. The probability to belong to a specific class depended on the respondent's level of secondary education and whether she has been vaccinated against HPV. Namely, girls attending higher levels of secondary education and HPV vaccinated girls had a higher chance to belong to latent class 3, than lower educated and non HPV vaccinated girls(Dutch secondary schools have different educational levels). Respondents belonging to latent class 3 preferred vaccination at age 12 years to age 9 years, which was not a significant preference for respondents who belong to latent class 1 and 2. Most of the estimated coefficients for each latent class had the expected sign and were significant in most cases (Table 4). Although all five HPV vaccination attributes significantly influenced girls' preferences, the preference heterogeneity was substantial. Respondents in all classes preferred a lower risk of mild side-effects and a higher degree

Table 4: Respondents' preferences for HPV vaccination based on a panel latent class model

	Latent Class 1	Latent Class 2	Latent Class 3
Attribute	Coeff.	Coeff.	Coeff.
Risk of mild side-effects (per 10%)	-0.49 ***	-0.41 ***	-0.30 ***
Degree of protection against cervical cancer (per 10%)	1.33 ***	0.40 ***	0.73 ***
Duration of protection:			
8 years (reference)	-0.50	-0.81	-0.89
25 years	0.84 ***	0.29 ***	-0.19 ***
Lifetime	-0.34 **	0.52 ***	1.07 ***
Age at vaccination:			
9 years (reference)	0.05	-0.29	-0.32
12 years	-0.12	-0.01	0.16 ***
14 years	0.07	0.30 ***	0.16 ***
Number of doses of the vaccine:			
2 doses (reference)	0.14	0.10	0.08
3 doses	-0.14 *	-0.10 ***	-0.08 **
Constant	-4.39 ***	1.73 ***	-4.98 ***
		Class probability model	
Constant	-0.0851	0.3705 **	-
Higher eduction	-0.0007 **	-0.0005 *	-
Vaccinated	-0.0005 *	-0.0005 *	-
		Class probability (%)	
Average class probability	31.0	45.5	23.5
		Model fits	
Log-likelihood		-4.545.47	
Pseudo R-squared		0.481	

Notes: (1) ***, **, * denotes significance at 1%, 5%, and 10%, respectively; (2) Effects coded variables used for protection duration, age at vaccination, and doses of the vaccine; (3) Coeff. = coefficient; (4) number of observations =7,976

of protection to a higher risk and a lower degree of protection; they also preferred 25 years of protection to 8 years of protection. Respondents belonging to class 1 preferred 25 years of protection to 8 years of protection, rather than lifetime protection to 8 years of protection. Respondents who belong to latent class 2 and 3 preferred 2 doses to 3 doses, and preferred vaccination at 14 years rather than at 9 years, whereas respondents belonging to latent class 1 showed no significant preference for the number of doses or the age of vaccination. Sensitivity analyses showed that excluding the data of ten out of 500 respondents (2%) who 'failed' the rationality test had no relevant impact on the size or relative importance of the attributes.

Trade-offs

Overall, respondents were willing to trade-off 7% (CI: 3.2% to 10.8%) of the degree of protection to have a 10% less risk of mild side-effects. To obtain protection against HPV

for 25 years instead of 8 years, they were willing to trade-off 18% (CI: 8.6% to 29.6%), and to obtain lifetime protection instead of 8 years of protection, they were willing to trade-off 21% (CI: -0.1% to 37.2%). Respondents were willing to trade-off 4% (CI: 1.2% to 5.9%) to receive 2 doses instead of 3 doses. To get a vaccination at age 12 or 14 years, instead of at 9 years, respondents were willing to trade-off 4% (CI: -2.4% to 8.6%) and 8% (CI: -0.6% to 16.7%), respectively (Table 5).

DCE rationality

The dominant choice set was answered correctly by 490/500 (98%) of the respondents; 83 respondents completed the ranking test incorrectly (e.g. giving the same rank to multiple attributes) and were excluded from this ranking analyses. The most important attributes according to the ranking test were: the degree of protection (70%); the duration of protection (17%); the risk of mild side-effects (8%); the number of doses (4%); and the age of vaccination (2%) (n=407). The trade-offs respondents were willing to make between the degree of protection and the other attributes indicated the following order of importance of attributes: duration of protection, followed by the risk of mild side-effects, the number of doses of the vaccine, and age at vaccination (Table 5). Thus, the ranking test supports the convergent validity of the DCE results.

The mean evaluations of the DCE questions were (range 1-5): 'unclear-clear' (M=3.48, SD=1.14), 'difficult-easy' (M=3.53, SD=1.14), 'annoying-pleasant' (M=2.82, SD=1.01), and 'too many questions-not too many questions' (M=2.56, SD=0.93).

Table 5: Respondents' trade-offs between degree of protection versus various aspects of a vaccination program as used in the present study

Change in levels	Willingness to trade degree of protection % (CI)	
Per 10% less **risk of mild side-effects**	6.7	(3.2 to 10.8)
A **protection duration** of 25 years instead of 8 years	17.8	(8.6 to 29.6)
A lifetime **protection** instead of 8 years	21.4	(-0.1 to 37.2)
A vaccination at **age** 12 years instead of 9 years	4.4	(-2.4 to 8.6)
A vaccination at **age** 14 years instead of 9 years	8.2	(-0.6 to 16.7)
A vaccination program consisting of 2 instead of 3 **doses**	3.5	(1.2 to 5.9)

Note: CI = 95% confidence interval based on the Krinsky Robb method adjusted for class probabilities

DISCUSSION

We used a DCE to determine girls' preferences for HPV vaccination almost 3 years after the much debated start of the HPV vaccination program. Overall, girls were willing to trade-off 18% of the degree of protection to obtain a vaccination with 25 years protection instead of 8 years protection, and trade-off 7% to have a 10% less risk of mild side-effects. To receive 2 doses of the vaccine instead of 3 doses, they were willing to trade-off 4% of the degree of protection. Furthermore, it appeared that higher educated girls and HPV vaccinated girls have a higher probability to opt for HPV vaccination if it is offered at age 12 years instead of at age 9 years, than girls with lower education levels or girls who were not vaccinated.

When comparing these reported trade-offs with those of our previous study in 2009 [13], the changes are not substantial. The risk of mild side-effects became less important: in 2011 girls were willing to trade off 7% of the degree of protection (CI: 3.2% to 10.8%) to obtain a 10% less risk of mild side-effects, while in 2009 they were willing to trade-off 18% (CI: 13.8% to 22.4%). Also, it became less important to obtain lifetime protection instead of 8 years (in 2011) or 6 years protection (in 2009), as this trade-off was no longer significant in 2011 (21%, CI: -0.1% to 37.2%) whereas it was in 2009 (38%, CI 32.1% to 44.3%). Also, age of vaccination at 12 years instead of at 9 years was no longer significant in 2011 (2011: 4%, CI: -2.4% to 8.6%; 2009: 7%, CI: 2.6% to 10.6%).

In summary, almost 3 years after initiation of the HPV vaccination campaign on the Netherlands, the risk of mild side-effects and age at vaccination seem to have become less important. Potentially, the girls had a better idea about which mild side-effects to expect and were less concerned about them. Also, the importance of the degree of protection may have gained value for the girls. The age of vaccination might be less of an issue in 2011 given the longer duration of protection, i.e. 8 years in 2011 compared with 6 years in 2009.

There was preference heterogeneity among the girls, i.e. higher educated girls and HPV vaccinated girls have a higher probability to opt for HPV vaccination if it is offered at age 12 years instead of at age 9 years, than girls with lower education levels or girls who were not vaccinated. Furthermore, the majority of girls (including higher educated girls and HPV vaccinated girls) also preferred vaccination at age 14 years to vaccination at age 9 years. In other words, most girls did not prefer vaccination at the age of 9 years. Overall, girls were willing to trade-off 3.5% of the degree of protection to receive 2 doses instead of 3 doses, and most girls also preferred a 2-dose scheme to the current 3-dose scheme. Recently, the Netherlands National Institute for Public Health and the Environment decided that a 2-dose scheme will be introduced, because 2 doses are found to provide as much protection as 3 doses as long as the vaccination is given before girls turn 15 years of age [30-31]. Since we showed that girls preferred a 2-dose scheme, this new strategy

may result in a higher vaccination uptake. We want to stress that this revised vaccination program needs to receive adequate publicity. Surprisingly, it seems that some girls preferred 25 years of protection to lifetime protection. The concept of 'lifetime' might be too vague for these young girls and they may be unable to correctly judge its value; a protection period of 25 years might be interpreted by them as a very long period and it may sound more 'concrete'.

A strength of the present study is the large number of respondents (n=500) and the high response rate (85%). A limitation might be that we did not include protection against genital warts as an attribute.

In conclusion, this study shows that, almost 3 years after the much debated start of the HPV vaccination program in the Netherlands, trade-offs that girls are willing to make have not changed substantially. The risk of mild side-effects and age at vaccination still influenced the girls' preferences, but seem to have become less important. This study shows that there was preference heterogeneity among the girls, with higher educated girls and HPV vaccinated girls having a higher probability to opt for HPV vaccination at a higher age, than girls with lower education levels or girls who were not vaccinated. Also, since most of the girls preferred vaccination at age 14 years to vaccination at age 9 years, we recommend not to lower the current target age of 12 years in national immunization program in countries such as the Netherlands, Denmark, Sweden, Norway and United Kingdom. We also recommend to introduce a 2-dose scheme (instead of the current 3-dose scheme), because the girls are far from indifferent to the choice between 2 and 3-dose scheme.

Authors' contributions

IJK and MB conceived the idea for the study. IJK supervised the execution of the study; EWBG, RH, IJK, MB, and JHR designed the questionnaire; RH was responsible for the recruitment of the sample; RH and EWBG were responsible for the database design and data entry; EWBG performed the statistical design and analyses; all authors contributed to the interpretation of the data; RH drafted the report. All authors revised the article critically and approved the final version to be published.

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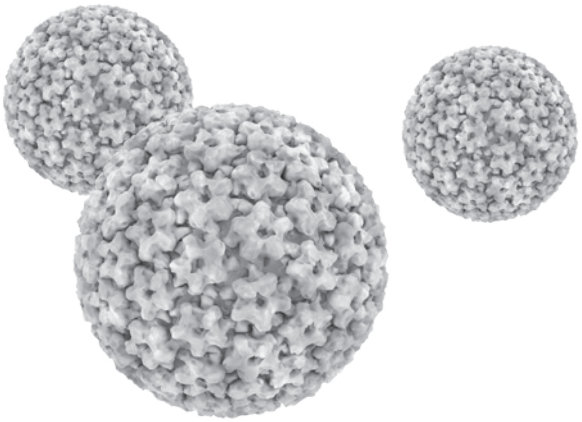

Chapter 7

Increasing girls' knowledge about human papillomavirus vaccination with a pretest and a national leaflet: a quasi-experimental study

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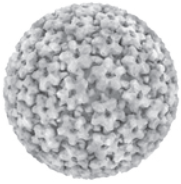

ABSTRACT

Background: Adolescent girls are at an age to be involved in the decision about HPV vaccination uptake and therefore need adequate information about the vaccination. This study assesses to what extent reading an official information leaflet about HPV contributes to girls' knowledge levels, and to what extent an increase in knowledge is boosted by a pre-test measurement.

Methods: Participants (girls aged 11-14 years) were systematically allocated to group A that completed a pre-test measurement (12 true/false statements) or to group B that did not complete it. Subsequently, both groups read the HPV leaflet and completed the post-test measurement.

Results: The response rate was 237/287 (83%). Pre-test scores in group A (M=3.6, *SD*=1.81, $p<0.001$) were lower than post-test mean knowledge scores (0-10) in group B (M=4.6, *SD*=2.05). Post-test knowledge scores in group A were higher than those in group B [6.2 (*SD*=2.06) versus 4.6 (*SD*=2.05), $p<0.001$]. In the post-test measurement, about a third of both groups knew that vaccinations do not give 100% protection against cervical cancer and that the duration of protection is unknown.

Conclusions: Reading the information leaflet had a positive effect on knowledge, even more so when boosted by a pre-test measurement. However, knowledge on the degree and duration of protection against cervical cancer remained limited. Focusing girls' attention on important aspects before they start reading the leaflet (e.g. by including a quiz on the first page) may serve to raise their awareness of these aspects.

BACKGROUND

Young adolescent girls are at an age to be involved in decisions about vaccination uptake. Countries like the United Kingdom, Canada, Australia and the Netherlands offer human papillomavirus (HPV) vaccine to girls at an age between 11 and 14 years. Girls need access to adequate information about HPV and the vaccination to be well informed about the risks/benefits of the vaccination. However, decisions about uptake are often made without sufficient information (1). It is important that girls know, for example, that: HPV is transmitted through sexual activity and has a lifetime risk of 75-80% (2-3); that although HPV infections are common, most infections clear within 2 years (4-5); that an HPV infection is a necessary factor in the development of cervical cancer (6); and that the vaccine does not provide full protection against HPV infections (it does protect against HPV 16 and 18 which are responsible for 71% of all cervical cancers (7)). Furthermore, a positive association has been found between knowledge on HPV and uptake (8-9).

Although knowledge on vaccine has been assessed among women (10-12) and adolescents (13), the impact of official information leaflets on knowledge among young adolescents has not yet been examined. This study assesses i) the extent to which girls' knowledge levels about HPV vaccination increase after reading the official leaflet that all girls in the Netherlands receive prior to the vaccination offer, and ii) to what extent an increase in knowledge may be boosted by a pre-test measurement.

METHODS

Participants

Girls aged 11-14 years were recruited from three secondary public schools (state funded: one urban, two rural), whilst attending their first year there. One of the authors (PAWHS) approached schools in different regions by telephone and asked if they were willing to cooperate. The number of participants was based on feasibility; however, a post-hoc power analysis showed that the power was 0.992.

Design

In the Netherlands girls are offered the bivalent vaccine against HPV. All girls eligible for HPV vaccination receive an information leaflet about HPV and vaccination characteristics, sent by mail to their home address by the municipal health service. The leaflet includes information on how HPV is spread, the incidence of cervical cancer, the degree/duration of protection of the vaccine, the risk and symptoms of mild side-effects, and the need of a

pap smear in both vaccinated and unvaccinated women. To assess girls' knowledge levels about HPV and HPV vaccination after reading this information leaflet, we asked girls to read the leaflet (in their classroom) and to then complete a post-test measurement.

To assess the increase in girls' knowledge levels about HPV vaccination, we needed to know the pre-reading knowledge levels and introduced a pre-test measurement. Since we acknowledged that a pre-test measurement could prompt more attentive reading of the leaflet and boost knowledge increase, a second group was introduced that did not complete a pre-test measurement. This resulted in the following design with equal numbers in both groups: girls present in the classroom were assigned to either group A (seated at one side of the classroom) which completed a pre-test measurement, then read the leaflet and immediately completed a post-test measurement; or group B (seated at the other side of the classroom) which read the leaflet and then completed the post-test measurement. There was no follow-up time between completing all the measurements and reading the leaflet.

To assess to what extent the girls' knowledge levels about HPV vaccination increased after reading the leaflet, we compared knowledge scores of the pre-test measurement of group A with the post-test measurement of group B (Figure 1), assuming that the demographic characteristics of group A and B were similar. We hypothesized that the total knowledge score would increase after reading the leaflet.

To assess the effect of a pre-test measurement, prompting more attentive reading of the leaflet and boosting knowledge increase, we compared the post-test measurements of group A and B (Figure 1). We hypothesized that, after reading the leaflet, the total knowledge score of group A would be higher than that of group B.

It should be noted that in addressing the first research question the pre-test measurement serves as an assessment and the leaflet is interpreted as the intervention, whereas in addressing the second research question the pre-test measurement and the leaflet combined serve as the intervention (Figure 1).

Procedure

The study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Erasmus MC (MEC-2010-328). The parents of potentially participating girls received an information letter about the study and an opt-out form. Questionnaires were completed in December 2010 and January 2011 and were distributed to participants in their classrooms. A brief introduction was given on the process of completing questionnaires and reading the leaflet. Completion and reading together took 25-40 min.

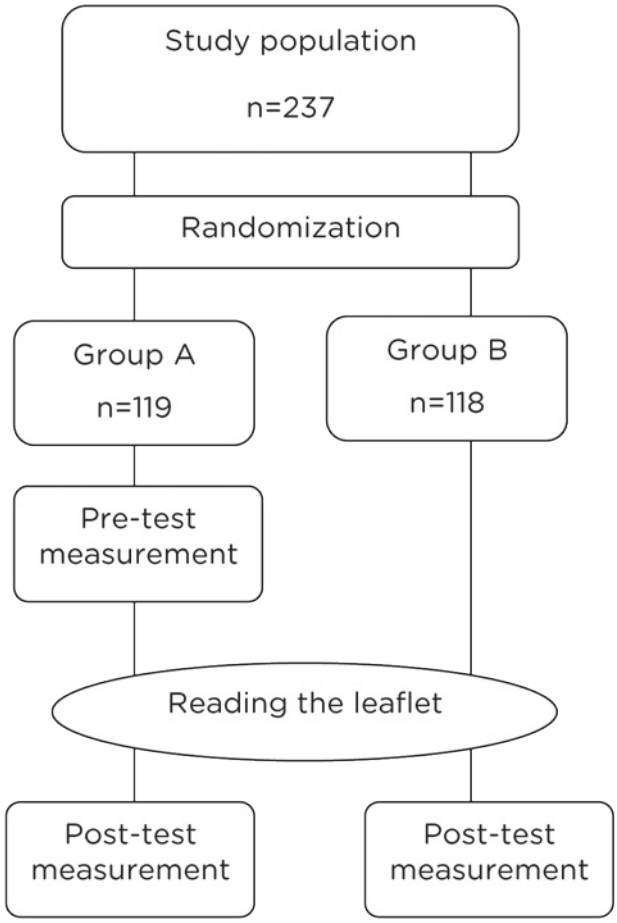

Figure 1 - Study design in answering the two research questions

Questionnaire

The self-administered questionnaire assessed knowledge on HPV vaccination and demographic characteristics. Before presenting the questionnaire to the study population, it was piloted among three age-matched children and one teacher to evaluate its comprehensibility. Knowledge was assessed through 12 statements (Table 2). We considered eight of these statements to be essential aspects of vaccination, such as the degree/duration of protection against HPV through vaccination, and transmission of the virus. The remaining four items addressed details of the HPV vaccination, such as costs of vaccination and permission for vaccination. The correct answer to each statement could

be found in the leaflet. Answer options were 'absolutely true', 'possibly true', 'possibly not true' and 'absolutely not true'. We choose this response system to be able to assess respondents' uncertainty about their answers and to assess knowledge increase at a detailed level, i.e. the percentage of respondents in group A who were not sure about their answer before reading the leaflet (marked possibly true or not true) and were sure about the correct answer after reading the leaflet (marked 'absolutely true or not true') (Table 2). If a statement was true the following points were assigned: absolutely true: 1 point, possibly true: 0 points, possibly not true: 0 points, and absolutely not true: 0 points. If a statement was not true, then the following points were assigned: absolutely not true: 1 point, possibly not true: 0 points, possibly true: 0 points, and absolutely true: 0 points. To facilitate interpretation of the total knowledge score, results were transformed to a 0-10 scale.

In addition, we asked girls if they were already vaccinated against HPV. If girls had not been vaccinated, we addressed their intention to get vaccinated against HPV on a 10-point Likert scale (1=definitely not, 10=definitely) with the following question: 'Do you intend to get vaccinated against HPV?'

Analyses

First, to assess whether knowledge on HPV vaccination increased after reading the leaflet, an independent samples t-test was used to analyse the difference in total knowledge scores between the pre-test measurement of group A and the post-test measurement of group B. Second, to assess to what extent an increase in knowledge was boosted by a pre-test measurement, an independent samples t-test was used to assess differences in total knowledge scores between the post-test measurements of group A and B. We assumed that pre-test knowledge levels would be similar in both groups. Cohen's effect sizes were calculated (14). Third, Chi-square tests were used to assess whether the number of correct answers per statement differed significantly between the pre-test measurement of group A and the post-test measurement of group B, and between the post-test measurements of both groups (Table 2). Differences between group A and B in background variables were assessed using Mann-Whitney U tests for continuous variables and Chi-square tests for categorical variables.

RESULTS

Participants

The response rate was 237/287 (83%). Non-participation was due to absenteeism from school or lack of parental consent to participate. The mean age of the participants was 12.2 (*SD* group A=0.50, *SD* group B=0.45) years and almost all participants were born in the Netherlands (group A: 96.6%; group B: 94.9%). The majority of participants had high (group A: 41.2%; group B: 39.0%) or intermediate (group A: 34.4%; group B: 39.0%) educational level (Dutch schools have different educational levels within a school year). About half of the participants stated they had a religious affiliation (group A: 55.6%; group B: 50%). Group A and B showed no significant differences regarding demographic characteristics and HPV vaccination history (Table 1).

Table 1 – Characteristics of the study participants

Characteristics	**Group A (n=119)**		**Group B (n=118)**		**p-value**
	Mean	(SD)	Mean	(SD)	
Age (years)	(12.2)	(0.50)	(12.2)	(0.45)	0.82
Age range (years)	11-14		11-13		
	n	(%)	n	(%)	
Educational level					0.76
Low	29	(24.4)	26	(22.0)	
Intermediate	41	(34.4)	46	(39.0)	
High	49	(41.2)	46	(39.0)	
Religion					0.40
None	52	(44.4)	59	(50.0)	
Christian	64	(54.7)	56	(47.5)	
Islam	1	(0.9)	1	(0.8)	
Other	0	(0.0)	2	(1.7)	
Country of birth of participants					0.74
The Netherlands	115	(96.6)	112	(94.9)	
Country of birth of parents					0.75
Both parents born in the Netherlands	102	(86.4)	97	(86.6)	
One parent born outside the Netherlands	9	(7.6)	9	(8.0)	
Both parents born outside the Netherlands	7	(5.9)	6	(5.4)	
HPV vaccinated before completion of questionnaire					
Yes	22	(18.5)	17	(14.5)	0.52
Intention if not vaccinated					0.26
Low	12	(12.5)	21	(21)	
Neutral	18	(18.8)	19	(19)	
High	66	(68.7)	60	(60)	

Note: Group A and B had no significant differences regarding demographic characteristics and HPV vaccination history

Comparison of knowledge scores before and after reading the leaflet

For these analyses, total knowledge scores of the pre-test measurement of group A (n=119) were compared with the scores of the post-test measurement of group B (n=118). As hypothesized, we found that total knowledge scores were significantly lower in group A before reading the leaflet (M=3.6, SD=1.81) than in group B that completed the questionnaire after (M=4.6, SD=2.05) reading the leaflet, t(235)=-3.941, $p<0.001$. Cohen's effect size was 0.52, indicating a moderate effect (14). Figure 2 shows the distribution of correct answers per knowledge statement about HPV and cervical cancer.

The number of correct answers to 5 of 12 statements was significantly lower in group A (n=119) before reading the leaflet than in group B (n=118) after reading the leaflet. For instance, statement 2 about safe sex and infection [group A: 25/119 (21.0%), group B:

Table 2 - Comparison of knowledge scores between group A and group B and within group A

No	Statement	Pre-test group A vs. post-test group B	Post-test group A vs. post-test group B	Group A: 'almost correct' at pre-test to 'absolutely correct' at post-test
		p-value		n (%)
1	HPV vaccinations completely protect against cervical cancer *(false)*.	0.003[1a]	0.169	9 (7.6)
2	Even if you only have safe sex you can be infected with HPV *(true)*.	0.001[1a]	0.079	32 (26.9)
3	All 12-year-old girls will be sent an invitation for HPV vaccinations without having to ask for it *(true)*.	0.851	0.007[2]	18 (15.1)
4	Legally, parents need to give permission for HPV vaccinations in 12-year-olds *(false)*.	<0.001[1a]	0.054	8 (6.7)
5	In spite of HPV vaccinations, Pap-smears from age ≥ 30 years are still recommended *(true)*.	<0.001[1a]	<0.001[2]	62 (52.1)
6	You can only have a Pap smear if you have first had HPV vaccinations *(false)*.	0.148	0.003[2]	16 (13.4)
7	HPV vaccinations can make you lose your hair *(false)*.	<0.001[1a]	0.013[2]	40 (33.6)
8	If you have been sexually active HPV vaccinations are still advised *(true)*.	0.265	0.002[2]	37 (31.1)
9	HPV vaccinations reduce the risk of getting cervical cancer *(true)*.	0.006[1b]	<0.001[2]	18 (15.1)
10	We know for a fact that HPV vaccinations protect against cervical cancer for a lifetime *(false)*.	0.175	0.319	18 (15.1)
11	HPV vaccinations reduce the risk of dying of cervical cancer *(true)*.	0.456	<0.001[2]	26 (21.8)
12	HPV vaccinations require several hundred dollars out-of-pocket expenses *(false)*.	0.131	0.999	21 (17.6)

[1a] *Percentage of correct answers in the post-test measurement in group B was significantly higher compared to the pre-test measurement in group A*

[1b] *Percentage of correct answers in the post-test measurement in group B was significantly lower compared to the pre-test measurement in group A*

[2] *Percentage of correct answers in the post-test measurement in group A was significantly higher compared to the post-test measurement in group B*

50/118 (42.4%); p=0.001], statement 1 about incomplete protection against cervical cancer [group A: 12/119 (10.1%), group B: 30/118 (25.4%); p=0.003], and statement 10 about unknown duration of protection against cervical cancer [group A: 18/119 (15.1%), group B: 27/118 (22.9%); p=0.175]. However, statement 9 about the risk reduction of getting cervical cancer after being vaccinated was answered correctly less often by group B after reading the leaflet than by group A before reading the leaflet (pre: 78.2%, post: 61.0%; p=0.006) (Figure 2) (Table 2).

We assessed the number of respondents in group A who had an 'almost correct' answer before reading the leaflet and an 'absolutely correct' answer after reading the leaflet. Respondents were most reassured by the leaflet about the correct answer considering the following statements: statement 5 about the recommendation of pap smears in spite of HPV vaccination 62/119 (52.1%); statement 7 about hair loss after vaccination 40/119 (33.6%); and statement 8 about sexual activity and vaccination 37/119 (31.1%) (Table 2).

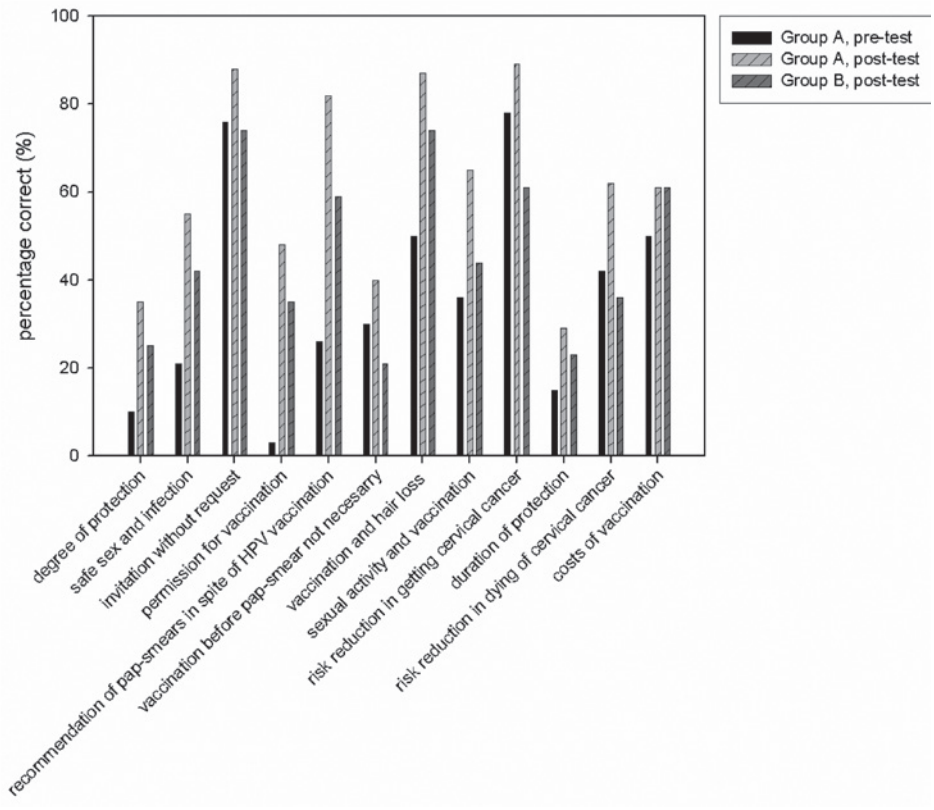

Figure 2 - Percentage of correct answers to the statements made by group A and B

Influence of pre-test measurement on knowledge scores at post-test measurement

Comparing knowledge scores of both post-tests between group A and B showed, as hypothesized, that group A (n=119) (M=6.2, SD=2.06) had a significantly higher total knowledge score at the post-test measurement than group B (n=118) (M=4.6, SD=2.05), $t(235)=5.805$, $p<0.001$). Cohen's effect size was 0.78, indicating a moderate effect (14). After completing a pre-test measurement and reading the leaflet (group A), the number of correct answers to 7 of 12 statements was significantly larger than after reading the leaflet only (group B) (Table 2).

DISCUSSION

This study examined the knowledge among girls aged 11-14 years about HPV and vaccination, and the extent of increase in knowledge after reading the official HPV vaccination leaflet used in the Dutch national immunization program. Firstly, total knowledge scores were higher after reading the information leaflet and we conclude that reading it had a positive effect on the knowledge levels of the girls. Secondly, post-leaflet total knowledge scores were higher in girls who had also completed the questionnaire *before* reading the leaflet and we conclude that completing this questionnaire had a positive effect on the knowledge levels.

Inclusion of a second group that did not complete a pre-test allowed to assess the effect of a pre-test measurement on knowledge scores. The characteristics of both groups were similar, indicating that systematically dividing the girls into two groups worked well and the groups were comparable. The higher post-leaflet knowledge scores in girls who had also completed the questionnaire before reading the leaflet are probably due to the girls' attention being prompted by the statements in the questionnaire, and their increased awareness of the knowledge they were supposed to have at the post-test measurement. This may have led to more attentive reading of the leaflet and thus being able to answer more statements correctly. Such a booster effect of a pre-test measurement, in fact acting as an intervention, is called the mere measurement effect (15). This effect was also found in a study among novice blood donors; people who completed a questionnaire about blood donation were more willing to give blood than those who had not completed a questionnaire (15).

The percentage of correct answers to some statements largely increased from a low percentage before reading the leaflet to a high percentage after reading the leaflet, e.g. the statements about whether girls need permission from their parents to get vaccinated and that, despite HPV vaccinations, pap smears are still recommended. The leaflet had a

positive effect on increased knowledge scores after reading it. Because some statements were already answered correctly by most girls before reading the leaflet, there was less room for improvement in knowledge. Surprisingly, knowledge on the degree/duration of protection against cervical cancer was low before reading the leaflet and remained relatively low after reading it. For instance, about 75% of the girls incorrectly thought that vaccination completely protects against cervical cancer and that protection lasts a lifetime. For optimal benefit from HPV vaccination, girls need to know that booster vaccinations might be needed in the future and that other preventive measures, such as screening, are still recommended. We advise additional education about the recommendation to participate in cervical cancer screening also after HPV vaccination. The group who completed the statements before *and* after reading the leaflet had better knowledge scores at the post-test measurement regarding all statements. With the exception of one statement, knowledge on the risk reduction of getting cervical cancer after HPV vaccination was worse *after* reading the leaflet in one group than before reading the leaflet in the other group. A possible explanation for this might be that girls who completed the pre-test measurement were better informed about HPV vaccination before completing the pre-test and reading the leaflet; however, their knowledge on this item increased after reading the leaflet. For this reason, we suggest that this specific item be thoroughly revised when the leaflet is e.g. updated.

We acknowledge that it is preferable to use larger groups, and to randomise in a more sophisticated way than simply dividing one side of the classroom from the other. Overall, to improve girls' understanding of the purpose of vaccination and the degree/duration of protection against cervical cancer, we recommend that information be unambiguous and that the key points should be clearly outlined on a prioritized list (16). This can be achieved by, e.g., editing or improving the current leaflet, or offering information on these important aspects at school or other relevant locations.

A limitation is that we only have data on the girls' intention to have (or not have) the vaccination, and lack information on the actual decision about uptake. Strengths of the study are its external validity: the use of an official leaflet which is sent to every 12-year-old girl in the Netherlands, the high response rate (83%), and the fact that the leaflet addresses a choice that participants have to make in real life. However, reading the leaflet at school is different from reading it at home and, due to non-probability sampling, the results may not represent the entire population.

Conclusion

This study shows that reading the information leaflet had a positive effect on girls' knowledge about HPV, which showed a further increase when boosted by a pre-test measurement. However, levels of knowledge regarding the degree/duration of protection against

cervical cancer remained low. Prompting girls' attention before they start reading the leaflet may raise their awareness of important aspects of HPV vaccination and may give better support in their decision-making process. This could, for example, be organized by conducting a quiz at school, by including a quiz on the first page of the leaflet, or by conducting a quiz on the internet which has the advantage of being able to provide tailored information based on a girl's knowledge score.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

IJK conceived the idea for the study, designed the protocol and supervised the performance of the study; All authors contributed to the design of the questionnaire; PAWHS performed the retrieval of the sample; PAWHS was responsible for the database design and data entry, and performed the preliminary analyses; RH performed the final analyses; IJK, RH, JHR, HR, IMCMdK and MvB discussed the interpretation of the results; PAWHS drafted a preliminary report and RH drafted a final report; all authors revised the article critically and approved the final version to be published.

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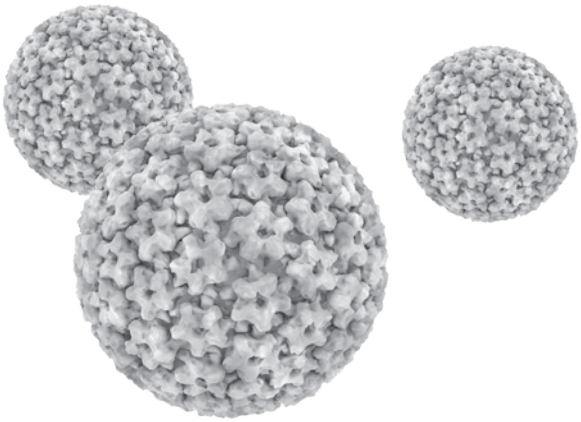
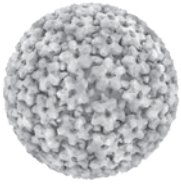


Chapter 8

Discussion



This thesis provides research into a range of aspects of HPV vaccination that girls and parents consider important, containing studies that started before the introduction of the vaccine into the National Immunization Program and ended three years after its introduction.

First, in this chapter the answers to the research questions will be given. Second, the methodological issues of the studies will be discussed. Next, a general discussion about the main findings will be given. Finally, recommendations for further research and practice, and general conclusions will be provided.

1. ANSWERS TO THE RESEARCH QUESTIONS

Which decisional strategies do parents use to develop an intention towards HPV vaccination for their daughters and which factors direct uptake intentions prior to the introduction of the vaccine program?

In a focus-group study amongst 36 parents having a daughter aged 8-15 years we found that some parents used a systematic approach to seeking information, e.g. checking websites and other sources and thus focused on content (i.e. central processing of information). Others mainly relied on their level of trust in the message source, like the government, or their level of distrust, for example the pharmaceutical industry (i.e. peripheral processing of information). It is known that attitudes based on such heuristic ways of seeking information are usually prone to information that contradicts these attitudes and thus are not stable.

Motivation to vaccinate was related to perceiving cervical cancer as a serious disease, perceiving one's daughter as being potentially susceptible to an HPV infection, and having experienced significant others having cancer. Motivation not to vaccinate was related to fear of long-term side effects of the vaccination and doubts about the effectiveness of HPV vaccination. In general, parents felt inadequately informed and lacked factual information about HPV, HPV infection risk and HPV vaccination.

We identified two mechanisms that are likely to influence the process of HPV vaccination decision-making: child-protection motivation (1); and decision-making responsibility (2).

Parents were motivated to protect their child irrespective of whether they did or did not want their daughter to be vaccinated. Although the outcome of their decision-making processes differed, in either case this could be attributable to anticipated regret of a potential decision to act or not to act. Our study suggests differences in the attribution of decision-making responsibility. Most parents indicated that they needed to make

the decision about HPV vaccination uptake, either by themselves or together with their daughter. This is important, given that this parental viewpoint appears to be at odds with the fact that girls aged 12 years and older do not legally need parental permission to get vaccinated.

Which parental determinants predict uptake of HPV vaccination by their daughters?

In a longitudinal study amongst parents having a daughter eligible for HPV vaccination we measured predictors of uptake at baseline (N=1762) in June 2009 and uptake at follow-up (N=793) in November 2011. We showed that uptake was predicted by intention, having to decide sooner (in 2010) or later (in 2011) about uptake, and anticipated regret and worry about the consequences of abstaining from HPV vaccination. Ambivalence, which is having simultaneous positive and negative evaluations of an attitude object (in this case HPV vaccination), played an important role. We observed that ambivalence towards HPV vaccination at baseline moderated the relationship between the attitude towards HPV vaccination (as assessed at baseline) and uptake (as assessed at follow-up), with the attitude-uptake relationship being stronger when ambivalence levels were higher. This means that parents with a positive attitude and a high level of ambivalence towards HPV vaccination were more likely to have their daughter vaccinated than parents with a positive attitude and a low level of ambivalence. This finding could be explained in two ways. First, ambivalence is characterized as being subjectively uncomfortable and people may be motivated to resolve the conflicting evaluations that they hold [1] by searching for information. Second, earlier studies found that ambivalent people processed pro-attitudinal messages to a greater extent than counter-attitudinal messages, probably because pro-attitudinal messages are more likely to reduce ambivalence [2-3]. Taking these two mechanisms together, it is likely that in our study ambivalent parents with a positive attitude towards HPV vaccination processed 'positive' messages about HPV vaccination to a greater extent than 'negative' messages, and were therefore more likely to have their daughter vaccinated.

HPV vaccination uptake was most strongly predicted by a positive parental intention. In turn, HPV vaccination intention was positively associated with parental trust in the vaccine, the perception that the vaccine was endorsed by significant others in their lives and the motivation to comply with that social norm, and anticipated regret and worry (which also predicted uptake). Positive intention was negatively associated with educational level and perceived parental responsibility for a child's health.

Knowledge did not predict uptake or intention. Importantly, however, knowledge about the duration of protection was low at both baseline and follow-up. At baseline, 62% of

the parents thought that protection lasts 30 years or even lifelong. At follow-up, this percentage had only slightly increased to 66%.

Furthermore, we showed that a more positive attitude towards HPV vaccination over time was associated with an increase in trust in the vaccine and in social norms over time, and a decrease in ambivalence towards HPV vaccination over time. This latter factor was related to an increase in feeling informed about HPV vaccination and an increase in trust in the vaccine over time. In summary, over time parents felt better informed, became less ambivalent and had more trust in the vaccine.

How are various aspects of HPV vaccination associated with parents' preferences for uptake by their daughters, and which trade-offs are parents willing to make between these aspects?

We used a Discrete Choice Experiment (DCE) to assess parents' (N=302) preferences for attributes of HPV vaccination: i.e. degree of protection against cervical cancer, duration of protection, risk of serious side effects, and age at vaccination. Parents preferred a higher protection rate and a longer duration of protection to a lower protection rate and a shorter duration of protection. Also, parents preferred an HPV vaccination program associated with lower levels of serious side effects. As these findings may seem logical, they may indicate that parents understood the DCE task. Parents did not prefer vaccination at age 12 to vaccination at the age of 9, but they did prefer vaccination at age 14 to vaccination at age 9.

Parents were willing to trade off the degree of protection against cervical cancer in order to gain improvement in the levels of the other attributes. In order to obtain an HPV vaccination with a risk of serious side effects of 1/750,000 instead of 1/150,000, parents were willing to trade off 21% of the degree of protection. They were willing to trade off 11% of the degree of protection to obtain lifetime protection instead of 25 years. To raise the age at vaccination to 14 rather than of 9, parents were willing to trade off 10% of the degree of protection.

Furthermore, we calculated the mean uptake of a base-case scenario compared to no vaccination. The base-case corresponded most to what was known about the characteristics of the HPV vaccination program at the time we conducted our study: i.e. an HPV vaccination program at the age of 12 years, a 1/150,000 risk of serious side effects, a duration of protection of 6 years, and a 70% degree of protection. The expected uptake based on this base case was 63.3%. In particular, an increase in the duration of protection from 6 years to lifetime would result in a relatively large increase in the expected uptake (i.e. an absolute increase of 12.2%). On the other hand, an increased risk of serious side effects from 1/150,000 to 1/30,000 would result in a decrease in the expected uptake of 13.4% (Figure 1).

What are girls' preferences for HPV vaccination and are they willing to trade off between protection against cervical cancer and other characteristics of HPV vaccination?

The preferences of girls aged 12-16 years (N=312) regarding HPV vaccination were measured during the media debates about HPV vaccination. Girls preferred HPV vaccination that generated a higher degree of protection and with a longer protection duration to an HPV vaccination that generates a lower degree of protection and a shorter protection duration. Furthermore, girls preferred an HPV vaccination program with a lower risk of serious and mild side effects. Girls did not prefer vaccination at age 14 to vaccination at age 9. However, they did prefer vaccination at age 12 to vaccination at age 9.

On average, girls were willing to trade off 38% protection against cervical cancer to obtain HPV vaccination that would provide lifetime protection instead of a protection duration of 6 years. Girls were willing to trade off 17% protection against cervical cancer to obtain a vaccination with a risk of serious side effects of 1/750,000 instead of 1/150,000, 9% protection against cervical cancer to get an HPV vaccination that had a 5% lower risk of mild side effects, and 7% protection against cervical cancer to get an HPV vaccination at age 12 instead of age 9. Considering the relative trade-off between the risk of mild and serious side effects, girls were willing to accept a 9.7% increased risk of mild side effects if the risk of serious side effects decreased from 1/150,000 to 1/750,000.

As we did for parents, we also calculated the mean uptake of a base-case scenario compared to no vaccination for girls. This base case represents HPV vaccination at the age of 12, a 1/30 risk of mild side effects, a 1/150,000 risk of serious side effects, a protection duration of 6 years, and a 70% protection rate against cervical cancer. We found an expected uptake of the base-case HPV vaccination program of approximately 77%. Relatively large effects on the average expected uptake were especially measured for an increased risk of serious side effects, from 1/150,000 to 1/30,000 (a decrease of 14.6%), lifetime protection instead of a protection duration of 6 years (an increase of 12.0%) and a decrease in protection against cervical cancer from 70% to 50% (a decrease of 7.3%) (Figure 1).

To what extent have girls' preferences changed almost three years after the much-debated start of the HPV vaccination program?

In 2011 we again used a DCE to assess the preferences of girls aged 11-15 (N=500) for HPV vaccination. In this new sample we found that three years after the start of the vaccination program the risk of mild side effects had become less important: in 2009 girls were willing to trade off 18% of the degree of protection (CI: 13.8% to 22.4%) to obtain a reduction of 10% in the risk of mild side effects, while in 2011 they were willing to trade off 7%

(CI: 3.2% to 10.8%). Second, it became less important to obtain lifetime protection over a protection rate of 8 years (in 2011) or 6 years (in 2009), as this trade-off was no longer significant in 2011 (2011: 21%, CI: -0.1% to 37.2%; 2009: 38%, CI 32.1% to 44.3%). Third, age of 12 years at vaccination instead of 9 years was no longer significant in 2011 (2011: 4%, CI: -2.4% to 8.6%; 2009: 7%, CI: 2.6% to 10.6%). In summary, almost 3 years after the initiation of the HPV vaccination campaign in the Netherlands, the risk of mild side effects and age at vaccination seem to have become less important factors in decision-making. Potentially, the girls had a better idea about which mild side effects to expect and were less concerned about them. Also, the importance of the degree of protection may have increased for the girls. The age of vaccination might be less of an issue in 2011 given that the duration of protection has been known to be at least 2 years longer, i.e. 8 years in 2011 compared with 6 years in 2009.

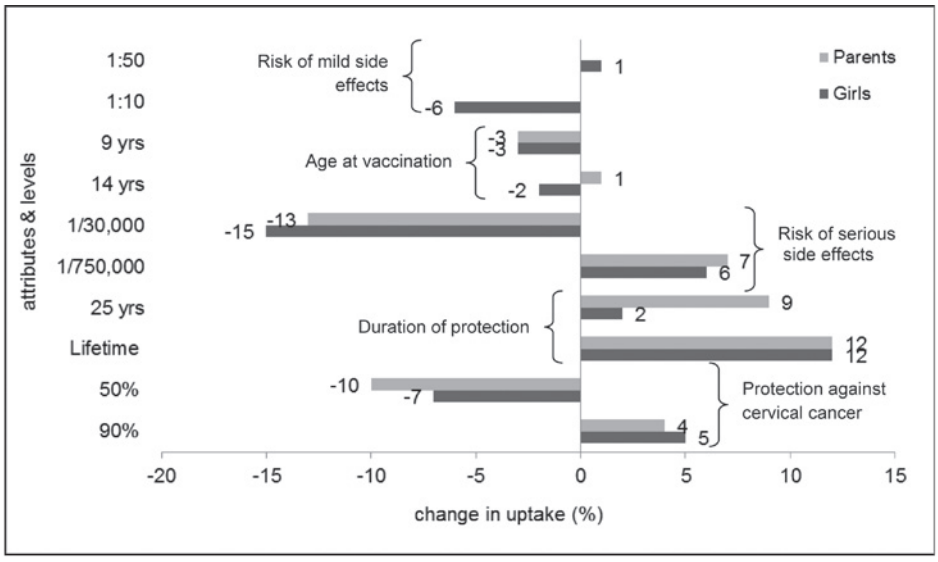


Figure 1. Univariate marginal estimates for change in the predicted probability of participation of parents and girls; highest and lowest value for attributes versus base case.

To what extent does an official information leaflet about HPV contribute to girls' knowledge levels?

In a quasi-experimental study among girls aged 11-14 years (N=237) we assessed the contribution of an official information leaflet to girls' knowledge levels. We firstly showed that knowledge scores were higher after reading the information leaflet. Secondly, post-leaflet total knowledge scores were higher in girls who had also completed the questionnaire *before* reading the leaflet and we conclude that completing this question-

naire had a positive effect on knowledge levels. The percentage of correct answers to some statements largely increased from a low percentage before reading the leaflet to a high percentage after reading the leaflet, e.g. the statements about whether girls need permission from their parents to get vaccinated and the statement that, despite HPV vaccinations, Pap smears are still recommended. Of note, knowledge about the degree/duration of protection against cervical cancer was low before reading the leaflet and remained relatively low after reading it. For instance, about 75% of the girls incorrectly thought that vaccination completely protects against cervical cancer and that protection lasts a lifetime.

2. METHODOLOGICAL CONSIDERATIONS

The results of this thesis should be interpreted in light of certain methodological considerations.

Selection bias

First, in our studies aimed at parents, the respondents were mainly mothers. In the focus-group study (chapter 2) and the longitudinal study (chapter 3) 94% of the respondents were mothers. In the DCE study (chapter 4) 90% were mothers. This seems common in studies assessing parental attitudes regarding HPV vaccination [4-6]. A study about the determinants of HPV vaccination intentions among Dutch girls and their mothers showed that 6% of the parent couples had a different opinion about the uptake of their daughter [7]. Though this number is low, it would be worthwhile to assess whether fathers and mothers share the same opinion about HPV vaccination. Second, in all our studies most respondents had an intermediate or high educational level, so girls and parents with a low educational level were underrepresented. Our samples may therefore not be representative of the general population. This may limit the external validity of our results, especially since the longitudinal study at baseline (chapter 3), and the DCE study among parents (chapter 4) had a low response rate (about 30%). We did not have information about the characteristics of the non-responders and thus were not able to compare them with those of the responders.

Actual uptake

For good internal validity, it is better to measure actual behavior instead of the intention to perform a certain behavior. For the focus-group study (chapter 2) we have data on parents' intention to have their daughter vaccinated, but do not know what the actual

rate of uptake was. In the three DCE studies (chapters 4-6) and the quasi-experimental study (chapter 7), some girls had already been vaccinated at the time they completed the questionnaire. If girls were not vaccinated we measured their intention to get vaccinated. The fact that we have no data about actual uptake may limit the study's internal validity. However, in our longitudinal study described in chapter 3 we show that intention was a strong predictor of uptake. Therefore, this weakness probably has a limited influence on the results.

Discrete Choice Experiments

Attribute selection

In our DCE studies we selected the most relevant attributes based on the literature, interviews with experts in the field of HPV vaccination, and focus-group data; however, this careful procedure does not guarantee that we included all attributes that are relevant to girls' and parents' preferences about HPV vaccination. For example, we did not include genital warts protection as an attribute of HPV vaccination, as the Dutch vaccination program offers only the bivalent vaccine, which provides no protection against HPV types causing genital warts. However, girls and parents may well have a preference for HPV vaccines offering protection against genital warts.

Understanding risks

In our discrete choice experiments girls and parents had to compare risks and effectiveness rates. This may have caused difficulties. For example, in two DCE studies (chapters 4 and 5), respondents had to compare risk ratios of serious side effects of 1:30,000, 1:150,000 and 1:750,000. We used several methods to clarify these risks: we described the risks in words (i.e. the risk of serious side effects is small, very small or extremely small) and gave extra information phrased as: "Of 150,000 persons one person will experience serious side effects and 149,999 persons will not" (and vice versa for the other risks), and "By way of comparison: each year 100,000 12-year-old girls are invited to get vaccinated against cervical cancer." The degree of protection was illustrated with bar graphs. For the study described in chapter 5 the risk of mild side effects was illustrated with pie charts.

For the study described in chapter 6 we optimized the illustration of risks and effectiveness by using pictographs (icon array), which is a matrix of elements that are shaded in different colors to represent the proportion that will be prevented from getting cervical cancer after vaccination and the proportion that will experience mild side effects [8]. Because formats such as "1 in x", like 1:30 versus 1:50, consistently perform worse [9], we opted to keep the denominator constant: 1:30, 10:30 and 20:30 when describing the risks

of mild side effects and we described the denominator of 30 as a classroom, in which 1, 10 or 20 classmates would experience mild side effects.

In spite of the measures described above, people may still have encountered difficulties understanding the numbers and the risks. We used a number of methods to assess whether people understood the meaning of the attributes and the levels.

In all our DCE studies we included a dominant choice test. In such a set one of two HPV vaccination alternatives was characterized by equal or logically preferable levels on all attributes; logically, everyone should prefer this alternative. Also, parents and girls were asked to rank the attributes of HPV vaccination from most important to least important. We compared the ranking with the preferences shown in the DCE and assessed whether these were consistent. Furthermore, in the DCE study described in chapter 4 we included the Subjective Numeracy Scale to gain more insight into parents' numeracy. This scale correlates well with objective measures of numeracy skills [10-11].

We made every attempt to illustrate the risks and effectiveness rates as completely as possible and believe that overall, girls and parents understood these numbers.

3. GENERAL DISCUSSION

Our results provide some insight into reasons for the low rates of HPV vaccine uptake in the Netherlands. The uptake rate among 13- to 16-year-old girls in the 2009 catch-up campaign was 52% [12]. In 2010, 56% of all eligible 12-year-old girls were vaccinated against HPV. In 2011 the uptake rate was 58% [13] and in 2012 the uptake rate increased to 61% [14]. In Europe, uptake rates vary considerably between countries (range 17-84%) [15]. According to the Netherlands' National Institute for Public Health and the Environment, the lower than expected rate of uptake was caused by the circulation of myths about the vaccine [16]. For example, one of these myths was about a risk of death or paralysis due to the vaccination. Our studies confirm that parents were afraid of serious side effects and had doubts about the effectiveness of the vaccine. Another study conducted in the Netherlands showed that the strongest determinants of not accepting HPV vaccination were: limited information about the vaccine provided by the government, limited trust that the government would stop vaccinations if they caused serious side effects and concerns related to religion and to vaccine safety and effectiveness [17].

Our studies also show that over time parents felt better informed, became less ambivalent and had more trust in the vaccine. The risk of mild side effects seems to have become less of a concern to girls. Also, currently, more is known about the vaccine than when it was introduced in 2009. Follow-up data on young women who have received the HPV vaccine, which are currently available for 9.4 years, show a sustained efficacy against HPV 16 and 18 [18]. Statistical modeling predicts slow decay of the vaccine-induced

antibodies over a period of at least 20 years. Assuming that if the long-term persistence of antibodies has a similar relevance for protection to that observed with some other vaccines, a booster may not be needed until a considerable period of time has passed after the initial vaccination [19].

Although we found that parents feared long-term side effects, the vaccine appears to be safe. The Centers for Disease Control and Prevention (CDC) made the following statement about the bivalent vaccine: "the bivalent vaccine is safe, it has been in use around the world for several years and has been very safe. However, any medicine can potentially cause a serious problem, such as a severe allergic reaction. The risk of a vaccine causing a serious injury, or death, is extremely small. Life-threatening allergic reactions from vaccines are very rare" [20]. Also, a large cohort study found no evidence supporting associations between exposure to the quadrivalent HPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events [21]. Furthermore, the Netherlands' National Institute for Public Health and the Environment states that no serious side effects of HPV vaccination are known or have been reported [22].

However, although the safety of the vaccine has become increasingly clear, rates of vaccine uptake by Dutch girls have increased by only a moderate extent. One explanation might be that the introduction of the vaccine into the National Immunization Program (NIP) might have been too hasty. For example, our focus-group study showed that before the introduction of the vaccine, parents felt inadequately informed and lacked factual information about HPV, HPV infection risk and HPV vaccination. In our longitudinal study we found that parents who had to decide later (i.e. in 2011) about uptake had their daughter vaccinated more often than parents who had to decide earlier (i.e. in 2010). An explanation for this might be the amount of time that passed between the baseline questionnaire (2009), when an intense societal debate was ongoing, and the actual decision about vaccination uptake. In 2011 this debate probably had less impact on the uptake decision than it did in 2010. Also, parents who made the decision later versus earlier probably felt more reassured about the vaccine's safety. This suggests that if parents and girls had been more aware of the link between HPV and cervical cancer, and the forthcoming possibility of vaccination in a much earlier phase than when the first invitations were sent, they might have been more positive about vaccination. Openness about certain issues, such as uncertainties about the duration of protection provided by HPV vaccination, could potentially have prevented the development of rumors that circulated about the vaccine, which raised fears about risks of infertility or paralysis after vaccination.

Possibly, parents and girls are not aware of the low numbers of adverse events related to HPV vaccinations. According to our studies, if parents and girls were presented with the likelihood of an extremely small risk of serious side effects (i.e. 1:750,000) compared to a very small risk (i.e. 1:150,000), uptake would increase by 6% in the study among girls

and by 7% in the study among parents. In order to make an informed choice, parents and girls should be knowledgeable about important aspects of HPV vaccination. One of those aspects is the vaccine's safety. While rates of serious side effects were unknown at the time of the introduction of HPV vaccination in the National Immunization Program, we currently know that the risk of a vaccine causing a serious injury, or death, is extremely small [20] and that in the Netherlands no serious side effects of HPV vaccination are known or have been reported [22]. Parental knowledge of this seems to be low, as indicated by the low rates of uptake. In other words, when parents and girls have to decide about uptake, they should know that current knowledge shows that there are no serious side effects. Hence, if parents and girls are aware of the vaccine's safety, uptake might increase. It would therefore be a good idea to give more attention to the vaccine's safety in the media, at school, and during visits to the general practitioner. Since our study showed that social norms (including the opinion of one's general practitioner) influenced the intention to get vaccinated, the general practitioner may play a role in explaining the advantages and safety of HPV vaccination.

The vaccination program of countries with a high rate of uptake may provide examples with which to optimize the Dutch HPV vaccination program from a public health viewpoint. For example, in Scotland in the 2008/2009 school year, 92% of eligible girls were vaccinated against HPV. Three years later, the uptake rate in Scotland is still around 90% (91%) [23]. Belgium (Flemish region), Scotland, England and Australia also have high uptake rates (range 71-86%) (Table 1). All these countries offer the vaccine through a school-based program. There are also other reasons for the high rates of uptake reported elsewhere. For example, in Scotland, it was concluded that "a structured, managed approach to the preparation of the delivery of new immunisation programmes is essential in achieving high and inclusive uptake" [24]. "This structured approach allowed for transparency of processes and accountability for decision making and it provided a process that could be reviewed at key stages." Also, a "school-based delivery and tailored communication directed at adolescent girls played a role in the achievement of the high uptake" [24]. In Denmark, where the uptake rate is 83%, Poulsen (2014) states that the key factors for a high uptake rate included "transparency in decision-making and communication of evidence and uncertainties which created trust and credibility", "careful planning and communication and the policy to keep doctors and other key players informed from an early stage". But also "well-developed information material and support from stakeholders were the basis for positive articles in the media." "Preparation for adverse event[s], misinformation and rumors formed the basis for a quick response from authorities to the press and maintained public confidence" [25]. Furthermore, as suggested by Zimet et al. (2013), a useful approach may be to "reframe non-vaccination as an active decision, comparable to vaccination, introducing the notion that there is risk associated with not receiving the HPV vaccine" [26].

Reasons for low rates of uptake are also reported. The low overall uptake in the United States of 32% of girls aged 13-17 years, for example, may be due to e.g. "inadequate provider recommendations", "provider reimbursement concerns", and the "infrequent use of reminder/recall systems that would foster completion of the 3-dose series and factors such as parental hesitancy, and health-care access" [27-28].

Overall, to optimize the HPV vaccination program in the Netherlands from a public health viewpoint, more emphasis should be placed on the vaccine's safety in the leaflet and the media. The leaflets used in countries with high uptake rates contain some information that may be useful to include in the Dutch leaflet; for example, it might state that the vaccine meets the high safety standards required for it to be used in the Netherlands and other European countries; serious side effects are extremely rare; millions of doses of the vaccine have been administered to girls worldwide. Furthermore, for the implementation of future vaccines, more transparency in decision-making may be needed as well as better preparation for misinformation and possible rumors.

Table 1: Overview of free HPV vaccination programs targeted at girls aged 12-13 in various countries

Country	Uptake (%); year	Delivery infrastructure	Information in leaflet about the vaccine's safety
Netherlands [29]	61; 2012	Central locations outside school	Rumors about fatalities and infertility after vaccination are refuted
Australia [30]	71; 2011	SBS	Text: The HPV vaccine has been tested to ensure it is safe for males and females, and more than seven million doses of the HPV vaccine have been distributed in Australia so far. The vaccination program includes safety monitoring to detect and manage any side effects. If you have any concerns following your child's vaccination, contact your doctor, immunisation provider or state or territory health department.
Belgium (Flemish region) [31]	82; 2012	SBS	Text: the vaccine is safe
England [32]	86; 2012	SBS	Text: More serious side effects are extremely rare. The vaccine meets the rigorous safety standards required for it to be used in the UK and other European countries. Tens of millions of doses of HPV vaccine have been given to girls worldwide.
Scotland [33]	91; 2012	SBS	Text: The vaccine meets the high safety standards required for it to be used in the UK and other European countries. Clinical trials with thousands of young women have shown that the vaccine is very safe. Very rarely, some people can have a severe reaction soon after immunisation, which causes breathing difficulties and may cause them to collapse. This is called an anaphylactic reaction. These reactions are extremely rare and nurses are fully trained to deal with them.

Note: SBS: school-based program

Effects of changes in the HPV vaccination program

Our DCE studies give information about the expected rates of uptake when a characteristic of the HPV vaccination program changes. In the future, it is likely that a HPV vaccine will be available that has an effectiveness rate of 90% against HPV types that cause cervical cancer, instead of the current effectiveness rate of 70% [34]. In 2009, based on parents' preferences, we assumed an uptake rate of 63% for a HPV vaccination program at the age of 12 years, a 1/150,000 risk of serious side effects, a duration of protection of 6 years, and a 70% degree of protection. If the degree of protection rose to 90% (all other factors being equal), then uptake would increase by 4%, to 67%. Based on girls' preferences, we assumed an expected uptake of 77%. If the degree of protection rose to 90% instead of 70%, then uptake would increase by 5%, to 82%.

Starting in 2014 Dutch girls are being given two vaccinations instead of three, because two doses have been found to provide as much protection as three doses as long as the vaccination is given before girls turn 15 years of age [35-36]. Our study showed that most girls preferred a 2-dose scheme to a 3-dose scheme, and, overall, girls were even willing to trade off 3.5% of the degree of protection to receive two doses instead of three doses. This suggests that the new strategy may result in a higher vaccination uptake.

4. RECOMMENDATIONS FOR FURTHER RESEARCH

- We recommend that in future research about HPV vaccination ways are sought to include higher numbers of parents and girls with a low educational level and to include more fathers.

-To be able to assess whether parents and girls base their decision on the correct information or instead on myths about HPV vaccination, it is important to know their reasons for declining or accepting the vaccine. These can be determined, for example, through a questionnaire study, which includes open questions about reasons for participation and items assessing the understanding of HPV vaccination. This might give insight into whether the rumors that have circulated, e.g. about becoming infertile or paralyzed after vaccination, still have an impact on girls' and parents' decisions about HPV vaccination uptake. If so, extra efforts will have to be made to invalidate these rumors. Such a study might also show whether parents and girls are aware of the characteristics of the vaccine in terms of safety and its protection against HPV, both in the sense of extent and duration of protection. Study findings may then help determine new information policies about HPV vaccination.

5. RECOMMENDATIONS FOR POLICY AND PRACTICE

- To facilitate informed decision-making, we recommend that campaigns provide clear information about HPV vaccination, explaining its advantages and the vaccine's safety, but also disclosing potential disadvantages and unknown factors (e.g. the duration of protection).

- To make girls aware that the duration of protection is not known and that the vaccine does not provide complete protection against cervical cancer, it is important that educational material clearly states that booster vaccinations might be needed in the future and that screening for cervical cancer is still recommended.

- To trigger girls' attention about important aspects of HPV vaccination, a quiz about the vaccination can be completed before they start reading the leaflet, e.g. by conducting a quiz on the internet.

- To better inform target groups about a new vaccine, the link between the disease and the vaccine has to be made clear. We recommend exploring the decisional strategies used by the target group/parents, e.g. by conducting focus-group discussions. If target groups appear to use heuristic cues (e.g. trusting the message source) as a primary route for vaccination decision-making, they may have intentions about uptake that can easily be changed or they may tend to make decisions that are not well-informed. This could be prevented by making messages more personally relevant, providing information multiple times, and by stimulating active learning.

- To make HPV-vaccinated women aware of the recommendation to have Pap smears, we recommend including information about reasons to have a Pap smear in materials about cervical screening.

- To assess whether vaccinated girls participate in screening, we recommend that their screening uptake be monitored, because they might believe that screening is unnecessary.

6. MAIN CONCLUSIONS

- Before the introduction of the vaccine, some parents perceived a lack of information and felt insecure about the safety and effectiveness of HPV vaccines.

- Uptake of HPV vaccination was predicted by intention, having to decide about uptake earlier rather than later (i.e. in 2011 or 2010), and anticipated regret/worry about abstaining from vaccination. Anticipated regret was a common predictor of intention and uptake and thus an important factor in the decision-making process about HPV vaccination.

- Parents' preferences for HPV vaccination were influenced by the degree of protection against cervical cancer, the duration of protection, the risk of serious side effects, and their daughter's age at vaccination. Based on the trade-offs parents were willing to make, uptake would increase if new evidence indicated outcomes would be better than they are currently understood, particularly for the degree and duration of protection.

- Girls made trade-offs between protection against cervical cancer and other characteristics of HPV vaccination. In particular, the degree of protection against cervical cancer, protection duration, and risk of serious side effects influenced HPV vaccination preferences.

- Reading the information leaflet had a positive effect on girls' knowledge about HPV, which showed a further increase when boosted by a pre-test measurement. Still, knowledge about the degree and duration of protection against cervical cancer remained relatively low after reading the leaflet. This aspect of protection is important for informed decision- making.

- Over time, parents felt better informed, became less ambivalent and had more trust in the vaccine.

- Almost three years after the much-debated start of the HPV vaccination program, the risk of mild side effects and age at vaccination still influenced girls' preferences, but seem to have become less important.

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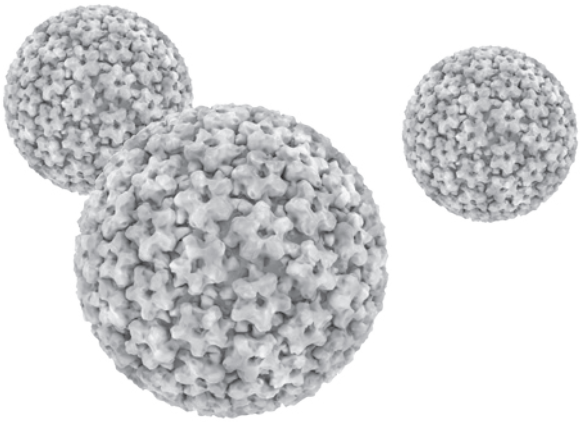

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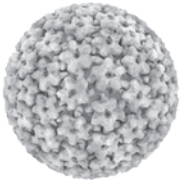


In Europe 60,000 women are diagnosed with cervical cancer annually. In the Netherlands, about 700 women are diagnosed with cervical cancer each year and about 200 to 250 women die from the disease. Cervical cancer can only develop in the presence of infection with a high-risk type of human papillomavirus (HPV). To lower the risk of cervical cancer, women can get routine screenings to detect precancerous tissue changes in the cervix. In the Netherlands, such screenings are available to women aged 30-60 years and can be undergone once every 5 years.

In 2010 the Netherlands' National Immunisation Programme (NIP), which is free of charge and voluntary, was extended to include the bivalent HPV vaccine for 12-year-old girls. This vaccine protects against HPV 16 and 18, which cause about 70% of all cervical cancer cases. Eligible girls receive an information leaflet and invitation to be vaccinated at their home address. In the Netherlands, 12-year-old girls do not need parental permission to make a decision about uptake, though in practice parents play a considerable role in decision-making about the uptake of HPV vaccinations. General acceptance of HPV vaccination by parents and girls cannot be taken for granted, as has been shown by relatively low uptake rates in the Netherlands. In 2010, 56% of all 12-year-old girls were vaccinated against HPV and in 2012 the rate of uptake had increased to 61%. This thesis describes research into a range of aspects of HPV vaccination that girls and parents consider important, as well as their attitudes towards HPV vaccination, knowledge about HPV vaccination, and other determinants of uptake.

The following research questions are addressed:

1. Which decisional strategies do parents use to develop an intention towards HPV vaccination for their daughters and which factors direct uptake intentions prior to the introduction of the vaccine program?
2. Which parental determinants predict uptake of HPV vaccination by their daughters?
3. How are various aspects of HPV vaccination associated with parents' preferences for uptake by their daughters, and which trade-offs are parents willing to make between these aspects?
4. What are girls' preferences for HPV vaccination and are they willing to trade off between protection against cervical cancer and other characteristics of HPV vaccination?
5. To what extent have girls' preferences changed almost three years after the much-debated start of the HPV vaccination program?
6. To what extent does an official information leaflet about HPV contribute to girls' knowledge levels?

In **Chapter 2** we explored the decisional strategies that parents used to develop an intention towards HPV vaccination prior to an initial administration of the vaccine. In a focus-group study we found that some parents used an approach of systematically seek-

ing information as a way to prepare to make a decision, while others relied on trust in the message source. Generally, parents believed it was important to protect their child against negative outcomes that could result from vaccinating or from not vaccinating, and felt it was their responsibility to decide about uptake. Perceptions about their child's susceptibility to an HPV infection, the vaccine's effectiveness and the possibility of serious side effects were most important in the HPV vaccination decision-making process.

Chapter 3 describes the parental predictors for HPV vaccination uptake by their daughters. We showed that intention, timing of the decision (just after the vaccine had been introduced or later on), and anticipated regret and worry about abstaining from vaccination were predictors of uptake. Anticipated regret was a common predictor of intention and uptake and thus an important factor in the decision-making process about HPV vaccination. In turn, predictors of intention, like social norms and trust in the vaccine, were also important when deciding about HPV vaccination.

In **Chapter 4** we used a Discrete Choice Experiment (DCE) to assess parents' preferences for HPV vaccination and the trade-offs they were willing to make between characteristics of HPV vaccination. In DCEs, it is assumed that a medical intervention, such as a vaccination program, can be described by its characteristics (e.g. duration of protection), and by variants of that characteristic (e.g. a duration of protection of 6 years, 25 years or lifetime). The DCE questions offered three choices: two HPV vaccination alternatives with varying levels of the characteristics and a possibility to opt out (i.e. no vaccination). Parents were asked to choose the alternative that most appealed to them. We found that parents' preferences for HPV vaccination were influenced by the degree of protection against cervical cancer, the duration of protection, the risk of serious side effects, and the girl's age at vaccination. We concluded that rates of uptake could rise if the age ranges within which a girl is entitled to free HPV vaccinations are broadened. Based on the trade-offs parents were willing to make, we conclude that uptake would increase if new evidence indicated outcomes were found to be better than they are currently understood, particularly for degree and duration of protection.

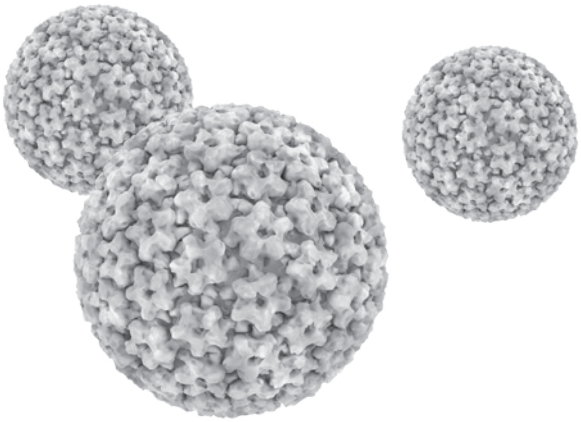
In **Chapter 5** we used a DCE to investigate if girls made trade-offs between various aspects of HPV vaccination, and to elicit the weight that girls placed on these characteristics during the media debates about HPV vaccination. We showed that degree of protection against cervical cancer, duration of protection, risk of serious side effects (e.g. requiring hospitalization), risk of mild side effects (e.g. nausea), and age at vaccination all proved to influence girls' preferences for HPV vaccination. On average, girls were willing to accept less protection against cervical cancer to obtain a longer duration of protection, or lower risks of serious or mild side effects. An increase in protection duration, an increase in

the risk of serious side effects, or a decrease in the degree of protection against cervical cancer all had a relatively large impact on the average expected uptake.

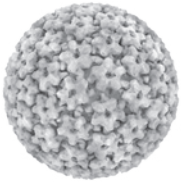
In **Chapter 6** we also used a DCE to assess girls' preferences for HPV vaccination and the trade-offs they are willing to make. We assessed these preferences and trade-offs almost three years after the much-debated start of the HPV vaccination program, in order to assess whether girls' preferences had changed after that time. We showed that the risk of mild side effects became less important. Also, it became less important to obtain lifetime protection compared to 8 years of protection. Age at vaccination of 12 years instead of 9 years also became less important. Furthermore, we showed that girls with higher levels of education and HPV-vaccinated girls have a higher probability of opting for HPV vaccination if it is offered at age 12 instead of at age 9, than girls with lower education levels or girls who were not vaccinated.

In **Chapter 7** we present the results of a quasi-experimental study in which we assessed the extent to which reading an official information leaflet about HPV contributed to girls' knowledge levels, and the extent to which an increase in knowledge was boosted by a pre-test measurement. This study showed that reading the information leaflet had a positive effect on girls' knowledge about HPV, which showed a further increase when boosted by a pre-test measurement. However, levels of knowledge regarding the degree and duration of protection against cervical cancer remained low. Therefore, the leaflet should be improved. Prompting girls' attention before they start reading the leaflet may raise their awareness of important aspects of HPV vaccination and may better support their decision-making process.

Finally, in **Chapter 8** the results of this thesis are discussed and recommendations for further research and practice are given. To facilitate informed decision-making, we recommend that campaigns provide clear information about HPV vaccination, explaining its advantages and the vaccine's safety, but also disclosing potential disadvantages and unknown factors. To better inform target groups about a new vaccine, the link between the disease and the vaccine has to be made clear. We recommend exploring which decisional strategies the target groups/parents use. To make girls aware of the unknown duration of protection and that the vaccine does not provide full protection against cervical cancer, it is important that educational material clearly states that booster vaccinations might be needed in the future and that screening for cervical cancer is still recommended. Further, we recommend performing future studies on the reasons for accepting or declining HPV vaccination, to assess whether parents and girls base their decision on the correct information or instead on myths about HPV vaccination.



Samenvatting



In Europa worden jaarlijks 60.000 vrouwen gediagnosticeerd met baarmoederhalskanker. In Nederland krijgen elk jaar 700 vrouwen te horen dat zij baarmoederhalskanker hebben, waarvan 200 tot 250 vrouwen aan de ziekte overlijden. Baarmoederhalskanker ontstaat door een infectie met een hoog risico humaan papillomavirus (HPV). Om het risico op baarmoederhalskanker te verkleinen worden vrouwen uitgenodigd om deel te nemen aan screening, waarbij voorstadia van baarmoederhalskanker worden opgespoord. In Nederland ontvangen vrouwen van 30 tot 60 jaar elke 5 jaar een uitnodiging voor baarmoederhalskanker screening.

In 2010 is de vaccinatie tegen baarmoederhalskanker opgenomen in het Nederlands Rijksvaccinatieprogramma. Dit vaccin is vrijwillig en wordt gratis aangeboden aan 12-jarige meisjes. Het vaccin beschermt tegen twee types HPV: HPV16 en HPV18, welke ongeveer 70% van alle gevallen van baarmoederhalskanker veroorzaken. Meisjes ontvangen thuis een informatiefolder en een oproep voor de vaccinatie. In Nederland hebben meisjes van 12 jaar of ouder geen toestemming van hun ouders nodig om gevaccineerd te worden, hoewel in de praktijk ouders een grote rol spelen in de beslissing om wel of niet te vaccineren. Algemene acceptatie van de HPV vaccinatie door ouders en meisjes kan niet zomaar worden aangenomen, zoals wel blijkt uit de relatief lage opkomst. In 2010 is 56% van alle meisjes gevaccineerd en in 2012 is dit percentage gestegen tot 61%. In dit proefschrift wordt de aspecten van HPV vaccinatie beschreven die meisjes en ouders belangrijk vinden. Ook worden hun attitude en kennis ten aanzien van HPV vaccinatie beschreven en de determinanten om wel of niet te vaccineren.

De volgende onderzoeksvragen worden beantwoord:

1. Welke beslissingsstrategieën gebruiken ouders om een intentie ten aanzien van HPV vaccinatie te vormen en welke factoren hebben invloed op die intenties, voordat het vaccin werd opgenomen in het Rijksvaccinatieprogramma?
2. Welke determinanten voorspellen bij ouders de deelname van hun dochter aan de HPV vaccinatie?
3. Hoe zijn karakteristieken van HPV vaccinatie geassocieerd met de voorkeuren van ouders ten aanzien van HPV vaccinatie en welke afwegingen zijn ouders bereid te maken tussen deze karakteristieken?
4. Wat zijn de voorkeuren van meisjes ten aanzien van HPV vaccinatie en zijn ze bereid om afwegingen te maken tussen de mate van bescherming en andere karakteristieken van HPV vaccinatie?
5. In welke mate zijn de voorkeuren van meisjes veranderd 3 jaar na de veelbesproken start van het HPV vaccinatieprogramma?
6. In welke mate draagt de officiële informatiefolder bij aan de kennis van meisjes over HPV vaccinatie?

In **Hoofdstuk 2** onderzochten we de beslissingsstrategieën die ouders gebruikten om een intentie ten aanzien van HPV vaccinatie te vormen. In een focusgroep onderzoek vonden we dat sommige ouders systematisch naar informatie zochten, terwijl anderen alleen vertrouwden op de bron van de informatie. Over het algemeen vonden ouders dat het belangrijk is om hun kind te beschermen tegen negatieve gevolgen die het resultaat konden zijn van wel of niet laten vaccineren. Tevens vonden ouders dat het hun verantwoordelijkheid is om te beslissen over de beslissing over vaccinatie. In de besluitvorming over HPV vaccinatie waren waargenomen vatbaarheid voor een HPV infectie, de effectiviteit van het vaccin en de mogelijkheid van ernstige bijwerkingen het meest belangrijk.

Hoofdstuk 3 beschrijft de determinanten bij ouders die de deelname van hun dochter aan de HPV vaccinatie voorspellen. Deze determinanten zijn: intentie, het moeten beslissen over wel of niet vaccineren vlak na de introductie van het vaccin of later, en geanticipeerde spijt en zorgen als je je dochter niet zou laten vaccineren. Geanticipeerde spijt was ook geassocieerd met intentie en daarom belangrijk in de besluitvorming rondom HPV vaccinatie. Daarnaast waren sociale norm en vertrouwen in het vaccin ook geassocieerd met intentie en zijn dus ook belangrijk in de besluitvorming.

In **Hoofdstuk 4** gebruikten we een discreet keuze experiment (DCE) om de voorkeuren van ouders ten aanzien van HPV vaccinatie vast te stellen en de afwegingen die zij bereid waren te maken tussen karakteristieken van HPV vaccinatie. In een DCE wordt een medische interventie, in dit geval een vaccinatieprogramma, beschreven aan de hand van zijn karakteristieken (bijvoorbeeld de duur van de bescherming). Deze karakteristieken bestaan uit een aantal varianten (levels), bijvoorbeeld een beschermingsduur van 6 jaar, 25 jaar en levenslang. De DCE vragen bestonden uit drie opties: twee HPV vaccinatie alternatieven met verschillende levels van de karakteristieken en een optie 'geen vaccinatie'. Ouders moesten steeds het alternatief kiezen dat hen het meest aansprak. We constateerden dat de voorkeuren van ouders ten aanzien van HPV vaccinatie werden beïnvloed door: de mate van bescherming tegen baarmoederhalskanker, de duur van de bescherming, het risico op ernstige bijwerkingen en de leeftijd waarop gevaccineerd wordt. We concluderen dat de opkomst zou kunnen stijgen als de leeftijdsgroep waarop een meisje gratis gevaccineerd kan worden breder zou zijn. Als we naar de afwegingen kijken die ouders bereid zijn te maken, kunnen we concluderen dat de opkomst zal stijgen als blijkt dat met name de mate en duur van bescherming gunstiger zijn dan ze nu zijn.

In **Hoofdstuk 5** gebruikten we een DCE om tijdens de discussies in de media rondom HPV vaccinatie te onderzoeken of meisjes afwegingen maakten tussen verschillende karakteristieken van HPV vaccinatie en hoe zwaar deze karakteristieken wogen. Hieruit bleek dat de mate van bescherming tegen baarmoederhalskanker, de duur van de be-

scherming, het risico op ernstige (bijvoorbeeld ziekenhuisopname) en milde bijwerkingen (bijvoorbeeld misselijkheid) en leeftijd waarop gevaccineerd wordt, allemaal invloed hadden op hun voorkeuren voor HPV vaccinatie. Gemiddeld waren meisjes bereid om een vaccin met minder bescherming tegen baarmoederhalskanker te krijgen , als de duur van de bescherming langer was of als het risico op ernstige en milde bijwerkingen kleiner was. Een aantal veranderingen zou een relatieve grote invloed hebben op de gemiddelde verwachte opkomst. Namelijk een toename in de duur van de bescherming, een toename in het risico op ernstige bijwerkingen of een afname in de mate van bescherming tegen baarmoederhalskanker.

In **Hoofdstuk 6** gebruikten we ook een DCE om de voorkeuren van meisjes ten aanzien van HPV vaccinatie vast te stellen en de afwegingen die ze bereid waren te maken. Deze voorkeuren en afwegingen hebben we ongeveer 3 jaar na de veelbesproken start van de HPV vaccinatie onderzocht, zodat we kunnen vaststellen of de voorkeuren van meisjes veranderd zijn na 3 jaar. We lieten zien dat het risico op milde bijwerkingen minder belangrijk is geworden. Ook werd het minder belangrijk om levenslange bescherming te hebben in plaats van 8 jaar. Tevens werd vaccineren op 12 jarige leeftijd in plaats van 9 jarige leeftijd minder belangrijk. Daarnaast lieten we zien dat meisjes verschilden in hun voorkeuren. Meisjes die hoger opgeleid zijn en meisjes die al gevaccineerd waren tegen HPV hadden een grotere kans om een vaccinatie te kiezen die aangeboden wordt op 12 jarige leeftijd in plaats van 9 jarige leeftijd, dan meisjes die lager opgeleid zijn of meisjes die niet gevaccineerd waren.

In **Hoofdstuk 7** presenteren we de resultaten van een quasi-experimentele studie waarin we onderzochten in welke mate de informatiefolder over HPV vaccinatie bijdraagt aan de kennis van meisjes en in hoeverre kennistoename versterkt wordt door een voormeting. Deze studie liet zien dat het lezen van de folder een positief effect had op de kennis van de meisjes over HPV. Het invullen van een vragenlijst voor het lezen van de folder zorgde voor een nog grotere toename in kennis. Daarentegen bleef kennis over de duur en mate van bescherming laag. De folder dient daarom verbeterd te worden. Het trekken van de aandacht van meisjes over HPV vaccinatie voordat ze de folder lezen kan hun bewustzijn verhogen over belangrijke aspecten van HPV vaccinatie en betere ondersteuning geven in hun besluitvorming.

Tenslotte bevat **Hoofdstuk 8** een algemene discussie van de resultaten van dit proefschrift en worden er aanbevelingen voor de praktijk en toekomstig onderzoek gegeven. Om geïnformeerde besluitvorming te ondersteunen, bevelen we aan dat campagnes duidelijke informatie geven over HPV vaccinatie: de voordelen en veiligheid van vaccinatie beschrijven, maar ook mogelijke nadelen en onbekende factoren openbaar maken.

Om een doelgroep beter te informeren over een nieuw vaccin, dient de link tussen de ziekte en het vaccin duidelijk gemaakt te worden. We bevelen aan dat er eerst uitgezocht wordt welke beslissingsstrategieën de doelgroep/ouders gebruiken. Om meisjes bewust te maken van de onbekende beschermingsduur en de onvolledige bescherming tegen baarmoederhalskanker, is het belangrijk dat informatiemateriaal duidelijk weergeeft dat herhaalvaccinaties misschien nodig zijn in de toekomst en dat screening op baarmoederhalskanker nog steeds wordt aanbevolen. Tot slot bevelen we aan om toekomstige studies te doen naar de redenen om wel of niet te vaccineren, zodat vastgesteld kan worden of ouders en meisjes hun keuze baseren op de juiste informatie of 'indianenverhalen' rondom HPV vaccinatie.

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Promoveren is als bevallen: de laatste loodjes wegen het zwaarst. Maar na de verlossende woorden 'hora est!' en de ontvangst van je bul zit je op een roze wolk. Nu mijn proefschrift af is en deze 'bevalling' er bijna op zit, wil ik graag iedereen bedanken die direct of indirect heeft bijgedragen aan de totstandkoming van dit proefschrift.

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Begeleidingsgroep en co-auteurs

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Lieve Dirk, een lach van jou doet alle (promotie)stress verdwijnen.

ABOUT THE AUTHOR

Robine Hofman was born on December 21, 1983 in Enschede, the Netherlands. In 2002, she finished her secondary education and she completed her bachelor degree in psychology in 2007 at the University of Groningen. In 2008, she obtained her master degree in social psychology. In October 2008, she started as a junior researcher at the Department of Public Health at the Erasmus University Medical Centre in Rotterdam. During this period, she performed researches in the decision-making of girls and parents about HPV vaccination uptake, as described in this thesis.

OVER DE AUTEUR

Robine Hofman is geboren op 21 december 1983 in Enschede. Ze behaalde in 2002 haar gymnasium diploma, waarna ze psychologie ging studeren in Groningen. In 2007 behaalde zij haar bachelor diploma en in 2008 haar master diploma in sociale psychologie. In oktober 2008 begon zij als junior onderzoeker op de afdeling Maatschappelijke Gezondheidszorg van het Erasmus Medisch Centrum Rotterdam. Hier heeft zij onderzoek gedaan naar de besluitvorming van meisjes en ouders ten aanzien van HPV vaccinatie, zoals beschreven is in dit proefschrift.

PUBLICATIONS

de Bekker-Grob EW, **Hofman R**, Donkers B, van Ballegooijen M, Helmerhorst TJ, Raat H, Korfage IJ. *Girls' preferences for HPV vaccination: A discrete choice experiment.* Vaccine. 2010;28:6692-7.

Hofman R, van Empelen P, Vogel I, Raat H, van Ballegooijen M, Korfage IJ. *Parental decisional strategies regarding HPV vaccination before media debates: a focus-group study.* Journal of Health Communication. 2013;18:866-80.

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Hofman R, van Empelen P, Richardus JH, de Kok IMCM, de Koning HJ, van Ballegooijen M, Korfage IJ. *Predictors of HPV vaccination uptake: a longitudinal study among parents.* Health Education Research. 2014;1:83-96.

Hofman R, de Bekker-Grob EW, Raat H, Helmerhorst TJ, van Ballegooijen M, Korfage IJ. *Parents' preferences for vaccinating daughters against human papillomavirus in the Netherlands: a discrete choice experiment.* BMC Public Health. 2014;14:454.

Hofman R, de Bekker-Grob EW, Richardus JH, de Koning HJ, van Ballegooijen M, Korfage IJ. *Have preferences of girls changed almost 3 years after the much debated start of the HPV vaccination program? A discrete choice experiment.* Plos One. 2014;9:e104772

PHD PORTFOLIO

Summary of PhD training

Name PhD student:	Robine Hofman
Erasmus MC Department:	Public Health
PhD period:	2008-2012
Promotor:	prof.dr. H.J. de Koning
Co-promotor	dr. I.J. Korfage

1. PhD training		
	Year	**Workload (Hours/ECTS)**
General courses		
- Planning and evaluation of screening	2009	1.4 ECTS
- Principles of research in medicine	2009	0.7 ECTS
- Introduction to data-analysis	2009	0.9 ECTS
- Study design	2009	4.3 ECTS
- Biomedical English writing and communication	2010	4.0 ECTS
- Regression analysis	2010	1.9 ECTS
- Using discrete choice experiments in health economics: theoretical and practical issues	2010	17 hours
- Basiscursus oncologie	2011	36 hours
Seminars/Meetings		
- Seminars and symposia at the department of Public Health, Erasmus MC, Rotterdam	2008-2012	116 hours
- Meetings and Masterclasses of the Dutch Cancer Society, Utrecht	2008-2011	40 hours
- Attending and/or organizing Risk perception – Informed decision making – Quality of life (RIQ) meetings, department of Public Health, Erasmus MC, Rotterdam	2009/2010	20 hours
- Transmissiedag, RIVM, Amersfoort	2009	8 hours
- Vaccinatiedagen, Groningen	2010	16 hours
Presentations/Posters		
- Society of Medical Decision Making, poster presentation, Hollywood, United States	2009	20 hours
- Researchmeeting, oral presentation, department of Public Health, Erasmus MC, Rotterdam	2009	20 hours
- Society of Medical Decision Making, oral presentation, Toronto, Canada	2010	40 hours
- Society of Medical Decision Making, poster presentations, Chicago, United States	2011	24 hours
- Subjective Probability, Utility, and Decision Making conference, poster presentation, London, United Kingdom	2011	15 hours
(Inter)national conferences		
- Society of Medical Decision Making, Hollywood, United States	2009	24 hours
- Society of Medical Decision Making, Toronto, Canada	2010	24 hours
- WEON, vereniging voor epidemiologie, Nijmegen	2010	16 hours
- Society of Medical Decision Making, Chicago, United States	2011	24 hours
- Subjective Probability, Utility, and Decision Making conference, London, United Kingdom	2011	29 hours
2. Teaching		
- Supervising two students health sciences for internship	2010	22 hours
- Supervising medical students 'Community projecten'	2010	20 hours