

Biologie & Medizin

HPV Vaccination for Male Adolescents?

EPIDEMIOLOGIC AND ECONOMIC CONSIDERA-TIONS CONCERNING THE HPV VACCINATION

In this paper, the adolescents' knowledge levels of HPV and attitude towards the HPV vaccination for boys were examined. Furthermore, a model of the HPV transmission was created to determine the impact of the immunization rates on the number of HPV infections. The epidemiologic and economic benefit of different immunisation rates was analysed. 30% of HPV infections in females could be averted if the boys who are willing to have the HPV vaccination were vaccinated, too.

DIE JUNGFORSCHERIN



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1. Introduction

1.1 Human Papillomaviruses

Human papillomaviruses fall into two groups regarding clinical disease: Low-risk types (LR HPVs) or high-risk types (HR HPVs). The low-risk types lead to the majority of benign skin and genital warts. High-risk types can cause different types of cancer. HR HPV-16 and HR HPV-18 alone cause at least 70% of cervical cancers all over the world [23].

Different transmission ways are possible. HPV types which cause cervical cancer or genital warts are transmitted by sexual activity. HPV infection and virus growth are limited to the squamous epithelia of humans, which can for example be found in the oesophagus, mouth and vagina. The process of the infection is relatively slow; it takes 12–24 hours for initiation of transcription. HPV is highly infectious. It has an incubation time of 3 weeks to 8 months or more [23, 25, 26].

1.2 Responses to Infection by Human Papillomavirus

There are several risk factors which increase a person's likelihood of an infection with HPV. The most important ones are a large number of lifetime sexual partners, cigarette smoking, and immunosuppression. In most cases, HPV infections are cleared naturally. However, an infection with certain HPV can lead to benign lesions (skin warts or genital warts) and/or cancer. In nearly all cases, cervical cancer is associated with HPV infection. However, HPVs are also involved in other types of cancer, amongst them the cancer of the anogenital region, the oral cavity, and the larynx. Men who have sex with men have an increased risk of anal cancer caused by HPV [4, 12].

1.2.1 Cervical Cancer

Infections by human papillomaviruses are initiated at the basal layer of the

epithelium. The life cycle involves three phases; sequential expression of viral genes leads to viral DNA replication and to the production of infective virions. Viral DNA integration causes the overexpression of two oncoproteins, E6 and E7. These promote the immortalization and transformation of infected cells [1, 4]. This way, cervical cells can become abnormal in appearance, called dysplasia. When dysplastic cells become malignant, the first stage which can be detected is CIS (carcinoma in situ). CIS is a noninvasive cervical cancer. These cells can eventually become invasive [19].

Infections with high-risk HPVs, for example type 16 and 18, can lead to several forms of cancer, in the majority of cases to cervical cancer. "Cervical cancer is a cancer arising from the cervix. It is due to the abnormal growth of cells that have the ability to invade or spread to other parts of the body." [27]. Normally, there are no symptoms in the earlier stages, but later on, symptoms such as pelvic pain, abnormal vaginal bleeding or pain during sexual intercourse may occur. Several types of cervical cancer exist. Approximately 90% of cervical cancers are squamous cell carcinomas. The rest are adenocarcinomas and a low number of other types [27]. Cervical cancer is the third most prevalent cancer which affects women worldwide (in developing countries, it ranks second). Additionally, it is the fourth most common death from cancer. It is responsible for 275'000 deaths per year and it is annually diagnosed in 500'000 women [2, 14].

1.2.2 Genital Warts

High-risk HPVs cause cervical cancer, whereas low-risk HPVs are rarely involved in cervical cancer. However, low-risk HPVs are the cause of genital warts. Even though a lot of HPV types can cause genital warts, 90% of genital warts are caused by only two low-risk HPV types: HPV-6 and HPV-11 [23]. Warts are noncancerous skin growths. In most people who are infected with genital wart-causing HPV types the infection is cleared naturally and therefore they do not develop warts. However, they can still transmit the virus to other people. Genital warts are quite infectious [25].

1.3 Prevention

Factors such as monogamy, personal hygiene, late commencement of sexual activity, and use of barrier contraceptive methods contribute to the primary prevention of HPV infection. Barrier contraceptive methods are contraceptive methods which block the sperm from entering the uterus (for example condoms or diaphragms); however, they are only partially efficient in preventing HPV infection Prophylactic [1]. strategies which induce effective immune responses, for example vaccines, can be protective against subsequent HPV infection. The goal of the vaccines is to prevent cervical cancer and/or genital warts [3]. Currently, there are two capsidbased vaccines for the protection against HPV infection which are approved by the FDA (USA Food and Drug Administration), Gardasil and Cervarix [10].

Gardasil is a quadrivalent vaccine based on virus-like particles (VLPs). It contains VLPs for HPV types 6, 11, 16, and 18, but also offers some cross-protection to closely related HPV types. This vaccine is recommended for females and males who are between 9 and 26 years old. It is injected intramuscularly in a threedose regimen; after the initial injection there are two subsequent doses (two and six months later). Gardasil is the vaccine the school health service St. Gallen currently uses to vaccinate girls [3, 10]. Cervarix is a bivalent vaccine which contains VLPs for HPV types 16 and 18. Like Gardasil, it offers some crossprotection to closely related HPV types. It is recommended for females who are between 9 and 29 years old [10].

The BAG (Bundesamt für Gesundheit, Federal Office of Public Health) and

EKIF (Eidgenössische Kommission für Impffragen, Confederate Commission Questions for of Vaccinations) recommend the HPV vaccination to all adolescents aged between 11 and 14 years, since vaccination before sexual debut (before exposure to HPV) will lead to the greatest public health benefit. The vaccination has been recommended for girls since 2007 because they are mainly affected by HPV. Within the frame of the cantonal calendar of vaccination the vaccination is free for girls who are between 11 and 14 years old. The vaccination might also benefit females aged from 15 to 26, which is why it is free of charge for them as well. As of recently (since 1 July 2016), the HPV vaccination for male adolescents is also recommended and the HPV vaccination is also costless for males aged 11 to 26 years [3, 8, 16].

Both vaccines are highly immunogenic, are shown to be well-tolerated, and prove to be efficacious in protecting against infection with HPV-16 and HPV-18 (and for Gardasil also HPV-6 and HPV-11) [3]. Potential reasons for parents not to have their children vaccinated are vaccine cost, concerns about the vaccine's effect on sexual behaviour, low perceived risk of HPV infection, and fear of potential side effects. Additionally, parents of boys stated that they did not want to vaccinate their sons because of the perceived lack of direct benefit [15]. Protective HPV vaccines are considerably successful. But still, there is a lack of crossprotection against many HPV types which are associated with malignancies. Modifications of protective vaccines are under development and testing [10].

1.4 Questions and Theses of this Paper

In recent years, HPV and cervical cancer have received increased attention. HPV vaccination of adolescent girls has been implemented in many countries. One limitation of the current vaccine policy in females is the low vaccination coverage: Currently, 70% of the females are vaccinated in St. Gallen (Angela Walt, personal communication, 9 September 2014). A major point of debate is whether boys should also be vaccinated against HPV or not. Boys can suffer from HPV-associated warts, but also from HPV-associated cancers, such as anal cancer. More importantly, asymptomatic infection of the penis is the main route of transmission of the virus to females. The aim of this paper is to find out if boys are willing to have the vaccination and if immunisation of boys would result in a benefit for the whole population. Epidemiologic and economic consequences of boys being vaccinated will be evaluated. Another goal is to show the knowledge level of HPV in adolescents, since immunisation rates are linked to knowledge levels.

The following research theses were defined:

- The HPV vaccination for boys will be accepted by the adolescents and the adolescents are well-informed about HPV.
- Boys being vaccinated against HPV will result in epidemiologic and economic benefit.

2. Material and Methods

2.1 Survey

I was offered the opportunity to conduct the survey in cooperation with the school health service St. Gallen. Two different questionnaires in German were created, one for the boys and one for the girls. Each questionnaire contained seven questions. The first four questions aimed at showing the level of knowledge about HPV and the HPV vaccination, whereas the last three questions asked the male and female adolescents their opinions concerning the HPV vaccination for boys. The questions were the same for the male and female adolescents; just adapted to the perspective of the girls and boys, respectively. In order to have a



realistic result, there were three answer possibilities in the first four questions. Two of these answer possibilities were in the form of a statement. One statement was correct and the other statement was incorrect. The third possibility was the answer "I do not know". The questionnaires can be found on page 10 and 13.

On 25 August 2014 the questionnaires were handed in to the school health service of the city of St. Gallen. The survey took place from 29 August to 21 November 2014. The school service conducted a compulsory examination with students who attended secondary school (ninth grade). They were about 15 years old and came from St. Gallen and surrounding areas. The students had attended an information event concerning HPV and the HPV vaccination in the seventh grade. During the time in which the survey took place, I was given questionnaires from between one and five classes every week by the school health service. In total, 307 questionnaires were handed out to the students. All questionnaires were returned to me, but three questionnaires were invalid. Therefore, 304 questionnaires were evaluated. 158 boys and 146 girls participated in the survey. An Excel spreadsheet was filled with the data and the sums and mean values for the boys and the girls were calculated.

2.2 Model

The aim was to create a model which shows the factors that influence the rate of infection. The model, which can be seen in figure 1, was the base for the further calculations of this paper. Figure 2 shows the parameters and model equations and table 1 displays the abbreviations which were used in the model.

The program used to create the model is called Dynasys (Version 2.0.2, Modsim,



Fig. 1. A model created by means of the program "Dynasys" shows the factors that influence the rate of infection

2014). Dynasys is a tool which enables the modelling and simulation of a dynamic system. It is developed as a flow diagram based on parameters, exogenous quantities, table functions, intermediate sizes, state variables and changes of state. The numerical method used to calculate the simulations is either the Euler or the Runge-Kutta method. Dynasys provides the results in the form of a spreadsheet or a diagram (time or phase diagram) [18].

The aspiration was to show the influence of the HPV vaccination on the first five years of sexual activity in young adults. One month was determined as one time interval. As it was found in [7], the median age of the first sexual intercourse is 18.5 years for males and females. Therefore, the model was applied to adults who are between 18 and 23 years old. I wanted to find out how many women were infected with HPV after five years (60 time intervals) depending on the immunisation rates. The results were the basis for two considerations, the epidemiologic model and the cost assessment model. The number of infected males or females is influenced by several parameters. One parameter is the total number of males and females, out of which some are infected (the starting value of infected males and females). Due to the immunisation rates, some males and females are immune against HPV infection. The HPV transmission is also influenced by the proportion of males and females of the population who are sexually active, the number of partners per month, the probability of the virus transmission, the proportion of infected males and females, and the clearance rate.

In this model, the initial point was the total number of males and females, respectively. As the number had to be high enough in order to provide reliable results, it was determined as 10,000 in each case. [20] revealed that in this scenario 70 males and 650 females would be infected with HPV-16 or HPV-18 in the beginning. These numbers were the starting values of infected males and females.

The immunisation rates were varied in order to find out which immunisation rate in males and females would result in the greatest epidemiologic and economic benefit. I was particularly interested in eight scenarios. These were: No vaccinations (0% vaccinated people), the current situation (70% of the females and no males vaccinated), a realistic scenario (70% of females and

Zustandsgleichung	
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Zustandsänderung	en
Increase_Infecte	d_M = (Sexually_Active_Proportion_M*Probability_Virus_Transmission_M*
	Proportion_of_Infected_F*Partners_per_Month_M*Susceptible_M)-Clearance_Rate_M*Infected_N
Increase_Infecter	<pre>d_F = (Sexually_Active_Proportion_F*Probability_Virus_Transmission_F*</pre>
	Proportion_of_Infected_M*Partners_per_Month_F*Susceptible_F)-Clearance_Rate_F*Infected_F
Parameter	
Partners_per_Mo	nth_M = 0.08
Probability_Virus	_Transmission_M = 0.6
Sexually_Active_I	Proportion_M = 0.8
Total_M = 10000	
Immunisation_R	ate_M = 0
Partners_per_Mo	nth_F = 0.08
Probability_Virus	_Transmission_F = 0.6
Immunisation_R	ate_F = 0
Sexually_Active_I	Proportion_F = 0.8
Total_F = 10000	
Clearance_Rate	M = 0.01
Clearance_Rate	_F = 0.01
Zwischenwerte	
Susceptible_M =	(Total_M-Infected_M)*(1-Immunisation_Rate_M)
Susceptible_F =	(Total_F-Infected_F)*(1-Immunisation_Rate_F)
Proportion_of_In	/ected_M = Infected_M/Total_M
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Fig. 2. The equations and parameters which were used in the model



males vaccinated), the optimal scenario for females (90% of the females and no males vaccinated), the optimal scenario (90% of females and males vaccinated), light vaccination coverage (45% of females and males vaccinated), current rate in females and light vaccination coverage in males (70% of females and 30% of males vaccinated), and the maximal rates (100% in females and males). In addition to these scenarios, the number of infected males and females after five years were calculated for various immunisation rates in order to receive a precise three-dimensional model. The immunisation rates used for the calculations were 0, 0.1, 0.3, 0.45, 0.7, 0.9, and 1 in males and females.

Tab. 1. The abbreviations which were used in the model			
Infected_M	The number of infected males		
Infected_F	The number of infected females		
Sexually_Active_Proportion_M	The sexually active proportion in the male population		
Sexually_Active_Proportion_F	The sexually active proportion in the female population		
Probability_Virus_Transmission_M	The probability for males to cont- ract a HPV infection per partnership		
Probability_Virus_Transmission_F	The probability for females to cont- ract a HPV infection per partnership		
Proportion_of_Infected_M	The number of infected males divi- ded by the total number of males		
Proportion_of_Infected_F	The number of infected females divided by the total number of females		
Susceptible_M	The males who can be infected		
Susceptible_F	The females who can be infected		
Total_M	The total number of males		
Total_F	The total number of females		
Immunisation_Rate_M	The immunisation rate in males		
Immunisation_Rate_F	The immunisation rate in females		
Clearance_Rate_M	The proportion of the infected males who heal the infection		
Clearance_Rate_F	The proportion of the infected females who heal the infection		
Partners_per_Month_M	The number of partners per month in males		
Partners_per_Month_F	The number of partners per month in females		

The number of susceptible males/females is influenced by the total number of males/females, the immunisation rate and the number of infected males/ females.

It was found out in [7] that 80% of the males and females who are 20 years old are sexually active. This represents the age group of the model. Hence, the parameter sexually active proportion of the population was determined as 0.8 for both males and females.

In the absence of published data, an estimated value of 0.08 partners per month was chosen (all estimates were selected after personal discussion with an expert in infectious diseases, Pietro Vernazza, 27 February 2016).

Per sexual contact with an infected person, the probability of HPV transmission is about 0.1. However, this model was not based on single sexual contacts, but on partnerships. As there was no data about the probability of HPV transmission in a partnership where one person is infected, this parameter was estimated at 0.6.

To calculate the proportion of infected males, the number of infected males was divided by the total number of males. The same calculations were done for the women.

The clearance rate is the proportion of the infected people who heal the infection. In the absence of published data, the clearance rate per month was estimated at 0.01.

2.2.1 Epidemiologic Model

By means of the model the number of males and females who were infected with HPV after five years was calculated. Furthermore, the vaccination costs were calculated to be able to compare the benefit to the costs. The immunisation costs approximately 300 CHF per adolescent (Pietro Vernazza, personal communication, 18 March 2016). To find out the vaccination costs, I multiplied the immunisation rate in the male adolescents by the total number of males (10,000) and by 300 CHF. The same calculations were conducted for the females. The vaccination costs were the sum of the two values.

An Excel spreadsheet was filled with the number of infected women and men after 60 time intervals. The numbers were rounded to tens. Then, the averted infections were calculated by subtracting the number of infected males/females at the current immunisation rates from the number of infected males/females when no one was vaccinated. The number of averted infections in females was displayed in a three-dimensional model which was created with Matlab. Furthermore, the costs per averted infection in females were calculated (vaccination costs divided by the number of averted infections in females). The results were rounded to tens. Also, the number of averted infections in females per vaccination was calculated by dividing the number of averted infections in females by the number of vaccinations and rounded the results to two decimal places. The eight different scenarios, the corresponding immunisation rates, the number of averted infections in males and females, and the number of averted infections in females per vaccination were displayed in a table.

2.2.2 Cost Assessment Model

In this model, the goal was to find out which immunisation rates in males and females would result in the best costbenefit ratio. The cost-benefit ratio is an expression for the ratio between expenses for preventive measures (vaccinations) and the money which could be saved when there was no need for treatment of HPV-caused diseases. Firstly, the numbers of infected girls after 60 time intervals depending on the immunisation rate were compared. These numbers were calculated with the help of Dynasys and then an Excel spreadsheet was filled with the results. For the vaccination costs, the same calculations were conducted as in the epidemiologic model. Again, an Excel spreadsheet was filled with the costs.

I wanted to find out how much money was saved because there was no need for the treatment of HPV-caused diseases. Firstly, the number of infected females after 60 time intervals (at the given vaccination rates) was subtracted from the number of infected women after 60 time intervals when no one was vaccinated. The result was the number of averted infections in females. To determine the costs, the relevant number is the number of females who develop carcinoma. Therefore the number of infected females was multiplied by the rate that expressed how many of the infected women would develop carcinoma in the following

years. It was stated in [7] that the cure rate is 0.9, therefore the wanted rate was 0.1. Lastly, the result was multiplied by the costs for the treatment of a disease caused by HPV. For the treatment costs, an estimated value of 75000 CHF was chosen as there was no published data.

In the end, the vaccination costs were subtracted from the saved money and the results were rounded to ten thousands. The final costs were displayed in an Excel spreadsheet.

3. Results

3.1 Survey

The knowledge of HPV in girls and boys differs, as <u>table 2</u> shows. The first question asked them about the information event about HPV and about

Tab. 2. Means of the answers to questions concerning knowledge about HPV displayed as percentages (rounded). The correct answer to each question is marked in green, the incorrect answer is marked in red, and the answer "I do not know" is not marked.

Questionnumber	Answer1	Answer 2	Answer 3
1 (male): Do you remember the infor- mation event about HPV which took place in seventh grade?	56%	23%	21%
1 (female): Do you remember the information event about HPV which took place in seventh grade?	62%	25%	13%
2 (male): Do you know how HPV is transmitted?	4%	79%	17%
2 (female): Do you know how HPV is transmitted?	5%	84%	12%
3 (male): Do you know what the con- sequences of an HPV infection might be for you?	19%	35%	46%
3 (female): Do you know what the consequences of an HPV infection might be for you?	50%	33%	17%
4 (male): Do you know why boys can also be vaccinated against HPV although only girls can suffer from cervical cancer?	53%	19%	29%
4 (female): Do you know why boys can also be vaccinated against HPV although only girls can suffer from cervical cancer?	73%	10%	18%



the HPV vaccination. About 6% more girls than boys remembered it correctly. In the second question, the participants

were asked how HPV is transmitted. 79% of the 158 boys who participated knew that human papillomaviruses

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Tab. 3. Means of the answers to questions concerning the adolescents' attitude towards HPV vaccination for boys displayed as percentages (rounded)

Questionnumber	Yes	No
5 (male): Would you have the vaccination if it was provided for boys?	68%	32%
5 (female): Do you support the HPV vaccination for boys?	96%	4%
6 (male): Do you hope to be better protected against genital warts through the vaccination?	77%	23%
6 (female): Do you hope to be better protected against genital warts and cervical cancer by boys being vaccinated against HPV?	96%	4%
7 (male): Do you think it is necessary to vaccinate boys although they are not directly affected by cervical cancer?	54%	46%
7 (female): Do you think it is necessary to vacci- nate boys although they are not directly affected by cervical cancer?	78%	22%





are transmitted via unprotected sexual intercourse; on the other hand, 17% did not know how HPV is transmitted. The rest chose the incorrect answer. Compared to these numbers, 83% of the girls knew how the viruses are transmitted. 12% said that they did not know how the transmission works, and 5% (slightly more than the boys' result) picked the incorrect answer. Question 3 asked the adolescents about the consequences of an infection with HPV. 46% of the boys answered the question with "I do not know" and 19% thought that they could contract testicular cancer. 35% chose the correct answer. 50% of the girls thought that they would contract a uterus inflammation in case of an infection with HPV. About one third (33%) of the female participants knew that they could get cervical cancer or genital warts. In question 4, the students were asked whether they knew why boys should also be vaccinated against HPV. 20% more girls than boys gave the correct answer.

Not only concerning the level of knowledge but also in their attitude towards the HPV vaccination for male adolescents there were differences in boys and girls, as table 3 indicates. In question 5, the boys were asked whether they would have the HPV vaccination if the school health service provided the service for them or not. More than two thirds (68%) of the boys said that they would have the vaccination against HPV if the service was provided to them. The girls were asked whether they approved of boys being vaccinated or not. 96% of the participating girls were supportive of boys being vaccinated against HPV. In question 6, the goal was to find out whether the adolescents hoped that they would be better protected against genital warts (and against cervical cancer for the girls) if boys were vaccinated. 77% of the boys and 96% of the girls hoped to be better protected. Question 7 was about the necessity of boys also being vaccinated. 54% of the boys and 78% of the girls thought that it was necessary to vaccinate the boys against HPV.

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3.2 Model

The epidemiologic model determines the number of averted infections in females after five years; the results are represented in <u>figure 3</u>. In <u>table 4</u>, the different scenarios, the corresponding immunisation rates, the number of averted infections in females and males, and the number of averted infections in females per vaccination are displayed. The cost difference and costs per averted infection in females were also calculated.

The second scenario simulated the current situation. 70% of the females and no males were vaccinated. Due to the immunisation, 980 infections in females and 590 infections in males were averted. One vaccination averted 0.14 infections in females, and each averted infection in females came at a cost of 2140 CHF. The difference between saved money and vaccination costs equalled 5.25 million CHF.

The realistic scenario was determined under the assumption that the immunisation rate in girls has now reached a maximum at 70% and that boys would get vaccinated at the same rate, which was also supported by the results from the survey. These rates resulted in 1180 averted infections in females. Therefore, 200 infections in females could be averted by increasing the immunisation rate in boys from 0% to 70%. In males, 1310 infections could be averted. One averted infection in females came at a cost of 3560 CHF; per vaccination, 0.08 infections in females were averted. The cost difference equalled 4.65 million CHF.

The scenario with the highest cost difference was the optimal scenario in females (when 90% of the females were vaccinated). Then, the difference between saved money and vaccination costs equalled 6.23 million CHF.

The scenarios with the highest number of averted infections were the "maximal

rates" scenario and the optimal scenario. When 100% of the population were vaccinated, 1290 infections in females and 1580 infections in males were averted. The immunisation rate of 90% in males and females resulted in 1280 averted infections in females and 1500 averted infections in males.

4. Discussion

The aim of this paper was to evaluate whether additional vaccination of boys would help to minimise disease burden of HPV infection in women. I first evaluated if the boys were willing to undergo vaccination for a disease that mainly affects females. In fact, the results of the survey demonstrated that this was the case. 68% of the boys stated that they would have the vaccination if the school health service provided the service to them. The girls were supportive of boys being vaccinated: 96% of them approved HPV vaccination for boys.

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Tab. 4. The immunisation rates, the numbers of averted infections in males and females, and the number of averted infections per vaccination for the different scenarios. The number of averted infections is the difference between the number of infected females or males at the current immunisation rates and 1,650 infected females respectively 1,620 infected males when 0% were vaccinated.

Scenario	Immunisation rates (F, M)	Averted infec- tions (F)	Averted infec- tions (M)	Averted infec- tions (F) per vaccination
No vaccinations	0%, 0%	0	0	-
Current situation	70%, 0%	980	590	0.14
Realistic scenario	70%, 70%	1180	1310	0.08
Optimal scenario (females)	90%, 0%	1190	730	0.13
Optimal scenario	90%, 90%	1280	1500	0.07
Light vaccination coverage	45%, 45%	940	1000	0.10
Current rate in females, light vaccination coverage in males	70%, 30%	1070	910	0.11
Maximal rates	100%, 100%	1290	1580	0.06





	Fragebogen Mädchen, 9. Oberstufe, Herbst 2014
1.	 Kannst du dich noch an die Informationen zur HPV-Impfung i der ersten Oberstufe erinnern? Ja, wir wurden über die Impfung informiert und darüber, wie man sich vor einer Infektion mit den HP-Viren schützen kann. Ja, wir wurden über die Impfung und über die verschiedenen Behandlungsmöglichkeiten von Gebärmutterhalskrebs informiert. Nein, daran kann ich mich nicht mehr erinnern.
2.	 Weisst du, wie die HP-Viren übertragen werden? Ja, die Viren werden durch Berührung übertragen. Ja, die Viren werden durch ungeschützten sexuellen Kontakt übertragen. Nein, ich weiss es nicht.
3.	 Bist du darüber informiert, welche Folgen eine Infektion mit dem HP-Virus für dich haben könnte? Ja, es ist möglich, dass ich eine Gebärmutterentzündung bekomme. Ja, es ist möglich, dass ich Krebs oder Genitalwarzen bekomme. Nein, ich weiss es nicht.
4.	 Weisst du, warum auch Jungen gegen HPV geimpft werden sollten, obwohl nur Mädchen an Gebärmutterhalskrebs erkranken können? Ja, weil Jungen die Viren auf Mädchen übertragen können. Ja, weil die Impfung auch vor anderen Infektionskrankheiten schützt. Nein, ich weiss es nicht.
5.	Würdest du es unterstützen, dass auch die jungen Männer gegen HPV geimpft werden? Da Nein
6.	Erhoffst du dir, dass du einen erhöhten Schutz gegen Genitalwarzen und Gebärmutterhalskrebs hast, wenn die Jungen auch geimpft werden?

Ja
Nein

7. Findest du es nötig, die jungen Männer zu impfen, obwohl sie nicht direkt von Gebärmutterhalskrebs betroffen sind?

Ja
Nein

The second question was whether vaccination of boys at the rate found in the survey (around 70%) would in fact result in a lower number of infected women. Doubling the cost of vaccination by vaccinating girls and boys at the current rate for girls resulted in a reduction of infections in females by 30% compared to the current situation. However, among the eight theoretical strategies for immunisation rates in males and females, the "current situation" scenario had the highest number of averted infections in females per vaccination (one vaccination averted 0.14 infections in females), and therefore was the most efficient scenario.

At relatively low knowledge levels, almost 70% of the males said that they were willing to have the vaccination. The survey showed that the male adolescents did have a certain level of knowledge, but they were not well-informed about HPV since there were several knowledge gaps. Generally, the girls were better informed about HPV and the HPV vaccination than the boys were. Nevertheless, the girls were not well-informed about HPV as they had certain misconceptions. The first research hypothesis stated that the HPV vaccination for boys would be accepted by the adolescents and that they were well-informed about HPV. This hypothesis was only partly confirmed, as the adolescents responding the survey approved vaccination of boys despite limited knowledge about the biology and consequences of HPV infection. Higher knowledge levels would enable the adolescents and young adults to protect themselves better against HPV. Furthermore, increasing knowledge levels by launching an information campaign might result in a higher willingness of the boys and of the girls to have the HPV vaccination, as immunisation rates are linked to knowledge levels.

The higher the immunisation rates were, the more infections could be averted. Therefore, the scenario in which 100% of males and females were vaccinated resulted in the highest number of averted infections. However, these rates did not result in a high efficiency nor in more economic benefit than the current rates. The same accounted for the optimal scenario: When 90% of the males and females were vaccinated, the number of averted infections was high, but the cost difference and the efficiency were low.

Halving the number of vaccinations by vaccinating 90% of the females and no males, the averted infections in females were reduced by 7%. These immunisation rates prevented a high number of infections in females at a relatively low number of vaccinations; hence, a high efficiency was found for this scenario. Furthermore, among the eight scenarios, the highest cost difference between saved money and vaccination costs occurred in this scenario. Therefore, these rates might be worth striving for. However, the immunisation rate in females might have reached its maximum at 70% under current circumstances, as there has been no upward tendency lately (Pietro Vernazza, personal communication, 18 March 2016). In order to increase the immunisation rate in girls from 70% to 90%, an enormous immunisation campaign would have to be launched, resulting in huge cost.

Vaccinating 45% of the boys and girls resulted in 54% more infections in females compared to using the same number of vaccinations by vaccinating 90% of the girls.

The first priority of a vaccination programme should be to avert infections and in this way prevent HPV from spreading. However, economic considerations and the efficiency also have to be taken into account. It is important to weigh the advantages and disadvantages of the different immunisation rates and to come to a compromise over the different interests. In addition, there are limitations to the immunisation rates which result from the restricted willingness of the population to have the vaccination. An immunisation rate of 90% in females and 0% in males would result in the greatest economic benefit, in a good efficiency, and in a high number of averted infections. Therefore, this scenario seems to be worth aspiring to. However, under the present circumstances, only 70% of the girls are willing to have the vaccination (Angela Walt, personal communication, 9 September 2014). Increasing this proportion by launching a campaign would involve high cost and effort. Therefore, it would make more sense to vaccinate the 70% of the boys who stated that they were ready to undergo vaccination in addition to 70% of the girls. This way, a high number of infections in females could be prevented without having to launch an expensive campaign. Vaccinating boys and girls would also limit the number of infections in boys, which might further reduce morbidity in males. Males are affected by HPV as well due to penile, oral, and anal cancers. In particular men who have sex with men have an increased risk of contracting HPV-caused cancer. They would benefit directly from being vaccinated against HPV. This fact was not scope of this study [6, 12]. The second research hypothesis stated that vaccinating the boys would result in epidemiologic and economic benefit. It was partly confirmed: The epidemiologic model revealed that boys being vaccinated would reduce the number of infections, but the cost assessment model showed that the highest differences occurred when no males and a high number of females were vaccinated.

[11] and [22] have shown that boys were moderately willing to have the HPV vaccination (on average 35% of them would have the vaccination). About half of the boys were indecisive. In this survey, the proportion of boys who would have the vaccination was higher, but they did not have the option to say that they did not know whether yes or no. More or less, the results of the survey corresponded to the results of these studies. It was demonstrated by [13], [22], and [24] that females had greater knowledge of HPV than males. This corresponds to my results. However, as in my results, the adolescents had some misunderstandings. Knowledge levels in the other studies were generally lower than the ones I had found out, but one has to take into account that the students who took part in my survey had attended an information event two years before.

For the questions which tested the adolescents' knowledge about HPV, I offered three answer possibilities. One possibility was a correct statement, another possibility was an incorrect statement, and the third possibility was to say that they did not know the answer. Therefore, the survey did not only rely on the statement of the participants on whether they knew or did not know the answer, but I could also see the percentage of participants who thought that they knew the correct answer but actually did not. This increases the validity of the results. For the last four questions, the students could only answer yes or no. They were not able to express their precise opinion, for example that they wish to have more information before having the vaccination. In retrospect, I would give them the opportunity to express their opinion more precisely. The number of participants was quite high. The results of this survey can only be applied to adolescents who are between 14 and 16 years old and who come from the German-speaking part of Switzerland. For this group of adolescents, the results are fairly representative, but not necessarily for other groups. In order to know how the adolescents' knowledge of HPV and attitude towards the HPV vaccination for boys in Switzerland is, it would be necessary to conduct surveys with students from all parts of Switzerland as there are cultural differences between the different language regions of Switzerland.



Other studies confirmed the results from the epidemiologic model: [17] concluded that HPV vaccination would decrease the numbers of HPV infections. precancerous lesions and cervical cancer. [6] revealed that vaccinating 70% of the females would reduce HPV-16/18 prevalence in females by 65% in about 40 years, whereas vaccinating 70% of the males and females would reduce the prevalence in females by 85% in 40 years. This corresponds to the results of the model in as much as vaccinating the males and females resulted in more averted infections in females than just vaccinating the females. However, the epidemiologic model calculated the number of infected females after five years. When 70% of the females and no males were vaccinated, the decrease of HPV infections in females equalled 59% in five years; when 70% of the males and females were vaccinated, the number of infections in females decreased by 72%. The decrease of HPV-16/18 prevalence was more rapid in the epidemiologic model than in the model of the study which it was compared to, reaching almost the same results in five instead of 40 years. This difference might be due to different modelling of the HPV transmission and due to different parameters. Nevertheless, the results of the models showed the same tendency and confirmed that vaccinating the girls might be effective, but vaccinating girls and boys would help to prevent HPV from speading by averting additional infections. The results of the cost assessment model were confirmed by [9], stating that a higher vaccination coverage in females would be more cost-effective and effective than a higher coverage in boys. More precisely, this study has found out that having an immunisation rate of 90% in female adolescents is more profitable than vaccinating 71% of both boys and girls. Therefore, my results correspond to the results of this study. [5] has shown that vaccinating young girls against HPV might be cost-effective, but vaccinating boys against HPV might not be cost-effective in countries that can reach high immunisation rates in girls.

In order to create the "Dynasys" model, I had to simplify the transmission of HPV. I restricted the model to the sexual transmission and I left out other routes of transmission (for example from mother to child during birth) which are not common, but possible. In addition, I only included sexual intercourse between males and females and I did not take homosexual sex into account.

A very important factor in the spread of a sexually transmitted disease is the heterogeneity of the sexual behaviour (for example the rate of sexual partner change). In a few people, this rate is very high; these people have an enormous influence on the HPV spread. However, I was not able to include this heterogeneity in my model, since this would be beyond my abilities.

Another limitation to the credibility of the model is that some of the parameters had to be estimated due to absence of published data. Furthermore, I assumed that having the vaccination would result in complete immunity. However, this is not the case. Gardasil protects against HPV-types 6, 11, 16, and 18. Most cases of cervical cancer and genital warts are caused by these HPV-types, but there are also other HPV-types which can cause cancer. In the first attempt of modelling the HPV transmission, the model was based on random matings instead of partnerships. However, this does not reflect reality. Additionally, I did not restrict myself to a certain number of time intervals but instead wanted to find out how many time intervals it would take to infect all the unvaccinated women with HPV.

Moreover, no clearance rate was included. As a consequence, the results were implausible. However, in the second attempt, the model was based on partnerships instead of random matings and an average number of partners per time interval (one month) was determined. A limit of time intervals and the clearance rate were also included, which increased the plausibility of the model.

The results of the cost assessment model should be treated with a certain caution. The cost assessment model only gives a rough approximation of the resulting cost difference. In reality, these cost assessments are complex calculations including various factors which could not be considered in this model. Furthermore, for the treatment costs an estimated average value of 75000 CHF was chosen, causing the results to be more imprecise. The cost assessment model of this paper is not an in-depth analysis of the economic consequences, but still gives an idea of the possible resulting costs of the different scenarios.

All of these simplifications reduce the validity of the results. Nevertheless, the model gives a good impression of how the immunisation rates influence the rate of HPV transmission in young adults. Also, other studies in this field of research came to similar results as I did.

5. Conclusions

Both male and female adolescents had some basic knowledge about HPV. However, there were some misunderstandings and knowledge gaps. Due to the prevalence of HPV, more information is needed. It would make sense to raise the awareness of adolescents about HPV. The school health service already organizes an information event and distributes brochures to students. Still, there are several possibilities to increase the student's knowledge level, for example through a second information event. This way, the school doctors could teach students the fundamental knowledge in the first event and build upon these basics in the second one. Another possibility is to inform the students through their schools. Teachers could tell their students in sexual education lessons about HPV. Furthermore,

parents should be better informed about HPV. The parents could consequently inform their children about HPV explaining to them the reasons why they should or should not be vaccinated. As the knowledge level about HPV was lower in boys than in girls, especially the boys should receive more information. High knowledge levels enable the adolescents to protect themselves better against HPV. An additional effect is that the immunisation rate is linked to the knowledge level; higher knowledge levels might have a positive effect on the immunisation rate which means that the vaccination programme would benefit. Therefore, an information campaign should be launched.

The model showed that the rates which would result in the highest number of averted infections are the maximal rates (100% in males and females), but among the eight scenarios the best efficiency was found for the scenario which simulated the current situation; then, the immunisation rates were 70% in females and 0% in males. However, the highest cost difference occurred when 90% of the females and no males were vaccinated. Taking into account all of the results, an immunisation rate of 90% in females seems to be desirable, as the efficiency was quite high, many infections in females were averted, and the cost difference was high. However, increasing the immunisation rate in girls from 70% to 90% would involve great effort and cost, as an enormous vaccination campaign would have to be launched to motivate more girls to have the vaccination. But the survey demonstrated that almost 70% of the boys would have the vaccination if it was provided to them. Vaccinating 70% of the boys in addition to 70% of the girls would reduce the number of infections in females by 30% compared to the current situation. Therefore, it would make sense for the school health service to launch the HPV vaccination programme not only for girls, but for boys, too. This has previously been considered. As a substantial proportion of the boys were willing to have the

Nur eine Antwort pro Frage möglich

1.



Fragebogen Jungen, 9. Oberstufe, Herbst 2014 Kannst du dich noch an die Informationen zur HPV-Impfung in der ersten Oberstufe erinnern? Ja, wir wurden über die Impfung informiert und darüber, wie man sich vor einer Infektion mit den HP-Viren schützen kann. Ja, wir wurden über die Impfung und über die verschiedenen Behandlungsmöglichkeiten von Gebärmutterhalskrebs informiert.

- Nein, daran kann ich mich nicht mehr erinnern.
- 2. Weisst du, wie die HP-Viren übertragen werden?
 - Ja, die Viren werden durch Berührung übertragen.
 - Ja, die Viren werden durch ungeschützten sexuellen Kontakt übertragen.
 - Nein, ich weiss es nicht.
- 3. Bist du darüber informiert, welche Folgen eine Infektion mit dem HP-Virus für dich haben könnte?
 - Ja, es ist möglich, dass ich Hodenkrebs bekomme.
 - Ja, es ist möglich, dass ich Genitalwarzen bekomme.
 - Nein, ich weiss es nicht.
- 4. Weisst du, warum auch Jungen gegen HPV geimpft werden sollten, obwohl nur Mädchen an Gebärmutterhalskrebs erkranken können?
 - Ja, weil Jungen die Viren auf Mädchen übertragen können.
 - Ja, weil die Impfung die Jungen auch vor anderen Infektionskrankheiten schützt.
 - Nein, ich weiss es nicht.
- 5. Würdest du dich, wenn die Impfung auch für Jungen zugelassen wird, impfen lassen?
 - 🔲 Ja
 - Nein
- 6. Erhoffst du dir, dass du nach der Impfung einen erhöhten Schutz gegen Genitalwarzen hast?
 - 📙 Ja
 - Nein
- 7. Findest du es nötig, die jungen Männer zu impfen, obwohl sie nicht direkt von Gebärmutterhalskrebs betroffen sind?
 - Ja
 - Nein



vaccination, the programme would meet with considerable success.

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More research should be conducted in order to find out which immunisation rates would result in the greatest public health benefit. For that purpose, more sophisticated models need to be created. Furthermore, the analyses are to be expanded and should include all age groups relevant to the HPV vaccination. Additionally, in-depth analyses of the consequential costs should be carried out. Also, the model only had a look at the effect of vaccinating males and females after five years, but did not evaluate the long-term consequences of vaccinating the population at certain rates. This should also be done in order to be able to determine the optimal immunisation rates.

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