Modeling the consequences of regional heterogeneity in human papillomavirus (HPV) vaccination uptake on transmission in Switzerland

Maurane Riesen\textsuperscript{a,b,*}, Victor Garcia\textsuperscript{a}, Nicola Low\textsuperscript{a}, Christian L. Althaus\textsuperscript{a}

\textsuperscript{a}Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
\textsuperscript{b}Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

Abstract

Background: Completed human papillomavirus (HPV) vaccination by age 16 years among women in Switzerland ranges from 17 to 75% across 26 cantons. The consequences of regional heterogeneity in vaccination coverage on transmission and prevalence of HPV-16 are unclear.

Methods: We developed a deterministic, population-based model that describes HPV-16 transmission among young adults within and between the 26 cantons of Switzerland. We parameterized the model using sexual behavior data from Switzerland and data from the Swiss National Vaccination Coverage Survey. First, we investigated the general consequences of heterogeneity in vaccination uptake between two sub-populations. We then compared the predicted prevalence of HPV-16 after the introduction of heterogeneous HPV vaccination uptake in all of Switzerland with homogeneous vaccination at an uptake that is identical to the national average (52%).

Results: HPV-16 prevalence in women is 3.34% when vaccination is introduced and begins to diverge across cantons, ranging from 0.14 to 1.09% after 15 years of vaccination. After the same time period, overall prevalence of HPV-16 in Switzerland is only marginally higher (0.55 %) with heterogeneous vaccination uptake than with homogeneous uptake (0.49%). Assuming inter-cantonal sexual mixing, cantons with low vaccination uptake benefit from a reduction in prevalence at the expense of cantons with high vaccination uptake.

Conclusions: Regional variations in uptake diminish the overall effect of vaccination on HPV-16 prevalence in Switzerland, although the effect size is small. Cantonal efforts towards HPV-prevalence reduction by increasing vaccination uptake are impaired by cantons with low vaccination uptake. Harmonization of cantonal vaccination programs would reduce inter-cantonal differences in HPV-16 prevalence.

Keywords: human papillomavirus, vaccination, sexual behavior, mathematical model, Switzerland

1. Introduction

The first vaccine against human papillomavirus (HPV) was licensed in 2006 and is now widely used in many countries. At the population-level, HPV vaccination has led to a substantial reduction in the prevalence of the targeted HPV types (HPV-16/18/6/11 for the quadrivalent vaccine) as well as anogenital warts [1]. Most vaccination programs target girls or young women before they become sexually active. Regional differences in vaccination uptake have emerged in some countries after implementation of the vaccination programs [2, 3]. These differences are very pronounced in Switzerland where the proportion of 16 year old girls completing the three dose vaccination schedule ranges from 17 to 75% in 26 cantons (states) (Fig. 1) [4, 5]. The cantonal heterogeneity in vaccination uptake can be partly explained by differences in the way the vaccine is offered to girls and young women (e.g., school-based programs, general practitioners or gynecologist). Other factors, such as cultural differences between the cantons might play a role too. To date, the potential epidemiological consequences of regional variation in vaccination uptake on transmission and prevalence of HPV in Switzerland and other countries are not well understood.

Mathematical models have played an important role in estimating the expected impact of vaccination on the transmission of HPV [6–8] and other infections [9]. Investigating the consequences of spatial heterogeneity in vaccination uptake has received less attention, with some mentionable exceptions. Studies on measles vaccination [10, 11] and canine rabies [12] showed that spatial vaccination heterogeneity leads to less effective control of the targeted disease when compared with homogeneous vaccination. The debate about heterogeneity in HPV vaccination uptake has focused on sex-specific vaccination [13, 14]. Sex-specific vaccination is expected to be more beneficial than homogeneous (male/female) vaccination in a heterosexual population because both sexes are required for transmission. Therefore if only one sex is targeted by the

\*Corresponding author.

Email addresses: maurane.riesen@ispm.unibe.ch (Maurane Riesen), vic-garcia@gmx.net (Victor Garcia), nicola.low@ispm.unibe.ch (Nicola Low), christian.althaus@alumni.ethz.ch (Christian L. Althaus)
The aim of this study was to investigate the impact of heterogeneous vaccination uptake and different sexual mixing scenarios on the prevalence of HPV-16 in Switzerland. We developed a mathematical model of HPV-16 transmission among young heterosexual adults. We parameterized the model using Swiss sexual behavior data and calculated the pre-vaccination prevalence and the basic reproduction number ($R_0$) of HPV-16. First, we investigated the general consequences of heterogeneous vaccination uptake in a simple model with two sub-populations. We then simulated the transmission of HPV-16 within and between the 26 cantons of Switzerland assuming three different scenarios for inter-cantonal sexual mixing. We compared the predicted post-vaccination prevalence of HPV-16 after the introduction of heterogeneous HPV vaccination uptake with a default scenario of homogeneous vaccination.

2. Methods

2.1. HPV-16 transmission model

We developed a deterministic, population-based model of HPV transmission that is based on well-established work on sexually transmitted infections (STIs) [17–19]. For simplicity, we focused on HPV-16 only as it is the most common oncogenic type in women worldwide [20] and responsible for more than 50% of invasive cervical cancers [21]. We implemented the spatial (cantonal) structure into a meta-population model, and considered the population of 18–24 year old heterosexual Swiss adults who can be susceptible ($S$), infected ($I$), recovered ($R$), or vaccinated ($V$). These compartments are further divided into sub-compartments that reflect the individuals’ sex, sub-population/canton and sexual activity level, and can be described by the following system of ordinary differential equations (ODEs):

\[
\frac{dS_{skr}}{dt} = (1 - p_{sk})\mu N_{sk} - \lambda_{sk} S_{skr} + \omega R_{skr} - \mu S_{skr} - m S_{skr} + m_n \sum_u S_{sku},
\]

\[
\frac{dI_{skr}}{dt} = \lambda_{sk} S_{skr} - \gamma I_{skr} - \mu I_{skr} - m I_{skr} + m_n \sum_u I_{sku},
\]

\[
\frac{dR_{skr}}{dt} = \gamma I_{skr} - \omega R_{skr} - \mu R_{skr} - m R_{skr} + m_n \sum_u R_{sku},
\]

\[
\frac{dV_{skr}}{dt} = p_{sk}\mu N_{sk} - \nu V_{skr} - m V_{skr} + m_n \sum_u V_{sku}.
\]

Here, the subscripts $s$, $k$, and $r$ denote sex, sub-population/canton and sexual activity group, respectively. Susceptible individuals ($S$) can become infected at rate $\lambda_{skr}$ (force of infection). Infected individuals ($I$) spontaneously clear HPV-16 at rate $\gamma$ to become temporarily immune. Recovered individuals ($R$) lose their immunity at rate $\omega$ and become susceptible again. All individuals enter and leave the population at rate $\mu$ with $N_{skr} = S_{skr} + I_{skr} + R_{skr} + V_{skr}$ being the population size of individuals that have sex $s$, reside in sub-population/canton $k$ and belong to sexual activity group $r$. $p_{sk}$ is the sub-population- or canton-specific proportion of individuals that are vaccinated upon entering the population. We assumed vaccine efficacy is 100% (3 doses) and last for an individual’s sexual lifetime. Individuals can change their sexual behavior at rate $m$, i.e., they are redistributed to either the same or another sexual activity group proportional to the size of the target group [19, 22].
2.2. Data and parameters

2.2.1. Vaccination uptake

We used data from the Swiss National Vaccination Coverage Surveys (SNVCS) to obtain the proportion of women who are vaccinated in each canton (Fig. 1, Supplementary Material). The SNVCS monitor immunization coverage of children and adolescents and compiles them into three-year bands. For HPV vaccination, the surveys focus on 16-year-old girls. In this study, we used data from the last available survey period (2011–2013), except for the canton of Geneva (GE) and Appenzell Innerrhoden (AI) where we used data from the years 2010 and 2014, respectively. Two HPV vaccines are currently authorized in Switzerland: Gardasil® (Sanofi Pasteur MSD) which targets four HPV types (HPV-6/11/16/18), and Cervarix® (GlaxoSmithKline) which targets two HPV types (HPV-16/18). 95% of vaccinated women received the quadrivalent vaccine [4]. We used the proportion of fully vaccinated women (completed three doses) as a model parameter.

Although Switzerland adopted the two-dose HPV vaccination schedule in 2012, we assumed that this had not been implemented in the cantonal programs at the time the surveys were done. We did not consider HPV vaccination in boys and young men, as uptake in Switzerland is negligible at present.

2.2.2. Sexual behavior

We used data from the SIR (Screening, Impfung und Risiko faktoren) survey [4]. The Swiss Federal Office of Public Health (FOPH) conducted this survey in 2014 and collected data on the sexual behavior of 18–24-year-old Swiss women (n = 1,291). We categorised the study participants into two sexual activity groups and estimated the sexual partner change rate by assuming that the reported numbers of new heterosexual partners in the last year can be described by two Poisson distributions, weighted by the proportion of individuals in each sexual activity group [19, 23]. The survey did not include men, so we assumed their sexual activity to be the same as for women. Furthermore, we assumed that sexual behavior does not differ between cantons.

2.2.3. Inter-cantonal mixing

We used mobility data from the Swiss Federal Office for Spatial Development (ARE) as a proxy for sexual mixing between different cantons. The data set contains average daily commuting data by public transport and individual vehicles from Monday to Friday in 2010 [24].

2.2.4. Other parameters

We used publicly available data about the number of 18–24-year-olds in each canton in 2013 from the website of the Swiss Federal Statistical Office (FSO) [25] (Supplementary Material). Parameters that describe the transmission and life-history of HPV-16 were informed by the literature [26, 27] and assumed to be the same for women and men. All parameter values and their sources are specified in Table 1.

2.3. Sexual mixing and force of infection

The force of infection, \( \lambda_{kr} \), depends on assumptions about sexual contact preferences between individuals from different sexual activity groups and sub-populations/cantons. We devised three different scenarios of increasing complexity to account for different spatial mixing patterns (Fig. 2):

1. **Assortative sexual mixing**: Sexual contacts only occur between individuals from the same sub-population/canton.
2. **Proportional sexual mixing**: A fraction of sexual contacts occur between individuals from the same sub-population/canton, while the remaining contacts are proportionally distributed across all sub-populations/cantons.
3. **Mobility-informed sexual mixing**: Swiss mobility data are used as a proxy for inter-cantonal sexual mixing.

2.3.1. Assortative and proportional sexual mixing

The first two scenarios where we assumed fully assortative or proportional mixing between sub-populations/cantons result in the following force of infection:

\[
\lambda_{kr} = \beta c_{r} \sum_{k'c'} \rho_{k'k}^{r} \frac{I_{k'r}}{N_{k'r}},
\]

where \( \beta \) is the per partnership transmission probability and \( c_{r} \) is the sexual partner change rate for individuals of sexual activity group \( r \). The elements of the sexual mixing matrix

\[
\rho_{k'k}^{r} = \rho_{k'k} \delta_{k'} + (1 - \epsilon_{k}) \sum_{s} c_{s} N_{s,k} \left( \frac{c_{s} N_{s,k'}}{\sum_{s} c_{s} N_{s,k'}} \right)
\]

\[
\times \left( \epsilon_{r} \delta_{r'} + (1 - \epsilon_{r}) \frac{c_{r} N_{r,k'}}{\sum_{r} c_{r} N_{r,k'}} \right)
\]

describe the conditional probability of an individual of sex \( s \) sub-population/canton \( k \) and sexual activity group \( r \) to have a sexual contact with an individual of the opposite sex \( s' \), sub-population/canton \( k' \) and sexual activity group \( r' \). \( \epsilon_{k} \) and \( \epsilon_{r} \) are the sexual mixing coefficients with respect to sub-population/canton and sexual activity group, respectively. Values of 1 represent fully assortative mixing where individuals only have sexual contacts with other individuals from the same sub-population/canton or sexual activity group. A value of 0 corresponds to proportional (random) mixing where sexual partners are chosen in proportion to the size of their sub-population/canton and their sexual activity group. \( \delta_{k'} \) and \( \delta_{r'} \) are the Kronecker deltas that are equal to 1 if \( k = k' \) or \( r = r' \) and to 0 otherwise. In the first scenario (assortative sexual mixing), we set \( \epsilon_{k} = 1 \). In the second scenario (proportional sexual mixing), we set \( \epsilon_{k} \) to 0.6 (model with two sub-populations) and 0.8 (canontal model). Throughout all simulations, we set \( \epsilon_{r} = 0.5 \), which corresponds to partially assortative mixing with respect to sexual activity [19, 22].
The force of infection for the mobility-informed sexual mixing scenario is 80% (Supplementary Material Fig. S.1), i.e., the proportion of intra-cantonal heterosexual contacts across all cantons is 

\[ \sigma_{kk} = \frac{P_{\text{mob}}}{N_k}, \]

We then replaced the diagonal entries of \( \sigma_{kk} \) with the sum of all entries that are outside canton \( k \):

\[ \sigma_{i,k} = 1 - \sum_{i \neq k} \sigma_{i,k}. \]

The force of infection for the mobility-informed sexual mixing scenario is given by Eq. 6 with \( \rho_{sk,k'} \) being replaced by \( \rho_{sk,k'} \cdot \sigma_{sk,k'} \). We chose the scaling factor \( s \) such that the weighted proportion of intra-cantonal heterosexual contacts across all cantons is 80% (Supplementary Material Fig. S.1), i.e., is the same as in the proportional sexual mixing scenario:

\[ \sum_k \sigma_{ik} \frac{N_k}{\sum_k N_k} = 0.8. \]

### 2.4. Model simulations

We simulated the different model scenarios by numerically integrating the ODEs until the system approached the endemic pre-vaccination equilibrium (\( p_{sk} = 0 \)). We then initiated the HPV vaccination program by setting \( p_{sk} > 0 \), and ran the model for a further number of years. The ODEs were solved in the R software environment for statistical computing [28] using the function ode from the package deSolve. We calculated the basic reproduction number (\( R_0 \)) using the next-generation matrix method as described by Diekmann et al. [29, 30] (Supplementary Material Section 1). This allowed us to compute the vaccination threshold \( V_C = 1 - 1/R_0 \). All code files can be downloaded from GitHub.

### 3. Results

#### 3.1. HPV-16 dynamics

Using the parameters from Table 1, the transmission model provides a realistic description of the HPV-16 dynamics in Switzerland. The pre-vaccination prevalence of HPV-16 is 3.34% among 18–24 year olds. While this is somewhat lower than the expected and observed HPV-16 prevalence in Britain (Supplementary Material Section 2, Table S.3), it is in the range that is typically observed among women in other European countries [20]. The functional relationship between vaccination coverage and the reduction in HPV-16 prevalence 2 to 4 years post-vaccination is in good agreement with the findings of a systematic review (Supplementary Material Section 3, Fig. S.2) [1]. The basic reproduction number, \( R_0 \), of HPV-16 in our model is 1.29. This value corresponds to a vaccination threshold of 22% in the general population. If vaccination is targeting only one sex, the threshold increases to 39%.

#### 3.2. Vaccination in two sub-populations

To better understand the effects of spatially heterogeneous vaccination uptake on infection transmission, we focused on a simplified model with just two sub-populations of the same size. We calculated the expected HPV-16 prevalence after 50 years post-vaccination.
Fig. 2. Chord diagrams of inter-cantonal sexual mixing. The diagrams show the number of sexual contacts between individuals from different cantons. For the scenarios where sexual mixing between cantons occurs (proportional and mobility-informed sexual mixing), we excluded the sexual contacts between individuals that reside in the same canton for better visibility. Cantons with a French-, German- or Italian-speaking majority are indicated in blue, beige and red, respectively. Acronyms for canton names are explained in the Supplementary Material Table S.1

Fig. 3. Heterogeneous vaccination uptake and HPV-16 prevalence. The graphs show the expected prevalence of HPV-16 after 50 years of vaccinating two sub-populations at different coverage rates. a) HPV-16 prevalence when there is no sexual mixing between the two populations. b) HPV-16 prevalence when 20% of sexual contacts are made between the two populations ($\varepsilon_k = 0.6$). c) Difference in HPV-16 prevalence between scenario a and b.
years of vaccinating the two sub-populations at different cov–267 erage rates (Fig. 3). In the first scenario, we assumed fully AS–268 sortative sexual mixing between the two sub-populations, i.e., sexual contacts only occur between individuals from the same sub-population (Fig. 3a). The concave relation between vacc–270 cination coverage in the two sub-populations and the expected prevalence of HPV-16 overall indicates that homogeneous vacc–273 cination uptake always has the largest effect on reducing prev–276 alence. For example, a vaccination coverage of 25% in both sub–275 populations results in a lower prevalence than vaccinating ei–276 ther of them at 50%. In the second scenario, we assumed a certain level of proportional mixing where 20% of sexual con–278 tacts are made with individuals from the other sub-population (Fig. 3b). Sexual mixing between the two sub-populations di–280 minishes the negative effect of heterogeneous vaccination up–281 take, but homogeneous vaccination still results in the lowest prevalence of HPV-16. Fig. 3c shows the difference in the ex–283 pected HPV-16 prevalence between the first (no sexual mixing) and second (sexual mixing be–285 tween the sub-populations) scenario. The higher the difference, the stronger the effect of sexual mixing is in reducing the negative consequences of heterogeneous vaccination uptake. This is par–286 ticularly the case when vaccination is highly heterogeneous, i.e., when uptake is very high in one sub-population and very low in the other sub-population. In summary, these results il–290 lustrate that spatially heterogeneous vaccination uptake dimin–292 ishes the effect of vaccination on reducing HPV-16 prevalence, but that sexual mixing between sub-populations can limit these undesired consequences by ‘homogenizing’ the overall population.

3.3. Transmission of HPV-16 within and between cantons

We extended our analysis of heterogeneous vaccination up–297 take by simulating the transmission of HPV-16 within and be–298 tween the 26 cantons of Switzerland. The observed dynamics generalize some of the insights from the simplified model with two sub-populations. After vaccination is introduced, HPV-16 preva–298 lence begins to diverge across cantons (Fig. 4). After 15 years of vaccination, the range of expected HPV-16 prevalences depends on the assumed scenario for sexual mixing between cantons (see Methods). For fully assortative mixing, the highest and lowest prevalence are 2.40% (ZG, 17% vaccination coverage) and 0.12% (VS, 75% vaccination coverage), respectively (Fig. 4a). The range of cantonal HPV-16 prevalence narrows if sexual mixing between cantons is taken into account. The cantonal prevalence ranges from 1.28% to 0.23% for proportion–291 tional mixing (Fig. 4b), and from 1.09% to 0.14% for mobility–293 informed mixing (Fig. 4c). Thus, sexual mixing between can–295 tons again ‘homogenizes’ the infection dynamics and the effect of vaccination on reducing prevalence.

This effect is also reflected in the overall prevalence of HPV–297 16 in Switzerland. The national prevalence of HPV-16 is–298 slightly higher under heterogeneous vaccination uptake com–299 pared with homogeneous uptake (Fig. 4a). This difference be–301 comes smaller in the two scenarios that assume sexual mixing between the two cantons (Fig. 4b and 4c). In the most realistic scenario (mobility-informed mixing), the national prevalence of HPV-16 is expected to drop to 0.55% after 15 years of heterogeneous vaccination uptake, while homogeneous vaccination uptake would drop the prevalence to 0.49%. The result that heterogeneous vaccination uptake yields a slightly higher HPV-16 prevalence compared with homogeneous uptake is robust to different assumptions about sexual activity, cantonal population sizes and the overall vaccination uptake ((Supplementary Material, Table S.4)).

Inter-cantonal sexual mixing helps to reduce the prevalence of HPV-16 in cantons with low vaccination coverage at the expense of cantons with high vaccination coverage. At the national level, increasing sexual mixing between cantons always results in a lower HPV-16 prevalence (Fig. 5, dashed red lines), while the effect of sexual mixing at the cantonal level is more intricate. The number of cantons that achieve a specific reduction in prevalence – expressed as relative risk (RR) reduction – can either decrease or increase with varying degrees of sexual mixing (Fig. 5). For example, high levels of sexual mixing between cantons (low \(\epsilon_k\)) increase the number of cantons that achieve a 50% reduction in prevalence after 15 years of vacci–304 nation (Fig. 5a). In contrast, low levels of sexual mixing be–305 tween cantons (high \(\epsilon_k\)) are required to increase the number of cantons that achieve a RR reduction of 90%. On a timescale of 50 years, the number of cantons that reach a RR reduction of 99% is lowest for low, but realistic, levels of sexual mixing between cantons (\(\epsilon_k = 0.85 - 0.95\)) (Fig. 5b). These levels of sexual mixing prevent the elimination of HPV-16 in high-coverage cantons, but they are too low for low-coverage cantons to sufficiently benefit from the herd immunity of high-coverage cantons.

4. Discussion

Uptake of HPV vaccination in 16 year old girls in Switzerland shows pronounced differences between different cantons ranging from 17 to 75%. We used a dynamic transmission model to study the expected consequences of this spatial heterogeneity in vaccination uptake on the transmission and prevalence of HPV-16 in Switzerland. Using a simple model with just two sub-populations, we found that heterogeneous vaccination uptake can diminish the effect of vaccination on reducing HPV-16 prevalence. This effect is strongest when vaccination is highly heterogeneous, i.e., when uptake is very high in one sub-population and very low in the other sub-population. These results were then corroborated with an extended model simulating the transmission of HPV-16 within and between the 26 cantons of Switzerland. Homogeneous vaccination uptake would generate a lower national HPV-16 prevalence compared to heterogeneous vaccination uptake, but the overall differences in prevalence are very small. We found that inter-cantonal sexual mixing ‘homogenizes’ the infection dynamics, limits the undesired consequences of heterogeneous vaccination uptake, and reduces the inter-cantonal differences in HPV-16 prevalence.

This study describes the transmission of HPV-16 in Switzerland using a mathematical model to investigate how spatial heterogeneity in vaccination uptake affects prevalence. The example of Switzerland provides sufficient data for parameterizing...
Fig. 4. Cantonal and national prevalence of HPV-16 after vaccine introduction. 
a) Fully assortative mixing (no sexual mixing between cantons). b) Proportional mixing (20% of sexual contacts are proportionally distributed over all of Switzerland). c) Mobility-informed mixing. Grey lines represent cantonal HPV-16 prevalence. The black and red lines correspond to the national prevalence for heterogeneous and homogeneous vaccination uptake, respectively.

Fig. 5. Relationship between inter-cantonal sexual mixing and HPV-16 prevalence. The graphs show the number of cantons that achieve a specific relative risk (RR) reduction after 15 years (a) and 50 years (b) of vaccination. The dashed red lines correspond to the national prevalence which is lowest if sexual mixing is completely proportional ($\epsilon_k = 0$). For all simulations, we used the proportional sexual mixing scenario.
a dynamic transmission model while exhibiting large variation in HPV-16 vaccine deployment. Using Swiss sexual behavior data, the model provided a realistic description of HPV-16 transmission in Switzerland, and allowed us to investigate the expected effect of HPV vaccination. Our results do not change qualitatively when the number of cantons or parameter values are varied within reasonable ranges. In the absence of data decribing inter-cantonal sexual mixing in Switzerland, we used commuting data and explored three different scenarios. The two scenarios that assumed partial sexual mixing between cantons – proportional sexual mixing and mobility-informed mixing – gave rise to a similar pattern, strengthening the validity of our findings.

Our study has a number of limitations that need to be consid-
ered when interpreting the findings. First, we used a relatively simple model to describe the transmission of HPV-16, not tak-
ing into account potential sex-specific differences in sexual be-
havior and the infection life-history. Owing to our focus on the transmission and prevalence of HPV-16, we did not in-
clude the progression of HPV infections to cervical intraep-
thelial neoplasia (CIN), as some modeling studies have done in different populations and its relationship with di-

Our results need to be interpreted in the context of the cur-
rent HPV literature considering heterogeneity in vaccination. The finding that decreasing heterogeneity in vaccination up-
take increases impact helps to interpret the result by Durham et al. [15] who showed that vaccination efforts should be targeted towards low-vaccination states in the USA. Increasing vaccina-
tion uptake in populations with low-vaccination uptake has the strongest effect for reducing vaccination heterogeneity overall. The study by Shafer et al. [16] on unequal HPV vaccination uptake among different ethnic groups in Canada, suggests that heterogeneous vaccination can lead to cross-over effects across groups and depends on the amount of sexual mixing between the groups. Our study corroborates these findings and illus-

We showed that the effect of cantonal variations in vacci-
nation uptake on reducing the overall effect of vaccination on HPV-16 prevalence in Switzerland is small. This result is remarkable as eight cantons (ZG, AR, SZ, OW, AI, TG, BE and TI) have a vaccination uptake that is below the vaccina-
tion threshold in our model (39.6%). In contrast, all cantons are above this threshold assuming homogeneous vaccination at an uptake that is identical to the national average (52%). One might expect that the effects of herd immunity in the lat-
ter scenario would result in a substantially lower prevalence of HPV-16 compared with heterogeneous uptake. However, we compared the expected prevalence after 15 years of vaccination using our model even for populations with low vaccination uptake has the effect for reducing vaccination heterogeneity overall. Our study has a number of limitations that need to be considered when interpreting the findings. First, we used a relatively simple model to describe the transmission of HPV-16, not taking into account potential sex-specific differences in sexual behavior and the infection life-history. Owing to our focus on the transmission and prevalence of HPV-16, we did not include the progression of HPV infections to cervical intraepithelial neoplasia (CIN), as some modeling studies have done in different populations and its relationship with differences.
direct effects of vaccination efforts in other (particularly neigh-
boring) cantons and how these effects are dissipated via intra-
cantonal sexual mixing. For the most plausible scenario for-
inter-cantonal mixing (mobility-informed sexual mixing), we,
found that cantons with high vaccination coverage experience
a less effective reduction in HPV-16 prevalence to what would
be expected if they were isolated (assortative sexual mixing).
Conversely, this effect benefits those cantons with a low vac-
cination uptake that achieve a higher reduction in prevalence
as to what would be expected in absence of intra-cantonal sexual
mixing. The intensity of cantonal dissipation of vaccination ef-
forts is again mediated by intra-cantonal sexual mixing. The
number of cantons that surpass a pre-defined relative risk re-
duction is highly sensitive to the level of assortative mixing be-
tween cantons (Fig. 5). The results of this study suggest that a
harmonization of programs between cantons, and a reduction in
vaccination heterogeneity, would result in a stronger effect of
vaccination on reducing HPV-16 prevalence in Switzerland.
The generality of our results on the effects of spatial hetero-
\[516\] geneity in vaccination uptake are also relevant for the planning
of vaccination programs in other countries, and in the context of
infectious diseases other than HPV.

In summary, we found that spatial heterogeneity in HPV vac-
cination uptake is expected to diminish the effect of vaccination
on HPV-16 prevalence, but the overall effect is small. In the
context of Switzerland, this means that cantonal efforts towards
a reduction of HPV-prevalence are impaired by cantons with low vaccination uptake. Harmonization of cantonal vaccination
programs would reduce inter-cantonal differences in HPV-16
prevalence.

Acknowledgment

We would like to thank the Swiss Federal Office of Public
Health (FOPH), the Swiss Federal Office for Spatial Develop-
ment (ARE), and the investigators of the British National Sur-
vey of Sexual Attitudes and Lifestyles (NatSAL) for providing
access to the data used in this study. We would also like to
thank J.A. Bogaards for his valuable comments on our study.

Funding: This study was supported by the Swiss Cancer
League and the Swiss Cancer Research Foundation (# 3049-08-
2012).

References

1. M. Drollet, E. Benard, M.-C. Boily, H. Ali, L. Baadour, H. Bauer, S. Bed-
Kjaer, E. V. Kliever, P. Leenens-Mellouki, L. Markowitz, A. Mbuogu, D. Misher, L. Nicolai, J. Oliphant, K. G. Pollock, K. Soldan, P. Sommen,
berg, S. N. Tabrizi, C. Tanton, M. Brisson, Population-level impact and
herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis, Lancet Infectious Diseases 15 (5)
agd.admin.ch/bag/de/home/themen/mensch-gesundheit/vertragbare-techniken/ma

2012).
2. J. S. Smith, L. Lindsay, B. Hoots, J. Keys, S. Franceschi, R. Winer, G. M.
4. L. A. Shafer, I. Jeffrey, B. Elias, B. Shearer, K. Canfell, E. Kliewer, Quantifying the impact of dissimilar HPV vaccination uptake among Manito-
José, Cervical Human Papillomavirus Prevalence in 5 Continents: Meta-
9. J. S. Smith, L. Lindsay, B. Hoots, I. Keys, S. Franceschi, R. Winer, G. M.
10. C. L. Althaus, M. Choisy, S. A. Azlin, Number of sex acts matters for heterosexual transmission and control of Chlamydia trachomatis, PeerJ.


