A mathematical model for Human Papillomavirus (HPV) vaccination strategies in a random network

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Abstract

In this paper we consider a random network model for sexual contacts in a population developed from real statistical data in order to assess vaccination policies against sexually transmitted diseases (STDs). The model is constructed by imposing a constraint requiring that individuals of a given sex, in a given age-group, would have an average connectivity as that obtained in statistic surveys.

In this model the disease is transmitted stochastically according to a set of probability of infection parameters that depend on the age-group. We are, in particular, interested on Human Papillomaviruses infections (HPV), characterized by a high infectivity and prevalence among the population. By building a network of up to one thousand nodes we are able to obtain a stationary state under the assumption of constant population. Starting with this model we will simulate several scenarios for vaccination against HPV by using the recent HPV ninevalent vaccine, which prevents against several oncogenic genotypes of the virus.

Three different scenarios are simulated: only girls are vaccinated, only boys are vaccinated or both sexes are vaccinated (gender neutral vaccination). Important levels of herd immunity are observed if only one sex is vaccinated and the scenario in which only boys are vaccinated is plausible in terms of cost-effectiveness. However, the serious consequences for women infected with oncogenic genotypes speak

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against this latter scenario. Conclusions about global vaccination programs are finally discussed in terms of our model.

Keywords: Human Papillomavirus (HPV), Network mathematical model, Lifetime sexual partner (LSP), Vaccination strategy, Cost-effectiveness.

1 Introduction

Mathematical modeling of the transmission of infectious diseases is a very classical topic in applied mathematics. As early as 1766, D. Bernoulli developed a simple mathematical account for the spread of smallpox and the estimation of the efficacy of the inoculations with cowpox [1]. In the XXth century, the discipline of mathematical epidemiology developed into a full research area with the works of Kermack and McKendrick and other [2, 3, 4].

Continuous models, although still useful in some contexts, should be considered outdated for many purposes. In particular, in a continuous model it is not possible to make distinctions among individuals and to track their clinical history by labels such as age, sex, previous illnesses, infections, etc. The use of mass action terms implies, necessarily, a mean-field approximation.

The main difference with the network models is that in them we can follow any individual and implement a given vaccination policy by selecting these individuals according to their clinical record. This would be very difficult, or impossible to do, in a continuous differential model without increasing the number of compartments and equations and, even in such a case, the mass contact approach does not incorporate the essential discreteness of the infection process of one individual to another. Moreover, by targeted vaccination of highly connected individuals we can improve the control of the infectious diseases in a way that it is not observed in purely continuous models [5]. For that reason, the debate about the use of targeted or mass vaccination campaigns in the control of smallpox has mainly been addressed within the framework of network models [6, 7].

Despite the high public health impact of sexually transmitted diseases there is not enough research invested in the analysis of large networks with the objective of simulating the transmission and control of these infections. In particular, HPV are the sexually transmitted infections with the highest prevalence in the world. The total cost of treatment of lesions caused by several HPV genotypes exceeded 3.8 billion dollars per year only in the U.S. [8]. The overall cost in Spain alone was 47 million euro per year by 2007 [9].

The development of the quadrivalent vaccine against HPV oncogenic genotypes 16 and 18 as well as the types 6 and 11 responsible of most of

the genital warts, have allowed the control of HPV infections and diseases because of its high immunity response [10]. The present moment is particularly timely for the study of network models of HPV transmission as they can provide the better way to simulate different vaccination strategies and provide recommendations for public health decisions in this area.

The objective of this paper is to apply a sophisticated network model for HPV transmission, we have been developing in the last five years, to the spread and control of HPV in Spain. Our model takes into account a large number of individuals with age structure and an average number of connections that fits real statistical data. The transmission of the disease is modeled using a probabilistic approach with the goal of obtaining the disease prevalence provided by the so-called CLEOPATRE study [9]. This model has been able to predict the fast decrease in the number of cases of wart lesions found in Australia after a vaccination campaign including a catch-up in women up to 26 years of age [5, 11]. This prediction is a successful outcome of the network model that would have been very difficult to explain within the limited context of continuous models.

In this paper we will provide an exhaustive analysis of possible vaccination campaigns and their results in the future several decades from now. In principle, vaccination campaigns are being implemented by the vaccination of girls at early adolescence with typical coverages of 70%. The rationale for the vaccination of girls is that the majority of heterosexual boys would be also protected by the herd immunity effect, specially in the case of a sexually transmitted disease. On the other hand, oncogenic HPV genotypes prevented by the ninevalent vaccine are known for being responsible of about a 90% of the cases of cancer [12].

Our approach by the means of networks will allow us to obtain a more realistic prediction for the time evolution of the number of infections and the decline in the manifestation of diseases in the form of genital warts or cancer. These results are interesting from the point of view of mathematical epidemiology because we seek to answer the question of the optimal strategy for vaccination in a sexually transmitted disease. Therefore, they have also important implications for public health policy in terms of the control of severe disease cases and cost-effectiveness of the vaccination strategy.

The layout of this paper is as follows. In Section 2 we discuss the implementation and calibration of the network model. Section 3 is devoted to the application to different vaccination strategies and the discussion of the cost-effectiveness from a public health perspective. The paper ends with some discussions and conclusions.

2 Building the network from statistical and demographic data

2.1 Data

We retrieve demographic data from [13], per sex and age group from 14-64 years old. The data are drawn in Figure 1.

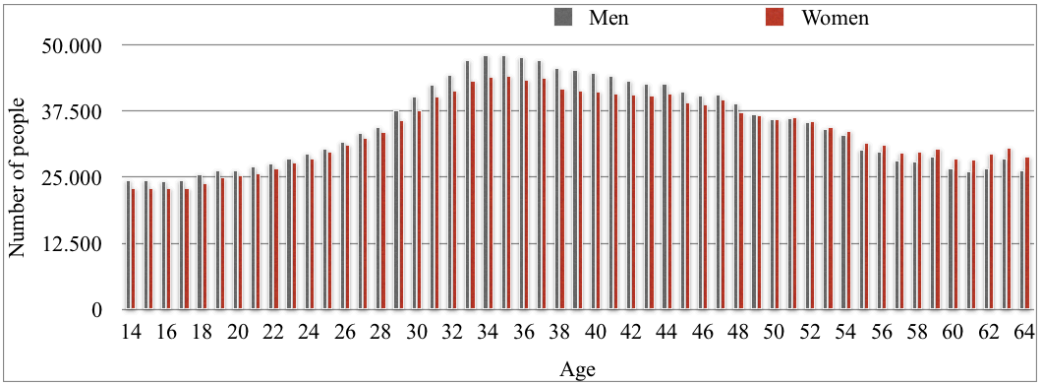


Figure 1: Number of men and women per age from 14 to 64 years old [13]. 50.76% of people aged $14-64$ are men and 49.24% are women.

Also, in 2003 a survey was conducted in Spain with the objective of obtaining statistical information about the number of lifetime sexual partners (LSP) until a certain age both for men and women [14]. The data was aggregated in three age groups, namely: from 14 to 29 years old, from 30 to 39 years old and from 40 to 64 years old. The results from the so-called Health and Sexual Habits Survey are given in Table 1. From this table we also see that men tend to have more LSP than women.

The Health and Sexual Habits Survey [14] says that 3.88% of men are men who have sex with men (MSM). The dynamics of this subpopulation is different because their LSP are also MSM and the average connectivity is also larger than among the heterosexual network as shown in Table 2 [15].

2.2 Building the network

Let us build a LSP network with a given number of nodes with the demographic structure retrieved from [13] (Figure 1) and with LSP according to the data in Tables 1 and 2.

Due to the uncertainty in the data of LSP given in Table 1, it will be necessary to introduce as a parameter of the network, the average number of

MALES

Age	0 LSP	1 LSP	2 LSP	3 – 4 LSP	5 – 9 LSP	10 or more LSP
14 – 29	0.107	0.207	0.131	0.225	0.168	0.162
30 – 39	0.027	0.225	0.128	0.21	0.17	0.24
40 – 65	0.019	0.268	0.14	0.193	0.163	0.217

FEMALES

Age	0 LSP	1 LSP	2 LSP	3 – 4 LSP	5 – 9 LSP	10 or more LSP
14 – 29	0.138	0.43	0.186	0.158	0.056	0.032
30 – 39	0.029	0.501	0.168	0.177	0.077	0.048
40 – 65	0.017	0.652	0.138	0.118	0.039	0.036

Table 1: Proportion of males and females per number of LSP per age group.

Age group	No. LSP	Age group	No. LSP
14 – 19	18	40 – 49	59
20 – 24	25	50 – 59	50
25 – 29	33	60 – 85+	56
30 – 39	45	**Average**	**39**

Table 2: Average number of LSP of men who have sex with men (MSM) per age group and the global average [15].

LSP of the heterosexual men, k, in order to establish the network properly. From [15], k should be around 8.

Also, we consider nodes representing heterosexual men and women, and MSM. However, we are not going to consider women who have sex with women (WSW) because the numbers of women who have sex exclusively with women are very small, and the higher prevalence in WSW is likely to be in women having sex with both men and women [16]. The latter reported significantly greater male partner numbers and sexually transmitted infection diagnoses [17]. Thus, the effect of the WSW in the HPV transmission dynamics will be included in some way in the women with a high number of male sexual partners.

2.2.1 Labeling the nodes

We label randomly each node by gender (heterosexual man, woman or MSM) and then by the age, following the demographic structure (Figure 1).

Now, for all the nodes labeled as women and heterosexual men, we select the row of the Table 1 corresponding to its sex and age group. Then, we

select randomly a group of LSP which the node is going to belong following the proportions of this Table 1. If the node belongs to the group

- 0 LSP, 1 LSP or 2 LSP, it is labeled as having 0 LSP, 1 LSP or 2 LSP, respectively;
- 3-4 LSP, it is labeled randomly with 3 LSP or 4 LSP;
- 5-9 LSP, it is labeled randomly with 5, 6, 7, 8 or 9;
- 10 or model LSP, the exact number of LSP will be labeled later.

In this heterosexual subnetwork, the total number of labeled LSP in heterosexual men should be equal to the total number of labeled LSP in women. Furthermore, the total number of LSP of the heterosexual men (and consequently women) is $N = k\times$ number of the heterosexual men. Thus, the difference between N and the total number of LSP of men already labeled are going to be used to label the heterosexual men nodes with 10 or more LSP, with the obvious caveat that all the labels should be 10 or more. In a similar way, N minus the total number of LSP of women already labeled are going to be used to label the women nodes with 10 or more LSP.

Now, the LSP of the MSM nodes are assigned by age group using the Table 2.

At this point, all the nodes are labeled by gender, age and LSP (Figure 2), but the sexual partners are not still paired.

2.2.2 Node pairing

First, we connect the women population and the heterosexual men population of nodes in such a way that a bipartite graph is obtained, building the heterosexual subnetwork. The assignment of partners is carried out using a Greedy Randomized Adaptive Search Procedure (GRASP) algorithm [18] and taking into account the principle of assortativity (individuals with similar age and similar number of partners are connected more likely). The weight function defining the assortativity is stated as follows:

$$\pi(i,j) = \left\{ \begin{array}{ll} |nLSP[i] - nLSP[j]| & nLSP[i], nLSP[j] \leq 4 \\ 0 & nLSP[i], nLSP[j] > 4 \\ 100 & \text{otherwise} \end{array} \right\} \quad (1)$$

$$+|Age[i] - Age[j] - 1.8| \ ,$$

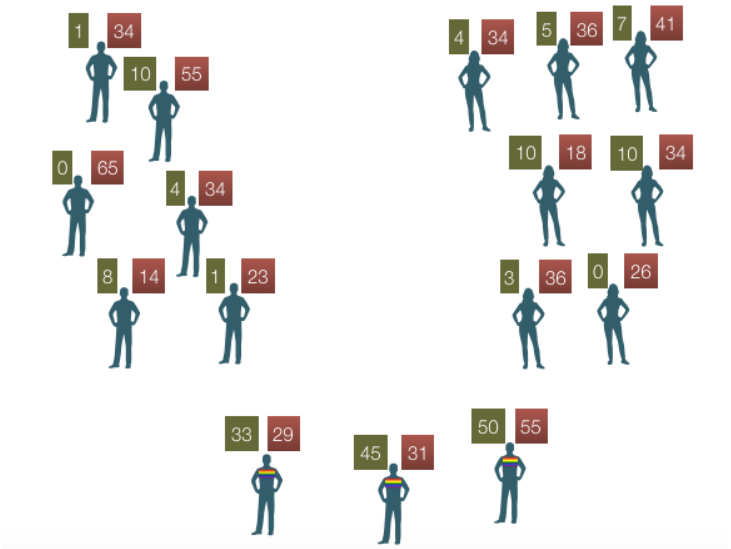


Figure 2: Example of the result of the labeling process. On the left are the heterosexual men, on the left the women. The MSM are in the bottom. Each node has two labels: the green one is the number of LSP and the red one the age. Now, we have to create the LSP assigning pairs of nodes.

where $nLSP[i]$ denote the number of LSP and $Age[i]$ the age of node i.

Looking at the Table 1, we can see that most of the people are in the groups with 4 or less LSP. Therefore, we assume two different groups of sexual behavior: 4 or less LSP and 5 or more LSP. Thus, for the first term of (1), we assume that it is more likely that people in the same group are sexual partners. A high value, for instance 100, on the one hand, forces that the sexual partners of different groups are created when almost all the same-group sexual partners have been already assigned, and on the other hand, shows that the age is less important when the people has a high number of LSP. Furthermore, for people with 4 or less LSP, we establish differences depending on their LSP.

The second term in (1) implies an increasing weight for partners whose age is very different from 1.8 years. Some studies in Spain indicate that the average difference of age among the partners in a couple is 1.8 years [19].

Using the same algorithm GRASP with the same weight function (1), we build the MSM subnetwork. It is clear that the MSM subnetwork is not bipartite.

It is well known that MSM have also women as sexual partners [20] and we have also to include some links among the MSM population and some women. Unfortunately, precise data about that are still unknown. Therefore, we are

going to assume that every MSM individual may have a link with a woman with 5 or more contacts. So, both populations are not isolated, creating a bridge between the heterosexual and the MSM subnetworks where the infection may circulate from one to another.

An example of a small LSP network can be seen in Figure 3. Further details on the algorithm for building the sexual contact network can be found in previous publications [5, 21].

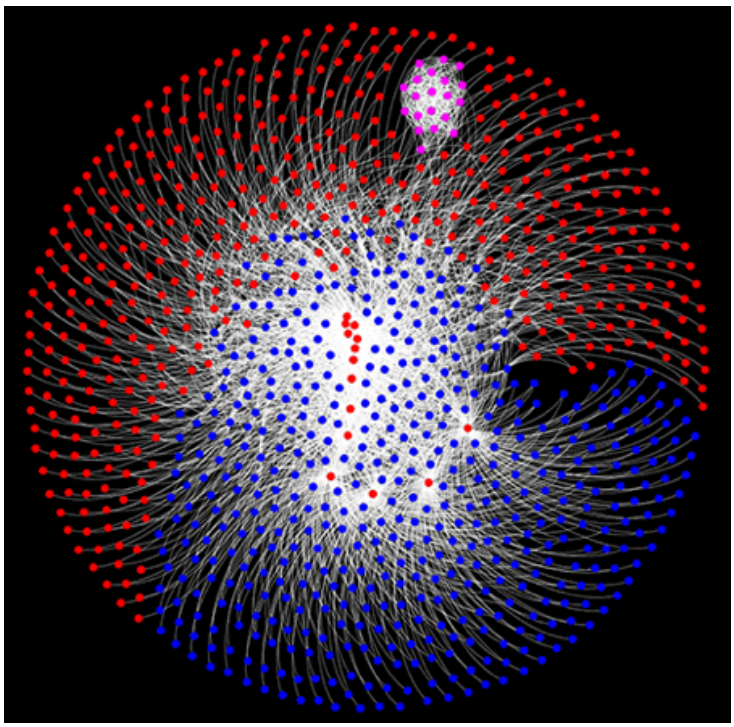


Figure 3: LSP network. Red points are women, blue points heterosexual men and pink points MSM.

2.2.3 HPV transmission dynamics definition

Once the network model has been built we analyzed the transmission of the HPV infection. Taking into account that the ninevalent HPV vaccine prevents the infection against the oncogenic types 16, 18, 31, 33, 45, 52, and 58 (responsible of 90% of cancers related to HPV) and HPV 6/11 (responsible of 90% of genital warts cases related to HPV), three types of infection are considered:

- infection of oncogenic HPV by oncogenic genotypes 16, 18, 31, 33, 45, 52 or 58;

- HPV 6/11 infection by the genotypes 6 or 11;
- and co-infection by oncogenic HPV and HPV 6/11.

The simulation is based upon a stochastic implementation of a Susceptible - Infectious - Susceptible (SIS) model with the following parameters:

- the average clearing (recovery) times from oncogenic HPV or HPV 6/11 infection (2 parameters);
- four parameters determining if the oncogenic HPV or HPV 6/11 infection is transmitted from a man or woman to his/her partner;
- the global frequency (probability) of having a sexual contact per age group and time step (4 parameters).

After generating the network with a large number of individuals ($100,000$ in this case) we perform simulations by starting with an initial condition in which a small fraction of the population is infected. Then, we carry out the evolution of the disease and follow the number of infected individuals with oncogenic HPV or HPV 6/11 genotypes. After a warm-up period and taking into account the results of many simulations we are able to select the best fit with the results of incidence in women obtained in the CLEOPATRE study [9]. This optimization uses a version of the PSO algorithm [22] and the details of teh calibration and the obtained results can be seen in Table 3 [23]. The obtained model parameter values are in agreement with the medical literature.

Once the parameters have been calibrated in this way for Spain we are prepared to simulate different vaccination scenarios to be discussed in the next section.

3 Vaccination strategies and herd immunity effects

The objective of this section is to discuss the result of the simulation of several scenarios with different vaccination strategies to gauge their impact in the vaccinated and unvaccinated individuals. After performing a vaccination campaign with a sufficient level of coverage, it is common in many diseases to obtain a beneficial side-effect in the form of the decrease of the number of infected individuals also among the unvaccinated individuals. This is known as the herd immunity effect. As it is very difficult that for a vaccination

Model parameter	Mean	95% confidence interval
Average LSP men	8.63	$[7.15, 9.86]$
Average time clearing oncogenic HPV	1.08	$[0.88, 1.19]$
Average time clearing HPV 6/11	0.60	$[0.52, 0.82]$
Probability a woman transmits HPV 6/11	0.23	$[0.21, 0.29]$
Probability a man transmits HPV 6/11	0.28	$[0.22, 0.37]$
Probability a woman transmits oncogenic HPV	0.81	$[0.68, 0.95]$
Probability a man transmits oncogenic HPV	0.91	$[0.74, 0.97]$
Frequency, 14-17 years old	0.1098	$[0.0485, 0.1542]$
Frequency, 18-29 years old	0.0776	$[0.0568, 0.0981]$
Frequency, 30-39 years old	0.0620	$[0.0024, 0.0935]$
Frequency, 40-65 years old	0.0190	$[0.0046, 0.0553]$

Table 3: Mean and the 95% confidence interval of the model calibrated parameters [23]. Times are in years and probabilities are given as a fraction of unity.

campaign to reach all susceptible individuals and the coverages typically do not rise much over 70 %, it is important to estimate the extension and duration of the herd immunity effect to determine if we could expect new cases of the HPV disease in the future.

We have considered three different scenarios:

1. Only 12-13 years old girls are vaccinated with a 75 % coverage.
2. Only 12-13 years old boys are vaccinated with a 75 % coverage.
3. Both 12-13 years old girls and boys are vaccinated (gender neutral) at a 75 % coverage.

Special vaccination campaigns, known as catch-up vaccination, are not considered because the vaccine effectiveness drops (to levels of $20\% - 54\%$ on cervical abnormalities) if the individuals have previously been in contact with the virus [24]. This is the main reason why girls and boys are vaccinated in ages (12-13 years old) before having the first sexual contact.

Then, we calculate the decline of the prevalence of oncogenic HPV and HPV 6/11 on women, men and MSM (MSM are also included in men) over time measured as

$$D_t = 100\left(1 - \frac{P_t}{P}\right), \tag{2}$$

where D_t is the decline of the HPV infection in the time instant t, P_t is the prevalence of the HPV in the time instant t and P is the prevalence of the HPV just before the vaccination program starts.

Taking into account the short period of time in developing genital warts when infected by HPV 6/11 (6 months), we can assume that HPV 6/11 decline also shows the decline in genital wart cases. We cannot say the same for oncogenic HPV because the developing time is around 20 years [25].

The herd immunity is going to be measured as the difference between the vaccination coverage and the percentage of decline. The more herd immunity the more beneficial indirect effect on unvaccinated.

The results for the comparison between the first and second scenarios are shown in Figure 4. In these figures we plot both the average values (dashed lines) and the error bounds (solid lines) with a 95% confidence. We observe that, if only girls are vaccinated, we can reach an important herd immunity effect for men of about 60% who are not vaccinated. Reciprocally, if only boys are vaccinated, we will have a herd immunity of about 70% for women. So, in terms of protection for the global population against genotypes 6 and 11 we could say that the vaccination of only boys is more cost-effective. Anyway, this conclusion ignores the fact that lesions in women evolve, in some cases, to cervical cancer and, consequently, their vaccination is required to prevent most serious diseases in this case.

The reason for the lesser herd immunity effect in men in scenario 1 is the MSM population as shown in Figure 4(c). If only girls are vaccinated the herd immunity effect in MSM is almost nonexistent (within the confident interval) because there is not decline. On the other hand, a small herd immunity is found if all the male population is vaccinated at 75% coverage, around 5%, because the decline achieves around 80%. This difference in the herd immunity effect between scenarios 1 and 2 may be higher in case the percentage of MSM increase.

Similarly, in Figure 5 we compare scenario 1 (only girls are vaccinated) with scenario 3 (gender neutral vaccination).

We see that in scenario 3 we obtain, by means of the herd immunity, almost complete protection of the female population and around 95 % protection for men. The difference, as before, are the MSM that, as shown in Figure 5(c), only attain an inconspicuous increment of 5 % extra protection by herd immunity.

In the previous discussion we have been concerned with HPV genotypes 6 and 11, which are the main cause of genital warts but the most serious diseases are directly caused by oncoviruses 16, 18, 31, 33, 45, 52, and 58.

In Figure 6(a) we have plotted the decline in the number of oncogenic HPV infections in women vs time. This is related also with the expected

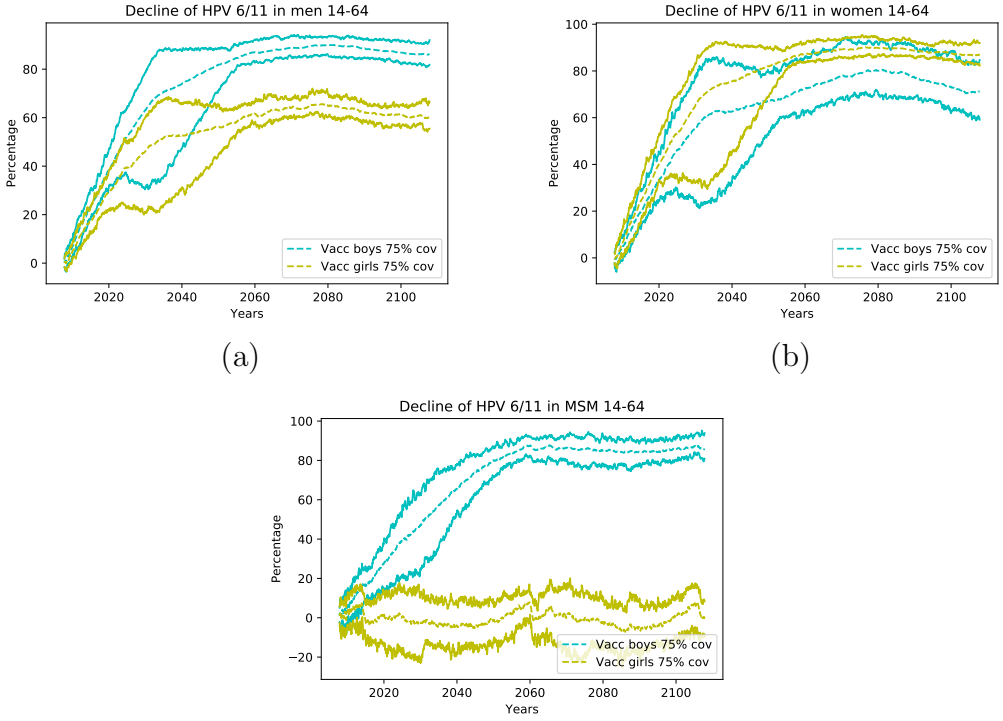


Figure 4: Comparative of the decline in the number of infections caused by HPV 6/11 for the scenario 2 (upper curves) and 1 (lower curves) in men (a), women (b) and MSM (c).

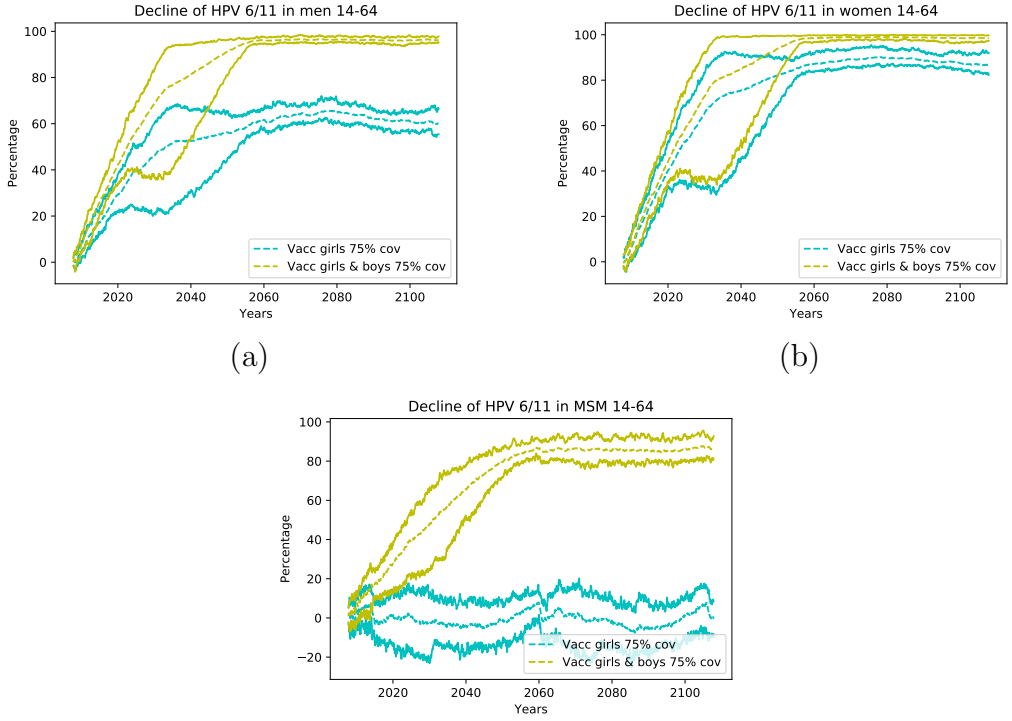
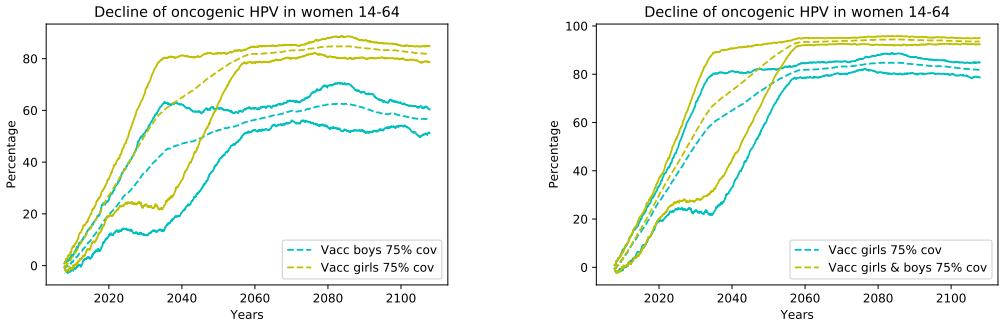


Figure 5: Comparative of the decline in the number of infections caused by HPV 6/11 for the scenario 3 (upper curves) and 1 (lower curves) in men (a), women (b) and MSM (c).



(a) (b)

Figure 6: Decline in the number of infections caused by oncogenic HPV viruses in women. (a) for the scenario 1 (upper curves) and 2 (lower curves); (b) for the scenario 3 (upper curves) and 1 (lower curves).

number of cervical cancers but there is a delay of 20 years among the infection and the development of the disease [25]. We see that the herd immunity effect if only boys are vaccinated is not enough to protect the whole female population from this disease and, consequently, it may not be recommended.

Finally in Figure 6(b) we have shown the decline when both sexes are vaccinated vs the case in which only girls are vaccinated. We see that the vaccination of both sexes at 75 % coverage leads to an important immunity effect in women allowing for an, almost complete, eradication of infections and lesions from HPV oncoviruses in the next forty/fifty years.

4 Conclusions

In this paper we have discussed and analyzed a random network model for the evolution of HPV infections in Spain after the implementation of the vaccination campaigns. The network model we have implemented is the most sophisticated one, to the best of our knowledge, used to the moment to analyze this problem. To make the model as realistic as possible we have used a GRASP assignment algorithm [18] and assortativity to connect the people in the network in such a way that the average number of lifetime sexual partners coincide with the reports in the statistical survey for each age group. We have resorted to networks for the simulation of the disease because they are more appropriate than traditional models based upon differential equations [5, 6, 7].

In the network we are able to follow the clinical record of each individual and label them according to their age, sex, status with respect to the

infections (susceptible, infected, etc.) and status with respect to the vaccine (vaccinated or unvaccinated) as well as the age at which they received the vaccination dose. By considering a probabilistic model we can follow the evolution of the infection by analyzing the transmission from one individual to another. Our model takes also into account the MSM population in which the average number of connections is typically higher than among the heterosexual population.

An important factor in any vaccination campaign is the emergence of the herd immunity effect. For several reasons, most vaccination campaigns are not universal and, even if recommended for all people in a certain age group, we have always a proportion of unvaccinated individuals. These individuals may be responsible for the resilient manifestation of the infectious disease. On the other hand, even if the infectious agent still circulates among this unvaccinated population we may find that a significant proportion of individuals in this subpopulation may benefit from the vaccination of the rest of the population. This is particularly clear for sexually transmitted diseases when one of the sexes is vaccinated at a moderate or high coverage from the very beginning of the vaccination program. In the case of HPV we have found that, when only girls are vaccinated, there is not indirect protection of the MSM population.

We conclude that, albeit the MSM population is sparsely connected with the female population, the herd immunity protection of this subpopulation is almost nonexistent. The problem is worsened by the fact that MSM forms a random network more densely connected than the heterosexual subpopulations, the MSM population may act as a reservoir of HPV infections and, moreover, they are part or a single network instead of two subnetworks in a bipartite graph.

We have simulated three scenarios corresponding to the vaccination of only girls at early adolescence, only boys or both sexes. The coverage was assumed to be constant and around the present value of 75 %.

Obviously, the most effective campaign would be the vaccination of both sexes which allows for an almost perfect protection for the female population against HPV oncoviruses and low-risk viruses after 40/50 years from the beginning of the vaccination campaign. On the other hand, the vaccination of boys only allows for a partial control of the infections in the MSM subpopulation (where the herd immunity effect is marginal) but with the undesirable side effect of keeping a percentage of the female population at risk. Taking into account that the most serious diseases appear more frequently in women (cervical cancer), this strategy cannot be recommended even if the herd immunity effect is larger for women than for men (because of the MSM high connectivity).

The robustness of these results in a changing population in which sexual habits could evolve in the future is also a necessary situation to consider in future simulations. We are currently improving the model from the point of view of social evolution and we will publish the results elsewhere.

Conflict of interest

This work does not have any conflicts of interest.

Acknowledgements

This work has been partially supported by the Ministerio de Economía, Industria y Competitividad grant MTM2017-89664-P.

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