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Article

Random network models to predict the long term impact of HPV vaccination on genital warts

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Abstract: HPV vaccine induces a herd immunity effect in genital warts when a large number of the population is vaccinated. That aspect should be taken into account when devising new vaccine strategies, like vaccination at older ages or male vaccination. Therefore it is important to develop mathematical models with good predictive capacities. We devised a sexual contact network that was calibrated to simulate the Spanish epidemiology of different HPV genotypes. Through this model we simulated the scenario that occurred in Australia in 2007, where 12-13 year-old girls where vaccinated with a three-dose schedule of a vaccine containing genotypes 6 and 11, that protect against genital warts, and also a catch-up program in women up to 26 years of age. Vaccine coverage were 73% in girls with three doses and with coverage rates decreasing with age until 52% for $20-26$ year-olds. A fast 59% reduction in the genital warts diagnoses occurred in the model in the first years after the start of the program, similar to what was described in the literature.

Keywords: human papillomavirus; network model; vaccination strategies

1. Introduction

Human papillomaviruses (HPV) encompass more than 100 genotypes of viruses that infect cutaneous, genital and respiratory epithelia of humans worldwide. These are divided into high risk (HR), those that are directly related to the origin of cancers, and low risk (LR) genotypes that provoke mucocutaneous lesions. HPV 16 and 18 are responsible for about 70% of cervical cancers, and different proportion of other malignancies: vaginal, anal, mouth and throat, etc. HPV 6 and 11 are responsible for over 90% of genital warts (GW). High risk genotypes are the direct cause of clinically important diseases such as cervical carcinoma associated with the oncoviruses HPV 16 and 18. In recent years, about $500,000$ new cases were diagnosed annually and $200,000$ women died as a consequence of the progression of cervical dysplasias to invasive carcinomas [1].

HPV is the most common sexually transmitted infection (STI) in the world. It is estimated that about 1 million new cases of GW are reported each year and the cost of treatment is increased by the tendency of these warts to recur after initial clearance. The cost of the treatment of genital warts was estimated to exceed \$ 3.8 billion in the U.S. in 1997 [2]. In Spain there were $35,000$ cases in women in 2007 with an overall annual cost of € 47 millions [23].

Two vaccines consisting of non-infectious HPV virus-like particles (VLP) [3] containing the capsid protein L1 of the virus but not the viral DNA. They induce a high immune response and prevent premalignant lesions. Both vaccines contain genotypes 16 and 18, and one of them adds VLP against genotypes 6 and 11 (HPV4).

In the Region of Valencia, Spain, the vaccine is administered to < 15 girls. Similar vaccination strategies of this kind were modelled by Elbasha et al. [4,5] by means of a compartmental model with 17 age groups for each gender. This model focuses mainly on the development of cervical intraepithelial neoplasia (CIN) and its progression from CIN1 to CIN3. According to these authors vaccination must be implemented for adolescent girls aged between 12 and 14 years. Elbasha et al. also found some evidences that the vaccination of boys could also be cost-effective [4]. By vaccinating girls alone an 83% reduction in the incidence of GW is expected but this reduction is increased to 97% if boys are also vaccinated.

In recent works [6,24] a decrease on the number of infected persons and the number of persons with GW is already reported for Australia after two years of administering vaccinations to young girls. It showed both direct and indirect protection in males. These results were more impressive than the predictions of the continuous models. A Bayesian model for HPV vaccination was then proposed by Bogaards et al. [29] and focused on the herd immunity effect of the female vaccination on the male population in a static picture. A dynamic understanding for the short and long term effects of vaccination policies is, however, still necessary and even more so with HPV vaccines because their benefit to the whole population is to be observed in the time span of several decades.

New vaccination schedules, specially vaccination in boys, should take into account the herd immunity effect vaccination in girls (in mainly heterosexual societies), therefore models that simulate STI would be important. Network models are those models in which the relations of the individuals (represented by network sites) are taken into account by means of the network bonds. Random network models have been successfully applied to other infectious diseases such as the Respiratory Syncytial Virus pandemic [7] as well as other social pandemics such as obesity [8].

STI are more likely to produce large-scale infections than other transmissible diseases, such as respiratory transmitted diseases, because the efficacy of sexual contacts for the infection is large and the infectious agent has long latency periods as in the case of HIV or HPV. Moreover, neither the carrier nor his/her partner are aware of their exposure. For example, it has been estimated that around $40 - 50\%$ of contacts are capable of transmitting HPV [9]. On the other hand, some STIs are caused by oncoviruses such as Hepatitis B or HPV, which increase the death rate of people who develop the disease.

In order to predict the evolution of these diseases we need a reliable model of the underlying social network in which the infection builds up. Individuals who change partners or have several partners simultaneously, are the hubs favouring the spread of STI. The distribution of degrees of the nodes in the network and the average chemical path from an infected individual to a susceptible one, are important parameters controlling the final extension of a new STI in a population and the speed at which it spreads. However, most models are based on some assumptions, which could not be valid for certain populations. Some studies claimed that the web of human sexual contacts is a scale-free network characterized by a power-law distribution for the number of individuals with a certain degree of connectivity, k: $P(k) \propto 1/k^{\alpha}$ with a value of α in the range $2 < \alpha < 3$, and slightly smaller for males than for females [10]. Although $P(k)$ provides some valuable information about the network, it is not a sufficient prescription on how to build it for a given population size. Moreover, a power-law distribution of contacts could not be representative of some populations, or could vary from country to country. For example, it has been found that a densely connected core appears without the need of a high connectivity degree in the Jefferson High School's network [11].

Some field studies have ascertained the structure of moderate size real networks of sexual contacts. In 2004, Bearman et al. published the results for a set of 800 adolescents in a midsized town of the United States [11]. They showed that the structure of this network is a big cluster with a ring and extended filaments which contained most of the adolescents implying that, potentially, the infection of an individual could spread to the whole of the population, given sufficient time and infectivity. A similar study was performed in 2007 at the Likoma Island in Malawi with the idea of predicting and explaining the expansion of HIV in sub-Saharan populations [12]. That study disclosed that the sexual network contained many cycles, in contrast with the single cycle at Jefferson High School. For that reason, it was speculated that superimposed cycles could be the explanation of the high prevalence of HIV infection in small populations of Africa.

Some recent studies reveal that the evolution of partnerships is also an important factor in the transmission of STIs. In particular, they pointed out that the following items should be considered: (i) the cumulative distribution of the lifetime number of partners, (ii) the distribution of partnership durations, (iii) the distribution of gap lengths between partnerships, and (iv) the number of recent partners. A method for building up networks considering these items has been developed by Schmid and Kretzschmar [13]. However, this information is not available in most surveys, and we therefore face the problem of developing reasonable models for STIs in many countries where information about sexual behaviour is scarce. For example, in the case of Spain, there is only available data about the number of sexual contacts in a lifetime from surveys. This is sufficient for building a sexual network for the transmission of HPV or other diseases with lifetime consequences and progression. In these cases, the important fact is whether the individual has had a contact with risk of infection. The remaining aspects of the network such as the duration of partnership and the time intervals among them can be incorporated effectively into a probability of transmission parameter.

In this paper we show how to build a network model for sexual contacts from the usual statistical data in surveys concerning the number of partners in a lifetime. We consider both heterosexual men and men who have sex with men (MSM) populations and the connections among them. We perform simulations over this network substrate on the HPV infections by different genogroups including both LR and HR infections. In particular, we show that for the case of Australia the strategy of a vaccination for $12-13$ year-old girls plus catch-up lead to a considerable reduction in the number of cases of infection by HPV 6 and/or 11 (which are the main cause of GW). For women in the $14-26$ age-group we obtain a decrease of 59% after $3.6-4.6$ years and 39% in men after $3-3.75$ years. These results agree with the conclusions of the study by Ali et al. [24].

2. Materials and Methods

2.1. Origin of the data

Data from the region of Valencia (Spain) was collected from the Valencian Institute of Statistics (2013) [14]. Lifetime sexual partners for an individual (LSP) was obtained from the Health and Sexual Habits Survey of 2003 [15], and summarized in Table 1.

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

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

Some features of the distribution of contacts were: (i) The percentage of males and females with no partners is very similar in each age-group (ii) The proportion of women with a single partner is, approximately, two times larger than men with only one partner (iii) The percentage of men with two or more partners is always larger than that of women except for women in the age-groups $14-29$, and $30-39$ in the case of two partners. The asymmetry in the behaviour of males and females should be taken into account in the construction of the network.

2.2. Network model

In mathematical terms:

$$\sum_{i=1}^{M} LSP_i = \sum_{j=1}^{F} LSP_j \,. \tag{1}$$

The estimation of sexual partners: there are some approaches to the number of LSP in males and females [16,17] that are difficult to match. Generally speaking, males tend to overestimate the number of their sexual partners and females tend to underestimate it. Therefore, we considered the average LSP male value, $\langle k \rangle_m$, and calibrated the network so that results were consistent with data of Table 1, and estimated that the number of LSP in males in Spain was at least 4.5. The network was built with a total of $500,000$ nodes, which requires a substantial computational power.

2.3. Semi-random construction

From Table 1 (proportion of male LSP aged 14-29) we have the following list: $(0.107, 0.314, 0.445, 0.67, 0.838, 1)$ for the accumulated proportion of males with less or equal than a given LSP number. Now, we randomly generate a number r between 0 and 1 and assign the number of contacts to every male node in the $14-29$ age group, in the network as follows:

- $r \leq 0.107$ say that the corresponding male does not have LSP,
- $0.107 < r \leq 0.314$ say that the corresponding male has one LSP,
- $0.314 < r \leq 0.445$ say that the corresponding male has two LSP,
- $0.445 < r \leq 0.67$ say that the corresponding male has three or four LSP uniformly distributed.
- $0.67 < r \leq< 0.838$ say that the corresponding male has five to nine LSP uniformly distributed.
- $0.838 < r \leq 1$ say that the corresponding male has 10 or more LSP.

Every node in the network is labelled by its gender and age randomly assigned according to the population histogram. The assignment of the number of bonds, as another label of the node, is not so straightforward since we must guarantee that the condition in Eq. (1) is verified. In order to fulfill this condition we take advantage of the uncertainty of statistics reports concerning individuals with 10 or more lifetime sexual partners. Starting with the males, we assign the number of LSP up to 9 partners and, for 10 or more partners proceed as follows: let i_{max} be the number of males with 9 or less partners. The unassigned males should be $M - i_{\text{max}}$ and the number of bonds that should be distributed among them is $M \langle k \rangle_m - \sum_{i=1}^{i_{\text{max}}} LSP_i$. By Euclidian division, this quantity can be expressed as $(M - i_{\text{max}})n_m + r_m$, where $n_m \geq 10$. In our procedure we assign a random number of bonds, uniformly distributed, in the interval $[10, 2n_m - 10]$ to every male with 10 or more LSP, i. e., to the $M - i_{\text{max}}$ unassigned males.

Now, we denote as p_m the total number of bonds of the male population. We must take into account, as expressed in Eq. (1), that the total number of bonds of the female population should be the same. To impose that condition we proceed as follows: (i) Assign the number of bonds to the females with 9 or less partners following the statistical data in Table 1. (ii) The sum of all female LSP in this group of j_{max} members will be denoted by s_f. Then $n_f = F - j_{\text{max}}$ is the number of females with 10 or more LSP. (iii) The number of bonds starting in the males and still unassigned to a female is $p_m - s_f = q_f n_f + r_f$, where $0 \leq r_f < n_f$ and $n_f \geq 10$. (iv) We assign $q_f + 1$ bonds to r_f females still unassigned and q_f bonds to the rest of $n_f - r_f$ females. The steps of this algorithm are also enumerated in the flow diagram in Fig. 1.

Notice that for men and women with more than 10 LSP we assign their LSP in the most equitable way, assuming that all of them have, more or less, the same number of LSP. Thus, we have a lot of hubs with low number of contacts instead of a few hubs with a lot of contacts.

Under the point of view of STI transmission, the latter situation leads to a faster transmission if the hub is infected and also, if the hub is vaccinated the transmission is cut faster. Therefore, due to the lack of data about people with 10 or more LSP, we make the decision of being conservative in the transmission of the disease and in the effect of the vaccination campaigns.

Notice that this procedure implies that the condition in Eq. (1) is verified. After this procedure we have obtained the following lists:

- $AgeMale\,[i]$ is the age of the i-th male, $i = 1, \ldots, M$.
- $AgeFemale\,[i]$ is the age of the i-th female, $i = 1, \ldots, F$.
- $kMale\,[i]$ is the number of lifetime sexual partners for the i-th male, $i = 1, \ldots, M$.
- $kFemale\,[i]$ is the number of lifetime sexual partners for the i-th female, $i = 1, \ldots, F$.

These lists will be used to perform the connections of males and females and build the network. Note that, in Table 1, there are more females than males with few LSP (comparing male and female percentages). It implies that there will be few women with a very large number of LSP. This fact suggests us to start the assignment procedure with women with the largest LSP. Otherwise, it would be possible that, when we have to assign LSP of men to a female with a large number of LSP, there will not be enough men with free sexual partners to be assigned and, for this female, it would be impossible to satisfy the condition that the degree of each node was the number of its LSP.

The assignment of partners was carried out by considering a principle of psychological similarity [18] or assortativity. Hence, we are going to define a weight function assuming that: Women with few LSP usually match men with few LSP; people with 4 or more LSP use to join with people with 4 or more LSP; and couples where one of them has a large number of LSP and the other few LSP will be uncommon. Then, for the woman i and the man j we define the following weight function:

$$\pi(i,j) = \left\{ \begin{array}{ll} |kFemale[i] - kMale[j]| & kFemale[i], kMale[j] \leq 4 \\ 0 & kFemale[i], kMale[j] > 4 \\ 100 & \text{otherwise} \end{array} \right\} \tag{2}$$

$$+|AgeFemale[i] - AgeMale[j] - 1.8|.$$

The combined weight function, which takes into account the age difference of the partners, $|AgeFemale[i] - AgeMale[j] - 1.8|$ is defined in this way because some studies show that the average age difference among the members of a couple in Spain is 1.8 years [19].

The MSM population (around a 3.88 % of the total male population in Spain) can also be incorporated into the model but in this subpopulation the connectivity would be larger than the heterosexual network. The MSM population would also be connected with the heterosexual one by links with women in such a way that every MSM individual has a link with a woman with 5 or more contacts [22]. The assignment of links is then performed by the GRASP algorithm [20,21]. Details about the construction of the whole network have been provided in previous studies [22,25].

2.4. The dynamics of HPV transmission in the sexual network

To implement the simulation of the transmission of HPV among the individuals in the network, a standard epidemiological model with susceptible and infected states and 3 types of infection (HR, LR and co-infection) was carried out.

The epidemiological model is defined by the following parameters:

- We need some probabilities to determine if a sexual partner is going to produce a contagion of another partner in a given time stage. These parameters are different for each age group: $14-17$, $18-29$, $30-39$ and $40-65$.
- Average time an individual infected by a HR HPV clears the infection and recovers.
- A similar parameter for clearing the LR HPV infection.

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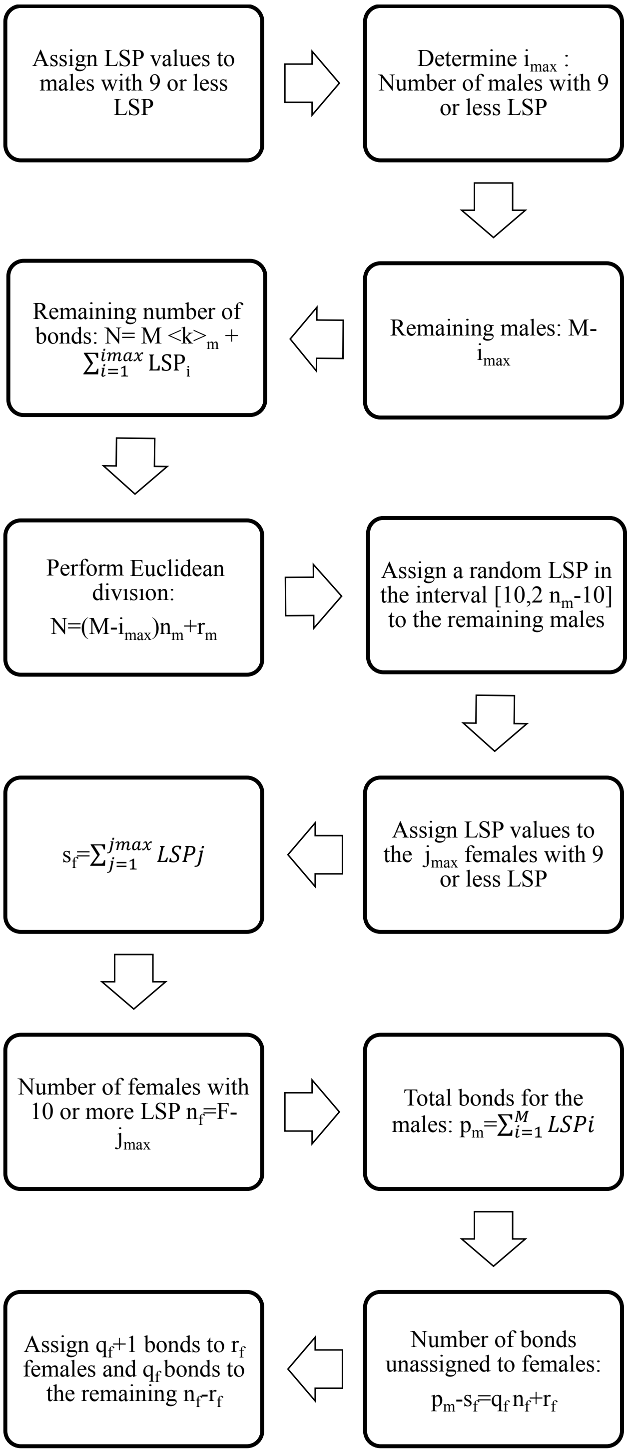

Figure 1. Flow diagram for the algorithm corresponding to the assignment of a number of LSP to every male and female in the network.

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- If a partner produces the contagion of his/her partner we need another four parameters to determine if the high or low risk HPV infection is transmitted from man to woman and vice versa.

Another additional parameter is necessary to generate the network. This is the average number of lifetime sexual partners for men (parameter k). Simulations are run by generating a network and carrying out a large number of epidemic evolution time-steps starting with a number of individuals infected by both HPV types as given by the CLEOPATRE study [23]. After the warm-up period we obtain a stable situation and we can proceed with the calibration by comparing the model predictions with real data and deducing the most probable values of the set of parameters.

We have used a calibration procedure using the Particle Swarm Optimization (PSO) algorithm. The prevalence data for each age group is listed in Table 2:

Table 2. Prevalence of HR- and LR-infected women per age groups from the CLEOPATRE study [23]. Co-infections are included in both HR- and LR-infected. Mean and 95% confidence intervals.

Women	HR-infected	LR-infected
$18-29$ y.o.	$24.10\%,\ [21.33\%, 26.98\%]$	$6.36\%,\ [4.71\%, 8.07\%]$
$30-39$ y.o.	$11.01\%,\ [7.54\%, 15.09\%]$	$1.26\%,\ [0.0\%, 3.14\%]$
$40-64$ y.o.	$5.96\%,\ [4.29\%, 7.8\%]$	$2.37\%,\ [1.22\%, 3.68\%]$
$18-64$ y.o.	$16.23\%, [14.52\%, 17.97\%]$	$4.41\%,\ [3.42\%, 5.45\%]$

Note that the network building and the transmission parameters involve randomness and uncertainty due to the random processes used in the network building and the transmission dynamics of the HPV. This fact is going to be taken into account in the calibration and simulation.

To check the reliability of the model and the calibration, we simulated the HPV vaccination campaign carried out in Australia [24], and compared them with the actual impact published [24]. In 2007, Australian health authorities started a vaccination program for the $12-13$ year-old girls with a coverage of 73% (83% in the first dose, 80% in the second dose and 73% in the third dose). Also, from 2007 to 2009 there was a catch-up vaccination program for women aged $13-26$ with a decreasing coverage with age until 52% in women aged $20-26$. Their results can be summarized:

- Two years after the vaccine was introduced, the proportion of GW diagnosed declined by a 59% in vaccine eligible young women aged $12-26$ years in 2007, and by 39% in heterosexual men of the same age.
- No significant decline was observed in older women or men (older than 26 years old), non-resident young women, or men who have sex with men.

Two different scenarios were considered to be simulated:

- Scenario 1: vaccination of 83% of the 14 year-old girls (or younger girls) plus a catch-up with coverage 73% for $14-26$ year-old women.
- Scenario 2: vaccination of 73% of 14 year-old girls (or younger girls) plus a catch-up with a vaccination coverage of 52% for $14-26$ year-old women.

These simulations represented the upper and lower bounds of the scenario implemented in Australia. The assumed effectiveness of the vaccine was 96.5%.

Due to the randomness of the simulations, we will show the average and confidence intervals among the 30 simulations per every scenario we have considered above.

2.5. Calculation of the number of infections

We call I the number of infected women of LR HPV 6 and/or 11 just before the starting of the vaccination campaign; we call $V = (v_1, \ldots, v_N)$ to the number of infected women of LR HPV 6 and/or

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11 every month from the starting of the vaccination program until the end of the simulation. Then the vector

$$100 \times \left(1 - \frac{v_1}{I}, \ldots, 1 - \frac{v_N}{I}\right) , \tag{3}$$

is a measure of the percentage of decline of number of infected women of LR HPV 6 and/or 11 after the beginning of the vaccination campaign. This will be also applied to men and MSM.

In order to compare GW data given in [24] with our model, results referred to infected women of LR HPV 6 and/or 11, we should take into account that whether a fixed proportion of HPV 6 and/or 11 infected develop warts, the percentage of decline in warts and in infected women of LR HPV 6 and/or 11, will be comparable.

3. Results

After calibration, the model predicted an average number of LSP in men of 7.7; CI95% $[7.3, 8.5]$, with an average duration of an infection due to LR genotypes of 0.5 CI95% $[0.3, 0.8]$ years, for men and women.

The transmission probability from women for LR genotypes is 0.58 CI95% $[0.57, 0.59]$. And from men is 0.63 CI95% $[0.49, 0.72]$.

3.1. *The case of Australia*

Figure 2 shows the percentage of women aged $14 - 26$ infected after starting the vaccination program in both simulated scenarios. The fast decrease in both scenarios can be seen at the very beginning.

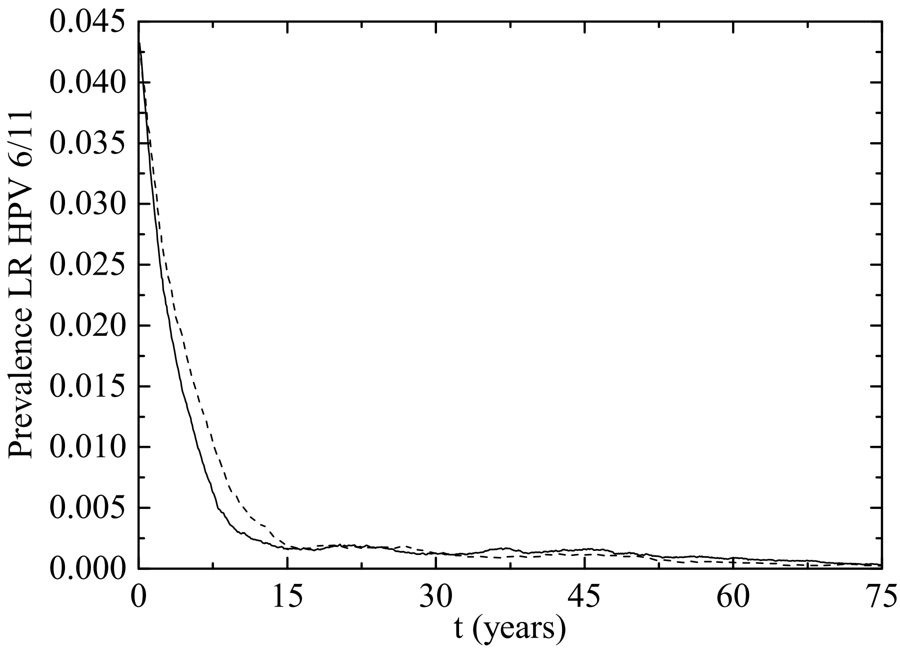

Figure 2. Percentage of women aged $14 - 26$ infected of LR HPV 6 and/or 11 after the implementation of the vaccination program (Scenario 1: solid line and Scenario 2: dotted line).

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In Figure 3 we have plotted the same data as in Figure 2 but under other point of view: the average percentage of decline of women infected of LR HPV 6 and/or 11. As the vaccination program progresses over time the percentage of decline, obviously, grows.

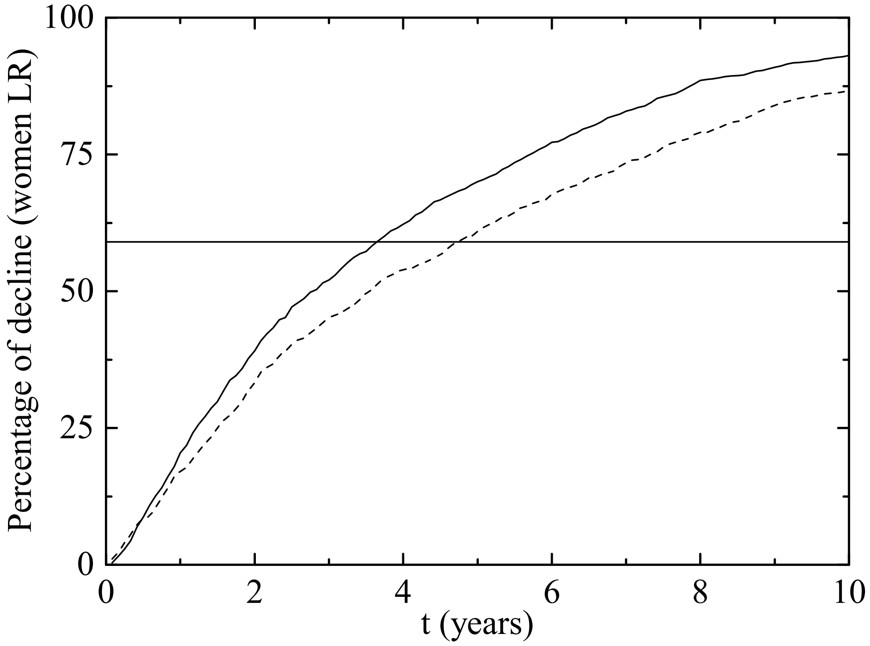

Figure 3. Percentage of decline of women aged $14 - 26$ infected of LR HPV 6 and/or 11 (and consequently of GW) after the implementation of the vaccination program in both scenarios (Scenario 1: solid line and Scenario 2: dotted line). The horizontal line represents the percentage of decline in Australian women wart cases after 2 years.

In our model simulation, after 2 years of the beginning of the vaccination program, a decline of $33.3\% - 39.1\%$ has occurred in women and $3.6 - 4.6$ years were necessary to reach the Australian 59% decline rate in GW.

In men aged $14 - 26$, Figure 4, there was a decline of $23.1\% - 30.5\%$ after two years and $3 - 3.75$ years were necessary to reach the Australian 39% decline rate of infection. No significant impact on the rate of infection was observed in women or men aged $27 - 64$ in the first 10 years after the implementation of the vaccination program (Figure 5). It can be explained by the fact that, usually, individuals have sexual intercourses with people with, more or less, the same age.

The herd-immunity effect in both scenarios is shown in Figure 6 for heterosexual men and Figure 8 for MSM. Notice that in men and MSM any decline is due to herd immunity. The decline of GW in the whole female population is given in Figure 7. This is predicted when the lines representing their decline are over the vaccination line also shown in this figure. We see that the herd-immunity effect starts after 2.58-2.91 years when 11.2 % - 14.45 % of women are vaccinated

Notice that the herd immunity effect is very clear within the 90% confidence interval both for heterosexual men and women but it is uncertain in the MSM population. In the best case scenario the MSM subpopulation achieves a large protection level but there are other situations in which it remains largely unprotected and the VPH strains still circulate among them for many years. This could be attributed to the way in which the MSM individuals are connected: with a very large number of LSP among them and some casual links with women with large LSP. If these women, acting like

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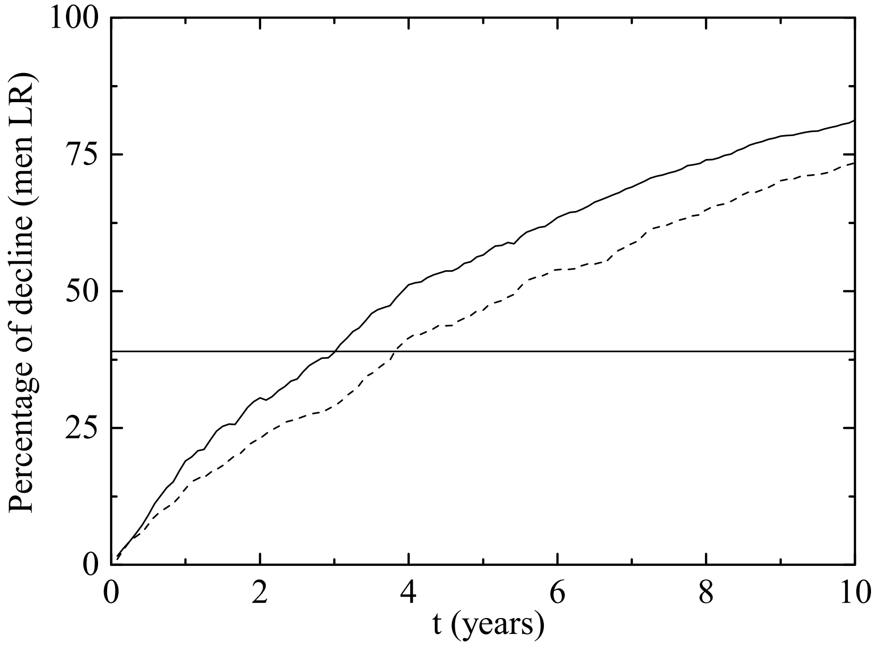

Figure 4. The same as Fig. 3 but for men aged 14 − 26.

hubs in the network, are vaccinated we obtain a fast eradication of the disease in the MSM population and this would be the best scenario.

4. Discussion

The random network of sexually transmitted HPV including up to 500,000 nodes, was developed to fit the data of surveys concerning the number of sexual partners throughout life [22,25]. Standard continuous models are insufficient to accurately predict transmission because they do not account for the individual to individual transmission of the infection, the role of hubs in disseminating the virus through the rest of the population and neither the vaccination campaigns targeting specific groups of individuals.

This network has successfully been applied to the stable state of infections by LR and HR HPV genotypes in Spain [22]. In this study we mimicked the results found in the HPV vaccination campaign of Australia [6,24], and showed very reliable results.

Model predictions in key epidemiological data was always within the range of the published results. So, the 7.7 number of LSP is close to the 8 published in Spain [27]. Also, the average duration of infection for LR genotypes are similar to the reported, that is 0.5-1.12 for the LR genotypes [4,9,26]. The transmission probability from women and men also is closed to the parameters used previously [4,26]. All this reassures the reliability of the model.

Models based upon continuous differential equations predict a slower decrease in the number of infected individuals after implementing similar vaccination campaigns [4,5]. Hence, the case of the HPV vaccination in Australia provides one of the best real scenarios for testing new network models in mathematical epidemiology. There is an on-going debate on the pertinence of an approach based upon networks on epidemiology [28] and this work contributes to show the necessity of such an approach in many cases, in particular, in those corresponding to STI.

To validate the model, we used the Australian experience, with two different vaccination coverages: routinely vaccination campaign for 12 − 13 year-old girls with a coverage of 73% and

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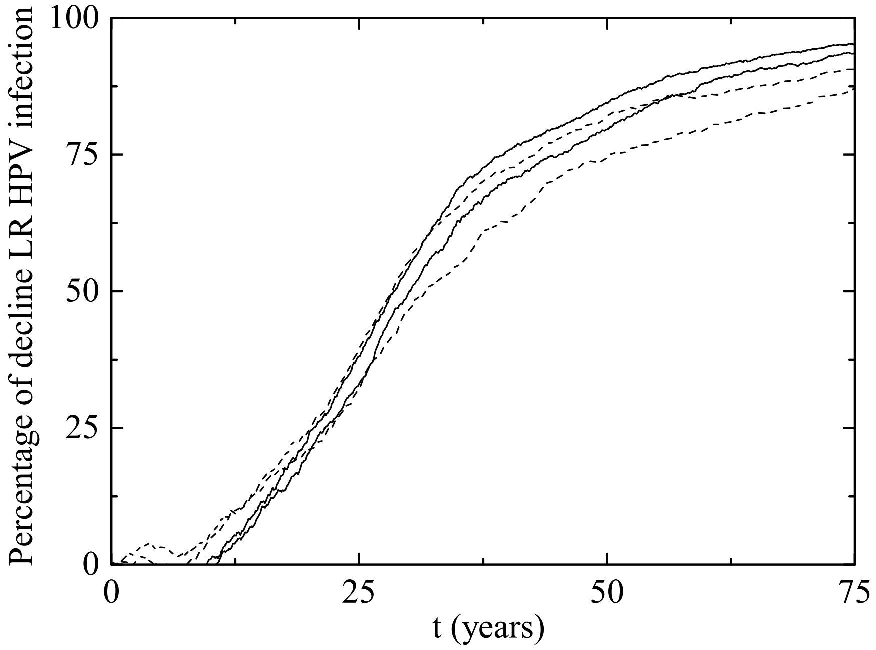

Figure 5. Percentage of decline of men and women aged 27 – 64 infected of LR HPV 6 and/or 11 (and consequently of GW) after the implementation of the vaccination program in both scenarios. The upper solid line corresponds to women in Scenario 1 and the lower solid line corresponds to women in Scenario 2. The upper and lower dotted lines correspond to men in Scenarios 1 and 2, respectively. Notice that no significant decline is observed in women or men aged 27 – 64 in almost the first 10 years.

83% and a catch-up program in the 14 – 26 age group with an average coverage of 52% and 73%. This program revealed an important herd effect [24], so that vaccination decreased the incidence of GW even in the non-vaccinated men because of the protection of infection conferred by the vaccine, and the decreased transmission of the virus.

The model predicted a fast decline in the number of infections paralel to the decline in the number of GW in Australia. However, this model was built with Spanish data on sexual behavior [15] and prevalence of HPV infection [23], that might differ to the Australian one, and may explain the minor differences found between the model and the actual data published. Another potential cause of these differences could be the need for a three dose schedule that we simulated, when it has been proposed that with one dose the short term protection against GW is practically of 100% [24]. Herd immunity in this model of STI is predicted much sooner than in other highly transmitted aerial transported infectious diseases as influenza or RSV, due to the structure of the network. This supports the need to build appropriate LSP networks.

Other models have also predicted the protection of males by vaccinating girls and women, but only on heterosexual men, as the Bayesian model used by Bogaards et al. [29]. The model of Bogaards et al. uses Bayesian techniques to study the herd immunity effect. However, in contrast with our model, this one does not take into account the dynamics of the HPV transmission, the importance of age-groups and the different roles they play in the propagation of these viruses or the links among the MSM subpopulation and the heterosexual network. In this sense, a network model is required to study the impact of the vaccination strategies in short, medium and long time scales.

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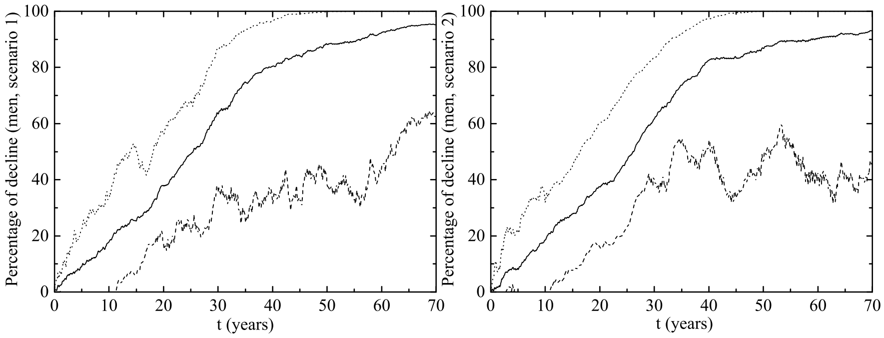

Figure 6. Herd immunity effect of the vaccination program in Australia on heterosexual men. Left figure (Scenario 1) and right figure (Scenario 2). The upper dotted and the lower dashed lines correspond to an interval of 90% confidence. Solid line is the average evolution of the decline in GW.

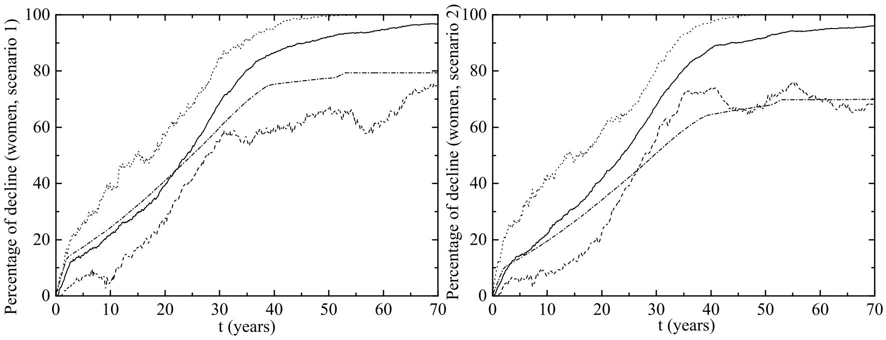

Figure 7. Percentage of decline in GW cases for women for the vaccination program in Australia. Left figure (Scenario 1) and right figure (Scenario 2). The upper dotted and the lower dashed lines correspond to an interval of 90% confidence. Solid line is the average evolution of the decline in GW for the whole female population and the dashed-dotted line is percentage of vaccinated women. Notice the herd immunity effect also contributes to the decline in the number of infections for unvaccinated women. This can be seen when the decline lines are over the vaccination line.

Vaccination strategies should seek an optimal effectiveness and efficiency. The impact of vaccination in males should always consider the herd immunity of vaccinating girls. However, it is shown that vaccination of women leaves heterosexual males only partially protected at least in the first 10 years after vaccination, however MSM take 50 years on average, to have a decrease in the incidence of infection of 50%. This can be the consequence of the large LSP numbers for MSM and their casual connections with women with large LSP numbers in the heterosexual subnetwork.

The model considers a quiet close community, where there is no much contact with other communities. This may not be the case of Spain, that in 2016 received over 75 million tourists [30], representing nearly double than the number of inhabitants of Spain, and when sexual contacts are frequent. This may bias the result, as the herd immunity in Spain may not be so clear as in countries with less tourism.

Another issue that we must take into account, is the modelling of the population with a high number of contacts because these individuals are hubs in the network whose vaccination may induce a faster decline of the virus prevalence. Our approach is rather conservative in the assignment of LSP for men and women with 10 or more links because we assume that all of them have similar LSP. However, it is expected that individuals with extreme values of LSP are favouring the transmission of HPV in such a way that a targeted vaccination can show its benefit in a very short time.

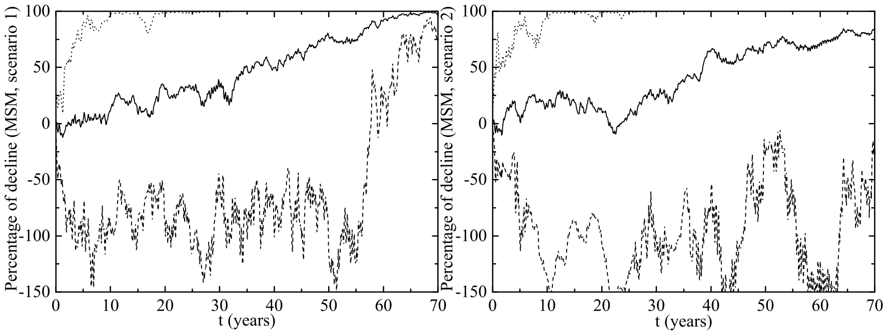

Figure 8. The same as Fig. 6 but for MSM.

Supplementary Materials: further details and results about the building of lifetime sexual partner networks can be found here: lsp.imm.upv.es

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Abbreviations

The following abbreviations are used in this paper:

VLP	Virus-like particles
STI	Sexually transmitted infection
HPV	Human papillomavirus
LSP	Lifetime sexual partner
HIV	Human immunodeficiency virus
PSO	Particle Swarm Optimization
MSM	Men having sex with men
GW	Genital warts

Bibliography

1. Sirjänen, K.; Sirjänen, S. Papillomavirus Infections in Human Pathology. John Wiley & Sons: Chichester, West Sussex, UK, 2000.
2. Roberts, J. S. C. Vaccine for Genital Warts. In *Vaccines for Human Papillomavirus Infections and Anogenital disease*; Tindle, R. W.; Medical Intellegence Unit 14, R. G. Landes Company: Austin, Texas, 1999.
3. McNeil, C. Who invented the VLP Cervical Cancer Vaccines ?. *Journal of the National Cancer Institute* **2006**, *98 (7)*, 433.
4. Elbasha E. H.; Dasbach E. J.; Insinga R. P. Model for assessing human papillomavirus vaccination strategies. *Emerg. Infect. Dis.* **2007**, *13(1)*, 28–41.
5. Elbasha E. H.; Galvani A. P. Vaccination against multiple HPV types. *Math. Biosci.* **2005**, *197*, 88–117.
6. Fairley G.; Hocking J.; Chen M.; Donovan, B. C. Rapid decline in warts after national quadrivalent HPV vaccine program. The 25th International Papillomavirus Conference; 2009 May 8-14; Malmo, Sweden.
7. Acedo L.; Moraño J. A.; Villanueva R. J.; Villanueva-Oller J.; Díez-Domingo J. Using random networks to study the dynamics of respiratory syncytial virus (RSV) in the Spanish region of Valencia. *Math. Comp. Mod.* **2011**, *54(7-8)*, 1650-1654.
8. Christakis N. A.; Fowler J. H. The Spread of Obesity in a Large Social Network over 32 Years. *N. Eng. J. Med.* **2007**, *357*, 370-379.

9. Burchell A.; Richardson H.; Mahmud S. M.; Trottier H.; Tellier P. P.; Hanley J.; Coutlée F.; Franco E. L. Modeling the Sexual Transmissibility of Human Papillomavirus Infection using Stochastic Computer Simulation and Empirical Data from a Cohort Study of Young Women in Montreal, Canada. *American Journal of Epidemology* **2006**, *169(3)*, 534-543.
10. Liljeros F.; Edling C. R.; Nunes L. A.; Stanley H. E.; Åberg Y. The web of human sexual contacts. *Nature* **2001**, *411*, 907-908.
11. Bearman P. S.; Moody J.; Stovel K. Chains of Affection: The Structure of Adolescent Romantic and Sexual Networks. *American Journal of Sociology* **2004**, *110(1)*, 44-91.
12. Helleringer S.; Kohler H. P. Sexual network structure and the spread of HIV in Africa: evidence from Likoma Island, Malawi. *AIDS* **2007**, *21*, 2323-2332.
13. Schmid B. V.; Kretzschmar M. Determinants of sexual network structure and their impact on cumulative network measures. *PLOS Computational Biology* **2012**, *8(4)*, e1002470.
14. Valentian Institute of Statistics, http://www.ive.es
15. Encuesta de salud y hábitos sexuales 2003. Instituto Nacional de Estadística, http://www.ine.es
16. Chandra A.; Mosher W. D.; Copen C. Sexual Behavior, Sexual Attraction, and Sexual Identity in the United States: Data From the 2006–2008. National Survey of Family Growth, National Health Statistic Reports, No. 36, March 3, 2011. http://www.cdc.gov/nchs/data/nhsr/nhsr036.pdf
17. Key Statistics from the National Survey of Family Growth, http://www.cdc.gov/nchs/nsfg/key_statistics/n.htm
18. Gentner D.; Markman A. B. Structure mapping in analogy and similarity. *American Psychologist* **1997**, *52(1)*, 45-56.
19. Miret P.; La similitud entre los componentes de las parejas jóvenes en España en la primera década del siglo XXI. ¿ Cada vez más iguales ?. (The similarity among the components of young couples in Spain in the first decade of the XXIst century. ¿ Increasingly equal ?.) *Revista de Estudios de Juventud* **2010**, *90*, 225-255, http://www.injuve.es/sites/default/files/RJ90-16.pdf
20. Cormen T. H.; Leiserson C. E.; Rivest R. L.; Stein C. Introduction to Algorithms. MIT Press and McGraw-Hill, 1990.
21. Feo T. A.; Resende M. G. C. Greedy Randomized Adaptive Search Procedures. *Journal of Global Optimization* **1995**, *6(2)*, 109-133.
22. Acedo L.; Burgos C.; Hidalgo J. I.; Sánchez-Alonso V.; Villanueva R. J.; Villanueva-Oller J. Calibrating a large network model describing the transmission dynamics of the human papillomavirus using a particle swarm optimization algorithm in a distributed computing environment. *The International Journal of High Performance Computing Applications* **2017**, doi: 10.1177/1094342017697862
23. Castellsagué X.; Iftner T.; Roura E.; et al. Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: the CLEOPATRE study. *Journal of Medical Virology* **2012**, *84(6)*, 947–956. DOI: 10.1002/jmv.23282.
24. Ali H.; Donovan B.; Wand H.; Read T. R. H.; Regan D. G.; Grulich A. E.; Fairley C. K.; Guy R. J. Genital warts in young australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* **2013**, *346*, f2032.
25. Acedo L.; Martí R.; Palmi F.; Sánchez-Alonso V.; Santonja F. J.; Villanueva R. J., Villanueva-Oller J. Building lifetime heterosexual partner networks. In L. Jódar, E. de la Poza, and L. Acedo, editors, Modeling human behavior. Individuals and organizations, chapter 19, pages 235-251. Nova publishers, 2017.
26. Nyitray A.G.; Chang M.; Villa L.L.; Carvalho da Silva R.J.; Baggio M.L; Abrahamsen M.; Papenfuss M.; Quiterio M.; Salmerón J.; Lazcano-Ponce E.; Giuliano A.R. The Natural History of Genital Human Papillomavirus Among HIV-Negative Men Having Sex With Men and Men Having Sex With Women, *J Infect Dis* **2015** *212 (2)*: 202-212. DOI: 10.1093/infdis/jiv061.
27. Estudio de conducta sexual entre homosexuales (Study of sexual behavior among MSM). Durex, 2002.
28. Eubank S.; Anil Kumar V. S.; Marathe M. V.; et al. Structure of social contact networks and their impact on epidemics. *DIMACS Ser. Discrete Math. Theoret. Comput. Sci.* **2006**, *70*, 181–214.
29. Bogaards J. A.; Wallinga J.; Brakenhoff R. H.; Meijer Chris J. L. M.; Berkhof J. Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: bayesian evidence synthesis, *BMJ* **2015**; *350* :h2016.

Peer-reviewed version available at *Viruses* **2017**, *9*, 300; doi:10.3390/v9100300

30. Press release from the Instituto Nacional de Estadística, Spain. http://www.ine.es/daco/daco42/frontur/frontur1216.pdf