Studying possible outcomes in a model of sexually transmitted virus (HPV) causing cervical cancer for Poland

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Abstract. The aim of this paper is to supplement knowledge about the spread of sexually transmitted diseases through computer simulations. The model has aggregated the most important properties of HPV infections and development of cervical cancer in demographically changing Polish society. The main goal is the authoritative analysis of the potential epidemiological control strategies and their impact on situation in Poland in the future 25 years. Constructed model shows indication that vaccination with screening organized alongside would be effective measures against cervical cancer. It also alarms authorities that processes like aging of society and increase of sexual activity (which are taking place in Poland at the moment) could recall epidemic, if prevention would not act properly.

Keywords: epidemic modeling; social model simulation; system research; STI; HPV; cervical cancer

1 Introduction

Human papillomavirus, or HPV, is a sexually transmitted virus infection, which is not only the main, but also necessary risk factor for developing cervical cancer [2], [4], [1] - second most common type of cancer in women. Accordingly, these infections are quite widespread - in 1990s it has been shown that about 70 percent of the sexually active population have acquired a virus of this type at some point of their lives [7]. Out of 30 types of HPV virus that are known to infect genital areas, 15 are high risk or oncogenic, although it might pass as long as twenty years for cancer to develop from the time one gets infected by such a virus [3]. Among the oncogenic HPVs, the most severe one is type 16, present in about half of all cervical cancer cases [4]. Recent studies have shown that the main safety precaution with respect to cervical cancer is going to be a combination of vaccination and screening - since only type specific vaccines are available and there are as many as 15 high risk HPVs. As well as that, screening alone, although a very reliable method for all age groups [2], has decreased cancer incidences in developed countries, but globally, licensing proper vaccines would be of great importance, especially since the morbidity of cervical cancer is high in developing countries [3]. However, even when a proper vaccine is introduced, it will take time for the decrease in the incidences (and fatality) of cervical cancer to become visible, due to the slow progression of such cancers; this also confirms that screening should be organized along with the vaccination [2].
Given that the infection is transmittable via sexual contact, vaccinating a certain amount of females alone would be a better strategy than vaccinating the same amount of both sexes, and

there have already been studies that confirmed this assumption [3]. Another reason to decide for women particularly is that the possible consequences of infection are much more severe in females (cervical cancer).

Table 1. Proportions of activity groups [4]

Age (years)	Highest activity	Moderately high activity	Moderate activity	Lowest activity
$15-19$	0.015	0.03	0.135	0.82
$20-24$	0.015	0.025	0.34	0.62
$25-34$	0.01	0.02	0.21	0.76
$35-64$	0.005	0.01	0.09	0.895

Table 2. Mean rates of sexual partner change (new partners per year) for activity groups [4]

Age (years)	Highest activity	Moderately high activity	Moderate activity	Lowest activity
$15-19$	15	3.50	1.34	0.48
$20-24$	17.5	0.96	0.38	0.14
$25-34$	15	0.67	0.21	0.08
$35-64*$	7.5	0.45	0.08	0.04

Investigation of sexuality. Investigation of sexuality is not an easy task, especially in Poland (this middle-income country is classified by WHO in the field of sexually transmitted diseases at the level of countries of the third world [8]). There are no recorded data, perfect research methods or fully verifiable results anywhere in the world and more so in Poland. In this study we decide to use results of a Finish survey (Table 1) and adjust them to the Polish reality. Adjustsing was done by fitting real cancer cases (Figure 2) and scaling parameter was around 0.35 in 90th. This means, that values from Finish suveys must be divided by around 3. None of the surveys from other coutries have as high respondent rate as in Finland. Moreover, all other surveys show bias. For example in south- and east-european studies males report much more sexual partners than females.

Mathematical modeling. The area of epidemic modeling is explored by researchers from different academic backgrounds: physicians, physicists, mathematicians, statisticians, computer scientists, geographers (spacial epidemiology) and sociologists. All of them have something to add and this project is based on different approaches from mathematical to computational approach (simulations) and it also comprises concepts of physics, sociological and statistical analysis [11]. This work is specious, because it is interdisciplinary and shedding light on methods which have not been used very much in epidemiology until this moment. Epidemiological models based on human-to-human transmission from differential equation point of view do exist in older literature [12], but in more recent work in the area, agent-based models appear more often. Mathematical models and computer simulation start to play significant role as quantity of social interactions [13] is enormous, but more important than simulations are real data especially register-based.

Environment of study. The core of this research are computer simulations. First, a model that represents sexually active population of Poles was developed. The model operates on the

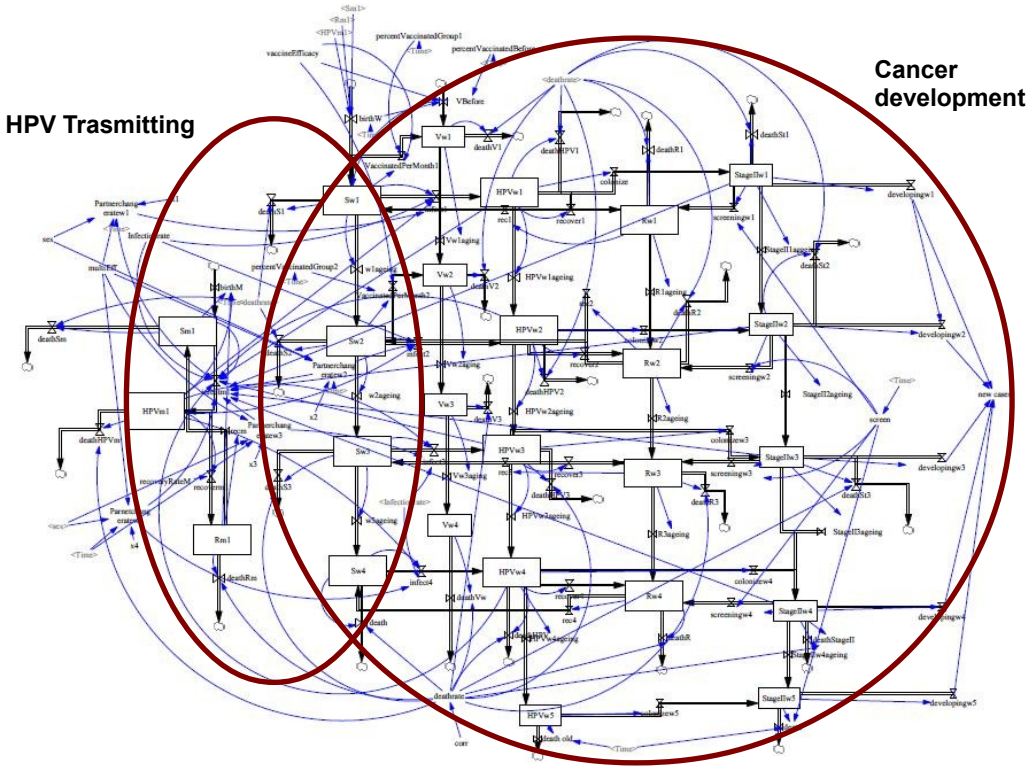


Fig. 1. Concept of model in Vensim

level of the whole country (action and state of agents are simulated at the level of the whole country [9], [10] - above 20 million people for Poland). In this study, however, we limit ourselves to the standard epidemic models, where categories of population are subgroups based on the model of SIR (Susceptible-Infected-Removed) [10]. We built the model describing the epidemiology and consequences of HPV for Poland in the environment of Vensim (Figure 1) based on our previous model for Sweden [14]. We adapted it to the demographic structure of Poles (unfortunately most of the parameters concerning sexuality and medical properties were estimated based on data for other populations - mostly Nordic - Table 3). The results obtained for vaccination strategies agreed with the work of scientists sponsored by the Merc AND Co [15] and GalaxySmith [16] (vaccine producers). Model contains age structure, because sexual behavior, as well as other medical parameters, is age depended. The existing model consists only of the main fraction of the population (heterosexual [17]) and takes into account the demographic changes over form last 25 years and predicts for next 25. Sexuality (number of new sexual partners in a given time interval) was randomly chosen in every step of simulation from empirical distribution for subgroup from given age category. Unfortunately, we do not have Polish data with such resolution. Only few of the Polish studies about sexuality consider aspects interesting for us and none of them was performed on big enough, representative sample (according Izdebski's research [18]). We observe the change of sexual behavior (average number of partners is increasing over time [19]), and the model will replicate that.

2 Problem statement

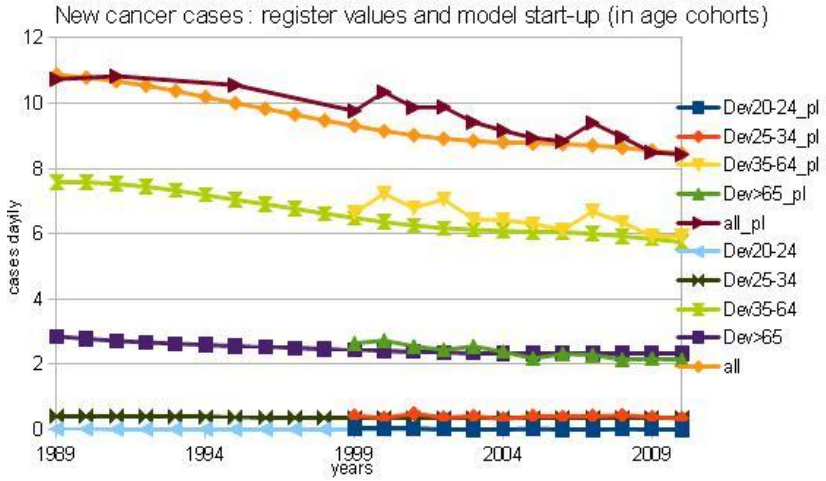


Fig. 2. Fitting area for calibaring model parameters. Development rates

The time between getting infected by HPV and developing cancer can be twenty years or more, therefore a dynamic model of human behavior would be very useful, so that simulations can be made and different scenarios compared [3].
Our model is based on HPV transition between people due to heterosexual contact. We assume that women infected by HPV could recover and acquire temporal immunity or could be long-term colonized by the virus and could then develop cancer. The model helps us understand the process and predict possible realizations and allows us to give suggestions on how to cope with an outbreak. We test the following scenarios:
a) no obligatory vaccination or vaccination of 14 years old girls (before sexual debut - the optimal srategy according to [4], [4],[3], [1], [16]);
b) with 50% or 75% of sexuality (linear) increase;
c) for different health care progress in effective screening frequencies of testing for cell pathology until frequency up to every 2.5 or 7.5 years.

3 Methods and Model Design [1]

We model part of Polish population which is sexually active ($15 - 64$ years old). We assume a temporal naturally acquired immunity and lifelong vaccine acquired immunity, with given efficacy. Male population is divided into 3 stages: Susceptible (Sm), Infectious (HPVm), Recovered (Rm) and population is dynamic due to natural birth and death rates. For women, apart from Sw, HPVw, Rw, additional stages Long-term colonized (StageIIw), Vaccinated (Vw) and Having cancer (Cancer), are allowed and all except Cancer are divided into different age groups. We also introduced changing of society by aging, birth and death (which was set to affect older groups much more than younger ones). We assume that around the age of 65 people are not

[1] code in Vensim is avaible: http://th.if.uj.edu.pl/ gulakov/hpv$_{m}$***odel.mdl***

changing partners, so death rate means not natural death, but rather removing from sexually active society. We are still tracing women above 65, who were already infected (in stage HPV or StageII) and can develop the cancer. We also allow dying in sexually active lifespan due to some other cause, with age-dependent death rate. Birth, which is actually to be understood as turning 15 years and potentially beginning a sexual life is interpolated from register data for time up until 2013 (now) and extrapolated for near future. In our model, Polish society is slowly aging in waves (as it seems to be happening in reality, due to specific demographic structure (Figure 4(a),4(b)). Medical properties of cancer developing are known to be age-dependent as well as sexual activity, so we decided to choose age groups with respect to data form reports. We used reports of Finish sexuality, in which the society is divided in groups of 5 years intervals. Cancer development properties were set up seperatly for all age-cohorts. As a trade-off for having the smallest numbers of groups, but caching main differences in behavior, we choose to devide women into the following age cohorts.
1) $15-19$ (initiation of sexual live)
2) $20-24$ (most active sexual group)
3) $25-34$ (stabilization of sexual live)
4) $35-64$ (sexual stagnation and stronger susceptibility to cancer)
5) ≥ 65 (no sexuality and cancer development)

Time

Simulations cover 50 years, from 1989 until 2039 (around 25 before the present year - 2013, to

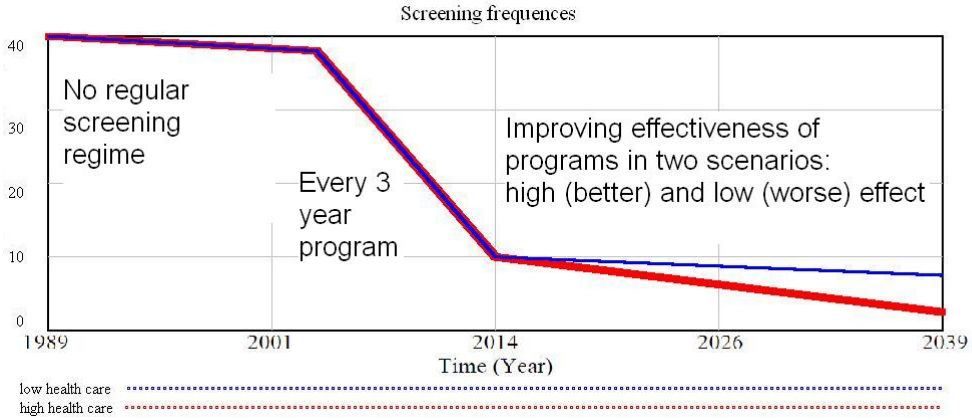


Fig. 3. Screening frequencies (every x years)

fit model parameters and around 25 years afterwards, to predict the future situation). Starting year - 1989 was chosen because of political transformation in Poland. This is when a collapse of social norms began, like those about sexuality. Moreover, before that date, there is no full registry on new cancer cases and until 1999 only part of the data are available (since 1999 National Cancer Registry [20] has been publishing very detailed data on-line). Another important change happened around 2006, when Poland introduced popular screening program. At present (2013), it is recommended to women between 25 and 60 to screen every 3 years, but only little above

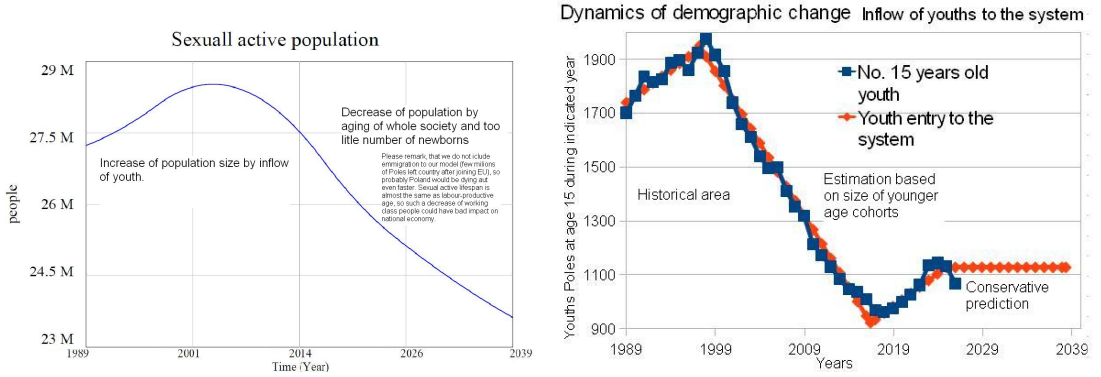
Table 3. Model parameters.

Parameter name	Description	Value	Reference
inflow	daily inflow of youth rate in Poland	Figure 4(b)	aprox. [5]
deathrate	daily death rate in Poland	sex, age and population depended	aprox. [5], [22]
Infectionrate	Infectivity per partnership	0.5	[15],[3]
Partner-changrate$w1-4$	Partner change rates in women	Stochastic, from Table 1-2	[4]
colonize$w1-5$	HPV progression rate to Stage II (per months)	Age $15-24$: $(0.1*(0.1/72+0.2/36)$ $25-34$: $0.5*(0.1/72+0.2/36)$ $35-64$: $0.35/72+0.2/36$ ≥ 65: $1.2*(0.35/72+0.2/36)$	[4] and [22]
recover$1-5$	HPV regression rate to immune (per month)	Age $15-34$: $0.6/18$ ≥ 35: $0.15/18$	[4]
screening$1-5$	Natural rate from stageII to immune (per month)	Age $15-34$: $0.65/72$ ≥ 35: $0.4/72$	[4]
developing$2-5$	Rate from stageII to cancer (per month)	$15-24$: $(0.1*(0.13/120)$ $25-34$: $0.5*(0.13/120)$ $35-64$: $0.13/120$ ≥ 65: $1.2*(0.13/120)$	[4], [22]
PercentVaccinated-Before and *Group*$1-2$	vaccinated before corresponding cohorts	90% 5%	own assump.
vaccineEfficacy	Percent of women for whom the vaccine works	95%	[1]
survive	5-year survival rate	0.41	[21]
screen	Frequency of screening up to	2.5 or 7.5 years	own assump.
sexuallity	Linear increase of sexuallity	50% or 75%	own assump.
recoveryRateM	Recovery rate from HPV for men (per month)	$0.4/18$	[4]
immunityLost	Rate from R to S for all (per month)	$7.5/12$	[4], [3]
multistrain	Sum effect of HPV 16 and 18	2	own assump.

20% of them do it [23] (effective screening frequency is around every 15 years). To capture this in the model, we differentiate screening values into 3 periods (Figure 3):
- until 2005: there was no regular screening, and tests are done when physicians ask for that,
- $2006-2015$: when regular screening procedures are introduced,

- 2016 – 2039: where we predict that screening effectiveness will be continuously improving (starting from every 10 years, which means that 1/3 of women will follow 'every 3 years rule').
We choose only 25 years timespan for prediction, because of the rapid change in medical treatments. For example, screening test in our model is allowed to detect only women "permanently" colonized, in StageII, but there already exist PCR-tests (where even genomic sequence can be obtained), which detect presence of virus in every stage. However, they are too expensive for common use now. Demographic prediction also cannot look too much ahead, because we did not take into account factors such as migration. Time step of simulation is 0.1 day (it has to be very small to avoid averaging because of stochastic character of simulation).

Demographics. Population in this model consists of sexually active Poles, who are leaving the



(a) Population size in time

(b) Inflow fitted with birth rates

Fig. 4. Demographics

system after reaching 65 years old. Exception are women from subgroups HPVw and StageII, who can still develop cancer until their death caused by any other factors (natural death). Life expectancy of those women is growing according to Statistics Polland - GUS [5] and it is modeled as linear increase for the whole time horizon of simulation. All agents could leave system due to natural death rate which is a function of population size, age and sex. Inflow to the system are the young of age 15 (respectively more boys than girls according to GUS). We can extrapolate number of the young coming into the system for the next 15 years of simulation (until 2027) by scaling number of young Poles who will grow up and start their sexual life in future. We can observe two characteristics of Poland - wave structure, and birth rate is mainly decreasing (Figure 4(b)). In effect population is aging and dying out. After the pick year in the number of the young coming into the system, which is around 2035, this number would probably decrease (as it can be observed in first years after pick). We decided not to follow this prediction, and following the rule to be as much conservative as possible, the rates of coming in later years (after 2035) are assumed constant. In effect, Polish sexually active population (corresponding to workers age span) will decrease from 27.5 in 2013 to 23.5 million in 2039 (Figure 4(a)). This value alone should alarm the authorities, and probably it is overestimated, since emigration of Polish citizens has not been taken into account.

Transition. Transition of disease can take place due to sexual contact, with given probabil-

ity. It has been estimated in other paper between 0.4 to 0.6, so we choose it as 0.5. With respect to Finish data set, individuals in our model have a randomly chosen number of new contacts each day, which follows the empirical distribution for given age groups from the Finish surveys (rescaled to Poland). Stochasticity was introduced not at the level of individuals, but at the level of subgroup (limitation of Vensim). One can understand that all people in a given subgroup can be very active or passive, at different iterations. We introduce change of sexuality as a linear increase of newborn's sexuality (the young at age 15 coming into the system) during 50 years of simulation. In the older age categories, sexuality increase is delayed, and agent bring their 'sexual liberality' by aging (coming from younger to the older subgroup).

Cancer developing. Once a woman is infected, she can either recover or be "permanently"

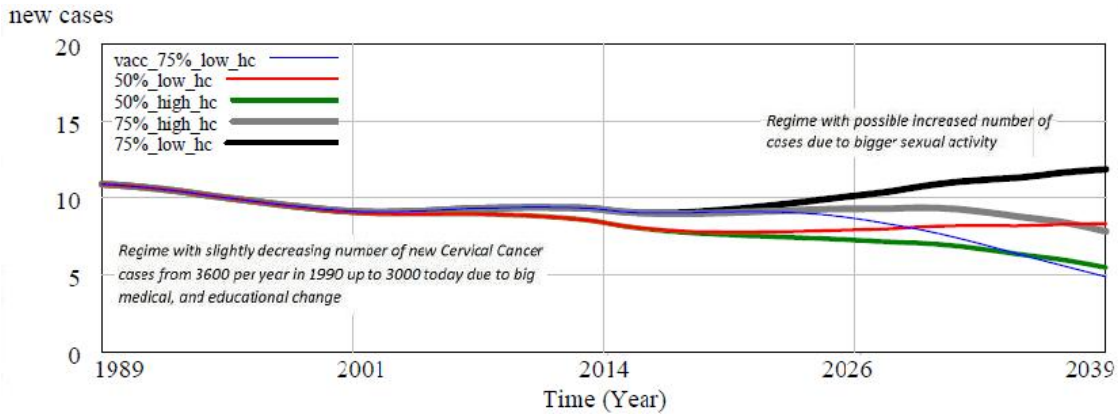


Fig. 5. New cancer cases per day, for different scenarios

colonized. From colonized state, she can be screened according to the program, or for other reasons, and find out about the infection. We assume that disease is curable in 100% of the cases if treated at this stage. Those women at the stage StageII who haven't been screened have a risk of developing cancer. Once a woman has acquired cancer, she can either survive or die, with given probabilities.

Immunity. Agents acquire temporal immunity due to natural recovery (and are moved from HPV or SrageII to R), but after some time they lose immunity and became Susceptible (S). Moreover, recovering from HPV does not protect against new infections forever, even for the same strain, and other modelers assume immunity period of 5 or 10 years [1,4].

Vaccination. We decided to vaccinate obligatory (in one scenario) only 14 years old girls (vaccination takes place before sexual debut) This is represented as a flow of the fraction covered by vaccination straight from birth flow to stage vaccinated (Vw) then they stay in this set of stages until death (life-long vaccine). We allow vaccinating older cohort of girls $(20 - 24)$ up to 5% of subgroup population (for all scenarios). It represents voluntary decision of some girls or their parents (it's recommended by vaccine producers to vaccinate up to 26 years old girls). In the model it is implemented as the flow from the Susceptible (Sw) to Vaccinated (Vw).

4 Results and Validation

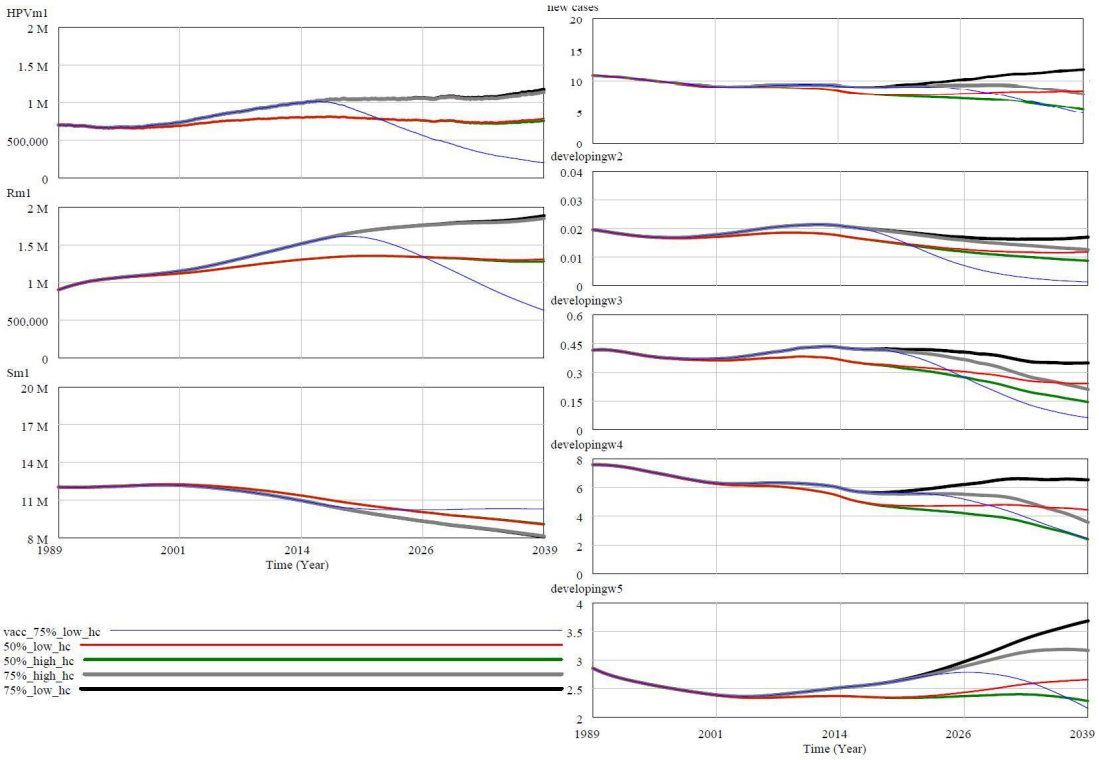


Fig. 6. Chosen stocks and flows in time. Flows show number of women who developed cancer per day for given age cohorts: development2: 20-24, development3: 25-34, development4: 35-64, development5: over 65. Stocks show number of men in stages: Sm, HPVm, Rm (subpopulation size in time)

Performed simulations agreed in historical area (Figure 2) for all new cancer cases [20] registered (since 1989) and also for given age-cohorts (registry made since 1999). Possible regimes of future states show increase or decrease of new cancer case (Figure 5). Only vaccination will allow Poles to continue process of decreasing cancer prevalence in Poland. For other scenarios for different health care level or sexuality increase it could be better of worse, but even most pessimistic assumptions (75% of sexulatity increase and effective screening frequency at the level of every 7.5 year) are still not the worst possible as we can imagine.
We show trajectories of different stocks and flow of model (Figure 7, 6) to check if possible outcomes seem to be realistic and validate model this way. We can observe huge increase of HPV (in both stages) and cancer prevalence in cohort of oldest woman (Figure 7, 6 StageIIw5, HPVw5 and development5), which was already predicted by other cancer researchers [20], [23].

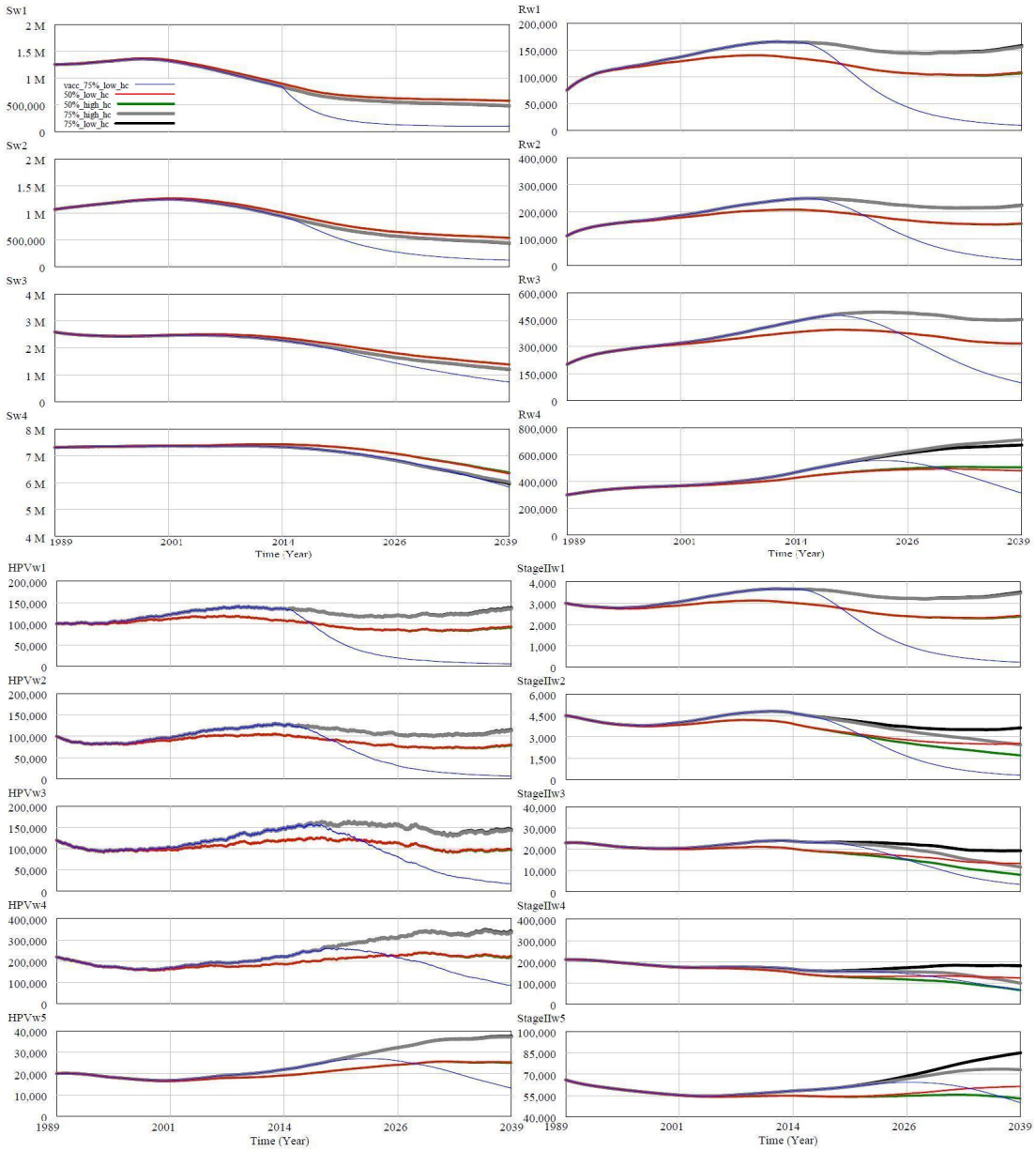


Fig. 7. Subpopulation size in time (number of women in stages: Sw, HPVw, Rw or StageIIw for given age cohorts. 1: 15-19, 2: 20-24, 3: 25-34, 4: 35-64, 5: over 65

5 Conclusion and discussion

We compared trajectories of new cancer cases detection for all scenarios (Figure 5). Fitted plateau (with small decay - Figure 2) in the first 25 years of simulation (1989-2014) corresponds to the

situation in Poland (around $10 - 9$ deaths per day), so this setting of the model can be used to test alternative scenarios. The best strategy, in the long run and with respect to the total number of cervical cancer cases, is to vaccinate girls before starting sexual life (we even chose to test these scenarios at the worst values of other control parameters), and this could be expected taking into account corresponding studies from other countries. For scenarios without vaccination, we also found that it is necessary to stay with short screening intervals, because it also has a big impact on results. If sexuality would increase about 75% or more, we could observe a change in trend, and growing number of new cancer cases in near future. Our feeling might be that such an increase of sexuality is not too much, because it was estimated that at this point Poles have less than 2 times lifelong sexual partners than Swedes or Finns. Moreover aging of Polish society is also involved in growing oncological problems. The intervention seems to be needed, because we tried to be as much conservative as possible (model parameters mostly approach expected value from lower side).

Our approach could be extended to be more realistic. This model takes into account HPV just as one aggressive strain. There are at least two pathogens: type 16 and type 18 [4], which can cause cancer and existing vaccines are protecting from both of them. A multistrain model would of course be more realistic, but at least two times more parameters would be needed. In order to imitate multistrain reality, we needed to increase the amount of infection, so we multiplied the partner change rates by 2. By that we assume that properties of both strains are the same, and that infection or cancer development have to be independent processes. This is not true in general, but epidemiology of type 16 and type 18 is similar. Also, evolution helps us justify the independence assumption, because those strains are fighting against each other, and it is very rare to be colonized by both of them (after the secondary infection only one will survive). We assume that vaccine acquired immunity is lifelong, but it is already known not to be true [4]. The trials of this vaccine have not been running for more than 20 years and no longitudinal studies have been done. However, some of the women have lost their immunity after only 10 years. As suggested by geographers working in spatial epidemiology, aspects such as education and whether one lives in urban or rural area also have a great impact on parameters such as sexual activity, and it would be more realistic if these aspects were taken into account as well. However, it is difficult to find data on activity with respect to such factors, and further disaggregation of the population would lead to a hardly tractable model. Moreover, the model is already very complex (with more than 100 parameters), but we did our best to validate it by sensitivity analyses of parameters and functional of control variables (Figure 7, 6).

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