

Network based mathematical modelling of HPV transmission and cervical cancer in Germany

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BACKGROUND AND OBJECTIVES

Worldwide, there are an estimated 569,800 cervical cancer cases per year due to an infection with human papilloma viruses (HPV) which is associated with about 311,400 deaths every year. Despite recommendations for screening programs and HPV vaccinations by the German Standing Committee on Vaccination (STIKO), Germany is facing about 4,600 cervical cancer cases and 2,000 deaths per year [1]. Considering Germany's low vaccination rate of 44.6% in female teenagers [2] compared to other western countries like Denmark (81%) or Sweden (78.5%) [3], and the recent recommendation for the vaccination of boys, it is of ever more importance to establish a tool providing the ability to precisely estimate potential interventions for the reduction of cervical cancer cases. Our aim was the development of a network based mathematical model, describing the transmission of HPV, incidences of cervical cancer as well as the evaluation of potential implications of policy and behavioral changes on the spreading and prevalence of infections and mortality due to cervical cancer.

METHODS

The underlying stochastic, dynamic, individual based network model used in an open population modelling approach was implemented in the R programming language (version 3.6) within the EpiModel package [5]. A network approach allows the modelling of individuals as separate nodes and dynamic stochastic processes which might lead to a more precise and flexible modelling of individual interactions and impact of interventions [4]. The sexual network was governed by an exponential random graph model which allows relationships to form and dissolve stochastically. For computational reasons, the initial model population was set to 10,000 nodes with reasonable heterosexual interaction patterns and age distribution for men and women (ages 12 to 100; Fig. 2) to closely reflect the circumstances in the Saarland region of Germany. Net migration with flexible infection and coverage rates was implemented as well. Information regarding population aging, birth, immigration, emigration and natural death of individuals was taken from the Federal Statistical Office of Germany (DESTATIS) [6]. Model baseline, infection rates and cancerogenicity were calibrated on the number of cancer cases and deaths due to cervical cancer. The calibration end points were obtained from literature [8-10]. Both the bi- and the nonavalent vaccines were analyzed in different infection and coverage settings, (44.6% vaccination of women and 20% future vaccination of men). For each scenario 100 simulations were performed.

RESULTS

The chosen model was an extended susceptible-infected-recovered (SIR) model with individuals passing from a susceptible to an infected state after being infected via the formation of a relationship with an infected individual. Furthermore, individuals could pass from the infectious to a recovered as well as back to the susceptible state through recovery. Infections are subdivided into different HPV types on which the different vaccines and risk factors for cancer hinge. From all stages death and emigration were possible, but arrival into the system was limited to births and immigration into the susceptible compartment with different infection and vaccination rates, respectively (Fig. 1).

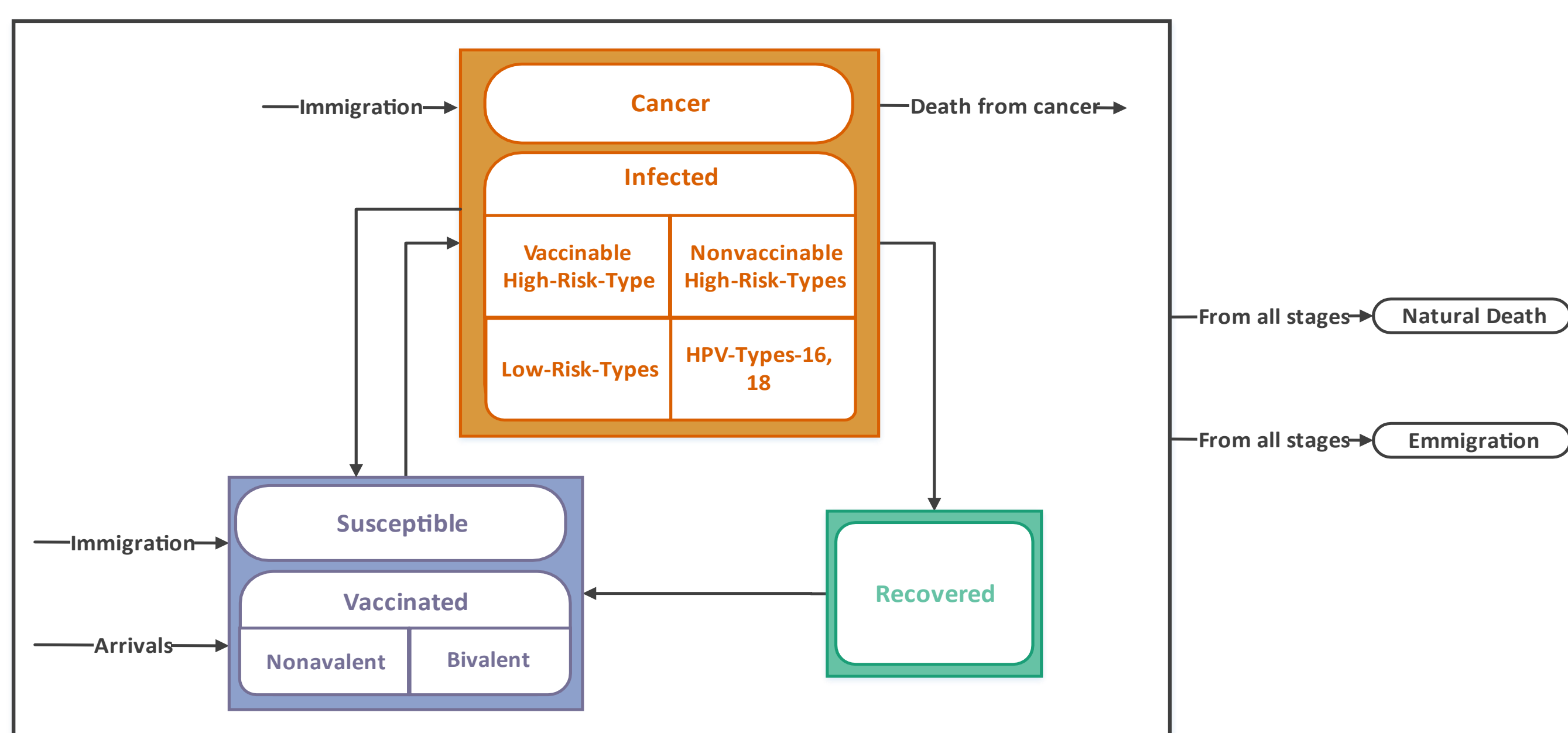


Figure 1: Schematic compartmental diagram for the spreading of HPV infections throughout the population based on a SIR compartment model, taking into account different demographic factors, HPV types and vaccines. The susceptible compartment is shown in blue, infected and its sub compartments in orange and recovered in green.

The above mentioned calibrations in combination with projections regarding the future demographic structure showed good concordance (Fig. 2-4). In addition the model predictions for cancer cases and deaths align well with literature extrapolations (Fig. 5-7). If only women are vaccinated the model shows a mean reduction by 25.8% for the HPV types 16/18 and 18.3% for vaccinable high risk types. This is amplified by the vaccination of men to values of 37.8% and 26.3%. In contrast the unspecific HPV prevalence does not decrease (Fig. 8). Over the course of the next 100 years, the model predicts an annual reduction of cervical cancer cases of 27.1% for the vaccination of women and of 34.1% if men are also vaccinated. Likewise, the annual number of cancer deaths is reduced by 23.1% and 38.4% per 100,000 women for these two scenarios. Depending on the actual vaccination turn out this might become even more amplified by the upcoming vaccinations for boys in Germany (Fig. 9).

CONCLUSION

A functional model for the description of the natural history and spreading of HPV has been developed. Furthermore, the model allows analyzing of potential impacts of behavioral parameters and policy changes on the prevalence of HPV and cervical cancer in the Saarland region.

However, especially in view of the over all low vaccination rate the level of acceptance for HPV vaccination for boys might prove to be a critical point.

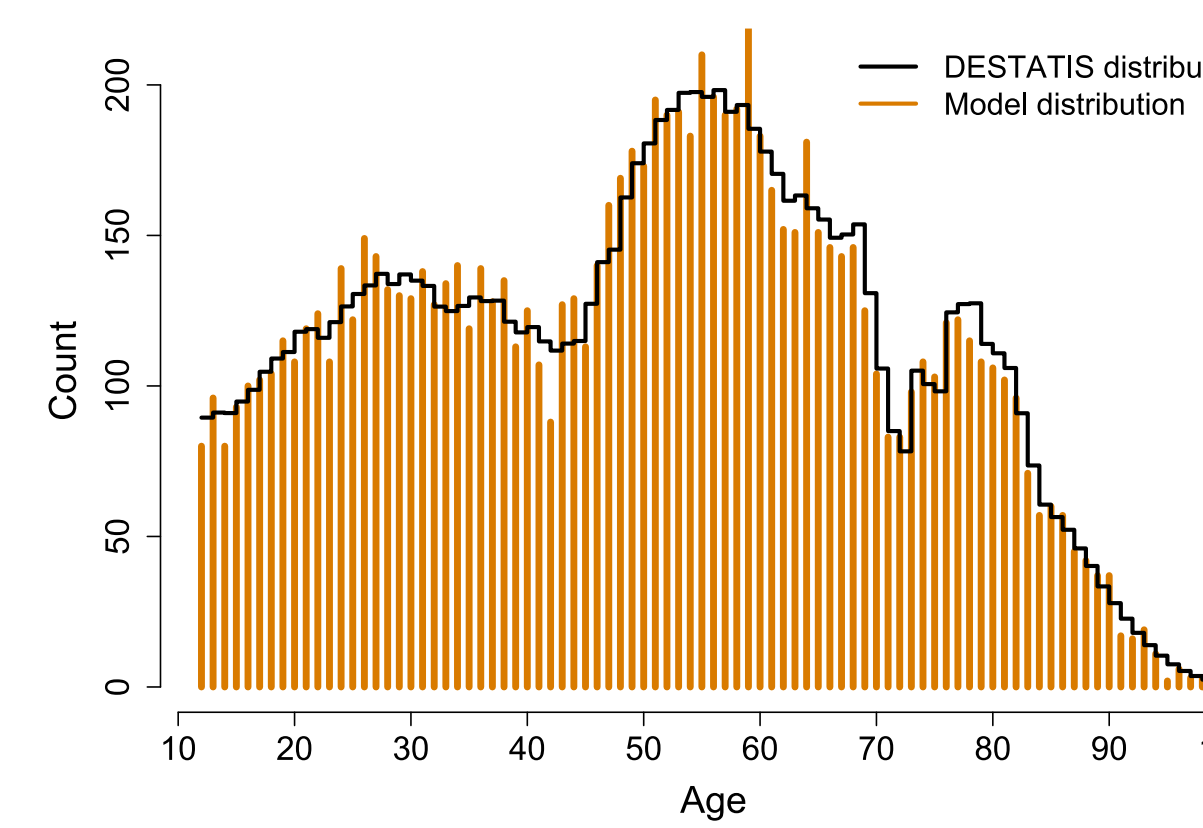


Figure 2: Initial age distribution modeled for a population of 10000 sampled from the age distribution for the Saarland region Germany provided by DESTATIS.

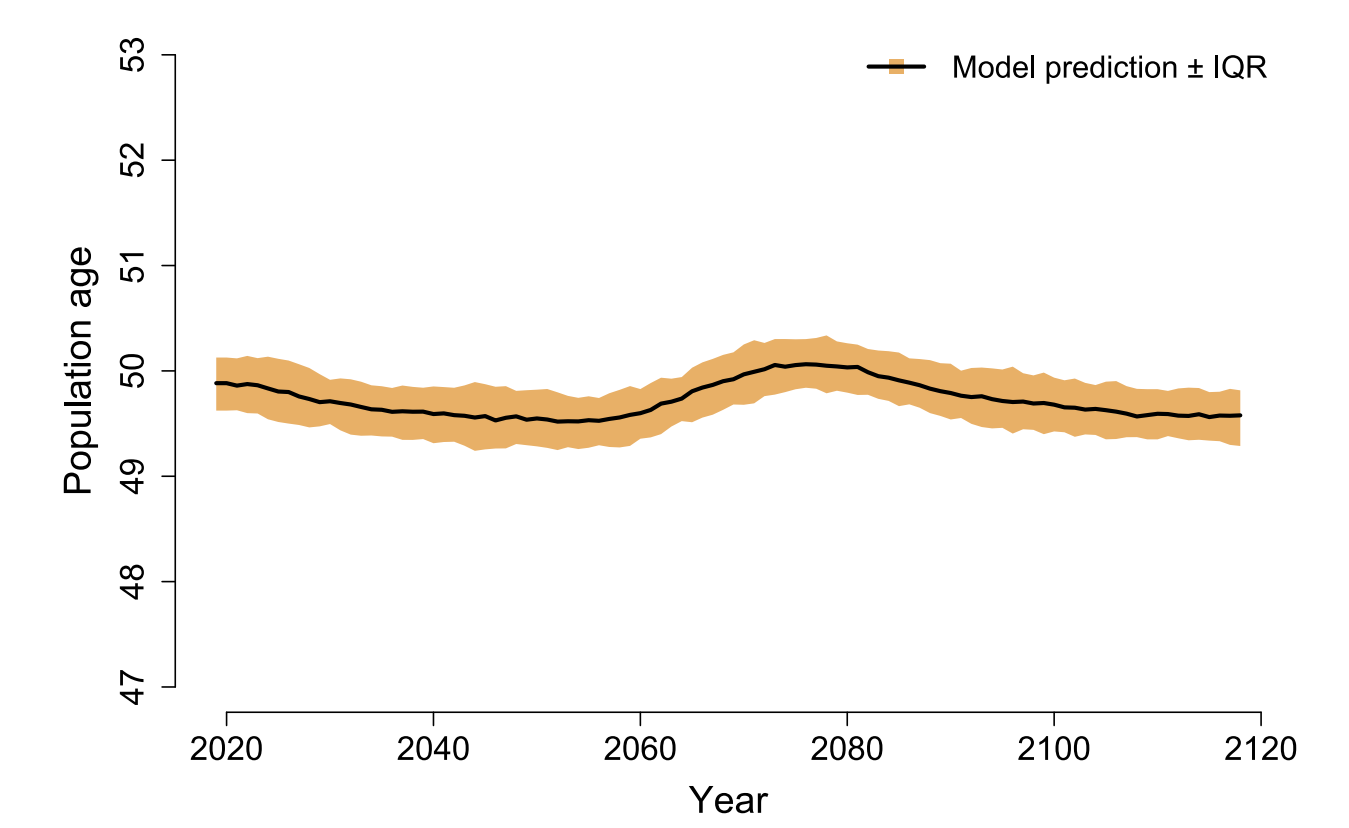


Figure 3: Model population median age for 10000 individuals for 100 simulations over the course of 100 years.

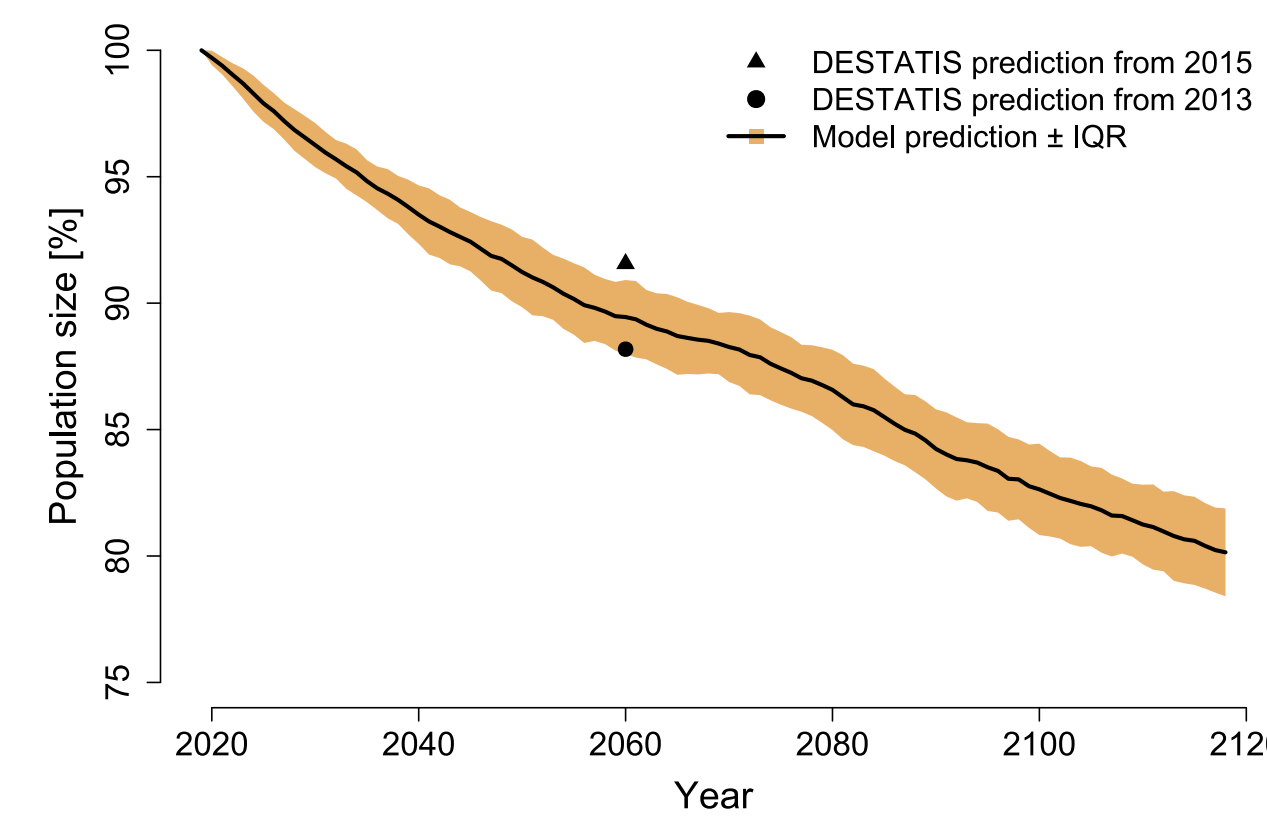


Figure 4: Predicted development of median relative population size over the next 100 years in comparison to predictions from 2015 and 2013 by DESTATIS for the year 2060.

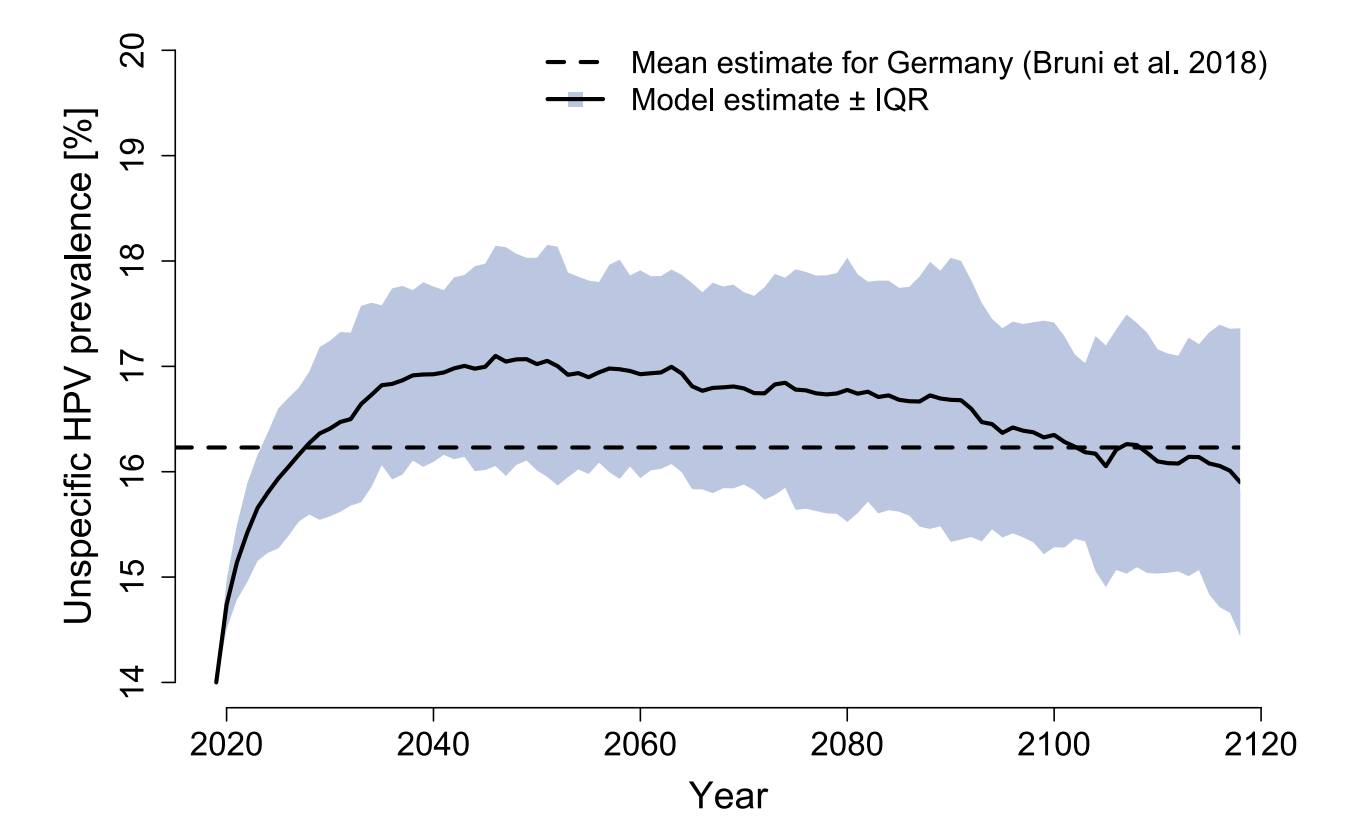


Figure 5: Median unspecific HPV prevalence over time in comparison to a mean estimate for Germany from literature.

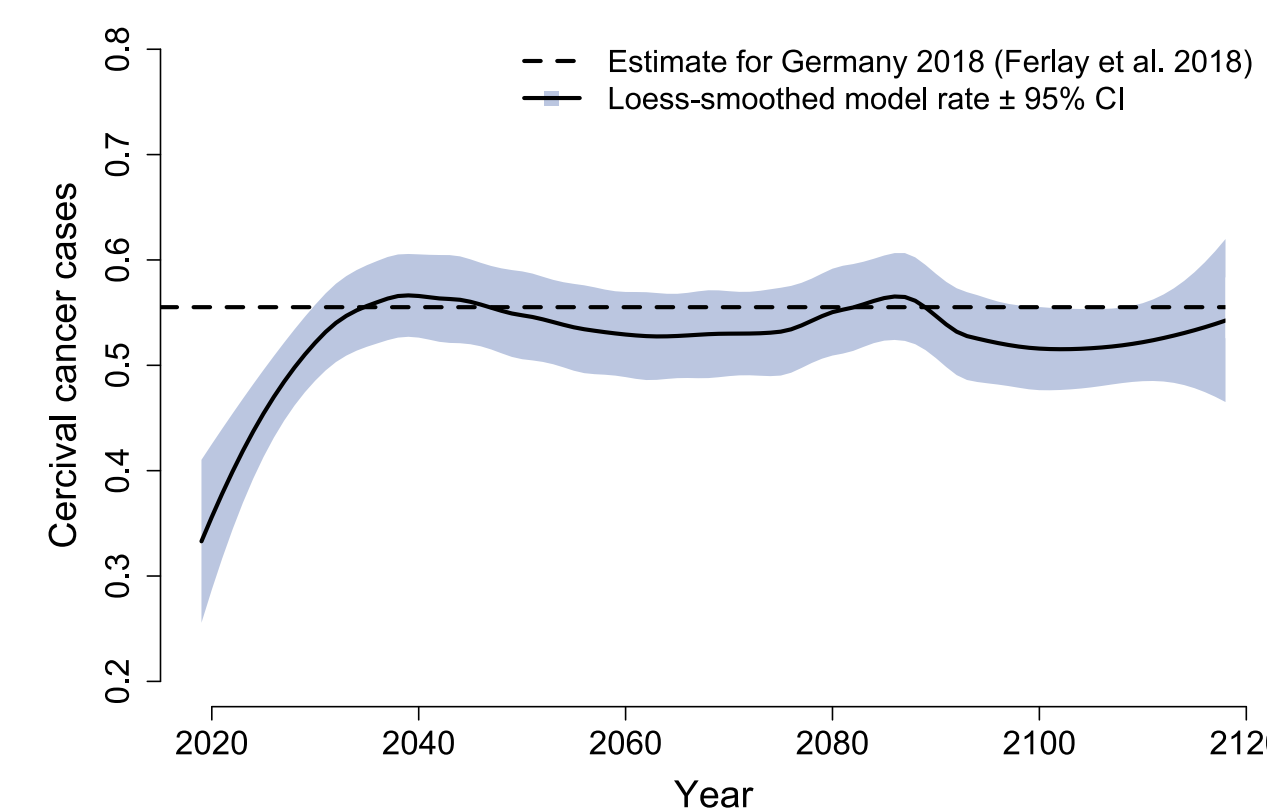


Figure 6: Model cervical cancer cases (adjusted by the expected median population decline) per 10,000 and per year (Loess curve) over the course of 100 years in comparison to an estimate for Germany from the literature.

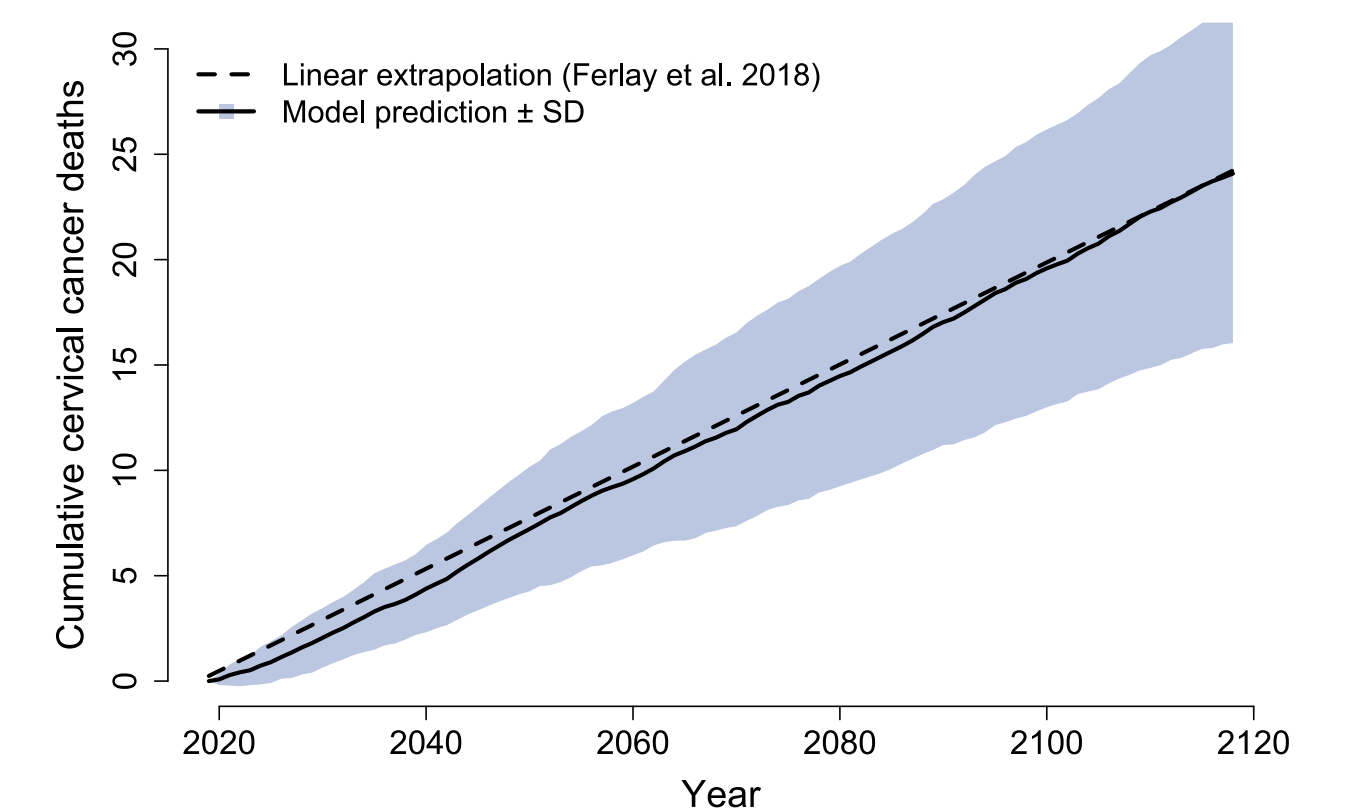


Figure 7: Predicted mean cumulative cervical cancer deaths per 10,000 over the course of 100 years in comparison to a fixed-rate extrapolation for Germany (rate provided by the literature).

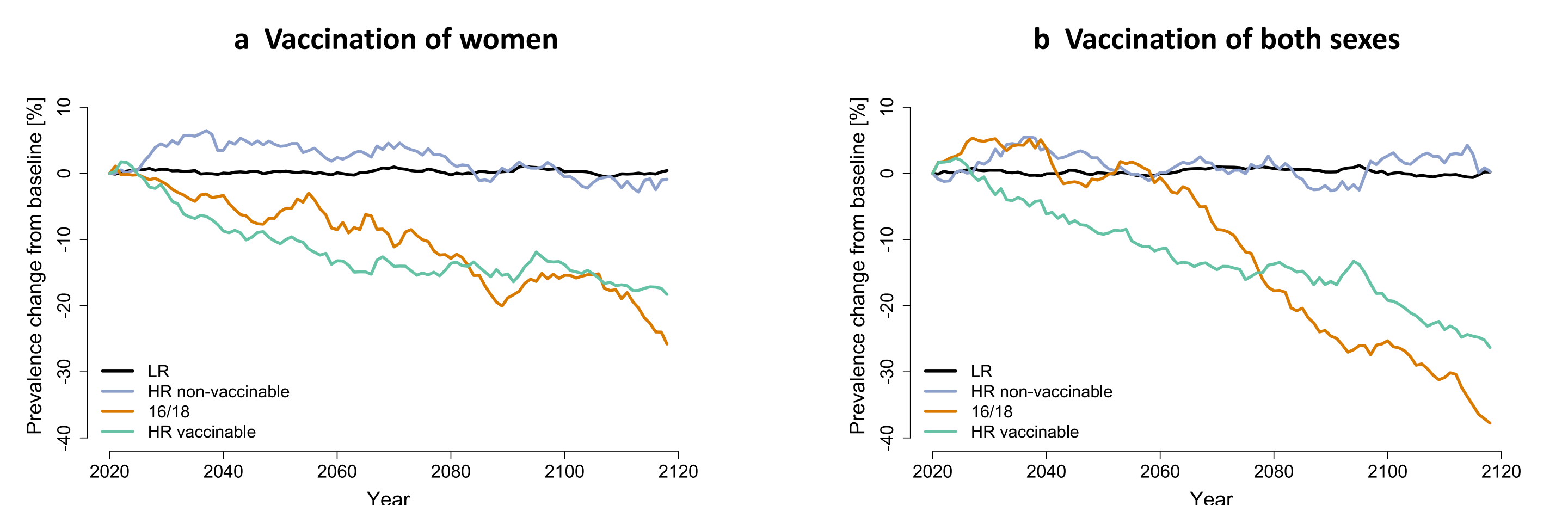


Figure 8: Change of the prevalence of HPV Types from baseline over time for women vaccination coverage of 44.6% (a) and for the additional vaccination of men at 20% coverage (b). HPV types are grouped by their ability to cause cancer and possibility to be vaccinated against them: 16/18 types, vaccinable high risks types (HR), non-vaccinable high risk types and low risk types (LR).

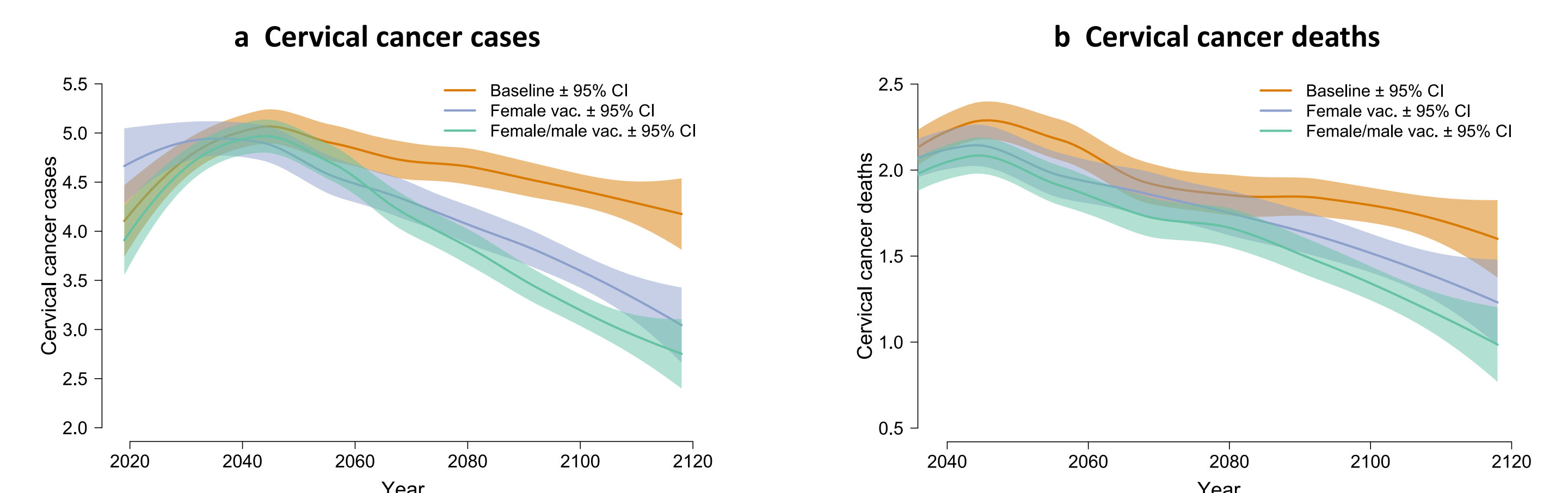


Figure 9: Number of cervical cancer cases (a) and cervical cancer deaths (b) per year, per 100,000 women. Comparison of the baseline model; no vaccination (orange), a scenario for vaccination of non-immigrated women with 44.6% coverage (blue) and a second scenario with additional vaccination of non-immigrated men with 20% coverage (green).

OUTLOOK

The model will be linked and calibrated with data provided by University Hospital Homburg as well as German healthcare providers for continual evaluations and additional recommendations regarding the prevention of cervix carcinoma in Germany.

[1] Ferlay et al., Estimating the global cancer incidence and mortality in 2018 : GLOBOCAN sources and methods, *Int. J. Cancer* 2018
 [2] Rieck et al., Aktuelles aus der KV-Impfsurveillance - Impfquoten ausgewählter Schutzimpfungen Deutschland, Robert Koch-Institut Epidemiologie und Gesundheitsberichterstattung 2018
 [3] Brotherton et al., HPV vaccination : Current global status, *Curr. Ob. Gyn. Rep.* 2015
 [4] Khanna et al., What can mathematical models tell us about the relationship between circular migration and HIV transmission dynamics?, *Math. Biosci. Eng.* 2015
 [5] Jenness et al., EpiModel : An R package for mathematical modeling of infectious disease over networks, *J. Stat. Softw.* 2018

[6] Statistisches Bundesamt, <https://www.destatis.de>
 [7] <https://www.aerzteblatt.de/int/archive/article/193180/Sexual-behavior-in-Germany-results-of-a-representative-survey>, 2019
 [8] Bruni et al., Human papillomavirus and related diseases in Germany, *Information Centre on HPV and Cancer* 2018
 [9] Reece et al., Condom use rates in a national probability sample of males and females ages 14 to 94 in the United States, *J. Sex. Med.* 2010
 [10] Iftner et al., Prevalence of low-risk and high-risk types of human papillomavirus and other risk factors for HPV infection in Germany within different age groups in women up to 30 years of age : an epidemiological observational study, *J. Med. Virol.* 2010