Mathematical modelling of HPV and HPV related cervical cancer elimination through vaccination in Barbados

Candidate number: E05763

Word Count: 9970 words

Date submitted: 14th October 2021

Abstract

Background: The human papillomavirus (HPV) is the strongest risk-factor for cervical cancer in women worldwide. Cervical cancer is the fourth most common cancer, and kills over 300,000 women each year. In Barbados, cervical cancer is the second leading cause of cancer death in women, with an associated mortality rate of 18.1 per 100,000 women. Recently, the World Health Organization (WHO) is urging countries to consider increasing vaccination coverage and screening efforts by 2030, as HPV is believed to be eliminable by the end of the century. Mathematical modelling has been historically used to assist in related policy-making decisions, and is used here to assess the efforts of Barbadian public health agencies to decrease HPV rates by forecasting incidence of HPV and cervical cancer for 2030 and 2100.

Methods: I used an age, gender, and sexual-activity stratified susceptible-infectious-susceptible (SIS) deterministic model to estimate HPV-16 and 18 incidence in Barbadian women aged 15-79 over time. The model was parameterized using publicly availably WHO data, estimates of sexual behaviour in Barbadian women, and fitted to pre-vaccination HPV serological data. Serological data was collected from 413 healthy women between age 18-65 from April 2010 to October 2012. I ran the fitted model for 100 years, and assessed the impact of different vaccination coverages on HPV incidence and cervical cancer incidence in women in the years 2030 and 2100.

Results: The best fitting model assumed proportional mixing and some intergenerational contact. At equilibrium, the fitted model led to 5134 infected women at any point. The current vaccine coverage of 30% girls and 27% boys aged <15 at 89% efficacy is predicted to prevent 48-52% of new HPV cases in 2030, and 78-86% in 2100, but never reaches a level to reduce cancer incidence <4 per 100,000. Vaccine coverages at or above 50% girls and 45% boys aged <15 reduce annual cancer incidence to <4 per 100,000 by 2100.

Discussion: The model was able to reproduce pre-vaccination HPV seroprevalence as observed in Barbados. All explored vaccine coverage levels lead to sharp reductions in HPV incidence, including the current coverage level. A vaccine coverage of at least 50% girls and 45% boys aged <15 may be enough to reduce cumulative cancer incidence to <4 per 100,000 by the end of the century. The model is affected by several limitations, particularly due to a lack of validating data. Future work should consider studying population characteristics, as well as post-vaccination HPV prevalence. Lastly, the nonavalent vaccine, which covers additional highly-prevalent HPV types present in Barbados, could be considered to further reduce the burden of HPV.

Statement of Author's role

The author of this report developed the research question, and with the guidance of the author's advisor, created and parameterized a relevant model in R. The author carried out all analyses and wrote up the final report. The author's advisor provided suggestions on how to design a transmission model in R and provided suggestions on how to simplify the model, but ultimately left all decisions up to the author and supported them wholeheartedly. The author's advisor read the pre-final report and made suggestions. The author has no conflicts of interest to declare.

Table of Contents

1. Introduction

1.1 Human Papillomavirus and cervical cancer

Invasive cervical cancer (ICC) is the fourth most common cancer in women worldwide.[1] An estimated 604,000 new cases are diagnosed each year, with between 311,000-342,000 deaths annually.[1,2] Distribution is differential, with low- and middle-income countries (LMIC) experiencing 85% of the burden.[2,3] However, ICC is a strong candidate for elimination due to its predominantly infectious origin, and is beginning to decline in incidence due to increased screening and vaccination efforts.[4] The human papillomavirus (HPV) was labelled as carcinogenic in 1995, and is a well-known risk factor for ICC, detected in over 99% of cases, and considered a necessary – although not sufficient – cause.[5–7] ICC risk-modifiers include age at sexual debut, sexual behaviour, smoking, immune deficiencies, coinfection with other sexually transmitted infections (STIs), contraception use, current age, socioeconomic status (SES), diet, and parity.[7,8] Additional HPV related diseases include vaginal, anal, vulvar, penile, and oropharyngeal cancers, various cutaneous and mucosal warts in both men and women, and recurrent respiratory papillomatosis.[7]

HPV is a small spherical double-stranded DNA virus belonging to the *Papillomaviridae* family that preferentially infects basal layers of epithelial cells.[9,10] Age-adjusted HPV prevalence is estimated at 9.9% globally.[11] Women younger than 25 years (y) experience most infections, with some regions seeing additional peaks in incidence following age 45y.[12] More than 100 HPV variants are known and classified as either high-risk or low-risk depending on oncogenicity.[13] The most prevalent high-risk variants are HPV-16, 18, 31, 33, 45, 52, 56, and 58.[11] Studies estimate more than 90% of ICCs are associated with these variants, with up to 70% associated with types 16 and 18.[14]

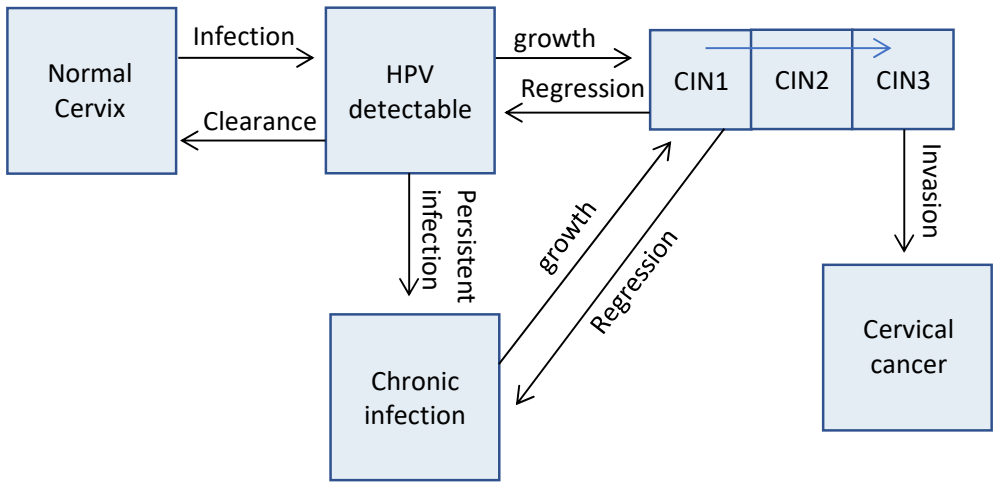
HPV induces cell machinery to replicate within the nuclei of infected cells until there are approximately 50-100 copies of itself before bursting from epithelial layers and infecting surrounding cells.[7,15] Around 90% of infections are benign and cleared naturally through the innate immune response within two years, although the genome may persist in infected cells for years.[9,15,16] High-risk types of HPV are troublesome due to the presence of E5, E6, and E7 proteins with the ability to inhibit p53 and pRB tumour-suppressor genes. Blocking these genes can increase cell cycle proliferation, weaken genome maintenance, and prevent apoptosis – increasing the probability of cancerous tumour growth.[9,17–19] Infection generally occurs through microscopic mucosal tears during sexual contact, but can transmit from mother-to-child at birth.[10,16–18]

Following HPV infection, the incubation period for microscopic growths is estimated at five years.[20] The incubation period toward ICC is around 10 years from initial infection, and usually occurs between ages 25-35y.[21] Studies in men and women find reinfection increases probability of malignant transformation. Additionally, these studies found that sexual behaviour and previous infection increases the risk of reinfection, with no evidence of homologous nor heterologous immunity to previously infected variants.[22,23]

Figure 1 highlights the natural history of HPV-derived ICC. Pre-cancerous disease begins as *cervical intraepithelial neoplasia* (CIN) when abnormal cellular growth occurs but is contained in the cervix. Pre-cancerous stages progress through CIN1, CIN2, and CIN3 depending on location of growth and risk of cancer development, followed by ICC stages I-IV as the tumour grows and spreads to nearby tissue.[24–26] Approximately 90% of ICC presents as squamous cell carcinoma, followed by nearly 10% adenocarcinoma; other cancer types are relatively rare.[24] There is conflicting evidence on whether specific cancer types lead to worse outcomes.[27–32] The 5-year survival rate of ICC ranges from 72-76%.[33–

[35] If diagnosed at an early stage, treatment involves radiotherapy, chemotherapy, and/or hysterectomy.[7,36]

Figure 1: Natural history of cervical HPV infection and invasive cervical cancer.



1.2 Prevention strategies

There are several methods to prevent HPV infection or, if already infected, detect HPV and cancerous changes early to pursue treatment. The simplest prevention method is the consistent and effective use of contraceptives such as condoms. However, studies found conflicting evidence on efficacy to prevent HPV transmission due to challenges in reliably measuring condom use.[37–40] Once infected, the best methods to detect infection, diagnose abnormal growth, and prevent further dysplasia is through regular HPV testing, pap-smear, endocervical curettage, or colposcopy; all suggested for women aged 21y and older.[7,41,42]

The most promising methods of preventing HPV transmission are routine non-infectious recombinant vaccines inducing neutralising antibodies to prevent future infections. One landmark study in over 1.6 million women and girls saw a 90% reduction in ICCs due to vaccinations between 2006 and 2017.[43]

There are currently three highly effective vaccines available for HPV: *Cervarix*, *Gardasil-4*, and *Gardasil-9*. Clinical trials found these vaccines safe and free of severe adverse-events in the recommended populations.[44–47] The bivalent *Cervarix* (protective against HPV-16 and 18) and quadrivalent *Gardasil-4* (protective against HPV-6, 11, 16, and 18) vaccines are most widely available with efficacy against new infection ranging from 89-100%, including slight protection against HPV-31 and 45, for at least 14 years following complete vaccination.[48–53]

The "second-generation" nonavalent *Gardasil-9* vaccine protects against HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58. Systematic reviews found the vaccine effective in females and males aged 9-26y.[54,55] Efficacy ranges between 96.7-97.4% against new infection and is estimated to prevent nearly 90% of neoplasia and ICC cases for at least six years.[44,56,57] This is noteworthy because HPV-45 is the third most common variant found amongst ICC cases, and efficacy against HPV-45 for "first-generation" vaccines is poor.[11] Some studies found that HPV-18 and 45 are both under-represented in pre-cancerous lesions, and commonly detected in younger ICC patients. These findings may suggest quicker progression to ICC after infection with these HPV-types, or even systematically missed diagnosis by screening programmes.[58]

While countries with HPV vaccination programmes tend to focus on two- or three-dose vaccination schedules for 9-25y old females, the World Health Organization (WHO) recommends two-dose schedules spaced six months apart for girls aged 9-14y, and three-dose schedules (second dose 1-2 months after the first, third dose six months after the first) for girls first vaccinated after age 15y and for younger immunocompromised girls.[59] Recent modelling studies further support these recommendations.[60,61] Studies found that, although some benefit exists in vaccinating males and older female age-groups, cost-effectiveness peaks while focusing vaccination efforts toward young girls because other groups in the population have little cancer burden and likely benefit from herd

immunity.[55,62,63] There is no evidence that vaccination assists with clearing current infection, nor does it prevent potential dysplasia if already infected.[64]

Vaccination is not without challenges, as vaccine hesitancy, uptake, and costs lead to variation in vaccine coverage.[65] Clinical recommendations are key to increasing uptake, but some physicians are apprehensive about vaccinating young populations.[66] The cost of vaccination may prove to be another major challenge, as they differ by country, but estimates range from USD $25 for each quadrivalent vaccine dose, and USD $196-240 for the nonavalent vaccine.[67,68] However, models propose that despite costs, vaccines have shown to be cost-effective.[61,69–71]

The nonavalent vaccine is believed to offer only slight advantages over the older generation vaccines, as both vaccine generations are highly effective against the most common HPV types.[44,59] As of 2018, 82 countries have some level of active HPV vaccination-programme.[72] Additionally, Gavi, the global vaccine alliance, recently began supporting LMICs to introduce HPV vaccines by assisting countries to access vaccines for as low as US $4.50 per dose.[73]

1.3 Barbados

Barbados is a small country located in the south-eastern Caribbean. Its population size is estimated at 287,000, with most people living in the urban south and west.[74,75] Approximately 148,000 (51.6%) of these are female.[74] United Nations World Population Prospects (UNWPP) estimates for 2020 place 16.8% of the total population below 15y, 13.1% between 15-24y, 12.8% between 25-34y, and 57.3% over the age of 35y.[74] Life expectancy at birth is 79y, the birth-rate is 10.96 per 1000, and the death-rate is 7.9 per 1000.[75]

Cervical cancer screening began in Barbados in July 1965.[76] In 2018, ICC was the fourth leading cancer nationally, and second leading cause of cancer-related deaths in Barbadian women, with approximately 38 new diagnosed cases and 27 deaths annually.[77] The crude mortality rate from ICC in Barbados is 18.1 per 100,000 women per year, compared to 11 per 100,000 regionally and 8.2 globally per 100,000 per year.[11,77] ICC mostly affects women over 45y.[78] A study in Barbadian women aged 18-65y found that before routine HPV vaccination was introduced to Barbados in 2014, HPV prevalence of any type was 33%, of which high-risk type HPV-45 was most prevalent, followed by 16, 52, and 58.[79] Importantly, with high rates of HPV-45, the genotypic distribution of HPV variants in Barbados is dissimilar to most populations.[79]

The HPV vaccine available in Barbados is a publicly funded 2-dose quadrivalent vaccine, offering only slight protection against HPV-45, and no protection to other high-prevalent variants, although these latter variants are less likely to affect ICC risk.[72,80] A similar study in Saint Vincent and the Grenadines also found HPV-45 most prevalent, and encouraged introduction of the nonavalent vaccine.[81]

The main target vaccination population in Barbados is 11-14y old girls, beginning in 2014; boys of the same age have been included in the programme since 2016.[72,77,80] There is no known information on catch-up campaigns or availability to older age-groups, nor coverage data on the nonavalent vaccine.[77] The Pan American Health Organisation (PAHO) and WHO estimated in 2018 (the first year data was available) vaccination coverage for final-dose at 25% for girls.[82,83] By 2019 (the most recent complete data available), this had increased to 30% for girls, and 27% in boys.[83]

A 2013 survey in Barbadian girls aged 15-19y found that 51% reported ever having sex, and 17.8% reported ever having intergenerational heterosexual intercourse (i.e. with a male 10y or older).[84] A more

recent 2020 cross-sectional study amongst male and female Barbadians found that 25% reported having had sex by 16y, which increased to 75% by 19y.[85] Regarding number of sexual partners, 44.7% of 15-19y old Barbadian women reported one partner, 18.9% reported two partners, 5% reported three partners, 3.3% reported four partners, and 3% reported five or more partners in the previous 12 months.[84] Overall, 80.6% of male and female Barbadians aged 15-49y reported a single sexual partner, while 19.4% reported multiple sexual partners.[85]

1.4 Mathematical modelling

Mathematical modelling is used to make public health recommendations and inform policy regarding control of infectious agents. It allows researchers and policy-makers to understand transmission dynamics in a population, and to project the potential impact of alternative strategies against transmission and disease. Modelling studies project that global elimination of ICC can be achieved by the end of the century.[86,87] Current herd immunity thresholds range from 50-80%, with studies suggesting that sustained 80% coverage could eventually eliminate all high-risk HPV types.[63,88,89] However, studies show that there are little herd effects on HPV types not specifically covered by a vaccine.[63,90]

1.5 HPV and cervical cancer elimination

Following the call for action in May 2018 toward global ICC elimination, the WHO released the global strategy to accelerate elimination of ICC as a public health problem in 2020, setting goals to achieve 90% HPV vaccination coverage in girls under 15y, 70% screening coverage by age 35y and again by 45y, and 90% of women with disease receiving treatment, by the year 2030.[91] This strategy includes reducing the age-adjusted incidence rate to 4 per 100,000 women per year in all countries.[3] On 17 November 2020, the Healthy Caribbean Coalition followed this with an open letter to Caribbean Community and Common Market (CARICOM) leaders calling for commitment to achieve the 2030 goals in the region.[92]

1.6. Aims and objectives

To date, no HPV modelling studies have specifically focussed on this population. The aim of this analysis is to project the current pathway towards elimination of HPV, and by extension, HPV-related ICC, in Barbadian women aged 15-79y.

This will be done through the following objectives:

1) What transmission patterns can explain the pre-vaccination HPV prevalence rates observed in Barbados?
2) What is the estimated prevalence and incidence of HPV and ICC in 2030 and 2100 if the current vaccine strategy is continued?
3) How would an increase in vaccination coverage affect these estimates?

2. Methods

2.1 Model structure

This study used a deterministic Susceptible-Infectious-Susceptible (SIS) transmission model inspired by previous HPV transmission models.[61,93,94] Figure 2 highlights the model structure. The model was stratified by gender (omitted from diagram as the model assumed identical structure for both genders), sexual-activity (low or high), and age-group (15-24y, 25-34y, or 35y+). In all compartments and parameters, subscripts refer to different model strata: *g* denotes gender (m for males, f for females); *a* denotes age-group (1 for 15-24, 2 for 25-34, 3 for 35+); and *r* denotes activity status (l for low-activity, h for high-activity). E.g. compartment $V_{f,1,h}$ refers to vaccinated females in age-group 15-24y in the low sexual-activity group.

Individuals entered the model at age 15y at a constant rate, α_1. This rate was multiplied by a proportion, $v_{g,r}$ (for vaccinated) or $u_{g,r}$, (for unvaccinated) depending on gender, sexual-activity group and vaccination status, and included vaccine coverage (by gender) and efficacy representing the vaccination strategy being explored. All individuals entered the model susceptible, assuming no sexual-activity before age 15y. To simplify the model, "death" (i.e. aging out at 79y) was assumed as all-cause, therefore HPV and cancer had no effect on this parameter

The model can be described by the following system of ordinary differential equations (equation 1):

$$\frac{dS_{g,1,l}}{dt} = -S_{g,1,l} * \lambda_{g,1,l} + I_{g,1,l} * \gamma + V_{g,1,l} * \delta + \alpha_1 * u_{g,l} - \alpha'_1 * S_{g,1,l}$$

$$\frac{dS_{g,1,h}}{dt} = -S_{g,1,h} * \lambda_{g,1,h} + I_{g,1,h} * \gamma + V_{g,1,h} * \delta + \alpha_1 * u_{g,h} - \alpha'_1 * S_{G,1,h}$$

$$\frac{dS_{g,2,l}}{dt} = -S_{g,2,l} * \lambda_{g,2,l} + I_{g,2,l} * \gamma + V_{g,2,l} * \delta + \alpha_2 * S_{g,1,l} + \alpha_2 * S_{g,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * S_{f,2,l}$$

$$\frac{dS_{g,2,h}}{dt} = -S_{g,2,h} * \lambda_{g,2,h} + I_{g,2,h} * \gamma + V_{g,2,h} * \delta + \alpha_2 * S_{g,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * S_{g,2,h}$$

$$\frac{dS_{g,3,l}}{dt} = -S_{g,3,l} * \lambda_{g,3,l} + I_{g,3,l} * \gamma + V_{g,3,l} * \delta + \alpha_3 * S_{g,2,l} + \alpha_3 * S_{g,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * S_{g,3,l}$$

$$\frac{dS_{g,3,h}}{dt} = -S_{g,3,h} * \lambda_{g,3,h} + I_{g,3,h} * \gamma + V_{g,3,h} * \delta + \alpha_3 * S_{g,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * S_{g,3,h}$$

$$\frac{dI_{g,1,l}}{dt} = +S_{g,1,l} * \lambda_{g,1,l} - I_{g,1,l} * \gamma - \alpha'_1 * I_{g,1,l}$$

$$\frac{dI_{g,1,h}}{dt} = +S_{g,1,h} * \lambda_{g,1,h} - I_{g,1,h} * \gamma - \alpha'_1 * I_{g,1,h}$$

$$\frac{dI_{g,2,l}}{dt} = +S_{g,2,l} * \lambda_{g,2,l} - I_{g,2,l} * \gamma + \alpha_2 * I_{g,1,l} + \alpha_2 * I_{g,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * I_{g,2,l}$$

$$\frac{dI_{g,2,h}}{dt} = +S_{g,2,h} * \lambda_{g,2,h} - I_{g,2,h} * \gamma + \alpha_2 * I_{g,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * I_{g,2,h}$$

$$\frac{dI_{g,3,l}}{dt} = +S_{g,3,l} * \lambda_{g,3,l} - I_{g,3,l} * \gamma + \alpha_3 * I_{g,2,l} + \alpha_3 * I_{g,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * I_{g,3,l}$$

$$\frac{dI_{g,3,h}}{dt} = +S_{g,3,h} * \lambda_{g,3,h} - I_{g,3,h} * \gamma + \alpha_3 * I_{g,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * I_{g,3,h}$$

$$\frac{dV_{g,1,l}}{dt} = -V_{g,1,l} * \delta + \alpha_1 * v_{g,l} - \alpha'_1 * V_{g,1,l}$$

$$\frac{dV_{g,1,h}}{dt} = -V_{g,1,h} * \delta + \alpha_1 * v_{g,h} - \alpha'_1 * V_{g,1,h}$$

$$\frac{dV_{g,2,l}}{dt} = -V_{g,2,l} * \delta + \alpha_2 * V_{g,1,l} + \alpha_2 * V_{g,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * V_{g,2,l}$$

$$\frac{dV_{g,2,h}}{dt} = -V_{g,2,h} * \delta + \alpha_2 * V_{g,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * V_{g,2,h}$$

$$\frac{dV_{g,3,l}}{dt} = -V_{g,3,l} * \delta + \alpha_3 * V_{g,2,l} + \alpha_3 * V_{g,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * V_{g,3,l}$$

$$\frac{dV_{g,3,h}}{dt} = -V_{g,3,h} * \delta + \alpha_3 * V_{g,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * V_{g,3,h}$$

(Equation 1)

Susceptible individuals of any gender *g*, age *a*, and activity-group *r* became infected at rate $\lambda_{g,a,r}$ (t) defined by equation 2 (detailed force of infection (FOI) in appendix equation 6).

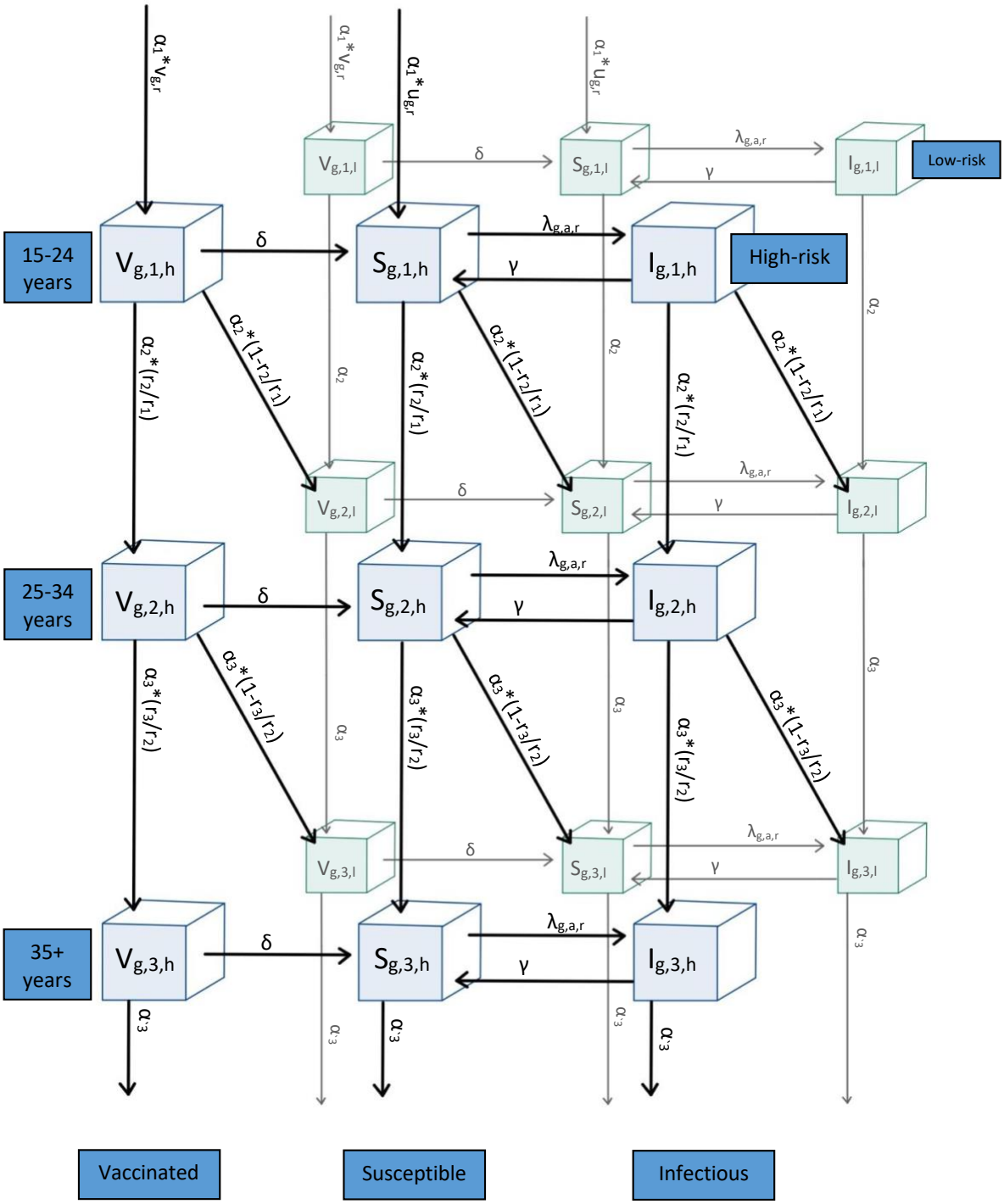
$$\lambda_{g,a,r}(t) = \sum_{i=1}^{3}\left(\sum_{r=1}^{2}\left(\beta_{ia,rj} * \frac{I_{i,j}(t)}{N_{i,j}(t)} * \mu_j\right)\right)$$

(Equation 2)

Here, age-groups 15-24y, 25-34y, and 35y+ are represented by *i* and *a* values 1, 2, and 3, while activity-groups low and high are represented by *j* and *r* values 1 and 2. $\beta_{ia,rj}$ represents the daily partnership rate of individuals in age-group *a* and activity-group *r* with individuals in age-group *i* and activity-group *j*. μ_j is a fitted value adjusting the probability of transmission following sexual-contact with infectious individuals in activity-group *j*.

Only heterosexual transmissions were modelled, therefore effective sexual-contact only considered as partnerships between females and males or visa-versa (full contact matrix found in appendix table A2). Infectious individuals cleared infections at a rate $\gamma = \frac{1}{D}$ $where\ D = \frac{-\log(1-0.9)}{365*2}$. This represented a cumulative proportion of 90% of infections clearing within two years.[16] I assumed that previous infections conferred no protection to future infections, and individuals returned to being susceptible after recovery from infection.

Figure 2: Detailed SIS model diagram showing the movement of individuals through compartments.



HPV prevalence in females in any year was calculated as the total number of cases at mid-point (1 July) of the year. Incidence was calculated by summing the total number of cases over the year (1 January to 31 December), stratified by the number of females in any group, and presented per 100,000. Symptomatic (i.e. cancer) cases were estimated outside the transmission model.

Differential equations were solved using the Runge-Kutta method in the *R deSolve* package, and ran for 100 years.[95] The full set of differential equations for each stratum are in the appendix (equation 7).

2.2 Model parameters

Table 1 lists all parameters used in the model, including definitions, calculations, and values. Demographic information was based on estimates from the United Nations World Population Prospects.[74] In 2021, the estimated population size for Barbados was 287,371.[74] Those younger than 15y were removed and the final population-size of 239,206 was used in the model. The population-size was assumed to remain stable for the duration of the simulation by equating the numbers of births and deaths. I assumed a rectangular population distribution, where after entry in the population, all individuals were assumed to survive until reaching the average life-expectancy of Barbados (79y), and were removed from the model thereafter. The number of people in each age-group were calculated proportional to the duration they spend in each age-group (equation 3):

$$\begin{bmatrix} N_1 \\ N_2 \\ N_3 \end{bmatrix} = \begin{bmatrix} age_1/(age_1 + age_2 + age_3) \\ age_2/(age_1 + age_2 + age_3) \\ age_3/(age_1 + age_2 + age_3) \end{bmatrix} * z, where \begin{bmatrix} age_1 \\ age_2 \\ age_3 \end{bmatrix} = \begin{bmatrix} 10 \\ 10 \\ L - 35 \end{bmatrix}$$

(Equation 3)

The average time an individual spent in an age-group was equal to the size of that age-group in years. These parameters also reflected Barbados' age distribution, and ensured a stable population distribution over time. The rate at which individuals entered the model mirrored the rate they left at age 79y in

order to maintain a stable population-size, with only the oldest age-group being removed. As aging occurred, the rates at which high-activity individuals aged into subsequent age-groups were adjusted by a proportion r_2/r_1 (for 25-34y) or r_3/r_2 (for 35y+) to reflect the observed reduction in people in the high-activity group in older age-groups.

HPV prevalence in Barbadians older than 35y did not differ substantially, and were therefore grouped together to simplify transmission. Likewise, although gender-ratios differ slightly in reality (51.6% female, 48.4% male), I assumed a 1:1 ratio of females to males to simplify population dynamics.

Table 1: Parameters used in the differential equations and model diagram.

Parameter	Definition and source	Value
$\lambda_{g,a,r}$	Force of infection of susceptible gender *g*.	Calculated in model, see appendix equation 6
L	Life expectancy in years, assumed to be 79y.[75]	$L = 79$
z	Total model population size.[74]	$z = 239206$
age_a	Age duration in each age-group *a*.	$\begin{bmatrix} age_1 \\ age_2 \\ age_3 \end{bmatrix} = \begin{bmatrix} 10 \\ 10 \\ L-35 \end{bmatrix}$
N_a	Population size in each age-group *a*.	$\begin{bmatrix} N_1 \\ N_2 \\ N_3 \end{bmatrix} = \begin{bmatrix} age_1/(age_1+age_2+age_3) \\ age_2/(age_1+age_2+age_3) \\ age_3/(age_1+age_2+age_3) \end{bmatrix} * z$
$N(t)$	Total population, at time *t*.	$N(t) = N_1(t) + N_2(t) + N_3(t)$
v_{pf}	Proportion of vaccinated females.	Varies throughout model for sensitivity analysis

Table 1 continued: Parameters used in the differential equations and model diagram.

Parameter	Definition and source	Value
v_{pm}	Proportion of vaccinated males.	Varies throughout model for sensitivity analysis
v_e	Vaccine efficacy, set at 89% or 100%.[48–53]	Varies throughout model for sensitivity analysis
α'_1	Rate at which individuals age out of the 15-24y compartment.	$\alpha'_1 = \frac{1}{(age_1 * 365)}$
α'_2	Rate at which individuals age out of the 25-34y compartment.	$\alpha'_2 = \frac{1}{(age_2 * 365)}$
α'_3	Rate at which individuals in the oldest age groups die and leave the model	$\alpha'_3 = \frac{1}{(age_3 * 365)}$
α_1	Rate at which individuals age into the model (i.e. "become 15y old").	$\alpha_1 = \alpha'_3 * N_3 * 0.5$
α_2	Rate at which individuals age into the 25-34y old compartment.	$\alpha_2 = \alpha'_1$

Table 1 continued: Parameters used in the differential equations and model diagram.

Parameter	Definition and source	Value
α_3	Rate at which individuals age into the 35y+ old compartment.	$\alpha_3 = \alpha'_2$
γ	Rate at which infectious individuals recover and re-enter the susceptible compartment.[16]	$\gamma = \frac{1}{D}$
δ	Rate at which vaccinated individuals lose protection and re-enter the susceptible compartment.[53]	$\delta = \frac{1}{365*14}$
μ_r	Fitted parameter adjusting daily partnership rates with infectious individuals who are in the low- or high-activity stratum.	Fitted in the model
r_a	Proportion of high-activity individuals in each age-group a.[79]	$\begin{bmatrix} r_1 \\ r_2 \\ r_3 \end{bmatrix} = \begin{bmatrix} 0.339 \\ 0.252 \\ 0.128 \end{bmatrix}$

Table 1 continued: Parameters used in the differential equations and model diagram.

Parameter	Definition and source	Value
$v_{g,r}$	Proportion of effectively vaccinated individuals entering the model depending on gender *g*.	$\begin{bmatrix} v_{f,l} \\ v_{f,h} \\ v_{m,l} \\ v_{m,h} \end{bmatrix} = \begin{bmatrix} 1 - r_1 * v_{pf} * v_e \\ r_1 * v_{pf} * v_e \\ 1 - r_1 * v_{pm} * v_e \\ r_1 * v_{pm} * v_e \end{bmatrix}$
$u_{g,r}$	Proportion of unprotected individuals entering the model depending on gender *g*.	$\begin{bmatrix} u_{f,l} \\ u_{f,h} \\ u_{m,l} \\ u_{m,h} \end{bmatrix} = \begin{bmatrix} 1 - r_1 * 1 - v_{pf} * v_e \\ r_1 * 1 - v_{pf} * v_e \\ 1 - r_1 * 1 - v_{pm} * v_e \\ r_1 ** 1 - v_{pm} * v_e \end{bmatrix}$
$c_{a,a}$	Proportion of partnerships made by contactors of each age with contactees of each age.[84]	See table 4
p_r	Average number of partnerships per day.	$\begin{bmatrix} p_l \\ p_h \end{bmatrix} = \begin{bmatrix} 0.002465753 \\ 0.008200666 \end{bmatrix}$ see section 2.4
$f_{a,rr}$	Proportion of contacts made by each activity-group within each age group.	$\begin{bmatrix} f_{1,ll} & f_{2,ll} & f_{3,ll} \\ f_{1,lh} & f_{2,lh} & f_{3,lh} \\ f_{1,hl} & f_{2,hl} & f_{3,hl} \\ f_{1,hh} & f_{2,hh} & f_{3,hh} \end{bmatrix} = \begin{bmatrix} 0.3695928 & 0.4715946 & 0.6719551 \\ 0.6304072 & 0.5284054 & 0.3280449 \\ 0.3695928 & 0.4715946 & 0.6719551 \\ 0.6304072 & 0.5284054 & 0.3280449 \end{bmatrix}$

g=gender, where m=male, f=female;

a=age, where 1=15-24y, 2=25-34y, 3=35y+;

r=sexual-activity, where l=low-activity, h=high-activity

I derived mixing matrices representing the daily rate at which new sexual partnership were acquired by combining several parameters. I combined the estimated total number of sexual partners per year by

sexual-activity group with the proportion of contacts made by people of certain age-groups, and the assumed proportion of contacts made by people in the low- or high-activity group based on an assumed Q-value, as introduced by Gupta et al.[96] Q represents the degree of mixing where Q=0 when partners are selected *proportionately*, Q=1 when partners are selected *with-like*, and Q<0 (i.e. negative values) when partners are selected purely *with-unlike*.[96] Using these parameters, I calculated daily partnership acquisition rates ($\beta_{ia,rj}$) between individuals in age-group *a* and sexual-activity group *r* with individuals of the opposite gender in age-group *i* and sexual-activity group j. I did so by combining the daily number of partnerships made by individuals in sexual-activity group *r*, where high- and low-activity individuals were grouped based on number of partners in the last 12 months and the number of partners were averaged; the proportion of partnerships made by individuals of age-group *a* with individuals of age-group *i*; and the proportion of partnerships made by individuals in age-group *a* and sexual-activity group *r* with individuals of sexual-activity group *j* based on a given Q-value ($f_{a,rj}$; table 1). The full calculation for these β parameters is shown in equation 4. The associated (heterosexual) contact matrix is found in table 2.

$$\beta_{ia,rj} = c_{i,a} * p_r * f_{a,rj}$$

(Equation 4)

Table 2: Contact matrix, where females of each age and sexual-activity group make partnerships with males of each group. The transpose of this matrix is used for male-female partnerships.

			Males					
			14-24y		24-34y		35y+	
			Low	High	Low	High	Low	High
Females	14-24y	Low	$\beta_{11,ll}$	$\beta_{11,lh}$	$\beta_{12,ll}$	$\beta_{12,lh}$	$\beta_{13,ll}$	$\beta_{13,lh}$
		High	$\beta_{11,hl}$	$\beta_{11,hh}$	$\beta_{12,hl}$	$\beta_{12,hh}$	$\beta_{13,hl}$	$\beta_{13,hh}$
	24-34y	Low	$\beta_{21,ll}$	$\beta_{21,lh}$	$\beta_{22,ll}$	$\beta_{22,lh}$	$\beta_{23,ll}$	$\beta_{23,lh}$
		High	$\beta_{21,hl}$	$\beta_{21,hh}$	$\beta_{22,hl}$	$\beta_{22,hh}$	$\beta_{23,hl}$	$\beta_{23,hh}$
	35y+	Low	$\beta_{31,ll}$	$\beta_{31,lh}$	$\beta_{32,ll}$	$\beta_{32,lh}$	$\beta_{33,ll}$	$\beta_{33,lh}$
		High	$\beta_{31,hl}$	$\beta_{31,hh}$	$\beta_{32,hl}$	$\beta_{32,hh}$	$\beta_{33,hl}$	$\beta_{33,hh}$

2.3 Calculating cancer incidence

I crudely calculated ICC incidence by multiplying HPV incidence using estimates from a cohort studying the 10-year risk of cervical dysplasia and cancer in women with HPV-16 and/or 18.[97] The cumulative proportions of women with HPV-16 or 18 (HPV-16/18) that developed CIN3 or ICC (CIN3/ICC) were 17.2% and 13.6% respectively, therefore the cumulative proportion of women with HPV-16/18 with this same outcome was calculated as $\frac{(0.172+0.136)}{2} = 15.4\%$. Assuming that nearly all women who develop CIN3/ICC do so within the observed 10 years after infection with HPV-16/18, the annual rate at which CIN3/ICC is developed was calculated as $-\frac{\log(1-0.99)}{10} = 0.46$, which corresponded to an average duration between infection and CIN3/ICC development of 2.17 years. CIN3/ICC incidence was therefore calculated by summing the total number of HPV infections over a year and applying the proportion

0.154 to that sum, and the time these cancers occurred was calculating by adding 2.17y to the time of infection.

I did not consider early cervical dysplasia, nor the age-specific rates of cancer progression, hence crude estimates were averaged across age-groups. It is critical to note that, because the 10-year cohort measured CIN3/ICC together, my model did as well.

2.4 Model fit and data

HPV prevalence estimates in Barbadian women aged 18-65 were derived using data provided by researchers at the University of the West Indies.[79] Their population-based study gathered independent samples from 426 healthy (i.e. ICC free) women aged 18-65y between 2010 to 2012 across three Barbadian clinics. Clinics were chosen due to centrality and size, and women were recruited and screened during routine pap tests. Participants were invited even if they had previously diagnosed untreated ICC or pap abnormalities, however, none had ICC. Referring to figure 1, these women were assumed to be in the *HPV detectable* stage.

Researchers detected HPV using Luminex-based HPV PCR genotyping methodology, and collected sexual behaviour and demographic information through self-administered questionnaires. The dataset contained detailed data, including participant's exact age, HPV variants detected, and each participant's self-reported number of sexual partners in the previous year. The dataset included 426 samples, but 14 participants included missing values, so the final dataset included 412 women.

I restricted the analysis to HPV-16 and 18 serotypes, and stratified prevalence by age-group and sexual-activity. Although they reported participant's exact age, I regrouped the dataset into 10-year age-bands

split at the midpoint of each decade-long age-group. HPV prevalence did not differ greatly after age 35y, so I recombined all individuals over age 35y into one group. Therefore the final age-groups included 56 (14%) women aged 15-24y, 133 (32%) aged 25-34y, and 223 (54%) aged 35y+. Sexual-activity was regrouped by number of partners in previous year into "low" (0-1 partners) and "high" (2-10 partners) activity, and used to calculate the proportion of women in the low and high-activity groups for each age-group. Because I only had access to data on females, I assumed that male demographic and characteristics mirrored those of females. Mean HPV prevalence and 95% binomial confidence intervals were calculated for each joint activity- and risk-group (table 3).

I limited the model fit exploration to two assumptions: one where individuals solely contacted those in their own age-group; and another where the majority of individuals contacted their own age-group, while 17.8% of 15-24y old individuals had intergenerational contact, based on a 2013 cross-sectional study in Barbadian girls (table 4).[84]

Table 3: HPV prevalence by sexual-activity group.

Sexual- activity	HPV prevalence	95% confidence interval
Low	2.00%	0.73-4.30%
High	8.11%	3.03-16.82%

Table 4: Proportion of contacts by age, based on Drakes 2013 data.[84]

	Contactee		
Contactor	**15-24y**	**25-34y**	**35y+**
15-24y	0.822	0.089	0.089
25-34y	0.089	0.911	0
35y+	0.089	0	0.911

The model was fit to pre-vaccination HPV prevalence estimates for Barbados by optimizing values for parameters μ_l and μ_h that adjust the FOI for susceptibles in the low- and high-activity groups, respectively. In each run, the model was initialized assuming nearly all individuals were HPV naive, with 50 initial infectious individuals in each gender, age-group, and activity-group to stimulate spread, and no vaccinated individuals (appendix table A1). Models were ran until equilibrium, determined by when the variance in the total number of susceptible individuals was <0.5 in the final 365 days of the simulation. Optimization was done through the Nelder-Mead algorithm in the *optimx* package in *R*.[98,99] I minimised the negative log-likelihood using a binomial likelihood to compare the modelled HPV infection prevalence in women at model equilibrium with observed values, stratified by age- and sexual-activity groups. The fitting procedure was repeated for different sets of parameter values, exploring different values of Q (ranging from 0.0 to 0.5) and different assumptions in partnering occurrences. The model that minimized the log-likelihood across these different parameter sets was selected as the final model.

2.5 Vaccine implementation

Barbados' vaccination programme includes only the quadrivalent vaccine. I implemented the current WHO reported vaccination coverage (30% female, 26% male) as the baseline strategy.[83] The vaccine was assumed to provide protection for, on average, 14 years.[53] Efficacy was set at 89% and assumed that

those “successfully” (i.e. effectively) vaccinated were fully protected, while the remaining were fully susceptible to infection. I was not concerned with vaccine dose schedules, so there was no ‘partial’ (i.e. partially vaccinated) protection. Vaccinated individuals reverted back to being susceptible at a rate $\delta = \frac{1}{365*14}$ representing 14 years of protection, on average.[53]

I used the steady state of the final fitted model at equilibrium as the starting point of the post-vaccination model, and assumed the model started at 1 January 2016 with WHO provided coverage estimates in males and females.[83] Increased coverage levels were explored at each additional 10th percentile in girls until 100% coverage was reached, with boy’s vaccination coverage set as 90% that of girls, as observed in the current coverage estimates. Vaccine strategies were compared through measuring HPV prevalence at the mid-point of the year, cumulative annual HPV incidence, and crude cumulative annual ICC incidence for each strategy in 2030 and 2100. All measures were presented per 100,000 women.

2.6 Modelling sensitivity analysis

I assumed 89% vaccine efficacy as baseline and performed sensitivity analysis for all strategies and results by assuming efficacy of 100%, repeating the analysis, and assessing the sensitivity of results to the assumed efficacy estimate.[48–53] As an ad hoc analysis, male vaccine coverage levels were set to 0% to determine whether male vaccination explained reductions in prevalence over time.

All analyses were done in *R* version 4.0.2.[100] Data were stored on an encrypted hard-drive. Ethical approval for the study was granted by the London School of Hygiene & Tropical Medicine Ethics Committee (ref 25418). Information on HPV’s natural history and data for model-parameters were searched on *PubMed* using relevant search-terms and through cross-referencing source bibliographies.

3. Results

3.1 Pre-vaccination transmission dynamics

Observed pre-vaccination prevalence of HPV-16/18 was highest in the youngest age-group at 11.32% (95% CI: 4.27-23.03%) and decreased with age, with HPV detected in 5.04% (95% CI: 1.87-10.65%) of 25-34y old women and 2.97% (95% CI: 1.10-6.35%) of those aged 35y+. By age-group, 66% of 15-24y, 75% of 25-34y, and 87% of 35y+ women had <2 partners in the previous year and were classified as low-activity, while 34%, 25% and 13% had ≥2 partners and were classified as high-activity.

All fitted models reached an equilibrium after a maximum of 60 years. Summary estimates from fitted models are shown in Table 5. The lowest negative log-likelihood was found for the model that used the Drakes data for mixing between age-groups and assumed proportional mixing (Q=0.0) for contacts between people in the low- and high-activity groups (figure 3).[84]

At equilibrium, this model led to an estimated prevalence of 5134 female HPV infections at any specific time-point, with most cases in high-activity 35y+ old followed by high-activity 25-34y old women. This was associated with a prevalence per 100,000 of 4292.65. Compared to the observed data, the modelled prevalence estimates for high-activity 15-24y (15.9%), low-activity 25-34y (5.7%), and low-activity 35y+ (1.8%) women were all within 2% of the observed point estimate. The model slightly underestimated high-activity 35y+ (5.7%) and low-activity 15-24y (5.4%) prevalence by >2%, and overestimated prevalence in high-activity 25-34y (16.4%) females by nearly 10%.

Figure 3: Model fit comparing modelled HPV prevalence in the final model to observational seroprevalence data in Barbadian women aged 15-79y. Panels represent high- and low-sexual activity groups.

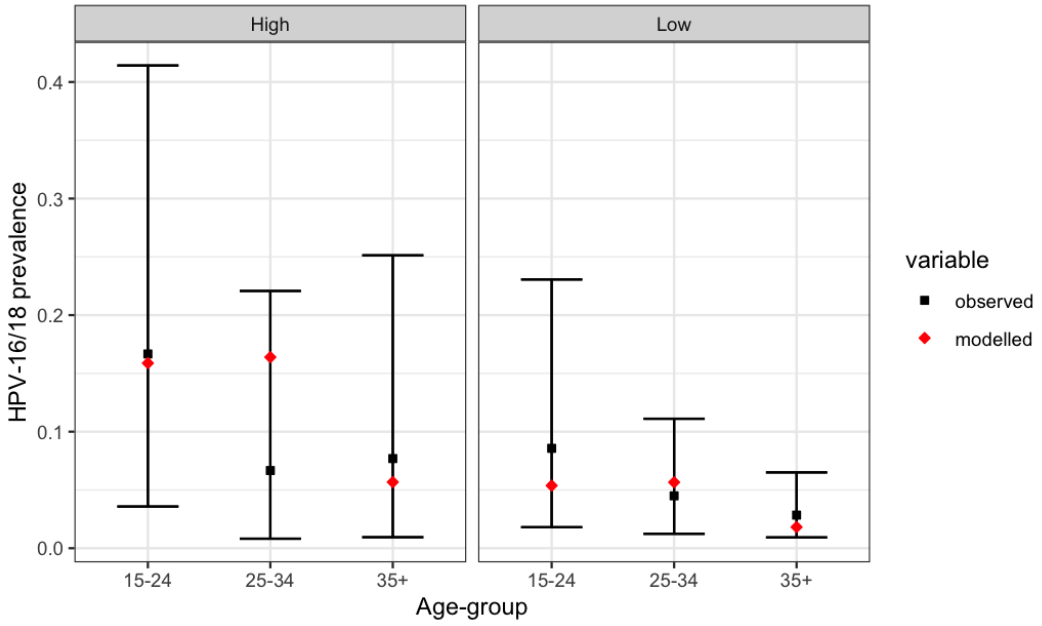


Table 5: Model-fit comparisons for different assumptions on intergenerational contact and Q-values.

	Simulation and justification					
Parameter	**No intergenerational contact**			**Some intergenerational contact[84]**		
Q-value	0.0	0.2	0.5	0.0	0.2	0.5
Years until equilibrium	50	60	60	60	50	60
-Log (likelihood)	16.98152	15.09119	15.0255	10.97375	11.66708	13.81676
μ_l	0.288798	0.000127	0.000857	0.000154	0.000141	0.46649
μ_h	0.874601	0.810575	0.653135	0.861074	0.760449	0.638528

l=low-activity, h=high-activity

3.2 Current vaccine coverage

Figure 4 presents stratified HPV prevalence over time as proportions of each age- and activity-group in women. The sharpest absolute decreases in infection are projected to occur in all high-activity women, as well as low-activity women aged 15-24y and 25-34y. From 2016, prevalence drops from 5.4% and 15.8% in low- and high-activity 15-24y women to 2.4% and 7.5% in 2030, and then to 1% and 3.3% in 2100 respectively. Prevalence in women aged 25-34y is projected to decrease from 5.7% in low-activity and 16.4% in high-activity from 2016, to 3.3% and 9.9% in 2030, and 1.4% and 4.3% in 2100. In 35y+ women, HPV prevalence is expected to drop from 1.8% and 5.7% in low- and high-activity women, to 1.0% and 3.3% in 2030, and again to 0.4% and 1.3% respectively by 2100. Most reductions begin tapering off between 2040 and 2060.

Figure 4: HPV prevalence in women over time after vaccine introduction in 2016. Prevalence is stratified by age- and activity-group and shown as a proportion in each group.

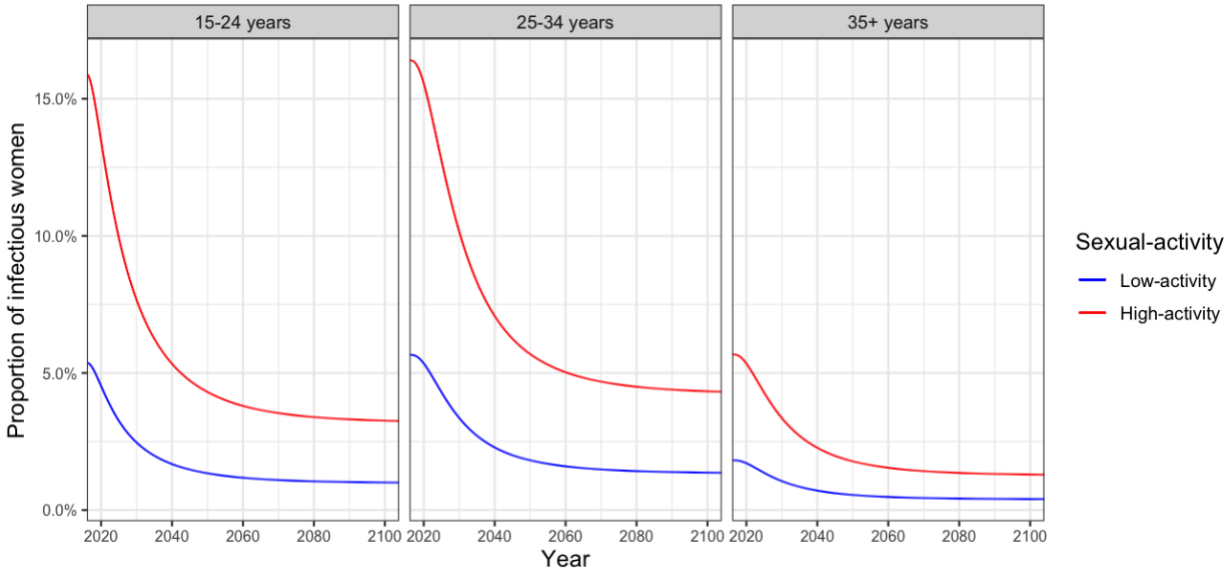


Table 6 shows the model output for the current strategy stratified by age-group. With 89% efficacy, the model projects HPV prevalence at 2030 mid-point of 4129.14 per 100,000 in 15-24y, 4960.18 per 100,000 in 25-34y, and 1320.64 per 100,000 in 35y+ old females. By 2100, HPV prevalence is projected to reduce by 57% to 1771.29 per 100,000 in 15-24y women, 57% to 2113.61 per 100,000 in 25-34y, and 61% to 517.90 per 100,000 in 35y+ women. Annual female HPV incidence in 2030 is projected to be 4976.96, 5573.12, and 1376.11 per 100,000 in each age-group respectively. Incidence in 2100 is projected to drop by 56% to 2214.50 per 100,000 for 14-25y , 56% to 2465.40 for 25-34y, and 59% to 559.38 in 35y+ women.

With the 89% effective model as baseline, and sensitivity analysis where efficacy was increased to 100%, the model projected prevalence per 100,000 in the year 2030 of 3969.94 for women aged 15-24y, 4612.96 for 25-34y, and 1222.52 for 35y+; reductions of 4%, 7%, and 7% compared to the baseline respectively. Prevalence predictions for 2100 are reduced by 38% to 1102.29 per 100,000, 35% to 1377.68 per 100,000, and 36% to 329.55 per 100,000 compared to baseline for each age-group respectively. Cumulative female HPV incidence at 100% compared to 89% efficacy is forecast to decrease by a further 11%, 7%, and 8% to 4425.42, 5162.92, and 1376.11 per 100,000 respectively in each age-group. In 2100, these will fall 38% to 1375.58 in 15-24y, 35% to 1609.11 in 25-34y, and 37% to 354.42 per 100,000 in 35y+ women.

Table 6: Prevalence and cumulative incidence of HPV by age-group in women with the current vaccination coverage (30% girls, 27% boys). All estimates are relative to strata size.

Age	Efficacy	Prevalence at year mid-point (per 100,000)		Cumulative female HPV incidence (per 100,000 women)	
		2030	2100	2030	2100
15-24y	89%	4129.14	1771.29	4976.96	2214.50
	100%	3969.94	1102.29	4425.42	1375.58
25-34y	89%	4960.18	2113.61	5573.12	2465.40
	100%	4612.96	1377.68	5162.92	1609.11
35y+	89%	1320.64	517.90	1376.11	559.38
	100%	1222.52	329.55	1263.84	354.42

For all ages (table 7), and under the current strategy and assuming 89% efficacy, the model projects 2328.14 per 100,000 prevalent female HPV cases at the mid-point of 2030. By 2100, this falls 59% to 963.08 per 100,000 women. Cumulative HPV incidence between 1 January and 31 December 2030 is projected to be 2594.57 per 100,000 women, which will drop 57% to 1115.81 per 100,000 women for the entire 2100 year. Cumulative CIN3/ICC incidence for the same time-points are expected to be 441.73 per 100,000 women, and decrease 61% to 172.25 per 100,000 respectively. Sensitivity analysis suggests that with 100% efficacy, these predictions will decrease 8%, 9%, and 7% in 2030, and a further 66%, 64%, and 68% in 2100, for prevalence, cumulative HPV incidence, and cumulative CIN3/ICC incidence respectively.

Compared to the pre-vaccination estimates, the model projects that the current strategy will have already prevented 18-20% (3968.71-4068.86) cumulative incident HPV cases per 100,000 women in

2021. In 2030, the current strategy is expected to prevent approximately 48-52% cumulative incident HPV cases per 100,000 women, and in 2100, 78-86% of incidence cases to be prevented. When allowed to run past the 100 year limit, this vaccine strategy never reached the WHO goals of cancer incidence <4 per 100,000.

3.3 Other vaccine strategies

Table 7 shows summary estimates for each vaccine strategy considered for 2030 and 2100, while figures 5 and 6 show the modelled prevalence over the whole model period. At equilibrium (i.e. no vaccinations in girls or boys aged <15y), the model led to 5134 HPV infections at any time-point, with a cumulative HPV incidence of 4978.21 per 100,000 women, and cumulative CIN3/ICC incidence of 766.64 per 100,000 women.

Compared to the baseline strategy of 30% girls and 26% boys at 89% efficacy (where HPV prevalence, HPV incidence, and CIN3/ICC were 2328.14, 2594.57, and 441.73 per 100,000 women respectively), increasing vaccination coverage to 40% girls and 36% boys at 89% efficacy is projected to reduce HPV prevalence at the mid-point of 2030 by 21% to 1845.53 per 100,000 women, cumulative HPV incidence by 22% to 2016.27 per 100,000 women, and cumulative CIN3/ICC incidence reduces 18% to 360.17 per 100,00. By 2100, female HPV prevalence will decrease another 71% to 194.31 per 100,000, with cumulative HPV incidence reduced 69% to 228.28, and cumulative CIN3/ICC incidence reduced 74% to 35.43 per 100,000 women. Sensitivity analysis of increased efficacy found projected reductions of 26%, 31%, and 26% for HPV prevalence, cumulative HPV incidence, and cumulative CIN3/ICC incidence respectively in 2030 compared to the baseline. These measures were projected to decline a further 72%, 67%, and 72% for each measure respectively in 2100.

Table 7: Model output of sensitivity analysis by entire cohort.

Vaccination strategy	Efficacy	Prevalence at year mid-point (per 100,000)		Female HPV incidence (per 100,000 women)		Cervical cancer incidence (per 100,000 women)	
		2030	2100	2030	2100	2030	2100
No vaccination (equilibrium)	-	4292.65	-	4978.21	-	766.64	-
30% girls, 27% boys (Current strategy)	89%	2328.14	963.08	2594.57	1115.81	441.73	172.25
	100%	2138.91	614.06	2367.07	710.02	409.92	110.16
40% girls, 36% boys	89%	1845.53	194.31	2016.27	222.28	360.17	35.43
	100%	1638.93	53.57	1771.07	60.25	324.71	10.02
50% girls, 45% boys	89%	1448.51	11.07	1546.81	12.18	291.63	2.14
	100%	1242.81	1.34	1306.93	1.43	255.35	0.27
60% girls, 54% boys	89%	1129.55	0.35	1176.14	0.36	235.07	0.07
	100%	937.35	0.02	956.78	0.02	200.05	0.01
70% girls, 63% boys	89%	878.25	0.01	890.11	0.01	189.10	<0.01
	100%	750.59	<0.01	698.94	<0.01	156.68	<0.01
80% girls, 72% boys	89%	683.14	<0.01	673.17	<0.01	152.17	<0.01
	100%	534.61	<0.01	512.10	<0.01	123.05	<0.01
90% girls, 81% boys	89%	533.14	<0.01	510.52	<0.01	122.75	<0.01
	100%	407.34	<0.01	377.82	<0.01	97.15	<0.01
100% girls, 90% boys	89%	418.41	<0.01	389.34	<0.01	99.44	<0.01
	100%	313.32	<0.01	281.55	<0.01	77.26	<0.01

Further increases in coverage follow these same patterns (figure 5 and 6). Notably, the 50% girls and 45% boys vaccination strategy is the first to reach the WHO goal of cancer incidence <4 per 100,000 at a time-point of interest. In particular, cumulative ICC incidence in 2100 is reduced to 2.14 and 0.27 per 100,000 women when efficacy is 89% and 100% respectively. In fact, this strategy projects that cumulative CIN3/ICC incidence first drops <4 per 100,000 in the year 2090. Any additional increases in coverage only reduce the necessary time to reach the WHO goal. Also of note is that starting in the 70% girls and 63% boys strategy, all measures will eventually reach <0.01 per 100,000 before the year 2100. In 2030, and depending on vaccine efficacy, coverage of 70-100% girls and 63-90% boys will lead to female HPV prevalence of anywhere from 313.32-878.25 per 100,000, cumulative HPV incidence of 281.55-890.11 per 100,000, and cumulative CIN3/ICC incidence of 77.26-189.10 per 100,000 women. Removing vaccinated males from each strategy led to an minimum-maximum difference of 33-170% HPV prevalence, 36-202% cumulative HPV incidence, and 29-137% cumulative CIN3/ICC incidence in women in 2030 compared to each corresponding scenario that included vaccination of males, which were projected to grow ≥148% in HPV prevalence, ≥148% HPV incidence, and ≥44% CIN3/ICC incidence by 2100.

Figure 5: Proportions of infectious women as a result of each vaccinate strategy with 89% vaccine efficacy.

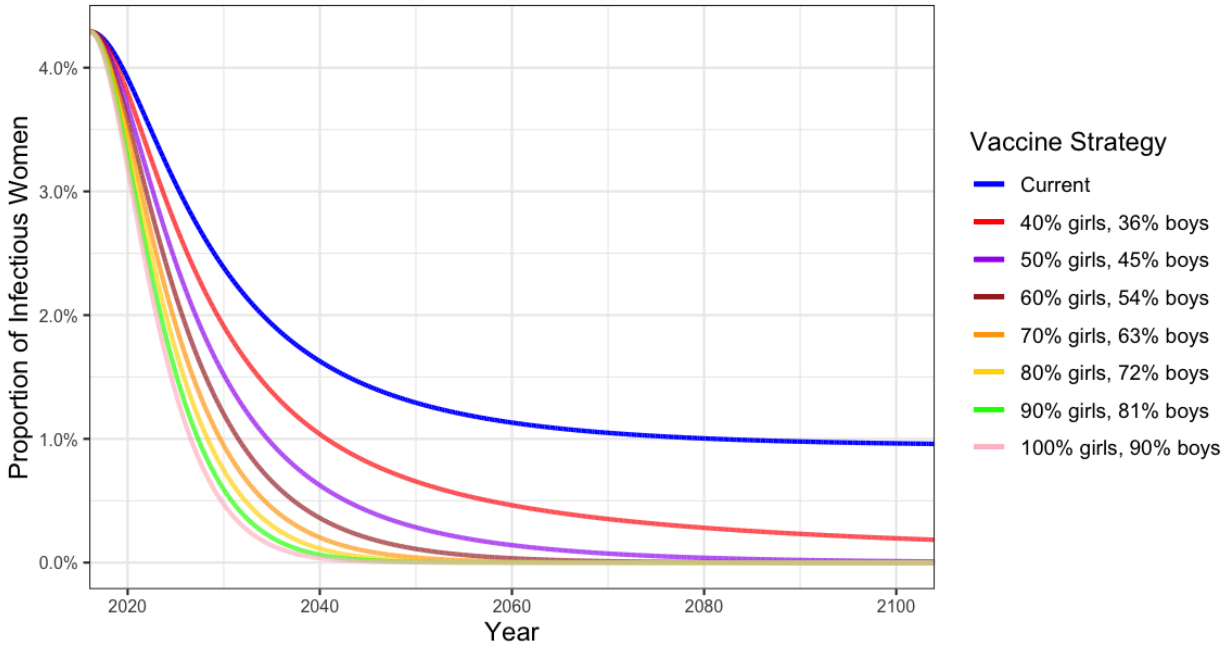
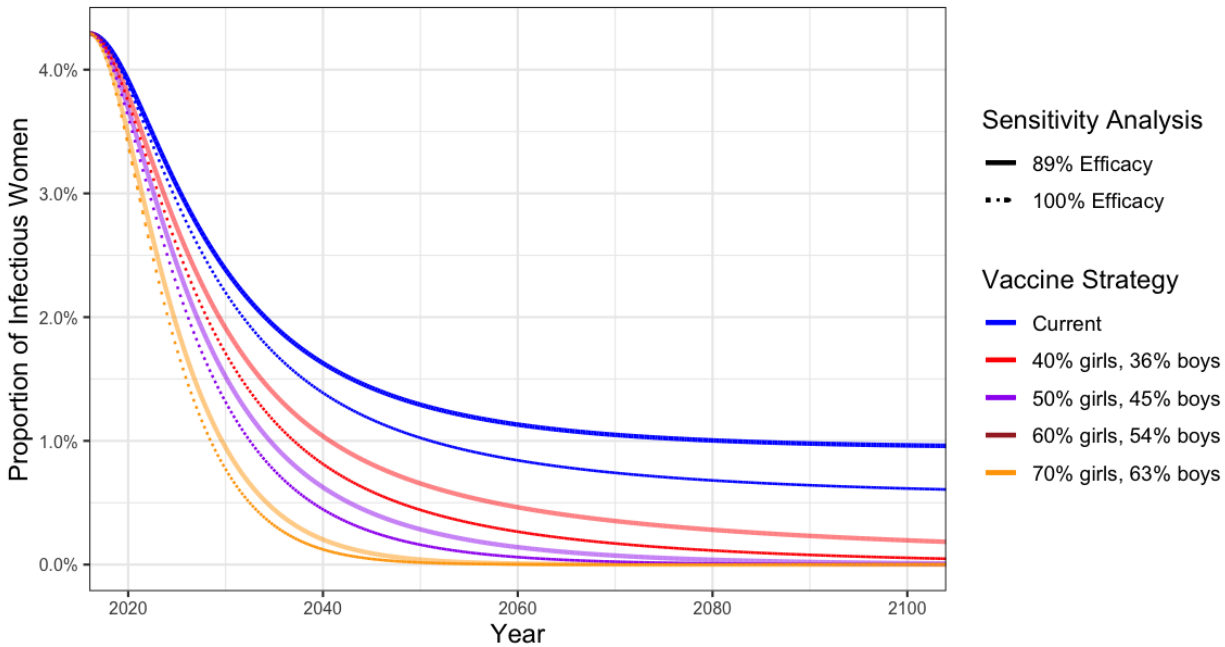


Figure 6: Proportions of infectious women in select vaccine strategies with sensitivity analysis of vaccine efficacy.



Figures 7 shows the proportions of women vaccinated over time at 89% efficacy. In total, when 30% of girls and 26% of boys <15y old are vaccinated each year and enter the model, we expect approximately 3.7% of all women to be vaccinated in 2030. By 2100, this will increase to 5.4% of all women. Increasing coverage estimates only serve to increase the total population vaccinated, with a maximum of 12.4% of women effectively vaccinated in 2030 (i.e. under the 100% girls, 90% boys strategy), and 17.9% of women effectively vaccinated in 2100.

Figure 7: Proportions of effectively vaccinated women (all age-groups combined) with 89% efficacy.

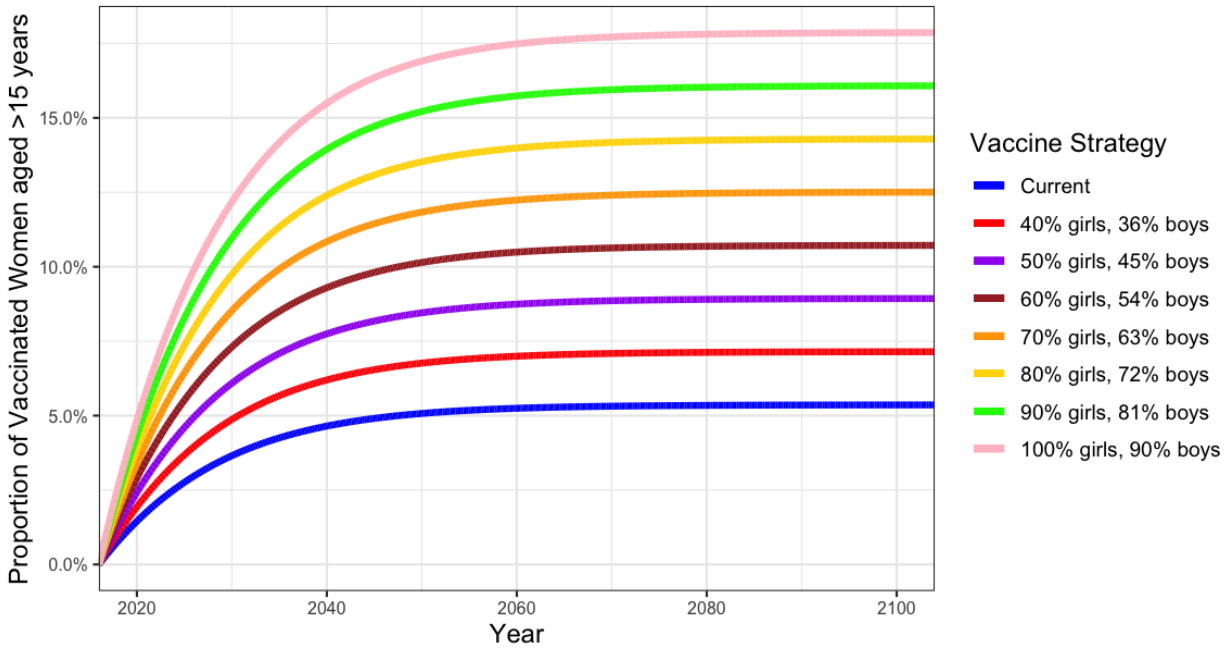
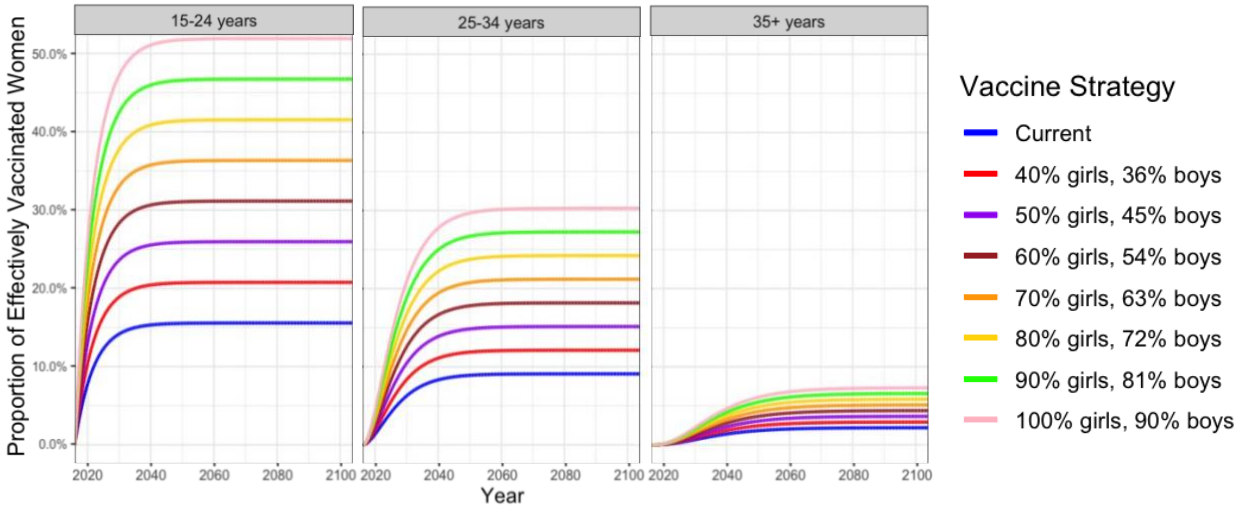


Figure 8 displays vaccine proportions by age-group. With the current coverage, and in 15-24y women, the model projects that 14.3% of women will be effectively vaccinated in 2030. In 25-34y olds, we expect only 6.5% effectively vaccinated women in 2030. And in 35y+ women, we should see only 0.7% of women effectively vaccinated. By 2100, we expect these proportions to increase, with 15.6%, 9.1%, and 2.2% of each age-group effectively vaccinated respectively. While each extended strategy increases these, we expect a limit of 47.6% of women aged 15-24y, 21.5% aged 25-34y, and 2.4% aged 35y+ in

2030. By 2100, these limits will increase to 51.9%, 30%, and 7.3% of women in each age-group respectively.

Figure 8: Proportions of effectively vaccinated women (by age-group) with 89% efficacy.



4. Discussion

4.1 Pre-vaccination model

HPV-16/18 prevalence in the pre-vaccination observations were highest in the youngest age-group. This is unsurprising and strongly supports research in other populations suggesting peak infection prevalence under age 25y.[12] Similarly, sexual partnership showing an inverse relationship with age supports findings that some younger individuals have a preference toward multiple sexual partners.[101] However, I must again point out that serological data in this population finds high prevalence of other HPV variants, notably HPV-45, and that the vaccine currently available in Barbados may only provide slight protection against this variant.[72]

Model fit prior to modelling transmission was particularly important due to very limited data on sexual-partnership rates in this population. The fitted model estimates had some overestimation in the high-activity 25-34y group. High-activity 35y+ and low-activity 15-24y olds were also slightly underestimated in the model, although the observed data had considerable confidence intervals. However, the final model provided a reasonable fit to the observed data. Ideally, post-vaccination serological surveys would occur in order to validate and improve the model fit.

4.2 Current coverage model

Under the current coverage, the model found that the highest proportion of female HPV infections occurred in the 24-35y age-group, although prevalence was similar to 15-24y olds, even when stratified by sexual-activity. Meanwhile the oldest age-group experienced the lowest risk of infection. Over time, the sharpest decreases in prevalence were seen in 15-24y and 25-34y olds (figure 4). However, because asymptomatic infection clearance is relatively rapid, this says nothing about whether older individuals had been infected in the past. By activity-group, we see that prevalence in the oldest high-activity women was not unlike low-activity women in the other two age-groups. Regardless, prevalence in the younger two groups was largely driven by high-activity women.

Overall, the current coverage, with projections of prevalence ranging from 614.06-2328.14 per 100,000 women, cumulative HPV incidence of 710.02-2594.57 per 100,000 women, and CIN3/ICC incidence from 110.16-441.73 per 100,000 women, suggests that coverage is not high enough in the current population to eliminate HPV, let alone ICC.

4.3 Increased coverage models

This model suggests that if effective HPV vaccination coverage remains at or below 40% of girls and 36% of boys <15y old, the WHO goals will not be reached by the end of the century. The model also suggests that upon reaching 50% coverage in girls and 45% in boys, it would be possible to not only reach this goal, but to achieve it at least one decade in advance.

One important caveat, is that my crude calculations combine CIN3 and ICC for the measure of cumulative incidence at each time point. Given this acknowledgement, I must point out that the 40% girls and 36% boys strategy reaches cumulative incidence of CIN3/ICC between 10.02-35.43 per 100,000. Although many CIN3 cases are expected to reach ICC if undiagnosed or untreated, these estimates may be skewed away from the null (i.e. less ICC cases if CIN3 are unmeasured).

4.4 The model in context

In general, my model projected sharp decreases in HPV-16/18 infections in the first two decades following the introduction of the quadrivalent vaccine. By 2030, all strategies predicted <2.5% of Barbadian women would be infected with these two variants. One explanation for this is that Barbados is one of few countries vaccinating boys due to the herd effect of vaccinating girls.[55,62,63] Removing male vaccinations from the model further supports this explanation, as this increases each measure from anywhere around 30-200%, depending on the strategy. Researchers and policy-makers need to consider this further, as it may be a viable solution to eliminating these diseases. However, this does not say anything about transmission between non-heterosexual men, which would require more specific data and in-depth exploration.

In many populations, infection peaks before age 25y and after age 45y.[12] In my model, infection peaked in all ages <35y, with similar prevalence in those aged 15-24y and 25-35y. I was unable to estimate prevalence in more narrow age-bands due to limitations of available data. Compared to the global prevalence of 9.9%, this model is considerably different, predicting that 3.6% of Barbadian women have HPV-16/18 in 2021 in correspondence with the observed estimates.[11] Estimates are likely confounded by HPV-type however, as pre-vaccination prevalence of HPV-16/18 was 9.5%, while HPV of any type was 33%.[79] Studies of similar pre-vaccination Caribbean populations in Trinidad and Jamaica found overall HPV prevalence to be 40.6% and 54% respectively.[102,103] It is currently not known why HPV prevalence in Caribbean populations is high, and more studies are needed to confirm that these estimates are consistent. It is also difficult to compare Barbados to global estimates because it is unclear how skewed estimates are by countries with little-to-no vaccine coverage.

Current herd immunity thresholds ranging from 50-80% suggest an R_0 of, on average, 2-5.[63,88,89] In my model, 40% coverage was not enough to eliminate HPV, suggesting that R_0 is at least 1.5. R_0 estimates could be calculated in this model using the Next Generation Matrix approach, but that is beyond the scope of this project, and estimates would be unreliable because the model does not include homogenous mixing, nor does it include all high-risk variants.

Although I don't model the symptomatic stage of HPV transmission directly, there is still much to be gained by estimating HPV prevalence and incidence over time. Even if my results are slightly biased, they otherwise show that HPV vaccination in Barbados is already relatively close to the coverage needed to eliminate ICC.

While vaccination is key to prevention, cervical screenings also plays a vital role in the reduction of ICC burden. Importantly, only 23% of countries providing services have ≥50% coverage.[3] In Barbados, screening in the form of cervical cytology is regularly available in both public and private settings. However, coverage estimates are not available.[104]

4.5 Limitations

Modelling the transmission of HPV is highly complex, and there are many limitations to this analysis. Compared to more prominent HPV models, I chose to simplify the parameters and dynamics in order to achieve my aims. I disregarded the complexity around progression of asymptomatic infection to symptomatic disease, opting to streamline ICC development by using a relatively simple rate. Cancer is understandably influenced by countless risk factors that are difficult to measure and nearly impossible to incorporate into a transmission model. Similarly, the proportion used to determine ICC incidence was based on estimates that combines CIN3 and ICC diagnosis into one cumulative risk.[97] Although the risk of CIN3 advancing to ICC is known to be high, and surveillance programmes aim to catch pre-cancerous and cancerous growth concurrently, I undoubtedly overestimated the number of ICC cases due to this merged risk. Additionally, because I assumed a fixed duration between infection and ICC occurrence, these estimates will be off; in reality, these durations differ between individuals. Similarly, an issue with SIS models is that they can "double-count" infections when a single individual is reinfected, therefore overestimating HPV incidence. However, HPV prevalence is relatively low, so this is not likely to substantially bias the results of this model. More complex models, such as individual-based models, could be used to overcome this problem. Fitting the model using maximum likelihood methods may also have issues identifying the ideal parameter, and don't provide uncertainty around estimated values. There are other complex algorithms, including Markov-Chain-Monte-Carlo methods, that may overcome this limitation. However, they were not used here because they are beyond the scope of this thesis.

My model contrasts with other transmission models. First, while I incorporated key elements of HPV transmission from other studies, other models focus on significantly larger populations, or generalize parameters to many countries at once. Second, I did not include screening, catch-up campaigns (which are non-existent in Barbados), partial immunity, coinfection, or incorporate disease progression, as I preferred a parsimonious structure.[61,93,94,105] However, the lack of disease progression may be considered a weakness in my model, as policy-makers may be interested in ICC burden in particular. Furthermore, my model not only doesn't model cancer directly, it combines measures of CIN3 and ICC. Third, my model runs on the assumption of a constant vaccine coverage with no variation each year. Coverage will naturally differ each year, which will lead to slight variance in HPV and future ICC incidence. Finally, my sensitivity analysis was limited to vaccine efficacy and coverage in order to simplify the results, while other models also include variation in vaccine protection and sexual behaviour.[94,105]

I also ignored certain parameters that might have provided accuracy to the model. The model may have been more accurate if age-groups were more detailed, and sexual-activity groups beyond 2 partners were divided. I did not account for non-natural deaths, nor did I consider death by ICC. In reality, this likely differs by age, with greater survival among younger individuals. A simpler death parameter allowed for a more parsimonious model with a stable population throughout the entire run. However, it is unlikely that Barbados' population size would remain stable over the next 100 years, and therefore might underestimate the burden of HPV due to the effect of increased population density. Another parameter that was simplified was the rate at which individuals clear HPV and become susceptible again. The relationship between an individual's age and their recovery time was also ignored. The rate at which vaccinated individuals lose their protection may have a similar relationship with age. However, vaccinating before sexual debut, and the constant rate at which protection is lost, may prevent this from

affecting my results much. Regarding vaccination, my strategy assumes an "all-or-nothing" modality, in which the vaccine efficacy determines those that have full immunity, while everyone else is assumed to be completely susceptible. In reality, the vaccine may have waning protection, whereby vaccinated individuals have a small, but growing, risk through time until they fully lose protection. However, recent studies suggest that the quadrivalent does not suffer from this, although the nonavalent vaccine may.[53,106]

My model did not account for any other prevention strategies. These include HPV prevention strategies, such as the use of condoms, as well as screening and treatment, which models suggest can decrease cancer incidence.[93,94] I also note that slight methodological limitations relate to the vaccination strategies themselves. First, I didn't account for the two years of vaccinations that girls received prior to the introduction of male vaccinations in 2016. Nor do I account for variance in age at which someone is considered fully vaccinated. However, these are unlikely to affect longer-term outcomes. Additionally, I did not account for how being vaccinated may change an individual's behaviour following sexual debut, although studies have found evidence that there is no increase in sexual behaviour in this regard.[107,108] The initial years of vaccination lead to the greatest reductions, whereas I was only interested in the medium to long-term estimates.

This model does not account for several transmission pathways. The greatest of these is that I only modelled heterosexual transmission. By ignoring non-heterosexual partnerships, the impact of HPV vaccination could be overestimated by my model, therefore underestimating incidence of HPV in the population as a whole, as non-heterosexual males and transgender populations are equally susceptible to infection. However, research into these populations require alternative in-depth analysis as these groups are small and likely would not substantially affect population-level transmission of HPV. Similarly,

HPV research and knowledge in males is sparce, and yet there is a non-zero risk of HPV infection and other HPV-related cancers in men; although these are a significantly smaller public health problem compared to ICC.[7] Furthermore, population data mong males was not present at this time, other than vaccine coverage. As such, the model mirrors parameters across the gender line. Therefore, outcomes are largely based on the assumption that males behave in the same way that females do. In truth, this is unlikely, and so my results could be either over- or underestimated, but to what length is challenging to say. Lastly, certain co-factors to infection need to be noted. There is some evidence of first-infection increasing the risk of future infections.[22,23] I may consequently underestimate the rate of HPV, although more complex model could model this. There is also growing evidence regarding the relationship between immunosuppression, coinfection with other STIs (particularly HIV), and HPV-related disease.[109–113] However, these relationships are complex, therefore I opted to omit immune deficiencies and coinfections from the model, but recognize that this may likewise lead to an underestimate in my outcomes, although this depends on prevalence of other STIs in Barbados. Lastly, I group HPV-16 and 18 together, average the rate at which they develop into cancer with equal weight, and ignore any potential interaction between variants. In Barbados, HPV-18 prevalence is significantly lower than 16, so individuals in the model should be much less likely to be infected with that type.

The final limitation of this study is that I was restricted by the data I had access to, and it is worth considering the limitations of these sources. The first of these, the cross-sectional Ward (2017) study, despite detailed serological data, is most likely to affect my results and warrants a thorough review. Their sample population included only healthy women (free of ICC) attending routine pap tests. Disease was not an exclusion criteria for a study, so it is possible that selection bias was present if symptomatic women were unable to participate in anyway. Likewise, the included women may represent a more health-aware group, and be less representative of the population as a whole. If so, this could confound

the observed prevalence estimates toward the null. Similarly, they collected information on other STIs, but these were limited to Chlamydia, Genital Warts, Herpes, and an undefined 'other'. HIV was notably absent from this list, despite known associations with HPV. Another limitation was their sample size of 413, potentially leading to unstable estimates within each stratum of HPV variant. Pelvic exams were completed on all participants, therefore (depending on test accuracy) there is not likely to be differential misclassification of outcome. One key point is that they explicitly excluded people with previous infections, therefore parameters reflect only those with first infection, and say nothing about reinfection rates. Those with previous infections may be at higher risk for infection and have higher prevalence than others. Another point is that their sample excludes girls aged <18y, therefore I am missing prevalence data in the first (and arguably most important) years of sexual-activity in this population. Depending on the average age of sexual-debut and average number of partners in those aged <18y, my estimates could be over- or underestimated. The use of self-reported questionnaires may have led to information bias. If present, this bias would have affected estimates of the number of partners in previous years, affecting transmission dynamics. Finally, missing data in their dataset was minuscule, and therefore unlikely to affect the analysis.

The second study (Drakes, 2013) was key to estimating intergenerational partnership data, but likewise has limitations. First, this study only samples 15-19y old girls, therefore this limits confidence to only females, and only in the first half of the youngest age-group. So my assumption that males and older age-groups mirror these intergenerational partnership rates may be a major limitation affecting transmission dynamics. Their study did not likely experience selection bias, as their two-stage sample frame used probability proportional to size and selected households randomly. However, their information on intergenerational mixing is not very detailed, and I would have preferred smaller intergenerational age-group estimates in this regard. Finally, although they did ensure confidentiality

and comfort, as well as a validated survey, there may still be information bias due to the sensitive nature of the survey, as well as recall bias in key information such as partner ages. If these are present, they would have an effect on estimates used to parameterize the model.

The third study (Khan, 2005) was used to estimate ICC incidence from the HPV predictions I model, and may be affected by several major limitations. The first is that despite a large sample size, the number of women experiencing their outcome of interest (CIN3/ICC) was small within each stratum of HPV variant (HPV-16: n=36; HPV-18: n=7). Although this reduces confidence, this would have only been due to random error due to the cohort design, rather than selection bias. Another limitation is that they recognize that some women were treated at the first sign of CIN2, and even CIN1 in some cases. When this occurred, these women were censored and follow-up ceased. This is important to note because if those women would have instead gone on to develop CIN3/ICC, then their incidence rates, and by extension my calculation for the development of CIN3/ICC, could be underestimated. Along these lines, the study only followed the cohort for 10 years, so it is possible that cancer development occurred after the end of follow-up, which may have biased their estimates downward. Lastly, they may have benefited from splitting CIN3 and ICC, as CIN3 occurs before ICC, therefore skewing their estimates toward the null. Likewise, these rates don't support other estimates of a 5-10 year incubation period.[20,21]

Most importantly, despite detailed HPV prevalence information, I limited myself to only HPV-16 and 18. This is noteworthy because other variants (particularly HPV-45) may be causing considerable ignored burden on the Barbadian population. And because studies have found HPV-45 highly prevalent in younger populations, there may be increased transmission of this variant if the model included it.[58] At the same time, studies preferentially focus on HPV-16/18, so validation and comparisons on HPV-45 are difficult to find. However, a key takeaway of this study is that little is known about the burden of HPV-45

on this population outside estimated prevalence. Barbados' vaccine programme does not cover HPV-45, and although there may be slight protection, findings and suggestions may ultimately be undermined by the threat HPV-45 poses on the population unless access to the nonavalent vaccine is promoted.

4.6 Future work and recommendations

Because of the sparsity of data in this population, there is much work to be done. In particular, post-vaccination seroprevalence surveys could determine how the current strategy has affected HPV prevalence in the years following introduction. This would also serve to validate my model, and allow for better corrections. Prevalence estimates in males would be particularly important to determine if contact patterns hold. Research on this topic would also greatly benefit from more knowledge around sexual-behaviour and partnership rates in different populations in Barbados, particularly males and non-heterosexual populations. This data would be key to improving the accuracy of transmission modelling, and would lead to more precise estimates. Lastly, and potentially most critical to the use of vaccination as a control measure, is the continued vaccine uptake and monitoring in the population. The WHO identified vaccine hesitancy as one of the top threats to global health.[114] It could be productive to explore current attitudes on vaccine programs in Barbados, especially because results show that the population is not far from reaching the coverage necessary to eliminate transmission by the end of the century. Official WHO estimates indicate that approximately 7% of girls and 6.72% of boys had been vaccinated in 2020.[83] It is, however, difficult to know if this is due to incomplete data, renewed vaccine hesitancy, or a result of decreased vaccinations due to the COVID-19 pandemic.

Presence of other HPV variants needs to be investigated further. This is acutely important due to the high prevalence of HPV-45 in Barbadian women.[79] If my model had considered these variants, I may have seen a different explanation of pre-vaccination contact patterns. Although this would have been

for naught, as the quadrivalent vaccine has only little effect, if any, on these variants.[63,90] At the same time, it must be recognized that the nonavalent vaccine is costly, therefore more consideration is needed on preventing differential access by SES.

5. Conclusions

This thesis sought to explain the transmission dynamics of HPV in Barbados, and to project a timeline for HPV and ICC elimination. While it did find that 50% of girls and 45% of boys could eliminate ICC related to HPV-16/18 in time for the WHO goal of <4 per 100,000, these predictions are unstable at best, and require more complex models and better data in order to say anything definitive. It must be reiterated that HPV-45 is highly prevalent in Barbados, and my model has little to no effect on transmission of this type, therefore the nonavalent vaccine should be introduced in a timely, albeit cost-effective, manner.

6. References

1. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER. 2021;0:1–41.
2. World Health Organization. Human Papillomavirus (HPV) and Cervical Cancer [Internet]. World Health Organization. 2020 [cited 2021 Feb 16]. Available from: https://www.who.int/news-%0Aroom/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer
3. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. World Health Organization. Geneva; 2020.
4. Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors. Eur J Cancer [Internet]. 2013;49(15):3262–73. Available from: http://dx.doi.org/10.1016/j.ejca.2013.04.024
5. Walboomers J, Jacobs M, Manos M, Bosch X, Kummer A, Shah K, et al. Human Papillomavirus is a Necessary Cause of Invasive Cervical Cancer Worldwide. J Pathol. 1999;189:12–9.
6. IARC Working Group. IARC monograph on the evaluation of carcinogenic risks to humans: human papillomaviruses. 1995 [Internet]. Vol. 64, IARC Scientific Publications. 1995. 428 p. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:IARC+Monographs+on+the+Evaluation+of+Carcinogenic+Risk+to+Humans.+Human+Papillomaviruses#5
7. Devita Jr V, Lawrence T, Rosenberg S. Cancer Principles & Practice of Oncology. 11th ed. Philadelphia: Wolters Kluwer; 2019.
8. Chelimo C, Wouldes TA, Cameron LD, Elwood JM. Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer. J Infect [Internet]. 2013;66(3):207–17. Available from: http://dx.doi.org/10.1016/j.jinf.2012.10.024

9. Van Doorslaer K, Burk RD. Evolution of human papillomavirus carcinogenicity [Internet]. 1st ed. Vol. 77, Advances in Virus Research. Elsevier Inc.; 2010. 41–62 p. Available from: http://dx.doi.org/10.1016/B978-0-12-385034-8.00002-8

10. Castellsagué X. Natural history and epidemiology of HPV infection and cervical cancer. Gynecol Oncol. 2008;110(3 SUPPL.2):4–7.

11. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. Human Papillomavirus and Related Diseases in the World- Summary report. ICO/IARC Inf Cent HPV Cancer (HPV Inf Centre) [Internet]. 2019;(June):307. Available from: https://hpvcentre.net/statistics/reports/XWX.pdf

12. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, De Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010;202(12):1789–99.

13. De Villiers EM, Fauquet C, Broker TR, Bernard HU, Zur Hausen H. Classification of papillomaviruses. Virology. 2004;324(1):17–27.

14. Burk RD, Harari A, Chen Z. Human papillomavirus genome variants. Virology. 2013;445(1–2):232–43.

15. Harden M, Munger K. Human papillomavirus molecular biology. Mutat Res. 2017;772:3–12.

16. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine. 2006;24(SUPPL. 3):42–51.

17. Longworth MS, Laimins LA. Pathogenesis of Human Papillomaviruses in Differentiating Epithelia. Microbiol Mol Biol Rev. 2004;68(2):362–72.

18. Stanley M. Pathology and epidemiology of HPV infection in females. Gynecol Oncol [Internet]. 2010;117(2 SUPPL.):S5. Available from: http://dx.doi.org/10.1016/j.ygyno.2010.01.024

19. Mirabello L, Clarke MA, Nelson CW, Dean M, Wentzensen N, Yeager M, et al. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. Viruses.

2018;10(2).

20. Woodman CBJ, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: A longitudinal cohort study. Lancet. 2001;357(9271):1831–6.

21. Schiffman M, Castle P, Jeronimo J. Human Papillomavirus and Cervical Cancer. Appl Phys B Lasers Opt. 2014;117(1):363–8.

22. Ranjeva SL, Baskerville EB, Dukic V, Villa LL, Lazcano-Ponce E, Giuliano AR, et al. Recurring infection with ecologically distinct HPV types can explain high prevalence and diversity. Proc Natl Acad Sci U S A. 2017;114(51):1–6.

23. Trottier H, Ferreira S, Thomann P, Costa M, Sobrinho J, Prado J, et al. HPV infection and re-infection in adult women: the role of sexual and natural immunity. Cancer Res. 2010;70(21):8569–77.

24. PDQ Adult Treatment Editorial Board. PDQ Cervical Cancer Treatment [Internet]. National Cancer Institute. 2020. Available from: https://www.cancer.gov/types/cervical/patient/cervical-treatment-pdq

25. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynecol Obstet. 2019;145(1):129–35.

26. Solomon D, Davey D, Kurman R, Moriarty A, Connor DO, Raab S, et al. The 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. J Am Med Assoc. 2002;287(16):2114–9.

27. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes after radical hysterectomy in patients with early-stage adenocarcinoma of uterine cervix. Br J Cancer [Internet]. 2010;102(12):1692–8. Available from: http://dx.doi.org/10.1038/sj.bjc.6605705

28. Bethwaite P, Yeong ML, Holloway L, Robson B, Duncan G, Lamb D. The prognosis of adenosquamous carcinomas of the uterine cervix. Br J Obstet Gynaecol. 1992;99(9):745–50.

29. Steren A, Nguyen H, Averette H, Estape R, Angioli R, Donato D, et al. Radical Hysterectomy for Stage IB Adenocarcinoma of the Cervix: The University of Miami Experience. Gynecol Oncol. 1993;48:355–9.

30. Lee YY, Choi CH, Kim TJ, Lee JW, Kim BG, Lee JH, et al. A comparison of pure adenocarcinoma and squamous cell carcinoma of the cervix after radical hysterectomy in stage IB-IIA. Gynecol Oncol [Internet]. 2011;120(3):439–43. Available from: http://dx.doi.org/10.1016/j.ygyno.2010.11.022

31. Galic V, Herzog TJ, Lewin SN, Neugut AI, Burke WM, Lu YS, et al. Prognostic significance of adenocarcinoma histology in women with cervical cancer. Gynecol Oncol [Internet]. 2012;125(2):287–91. Available from: http://dx.doi.org/10.1016/j.ygyno.2012.01.012

32. Eifel PJ, Burke TW, Morris M, Smith TL. Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. Vol. 59, Gynecologic Oncology. 1995. p. 38–44.

33. Lei J, Ploner A, Lagheden C, Eklund C, Nordqvist Kleppe S, Andrae B, et al. High-risk human papillomavirus status and prognosis in invasive cervical cancer: A nationwide cohort study. PLoS Med. 2018;15(10):1–15.

34. Balasubramaniam G, Gaidhani RH, Khan A, Saoba S, Mahantshetty U, Maheshwari A. Survival rate of cervical cancer from a study conducted in India. Indian J Med Sci. 2020;73(2):203–11.

35. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019. Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la santé / Statistique Canada, Centre canadien d'information sur la santé. 2019.

36. National Health Service. Cervical Cancer [Internet]. NHS. 2018 [cited 2021 Jul 23]. Available from: https://www.nhs.uk/conditions/cervical-cancer/

37. Manhart LE, Koutsky LA. Do Condoms Prevent Genital HPV Infection, External Genital Warts, or Cervical Neoplasia. Sex Transm Dis. 2002;29(11):725–35.

38. Devine OJ, Aral SO. The impact of inaccurate reporting of condom use and imperfect diagnosis of sexually transmitted disease infection in studies of condom effectiveness: A simulation-based assessment. Sex Transm Dis. 2004;31(10):588–95.

39. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ. 2004;82(6):454–61.

40. Burchell AN, Winer RL, de Sanjosé S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. Vaccine. 2006;24(SUPPL. 3):52–61.

41. National Cancer Institute. HPV and Pap Testing. NIH. 2019.

42. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2017;67(2):100–21.

43. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020;383(14):1340–8.

44. Serrano B, Alemany L, Tous S, Bruni L, Clifford GM, Weiss T, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. Infect Agent Cancer. 2012;7(1):1–13.

45. Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Hum Vaccines Immunother. 2016;12(6):1406–17.

46. Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink. Vaccine [Internet]. 2011;29(46):8279–84. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.08.106

47. Hviid A, Svanström H, Scheller NM, Grönlund O, Pasternak B, Arnheim-Dahlström L. Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases. J

Intern Med. 2018;283(2):154–65.

48. Howard M, Lytwyn A. The HPV vaccine: An analysis of the FUTURE II study. Can Fam Physician. 2007;53(12):2157–9.

49. Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res. 2009;2(10):868–78.

50. Apter D, Wheeler CM, Paavonen J, Castellsagué X, Garland SM, Skinner SR, et al. Efficacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precancer in young women: Final event-driven analysis of the randomized, double-blind PATRICIA trial. Clin Vaccine Immunol. 2015;22(4):361–73.

51. Haghsgenas MR, Mousavi T, Kheredmand M, Afshari M, Moosazadeh M. Efficacy of Human Papillomavirus L1 Protein Vaccines (Cervarix and Gardasil) in Reducing the Risk of Cervical Intraepithelial Neoplasia: A Meta-analysis. Int J PrevMed. 2017;8(44).

52. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases: Commentary. Colon and Rectum. 2007;1(3):687–96.

53. Kjaer SK, Nygård M, Sundström K, Dillner J, Tryggvadottir L, Munk C, et al. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries. EClinicalMedicine. 2020;23.

54. Moreira ED, Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, et al. Safety profile of the 9-valent HPV vaccine: A combined analysis of 7 phase III clinical trials. Pediatrics. 2016;138(2).

55. Yang DY, Bracken K. Update on the new 9-valent vaccine for human papillomavirus prevention. Can Fam Physician [Internet]. 2016;62(5):399–402. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27255620%0Ahttp://www.pubmedcentral.nih.gov/article

render.fcgi?artid=PMC4865336

56. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. Lancet. 2017;390(10108):2143–59.

57. Joura EA, Giuliano AR, Iversen O-E, Bouchard C, Mao C, Mehlsen J, et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. N Engl J Med. 2015;372(8):711–23.

58. Safaeian M, Schiffman M, Gage J, Solomon D, Wheeler CM, Castle PE. Detection of precancerous cervical lesions is differential by human papillomavirus type. Cancer Res. 2009;69(8):3262–6.

59. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017–Recommendations. Vaccine [Internet]. 2017;35(43):5753–5. Available from: http://dx.doi.org/10.1016/j.vaccine.2017.05.069

60. Prem K, Choi YH, Bénard É, Burger EA, Hadley L, Laprise JF, et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. medRxiv. 2021;1–27.

61. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: A PRIME modelling study. Lancet Glob Heal [Internet]. 2014;2(7):e406–14. Available from: http://dx.doi.org/10.1016/S2214-109X(14)70237-2

62. Canfell K, Chesson H, Kulasingam SL, Berkhof J, Kim JJ. Modeling Preventative Strategies against HPV-Related Disease in Developed Countries. Vaccine. 2012;30(0 5):F157–67.

63. Drolet M, Bénard É, Pérez N, Brisson M, Ali H, Boily MC, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019;394(10197):497–509.

64. Hildesheim A, Herrero R, Wacholder S, Rodriguez AC, Solomon D, Bratti MC, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting

infection: A randomized trial. J Am Med Assoc. 2007;298(7):743–53.

65. Chatterjee A. The next generation of HPV vaccines: Nonavalent vaccine V503 on the horizon. Expert Rev Vaccines. 2014;13(11):1279–90.

66. Hopkins TG, Wood N. Female human papillomavirus (HPV) vaccination: Global uptake and the impact of attitudes. Vaccine. 2013;31(13):1673–9.

67. Mennini FS, Bonanni P, Bianic F, Waure C, Baio G, Plazzotta G, et al. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. Cost Eff Resour Alloc. 2017;15(1):1–14.

68. Centers for Disease Control and Prevention (CDC). CDC Vaccine Price List. CDC. 2021.

69. Kim JJ, Simms KT, Killen J, Smith MA, Burger EA, Sy S, et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. PLoS Med [Internet]. 2021;18(3):1–15. Available from: http://dx.doi.org/10.1371/journal.pmed.1003534

70. Kosen S, Andrijono A, Ocviyanti D, Indriatmi W. The Cost-Effectiveness of Quadrivalent Human Papillomavirus Vaccination in Indonesia. Asian Pacific J Cancer Prev - APJCP. 2017;18(7):2011–7.

71. Jiang Y, Ni W, Wu J. Cost-effectiveness and value-based prices of the 9-valent human papillomavirus vaccine for the prevention of cervical cancer in China: An economic modelling analysis. BMJ Open. 2019;9(11).

72. Brotherton JML, Bloem PN. Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage. Best Pract Res Clin Obstet Gynaecol [Internet]. 2018;47(September):42–58. Available from: http://dx.doi.org/10.1016/j.bpobgyn.2017.08.010

73. Gavi the Vaccine Alliance. Human papillomavirus vaccine support. Gavi. 2021.

74. United Nations. Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019. 2019.

75. World Bank. Barbados [Internet]. World Bank Group. 2021 [cited 2021 Feb 13]. Available from:

https://data.worldbank.org/country/barbados?display=graph%22%3EBanco

76. Vaillant HW, Cummins GTM, Richart RM. An island-wide screening program for cervical neoplasia in Barbados. Am J Obstet Gynecol. 1968;101(7):943–6.

77. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. Human Papillomavirus and Related Diseases in Barbados. Summary Report 17 June 2019. ICO/IARC Inf Cent HPVand Cancer (HPV Inf Centre) [Internet]. 2019;(October). Available from: www.hpvcentre.com

78. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon, France; 2018.

79. Ward JM, Schmalenberg K, Antonishyn NA, Hambleton IR, Blackman EL, Levett PN, et al. Human papillomavirus genotype distribution in cervical samples among vaccine naïve Barbados women. Cancer Causes Control. 2017;28(11):1323–32.

80. Parellada C, Perez Carrega M., Carvalho AL., Prieto E, Monsanto H, Chashat-Cruz M. Evolution of gender-neutral HPV vaccination in National Immunization Calendars in Latin America and the Caribbean. Int J Infect Dis. 2018;73(82).

81. Andall-Brereton G, Brown E, Slater S, Holder Y, Luciani S, Lewis M, et al. Prevalence of high-risk human papillomavirus among women in two English-speaking Caribbean countries. Rev Panam Salud Publica/Pan Am J Public Heal. 2017;41(2):1–9.

82. PAHO. Barbados Cancer Country Profile 2020 [Internet]. 2020. Available from: https://www.paho.org/hq/index.php?option=com_docman&view=download&alias=51554-barbados-country-profile-2020&category_slug=4-cancer-country-profiles-2020&Itemid=270&lang=en

83. World Health Organization. Human papillomavirus (HPV) vaccination coverage [Internet]. WHO/UNICEF Joint Reporting Form on Immunization. 2021 [cited 2021 Sep 29]. Available from: https://immunizationdata.who.int/pages/coverage/hpv.html?CODE=BRB&ANTIGEN=HPV_FEM+

HPV_MALE&YEAR=

84. Drakes N, Landis RC, Perks C, Kumar A, Quimby K, Clarke C, et al. Prevalence and risk factors for inter-generational sex: a cross-sectional cluster survey of Barbadian females aged 15-19. BMC Womens Health. 2013;13(53):1–10.

85. Alok K, Nicole D, Shawna C, Keagan M, Jacqueline W. Risk taking sexual behaviors among young adults – findings from a cross sectional population based survey in Barbados. Int J Clin Virol. 2020;4(1):067–055.

86. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet. 2020;395(10224):575–90.

87. Jit M, Prem K, Benard E, Brisson M. From cervical cancer elimination to eradication of vaccine-type human papillomavirus: Feasibility, public health strategies and cost-effectiveness. Prev Med (Baltim) [Internet]. 2020;144(September):106354. Available from: https://doi.org/10.1016/j.ypmed.2020.106354

88. Anonychuk AM, Bauch CT, Merid MF, Van Kriekinge G, Demarteau N. A cost-utility analysis of cervical cancer vaccination in preadolescent Canadian females. BMC Public Health. 2009;9(401):1–13.

89. Brisson M, Bénard É, Drolet M, Bogaards JA, Baussano I, Vänskä S, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Heal. 2016;1(1):e8–17.

90. Christopher T, Pagan M, Klaric J, Beltran Th, Han J. HPV Vaccination Does Not Provide Herd Immunity for Unvaccinated Women or Cross-Protection for Nonvaccine HPV Types. Obstet Gynecol. 2016;127(p 4S).

91. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem and its associated goals and targets for the period 2020 – 2030. Vol. 2, United Nations General Assembly. 2020.

92. Healthy Caribbean Coalition. HCC Open Letter to CARICOM Heads of State and Government and Ministers of Health. Healthy Caribbean Coalition. 2020. p. 1–2.

93. Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: Results from a modelling study. Br J Cancer. 2004;91(3):530–6.

94. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis [Internet]. 2007;13(1):28–41. Available from: www.cdc.gov/eid%0Ahttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725801/pdf/06-0438.pdf

95. Soetaert K, Petzoldt T, Setzer WR. Solving Differential Equations in {R}: Package de{S}olve. J Stat Softw. 2010;33(9):1–25.

96. Gupta S, Anderson RM, May RM. Networks of sexual contacts: implications for the pattern of spread of HIV. AIDS. 1989;3(12).

97. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman MS, Scott DR, et al. The elevated 10-Year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005;97(14):1072–9.

98. Nash JC, Varadhan R. Unifying Optimization Algorithms to Aid Software System Users: optimx for R. J Stat Softw. 2011;43(9):1–14.

99. Nash JC. On Best Practice Optimization Methods in R. J Stat Softw. 2014;60(2):1–14.

100. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.

101. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global

burden of human papillomavirus and related diseases. Vaccine. 2012;30(SUPPL.5):F12–23.

102. Andall-Brereton GM, Hosein F, Salas RA, Mohammed W, Monteil MA, Goleski V, et al. Human papillomavirus genotypes and their prevalence in a cohort of women in Trinidad. Rev Panam Salud Publica/Pan Am J Public Heal. 2011;29(4):220–6.

103. Lewis-Bella K, Luciani S, Unger ER, Hariri S, McFarlane S, Steinau M, et al. Genital human papillomaviruses among women of reproductive age in Jamaica. Rev Panam Salud Publica/Pan Am J Public Heal. 2013;33(3):159–65.

104. ICO. Human Papillomavirus and Related Diseases Report - Barbados [Internet]. HPV Information Centre. 2016. Available from: www.hpvcentre.com

105. Elbasha EH, Dasbach EJ, Insinga RP. A multi-type HPV transmission model. Bull Math Biol. 2008;70(8):2126–76.

106. Kjaer SK, Nygård M, Sundström K, Munk C, Berger S, Dzabic M, et al. Long-term effectiveness of the nine-valent human papillomavirus vaccine in Scandinavian women: interim analysis after 8 years of follow-up. Hum Vaccines Immunother [Internet]. 2021;17(4):943–9. Available from: https://doi.org/10.1080/21645515.2020.1839292

107. Brouwer AF, Delinger RL, Eisenberg MC, Campredon LP, Walline HM, Carey TE, et al. HPV vaccination has not increased sexual activity or accelerated sexual debut in a college-aged cohort of men and women. BMC Public Health. 2019;19(1):1–8.

108. Smith LM, Kaufman JS, Strumpf EC, Lévesque LE. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: The Ontario Grade 8 HPV Vaccine Cohort Study. Cmaj. 2015;187(2):E74–81.

109. Chirenje ZM. HIV and cancer of the cervic. Best Pract Res Clin Obstet Gynaecol. 2005;19(2 SPEC. ISS.):269–76.

110. De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and

cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prev. 2008;17(6):545–54.

111. Reusser N, Downing C, Guidry J, Tyring S. HPV Carcinomas in Immunocompromised Patients. J Clin Med. 2015;4(2):260–81.

112. Wu ES, Urban RR, Krantz EM, Mugisha NM, Nakisige C, Schwartz SM, et al. The association between HIV infection and cervical cancer presentation and survival in Uganda. Gynecol Oncol Reports [Internet]. 2020;31(November 2019):100516. Available from: https://doi.org/10.1016/j.gore.2019.100516

113. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, Chiyapo S, et al. HIV infection and survival among women with cervical cancer. J Clin Oncol. 2016;34(31):3749–57.

114. World Health Organization. Thirteenth General Programme of Work 2019–2023. WHO Press. 2019;(April 2019):50.

7. Appendix

7.1 Initial model setup

Table A1: Initial values and model setup

Parameter	Value
Initial number of $S_{f,1,l}$	$N_1 * 0.5 * (1 - r_1) - 50 = 12302.75$
Initial number of $S_{f,1,h}$	$N_1 * 0.5 * (r_1) - 50 = 6285.221$
Initial number of $S_{f,2,l}$	$N_2 * 0.5 * (1 - r_2) - 50 = 13928.6$
Initial number of $S_{f,2,h}$	$N_2 * 0.5 * (r_2) - 50 = 4659.368$
Initial number of $S_{f,3,l}$	$N_3 * 0.5 * (1 - r_3) - 50 = 71652$
Initial number of $S_{f,3,h}$	$N_3 * 0.5 * (r_3) - 50 = 10475.06$
Initial number of $S_{m,1,l}$	$N_1 * 0.5 * (1 - r_1) - 50 = 12302.75$
Initial number of $S_{m,1,h}$	$N_1 * 0.5 * (r_1) - 50 = 6285.221$
Initial number of $S_{m,2,l}$	$N_2 * 0.5 * (1 - r_2) - 50 = 13928.6$
Initial number of $S_{m,2,h}$	$N_2 * 0.5 * (r_2) - 50 = 4659.368$
Initial number of $S_{m,3,l}$	$N_3 * 0.5 * (1 - r_3) - 50 = 71652$
Initial number of $S_{m,3,h}$	$N_3 * 0.5 * (r_3) - 50 = 10475.06$
Initial number of $I_{f,1,l}$	50
Initial number of $I_{f,1,h}$	50
Initial number of $I_{f,2,l}$	50
Initial number of $I_{f,2,h}$	50
Initial number of $I_{f,3,l}$	50
Initial number of $I_{f,3,h}$	50
Initial number of $I_{m,1,l}$	50

Table A1 continued: Initial values and model setup

Parameter	Value
Initial number of $I_{m,1,h}$	50
Initial number of $I_{m,2,l}$	50
Initial number of $I_{m,2,h}$	50
Initial number of $I_{m,3,l}$	50
Initial number of $I_{m,3,h}$	50
Initial number of $V_{f,1,l}$	0
Initial number of $V_{f,1,h}$	0
Initial number of $V_{f,2,l}$	0
Initial number of $V_{f,2,h}$	0
Initial number of $V_{f,3,l}$	0
Initial number of $V_{f,3,h}$	0
Initial number of $V_{m,1,l}$	0
Initial number of $V_{m,1,h}$	0
Initial number of $V_{m,2,l}$	0
Initial number of $V_{m,2,h}$	0
Initial number of $V_{m,3,l}$	0
Initial number of $V_{m,3,h}$	0
Modelling method	Runge-Kutta

7.2 Force of infection and beta parameters

Table A2: Full contact matrix.

			Males						Females					
			14-24y		24-34y		35y+		14-24y		24-34y		35y+	
			Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Females	14-24y	Low	$\beta_{11,ll}$	$\beta_{11,lh}$	$\beta_{12,ll}$	$\beta_{12,lh}$	$\beta_{13,ll}$	$\beta_{13,lh}$	0	0	0	0	0	0
		High	$\beta_{11,hl}$	$\beta_{11,hh}$	$\beta_{12,hl}$	$\beta_{12,hh}$	$\beta_{13,hl}$	$\beta_{13,hh}$	0	0	0	0	0	0
	24-34y	Low	$\beta_{21,ll}$	$\beta_{21,lh}$	$\beta_{22,ll}$	$\beta_{22,lh}$	$\beta_{23,ll}$	$\beta_{23,lh}$	0	0	0	0	0	0
		High	$\beta_{21,hl}$	$\beta_{21,hh}$	$\beta_{22,hl}$	$\beta_{22,hh}$	$\beta_{23,hl}$	$\beta_{23,hh}$	0	0	0	0	0	0
	35y+	Low	$\beta_{31,ll}$	$\beta_{31,lh}$	$\beta_{32,ll}$	$\beta_{32,lh}$	$\beta_{33,ll}$	$\beta_{33,lh}$	0	0	0	0	0	0
		High	$\beta_{31,hl}$	$\beta_{31,hh}$	$\beta_{32,hl}$	$\beta_{32,hh}$	$\beta_{33,hl}$	$\beta_{33,hh}$	0	0	0	0	0	0
Males	14-24y	Low	0	0	0	0	0	0	$\beta_{11,ll}$	$\beta_{11,lh}$	$\beta_{12,ll}$	$\beta_{12,lh}$	$\beta_{13,ll}$	$\beta_{13,lh}$
		High	0	0	0	0	0	0	$\beta_{11,hl}$	$\beta_{11,hh}$	$\beta_{12,hl}$	$\beta_{12,hh}$	$\beta_{13,hl}$	$\beta_{13,hh}$
	24-34y	Low	0	0	0	0	0	0	$\beta_{21,ll}$	$\beta_{21,lh}$	$\beta_{22,ll}$	$\beta_{22,lh}$	$\beta_{23,ll}$	$\beta_{23,lh}$
		High	0	0	0	0	0	0	$\beta_{21,hl}$	$\beta_{21,hh}$	$\beta_{22,hl}$	$\beta_{22,hh}$	$\beta_{23,hl}$	$\beta_{23,hh}$
	35y+	Low	0	0	0	0	0	0	$\beta_{31,ll}$	$\beta_{31,lh}$	$\beta_{32,ll}$	$\beta_{32,lh}$	$\beta_{33,ll}$	$\beta_{33,lh}$
		High	0	0	0	0	0	0	$\beta_{31,hl}$	$\beta_{31,hh}$	$\beta_{32,hl}$	$\beta_{32,hh}$	$\beta_{33,hl}$	$\beta_{33,hh}$

1=15-24y, 2=25-34y, 3 = 35y+;

l=low-activity, h=high-activity

Detailed beta parameter calculations, 1 is 15-24y old, 2 is 25-34y old, and 3 is 35y+olds, and where l is low-activity and h is high-activity.

$\beta_{11,ll} = c_{1,1} * p_l * Q_{1,ll} = 7.491088 * 10^{-04}$

$\beta_{11,lh} = c_{1,1} * p_l * Q_{1,lh} = 1.27774 * 10^{-03}$

$\beta_{12,ll} = c_{1,2} * p_l * Q_{2,ll} = 1.034924 * 10^{-04}$

$\beta_{12,lh} = c_{1,2} * p_l * Q_{2,lh} = 1.159597 * 10^{-04}$

$\beta_{13,ll} = c_{1,3} * p_l * Q_{3,ll} = 1.474619 * 10^{-04}$

$\beta_{13,lh} = c_{1,3} * p_l * Q_{3,lh} = 7.199012 * 10^{-05}$

$\beta_{11,hl} = c_{1,1} * p_h * Q_{1,hl} = 2.491405 * 10^{-03}$

$\beta_{11,hh} = c_{1,1} * p_h * Q_{1,hh} = 4.249542 * 10^{-03}$

$\beta_{12,hl} = c_{1,2} * p_h * Q_{2,hl} = 3.441977 * 10^{-04}$

$\beta_{12,hh} = c_{1,2} * p_h * Q_{2,hh} = 3.856616 * 10^{-04}$

$\beta_{13,hl} = c_{1,3} * p_h * Q_{3,hl} = 4.904327 * 10^{-04}$

$\beta_{13,hh} = c_{1,3} * p_h * Q_{3,hh} = 2.394266 * 10^{-04}$

$\beta_{21,ll} = c_{2,1} * p_l * Q_{1,ll} = 8.110789 * 10^{-05}$

$\beta_{21,lh} = c_{2,1} * p_l * Q_{1,lh} = 1.383442 * 10^{-04}$

$\beta_{22,ll} = c_{2,2} * p_l * Q_{2,ll} = 1.059344 * 10^{-03}$

$\beta_{22,lh} = c_{2,2} * p_l * Q_{2,lh} = 1.186958 * 10^{-03}$

$\beta_{23,ll} = c_{2,3} * p_l * Q_{3,ll} = 0.0$

$\beta_{23,lh} = c_{2,3} * p_l * Q_{3,lh} = 0.0$

$\beta_{21,hl} = c_{2,1} * p_h * Q_{1,hl} = 2.697507 * 10^{-04}$

$\beta_{21,hh} = c_{2,1} * p_h * Q_{1,hh} = 4.601086 * 10^{-04}$

$\beta_{22,hl} = c_{2,2} * p_h * Q_{2,hl} = 3.523192 * 10^{-03}$

$\beta_{22,hh} = c_{2,2} * p_h * Q_{2,hh} = 3.947615 * 10^{-03}$

$\beta_{23,hl} = c_{2,3} * p_h * Q_{3,hl} = 0.0$

$\beta_{23,hh} = c_{2,3} * p_h * Q_{3,hh} = 0.0$

$\beta_{31,ll} = c_{3,1} * p_l * Q_{1,ll} = 8.110789 * 10^{-05}$

$\beta_{31,lh} = c_{3,1} * p_l * Q_{1,lh} = 1.383442 * 10^{-04}$

$\beta_{32,ll} = c_{3,2} * p_l * Q_{2,ll} = 0.0$

$\beta_{32,lh} = c_{3,2} * p_l * Q_{2,lh} = 0.0$

$\beta_{33,ll} = c_{3,3} * p_l * Q_{3,ll} = 1.509414 * 10^{-03}$

$\beta_{33,lh} = c_{3,3} * p_l * Q_{3,lh} = 7.368877 * 10^{-04}$

$\beta_{31,hl} = c_{3,1} * p_h * Q_{1,hl} = 2.697507 * 10^{-04}$

$\beta_{31,hh} = c_{3,1} * p_h * Q_{1,hh} = 4.601086 * 10^{-04}$

$\beta_{32,hl} = c_{3,2} * p_h * Q_{2,hl} = 0.0$

$\beta_{32,hh} = c_{3,2} * p_h * Q_{2,hh} = 0.0$

$\beta_{33,hl} = c_{3,3} * p_h * Q_{3,hl} = 5.020047 * 10^{-03}$

$\beta_{33,hh} = c_{3,3} * p_h * Q_{3,hh} = 2.45076 * 10^{-03}$

(Equation 5)

Detailed Force of infections calculations, where m is male and f is female, 1 is 15-24y old, 2 is 25-34y old, and 3 is 35y+ olds, and where l is low-activity and h is high-activity.

$\lambda_{f,1,l} = \beta_{11,ll} * \frac{I_{m,1,l}}{N(t)} * \mu_l + \beta_{11,lh} * \frac{I_{m,1,h}}{N(t)} * \mu_h + \beta_{12,ll} * \frac{I_{m,2,l}}{N(t)} * \mu_l + \beta_{12,lh} * \frac{I_{m,2,h}}{N(t)} * \mu_h + \beta_{13,ll} * \frac{I_{m,3,l}}{N(t)} *$

$\mu_l + \beta_{13,lh} * \frac{I_{m,3,h}}{N(t)} * \mu_h$

$\lambda_{f,1,h} = \beta_{11,hl} * \frac{I_{m,1,l}}{N(t)} * \mu_l + \beta_{11,hh} * \frac{I_{m,1,h}}{N(t)} * \mu_h + \beta_{12,hl} * \frac{I_{m,2,l}}{N(t)} * \mu_l + \beta_{12,hh} * \frac{I_{m,2,h}}{N(t)} * \mu_h + \beta_{13,hl} * \frac{I_{m,3,l}}{N(t)} *$

$\mu_l + \beta_{13,hh} * \frac{I_{m,3,h}}{N(t)} * \mu_h$

$\lambda_{f,2,l} = \beta_{21,ll} * \frac{I_{m,1,l}}{N(t)} * \mu_l + \beta_{21,lh} * \frac{I_{m,1,h}}{N(t)} * \mu_h + \beta_{22,ll} * \frac{I_{m,2,l}}{N(t)} * \mu_l + \beta_{22,lh} * \frac{I_{m,2,h}}{N(t)} * \mu_h + \beta_{23,ll} * \frac{I_{m,3,l}}{N(t)} *$

$\mu_l + \beta_{23,lh} * \frac{I_{m,3,h}}{N(t)} * \mu_h$

$\lambda_{f,2,h} = \beta_{21,hl} * \frac{I_{m,1,l}}{N(t)} * \mu_l + \beta_{21,hh} * \frac{I_{m,1,h}}{N(t)} * \mu_h + \beta_{22,hl} * \frac{I_{m,2,l}}{N(t)} * \mu_l + \beta_{22,hh} * \frac{I_{m,2,h}}{N(t)} * \mu_h + \beta_{23,hl} * \frac{I_{m,3,l}}{N(t)} *$

$\mu_l + \beta_{23,hh} * \frac{I_{m,3,h}}{N(t)} * \mu_h$

$$\lambda_{f,3,l} = \beta_{31,ll} * \frac{I_{m,1,l}}{N(t)} * \mu_l + \beta_{31,lh} * \frac{I_{m,1,h}}{N(t)} * \mu_h + \beta_{31,ll} * \frac{I_{m,2,l}}{N(t)} * \mu_l + \beta_{32,lh} * \frac{I_{m,2,h}}{N(t)} * \mu_h + \beta_{33,ll} * \frac{I_{m,3,l}}{N(t)} * \mu_l + \beta_{33,lh} * \frac{I_{m,3,h}}{N(t)} * \mu_h$$

$$\lambda_{f,3,h} = \beta_{31,hl} * \frac{I_{m,1,l}}{N(t)} * \mu_l + \beta_{31,hh} * \frac{I_{m,1,h}}{N(t)} * \mu_h + \beta_{32,hl} * \frac{I_{m,2,l}}{N(t)} * \mu_l + \beta_{32,hh} * \frac{I_{m,2,h}}{N(t)} * \mu_h + \beta_{33,hl} * \frac{I_{m,3,l}}{N(t)} * \mu_l + \beta_{33,hh} * \frac{I_{m,3,h}}{N(t)} * \mu_h$$

$$\lambda_{m,1,l} = \beta_{11,ll} * \frac{I_{f,1,l}}{N(t)} * \mu_l + \beta_{11,hl} * \frac{I_{f,1,h}}{N(t)} * \mu_h + \beta_{21,ll} * \frac{I_{f,2,l}}{N(t)} * \mu_l + \beta_{21,hl} * \frac{I_{f,2,h}}{N(t)} * \mu_h + \beta_{31,ll} * \frac{I_{f,3,l}}{N(t)} * \mu_l + \beta_{31,hl} * \frac{I_{f,3,h}}{N(t)} * \mu_h$$

$$\lambda_{m,1,h} = \beta_{11,lh} * \frac{I_{f,1,l}}{N(t)} * \mu_l + \beta_{11,hh} * \frac{I_{f,1,h}}{N(t)} * \mu_h + \beta_{21,lh} * \frac{I_{f,2,l}}{N(t)} * \mu_l + \beta_{21,hh} * \frac{I_{f,2,h}}{N(t)} * \mu_h + \beta_{31,lh} * \frac{I_{f,3,l}}{N(t)} * \mu_l + \beta_{31,hh} * \frac{I_{f,3,h}}{N(t)} * \mu_h$$

$$\lambda_{m,2,l} = \beta_{12,ll} * \frac{I_{f,1,l}}{N(t)} * \mu_l + \beta_{12,hl} * \frac{I_{f,1,h}}{N(t)} * \mu_h + \beta_{22,ll} * \frac{I_{f,2,l}}{N(t)} * \mu_l + \beta_{22,hl} * \frac{I_{f,2,h}}{N(t)} * \mu_h + \beta_{32,ll} * \frac{I_{f,3,l}}{N(t)} * \mu_l + \beta_{32,hl} * \frac{I_{f,3,h}}{N(t)} * \mu_h$$

$$\lambda_{m,2,h} = \beta_{12,lh} * \frac{I_{f,1,l}}{N(t)} * \mu_l + \beta_{12,hh} * \frac{I_{f,1,h}}{N(t)} * \mu_h + \beta_{22,lh} * \frac{I_{f,2,l}}{N(t)} * \mu_l + \beta_{22,hh} * \frac{I_{f,2,h}}{N(t)} * \mu_h + \beta_{32,lh} * \frac{I_{f,3,l}}{N(t)} * \mu_l + \beta_{32,hh} * \frac{I_{f,3,h}}{N(t)} * \mu_h$$

$$\lambda_{m,3,l} = \beta_{13,ll} * \frac{I_{f,1,l}}{N(t)} * \mu_l + \beta_{13,hl} * \frac{I_{f,1,h}}{N(t)} * \mu_h + \beta_{32,ll} * \frac{I_{f,2,l}}{N(t)} * \mu_l + \beta_{23,hl} * \frac{I_{f,2,h}}{N(t)} * \mu_h + \beta_{33,ll} * \frac{I_{f,3,l}}{N(t)} * \mu_l + \beta_{33,hl} * \frac{I_{f,3,h}}{N(t)} * \mu_h$$

$$\lambda_{m,3,h} = \beta_{13,lh} * \frac{I_{f,1,l}}{N(t)} * \mu_l + \beta_{13,hh} * \frac{I_{f,1,h}}{N(t)} * \mu_h + \beta_{23,lh} * \frac{I_{f,2,l}}{N(t)} * \mu_l + \beta_{23,hh} * \frac{I_{f,2,h}}{N(t)} * \mu_h + \beta_{33,lh} * \frac{I_{f,3,l}}{N(t)} * \mu_l + \beta_{33,hh} * \frac{I_{f,3,h}}{N(t)} * \mu_h$$

(Equation 6)

Detailed differential equations, where m is male and f is female, 1 is 15-24y old, 2 is 25-34y old, and 3 is 35y+ old, and where l is low-activity and h is high-activity. All other parameters can be found in table 1 of the main report.

$$\frac{dS_{f,1,l}}{dt} = -S_{f,1,l} * \lambda_{f,1,l} + I_{f,1,l} * \gamma + V_{f,1,l} * \delta + \alpha_1 * u_{f,l} - \alpha'_1 * S_{f,1,l}$$

$$\frac{dS_{f,1,h}}{dt} = -S_{f,1,h} * \lambda_{f,1,h} + I_{f,1,h} * \gamma + V_{f,1,h} * \delta + \alpha_1 * u_{f,h} - \alpha'_1 * S_{f,1,h}$$

$$\frac{dS_{f,2,l}}{dt} = -S_{f,2,l} * \lambda_{f,2,l} + I_{f,2,l} * \gamma + V_{f,2,l} * \delta + \alpha_2 * S_{f,1,l} + \alpha_2 * S_{f,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * S_{f,2,l}$$

$$\frac{dS_{f,2,h}}{dt} = -S_{f,2,h} * \lambda_{f,2,h} + I_{f,2,h} * \gamma + V_{f,2,h} * \delta + \alpha_2 * S_{f,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * S_{f,2,h}$$

$$\frac{dS_{f,3,l}}{dt} = -S_{f,3,l} * \lambda_{f,3,l} + I_{f,3,l} * \gamma + V_{f,3,l} * \delta + \alpha_3 * S_{f,2,l} + \alpha_3 * S_{f,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * S_{f,3,l}$$

$$\frac{dS_{f,3,h}}{dt} = -S_{f,3,h} * \lambda_{f,3,h} + I_{f,3,h} * \gamma + V_{f,3,h} * \delta + \alpha_3 * S_{f,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * S_{f,3,h}$$

$$\frac{dS_{m,1,l}}{dt} = -S_{m,1,l} * \lambda_{m,1,l} + I_{m,1,l} * \gamma + V_{m,1,l} * \delta + \alpha_1 * u_{m,l} - \alpha'_1 * S_{m,1,l}$$

$$\frac{dS_{m,1,h}}{dt} = -S_{m,1,h} * \lambda_{m,1,h} + I_{m,1,h} * \gamma + V_{m,1,h} * \delta + \alpha_1 * u_{m,h} - \alpha'_1 * S_{m,1,h}$$

$$\frac{dS_{m,2,l}}{dt} = -S_{m,2,l} * \lambda_{m,2,l} + I_{m,2,l} * \gamma + V_{m,2,l} * \delta + \alpha_2 * S_{m,1,l} + \alpha_2 * S_{m,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * S_{m,2,l}$$

$$\frac{dS_{m,2,h}}{dt} = -S_{m,2,h} * \lambda_{m,2,h} + I_{m,2,h} * \gamma + V_{m,2,h} * \delta + \alpha_2 * S_{m,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * S_{m,2,h}$$

$$\frac{dS_{m,3,l}}{dt} = -S_{m,3,l} * \lambda_{m,3,l} + I_{m,3,l} * \gamma + V_{m,3,l} * \delta + \alpha_3 * S_{m,2,l} + \alpha_3 * S_{m,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * S_{m,3,l}$$

$$\frac{dS_{m,3,h}}{dt} = -S_{m,3,h} * \lambda_{m,3,h} + I_{m,3,h} * \gamma + V_{m,3,h} * \delta + \alpha_3 * S_{m,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * S_{m,3,h}$$

$$\frac{dI_{f,1,l}}{dt} = +S_{f,1,l} * \lambda_{f,1,l} - I_{f,1,l} * \gamma - \alpha'_1 * I_{f,1,l}$$

$$\frac{dI_{f,1,h}}{dt} = +S_{f,1,h} * \lambda_{f,1,h} - I_{f,1,h} * \gamma - \alpha'_1 * I_{f,1,h}$$

$$\frac{dI_{f,2,l}}{dt} = +S_{f,2,l} * \lambda_{f,2,l} - I_{f,2,l} * \gamma + \alpha_2 * I_{f,1,l} + \alpha_2 * I_{f,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * I_{f,2,l}$$

$$\frac{dI_{f,2,h}}{dt} = +S_{f,2,h} * \lambda_{f,2,h} - I_{f,2,h} * \gamma + \alpha_2 * I_{f,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * I_{f,2,h}$$

$$\frac{dI_{f,3,l}}{dt} = +S_{f,3,l} * \lambda_{f,3,l} - I_{f,3,l} * \gamma + \alpha_3 * I_{f,2,l} + \alpha_3 * I_{f,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * I_{f,3,l}$$

$$\frac{dI_{f,3,h}}{dt} = +S_{f,3,h} * \lambda_{f,3,h} - I_{f,3,h} * \gamma + \alpha_3 * I_{f,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * I_{f,3,h}$$

$$\frac{dI_{m,1,l}}{dt} = +S_{m,1,l} * \lambda_{m,1,l} - I_{m,1,l} * \gamma - \alpha'_1 * I_{m,1,l}$$

$$\frac{dI_{m,1,h}}{dt} = +S_{m,1,h} * \lambda_{m,1,h} - I_{m,1,h} * \gamma - \alpha'_1 * I_{m,1,h}$$

$$\frac{dI_{m,2,l}}{dt} = +S_{m,2,l} * \lambda_{m,2,l} - I_{m,2,l} * \gamma + \alpha_2 * I_{m,1,l} + \alpha_2 * I_{m,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * I_{m,2,l}$$

$$\frac{dI_{m,2,h}}{dt} = +S_{m,2,h} * \lambda_{m,2,h} - I_{m,2,h} * \gamma + \alpha_2 * I_{m,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * I_{m,2,h}$$

$$\frac{dI_{m,3,l}}{dt} = +S_{m,3,l} * \lambda_{m,3,l} - I_{m,3,l} * \gamma + \alpha_3 * I_{m,2,l} + \alpha_3 * I_{m,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * I_{m,3,l}$$

$$\frac{dI_{m,3,h}}{dt} = +S_{m,3,h} * \lambda_{m,3,h} - I_{m,3,h} * \gamma + \alpha_3 * I_{m,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * I_{m,3,h}$$

$$\frac{dV_{f,1,l}}{dt} = -V_{f,1,l} * \delta + \alpha_1 * v_{f,l} - \alpha'_1 * V_{f,1,l}$$

$$\frac{dV_{f,1,h}}{dt} = -V_{f,1,h} * \delta + \alpha_1 * v_{f,h} - \alpha'_1 * V_{f,1,h}$$

$$\frac{dV_{f,2,l}}{dt} = -V_{f,2,l} * \delta + \alpha_2 * V_{f,1,l} + \alpha_2 * V_{f,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * V_{f,2,l}$$

$$\frac{dV_{f,2,h}}{dt} = -V_{f,2,h} * \delta + \alpha_2 * V_{f,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * V_{f,2,h}$$

$$\frac{dV_{f,3,l}}{dt} = -V_{f,3,l} * \delta + \alpha_3 * V_{f,2,l} + \alpha_3 * V_{f,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * V_{f,3,l}$$

$$\frac{dV_{f,3,h}}{dt} = -V_{f,3,h} * \delta + \alpha_3 * V_{f,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * V_{f,3,h}$$

$$\frac{dV_{m,1,l}}{dt} = -V_{m,1,l} * \delta + \alpha_1 * v_{m,l} - \alpha'_1 * V_{m,1,l}$$

$$\frac{dV_{m,1,h}}{dt} = -V_{m,1,h} * \delta + \alpha_1 * v_{m,h} - \alpha'_1 * V_{m,1,h}$$

$$\frac{dV_{m,2,l}}{dt} = -V_{m,2,l} * \delta + \alpha_2 * V_{m,1,l} + \alpha_2 * V_{m,1,h} * \left(1 - \frac{r_2}{r_1}\right) - \alpha'_2 * V_{m,2,l}$$

$$\frac{dV_{m,2,h}}{dt} = -V_{m,2,h} * \delta + \alpha_2 * V_{m,1,h} * \left(\frac{r_2}{r_1}\right) - \alpha'_2 * V_{m,2,h}$$

$$\frac{dV_{m,3,l}}{dt} = -V_{m,3,l} * \delta + \alpha_3 * V_{m,2,l} + \alpha_3 * V_{m,2,h} * \left(1 - \frac{r_3}{r_2}\right) - \alpha'_3 * V_{m,3,l}$$

$$\frac{dV_{m,3,h}}{dt} = -V_{m,3,h} * \delta + \alpha_3 * V_{m,2,h} * \left(\frac{r_3}{r_2}\right) - \alpha'_3 * V_{m,3,h}$$

(Equation 7)

7.3 Detailed methods used to explore pre-vaccination transmission patterns

Table A3 Proportion of contacts by age using the assumption of no intergenerational contact.

	Contactee		
Contactor	**15-24y**	**25-34y**	**35y+**
15-24y	1	0	0
25-34y	0	1	0
35y+	0	0	1

Table A4 Proportion of contacts by age based on Drakes 2013 data.[84]

	Contactee		
Contactor	**15-24y**	**25-34y**	**35y+**
15-24y	0.822	0.089	0.089
25-34y	0.089	0.911	0
35y+	0.089	0	0.911

Table A5 Partner matrix 1 (Q = 0.0 “proportionate mixing”).

Contactor	**Contactee**	
	15-24y	
	Low	**High**
Low	0.3695928	0.6304072
High	0.3695928	0.6304072
	24-34y	
	Low	**High**
Low	0.4715946	0.5284054
High	0.4715946	0.5284054
	35y+	
	Low	**High**
Low	0.6719551	0.3280449
High	0.6719551	0.3280449

Table A6 Partner matrix 2 (Q = 0.2).

Contactor	Contactee	
	15-24y	
	Low	High
Low	0.4956742	0.5043258
High	0.2956742	0.7043258
	24-34y	
	Low	High
Low	0.5772757	0.4227243
High	0.3772757	0.6227243
	35y+	
	Low	High
Low	0.7375641	0.2624359
High	0.5375641	0.4624359

Table A7 Partner matrix 3 (Q = 0.5).

Contactor	Contactee	
	15-24y	
	Low	High
Low	0.6847964	0.3152036
High	0.1847964	0.8152036
	24-34y	
	Low	High
Low	0.7357973	0.2642027
High	0.2357973	0.7642027
	35y+	
	Low	High
Low	0.8359776	0.1640224
High	0.3359776	0.6640224