

Mathematical Assessment of anti-HPV Vaccines

Abba B. Gumel,
Department of Mathematics,
University of Manitoba, Winnipeg, Manitoba, Canada.

Biomat 2013, Fields Institute, November 6, 2013.



UNIVERSITY
OF MANITOBA

Burden of Some Infectious Diseases

- (i) **Smallpox (430 BC-1979):** over 300 million fatalities in the 19th century alone;
- (ii) **1918-1919 influenza pandemic (Spanish Flu):** 500 million people infected (1/3 of world's population at the time). Over 20 million fatalities (other estimates: 50-100 million deaths);
- (iii) **Plague (1340-1771):** over 75 million deaths;
- (iv) **Malaria (1600-to date):** 1-2 million deaths a year;
- (v) **HIV/AIDS (1981-to date):** over 25 million fatalities (33.4 million living with HIV/AIDS);
- (vi) **Cholera (1817-to date):** 8 pandemics.

Globalization and Public Health

International travel has long been associated with disease spread globally. Outbreak of infectious disease in one country can spread rapidly to other countries

“SARS has illustrated that we are constantly a short flight away from serious epidemic” (National Advisory Committee on SARS and Public Health, Canada; 2003)

We are vulnerable to what's happening in far away places

Role of Modelling in Disease Transmission Dynamics

Building and testing theories; assessing quantitative conjectures; providing insights on specific questions; determining sensitivities to changes in parameter values; estimating key parameters from data

Comparing, planning, implementing, evaluating and optimizing various detection, prevention, therapy and control programs

Identifying trends and making general forecasts

Early estimate of epidemiological thresholds (\mathcal{R}_0), prevalence, disease burden

Types of disease transmission models: deterministic, stochastic, network, discrete etc.

Public Health "Wish List" During New Epidemics

Estimation of reproduction number (\mathcal{R}_0) and other epidemiological thresholds

Qualitative nature of disease spread

- ◇ spreading speed (peak; disease "die out")
- ◇ is there multiple-waves phenomenon?

Estimation of disease burden: disease incidence, hospitalization, mortality

Assessment of control strategies: targeted; herd immunity, cost of interventions; optimal allocation of limited resources

Mathematical "Wish List"

Characterizing qualitative dynamics of the model (typically deterministic system of nonlinear differential equations): existence and asymptotic stability of solutions (equilibria, periodic); asymptotic stability (local vs. global); Conditions for disease persistence or elimination

Characterizing bifurcation type(s): forward; backward; Hopf; chaotic dynamics?

Statistical and computational aspects: data-fitting; parameter estimation; optimization (optimal control); sensitivity and uncertainty analysis; dynamic consistency; mathematical software design; high-performance computing

Human Papilloma virus (HPV)

Transmitted through sexual interactions and vertically

Commonest STI in Canada and USA; 75% of sexually-active people will have HPV at least once (CDC estimate: 79 million HPV cases in the USA currently; and 14 million new cases recorded annually)

Most HPV infections (90%) clear within two years

Persistent infection causes several diseases and conditions: cancers (notably cervical cancer in women) and genital warts (papillomas)

HPV Types

Caused by over 120 different serotypes (over 40 infect anogenital tract):
commonest types (6, 11, 16, 18)

Low or no oncogenic risk types (6, 11, 42, 44). Cause cervical cell abnormalities (usually resolved spontaneously, and do not lead to cancer); account for 90% of genital warts and respiratory papillomatosis

High oncogenic risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Cause cervical cell abnormalities, various anogenital cancers (cervical, anal, vaginal, vulvar, penile, throat, bladder etc.)

Over 70% of cervical cancer cases caused by HPV-16/18: Type-16 (50%). HPV DNA found in 99% of cervical cancer cases

Introduction Ctd.

HPV-16 and HPV-18 cause 70% of cervical cancer cases (due to the presence of two viral oncogenes, E6 and E7 genes, which bind to the human p53 tumor suppressor protein)

Symptoms: small bumpy warts, itching or burning around genitals

Incubation period: 1 month to 2 years (large number of cases not detected...asymptomatic transmission)

90% natural recovery. Those who do not clear infection develop persistent infection (increased risk of developing pre-cancerous lesions: **cervical intraepithelial neoplasia (CIN)**)

HPV and Cancer

Cancer	HPV Involvement
Cervix	100%
Cervix (CIS)	100%
Vulva	55%
Vaginal	55%
Penile	42%
Anal	88%
Larynx	42%
Oral	22%

Cervical Cancer

- ❑ One of the commonest cancers among women globally (breast, lung, colorectal, cervical)
- ❑ 250,000 deaths worldwide (12,000 in USA) annually
- ❑ 1,300 Canadian women diagnosed in 2009 (380 deaths)

Cervical Cancer Risk

- ◇ Women who do not have Pap ([Papanicolaou](#)) tests
- ◇ Women who do not follow up with testing or treatment after an abnormal Pap test
- ◇ Women who have persistent HPV
- ◇ Women who smoke
- ◇ Immuno-compromised women (HIV; organ transplant; steroid medications; chemotherapy)

Incidence and Mortality of Cervical Cancer (2008)

Region	Cervical cancer cases	Deaths
Africa	80,419	53,334
Americas	80,711	36,125
Asia	312,752	159,774
Europe	54,323	25,102
Oceania	1,595	781
World (Total)	529,828	275,128

Source: World Health Organization (<http://www.who.int>)

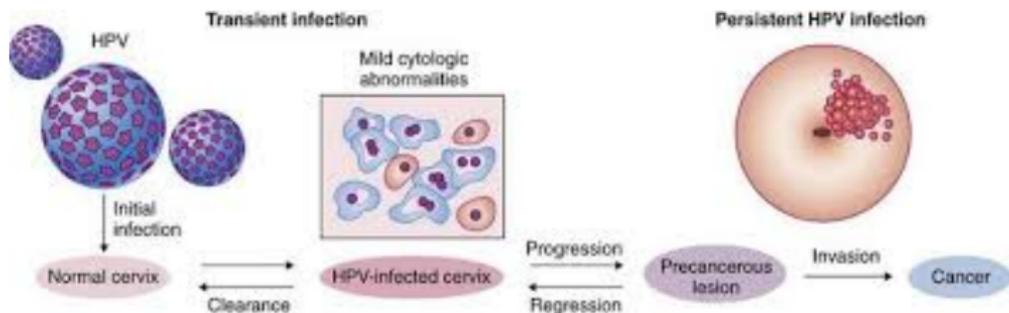
Estimated Annual Health Costs of Cervical Cancer

USA (Insinga et al., 2004)

- **Total: \$3.4 billion**
 - ◇ **Routine screening: \$2.1 billion**
 - ◇ **False positive tests: \$300 million**
 - ◇ **CIN: \$600 million**
 - ◇ **Invasive cervical cancer: \$350 million**

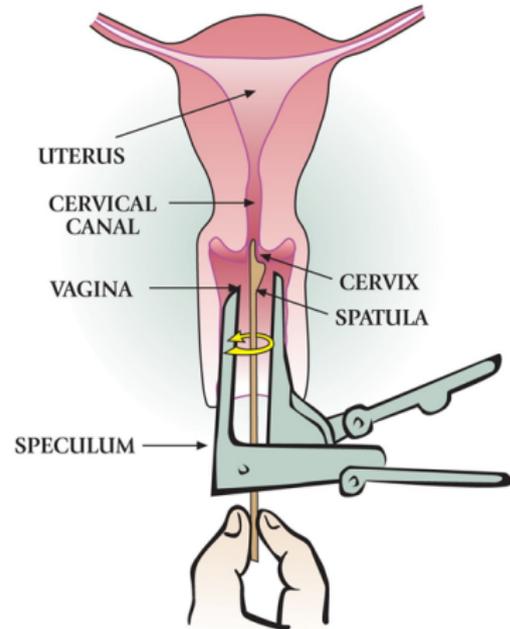
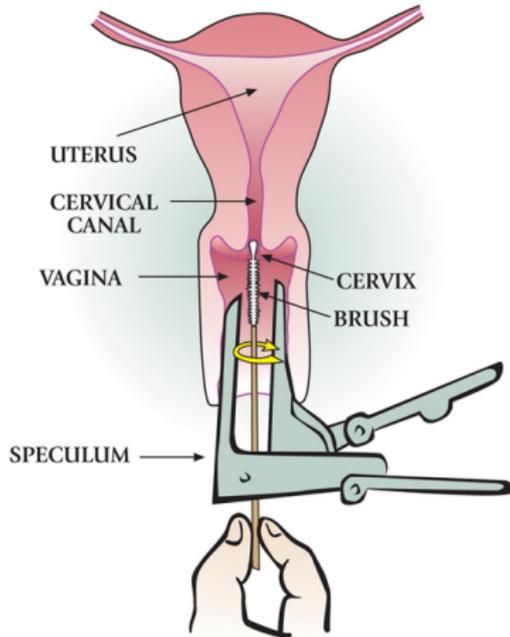
Cost of direct HPV-related interventions in BC (2005): CDN \$ 50 million
(BC CDC)

HPV: Natural History



Source: Cleveland Clinic

Control Strategies: Pap Screening



Source: Cancercare Manitoba

Pap Screening ctd.

Administered to women (typically starting at age 21, until 69) every three years: to detect HPV-induced (potentially cancerous) abnormal changes to woman's cervix (reduces incidence of cervical cancer)

All women (regardless of sexual orientation) who have ever been sexually active (intercourse, intimate touching etc.) to get regular Pap test (3 years after first sexual activity); some need Pap test every two years

Pap screening not necessary for women of age > 69 who have had three successive normal Pap results (except for those at high risk of cervical cancer)

Pap Screening ctd.

Screening for cervical cancer using the Pap test detects precursor lesions(allow for earlier and potentially less invasive treatment)

Recent Canadian study (Dickenson et al., CMAJ, 2013) suggests screening to commence at 25 years of age:

“so few cervical cancer cases diagnosed in women in their teens and 20s that there appears to be little benefit in screening women that young”

Control Strategies: Vaccination

Two vaccines approved by FDA in June 2006 (efficacy 90-100%):
administered in a 3-dose series within 6 months

Cervarix® (GlaxoSmithKline): bivalent (HPV2) 16, 18

- (i) prevents against cervical cancers and precancers
- (ii) females only (schedule: 0, 1, 6 months)
- (iii) cost: \$90 per dose

Gardasil® (Merck Inc.): quadrivalent (HPV4): 6, 11, 16, 18

- (a) prevents against cervical cancers, precancers and genital warts
- (b) females and males (9 through 26; schedule: 0,2,6 months)
- (c) cost: \$130 per dose
- (d) **not free for males in Canada**

HPV Vaccines ctd.

Vaccination of females

- (a) routine: 9 to 13 years of age
- (b) some benefits for 14-26 year olds (not previously vaccinated or not completed 3-dose series)
- (c) not recommended for < 9 or pregnant women (pregnancy test not required before vaccination)
 - ◇ females 26 years of age or younger with abnormal Pap test, positive HPV DNA, or genital warts may be vaccinated (vaccine will have no effect on existing disease or infection)

Vaccination of males: prevent genital warts; prevent female partners from getting cervical cancer

HPV Vaccines ctd.

Vaccine coverage in Canada: 55-85 (70)%

Systemic adverse reaction: pain (at body location it is given), nausea, fever, dizziness, diarrhea etc. Vaccines only cover some high risk HPV types

Consequently, regular Pap screening still important

Control Strategies: Treatment

Warts: chemical treatment methods (cryotherapy, podophyllin and trichloroacetic acid) and using creams

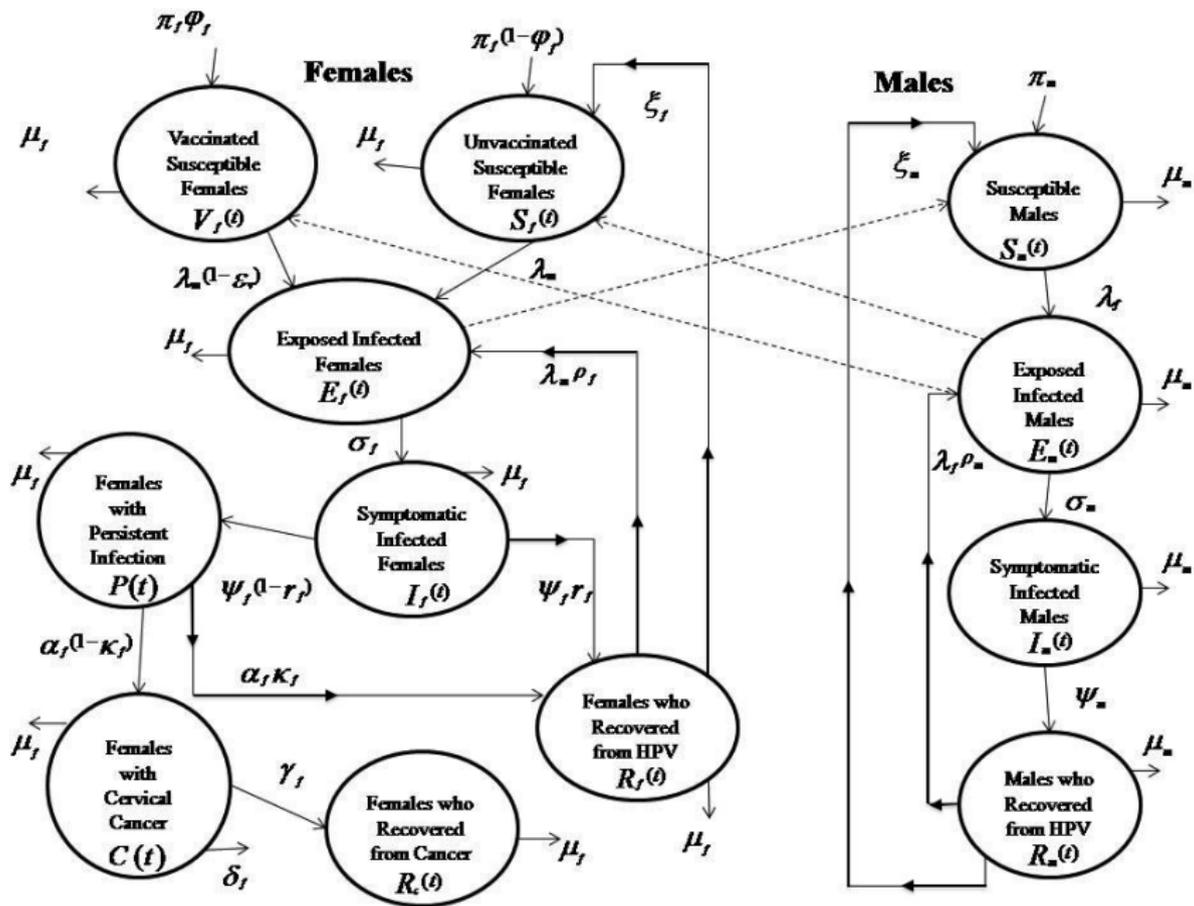
Cervical cancer: treatment depends on CIN stage

- ◇ pre-cancerous lesions can be successfully treated using loop electrosurgical excision procedure (which involves the removal of a cancerous tissue using a wire loop, or using laser therapy)
- ◇ If cancer is limited to the cervix, it can be removed using hysterectomy (removal of the cervix). Surgery or radiation therapy if it spreads to the anus and other genital areas

Correct and consistent condom use may

- (a) **have a protective effect on HPV acquisition**
- (b) **reduce the risk for HPV-associated diseases**
- (c) **mitigate the adverse consequences of infection with HPV**

Modeling Questions: Can the singular use of the *Gardasil* vaccine (for females) lead to effective control of HPV in a community? If yes, what coverage rate is required?



Model Equations

$$\begin{aligned}\frac{dS_f}{dt} &= \pi_f(1 - \phi_f) + \xi_f R_f - \frac{\beta_m c_f (\eta_m E_m + I_m)}{N_m} S_f - \mu_f S_f, \\ \frac{dV_f}{dt} &= \pi_f \phi_f - (1 - \varepsilon_v) \frac{\beta_m c_f (\eta_m E_m + I_m)}{N_m} V_f - \mu_f V_f, \\ \frac{dE_f}{dt} &= \frac{\beta_m c_f (\eta_m E_m + I_m)}{N_m} [S_f + (1 - \varepsilon_v) V_f + \rho_f R_f] - (\sigma_f + \mu_f) E_f, \\ \frac{dI_f}{dt} &= \sigma_f E_f - (\psi_f + \mu_f) I_f, \\ \frac{dP}{dt} &= \psi_f (1 - r_f) I_f - (\alpha_f + \mu_f) P, \\ \frac{dC}{dt} &= \alpha_f (1 - \kappa_f) P - (\gamma_f + \mu_f + \delta_f) C, \\ \frac{dR_c}{dt} &= \gamma_f C - \mu_f R_c,\end{aligned}\tag{1}$$

Model Equations Ctd.

$$\frac{dR_f}{dt} = \psi_f r_f I_f + \alpha_f \kappa_f P - \left[\rho_f \frac{\beta_m c_f (\eta_m E_m + I_m)}{N_m} + \xi_f + \mu_f \right] R_f,$$

$$\frac{dS_m}{dt} = \pi_m + \xi_m R_m - \frac{\beta_f c_f (\eta_f E_f + I_f + \theta_p P)}{N_m} S_m - \mu_m S_m,$$

$$\frac{dE_m}{dt} = \frac{\beta_f c_f (\eta_f E_f + I_f + \theta_p P)}{N_m} (S_m + \rho_m R_m) - (\sigma_m + \mu_m) E_m,$$

$$\frac{dI_m}{dt} = \sigma_m E_m - (\psi_m + \mu_m) I_m,$$

$$\frac{dR_m}{dt} = \psi_m I_m - \left[\rho_m \frac{\beta_f c_f (\eta_f E_f + I_f + \theta_p P)}{N_m} + \xi_m + \mu_m \right] R_m.$$

Theorem 1

The region

$$\mathcal{D} = \left\{ (S_f, V_f, E_f, I_f, P, C, R_c, R_f, S_m, E_m, I_m, R_m) \in \mathbb{R}_+^{12} : \right. \\ \left. N_f \leq \frac{\pi_f}{\mu_f}, N_m \leq \frac{\pi_m}{\mu_m} \right\}$$

is positively-invariant for the model (1).

Disease-free Equilibrium (DFE)

DFE:

$$\begin{aligned}\mathcal{E}_0^V &= (S_f^*, V_f^*, E_f^*, I_f^*, P^*, C^*, R_c^*, R_f^*, S_m^*, E_m^*, I_m^*, R_m^*) \\ &= (S_f^*, V_f^*, 0, 0, 0, 0, 0, 0, S_m^*, 0, 0, 0)\end{aligned}$$

Reproduction threshold:

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_m \mathcal{R}_f},$$

$$\mathcal{R}_m = \frac{\beta_f \mu_m}{g_5 \pi_m} \left(\frac{\eta_m g_5 + \sigma_m}{g_4} \right),$$

$$\mathcal{R}_f = \frac{\beta_m c_f^2 \pi_f (1 - \varepsilon_v \varphi_f)}{g_2 \mu_f} \left[\frac{\eta_f n_1 g_2 + \sigma_f (n_1 + \theta_p h_1)}{n_1 g_1} \right].$$

Local Asymptotic Stability of DFE

Theorem 2

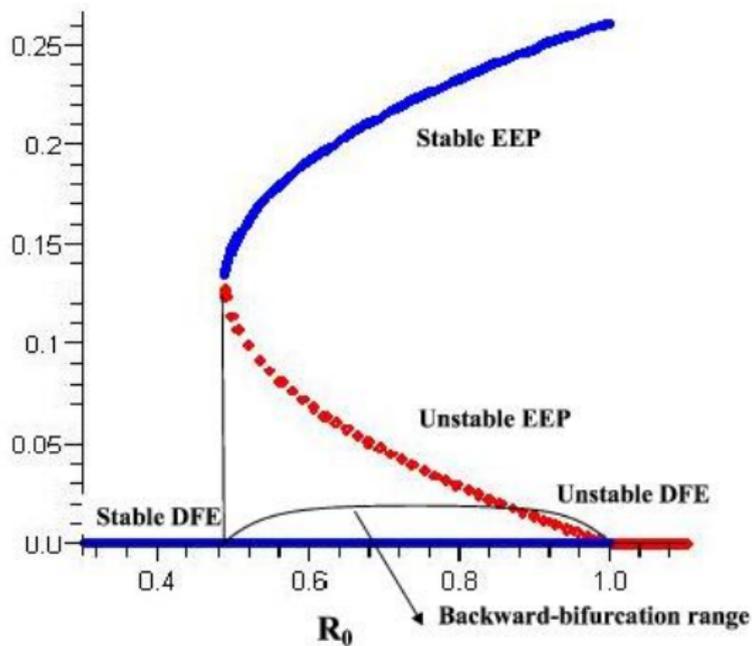
The DFE of the model (1) is LAS if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

Epidemiological implication: effective disease control feasible if $\mathcal{R}_0 < 1$ and initial conditions in the basin of attraction of DFE. Disease persists otherwise.

Theorem 3

The model undergoes a backward bifurcation at $\mathcal{R}_0 = 1$ under certain conditions.

Backward Bifurcation Diagram



Main Features of Backward Bifurcation

- (i) Co-existence of stable DFE and a stable endemic equilibrium when $\mathcal{R}_0 < 1$
- (ii) Endemic equilibrium that exists for \mathcal{R}_0 slightly above one has large infective population (the result of \mathcal{R}_0 rising above one is the sudden dramatic jump in the number of infected individuals; reducing \mathcal{R}_0 below unity would not (necessarily) eliminate the disease)
- (iii) Disease may still persist when $\mathcal{R}_0 < 1$ (disease control depends on initial conditions in this case)
- (iv) $\mathcal{R}_0 < 1$ is necessary but not sufficient for disease elimination

Backward bifurcation makes effective disease control difficult

Global Stability of DFE (special case)

Theorem 4

The DFE of the model (1) with $\rho_f = \rho_m = 0$ is GAS in \mathcal{D} if $\mathcal{R}_0 < 1$.

Proof based on using the Lyapunov function:

$$\begin{aligned}\mathcal{L} &= \frac{\beta_f c_f (\eta_f n_1 g_2 + \sigma_f n_1 + \theta_p \sigma_f h_1) (\eta_m g_5 + \sigma_m)}{n_1 g_1 g_2 g_4 \mathcal{R}_0^2} E_f \\ &+ \frac{\beta_f c_f (n_1 + \theta_p h_1) (\eta_m g_5 + \sigma_m)}{n_1 g_2 g_4 \mathcal{R}_0^2} I_f \\ &+ \frac{\beta_f c_f \theta_p (\eta_m g_5 + \sigma_m)}{n_1 g_4} P + \frac{(\eta_m g_5 + \sigma_m)}{g_4} E_m + I_m.\end{aligned}$$

Backward bifurcation caused by re-infection of recovered individuals.

Existence and Stability of EEP: special case

Theorem 5

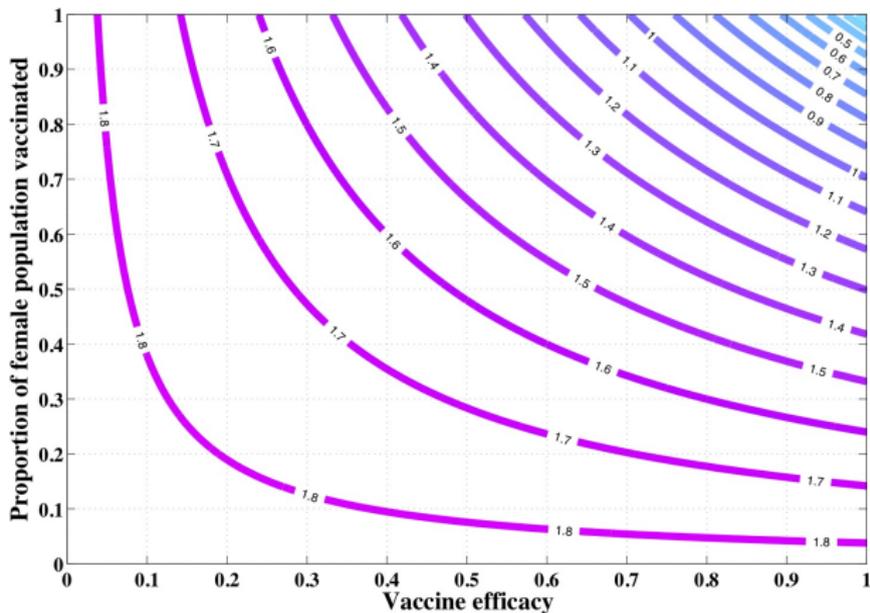
The model (1) could have 2 or more endemic equilibria if $\mathcal{R}_0 < 1$, and at least one positive endemic equilibrium whenever $\mathcal{R}_0 > 1$.

Theorem 6

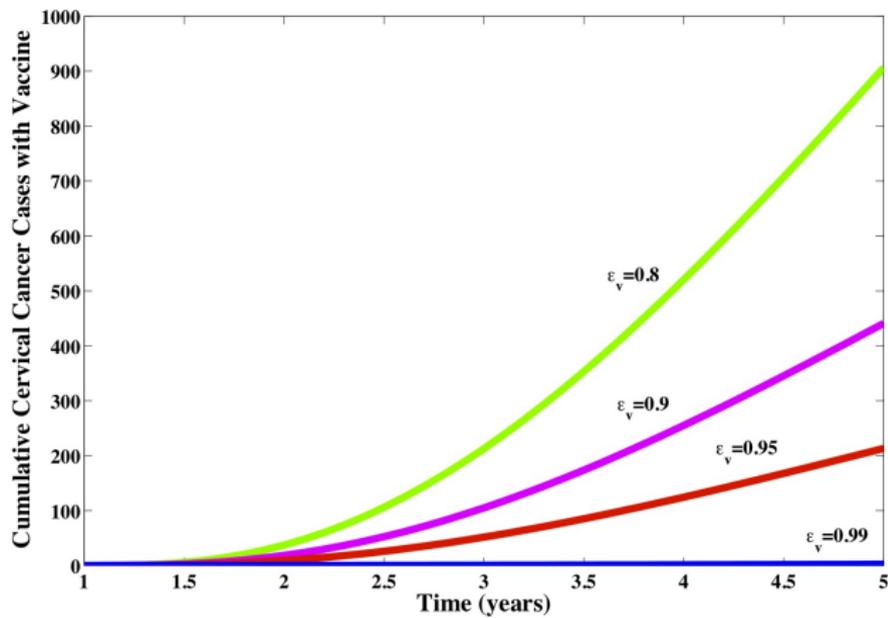
The unique EEP of the vaccination-free version of the model (1), with $\rho_f = \rho_m = 0$, is LAS whenever $\mathcal{R}_{01} = \mathcal{R}_0 |_{V_f = \varphi_f = 0} > 1$.

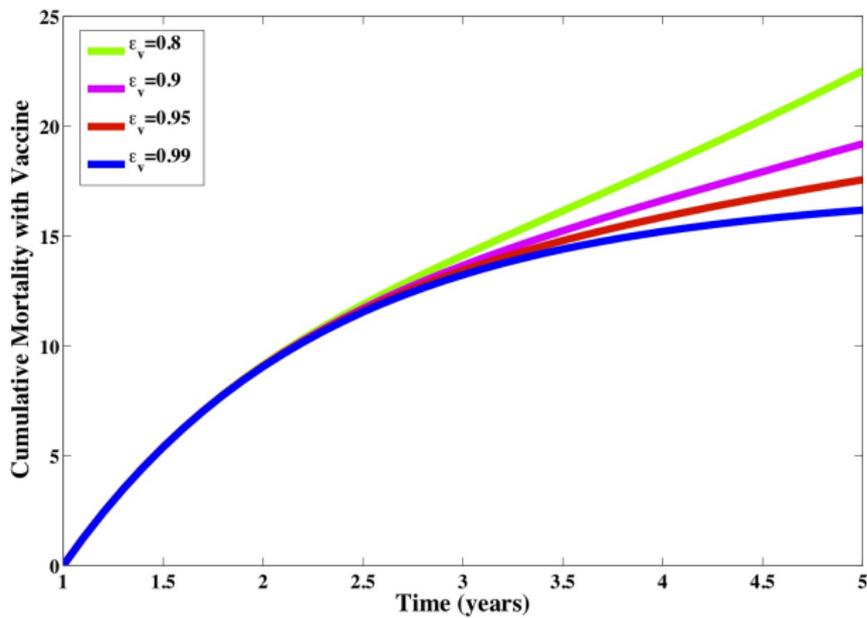
Proof based on using a Krasnasolskii's sub-linearity argument (Thieme, 1985)

Numerical Simulations



78% Gardasil coverage needed to make $R_0 < 1$

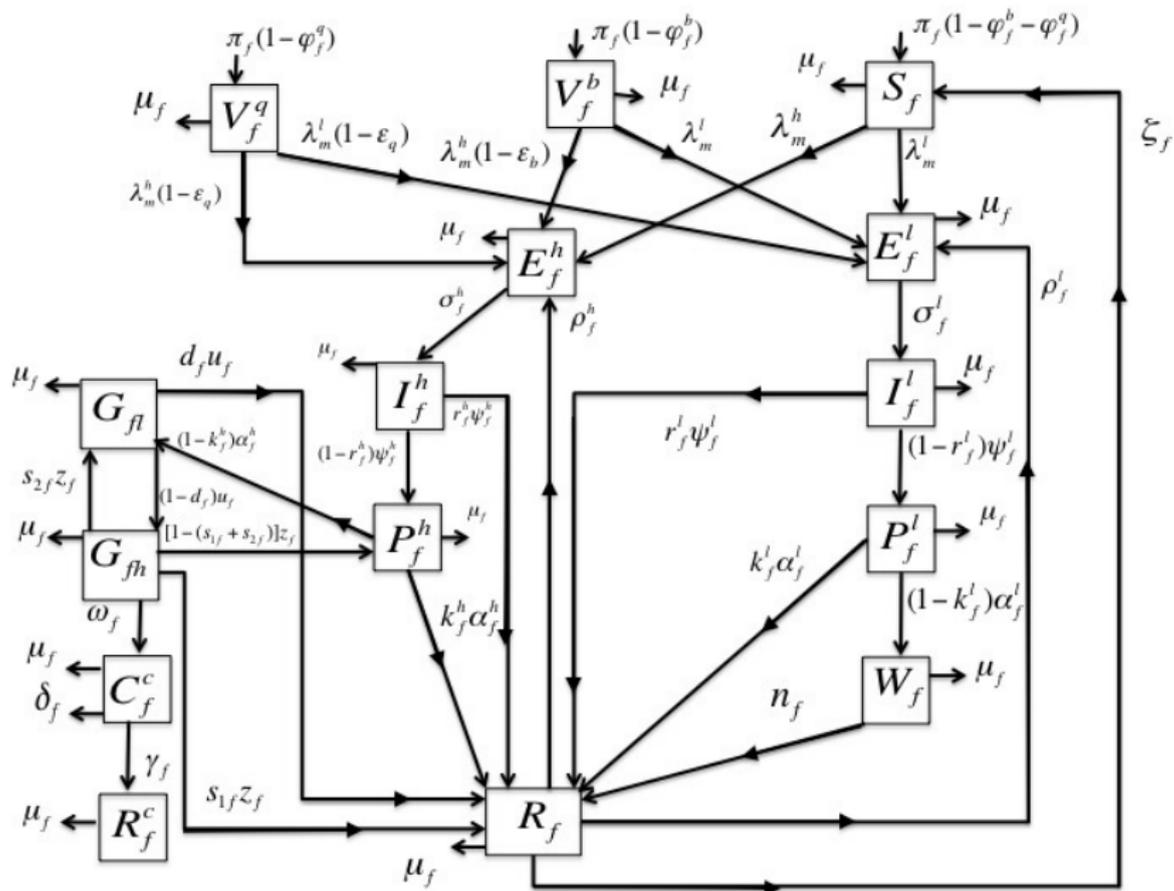


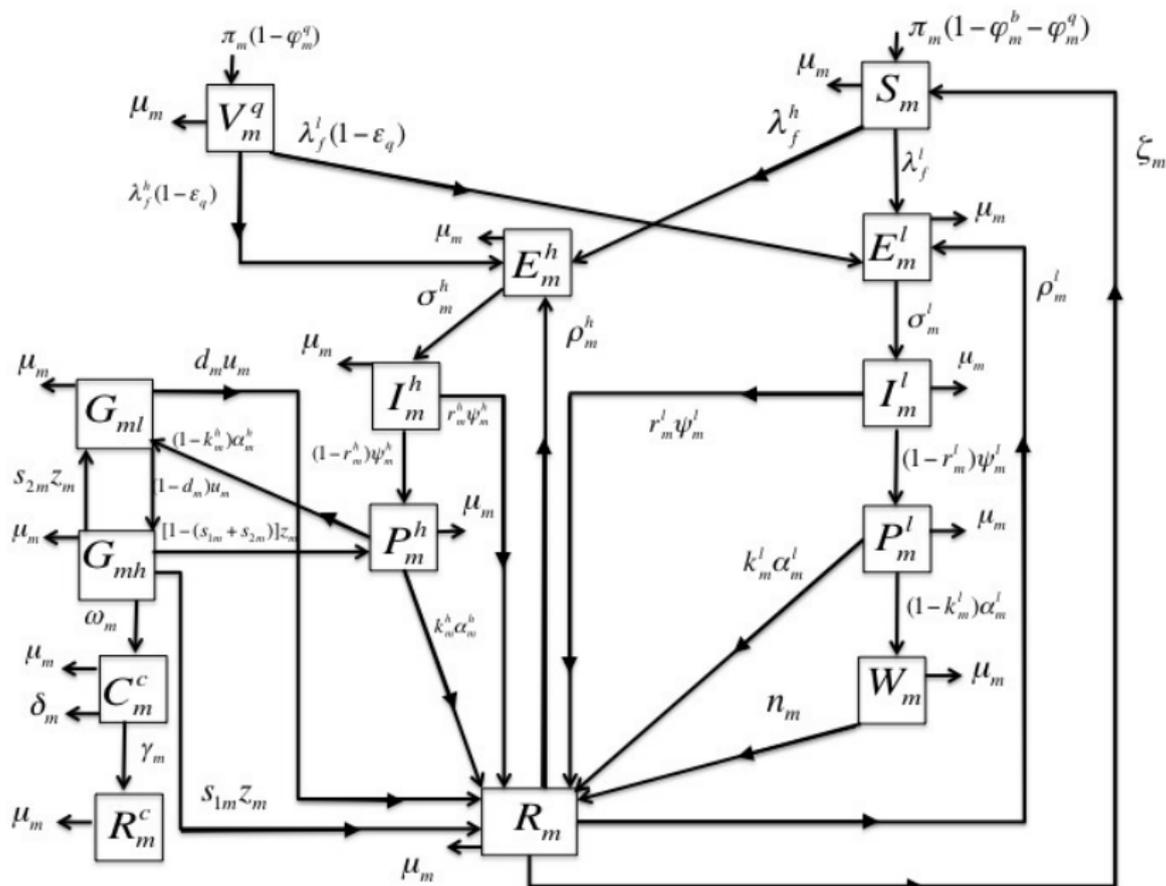


Extended Model

- (i) Incorporate dynamics of low- and high-risk HPV types (risk-structure);
- (ii) Incorporate dynamics of pre-cancerous and genital warts stages in females and males;
- (iii) Assess the community-wide impact of vaccinating males with the *Gardasil* vaccine (recent CDC recommendation).

Resulting model is a system of 29 nonlinear ODEs





$$\mathcal{R}_{fl} = \frac{\beta_m^l c_f \pi_f \mu_m (1 - \varepsilon_v \varphi_f^q) B_1}{\mu_f \pi_m \prod_{i=1}^3 D_i},$$

$$\mathcal{R}_{fh} = \frac{\beta_m^h c_f \pi_f \mu_m [1 - \varepsilon_v (\varphi_f^b + \varphi_f^q)] (Q_1 + Q_2 + Q_3)}{\mu_f \pi_m D_5 D_6 Q_4},$$

$$\mathcal{R}_{ml} = \frac{\beta_f^l c_f (1 - \varepsilon_v \varphi_m^q) B_2}{\prod_{i=1}^3 A_i},$$

$$\mathcal{R}_{mh} = \frac{\beta_f^h c_f (1 - \varepsilon_v \varphi_m^q) (Q_5 + Q_6 + Q_7)}{A_5 A_6 Q_8}.$$

Theorem 7

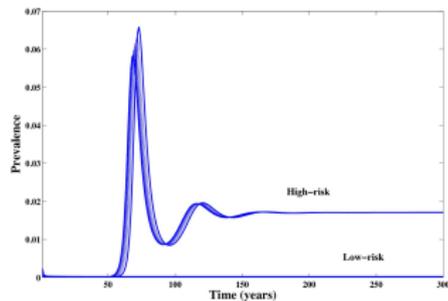
The DFE, \mathcal{E}_0^r , of the extended model is LAS if $\mathcal{R}_0^r < 1$, and unstable if $\mathcal{R}_0^r > 1$.

Theorem 8

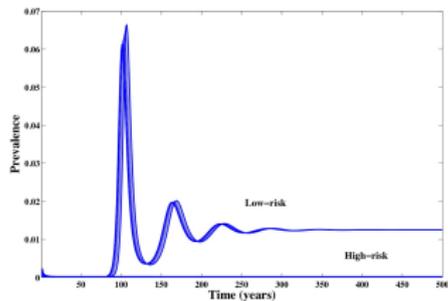
The extended model undergoes backward bifurcation at $\mathcal{R}_0^r = 1$ under a certain condition.

Possible non-trivial equilibria of the extended model: low-risk-only (\mathcal{E}_l) and high-risk-only (\mathcal{E}_h) boundary equilibria; co-existence equilibrium

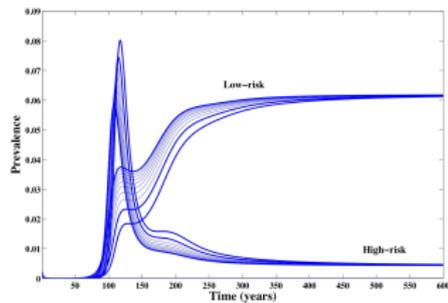
(A) $\mathcal{R}_l < 1 < \mathcal{R}_h$



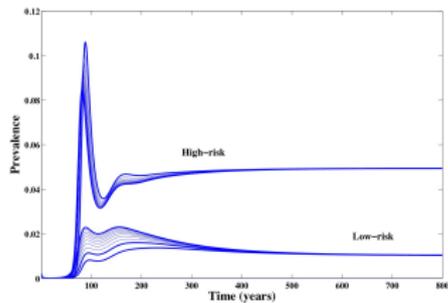
(B) $\mathcal{R}_h < 1 < \mathcal{R}_l$



(C) $\mathcal{R}_l > \mathcal{R}_h > 1$



(D) $\mathcal{R}_h > \mathcal{R}_l > 1$

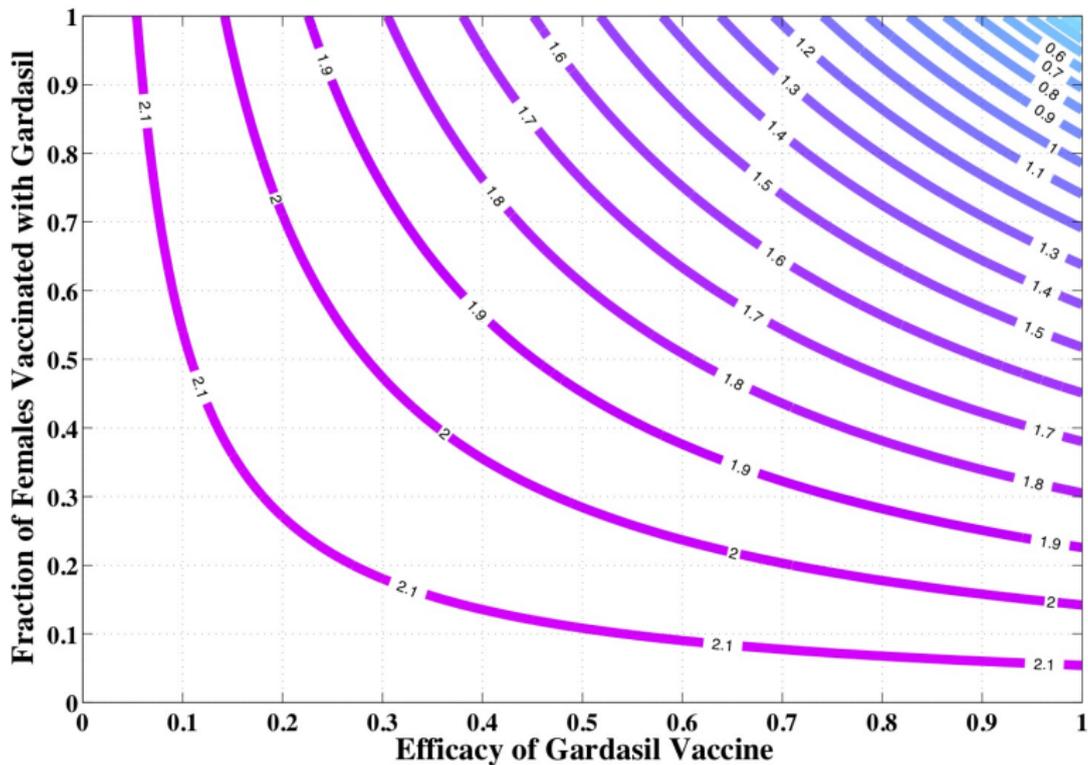


Conjecture 1

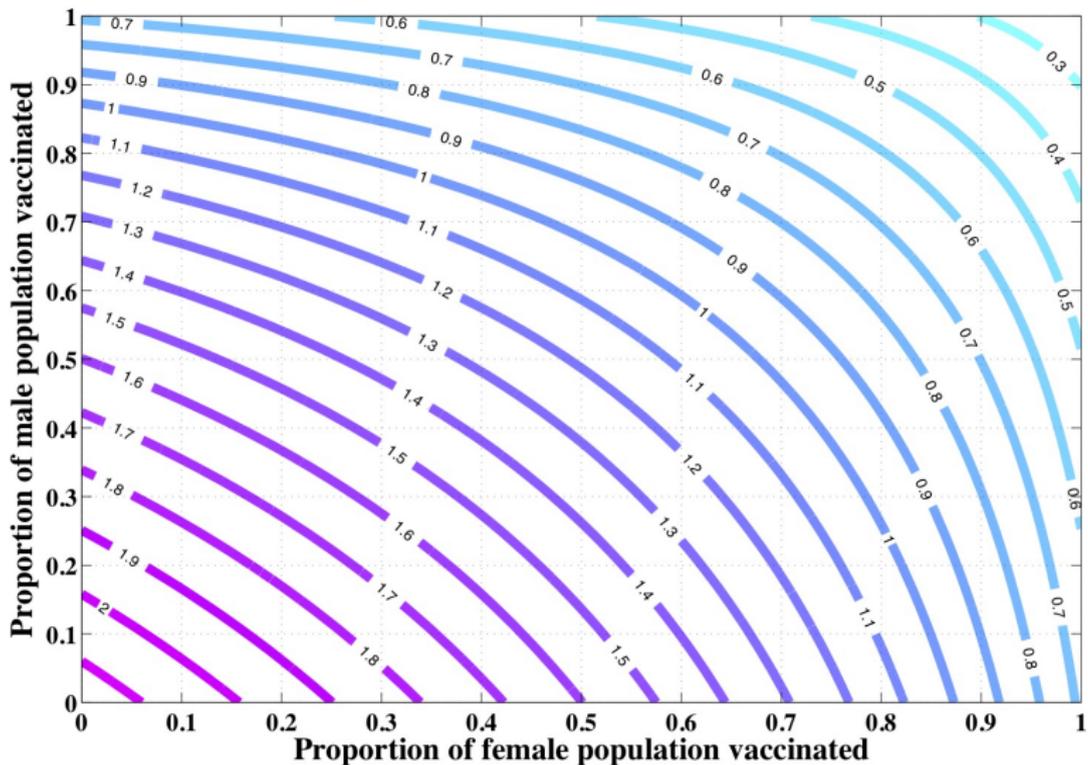
The extended model has at least one stable low-risk-only (high-risk-only) boundary equilibrium, $\mathcal{E}_\ell(\mathcal{E}_h)$, whenever $\mathcal{R}_i < 1 < \mathcal{R}_j$ (with $i, j = \{\ell, h\}$; $i \neq j$). In other words, the risk-structured model (??) undergoes competitive exclusion, with the HPV risk Type j driving out the HPV risk Type i to extinction, whenever $\mathcal{R}_i < 1 < \mathcal{R}_j$.

Conjecture 2

The extended model could have at least one stable co-existence endemic equilibrium, \mathcal{E}_r , whenever $1 < \mathcal{R}_i \leq \mathcal{R}_j$ (with $i, j = \{\ell, h\}$).



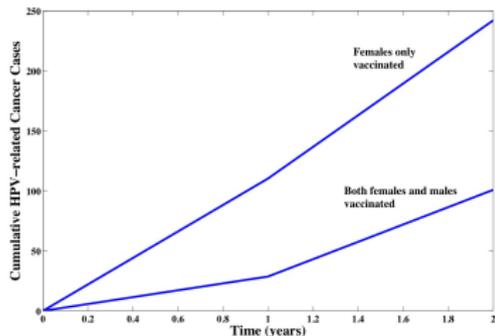
87% vaccine coverage needed to make $\mathcal{R}_{01}^r < 1$



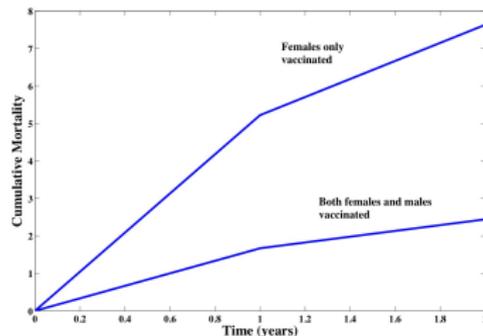
With 70% coverage (females); need 47% coverage in males to make $\mathcal{R}_{01}^r < 1$

Impact of *Gardasil* Vaccine: Females and Males

(A)



(B)



- (i) 250 cumulative cancer cases and 8 cumulative deaths if $\phi_f^q = 0.7$
- (ii) 100 cumulative cancer cases and 2 cumulative deaths if $\phi_f^q = \phi_m^q = 0.7$

Conclusions

- Presence of reinfection-induced backward bifurcation in HPV transmission dynamics;
- The singular use Gardasil for females can lead to effective control of HPV if coverage rate is high enough;
- With the current 70% Gardasil coverage for females, vaccinating 47% of new sexually-active males would lead to effective control of HPV in the community;
- Vaccinating males offers significant public health benefit.

Prospects of effective control of HPV using currently-available vaccines promising

Acknowledgements

Sponsors: NSERC of Canada; Merck Inc., USA.

Collaborators: A. Alsaleh (Graduate Student), E.H. Elbasha (Merck Inc., USA), S. Mahmud (Winnipeg Regional Health Authority), T. Malik (Postdoc), Jody Reimer (former undergraduate research student)