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INSIGHTS FROM EPIDEMIOLOGICAL GAME THEORY INTO GENDER-SPECIFIC VACCINATION AGAINST RUBELLA

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Abstract. Rubella is a highly contagious childhood disease that causes relatively mild symptoms. However, rubella can result in severe congenital defects, known as congenital rubella syndrome (CRS), if transmitted from a mother to a fetus. Consequently, women have higher incentive to vaccinate against rubella than men do. Within the population vaccination reduces transmission but also increases the average age of infection and possibly the risk of CRS among unvaccinated females. To evaluate how the balance among these factors results in optimal coverage of vaccination, we developed a game theoretic age-structured epidemiological model of rubella transmission and vaccination. We found that high levels of vaccination for both genders are most effective in maximizing average utility across the population by decreasing the risk of CRS and reducing transmission of rubella. By contrast, the demands for vaccines driven by self-interest among males and females are 0% and 100% acceptance, respectively, if the cost of vaccination is relatively low. Our results suggest that the rubella vaccination by males that is likely to be achieved on voluntary basis without additional incentives would have been far lower than the population optimum, if rubella vaccine were offered separately instead of combined with measles and mumps vaccination as the MMR vaccine.

1. **Introduction.** Rubella, commonly known as German measles, is a relatively mild infection with symptoms including rash and low-grade fever although many cases can be subclinical [1]. However, the infection in women during the first trimester of pregnancy can cause congenital defects in up to 85% of fetuses, a condition known as congenital rubella syndrome (CRS) [2], with declining percentages through the second trimester [3]. The major defects of CRS include deafness, cataracts, congenital heart diseases, microcephaly, and mental retardation [4]. It is estimated that more than 100,000 cases of CRS occur annually worldwide [5]. The

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largest numbers of rubella cases are reported from Belarus, Bulgaria, Kazakhstan, Poland, Ukraine, Argentina, Brazil, Mexico, and Venezuela [5].

Vaccination is the primary public health measure for reducing the transmission of rubella and has been implemented using different approaches in different countries. The most common strategy of rubella vaccination is based on a combined vaccine containing antigens against measles, mumps, and rubella, known as the MMR vaccine [1]. Another strategy of rubella vaccination involves using a single-antigen vaccine against rubella. In the UK, although the majority of children (89%) born in 2000-2002 were immunized with MMR, 5% of children received the single antigen vaccine [6]. In Japan, the MMR vaccine was replaced with the single-antigen rubella vaccine in 1994 due to the putative association of the MMR vaccine with a number of conditions, including autism, inflammatory bowel disease, and diabetes [7]. Since this shift in policy in Japan, the coverage of rubella vaccination has been relatively low [2]. Consequently, the rubella vaccination coverage has dropped dramatically especially for adolescents [2]. This raises concern over the likelihood of rubella epidemics and the occurrence of CRS in Japan if this trend continues [2].

Rubella vaccination provides direct protection against infection and reduces transmission in the population. However, vaccination also increases the average age of rubella infect, leading to a greater proportion (although not necessarily number) of rubella cases resulting in CRS. In addition, the benefits of vaccination are mitigated by costs and adverse effects of the vaccine. From a game-theoretic perspective, an individual adopts a strategy that will maximize personal utility taking into account that their probability of infection is determined by disease prevalence, which is in turn governed by the vaccination decisions made by the rest of the population. At the Nash equilibrium, no player can increase their individual utility by changing their own strategy. We define individual decisions of vaccination at the Nash equilibrium as the Nash strategy. The utilitarian vaccination strategy is defined as that which maximizes the total utility of the vaccination for the population by the balance between the benefits and costs of vaccination. Therefore, the utility calculation from the utilitarian perspective also includes the indirect benefits and costs of the vaccine to the population.

For other diseases, including influenza, smallpox, and HPV, it has previously been found that the vaccination level determined by Nash strategy is lower than that by the utilitarian strategy, since unvaccinated individuals can benefit from reduced transmission in a population [8][9][10][11][12][13][14]. However, we demonstrate that this generalization does not apply to the case of female rubella vaccination due to increasing disease severity with age and to the potentially conflicting incentives between genders. When men are vaccinated, women receive indirect protection against rubella infection by herd immunity as well as the risk of CRS, because vaccination increases the average age of infection. However men do not receive as much benefit as women by vaccinating themselves, because they do not bear the risk of CRS.

We present the first application of epidemiological game theoretic modeling to rubella vaccination. We use this approach to analyze the relationship between Nash and utilitarian vaccination strategies for rubella infection with severity that depends on both gender and age. We evaluate the impact of such discordance of incentives on vaccination and the resulting morbidity of rubella infection using epidemiological game theoretic analysis of individual versus population incentives. Our results highlight that the Nash level of male vaccination is much lower than the

utilitarian strategy, whereas the Nash and utilitarian strategies of female vaccination are in alignment at complete coverage across the population, when vaccination costs are relatively low. These results suggest that additional incentives would be required to raise male vaccination level close to the utilitarian strategy, if rubella vaccine is offered in a form of single antigen vaccine.

2. **Methods.**

2.1. **Epidemiological population model.** We developed a model (Eqs. (1)-(9)) of rubella transmission and vaccination, subdividing the population into juvenile (0-15 years, denoted by subscripts $1, \ldots, m$) and adult (over 15 years, denoted by subscript a) age classes. We also assume that juvenile class is subdivided into m age groups with equal age interval, $15/m$ years. Within each age class, individuals may be susceptible (S), infected (I), or immune (R). The latency period is ignored in this model, since our goal is to calculate infection cumulative probabilities among juveniles and adults using this population model, and incorporate them into utility calculation. Aging process is modeled through transferring individuals from the j^{th} age group to the $j+1^{th}$ ($j = 1, \ldots m$) age group at rate $m\theta$. In order to model the aging process properly, we use "linear chain trick," i.e. a gamma distribution of stage duration, and our parameter m controls the shape of the gamma distribution [15]. Specifically, when $m = 1$, we obtain an exponential distribution of stage duration, and as $m \to \infty$, the gamma approaches a single peak (a delta distribution) [15]. The two extremes are equivalent to assuming that individuals mature out of a stage either at a fixed rate or after a fixed period. Thus, changing m allows us to manipulate the variance of maturation times. We also assume that individuals die at rate μ_a for adults. Children are born and enter the model at a constant rate per capita, $\theta\mu_a/(\theta + \mu_a)$, such that the population size is asymptotically constant. We also assumed that the sizes of male and female population are equal.

We denote the average vaccination coverage of males and females, and the overall average by $\bar{\pi}_m$, $\bar{\pi}_f$, and $\bar{\pi}$ where $\bar{\pi} = 0.5(\bar{\pi}_m + \bar{\pi}_f)$. We defined p as a probability of vaccine failure and assumed $p = 0.05$ as a baseline value, given that the current rubella vaccine has 95% efficacy [4]. If successfully vaccinated or recovered from natural infection, individuals were assumed to have the lifelong immunity. Thus a proportion, $\bar{\pi}(1-p)$, of newly born children was assumed to be successfully vaccinated and enter the recovered class, and the rest, $1 - \bar{\pi}(1-p)$, enter a susceptible class. Given these assumptions, the epidemiological model of rubella transmission can be expressed by the following deterministic system of ordinary differential equations:

$$
\begin{aligned}
S_1' &= \{1 - \bar{\pi}(1-p)\}\Omega - (\lambda_1 + m\theta)S_1, && (1)\\
I_1' &= \lambda_1 S_1 - (\gamma + m\theta)I_1, && (2)\\
R_1' &= \bar{\pi}(1-p)\Omega + \gamma I_1 - m\theta R_1, && (3)\\
S_j' &= m\theta S_{j-1} - (\lambda_j + m\theta)S_j, \quad (j = 2, \ldots, m), && (4)\\
I_j' &= m\theta I_{j-1} + \lambda_j S_j - (\gamma + m\theta)I_j, \quad (j = 2, \ldots, m), && (5)\\
R_j' &= m\theta R_{j-1} + \gamma I_j - m\theta R_j, \quad (j = 2, \ldots, m), && (6)\\
S_a' &= m\theta S_m - (\lambda_a + \mu_a)S_a, && (7)\\
I_a' &= m\theta I_m + \lambda_a S_a - (\gamma + \mu_a)I_a, && (8)\\
R_a' &= m\theta R_m + \gamma I_a - \mu_a R_a && (9)
\end{aligned}
$$

where the force of infection is given by

$$\lambda_1 = \lambda_2 = \cdots = \lambda_m = \frac{\beta_1}{N}\Sigma_{j=1}^{m} I_j + \frac{\beta_2}{N} I_a,$$
$$\lambda_a = \frac{\beta_2}{N}(\Sigma_{j=1}^{m} I_j + I_a)$$

and $N = \Sigma_{j=1}^{m}(S_j + I_j + R_j) + S_a + I_a + R_a := K$ is the population size. In addition, we denote the juvenile and adult populations by $N_j = S_j + I_j + R_j := K_j$ $(j = 1, \ldots, m)$ and $N_a = S_a + I_a + R_a := K_a$, respectively. The sizes of juvenile and adult populations are asymptotically constant and hence, without loss of generality [16], we assume that the juvenile and adult populations are $K_j = \frac{\Omega}{m\theta}$ $(j = 1, \ldots, m)$ and $K_a = \frac{\Omega}{\mu_a}$, respectively, where $K = (\Sigma_{j=1}^{m} K_j) + K_a = \frac{\Omega(\theta+\mu_a)}{\theta\mu_a}$.

Eqs.(1)-(9) are rescaled by the introduction of the following variables: $i_j = I_j/K$, $r_j = R_j/K$ $(j = 1, \ldots, m)$, $i_a = I_a/K$, $r_a = R_a/K$ and $\Lambda = \Omega/K$:

$$i_1' = \lambda_1\left(\frac{\mu_a}{m(\theta+\mu_a)} - i_1 - r_1\right) - (\gamma + m\theta)i_1, \tag{10}$$
$$r_2' = \bar{\pi}(1-p)\Lambda + \gamma i_1 - m\theta r_1, \tag{11}$$
$$i_j' = m\theta i_{j-1} + \lambda_j\left(\frac{\mu_a}{m(\theta+\mu_a)} - i_j - r_j\right) - (\gamma + m\theta)i_j, \quad (j = 2, \ldots, m), \tag{12}$$
$$r_j' = m\theta r_{j-1} + \gamma i_j - m\theta r_j, \quad (j = 2, \ldots, m), \tag{13}$$
$$i_a' = m\theta i_m + \lambda_a\left(\frac{\theta}{\theta+\mu_a} - i_a - r_a\right) - (\gamma + \mu_a)i_a, \tag{14}$$
$$r_a' = m\theta r_m + \gamma i_a - \mu_a r_a \tag{15}$$

where the force of infection is given by

$$\lambda_1 = \lambda_2 = \cdots = \lambda_m = \beta_1(\Sigma_{j=1}^{m} i_j) + \beta_2 i_a,$$
$$\lambda_a = \beta_2(\Sigma_{j=1}^{m} i_j) + \beta_2 i_a.$$

In our model, we assumed that children have more contacts with other children than they do with adults or than adults have with each other. Therefore we used age-dependent transmission parameters of rubella, β_1 and β_2, for child-child interactions, and for all other interactions, respectively. The baseline parameters for β_1 and β_2 were parameterized to yield the approximately 80% and 97% cumulative probabilities of contracting rubella in the absence of vaccination, consistent with the prevaccination era during childhood and adulthood, respectively [17][18]. From our model, it was calculated that cumulative probabilities of contracting rubella in the absence of vaccination during childhood and adulthood are $1 - (m\theta)^m \prod_{j=1}^{m}(\frac{1}{\lambda_j^* + m\theta})$ and $(m\theta)^m(\frac{\mu_a}{\lambda_a^* + \mu_a}) \prod_{j=1}^{m}(\frac{1}{\lambda_j^* + m\theta})$, respectively. Here, λ_j^* and λ_a^* are calculated based on the prevalence in childhood and adulthood at endemic nonuniform steady state distributions. Using these formulae, β_1 and β_2 were estimated. Also, the rubella prevalence in childhood and adulthood were used to estimate cost of rubella infections in a prevaccination era. The duration of infection was assumed to be 11 days on average [19][20].

In the absence of vaccination, the basic reproduction ratio (R_0) when $m = 1$ is defined by

$$\max\left\{\frac{\mu_a}{\theta+\mu_a}\left(\frac{\beta_1}{\gamma+\theta} + \frac{\theta\beta_2}{(\gamma+\theta)(\gamma+\mu_a)}\right), \frac{\theta}{\theta+\mu_a}\left(\frac{\beta_2}{\gamma+\mu_a}\right)\right\}. \tag{16}$$

With a baseline parameter set and $m = 5$, R_0 is estimated at 5.3, which is consistent with the known basic reproductive ratio for rubella in the prevaccination era [19]. Unless otherwise specified, we used the following as a baseline parameter set, scaled to the population size, for simulations: $\mu_a = 1/65$ year^{-1}, $m = 5$, $\theta = 1/15$ year^{-1}, $\beta_1 = 368$ year^{-1}, $\beta_2 = 148$ year^{-1}, $\gamma = 30$ year^{-1}, and $p = 0.05$.

2.2. **Utility calculation.** To determine the average individual utility associated with vaccination strategy, we incorporated into the utility calculations the costs associated with vaccines including possible adverse effects, infection, and CRS. Men and women were assumed to contract and spread rubella equally, and are thus grouped together in the epidemiological model. However, the costs incurred during infection are greater for females than for males due to the risk of CRS, as are reflected in the utilities calculation. The model was parameterized from epidemiological and economic data (Table 1) to determine costs and benefits associated with a range of vaccination probability for individuals of each gender, which amounts to vaccination coverage for the population.

In our epidemiological model of rubella vaccination, vaccination behavior is modeled at the scales of both the population and the individual. The vaccination state (n) at the population scale is described by the equation, $dn/dt = G(n, \bar{\pi})$, where G is a nonlinear function vector (Eqs. (1)-(9)). We also assume that $n(t)$ is the distribution of individuals in each of six possible life-history states. For Eqs. (1)-(9) with $\bar{\pi} = 0$ (i.e. no vaccination), there is a non-uniform endemic steady state distribution of the form:

$$n^* = [s_1^*, i_1^*, r_1^*, s_2^*, i_2^*, r_2^*, \ldots, s_m^*, i_m^*, r_m^*, s_a^*, i_a^*, r_a^*]. \tag{17}$$

An individual-scale model can be expressed as a Markov process with transition rates derived from the population-scale model, Eqs. (1)-(9), under the assumption that the population has reached the endemic steady state distributions, n^*. Therefore, the state of an individual is described by $dx/dt = Q(n, \pi_g)x$, where Q is the transition-rate matrix of the life-history process and π_g is an individual's vaccination probability. The gender is denoted by subscript g ($g = m$ for males and $g = f$ for females). Here we define $x(t)$ as an individual's probability density over the life-history state space with a vaccination strategy, π_g, at time t. The transition rates between life-history states are governed by:

$$Q(n^*, \pi_g) = \begin{pmatrix} A_1 & 0 & 0 & 0 & 0 & 0 \\ B & A_2 & 0 & 0 & 0 & 0 \\ 0 & B & A_3 & 0 & 0 & 0 \\ & & \ddots & \ddots & & \\ 0 & 0 & \ddots & \ddots & 0 & 0 \\ 0 & 0 & 0 & B & A_m & 0 \\ 0 & 0 & 0 & 0 & B & A_a \end{pmatrix}, \tag{18}$$

where

$$A_1 = A_2 = \cdots = A_m = \begin{pmatrix} -\lambda_1^* - m\theta & 0 & 0 \\ \lambda_1^* & \gamma - m\theta & 0 \\ 0 & \gamma & -m\theta \end{pmatrix},$$

$$A_a = \begin{pmatrix} -\lambda_a^* - \mu_a & 0 & 0 \\ \lambda_a^* & \gamma - \mu_a & 0 \\ 0 & \gamma & -\mu_a \end{pmatrix}, \text{and } B = \begin{pmatrix} m\theta & 0 & 0 \\ 0 & m\theta & 0 \\ 0 & 0 & m\theta \end{pmatrix}.$$

The individual's risk of contracting disease is dependent on both population vaccination coverage, $\bar{\pi}$, via its impact on disease prevalence and an individual's

vaccination probability, π_g. All individuals enter the population as either a susceptible or an immune juvenile depending on their vaccination strategy (π_g), so an initial state of an individual is given by:

$$x(0) = [1 - \pi_g(1-p), 0, \pi_g(1-p), \rho_1, \rho_2, \cdots, \rho_m]^T \tag{19}$$

where $\rho_1 = \rho_2 = \cdots = \rho_m = [0, 0, 0]$.

The utility is defined as an expected payoff of a chosen vaccination strategy, calculated based on the disease prevalence, infection costs, and the vaccination costs. The vaccination cost to an individual occurs instantaneously upon vaccination. In contrast, the infection costs accumulate as individuals reside in the infected state. The expected cost of rubella infection in an adult woman is \$4374, whereas rubella infections in children and adult men are assumed to carry relatively small cost, \$42. The average costs of the rubella are calculated based on reported probabilities of complications and treatment costs (Table 1).

We define the average utility for residence in each state due to vaccination (ω_v) and infection for males ($\omega_{i,m}$) or for females ($\omega_{i,f}$). We also define the cost of infection among male (female) juveniles, the cost of infection among adult males (females) and the cost of vaccination by $c_{j,m,i}(c_{j,f,i})$, $c_{a,m,i}$ $(c_{a,f,i})$ and c_v, respectively. Using these definitions, we formulate the state-dependent utilities as follows:

$$\omega_{i,m} = [\eta_1, \eta_2, \cdots, \eta_m, \eta_{m+1}], \tag{20}$$

$$\omega_{i,f} = [\xi_1, \xi_2, \cdots, \xi_m, \xi_{m+1}], \tag{21}$$

$$\text{and } \omega_v = [0, 0, \frac{-c_v}{1-p}, \rho_1, \rho_2, \cdots, \rho_m] \tag{22}$$

where $\eta_1 = \eta_2 = \cdots = \eta_m = [0, -c_{j,m,i}, 0]$, $\eta_{m+1} = [0, -c_{a,m,i}, 0]$, $\xi_1 = \xi_2 = \cdots = \xi_m = [0, -c_{j,f,i}, 0]$, and $\xi_{m+1} = [0, -c_{a,f,i}, 0]$.

Using the infection probabilities from the epidemiological model (Eqs. (1)-(9)) and average utility, we can calculate the expected individual cost for both genders depending on his or her vaccine strategy at each level of population vaccine coverage. Under the assumptions that the population has reached its endemic steady state distribution and that the population size is asymptotically constant, we can calculate the expected utility of an individual with vaccination strategy π_g as follows:

$$U_g(\pi_g; \bar{\pi}) = \omega_v x(0) + \int_0^\infty e^{-\delta t} \omega_{i,g} x(t) dt \tag{23}$$

where $g = \begin{cases} m & \text{for males,} \\ f & \text{for females.} \end{cases}$

The discount rate δ (3% per year) is used to depreciate future values relative to current returns [21]. The expected utility of an individual with vaccination strategy π_g can be solved explicitly in terms of the transition matrix, $Q^* = Q(n^*(\bar{\pi}); \pi_g)$, and the initial state, $x(0)$:

$$U_g(\pi_g; \bar{\pi}) = [\omega_v + \omega_{i,g}(\delta I - Q^*)^{-1}] x(0) \tag{24}$$

where $g = m$ for males and $g = f$ for females, provided the Perron-Frobenius eigenvalue of Q^* is less than δ [22]. Similarly, the average utility is defined as the total societal cost per individual, i.e. $0.5(U_m(\pi_m; \bar{\pi}) + U_f(\pi_f; \bar{\pi}))$. The utilitarian strategy is calculated by maximizing the expected average utility [8][12].

Using endemic nonuniform steady state distributions, we can further calculate the utility of the vaccination strategy of males, π_m, and females, π_f, in a population with an average vaccination rate, $\bar{\pi}$, as follows:

$$U_g(\pi_g;\bar{\pi}) = -\pi_g c_v - (1-(1-p)\pi_g)\Phi_g(\bar{\pi}) \tag{25}$$

where

$$\begin{aligned}\Phi_g(\bar{\pi}) \quad = \quad & \frac{c_{j,g,i}}{(\lambda_1^* + m\theta + \delta)(\gamma + m\theta + \delta)} \Sigma_{k=1}^{m} (m\theta)^{k-1} \\ & \left(\Sigma_{n=1}^{k} \frac{\lambda_n^*}{(\gamma + m\theta + \delta)^{k-n} \Delta(n)} \right) \\ & + \frac{c_{a,g,i}(m\theta)^m}{(\lambda_1^* + m\theta + \delta)(\gamma + \mu_a + \delta)} \Sigma_{k=1}^{m} \frac{\lambda_k^*}{(\gamma + m\theta + \delta)^{m+1-k} \Delta(k)} \\ & + \frac{c_{a,g,i}(m\theta)^m \lambda_a^*}{(\lambda_1^* + m\theta + \delta)(\gamma + \mu_a + \delta)(\lambda_a^* + m\theta + \delta)\Delta(m)}\end{aligned}$$

for $g = \begin{cases} m & \text{for males,} \\ f & \text{for females.} \end{cases}$ Here we define $\Delta(k)$ as

$$\Delta(k) = \begin{cases} 1 & \text{for } k = 1, \\ \prod_{x=2}^{k} (\lambda_x^* + m\theta + \delta) & \text{for } k \geq 2. \end{cases}$$

The first term of Eq.(25) implies the cost of vaccination, and the second terms signify the costs associated with infections at all age groups. The Nash strategy in our model exists as a pair of individual vaccination levels for males and females, i.e. $(\bar{\pi}_m, \bar{\pi}_f)$. If an individual follows the Nash strategy, one experiences higher utility against alternative strategies, thus

$$U_m(\bar{\pi}_m;\bar{\pi}) \geq U_m(\pi_m;\bar{\pi}) \text{ and } U_f(\bar{\pi}_f;\bar{\pi}) \geq U_f(\pi_f;\bar{\pi}) \tag{26}$$

for all sets of strategies, $(\pi_m, \pi_f) \neq (\bar{\pi}_m, \bar{\pi}_f)$. Using Eq.(25), we derived the following inequality that is equivalent to Eq.(26), in order to identify the Nash strategy:

$$\bar{\pi_g}[-c_v + (1-p)\dot{\Phi}_g(\bar{\pi})] \geq \pi_g[-c_v + (1-p)\Phi_g(\bar{\pi})] \tag{27}$$

for all sets of strategies, $\pi_g \neq \bar{\pi}_g$, where $g = m$ (or f) for males (or females). Thus, $(1-p)\Phi_g$ signifies the individual cost-saving from averted infections by vaccination. Furthermore, since the benefit of vaccination is greater for females than for males due to cost-savings from averted CRS, it follows that $\Phi_m(\bar{\pi}) \leq \Phi_f(\bar{\pi})$ for all $\bar{\pi} \in [0,1]$, which we utilize to show the existence of Nash strategy.

3. **Results.** In the prevaccination era, the probabilities of rubella infection are 80% and 18% in childhood and in adulthood, respectively (Figure 1). However, as vaccine coverage level increases, the reduction in infection prevalence among susceptible juveniles is more dramatic than among susceptible adults, because the impact of vaccination is more direct and immediate to juveniles than to adults. In fact, at intermediate levels of coverage, the probability of rubella infections among adults increases with coverage level (Figure 1). This indicates that vaccination presents negative externalities by raising the average age of infection when vaccine coverage is not sufficiently high. However, when 87% of the population is vaccinated, the herd immunity threshold is achieved and transmission is terminated. For simulations, we used the following as a baseline parameter set: $\mu_a = 1/65$ year^{-1}, $m = 5$, $\theta = 1/15$

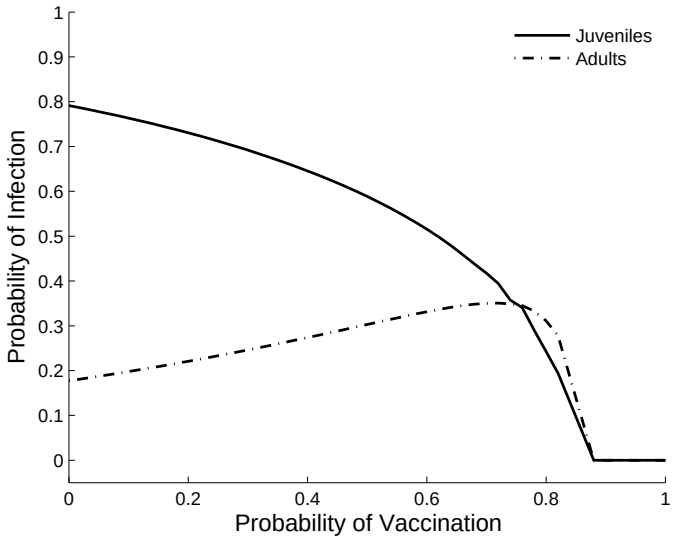


FIGURE 1. Probability of infection for unvaccinated individuals

year^{-1}, $\beta_1 = 368$ year^{-1}, $\beta_2 = 148$ year^{-1}, $\gamma = 30$ year^{-1}, and $p = 0.05$. This parameter set results in a basic reproductive ratio, estimated at 5.3.

Male vaccination further reduces the number of female adult infections when females are also vaccinated. Nonetheless, when the female vaccination level is relatively low, male vaccination presents negative vaccine externalities by raising the average age of infections and increases the risk of adult infection (as well as CRS) among females (Figure 2). Thus, when few females are vaccinated, male vaccination raises the total cost to a population by increasing the incidence of CRS. Fortunately, such male-dominated vaccination against rubella is an unlikely scenario as it contradicts the Nash strategies. The relative payoff of a vaccinated male compared to a male who rejected vaccination, $\Theta_m(\bar{\pi}) = [-c_v + (1-p)\Phi_m(\bar{\pi})]$, is nonpositive for all population vaccination coverage, $\bar{\pi} \in [0, 1]$ (Figure 3). This implies that men can expect little individual benefit from vaccination. Therefore, the male Nash strategy of rubella vaccination is 0% at all ranges of vaccine costs, because it will never be individually worthwhile for males to vaccinate (Figure 4). In contrast, the relative payoff of vaccination to a female, $\Theta_f(\bar{\pi}) = [-c_v + (1-p)\Phi_f(\bar{\pi})]$, is positive for low vaccination costs but increases initially and decreases eventually, as coverage levels increases (Figure 3). For all nonzero vaccination costs, the relative payoff for males is negative, making the Nash strategy for males to be 0% acceptance. When the vaccination costs are sufficiently low, i.e. up to \$355, the relative payoff for females is positive when $\bar{\pi} = 0.5$, making the Nash strategy for females to be 100%. For vaccine costs over \$355, both $\Theta_m(\bar{\pi})$ and $\Theta_f(\bar{\pi})$ are negative, thus the Nash strategies for males and females are both 0% acceptance. The existence of Nash strategy is examined using Eq.(27) and presented in detail using a baseline parameter set (Table 2).

At low vaccination costs, females can increase their utilities by accepting vaccination, although the benefit of vaccination for females decreases and erodes once

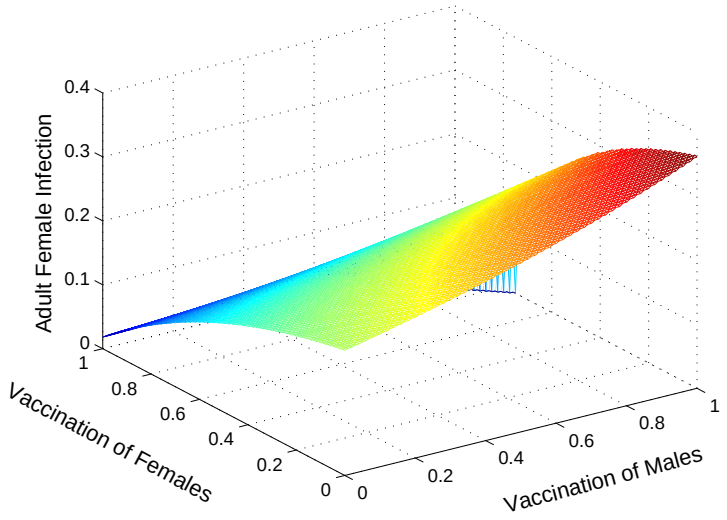
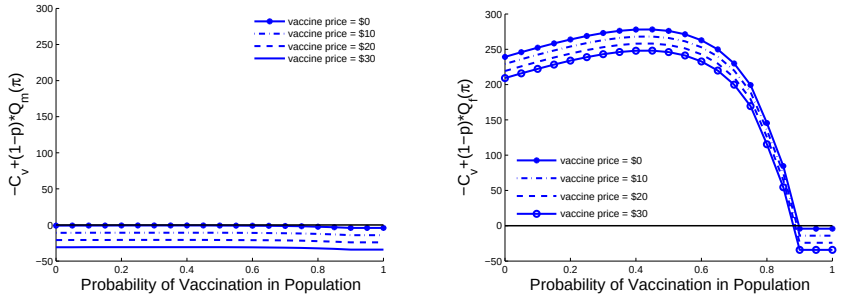


FIGURE 2. Probability of adult female infections per lifespan as female and male vaccine coverages are varied



(a) (b)

FIGURE 3. The expected cost saving, $-c_v + (1-p)\Phi_g(\bar{\pi})$, of a vaccinated individual is presented with varying probability of background vaccination. In general, females (b) are expected to benefit from vaccination more than males (a) since females can avoid the risk of CRS when vaccinated.

vaccination coverage becomes sufficiently high (Figure 3b). Therefore, when the costs of vaccination are under \$355, the female Nash strategy of rubella vaccination is 100% acceptance (Figure 4). For a range of vaccine cost values (\$251 − \$355), the Nash level of female vaccination will be 100%, whereas the utilitarian will be 0%. For vaccines priced over \$355, the Nash vaccination levels of both males and females are 0%. Thus, if the rubella vaccination program were voluntary and were offered as a single antigen vaccine at a price exceeding \$355, it would be difficult to motivate either gender to get vaccinated without offering additional incentives. In

contrast, for vaccination costs under \$15, the utilitarian strategy will be 100% and $74-76\%$ vaccination for females and males, respectively (Figure 4). For vaccination costs over \$15, male vaccination levels according to the utilitarian strategy start to decrease dramatically and become zero, whereas the utilitarian vaccination level for females is 100% for vaccination costs below \$251.

When mass vaccination is in effect, a reproductive ratio is reduced accordingly; thus, we carry out simulations with a lower R_0 in order to reflect reduced transmission due to vaccination. It is shown that both Nash strategy and utilitarian optimum decreases with lower basic reproductive ratio (Figure 5). It is estimated that when $R_0 = 3$, female Nash strategy of rubella vaccination is 100% acceptance when the costs of vaccination are under \$126. Also, for vaccination costs under \$8, the utilitarian strategy will be 100% and 48% vaccination for females and males, respectively (Figure 5). The female Nash strategy of rubella vaccination is 100% acceptance for vaccination costs up to \$32.

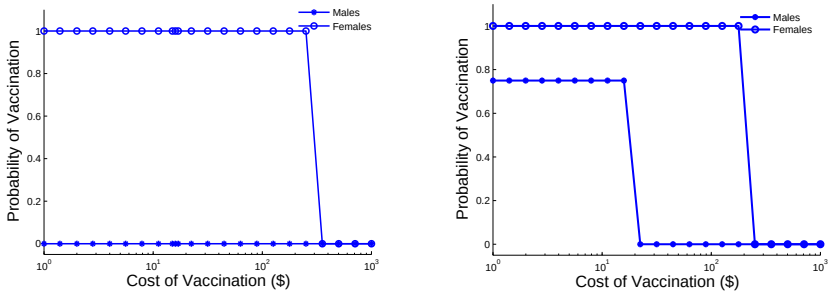


FIGURE 4. Nash (A) and Utilitarian (B) strategies for various vaccination costs when $R_0 = 5.3$ and the baseline parameter set used

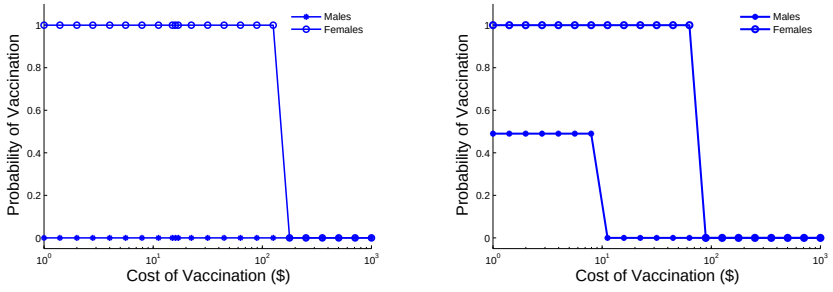


FIGURE 5. Nash (A) and Utilitarian (B) strategies for various vaccination costs when $R_0 = 3$ and the baseline parameter set used

4. **Discussion.** Rubella provides a prime example of a disease for which the benefits of vaccination differ by gender, resulting in conflicting incentives to vaccinate for men and women. To evaluate optimal coverage of vaccination for each gender and for the population, we developed an epidemiological game-theoretic model of rubella transmission. We determined how conflicting incentives may widen the discrepancy between Nash and utilitarian vaccination levels when disease severity increases with age and differs between men and women.

Rubella vaccination provides direct protection against infection with vaccinated individuals, as well as the positive externality of reduced transmission to unvaccinated individuals, which has an impact on the population beyond the individual. It has been previously found that routine vaccination programs increase the mean age at infection, and therefore increase the natural period of endemic dynamics [23]. For a seasonally forced infection, this may therefore lead to a change from regular annual epidemics to more complex patterns of disease incidence [23]. Our mode did not include the seasonality of rubella transmission, however this assumption suffices for the scope of our work, because we aim to estimate probability of infection during childhood and adulthood per lifetime from our population model. We found that the impact of this externality on the burden of disease is highly dependent on the extent of vaccination coverage. In general, at low vaccination coverage, additional vaccination is likely to increase the disease prevalence among adults, although it decreases the probability of juvenile infection. Furthermore, at low vaccine coverage among females, male vaccination raises the average age of infections and thus increases the risk of adult infection (as well as CRS) among females, causing negative vaccine externalities. Conversely, at high vaccination coverage among both genders, immunity is already widespread, so further vaccination will increase the level of seronegativity, reducing rubella prevalence to zero.

We found that the beneficial and detrimental outcomes of rubella vaccination generate conflicts between the Nash strategy for males and that for females, as the main impact of rubella vaccination is to prevent CRS. Our analysis showed that the Nash strategy is to vaccinate all females and no males. However, vaccinating exclusively women leaves those females for whom the vaccine failed unprotected from the risk of CRS. Therefore, this Nash strategy contrasts with the utilitarian strategy, which includes both males and females, although the utilitarian vaccination level for men is lower than for women. That is, when the vaccine is relatively inexpensive, the utilitarian strategy is to vaccinate all women and 75% of males, driving the force of infection to near zero. This indicates that the discrepancy between the Nash strategy and the utilitarian strategy is larger for males than for females. Thus, achieving a utilitarian vaccination level that includes the vaccination of men necessitates the provision of additional incentives beyond individual protection against rubella, given that there is little incentive for men to vaccinate. The utilitarian strategy highlights the importance of ensuring sufficiently high coverage levels in order to prevent a paradoxical increase in CRS when rubella vaccination is introduced in developing countries.

Our study predicts how vaccine price could affect the vaccine demand by both males and females. Increasing vaccination costs has a greater impact on individuals than on the population, because the positive externality of reduced transmission comes into play when optimizing the strategy for the population at greater extent than for the individual. If vaccination is priced below $355, benefit from vaccination is greater than its cost for females but not for males. In general, men need additional

incentives for vaccination across a range of vaccine costs, whereas women do not need incentives to achieve utilitarian optimum. In the United States, vaccinating both males and females against rubella is achieved by requiring MMR vaccination to attend school. Furthermore, by combining three vaccines in the standard vaccine schedule, males are provided additional incentives to get vaccinated against rubella. In the U.S., rubella vaccination was introduced in 1969 and the initial strategy was to vaccinate infants in order to eradicate the disease by abolishing its reservoir [3]. Therefore, pregnant women were still exposed to rubella, and the CRS incidence did not decrease sufficiently. Consequently, the rubella vaccination strategies in the U.S. were revised in the 1980s in order to include universal vaccination of infants of both genders as well as targeted vaccination of adolescent girls and adult women [3][24]. Since new vaccine strategies have been implemented, rubella is no longer endemic in the United States, and the number of children born with CRS has fallen from $20,000$ in 1964 to 6 in 2000 [4][25].

In contrast to the policy in the US, the Nash strategy corresponds to the vaccination strategy used by Japan, where single antigen rubella vaccines are recommended instead of MMR vaccines. Since this shift in policy in Japan, the coverage of rubella vaccination among adolescents has dropped dramatically, raising concern over the likelihood of increasing CRS incidence [2]. The history of policy changes for rubella vaccination in the UK is also interesting. In the UK, the single antigen rubella vaccine was first introduced in 1971, when it was administered to schoolgirls and susceptible women. It was not until 1988 that the MMR vaccine was introduced in the UK and the policy of vaccinating both male and female toddlers against rubella was implemented [26]. Such policy change in the UK essentially affected a switch from the Nash to the utilitarian strategy.

The importance of sufficient coverage levels for successful rubella vaccination is underscored by a 1993 rubella epidemic in Greece that yielded 25 CRS cases, following a decade of vaccination with coverage levels under 50% [27]. In addition, modeling results support the hypothesis that private sector MMR vaccinations could increase the incidence of CRS in developing countries without public rubella vaccination programs [28]. For instance, in South Africa, rubella vaccination is not part of the national program and uptake in the private sector is very limited. In fact, 10% of the rubella cases in South Africa are among persons aged over 14 years, thus there is a concern about CRS in newborns. It is also estimated that the number of CRS cases in China would increase 3-fold by 2050 without vaccination and that childhood vaccination with less than 50% coverage is predicted to increase CRS [29]. In a similar context, some countries such as India, Brazil and Ghana adopt the strategy of not vaccinating to allow the vast majority of children to contract rubella [30]. This strategy is effective when the average age of infection in the absence of vaccination is very young, such as in Ghana [19]. However, if immunity is already widespread, further vaccination increases the level of seronegativity [31], thus the externality of vaccination will be positive. A catch-up vaccination of children up to 15 years of age could reduce the risk of this paradoxical effect [3]. For example, in Romania, more than 70% of cases were among persons aged over 15 years between 1994 and 1998. In 2004 rubella-containing vaccine was added to the routine childhood schedule in addition to the adolescent female vaccination. Since the introduction of rubella vaccines, rubella cases among persons aged over 15 years were reduced to less than 20% of all cases [32]. However in the absence of those additional vaccine strategies, rubella vaccination among infants alone can

impose negative externalities. These findings underscore the importance of considering the impact on both CRS and rubella when adopting and selecting the rubella vaccination strategy in developed countries.

As a simple resolution to achieve sufficiently high vaccine coverage, combined immunization with other vaccines, such as with the MMR vaccine, is in effect in many countries, providing incentives for both men and women to get vaccinated at relatively low cost. This is because men do not have incentives to get vaccinated against rubella otherwise, implicating the potential difficulty in achieving sufficiently high coverage, as shown in our simulated Nash strategies. However, concerns about potential adverse effects associated with MMR can lead to adoption of single antigen vaccination instead. This study demonstrates that a voluntary vaccination program of rubella as a single antigen vaccine would require additional incentives for men to bring vaccination level in accord with utilitarian strategies.

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TABLE 1. The average costs associated with rubella infections [33]

Disease	Probability of occurrence (%)	Probability of hospitalization (%)	Number of hospitalization days	Cost of hospital-ization	No. of out patient visits	Cost per out patient visits	Days of home care if no hospitalization	Days of home care after hospitalization
Uncomplicated		0.10	2.58	$3135	0.54	$57.05	2.8	3
< 15 years	99.955							
> 15 years	69.955							
Thrombocytopenia	0.033	40	4.8	$22,776	5.91	$417.85	3.5	3
Encephalitis	0.013	100	8.7	$29,556	3.52	$337.95		7
Arthritis		4	3.75	$18,811	1.76	$140.07	1	7
< 15 years	0							
> 15 years	30							
Thrombocytopenia case fatality rate	0.46							
Encephalitis case fatality rate	5							
CRS	25							
Hospitalization for investigation	100	100	13.6	$39,934	1.53	$70.78		5
Heart surgery	35	100	8.9	$23,795				3.75
Cataract surgery	20	100	2.2	$5638				1.25
Annual special education cost	47		16 years	$16,750				
Mental retardation (Moderate/severe)	33(82/18)		50 years	($31,059/ $82,058)				
Deafness	45.6							
Blindness	1.4							
Death(first/second year of life)	10.60/0.40							
Spontaneous abortion	15				1	$594.26		3
Therapeutic abortion	59				1	$807.36		3
Stillbirth	1		1.81	$6253				3

TABLE 2. The existence of Nash strategy for a range of values of $\Theta_m(\bar{\pi})$ and $\Theta_f(\bar{\pi})$ where $\Theta_m(\bar{\pi}) = -c_v + (1-p)\dot{\Phi}_m(\bar{\pi})$ and $\Theta_f(\bar{\pi}) = -c_v + (1-p)\dot{\Phi}_f(\bar{\pi})$. (N/A=not applicable)
*not applicable due to the inequality, $\Phi_m(\bar{\pi}) < \Phi_f(\bar{\pi})$ for all $\bar{\pi} \in [0,1]$.

	$\Theta_m(\bar{\pi}) > 0$	$\Theta_m(\bar{\pi}) = 0$	$\Theta_m(\bar{\pi}) < 0$
$\Theta_f(\bar{\pi}) > 0$	N/A since $\Theta_m(\bar{\pi}) \leq 0$ for $c_v > 0$	N/A since $\forall \bar{\pi} \in (0, 0.5)$ s.t. $\Theta_m(\bar{\pi}) = 0$, it follows that $\Theta_f(\bar{\pi}) \leq 0$ (see Figure 4)	$\bar{\pi}_m = 0$, $\bar{\pi}_f = 1$ when c_v is low
$\Theta_f(\bar{\pi}) = 0$	N/A*	N/A*	$\bar{\pi}_m = 0$, $\bar{\pi}_f \in (0,1)$ when c_v is intermediate
$\Theta_f(\bar{\pi}) < 0$	N/A*	N/A*	$\bar{\pi}_m = 0$, $\bar{\pi}_f = 0$ when c_v is high