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## **OPEN** Age-Structured Population **Modeling of HPV-related Cervical Cancer in Texas and US**

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Human papillomavirus (HPV)-related cervical cancer is a major public health threat to women, with >10,000 new cases diagnosed annually in the United States between 2008 and 2012. Since HPV vaccines can protect against ~80% of HPV-associated cervical cancers, the economic and epidemiological impacts of HPV vaccination have been extensively investigated, particularly at the national level. However, vaccination policies are state-specific, and state-level models are required for state-specific policy decisions. This study adapted an age-structured population model to describe the dynamics of HPV-related cervical cancer in Texas, with model parameters calibrated for Texas. The Year 2000 parameter set was the start point, and the model's predictions from 2001–2010 were well matched with the real incidence numbers in 23 age groups, suggesting the validity of the model. Application of the model to the Year 2010 parameter set predicted that, over the next 10 decades, incidence would decrease rapidly within the first decade and more slowly thereafter. Sensitivity analysis determined the impact of selected parameters (e.g., vaccine coverage rate) on future disease incidence. When compared with the US parameter sets, the Texas population was more sensitive to changes in HPV transmission and vaccination (e.g., ~8% difference in the predicted disease decline).

Cancer of the uterine cervix is one of the most common cancers affecting women in the United States (US), ranking third in terms of incidence and mortality among all gynecologic cancers. In the US, 12,820 new cases of cervical cancer and 4,210 cervical cancer-related deaths are expected in 2017<sup>1</sup>. The incidence of cervical cancer in Texas is among the highest in the country, 8.7 cases per 100,000 women in 2013, compared with a national rate of 7.2 cases per 100,000 women<sup>2</sup>. About 1,300 new cases of cervical cancer are expected in Texas in 2017<sup>1</sup>.

Cervical cancer was once one of the leading causes of death among women in the US. However, with the introduction of the Pap test and the promotion of cancer screening and prevention programs in the 1950s, the incidence and mortality of invasive cervical cancer declined by more than 60% between 1955 and 1992<sup>1</sup>. Declines of cervical cancer incidence and mortality slowed down in recent decades: during the decade 2005–2014, incidence did not change significantly and mortality declined by an average of 0.8%<sup>1</sup>.

Nearly all cases of cervical cancers are associated with human papillomavirus (HPV) infection. HPV-16 and HPV-18 infection are highly oncogenic and account for the majority of HPV-related cervical cancer cases<sup>3</sup>. The first effective HPV vaccine became available in the US in 2006, and a national HPV vaccination program was implemented thereafter. The HPV vaccination program is expected to significantly reduce the incidence of

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HPV-related cervical cancers, but because of the latency period between HPV exposure and occurrence of cervical cancer, this decline is not expected for two to three decades.

HPV vaccination is recommended for all adolescents<sup>4</sup>. However, currently only 49.5% of females and 36.5% of males have been fully vaccinated, falling short of the national goal of 80% vaccination<sup>5</sup>. Currently vaccination-related legislation is state-specific<sup>6,7</sup>. therefore, understanding the effect of vaccination on a state level (as well as on a national level) is required to justify policy-based changes<sup>6</sup>. In Texas, the vaccination rate is lower than the national average, especially in males. The discrepancy between national and state vaccination rates as well as the differences between individual states necessitate further investigations on the state level<sup>8</sup>.

Studies on the economic and/or epidemiological impacts of HPV vaccination (e.g., cost-effectiveness for preventing HPV-related cervical cancer<sup>9-12</sup>) frequently call for the use of mathematical models, given the complexity of the long natural history of HPV-related cancers. In general, such mathematical models will include HPV transmission dynamics, progression and regression of cervical disease from premalignant to malignant states, screening strategies for early detection, and vaccination strategies for prevention<sup>13</sup>. Also, once established, a persistent HPV infection may progress to cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS), and finally invasive cervical cancer, so such models should allow for regression of disease and early detection and treatment through screening<sup>13,14</sup>. Considering the substantial heterogeneity in different age groups (e.g., behavior and vaccination coverage), it is suitable to employ age-structured population models, which are a system of ordinary differential equations (ODEs) generated by discretizing a first-order partial differential equation for population dynamics according to consecutive age groups<sup>15,16</sup>. In one of the many pioneering modeling efforts, Elbasha et al.<sup>17</sup> built a comprehensive age-structured model with all the aforementioned components and factors considered. While the natural history of cervical cancer is the best understood of all HPV-related cancers, new evidence is continually emerging that can be incorporated into existing models. For instance, Campos et al.<sup>18</sup> proposed an updated natural history model of cervical cancer by combining the CIN1 stage with the HPV-infected stage. Of course, age-structured ODE models are not the only possible model structure for this study; however, the recent work of Brisson et al.<sup>19</sup> selected and compared 16 transmission-dynamic models that differ in structure and data for parameter calibration, finding that the population-level prediction results of these models were concordant with each other.

In this study, our purpose was to build an age-structured population model that reflects our current understanding of the natural history of HPV-related cervical cancer, with the objective of understanding the incidence of HPV-related cervical cancer in Texas and the impact of HPV transmission and vaccination on that incidence. Our model incorporated several factors identified by Elbasha *et al.* Model parameter values for both Texas and the US were calibrated using Year 2000 and Year 2010 data. Starting from Year 2000, the model prediction results up to Year 2010 were compared with the real incidence numbers of cervical cancer of 23 age groups for model validation. Then the validated model was used to predict HPV-associated cervical cancer incidence rate in Texas. All the simulation and prediction results for Texas were compared with those of the US to highlight the similarities and differences between Texas and the national average. Note that although the same set of model equations were applied to both Texas and the US, the parameter values and initial conditions were different for Texas and the US. Although it is out of the scope of this study to derive state-specific parameter values for each other state, this work does provide a basis for further investigations of national- and state-level disease dynamics and impacts of HPV vaccination.

#### Results

**Model Development.** To build a model that would help us understand the impact of HPV transmission and vaccination on the incidence of HPV-related cervical cancer in Texas and compare Texas outcomes with the national-level results, we developed an age-structured mathematical model consisting of demographic, HPV epidemiological, and cervical cancer components. Briefly, the demographic component depicted the age- and sex-specific population dynamics of Texas and the US; the epidemiological component described HPV transmission, progression, and vaccination; and the cervical cancer component sketched the natural history of the disease. The resulting model is a large system of ODEs (a total of 6,003 ODEs) similar to the previous work of Elbasha and Dasbach<sup>20</sup>. Model parameters were calibrated from the literature or based on the best available data (Year 2000 to 2010) or knowledge of HPV and cervical cancer. Note that the Texas population is very different from the overall US population (e.g., the Hispanic or Latino percentage is 39.1% in Texas while it is around 17.8% of the total US population as of 2016, https://www.census.gov/quickfacts/TX). Therefore, the exact same model structures are used for both Texas and US, but two sets of parameter values and initial conditions are derived and employed for Texas and US, respectively.

**Model Validation.** The proposed model was validated by comparing model prediction results with real cervical cancer incidence numbers from Year 2001 to Year 2010, with the Year 2000 parameter values and initial conditions (Supplementary Texts S2 and S3) as the starting point. For this purpose, the 10-year incidence numbers reported in the Surveillance, Epidemiology, and End Results Program (SEER) and Texas Cancer Registry (TCR) databases for Texas and US from Year 2001 to 2010 were used (Fig. 1). Because there are no efficient identifiability analysis<sup>21</sup> and statistical inference<sup>22</sup> techniques for a large-scale nonlinear ODE system like our model, it is infeasible to perform model fitting here. However, Fig. 1 shows that, based on the parameter values and initial conditions calibrated in this study, the predicted incidence can reasonably match the observed data for all defined age groups (see Fig. 1a for the US results). For Texas (Fig. 1b), the predicted results from Years 2001 to 2010 are slightly larger than the real data for the older age groups (i.e., age  $\geq$ 40 years) while such an issue is not observed for the US results (likely because the US results are the sum of 50 states). This is primarily because no HPV vaccination had yet been implemented in Year 2001, but a constant vaccination rate was assumed for simplicity when performing model predictions, which did not adequately account for the time-varying characteristic of the



Figure 1. Model validation using real data for (a) the US and (b) Texas from 2001 to 2010. The red dots are real data points, and the blue lines are model prediction results. The number above each subfigure is the year.



#### **Incidence Prediction**

Figure 2. Model prediction for Texas and the US from 2011 to 2110.

vaccination rates between Year 2000 and 2010. The same set of data was used by Elbasha and Dasbach<sup>23</sup> for model validation, and they also reported mismatches between real data and model predictions for the older age groups. In comparison with Elbasha and Dasbach's work, our prediction results better matched the real data in the older age groups, possibly suggesting an improvement in model structure refinement and parameter value calibration.

**Prediction.** Instead of population total, here we predict cervical cancer incidence rate due to its usefulness in calculating cost effectiveness of HPV vaccination. The Year 2010 data were collected, and the model parameters were calibrated for predicting the future incidence rates over the next 100 years (Years 2011-2110), under the assumption that model parameter values remain the same as Year 2010 (Texts S4 and S5). As shown in Fig. 2, the predicted incidence rates in Year 2110 were ~50% lower for Texas and ~40% lower for the US than the rates in Year 2010. For Texas, starting from 4.96 cases (per 100,000 population) in Year 2010, the incidence rate monotonically decreased to 2.36 cases (per 100,000 population) in Year 2110, a 48% drop. Also, the incidence rate decline



was not constant: around Year 2030, the decline started to slow down. The US had an incidence of 4.62 (per 100,000) in Year 2010, which decreased to 2.79 (per 100,000) after 100 years. Like that in Texas, the US incidence rate dropped rapidly at the beginning and then more slowly after Year 2020. Also, the predicted US incidence rate was consistently higher than that of Texas after Year 2017, which clearly suggests a difference between national and state rates. Sensitivity analyses (described in the next section) showed that the Texas population was more sensitive to changes in disease dynamics and vaccination policies than the US population overall, which could explain the notable difference between the state- and national-level incidence predictions.

**Sensitivity analysis.** Sensitivity analyses were conducted to investigate the impacts of changes in several selected factors on the future incidence of HPV-related cervical cancer. These factors, which are considered to be important contributors to HPV-related cervical cancer and thus are often considered as parameters in predictive models for this disease<sup>17</sup>, include vaccine coverage rate, vaccination covered age group, rate of sexual partner change, degree of assortative mixing between age and sexual activity groups, heterogeneity in sexual partner acquisition rates, and the impact of vaccinate efficacy. We found that if the progression rates from CIN to CIS (i.e.,  $\pi_2$ ,  $\pi_3$ , and  $\pi_5$ ) were sufficiently small, model prediction results were not notably affected by the changes in these parameters. Therefore, the following sensitivity analyses were based on  $\pi_2 = 2.1$  (% per year),  $\pi_3 = 6.45$  (%per year), and  $\pi_5 = 0.62$  (%per year) and other Year 2010 parameter values. All the predicted incidence rates monotonically decreased from Year 2010 to 2110. Also, all the predicted incidence rates dropped rapidly in the first 10 years and then slowed down. The incidence was higher in Texas at the beginning of the time period but decreased faster than that of the US.

*Vaccine coverage rate* ( $\phi$ ). As shown in Fig. 3, when the vaccine uptake rate decreased by 50%, the Texas incidence increased by 4% at Year 2110 and, when the vaccine uptake rate increased by 50%, the Texas incidence decreased by 16.8%. The US incidence showed similar but smaller corresponding changes (2.3% and 9.6%, respectively). When the vaccine uptake rate was small (e.g., decreased by half), a rebound in the incidence occurred around Year 2025 for both Texas and the US, which might be a consequence of insufficient vaccine coverage.

*Vaccination covered age group.* The starting age of vaccination affects the incidence rate. To understand the effects of age-specific vaccination, we made predictions based on the assumption that people can receive vaccination two age groups earlier than existing vaccination coverage of 23 age groups (starting from age 9–10 years rather than age 13–14 years for females, starting from age 15–17 years rather than age 19 years for males). We then compared those results with the results of a similar analysis in which vaccination started two age groups later (starting from age 18 years for females and age 25–26 for males; details in Supplementary Table S1). Under those conditions, the incidence rates for both Texas and the US began to show more significant differences after Year 2050 (Fig. 4). The ratio of incidence rates between the two vaccination schedules for the US was 1.04 in 2050 and had increased to 1.09 by 2110. The corresponding ratios for Texas were 1.07 and 1.14, respectively. Thus, Texas had a lower incidence but a higher ratio from 2007 than the US. A saddle point occurred on the prediction curves for both Texas and the US around Year 2030. In short, earlier vaccination makes incidence rate decrease faster.

*Rate of sexual partner change*. The rate of sexual partner change for individuals was a parameter introduced by Elbasha *et al.*<sup>17</sup>. As shown in Fig. 5, increasing or decreasing the sexual partner change rate by 50% changed the incidence by approximately  $\pm 0.21$  cases (per 100,000 population) for TX and around  $\pm 0.13$  cases (per 100,000) for the US in Year 2040. If the sexual partner change rate were increased by 50%, there would be a rebound around Year 2040. The differences in the predicted incidence rates for a 50% increase or decrease in sexual partner change rate were more significant for Texas than for the US. At the end of the prediction period, a 50% increase in sexual partner change rate yielded a 0.07 per 100,000 higher incidence rate for Texas than for the US (the differences for TX and US are 0.1746 and 0.1068 per 100,000, respectively).



Figure 4. Sensitivity analysis: Vaccination covered age groups for Texas and the US.

Sensitivity Analysis - Rate of sexual partner change



Figure 5. Sensitivity analysis: Rates of sexual partner change for Texas and the US.



### Sensitivity Analysis – degree of assortative mixing

**Figure 6.** Sensitivity analysis: Degree of assortative mixing between age and sexual activity groups for Texas and the US.

Degree of assortative mixing between age and sexual activity groups. The degree of assortative mixing parameters  $(\varepsilon_1, \varepsilon_2, \text{and } \varepsilon_3)$  depicts the level of assortative mixing between different age and sexual activity groups. As shown in Fig. 6, the effects of a 50% change in these parameters on the predicted incidence rates were small. Smaller  $\varepsilon_1$  or  $\varepsilon_2$  values indicate a greater degree of assortative mixing.  $\varepsilon_3$  is for persons older than 60 years. The difference in the incidence rate for Texas and for the US increased slightly (ratio, 6% for Texas, 3% for US) at the end of prediction period (Year 2110).



Year Year Figure 8. Sensitivity analysis: Impact of vaccine efficacy for Texas and the US.

2100

Heterogeneity in sexual partner acquisition rates. To assess the impact of heterogeneity in sexual partner acquisition rates (i.e., different sexual behavior and various combinations of age and sexual activity groups), we consider three scenarios (1) heterogeneity in age groups only, (2) heterogeneity in sexual activity groups only, and (3) no heterogeneity, and we set (1)  $pc_i = 1$ , (2)  $pa_i = 1$ ,  $\overline{c_i} = 0.97$ , and (3)  $pc_i = 1$ ,  $pa_i = 1$ ,  $\overline{c_i} = 0.97$  as suggested by Elbasha et al.<sup>17</sup>; all the other parameters were fixed at default. Here  $pc_i$  and  $pa_i$  are the relative partner acquisition rates for sexual activity group l and for age group i, respectively;  $\bar{c}_i$  is the mean partner acquisition rate. Considering heterogeneity in sexual activity groups only, the predicted incidence was slightly lower than that predicted by default parameter values for both Texas and the US (Fig. 7); however, if scenarios (1) and (3) were considered, the predicted incidence was considerably lower than that for the default parameters from Year 2020 onward for both Texas and the US. As in the analyses of the other four factors, the Texas population was more sensitive to change in the heterogeneity parameter than the US population.

2020

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HPV vaccine efficacy. To study the impact of HPV vaccine efficacy on the incidence of HPV-related cervical cancer, sensitivity analyses were conducted by changing the values of parameters  $\psi_p^I$ ,  $\psi_p^I$ ,  $\psi_v^I$ ,  $\psi_{v_1}$  and  $\psi_{v_2}$ . The baseline values of  $\psi_{v_1}$  and  $\psi_{v_2}$  are 0.91 and 0.99, respectively; and the baseline values of  $\psi_p^I$  and  $\psi_p^I$  are 1 for female and 0 for male, respectively. Two scenarios were considered: (1) we decreased the values of  $\psi_p^I$  and ... by 50% and set the values of  $\psi_{v1}$  and  $\psi_{v2}$  at 0.5; (2) we decreased the  $\psi_p^I$  and  $\psi_p^{II}$  values by 75% and set the values of  $\psi_{v1}$  and  $\psi_{v2}$  at 0.75. As shown in Fig. 8, comparing the first scenario results with the baseline results, the incidence rates increased by ~0.31 cases (per 100,000 population) for TX and ~0.20 cases (per 100,000 population) for the US in Year 2050. Comparing the second scenario with the baseline results, the predicted incidence rates increased by 0.17 cases per 100,000 population for TX and 0.13 cases per 100,000 population for US in Year 2050. At the end of the prediction time window (Year 2110), under the first scenario, the incidence rate increased by ~0.21 cases (per 100,000 population) for TX and ~0.14 cases (per 100,000 population) for the US, respectively, compared with the baseline results. Under the second scenario, the predicted incidence increases were 0.10 and 0.07 per 100,000 population for TX and US, respectively, compared with the baseline results.

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Δ         Rate of hysterectomy         β           τ         Rate of progression from CIN 2 to CIN 3         9           τ         Rate of progression from CIN 1 to Cal extrical cancer         90           γ <sub>3</sub> Propertion of regression from CIN 1 to cal extrical cancer         90           γ <sub>3</sub> Propertion of regression from CIN 1 to cal extrical cancer         90           γ <sub>1</sub> Rative patters acquisition rate for sexual activity group         90           µ         Death rate         90           µ         Rative patters acquisition rate for age group         91           q <sub>4</sub> Rate of vaming immunity following recovery         91           γ <sub>4</sub> Rate of vaming immunity following recovery         91           γ <sub>6</sub> Reactivation rate, foll not sercooversion         92           q <sub>6</sub> Reactivation rate, foll not sercooversion         91           q <sub>6</sub> Reactivation rate in pattern who are recoverely vaccinated individuals with sercooversion         91           q <sub>6</sub> Reactor vaming immunity following r	Parameter	Definition	Reference
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μ         μ         μ         μ           ζ <sub>1</sub> Mean partner acquisition rate.         19           σ <sub>2</sub> Rate of vaning immunity following recovery         9           γ         Rate for ecovery from HPV infection         485           θ <sub>w</sub> Reactivation rate. following sero-conversion         485           θ <sub>w</sub> Reactivation rate. following sero-conversion         90           ψ <sub>2</sub> Degree of protection following area conversion         90           σ <sub>w</sub> Rate of vaning immunity following vaccination         90           σ <sub>w</sub> Rate of vaning immunity following vaccination         90           σ <sub>w</sub> Rate of vaning immunity following recovery         20           σ <sub>w</sub> Rate of vaning immunity following recovery of an infection in previously vaccinated individuals with seroconversion         81           σ <sub>w</sub> Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion         835           σ <sub>w</sub> Reactivation rate in patients who are recovered, vaccinated, and no seroconversion         835           σ <sub>w</sub> Reactivation rate in patients who are recovered, vaccinated, and no seroconversion         835           τ <sub>2</sub> Rate of regression from local to regional cervical cancer         90 <td< td=""><td>pa.</td><td>Relative partner acquisition rate for age group</td><td>18</td></td<>	pa.	Relative partner acquisition rate for age group	18
γ         Print of variang immunity following recovery         β           η         Rate of variang immunity following seroconversion         224           θ <sub>m</sub> Reactivation rate (dilowing seroconversion         224           θ <sub>m</sub> Reactivation rate (dilowing seroconversion         433           i         Probability of seroconversion following seroconversion         44           ψ <sub>m</sub> Degree of protection following seroconversion         46           ψ <sub>m</sub> Degree of protection following vaccination         47           atte of variang immunity following vaccination         47           atte of variang immunity following recovery         50           σ <sub>m</sub> Rate of variang immunity following recovery         50           σ <sub>m</sub> Rate of variang immunity following recovery of an infection in previously vaccinated individuals with seroconversion         835           σ <sub>m</sub> Rate of variang immunity following recovery of an infection in previously vaccinated individuals with seroconversion         845           σ <sub>m</sub> Rate of variang immunity following recovery of an infection in previously vaccinated individuals with seroconversion         845           σ <sub>m</sub> Reactivation rate in patients who are recovered, vaccinated, and no seroconversion         845           σ <sub>m</sub> Reactin fore forestorin following seroconversion, vaccinated<	7 m1	Mean partner acquisition rate	18
$g_{1}$ Rate of recovery from HPV infection8.57 $q_{u}$ Reactivation rate following seroconversion5.84 $\theta_{u}$ Reactivation rate, did not seroconversion6.61 $\psi_{v}$ Degree of protection following proconversion8 $\psi_{v}$ Degree of protection following no seroconversion8 $\psi_{v}$ Degree of protection following no seroconversion8 $\psi_{v}$ Degree of protection following seroconversion8 $\psi_{v}$ Degree of protection following secondersion8 $\sigma_{v}^{H}$ Rate of waning immunity following vaccination9 $\sigma_{v}^{H}$ Rate of waning immunity following recovery8 $\sigma_{w}$ Rate of vaning immunity following recovery of an infection in previously vaccinated individuals with seroconversionEstima $\theta_{w}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion8.58 $\theta_{w}$ Reactivation rate in patients who are recovered, vaccinated, and seroconversion8.58 $\psi_{w}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion8.58 $\chi_{w}$ Reactivation rate in patients who are recovered, vaccinated, and seroconversion8.58 $\chi_{w}$ Reactivation rate in patients who are recovered, vaccinated, and seroconversion8.58 $\chi_{w}$ Reactivation rate in patients who are recovered, vaccinated, and seroconversion8.59 $\chi_{w}$ React of regression from ICN 3 to CIN 29 $\pi_{w}$ Rate of progression from ICN 3 to CIN 29	<i>τ</i> <sub>j</sub>	Rate of waning immunity following recovery	20
1DataData Conversion13.9 $\theta_w$ Reactivation rate following seroconversion3.9 $d_w$ Probability of seroconversion following HPV clearance4.61 $\psi_w$ Degree of protection following no seroconversion3 $v_w$ Degree of protection following vaccination3 $\sigma_u^{(1)}$ Rate of waning immunity following vaccination3 $\sigma_u^{(2)}$ Rate of waning immunity following recovery3 $\sigma_w^{(1)}$ Rate of vaning immunity following recovery3 $\sigma_w^{(2)}$ Degree of protection following recovery3 $\sigma_w^{(2)}$ Rate of vaning immunity following recovery3 $\sigma_w^{(2)}$ Recativation rate in patients who are recovered, vaccinated, and seroconvertedEstima $\theta_w$ Regree of protection following recovery of an infection in previously vaccinated individuals with seroconversion3.59 $\chi_w^{(2)}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion3.59 $\chi_w^{(2)}$ Regree of protection following recovery of an infection in previously vaccinated individuals with seroconversion3.59 $\chi_w^{(2)}$ Degree of protection following seroconversion3.59 $\chi_w^{(2)}$ Reactivation rate in patients who are recovered, vaccinated, and no seroconversion3.59 $\chi_w^{(2)}$ Reactivation rate in patients who are recovered, vaccinated, and no seroconversion3.59 $\chi_w^{(2)}$ Rate of progression from CN 3 to CN 230 $\chi_w^{(2)}$ Rate of progression from CN 3 to CN 230 $\chi_w$	0 <sub>2</sub>	Rate of warming minimum y following recovery	36,37
$u_{ac}$ Reactivation rate, dd not sercoonvertihttps://dx $i$ Probability of sercoonversion following sercoonversion80 $\psi_{ac}$ Degree of protection following no sercoonversion80 $\psi_{ac}$ Degree of protection following no sercoonversion80 $\sigma_{ac}^{T}$ Rate of waning immunity following recovery82 $\sigma_{qc}$ Rate of waning immunity following recovery82 $\sigma_{qc}$ Rate of waning immunity following recovery of an infection in previously vacinated individuals with sercoonversionEstima $\psi_{qc}$ Degree of protection following recovery of an infection in previously vacinated individuals with sercoonversionEstima $\psi_{qc}$ Degree of protection following recovery of an infection in previously vacinated individuals with sercoonversionEstima $\psi_{qc}$ Reactivation rate in patients who are recovered, vacinated, and no sercoonvertedEstima $\theta_{qc}$ Reactivation rate in patients who are recovered, vacinated, and no sercoonversion83-87 $\chi_{22}$ Rate of regression from ICN 3 to CIN 280 $\tau_{22}$ Rate of progression from ICN 3 to CIN 280 $\tau_{qc}$ Rate of progression from local to regional cervical cancer80 $\psi_{qc}^{I}$ Degree of protection following sercoonversion, vaccinatedEstima $\psi_{qc}^{I}$ Degree of protection following sercoonversion, vaccinated81 $\tau_{qc}$ Rate of progression from ICN 3 to CIN 2.381 $\psi_{qc}^{I}$ Degree of protection following sercoonversion, vaccinated84 $\psi_{qc}^{I}$ Degree of protection f	A	Reactivation rate following seroconversion	37,38
$z_{ab}$ Probability of sero-conversion Glowing HPV clearance6.01 $\psi_n$ Degree of protection following sero-conversion20 $\psi_n$ Degree of protection following no sero-conversion20 $q_i^I$ Rate of waning immunity following vaccination20 $q_u^I$ Rate of waning immunity following recovery20 $\sigma_{q_u}$ Rate of waning immunity following recovery20 $\sigma_{q_u}$ Rate of waning immunity following recovery of an infection in previously vaccinated individuals with sero-conversionEstima $\psi_u$ Degree of protection following recovery of an infection in previously vaccinated individuals with sero-conversionEstima $\psi_u$ Degree of protection following recovery of an infection in previously vaccinated individuals with sero-conversionEstima $\theta_{u_u}$ Reactivation rate in patients who are recovered, vaccinated, and no sero-conversion8-9 $\chi$ Rate of local cervical cancer-associated death6 $prf$ Proportion of infections that are destined to be persistent6 $\pi_i$ Rate of progression from Iocal to regional cervical cancer80 $\pi_u^{II}$ Degree of protection following sero-conversion, vaccinatedEstima $\phi_i^{II}$ Degree of protection following sero-conversion, vaccinated40 $\psi_{ra}$ Degree of protection with 2 doses41 $\phi_{ra}$ Rate of rogression from Ibcal to CIN 2,361 $\phi_{ra}$ Rate of progression from HPV infection to CIN 2,361 $\phi_{ra}$ Rate of progression from HPV infection to CIN 2,361 $\phi_{r$	θ <sub>sz</sub>	Reactivation rate did not seroconvert	38,39
111 <th< td=""><td>U SZS</td><td>Probability of sero-conversion following HPV clearance</td><td>40,41</td></th<>	U SZS	Probability of sero-conversion following HPV clearance	40,41
$v_{ac}$ Degree of protection following no seroconversion30 $\sigma_{\mu}^{II}$ Rate of waning immunity following vaccination30 $\sigma_{q}^{II}$ Rate of waning immunity following vaccination30 $\sigma_{q}$ Rate of waning immunity following recovery30 $\sigma_{q}$ Rate of waning immunity following recovery31 $\psi_{q}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversionEstima $\psi_{q}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversionEstima $\theta_{qq}$ Reactivation rate in patients who are recovered, vaccinated, and no seroconversion84.9 $\chi_{q}$ Rate of protection following recovery of an infection in previously vaccinated individuals with seroconversion84.9 $\chi_{q}$ Rate of protection following recovery (vaccinated, and no seroconversion84.9 $\chi_{q}$ Rate of protection following recovery (vaccinated)30 $\chi_{q}$ Rate of progression from IO:13 to CIN 231 $\pi_{L}$ Rate of progression from local to regional cervical cancer39 $\psi_{q}^{I}$ Degree of protection following seroconversion, vaccinated81 $\psi_{q}^{I}$ Degree of protection following seroconversion, vaccinated81 $\psi_{q}$ Degree of protection with 1 dose41 $\psi_{q}$ Degree of protection with 2 doses41 $\phi_{q}$ Rate of progression from Drashthrough infection to CIN 2,345 $\phi_{q}$ Rate of progression from Drashthrough infection to CIN 2,341<	2/2	Degree of protection following seroconversion	20
$\tau_{a}^{-1}$ Degree of protection may be recent that $\sigma_{v}^{-1}$ Rate of waning immunity following vaccination20 $\sigma_{u}^{-1}$ Rate of waning immunity following recovery30 $\sigma_{u}^{-1}$ Rate of waning immunity following recovery30 $\sigma_{u}^{-1}$ Rate of protection following recovery of an infection in previously vaccinated individuals with seroconversionEstima $\psi_{u}^{-1}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversionEstima $\psi_{u}^{-1}$ Degree of protection state are associated death41 $\theta_{uy}$ Reactivation rate in patients who are recovered, vaccinated, and no seroconversion $23.9^{\circ}$ $\chi$ Rate of fora (croic) accarce-associated death41 $prf$ Proportion of infections that are destined to be persistent40 $\tau_{32}$ Rate of progression from local to regional cervical cancer20 $\pi_{R}$ Rate of progression from local to regional cervical cancer20 $\pi_{R}$ Rate of progression from local to regional cervical cancer20 $\phi_{L}^{-1}$ Degree of protection following seroconversion, vaccinatedEstima $\psi_{L}^{-1}$ Degree of protection following seroconversion, vaccinated41 $\psi_{L}^{-1}$ Degree of protection with 1 dose41 $\psi_{L}^{-1}$ Degree of protection with 2 doses41 $\psi_{L}^{-1}$ Degree of protection with 2 doses41 $\psi_{L}^{-1}$ Rate of progression from HPV infection to CIN 2,343 $\eta_{L}^{-1}$ Rate of progression from	$\psi_z$	Degree of protection following no seroconversion	20
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$\sigma_{qi}$ Kate of wanning immunity following recovery of an infection in previously vaccinated individuals with seroconversion $z^{-1}$ $\psi_{qi}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion84.9 $\theta_{qi}$ Reactivation rate in patients who are recovered, vaccinated, and seroconversion84.9 $\chi$ Rate of local cervical cancer-associated death4 $pf$ Proportion of infections that are destined to be persistent6 $r_{52}$ Rate of progression from ICN 3 to CIN 220 $\pi_k$ Rate of progression from local to regional cervical cancer20 $\pi_k$ Rate of progression from local to regional cervical cancer20 $\psi_p^I$ Degree of protection following seroconversion, vaccinatedEstima $\phi_1^I$ Proportion receiving only 1 doseEstima $\psi_{va}$ Degree of protection with 1 dose44 $\omega_{va}$ Degree of protection with 1 dose44 $\omega_{va}$ Degree of protection with 1 dose44 $\omega_{va}$ Degree of protection with 2 dosesEstima $\psi_{va}$ Degree of protection with 2 doses45 $\omega_{va}$ Degree of progression from HPV infection to CIN 2,345 $\theta_i$ Rate of progression from HPV infection to CIN 2,345 $\theta_i^{II}$ Rate of progression from HPV infection to CIN 2,345 $\theta_i^{II}$ Rate of progression from HPV infection to CIN 2,3Estima $\theta_i^{II}$ Rate of progression from HPV infection to CIN 2,3Estima $\theta_i^{II}$ Rate of pro	$\sigma_q$	Rate of waning immunity following recovery	20
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$\psi_{g_1}$ Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversionEstima $\theta_{ag}$ Reactivation rate in patients who are recovered, vaccinated, and seroconversion38.39 $\chi$ Rate of local cervical cancer-associated death41 $prf$ Proportion of infections that are destined to be persistent43 $\tau_{32}$ Rate of regression from ICN 3 to CIN 229 $\pi_L$ Rate of progression from local to regional cervical cancer29 $\psi_{g_1}^{P}$ Degree of protection following seroconversion, vaccinatedEstima $\psi_{g_1}^{P}$ Degree of protection following seroconversion, vaccinated44 $\phi_{11}$ Proportion receiving only 1 dose44 $\psi_{g_1}^{P}$ Degree of protection with 1 dose44 $\psi_{g_2}^{P}$ Degree of protection with 2 doses44 $\phi_{11}$ %Rate of progression from HPV infection to CIN 2,345 $\theta_{11}$ %Rate of progression from HPV infection to CIN 2,345 $\theta_{12}$ %Rate of progression from HPV infection to CIN 2,345 $\theta_{11}$ %Rate of progression from HPV infection to CIN 2,346 $\theta_{12}^{P}$ Rate of progression from HPV infection to CIN 2,346 $\theta_{11}^{P}$ Rate of progression from HPV infection to CIN 2,345 $\theta_{12}^{P}$ Rate of progression from HPV infection to CIN 2,345 $\theta_{11}^{P}$ Rate of progression from HPV infection to CIN 2,345 $\theta_{12}^{P}$ Rate of progression from HPV infection to CIN 2,345 $\theta_{12}^{P}$ <td< td=""><td><math>\psi_q</math></td><td>Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion</td><td>Estimated</td></td<>	$\psi_q$	Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion	Estimated
$\theta_{ag}$ Reactivation rate in patients who are recovered, vaccinated, and seroconvertedJestimation $\theta_{agh}$ Reactivation rate in patients who are recovered, vaccinated, and no seroconversion36.99 $\chi$ Rate of local cervical cancer-associated death42 $prf$ Proportion of infections that are destined to be persistent43 $\tau_{52}$ Rate of progression from ICN 3 to CIN 230 $\pi_{\mu}$ Rate of progression from local to regional cervical cancer20 $\pi_{g}$ Rate of progression from local to regional cervical cancer20 $\psi_{p}^{I}$ Degree of protection following seroconversion, vaccinatedEstimation $\psi_{p}^{I}$ Degree of protection following seroconversion, vaccinatedEstimation $\psi_{q}^{I}$ Degree of protection with 1 dose44 $\psi_{v2}$ Degree of protection with 1 dose44 $\psi_{v2}$ Degree of protection with 2 dosesEstimation $\alpha$ Relative rate of recovery from breakthrough infection30 $\theta$ %Rate of progression from CIN 2,345 $\theta_{r}$ %Rate of progression from CIN 2,345 $\theta_{r}$ Rate of progression from CIN 2,345 $\theta_{p}^{I}$ Rate of progression to CIN 2,345 $\theta_{r}^{IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII$	$\psi_{qs}$	Degree of protection following recovery of an infection in previously vaccinated individuals with seroconversion	Estimated
$b_{ap}$ Reactivation rate in patients who are recovered, vaccinated, and no seroconversion $200$ $\chi$ Rate of local cervical cancer-associated death42 $prf$ Proportion of infections that are destined to be persistent43 $\tau_{32}$ Rate of progression from CIN 3 to CIN 229 $\pi_L$ Rate of progression from local to regional cervical cancer29 $\pi_R$ Rate of progression from local to regional cervical cancer29 $\psi_p^{I}$ Degree of protection following seroconversion, vaccinatedEstima $\psi_p^{I}$ Degree of protection only 2 doseEstima $\phi_p$ Proportion receiving only 2 dosesEstima $\psi_{v1}$ Degree of protection with 1 dose44 $\psi_{v2}$ Degree of protection with 2 doses44 $\psi_{v2}$ Degree of protection with 2 doses44 $\phi_{v2}$ Degree of protection with 2 doses44 $\phi_{v2}$ Degree of protection with 2 doses44 $\phi_{v3}$ Relative rate of recovery from breakthrough infection30 $\theta$ %Rate of progression from HPV infection to CIN 2,345 $\sigma$ Rate of progression from HPV infection to CIN 2,345 $\theta_r$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_r$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_r$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_r$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_r$ Rate of progression from breakthrough infection to CIN 2,3<	$\theta_{sq}$	Reactivation rate in patients who are recovered, vaccinated, and seroconverted	Estimated
XRate of local cervical cancer-associated death42prfProportion of infections that are destined to be persistent43 $\tau_{32}$ Rate of regression from local to regional cervical cancer20 $\pi_{R}$ Rate of progression from local to regional cervical cancer20 $\pi_{R}$ Rate of progression from local to regional cervical cancer20 $\psi_{p}^{I}$ Degree of protection following seroconversion, vaccinatedEstima $\psi_{p}^{I}$ Degree of protection following seroconversion, vaccinatedEstima $\psi_{p}$ Degree of protection with 1 dose44 $\Phi_{2}$ Proportion receiving only 2 dosesEstima $\psi_{r4}$ Degree of protection with 2 doses44 $\phi_{r4}$ Degree of protection with 2 doses44 $\alpha$ Relative rate of recovery from breakthrough infection30 $\theta$ %Rate of progression from HPV infection to CIN 2,345 $\theta_{r}$ Recurrence rate of treated CIN 2,345 $\theta_{p}^{I}$ Recurrence rate of treated CIN 2,346 $\theta_{p}^{I}$ Rate of progression from HPV infection to CIN 2,345 $\theta_{p}^{I}$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_{p}^{I}$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_{p}^{I}$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_{p}^{I}$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_{p}^{I}$ Rate of progression to CIN2/3 in patients that are vaccinated with 1 dose, then are infectedEsti	$\theta_{sqs}$	Reactivation rate in patients who are recovered, vaccinated, and no seroconversion	42
prfProportion of intections that are destined to be persistent15 $\tau_{32}$ Rate of regression from CIN 3 to CIN 228 $\pi_L$ Rate of progression from local to regional cervical cancer29 $\pi_R$ Rate of progression from local to regional cervical cancer29 $\psi_p^J$ Degree of protection following seroconversion, vaccinatedEstimation $\phi_p^J$ Degree of protection following seroconversion, vaccinatedEstimation $\phi_1$ Proportion receiving only 1 doseEstimation $\phi_2$ Degree of protection with 1 dose44 $\psi_{va}^2$ Degree of protection with 2 doses44 $\alpha$ Relative rate of recovery from breakthrough infection39 $\theta$ %Rate of progression from HPV infection to CIN 2,345 $\theta_i$ %Rate of progression from CIN 2,3 to normal or HPV20 $\theta_r$ Recurrence rate of treated CIN 2,345 $\theta_p^H$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_p^H$ Rate of progression from breakthrough infection to CIN 2,345 $\theta_p^H$ Rate of progression from breakthrough infection to CIN 2,3Estimation $\Omega$ Cuer rate of local cervical cancer42 $\theta_p^H$ Rate of progression from breakthrough infection to CIN 2,3Estimation $\Omega$ Cuer rate of progression from breakthrough infection to CIN 2,3Estimation $\Omega$ Cuer rate of progression from breakthrough infection to CIN 2,3Estimation $\Omega$ Cuer rate of progression from breakthrough infection to CIN 2,3Estimating <td>X</td> <td>Rate of local cervical cancer-associated death</td> <td>42</td>	X	Rate of local cervical cancer-associated death	42
$\tau_{32}$ Rate of regression from CIN 3 to CIN 2 $\tau^{-0}$ $\pi_L$ Rate of progression from local to regional cervical cancer29 $\pi_R$ Rate of progression from local to regional cervical cancer29 $\psi_p^{II}$ Degree of protection following seroconversion, vaccinatedEstimat $\Phi_2$ Proportion receiving only 1 doseEstimat $\Phi_2$ Proportion receiving only 2 dosesEstimat $\psi_{v1}$ Degree of protection with 1 dose44 $\psi_{v1}$ Degree of protection with 2 doses44 $\alpha$ Relative rate of recovery from breakthrough infection30 $\theta$ %Rate of progression from HPV infection to CIN 2,345 $\sigma$ Reate of regression from CIN 2,3 to normal or HPV20 $\theta_r$ Recurrence rate of treated CIN 2,346 $\theta_p^{II}$ Rate of progression from breakthrough infection to CIN 2,346 $\theta_p^{II}$ Rate of progression from Dreakthrough infection to CIN 2,346 $\theta_r^{II}$ Rate of progression from Dreakthrough infection to CIN 2,345 $\sigma$ Recurrence rate of treated CIN 2,346 $\theta_p^{II}$ Rate of progression from breakthrough infection to CIN 2,346 $\theta_p^{II}$ Rate of progression from breakthrough infection to CIN 2,346 $\theta_p^{II}$ Rate of progression from breakthrough infection to CIN 2,345 $\sigma$ Cure rate of local cervical cancer42 $\theta_p^{II}$ Rate of progression to CIN2/3 in patients that are vaccinated with 2 doses, then are infectedEstimat $\theta_{row}$ Rate of	prf	Proportion of infections that are destined to be persistent	43
$\pi_L$ Rate of progression from local to regional cervical cancer $2^{ol}$ $\pi_R$ Rate of progression from local to regional cervical cancer $2^{ol}$ $\psi_p^{II}$ Degree of protection following seroconversion, vaccinatedEstima $\Phi_1$ Proportion receiving only 1 doseEstima $\Phi_2$ Proportion receiving only 2 dosesEstima $\psi_{vi}^{II}$ Degree of protection with 1 dose44 $\psi_{vi}^{I}$ Degree of protection with 2 doses44 $\alpha$ Relative rate of recovery from breakthrough infection $3^{ol}$ $\theta$ %Rate of progression from HPV infection to CIN 2,345 $\sigma_i$ Reat of progression from HPV infection to CIN 2,345 $\sigma_i$ Rate of progression from HPV infection to CIN 2,346 $\theta_r$ %Rate of progression from HPV infection to CIN 2,345 $\sigma_r$ Rate of progression from HPV infection to CIN 2,345 $\sigma_r$ Rate of progression from HPV infection to CIN 2,345 $\theta_r$ Recurrence rate of treated CIN 2,346 $\theta_p^{II}$ Rate of progression from breakthrough infection to CIN 2,3Estima $\Omega_r$ Cure rate of local cervical cancer42 $\theta_r^{IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII$	τ <sub>32</sub>	Rate of regression from CIN 3 to CIN 2	20
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Yem , accure uptake rate with mot door, mate persons	$\phi_{cm}$	Vaccine uptake rate with first dose, male persons	48,49
$\phi_d$ Vaccine uptake rate with first dose, female persons 48	$\phi_{cf}$	Vaccine uptake rate with first dose, female persons	48
$\kappa$ Detection rate of CIN 2,3, CIS 45	κ	Detection rate of CIN 2,3, CIS	45
$ \nu $ Detection rate of local cancer 42	ν	Detection rate of local cancer	42

 Table 1. Parameter notations, definitions, and sources.

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		Dimensions <i>i</i> =23 age groups <i>l</i> =3 sexual activity
Variable	Definition	groups c=2 gender groups
X	Susceptible, female persons	l, i, c+1
V1	Vaccinated with 1 dose	l, i, c+1
V2	Vaccinated with 2 doses	l, i, c+1
VS	Vaccinated with waned immunity	l, i, c+1
Y	Infected persons	l, i, c+1
UF	Persistently infected, only female	l, i, c
ZS	Recovered without sero-conversion	l, i, c+1
Z	Recovered with sero-conversion	l, i, c+1
WS	Infected vaccinated with waned immunity	l, i, c+1
W1	Infected vaccinated with 1 dose	l, i, c+1
W2	Infected vaccinated with 2 doses	l, i, c+1
PSF	Persistently infected vaccinated, only female	l, i, c
P1F	Persistently infected vaccinated with 1 dose, only female	l, i, c
P2F	Persistently infected vaccinated with 2 doses, only female	l, i, c
QS	Recovered vaccinated without sero-convertion	l, i, c+1
Q	Recovered vaccinated with sero-convertion	l, i, c+1
Hx	Population of females with hysterectomy	l, i, c
Ну	Population of females with hysterectomy that are infected	l, i, c
Hz	Population of females with hysterectomy that were infected, recovered, seroconverted	l, i, c
Hzs	Population of females with hysterectomy that were infected, recovered, not seroconverted	l, i, c
Hv1	Vaccinated with 1 dose, persons with hysterectomy	l, i, c
Hv2	Vaccinated with 2 doses, persons with hysterectomy	l, i, c
Hvs	Vaccinated with waned immunity, persons with hysterectomy	l, i, c
Hw	Infected vaccinated, persons with hysterectomy	l, i, c
Hqs	Recovered vaccinated without sero-convertion, persons with hysterectomy	l, i, c
Hq	Recovered vaccinated with sero-convertion, persons with hysterectomy	l, i, c
N	Total number of persons	l, i, c
CIN2	Undetected cervical intraepithelial neoplasia 2	l, i, c
CIN3	Undetected cervical intraepithelial neoplasia 3	l, i, c
CIS	Undetected carcinoma <i>in situ</i> 1	l, i, c
DCIN2	Detected cervical intraepithelial neoplasia 2	l, i, c
DCIN3	Detected cervical intraepithelial neoplasia 3	l, i, c
DCIS	Detected carcinoma <i>in situ</i> 1	lic
TCIN2	Treated cervical intraepithelial neoplasia 2	lic
TCIN3	Treated cervical intraepithelial neoplasia 3	l, i, c
TCIS	Treated carcinoma in situ	l, i, c
ICIN2	Infectious after treatment cervical intraepithelial neoplasia 2	l.i.c
ICIN3	Infectious after treatment cervical intraepithelial neoplasia 3	lic
ICIS	Infectious after treatment carcinoma in situ 1	lic
CCI	Undetected local cervical cancer	l, i, c
CCr	Undetected regional cervical cancer	l, i, c
CCd	Undetected distant cervical cancer	Lic
DCCl	Detected local cervical cancer	1
DCCr	Detected regional cervical cancer	1 i
DCCd	Detected distant cervical cancer	1 i
SCC	Cervical cancer survivals	1 i

Table 2. Variable notations, definitions, and dimensions.

#### Discussion

In this study, an age-structured HPV infectious disease model was adapted from the literature, updated, and validated for understanding the effects of HPV vaccination on cervical cancer progression in Texas and comparing them with those for the US overall. Model parameter values were taken from the literature or calibrated by using epidemiological data from Years 2000 to 2010. Model prediction results were validated against cervical cancer incidence for Years 2001–2010, matching the actual data well. The model shows a rapid initial decline of predicted incidence for the first 10 years and then a slower decrease after that. This predicted decreasing trend in incidence is consistent with the real trend observed over the past 7 years (2010–2017). As our study only considered the effect on HPV-16 and -18, the subsequent slower rate of decrease in cervical cancer incidence may represent incident cases due to other HPV types. Previous studies have demonstrated the lack of type-replacement following vaccination, supporting this trend. The model was then used to predict cervical cancer incidence rates for Texas and the US until Year 2110. Interestingly, when the progression rates from CIN to CIS were small, the five parameters used for the sensitivity analysis, parameters that are frequently chosen for this type of analysis, did not have a significant impact on the predicted cancer incidence<sup>24,25</sup>. More importantly, both the prediction and sensitivity analysis results suggested a clear difference between the Texas and the US populations in response to disease dynamics or policy changes.

Readers should be aware of several restrictions in this study. First, model fitting was not performed because of the lack of feasible regression techniques for large-scale ODE systems; therefore, parameter values were from the literature or estimated using available data or based on certain assumptions. A better match between model outputs and real data is expected if model fitting becomes feasible in the future. Second, a constant vaccination rate was assumed and thus might not truthfully capture the real evolution of vaccination strategy over time. Therefore, our prediction results may be conservative. Third, the age-structure model is of a very large scale, comprising more than 6,000 equations and a large number of parameters. Thorough interrogation of every aspect of this model (e.g., its robustness and predictive power) was not feasible in one study. Thus, one may consider reducing model complexity by dropping certain parameters or variables if their roles are trivial. Fourth, the proposed model was validated only by comparing the predicted cervical cancer incidence with the actual data from Years 2000 to 2010. When more data become available, further assessment of model validity is necessary to meet our goal of better assessing the health impacts of different vaccination strategies as well as their cost-effectiveness. Finally, solving a large system of ODEs repeatedly is computationally expensive. High performance computing techniques or alternative modeling approaches (e.g., microsimulation) may be considered in future work.

In summary, this study quantitatively investigated the HPV-related cervical cancer incidence in both Texas and the US using an age-structured model. The differences revealed via computer simulation and prediction in the Texas and US populations and disease dynamics suggest the necessity of further research work on the state level. These results provide a basis for future modeling of HPV-related cervical cancer incidence as well as the investigation of economic impacts of HPV vaccination related to prevention of cervical cancer.

#### Methods

**Age-structured model.** Building a mathematical model from scratch to depict population growth, HPV transmission, vaccination, and natural history of HPV-related cervical cancer demands tremendous effort and time. Therefore, we adapted the previously compared and validated nonlinear age-structured model framework proposed by Elbasha and colleagues<sup>17,19,20</sup>. This modeling framework comprises three major coupled components: the demographic, the epidemiological, and the cervical cancer natural history models for different sexes as well as different age groups. The demographic model describes the population dynamics of 23 consecutive age groups (from age 0–1 to age  $\geq$ 85 years); the HPV epidemiology model describes the incidence and progression of cervical cancer in women.

In the demographic model, individuals of one age group transfer to the next successive age group, except for the oldest (age  $\geq$ 85 years) group, at an age- and sex-specific rate. For example, the calibrated parameters suggested that around 13% of 8-year-old females from the second age group (age 1–8 years) move to the third age group (age 9–10 years) every year for both Texas and the US. The population size of an age group of specific sex depends on the proportions transferring from a younger group or into an older group and on cancer-related and non-cancer-related death. The population growth of the youngest age group is calculated from the birth rate because no younger population exists. In the epidemiological model, HPV transmission among subpopulations is specific to sex, age, and sexual activity. The female populations of various ages and sexual activity levels were further dichotomized by cervical cancer screen status (never or routine). Important subpopulations in this transmission model include susceptible individuals, infected individuals, persistently infected vaccinated individuals, and recovered vaccinated individuals. In the cancer natural history model, the pre-cancer and post-cancer stages consist of undetected CIN, treated CIN, infected treated CIN, benign hysterectomy, undetected cervical cancer, detected cervical cancer, and cervical cancer survivors.

Several changes were made to the model of Elbasha *et al.*<sup>17,20</sup> to reflect the current understanding of HPV transmission and cervical cancer progression. First, the updated natural history model of cervical cancer from Campos *et al.*<sup>18</sup> was incorporated into Elbasha *et al.*'s model, where CIN1 was combined with the HPV-infected state and CIN2 and CIN3 were treated as non-sequential states<sup>18</sup>. Second, Elbasha *et al.* made a distinction between two subtypes of undetected CIS; however, since the two CIS subtypes are not clinically distinguishable, CIS was not divided into two stages in our model. Third, the three-dose HPV vaccination strategy has recently been replaced by a two-dose strategy<sup>26</sup> therefore, the populations who received two or more doses were combined into one population in our model. Such a change affects many model structure details. For instance, the force of HPV infection ( $\lambda$ ) was determined by

$$\lambda_{k'\text{li}} = \beta_{k'} \frac{\sum_{j=1}^{23} \sum_{a=1}^{3} c_{klaij} \rho_{klaij} (Y_{kaj} + U_{kaj} + C_{kaj} + r_k (WS_{kaj} + P_{kaj}))}{O_{kaj}}$$

where  $c_{klaij}$  is the number of sexual partners,  $r_k$  is the relative infectivity of vaccine breakthrough cases,  $\rho_{klaij}$  is the probability of someone being in group k, l, a, i and j. Here, k denotes sex, l denotes sexual activity group, i denotes

age class, *a* denotes the sexual activity group that an opposite-sex partner was from, and *j* denotes the age class for the partner; *Y* and *U* denote infected and persistently infected persons, respectively; C includes undetected cervical cancer and detected cervical cancer populations; WS denotes infectious vaccinated persons. In a deviation from the model of Elbasha *et al.*, here *P* consists of *P*1 and *P*2 only, which denote the persistently infected vaccinated persons who receive one or two doses, respectively. Finally, the complete model equations are given in Supplementary Text S1; also, simplified model structure diagrams are provided in Supplementary Figures S1–S3.

**Model parameters.** Model parameter notations, definitions, and sources of parameter values are presented in Table 1; and model variable notations, definitions and dimensions are listed in Table 2. When certain parameter values were not available in the literature, parameters were calibrated on the basis of the best available data or knowledge on HPV infections and the natural history of cervical disease. For age group–specific parameters, sexual activity was divided into three levels according to number of sex partners<sup>27,28</sup> and screening characteristics (two levels), also categorized by age<sup>29</sup>. For previously infected or vaccinated individuals, we assumed that there exists no protection against future infection if no seroconversion was observed in these individuals. For a vaccinated individual with seroconversion, protection against future infection was assumed to be 100% because of the demonstrated efficacy of HPV vaccination<sup>30,31</sup>. Because Harper *et al.* showed no persistent infections following vaccination<sup>30</sup>, we assumed that no individuals with previous vaccination would develop premalignant cervical lesions if an infection occurred following vaccination.

The occurrence rate of undetected cervical premalignant disease was estimated from the sensitivity and specificity of the conventional Pap smear<sup>32</sup>. Patients with detected CIN3 or CIS were assumed to have received treatment according to standard practice. Since no data were available to estimate the number of undetected cervical cancer cases (those "patients" are not treated and thus incur minimal costs), the undetected cancer cases were ignored in our model.

**Simulation.** The model was implemented in MATLAB software (MathWorks, Natick, MA) and solved using the ode15s solver. All the simulation studies were conducted for both the Texas and the US populations. Specifically, the entire population was divided into two sex groups and 23 age groups (0 to <1, 1–8, 9–10, 11–12, 13–14, 15–17, 18, 19, 20–24, 25–26, 27–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and  $\geq$ 85 years). The population was further stratified into three sexual activity groups according to the number of partners (0–1, 2–4, and  $\geq$ 5 partners). The cervical cancer screening behavior for females was dichotomized into two categories (never or routine).

The US and Texas annual cancer incidence data by age group and cancer site were available from Year 2000 to 2010 in the SEER and TCR databases (https://seer.cancer.gov/ and https://www.dshs.texas.gov/tcr/). The Year 2000 data were used as initial conditions for the model to predict the Years 2001–2010 outcomes, and the Years 2001–2010 data were compared with the model prediction results for validation purposes. Similarly, using the Year 2010 data and parameter values in the model, the cervical cancer incidence rates from Year 2011 to 2110 were predicted for both Texas and the US. All parameter values and initial conditions for Texas and the US are listed in Supplementary Texts S2 and S3.

#### **Data Availability**

All the data used in this study are from public sources.

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#### **Author Contributions**

H.L.P. and C.Z. contributed to model development, computational analyses, and manuscript writing. S.T., L.R., L.X., K.D., C.F.W., and S.F. contributed to model refinement, model parameter calibration, and result interpretation. W.C. oversaw all the statistical issues and contributed to simulation and prediction studies. EMS contributed to model development and validation. W.C., L.R., D.R.L., and H.M. proposed the idea, oversaw the study, and significantly contributed to manuscript preparation. All authors have read and approved the final version of the manuscript.

#### **Additional Information**

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