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Estimated impact of human papillomavirus vaccines on infection burden: The effect of structural assumptions

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ABSTRACT

Mathematical models have been used to estimate the impact of human papillomavirus (HPV) vaccines on infection burden and cervical cancer. Models assume different mechanisms of naturally acquired immunity against re-infection, but processes of latency and reactivation of latent infection have not been explored. This study uses an individual-based dynamic model to simulate randomised controlled trials (RCTs) for vaccine efficacy, using different assumptions about naturally acquired immunity and viral latency after clearance of HPV infection. Model estimates of vaccine effectiveness are compared to those from published RCTs. We then estimate the impact of the bivalent vaccine on HPV-16 and -18 infection burden in South Africa under these different assumptions. When assuming no latency, simulated vaccine effectiveness overestimates results from RCTs and the model cannot match the observed difference in vaccine effectiveness between total vaccinated cohorts and more HPV-naïve cohorts. The reduction in HPV-16 and -18 burden by 2045, following roll-out of vaccination in 2014, does not depend on assumptions about natural immunity, but models that assume no latency predict ~25% greater reduction in HPV-16 and -18 burden than models that include reactivation of latent infection for all men and women. Mathematical models that do not allow for reactivation of latent HPV infections may therefore overestimate the long-term impact of HPV vaccines.

1. Introduction

Mathematical models of infection with human papillomavirus (HPV) and its progression to cervical cancer have been crucial in estimating the epidemiological and economic impact of cervical cancer prevention strategies such as vaccination and screening. There is general consensus in the literature on the progression of disease – persistent HPV infections progress to cervical cancer through two or three stages of pre-cancerous cervical disease [1]. On the other hand, there is uncertainty regarding the biological process after HPV is no longer detectable. Three possible events have been proposed in literature: (1) immediate susceptibility to re-infection with the same HPV type, (2) naturally acquired immunity against re-infection with the same HPV type and (3) viral latency that may reactivate [1].

There is evidence of both immunity and latency, but their extent and duration are difficult to estimate from epidemiological studies. It has been shown that only about 40–60% of women seroconvert following HPV infection [2] and this fraction is much lower for men and HIV positive women [3,4]. Beachler et al. [5] performed a systematic review and meta-analysis of studies that estimated the impact of HPV seropositivity on HPV re-detection. They estimate that seropositive women have a 30% reduced risk of re-detection compared to seronegative women, but no significant difference in risk of HPV re-detection could be shown in the studies in heterosexual men. The longitudinal studies with shorter follow-up found stronger protection against new HPV detection associated with baseline seropositivity, compared to studies with longer follow-up. This may indicate that natural immunity wanes over time, but reactivated latent infections could also account for some of the new HPV detection.

Maglennon et al. [6] have shown that inducing immune suppression in rabbits previously infected with papillomaviruses leads to detectable levels of virus. Such a study would be unethical in

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humans, but studies that included immune suppressed (HIV positive) women have shown new detection of HPV in women who reported no recent sexual activity, suggesting reactivation of latent infection is possible, particularly in immune-suppressed individuals [7,8]. In a review paper, Gravitt [9] concluded that not all recurrence of HPV infections can be explained by new sexual partners and subsequent analyses of longitudinal studies support this conclusion [10–13].

Epidemiological models of HPV natural history have used different assumptions about naturally acquired immunity. For example, some do not include such a state [14,15], while a number of models allow individuals to enter an immune state upon clearance and become susceptible again according to some rate [16–20]. In some models a proportion of individuals clearing HPV infection are assumed to obtain lifelong immunity and the remainder become susceptible to new infection upon clearance [21,22]. In another model, all individuals who clear an HPV infection are assumed to enter a lifelong partially immune state, with a constant reduced risk of being re-infected [23].

Only one model explicitly includes viral latency in the natural history of HPV. Korostil and Regan [24] developed a dynamical model of HPV-16 transmission in Australia where both men and women obtain naturally acquired immunity or enter the latently infected stage. In this model only women can experience reactivation of the infection and all the infections of latently infected women reactivate at menopause. Ranjeva et al [25] shows that a model that includes a higher risk of newly detected HPV for individuals with previous infections fits better to longitudinal HPV prevalence data than a memoryless model. The authors suggest that reactivation of latent infection or autoinoculation from other sites could explain this increased risk.

Models with different HPV natural history structures may fit equally well to epidemiological data from the pre-vaccine era, but may estimate different levels of vaccine effectiveness. Two highly effective HPV vaccines have been available for the last decade, and modelling studies have estimated the potential impact of these vaccines on HPV burden [26]. The current study uses an individual-based dynamic model to investigate how well model estimates of vaccine effectiveness compare to those in randomised controlled trials (RCTs) for different assumptions about naturally acquired immunity and viral latency after infection becomes undetectable. We then estimate the future impact of the bivalent vaccine on HPV-16 and -18 infection burden in South Africa under these different assumptions.

2. Methods

The individual-based model, MicroCOSM, was used to estimate the burden of HPV-16 and -18 in this analysis [27,28]. The model simulates, at weekly time steps, the HIV epidemic, infection with thirteen oncogenic HPV types and the underlying sexual network in the South African population. HPV types are independently simulated and HIV co-infection is assumed to increase duration of HPV infection and rates of reactivation of latent infections, where applicable. The HIV and sexual behaviour components are described in the appendix and in previous publications [27,28].

In this study, four distinct stages of HPV infection are considered: (1) Susceptible to HPV infection, (2) HPV DNA positive infection, (3) Latent HPV infection i.e. infection not detectable by nucleic acid amplification tests and (4) cleared infection with naturally acquired immunity to HPV re-infection (Fig. 1). Six different models of movement between these stages, as described in Table 1, are compared.

The six models are calibrated to South African type-specific HPV prevalence data (appendix Table A4) using a likelihood based approach. Prior distributions are specified for the key parameters

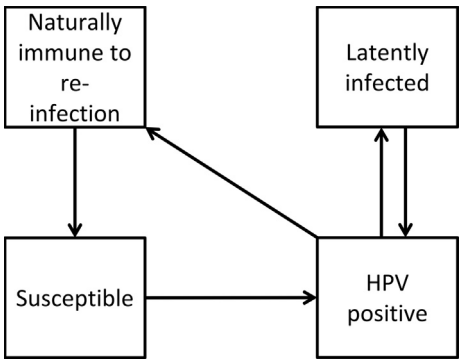

Fig. 1. Natural history of human papillomavirus in Model 1.

Table 1
Six structures for natural history of human papillomavirus.

Model Name	Description of possible events after HPV DNA becomes undetectable
Model 1	All individuals become either immune to re-infection or latently infected. Natural immunity wanes (individuals become susceptible again) and latent infections can reactivate (Fig. 1).
Model 2	All individuals become immune to re-infection and immunity wanes. No one becomes latently infected.
Model 3	All individuals become either immune to re-infection or latently infected. Immunity wanes and infections can only reactivate in HIV positive individuals.
Model 4	Women become either immune to re-infection or latently infected. Men become immune. Immunity wanes and infections can reactivate in women.
Model 5	All individuals become either immune to re-infection, latently infected or immediately susceptible to re-infection. Those who become immune remain immune forever. All latent infections can reactivate.
Model 6	All individuals become either partially immune to re-infection or latently infected. Latent infections can reactivate and the reduced risk of re-infection in the immune stage is lifelong and constant.

driving HPV infection: per sex-act transmission probabilities; durations of detectable and latent infection (both dependent on stage of HIV infection); duration of natural immunity; probability of becoming susceptible, naturally immune or latently infected after HPV clearance; and a parameter quantifying between study variability (appendix Table A2). Five hundred thousand parameter combinations are randomly sampled from the prior distributions for each HPV type. For each parameter combination, a likelihood value is calculated to quantify how well model estimates of HPV prevalence compare to data collected in observational studies. This likelihood value is used as a weight to resample 500 parameter combinations that represent the posterior distributions of the parameters [29]. More details on the calibration method, prior- and posterior distributions for HPV types 16 and 18, for each model structure, are given in the appendix (Tables A5 and A6).

2.1. Vaccine effectiveness

The samples of 500 parameter combinations from the posterior distributions of each HPV type and of each model structure are used to simulate RCTs of vaccine efficacy. Trials are simulated to correspond in design to the RCTs performed for young women (aged 15–25) [30,31] and women older than 25 [32]. For both types of trial, HIV negative women in the simulated population are enrolled in 2014 and randomised to receive the vaccine or not. Women are followed bi-annually for four years. Vaccine effectiveness is assessed at two levels of prophylactic efficacy against inci-

dent HPV16/18 infection through sexual contact: 100% or 95% of vaccinated women obtain lifelong protection (from here on called "take efficacy").

In the analysis of the simulated trial data, the outcome of interest is infection with HPV16/18 that persists for at least six months, similar to the primary outcomes in the RCTs [30–32]. In the analysis of Kreimer et al. [31], results were shown for the "modified total vaccinated cohort" (m-TVC), which excluded women who were HPV16/18 DNA positive at enrolment, and the "naïve total vaccinated cohort" (n-TVC), which excluded women DNA positive for any oncogenic HPV or seropositive for HPV16/18. In the study described by Harper [30], only the "naïve" cohort was enrolled in the study i.e. only women seronegative for HPV16/18 and DNA negative for all oncogenic HPV types were randomised to receive the vaccine. Results from the study in women aged 25 and older [32] are compared for the "total vaccinated cohort" (TVC) where women with prevalent infection or seropositive to HPV16/18 were not excluded, and the "according to protocol" cohort, where these women were excluded. To simplify notation in our analysis, we will label the latter cohort similar to the naïve cohort in younger women, i.e. n-TVC.

In the PATRICIA trial, which contributed ~75% of women in the combined analysis in [31], and in the trial described in [30], women who reported more than 6 lifetime partners (LTP) were excluded. Women tend to under-report total numbers of sexual partners [33]. We show results for simulated cohorts that only included women with <=6 LTP at baseline, but as a sensitivity analysis we also show results for cohorts without this exclusion criteria. To compare results to [32], we match distribution of the reported LTP in the RCT by ensuring that 75% of women enrolled in the simulated cohorts had fewer than 6 LTP. For older women, the under-reporting of LTP may be subject to not only social desirability bias, but also recall bias and therefore we also show results for simulated cohorts with no exclusion based on LTP. In our setting, with much higher HIV prevalence than in the vaccine RCT settings, the women with the highest numbers of partners are mostly excluded based on HIV-positive status.

We do not explicitly model HPV seropositivity, but consider two scenarios to approximate the effect of excluding women based on positive serostatus: (1) all women in the naturally immune stage are seropositive or (2), in addition, half of women in the latently infected stage are seropositive. There is an association between seropositivity and viral load [2], and since latent infections are undetectable, women in the latently infected stage are less likely to be seropositive.

2.2. Long term impact of vaccination

The sample of 500 parameter combinations from the posterior distributions are also used to simulate HPV infection up to 2045. Since 2014, the bivalent vaccine that protects against HPV types 16 and 18 has been administered in a two-dose schedule to 9 year-old girls at public schools in South Africa. We estimate the reduction in population level HPV-16 and -18 prevalence relative to the counterfactual in which there is no vaccination. Estimates are obtained assuming 100% of vaccinated women obtain lifelong protection against incident infection. Efficacy is assumed to be the same after HIV seroconversion. Vaccination uptake is assumed to have been 90% since 2014 [34,35] and to stay constant until 2045.

3. Results

The six model structures all fit well to type specific prevalence data (appendix Figs. A4 and A5) and the age patterns of overall HPV prevalence are consistent with data (appendix Fig. A6). The standard deviation of the parameter quantifying between-study variability is largest for Model 2, which may indicate worse fit than the other models (appendix Tables A5 and A6).

3.1. Vaccine effectiveness

Vaccine effectiveness for simulated RCTs of women aged 15–25, using the six model structures described in Table 1 is shown in Table 2. In the models that allowed for latency, vaccine effectiveness is estimated to be higher when excluding HPV-seropositive individuals (n-TVC analysis) than when including seropositive individuals (m-TVC analysis), with the difference being particularly substantial if women with higher numbers of partners are not excluded. This is consistent with the observations of Kreimer et al [31]. In contrast, Models 2 and 3 (which assume no or little HPV reactivation) estimate little change in effectiveness associated with different exclusion criteria. Models 2 and 3 are more consistent with observed vaccine effectiveness when assuming 95% prophylactic take efficacy than when assuming 100% prophylactic take efficacy; in the other models, either assumption could be consistent with observed effectiveness, depending on the extent to which high-risk women are excluded. In this analysis, only women who become HIV positive during the simulated trials contribute to reactivation in Model 3, and therefore results of Models 2 and 3 are very similar. This would not be the case if HIV positive women were included in the simulated RCTs.

Table 3 shows the simulated vaccine effectiveness when the vaccine is provided to women aged 25 and older. On average, estimates from Models 1 and 4–6 compare well to RCT estimates when simulated data match RCT data based on LTP distribution, for both the TVC and n-TVC if it is assumed that there is significant seropositivity during latent HPV infection. Confidence intervals around model estimates are wide due to very few incident cases in this low risk population. When all women are included in simulated cohorts, regardless of LTP, model estimates of effectiveness are lower. Wide confidence intervals around model and RCT estimates make it difficult to identify the model structures that are most consistent with the RCT data. Nevertheless, Model 2 produces higher levels of effectiveness than observed in RCTs [32], and only when an efficacy of 80% is assumed does Model 2 match the observed effectiveness in the RCT (results not shown).

3.2. Long term impact of vaccination

The six different HPV natural history structures estimate similar mean HPV-16 and -18 prevalence for males and females aged 15 or older in 2014, the year that vaccination is initiated in 9 year old girls (Table A9). All six model structures predict significant reduction in HPV16/18 prevalence by 2045, but with marked differences between structures with and without latency (Fig. 2). Model 1 predicts 66.5% (95% CI 52.5–83.3%) and 63.3% (48.5–86.1%) reduction in HPV-16 and -18 prevalence respectively. The model without any latency (Model 2) predicts much greater reduction in HPV-16 and -18 prevalence by 2045 (88.0% (77.4–96.5%) and 89.9% (73.2–100%) respectively). HPV16/18 prevalence also reduces substantially for men, through herd immunity. Although reductions in men are lower than for females and estimates have more uncertainty, reductions predicted for both men and women by the model without latency are ~25% greater than reductions predicted by the models with latency (Fig. 2). For men and women, reductions in prevalence for models 1, 5 and 6 are very similar, indicating that different structures for natural immunity do not play an important role in predicting the long term impact of vaccines. These results are based on the assumption that all vaccinated women experience

Table 2
Vaccine effectiveness against persistent HPV 16 or 18 infection among 15–25 year old women. Mean effectiveness among the 500 simulated trials is shown, along with the 2.5th and 97.5th percentiles.

	<=6 Lifetime partners			No limit on number of lifetime partners		
	m-TVC	n-TVC*	n-TVC**	m-TVC	n-TVC*	n-TVC**
Kreimer [31]	89.1 (86.8;91.0)	93.6 (91.2;95.5)	93.6 (91.2;95.5)	89.1 (86.8;91.0)	93.6 (91.2;95.5)	93.6 (91.2;95.5)
Harper [30]		96.0 (75.2;99.9)	96.0 (75.2;99.9)		96.0 (75.2;99.9)	96.0 (75.2;99.9)
100% prophylactic efficacy against HPV16/18 infection						
Model 1	95.9 (90.1;99.3)	97.2 (91.7;100)	98.5 (94.6;100)	86 (72.5;95)	90 (78.3;97.7)	94.4 (86.2;99.2)
Model 2	100 (100;100)	100 (100;100)	100 (100;100)	100 (100;100)	100 (100;100)	100 (100;100)
Model 3	99.7 (98.4;100)	99.9 (99;100)	100 (99.1;100)	98 (95;100)	99 (96.6;100)	99.5 (97.9;100)
Model 4	95.5 (89.1;99.3)	97 (91.7;100)	98.6 (95;100)	84.9 (71.2;95.8)	89.2 (76.7;97.5)	93.9 (85.6;99.2)
Model 5	95.4 (90.3;98.8)	96.8 (93.1;99.5)	98.4 (95.7;100)	84.3 (73.0;92.0)	88.3 (78.6;94.8)	93.4 (87.1;97.7)
Model 6	95.7 (90;99.2)	97 (92.2;100)	98.4 (95.1;100)	85.6 (75.7;92.9)	88.8 (79.5;95.7)	93.7 (87.2;98.5)
95% prophylactic efficacy against HPV16/18 infection						
Model 1	91.3 (85.4;96.5)	92.6 (86.5;98)	93.9 (88.5;98.3)	81.9 (68.6;91.4)	85.7 (74.8;94.2)	89.9 (82.1;96.3)
Model 2	95.5 (91.1;98.8)	95.5 (90.8;99.2)	95.5 (90.8;99.2)	95.4 (92.5;97.9)	95.4 (90.7;98.9)	95.4 (90.7;98.9)
Model 3	95 (90.8;98.4)	95.2 (90.5;99)	95.3 (90.5;99)	93.5 (89.3;96.7)	94.4 (89.8;98.2)	94.8 (90.3;98.4)
Model 4	91 (83.3;96.7)	92.4 (85.1;97.5)	93.9 (87.7;98.4)	81 (67.5;91.4)	84.9 (72.4;94)	89.4 (79.6;96)
Model 5	90.9 (85.3;95.2)	92.4 (87.2;96.4)	93.8 (89.6;97.0)	80.4 (70.0;88.7)	84.1 (74.7;91.6)	89.0 (82.1;94.2)
Model 6	91.1 (84.5;96.2)	92.4 (85.1;97.2)	93.8 (88.2;98.1)	81.5 (71;89.5)	84.6 (74.4;92.2)	89.3 (82.2;95.6)

m-TVC – In the modified total vaccinated cohort, women who were HPV16/18 DNA positive at enrolment were excluded.
n-TVC – In the naïve TVC, women who were HPV16/18 seropositive or DNA positive with any oncogenic type were excluded.
* Only women in the immune stage are seropositive.
** In addition, 50% of women in the latent stage are seropositive.

Table 3
Vaccine effectiveness against persistent HPV 16 or 18 infection among women aged 25 and older. Mean effectiveness among the 500 simulated trials is shown, along with the 2.5th and 97.5th percentiles.

	Matching LTP distribution			No limit on number of LTP		
	TVC	n-TVC*	n-TVC**	TVC	n-TVC*	n-TVC**
Skinner [32]	47.0 (25.4;62.7)	82.9 (53.8;95.1)	82.9 (53.8;95.1)	47.0 (25.4;62.7)	82.9 (53.8;95.1)	82.9 (53.8;95.1)
100% prophylactic efficacy against HPV16/18						
1	48.4 (−16.2;88.2)	56.3 (−21.4;100)	72.4 (−5.3;100)	40.2 (13.4;66.3)	46.9 (14.0;78.1)	62.6 (22.6;88.1)
2	80.2 (21.4;100)	100 (100;100)	100 (100;100)	76.3 (57.2;90.3)	100 (100;100)	100 (100;100)
3	77.5 (3.1;100)	95.2 (51.8;100)	98.4 (73.7;100)	70.6 (47.9;87.0)	91.0 (71.1;100)	95.7 (81.2;100)
4	44.6 (−40.8;91.9)	52.1 (−32.9;100)	69.3 (−28.3;100)	34.7 (5.1;65.3)	40.7 (5.0;76.1)	57.2 (20.0;86.4)
5	47 (−17.3;90.7)	55.3 (−19.6;100)	70.7 (−13.6;100)	33.4 (4.5;58.5)	40.0 (8.7;68.0)	58.4 (19.5;86.4)
6	46.6 (−25.5;90.1)	53.8 (−21;100)	71.1 (−18.3;100)	34.9 (6.4;60.8)	35.7 (0.6;63.4)	54.3 (15.7;84.5)
95% prophylactic efficacy against HPV16/18						
1	46.4 (−19.1;87.6)	53.5 (−24.5;100)	68.6 (−16.3;100)	38.4 (12.2;64.7)	44.8 (11.5;74.1)	59.7 (18.5;85.3)
2	76.8 (18.9;100)	95.9 (63.4;100)	95.9 (63.4;100)	73.0 (54.1;87.6)	95.6 (86.2;100)	95.6 (86.2;100)
3	74.7 (−3.9;100)	91.5 (42.5;100)	94.4 (52.5;100)	67.2 (43.1;84.3)	86.6 (65.9;100)	91.0 (71.4;100)
4	42.9 (−41.4;91.6)	50 (−34.2;100)	67.4 (−26;100)	33.2 (4.0;62.4)	39.1 (2.3;73.5)	54.7 (14.4;84.6)
5	44.5 (−21.2;88.3)	52.2 (−22;100)	67.4 (−20.8;100)	31.9 (3.0;56.9)	38.1 (7.6;66.6)	55.7 (16.9;83.6)
6	44.4 (−28.9;90)	51.1 (−23.8;100)	67.8 (−23.9;100)	33.4 (6.4;59.7)	34.1 (0.5;63.2)	51.7 (11.1;83.1)

TVC – In the total vaccinated cohort, women with prevalent infection or seropositive to HPV16/18 were not excluded.
n-TVC – In the naïve TVC, women with prevalent infection or seropositive to HPV16/18 were excluded.
* Only women in the immune stage are seropositive.
** In addition, 50% of women in the latent stage are seropositive.

lifelong protection against HPV acquisition. Results for three alternative assumptions are shown in the appendix (Figs. A7-9).

4. Discussion

In this study we consider six different models of HPV natural history that differ in terms of assumptions regarding natural immunity to re-infection and reactivation of latent infection after HPV DNA is no longer detectable. In simulated RCTs, vaccine effectiveness against persistent HPV16/18 infection is compared to estimates from RCTs. Among young women, the model without latency fails to match the relative difference in effectiveness when applying different DNA- and seropositivity exclusion criteria. In this model structure, all vaccinated women are equally protected against new detection of HPV16/18 and the additional exclusion of seropositive women and women who are DNA positive with other oncogenic HPV types reduces the number of cases and number exposed equally. In the model structures that include reactivation of latent infection, the higher risk women are more likely to have latent HPV16/18 infections. Reactivated infections will lead to vaccine effectiveness that is less than prophylactic vaccine efficacy, but the stricter the trial exclusion criteria are in excluding higher-risk women and women with prior/current infection, the smaller the difference between effectiveness and efficacy is likely to be.

For older women, the model without latency overestimates vaccine effectiveness. When no latency is assumed, simulated vaccine effectiveness is the same in younger and older women, in contrast to RCTs, which estimate a ~10% difference in effectiveness [30–32]. This observed age difference in vaccine effectiveness can only be matched by Model 2 if it is assumed that prophylactic vaccine efficacy is lower in older women than in younger women. Although various factors may influence vaccine induced immunity, antibody titre data suggest similar efficacy in vaccinated women in different

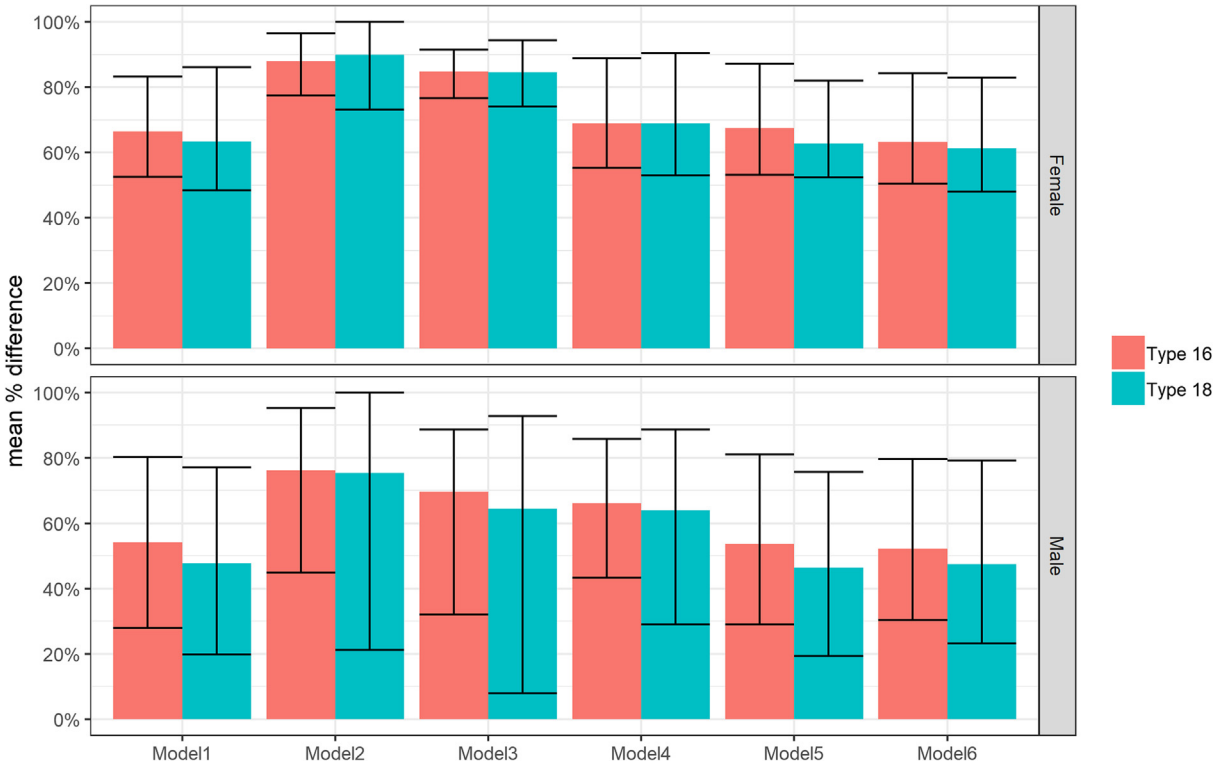

Fig. 2. Mean percentage reduction in HPV16/18 prevalence in 2045 for individuals aged 15+ with prophylactic vaccine efficacy of 100%. Vaccination coverage of 9 year olds girls is assumed constant between 2014 and 2045 at 90%.

age groups [30–32]. In the model structures that allow for reactivation of latent infection of all women, cases resulting from reactivation lead to vaccine effectiveness that better matches data.

In the analyses restricted to lower risk women, assumptions about natural immunity against re-infection did not have a clear impact on vaccine effectiveness. Assumptions about natural immunity also do not seem to play an important role in the long term impact of vaccination on HPV16/18 prevalence. For both men and women, there is a ∼25% difference in HPV prevalence in 2045 between Model 1 and Model 2. Latency and reactivation effectively increase the average duration of detectable HPV infection, which means that it takes longer for the vaccine to reduce the prevalence of HPV in Model 1 than in Model 2. We show impact on HPV prevalence for all ages (15+), as this will be a relevant predictor of cervical disease in 2045. In sensitivity analyses, we change assumptions about duration and degree of vaccine efficacy (Figs. A7-9). Although absolute values of estimates change, the substantial differences between estimates from Models 1 and 2 remain.

The results of this study could be generalizable to other settings. Although we compare results from models calibrated to South African data to results from RCTs performed in very different contexts, we do exclude women at baseline based on positive HIV status. Cost-effectiveness models of HPV-FASTER (strategies involving HPV testing and vaccinating women of all ages as cervical cancer prevention [36]) should consider the potential impact of reactivation of latent infections in the natural history assumptions.

The study has limitations. We do not explicitly include serostatus in the natural history of HPV and make crude assumptions about serostatus in this analysis to illustrate the effects of applying different exclusion criteria. A difference of ∼25% reduction in HPV burden between Models 1 and 2 does not directly imply ∼25% difference in cervical cancer reduction, but one would expect that model predictions of reduction in cervical cancer would also differ substantially if latency is allowed for or not. For a given model structure, parameter uncertainty leads to wide confidence intervals for model estimates and the confidence intervals around RCT point estimates are wide. This makes it difficult to judge which models are most consistent with the RCT data.

Although there is a growing body of evidence that HPV infections can become undetectable and reactivate to detectable levels, it is unknown whether reactivated infections in immunocompetent women are likely to persist to be of clinical significance [37]. In our model, reactivated infections are assumed to be as likely to persist at detectable levels as new infections. However, our estimated mean durations of latency are more than 15 years and therefore we do not simulate reactivation of intermittently-detectable infections, but only reactivations that could be of clinical significance. There is great uncertainty in this duration of latency, since there is no data to inform the parameter. Long term follow-up of cohorts such as those in [10–13], with viral load and sexual behaviour monitoring at regular intervals, could help inform this parameter.

5. Conclusion

This study argues that HPV natural history model structures that do not include reactivation of latent infections may not match the bivalent HPV vaccine effectiveness estimated in RCTs (which included sexually experienced women) as well as model structures that do include reactivation of latent infections. The choice of model structure also influences the predicted impact of HPV vaccination of sexually naïve women on HPV16/18 prevalence. Models that do not include a stage for latent HPV infection, and models in which only the infections of HIV-positive individuals can reactivate, may overestimate the long-term impact of HPV vaccination. Models that allow for latency may predict a slower decline in cer-

vical cancer incidence, which underscores the importance of ongoing screening programmes in addressing comprehensive prevention of cervical cancer.

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Author contributions

Cari van Schalkwyk: Conceived idea, performed analysis, wrote manuscript. **Jennifer Moodley**: Conceived idea, wrote manuscript. **Alex Welte**: Conceived idea, wrote manuscript. **Leigh F. Johnson**: Conceived idea, wrote manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.06.013.

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