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Validating the predicted impact of HPV vaccination on HPV prevalence, cervical lesions, and cervical cancer: A systematic review of population level data and modelling studies

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HIGHLIGHTS

- There is substantial impact of HPV vaccination on reducing HPV-related outcomes
- Models predicting the impact of HPV vaccination align with observed outcomes
- We can trust models to inform cervical screening strategies in vaccinated populations.

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ABSTRACT

Background. We compared model predictions with independently published primary data from population-based studies on the impact of HPV vaccination on HPV prevalence, cervical cancer and its precursors.

Methods. We searched Cochrane Library, EMBASE, MEDLINE, Web of Science for studies concerning high-income countries published between 2005 to June 2, 2023. Relative risk (RR) for HPV-related outcomes comparing the pre-vaccination and post-vaccination periods were collected from observational and modelling studies. The relationship between vaccination coverage and observed relative reductions was determined using meta-regressions, and we compared model prediction to observations.

Findings. We identified a total of 5649 potential articles, of which one systematic review, 14 observational studies and 32 modelling studies met our inclusion criteria. A clear relation was found between the RR of HPV diseases related outcomes in the pre- versus post-vaccination era and the vaccination coverage, with 23 out of 28 data points and 19 out of 20 data points showing significant reductions in HPV prevalence and CIN2+ prevalence respectively. Around 67 % (n/N = 12/18) of model predictions were more optimistic on HPV prevalence reductions compared to the 95 % CI of the meta-regression derived from observational studies. For CIN2+ lesions, 48 % (n/N = 31/64) of model predictions for CIN2+ outcomes fell within the 95 % CI.

Interpretation. Model predictions and observational data agree that HPV vaccination can have a substantial impact on HPV related outcomes on a population level. Despite large heterogeneity in observational data and modelling studies, it is particularly encouraging that model predictions on the impact of HPV vaccination on CIN2+ model lesions align with observational studies.

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Abbreviations: HPV, human papillomavirus; 2vHPV, bivalent vaccine against human papillomavirus; 4vHPV, quadrivalent vaccine against human papillomavirus; 9vHPV, nonavalent vaccine against human papillomavirus; CIN, cervical intraepithelial neoplasia; RCT, randomized controlled trial; RR, relative risk; SCC, squamous cell carcinoma; CI, confidence interval.

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Contents

1. Introduction

Human papillomavirus (HPV) associated cancers are a major public health burden with 730,000 cancer cases attributable to HPV infection reported worldwide in 2020 in both sexes [1]. Vaccination against HPV infection has been demonstrated to be highly effective in reducing the risk of developing cervical cancer in several randomized clinical trials [2]. Since 2006, bivalent (2vHPV), quadrivalent (4vHPV) and nonavalent (9vHPV) vaccines – protecting against high-risk HPV types HPV16/18, HPV16/18/6/11 and HPV16/18/6/11/31/33/45/52/58 respectively – have been implemented within national public health programmes in over 100 countries worldwide [3–7]. The population-level effects of these programs are expected to vary substantially between countries, depending on the vaccination coverage, type of vaccine, and implementation strategies (e.g. targeting girls only or gender neutral) [8,9]. Nevertheless, HPV vaccination will likely substantially affect the effectiveness and efficiency of cervical cancer screening strategies in vaccinated cohorts, as vaccinated women will be protected against many high-risk HPV infections, and unvaccinated women in vaccinated cohorts will have reduced risks due to herd immunity [10]. Careful revision of current screening guidelines in most countries is required to ensure that cervical cancer screening strategies remain effective and efficient [11,12].

Mathematical modelling has been key in shaping cervical cancer screening strategies in many countries [13–19], and will be an important tool in assessing optimal screening programs for vaccinated cohorts [20]. However, the introduction of HPV vaccination necessitates the addition of dynamic HPV transmission modelling to predict (herd-)immunity effects of vaccination strategies on the prevalence of HPV infections, pre-cancerous lesions (i.e. cervical intraepithelial neoplasia (CIN)), and/or cervical cancer in vaccinated cohorts. Although many modelling studies have already been performed [21], they usually lacked any real-world data to calibrate or validate the predicted impact of vaccination and herd immunity effects against, since population level vaccination strategies have only been implemented relatively recently. Hence, models differ substantially in their predictions of impact [21]. However, the rapidly emerging evidence from the maturing HPV vaccination programs on the impact of vaccination on HPV and cervical cancer outcomes allows us to now retrospectively validate previous model predictions against real-world data.

We systematically reviewed and validated modelling studies predicting the impact of HPV vaccination on HPV prevalence, CIN lesions, and cervical cancer incidence in high-income countries against real-world data. The search was limited to only high-income countries because these are most representative of a context with established vaccination and screening programs and are currently faced with the decision on how to shape cervical cancer screening for vaccinated cohorts. We performed three separate searches: (1) existing systematic reviews on population-level impacts of HPV vaccination; (2) empirical data studies published after the last systematic review; and (3) mathematical modelling studies on the population level impact of HPV vaccination. We then determined the relationship between vaccination coverage and observed relative reductions in HPV, CIN, and cervical cancer incidence, and assessed how model predictions compare to observations.

2. Methods

2.1. Search strategy and selection criteria

We followed the PRISMA guidelines [22], and performed three separate searches, in which we identified: (1) systematic reviews on primary data studies measuring the impact of HPV vaccination on HPV prevalence, CIN lesions, and/or cervical cancer, published between 2005 and June 2nd 2023; (2) primary data studies that were published between the last search date of the last published systematic review identified in search #1 and June 2nd 2023; and (3) modelling studies that predict the impact of HPV vaccination on HPV prevalence, CIN lesions, and/or cervical cancer published between 2005 and June 2nd 2023. We only included publications in English. Our searches were performed using Cochrane Library, EMBASE, MEDLINE, Web of Science, EconLit, and Google Scholar, and are described in more detail below. Full search terms can be found in Section S1 of the supplementary appendix.

2.2. Search 1: systematic reviews

We used MeSH and “all fields” search terms including “systematic review”, “HPV vaccination”, “impact”, “HPV prevalence”, “cervical intraepithelial neoplasia prevalence”, and “cervical cancer prevalence/incidence” and variation of these terms. Inclusion criteria were: (1) studies involved in the systematic review reported pre- and post-vaccination data on at least one HPV-related endpoint (genital HPV infection, CIN1+ or cervical cancer); (2) studies investigated the impact of real-world vaccination implementation strategies; (3) studies reported HPV vaccination coverage of the study population; (4) studies used the same population sources and recruitment methods before and after vaccination; (5) studies reported results for vaccinated cohorts rather than vaccinated individuals; (6) they examined the impact of HPV vaccination in a high income country, as defined by the World Bank fiscal year 2023; and (7) confidence intervals (CI) of the data

points were reported or could be calculated. Studies were excluded if: (1) they did not report any quantitative outcomes on frequency of the endpoints (prevalence or incidence); (2) no data were available for the pre- and post-vaccination periods; (3) they concerned a specific (high-risk) population such as HIV-infected people; (4) screening technology changed for the pre-and post-vaccination periods (e.g. from cytology to HPV test); (5) the study reported findings from clinical trials; and (6) a different study presented more recent results for the same target population and/or data collection method.

2.3. Search 2: primary data studies

In the second search, we used the same MeSH and "all fields" search terms as in the first search, changing only the "systematic review" term to "observational studies" and variations of this term\. Inclusion and exclusion criteria for the studies were the same as in the first search.

2.4. Search 3: modelling studies

In the third search, the MeSH search terms related to the type of the study were changed to "transmission models", "dynamic models" and variations of these terms. We applied the following inclusion criteria for the modelling studies: (1) the model(s) used were HPV transmission-dynamic mathematical models that were calibrated to epidemiological data; (2) studies reported outcomes on frequency of at least one HPV-related endpoint in both vaccinated and unvaccinated simulated cohorts; (3) studies reported HPV vaccination coverage; and (4) they simulated the impact of HPV vaccination in a high income country. Modelling studies were excluded if they studied a specific (high-risk) population. If more than one study was identified that reported the results from the same model and setting, only the most recent publication was included. If the same model was used for two different populations (e.g. from two different countries), both were included in our review.

2.5. Selection strategy and data extraction

Selection of the papers was performed in two rounds. In round one, screening of titles and abstracts of retrieved records for inclusion criteria was performed by two independent reviewers (EN and EJ). In round two, full texts were obtained from all studies included in round one and examined by two reviewers (EN and DB) to determine whether they met the inclusion criteria. Any disagreements between the two independent reviewers were resolved by consensus through discussion. EN and DB extracted the main study characteristics and outcomes using a standardized form. EJ checked the data extracted by the two authors for a randomly selected sample. No automation tools were used in the study selection process.

Data from studies within each of the systematic reviews were directly derived from the systematic reviews. Data were extracted systematically using a data extraction table covering both the main study characteristics and the primary outcomes of interest. The main study characteristics included the country, study population, sample size, age range of included population, period of data included, pre- and post-vaccination period, vaccine type, vaccine coverage and implementation strategy (i.e. targeting girls only, or gender neutral). The primary outcome was the relative risk (RR) of a specific condition post-vaccination compared to the pre-vaccination control group; i.e.: genital HPV infection with HPV16 and/or HPV18; CIN lesions divided in three groups according to the way data was reported (CIN1, CIN2/CIN2+ and CIN3/CIN3+); and cervical cancer. For those studies reporting results for different doses, different age-groups and different time periods since vaccination, we only included the highest doses, youngest age-group and longest time since vaccination, to obtain the best estimate of vaccination effect. If the same study reported results for different periods since vaccine introduction, but with different vaccine coverage for these time periods (i.e. coverage increased over time), we included all of them. For those studies reporting crude and adjusted estimates, we only included the adjusted ones. For the vaccination coverage, we included coverage for three doses, whenever possible, and the coverage among girls, in case a different coverage rate was reported for gender neutral vaccination. We performed a risk of bias assessment, following the framework from a previous review by Drolet et al. [9] From the identified modelling studies, we first stratified them by research group/model, as many papers will likely be based on the same or similar models. We then selected the most recent publication for each modelling group that quantifies the impact of vaccination on HPV prevalence, CIN lesions, and/or cancer by vaccination coverage level for a specific jurisdiction.

2.6. Analyses

Results were stratified by the type of outcome (i.e. HPV prevalence, CIN prevalence, or cervical cancer prevalence or incidence) and implementation strategy (i.e. targeting girls only or gender neutral). Results were visualized in forest plots for each of the outcomes of interest. The different categories are not mutually exclusive, thus studies may appear in more than one category if applicable. For instance, the same study may appear multiple times in one figure because it may report on various endpoints (i.e. different HPV types or CIN lesions), use different vaccination coverages, or examine different countries, vaccination scenarios and/or catch-up programs within the same study.

In the final step, we compared the results of the observational studies to the effects predicted by modelling studies by plotting the outcomes jointly in graphs. We again stratified the results by disease endpoint (HPV infection and CIN2+) and vaccination strategy (girls only vs gender neutral) and then we plotted them against stratified model estimates. We performed a random-effects meta-regression analysis to determine the association between vaccine coverage and the observed reductions of the different endpoints in the primary data studies. Weights were equal to the inverse of the study variance (i.e., studies with a larger population have a lower variance, and thus higher weight in the regression). Finally, we stratified by country so that we could directly compare the predicted effect with the observed effect for countries where both are reported. For CIN lesion outcomes, we only included primary data studies that had an observational time of at least five years and reported outcomes on CIN2+ for consistency with the modelling studies. If modelling studies for CIN2+ reported multiple time horizons, we only selected the longest time horizon in the base case. Sensitivity scenarios that include model outcomes for shorter horizons, exclude models considering nonavalent vaccination, and exclude models with a 100 year horizion can be found in figs. S3, S4 and S5 of the supplementary appendix. All analyses were performed using R version 4.2.1 and metafor package version 4.4–0.

3. Results

Figs. 1 and 2 show the flow charts of paper selection for the three separate searches. In the first search (i.e. the review of reviews), we identified 658 potentially eligible systematic reviews, of which one [9] met our inclusion criteria. The review described 18 unique studies [23–40]. In the second search, we identified 3790 additional observational studies published after the search date of the last systematic review, of which 14 met our inclusion criteria [25,41–47]. Therefore, we had a total of 32 studies, published between 2011 and 2023, covering 11 high-income countries (Fig. 1). Out of the 32 studies, 20 described observational data for genital HPV infection, 11 for CIN1+ lesions, and one for cervical cancer alone. In the third search, we identified 1201 potentially eligible modelling studies, of which 32 met our inclusion criteria, published between 2008 and 2019, involving 19 modelling groups and covering 18 high-income countries and with some studies appearing in multiple categories: seven for HPV infection [48–54], 11

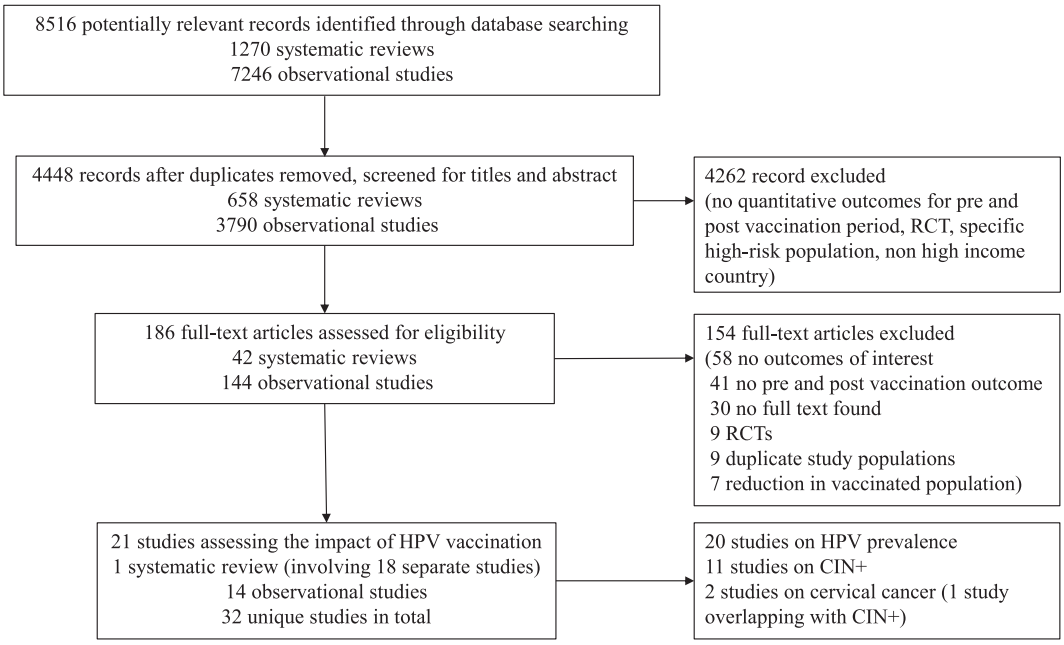

Fig. 1. Flow diagram of study selection process for the first and second searches *(systematic reviews and observational studies)*.

for CIN [52,55–64] and 26 for cervical cancer [52,55–79] (Fig. 2). Some studies evaluated multiple scenarios, yielding a total of 18 data points for genital HPV infection and 54 for CIN1+ lesions. We found none of the included studies to have a risk of serious bias (see supplementary appendix section S4).

Vaccine coverage in the data studies ranged from 1 % to 92 % (tables S1 and S2 supplementary appendix). Seven studies [25,36,38,43,47,80,81] reported a coverage less than or equal to 50 %, 17 studies [23,26–28,30,32,33,37,39,41,44–47,82–84] reported a coverage between 50 % and 80 %, and 12 studies [24,25,27–31,34,35,40,42,85] reported a coverage above 80 %. All 32 studies reported outcomes in settings where bivalent (nine studies) or quadrivalent (27 studies) vaccines were implemented in a routine vaccination program between the ages of 11 and 16. In 23 out of the 32 studies a catch-up vaccination campaign was also implemented. In three studies [27,30,40], the vaccine used switched during the study period, from bivalent to quadrivalent. The time between vaccination and analysis was shorter than 5 years in 16 of the data studies [24–28,30,32,33,35–40,47], between 5 and 10 years in 21 studies [23,27–31,34,36–40,42–45,47,82–85] and 10 years or longer in 5 studies [41,46,47,80,81]. Vaccine coverage in the modelling studies ranged from 30 % to 100 %, and several studies simulated more than one coverage level (tables S3 and S4

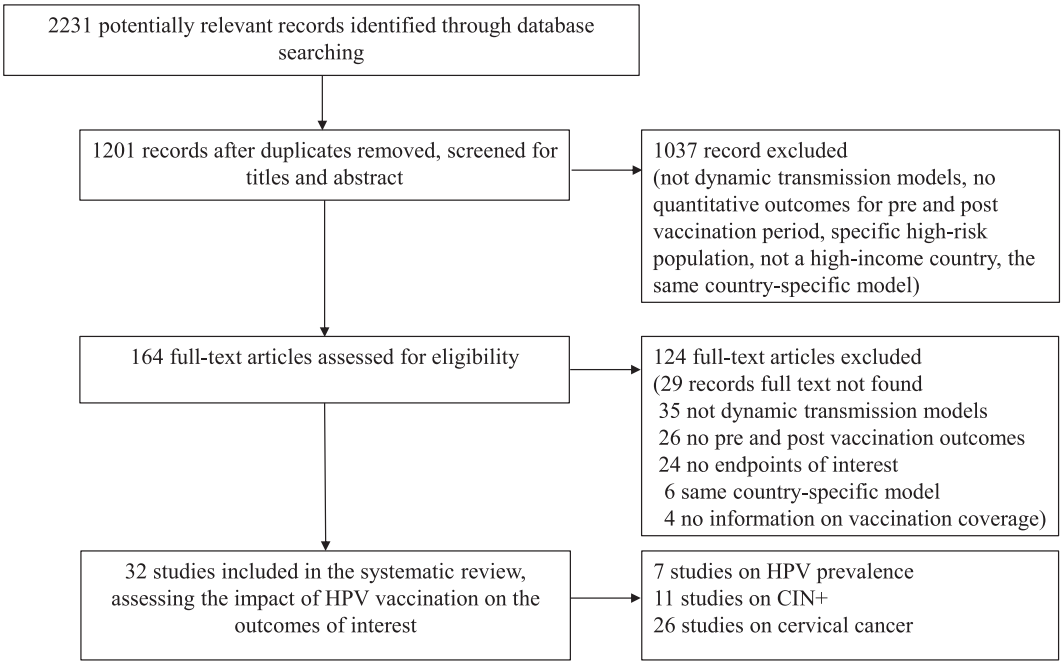

Fig. 2. Flow diagram of study selection process for the third search (*modelling studies*).

supplementary appendix). The 33 modelling studies simulated scenarios in which bivalent (15 studies) [48–52,54,57,58,63,67–69,74,75,77] or quadrivalent (21 studies) [50,51,53,55–57,59–63,65,68–73,76,78,79] vaccines were implemented, and five studies in which the nonavalent vaccine was implemented [64,66,68,72,76]. Four studies reported outcomes on two different vaccine types, i.e. bivalent and quadrivalent or bivalent and nonavalent [57,63,68,72]. The time horizon between vaccination and analysis was shorter than 50 years in 9 of the modelling studies [50,52,53,62,68–71,75] and 50 years or longer in 27 studies [48,49,51,54–67,70–79].

Fig. 3 shows the RR of genital HPV 16/18 infections in vaccinated versus unvaccinated cohorts as reported by primary data studies, stratified by implementation strategies and sorted by vaccination coverage. The 20 studies reported a cumulative total of 28 data points: 17 on girls-only (Fig. 3a) and 11 on gender neutral strategies (Fig. 3b). Twenty-three data points reported a significant reduction in HPV prevalence post vaccination, and 21 reported an RR below 0.5. RRs varied widely across the studies: from 0.02 [95 % CI 0.00–0.17] to 0.92 [95 % CI 0.78–1.08] in studies involving girls only vaccination and from 0.08 [95 % CI 0.01–0.60] to 0.91 [95 % CI 0.70–1.18] for gender neutral vaccination. Five reported no significant reduction, but mostly due to larg CIs, and one study (Dillner et al [25]) with barely any vaccination coverage (1 %).

Fig. 4 shows the RR for CIN1+ lesions among vaccinated cohorts in the included studies, stratified by implementation strategy (girls-only: Fig. 4a; gender neutral: Fig. 4b) and sorted by vaccine coverage. Eleven out of the 12 for girls only vaccination showed significant reductions in CIN or cervical cancer in women in vaccinated cohorts; RRs ranging between 0.03 [95 % CI 0.02–0.04] to 0.71 [95 % CI 0.64–0.80]. One study reported a higher risk of CIN2+ for women in vaccinated cohorts (RR = 1.06 [95 % CI 0.83–1.35]), with an average observational time of four years since vaccination, yet the finding was not significant. All eight data points involving gender neutral vaccination reported significant reductions in CIN or cervical cancer in women in vaccinated cohorts; RRs ranging between 0.35 [95 % CI 0.31–0.39] to 0.66 [95 % CI 0.63–0.69].

Fig. 5 shows model-predicted (red and blue) versus observed (black) RRs for HPV (Fig. 5a and b) and CIN2+ lesions (Fig. 5c and d) in vaccinated versus unvaccinated cohorts by vaccination coverage. The figures include a (weighted) meta-regression line for observational studies (solid black line, 95 % CI in grey), and are further stratified by vaccination strategy (i.e. girls-only in Fig. 5a and c and gender-neutral vaccination in Fig. 5b and d). The estimated I^2 statistic finds moderate between-study heterogeneity in all regressions except for Fig. 5d, where the low number of studies could explain an inaccurate estimate. The effect of vaccination coverage was found to be significantly negative in both HPV outcomes with a stronger albeit more uncertain effect for gender-neutral vaccination. The CIN2+ studies had a non-significant association with vaccination coverage due to the small number of data points. Modelling studies showed a large amount of heterogeneity in predicted impact. For instance, at coverage levels between 40 % and 60 %, model predicted RRs ranged between 0.10 and 0.44 for HPV, and 0.24 and 0.82 for CIN2+ of any HPV type. For HPV, only six out of the 18 model predictions fell within the 95 % CI of the mixed-effects meta-regression model of observational studies across both girls only and gender neutral vaccination settings, while the other 12 showed a more optimistic impact compared to the meta-regressions derived from observational studies. For CIN2+ outcomes, the model estimates seem more in line with observational findings, with 31 out of the 64 model predictions falling within the 95 % CI of the meta regression analyses. However, outcomes were also more heterogeneous, with 16 model estimates predicting an RR higher than the regression CI. Out of the 17 models predicting an RR lower than the meta-regression CI, 13 modelled vaccine-type-specific outcomes. Finally, when stratified by country (figs. S2 and S3 in the supplementary appendix), the model estimates and the observed RR align well, especially in more advanced disease. However, there are still some discrepancies between models

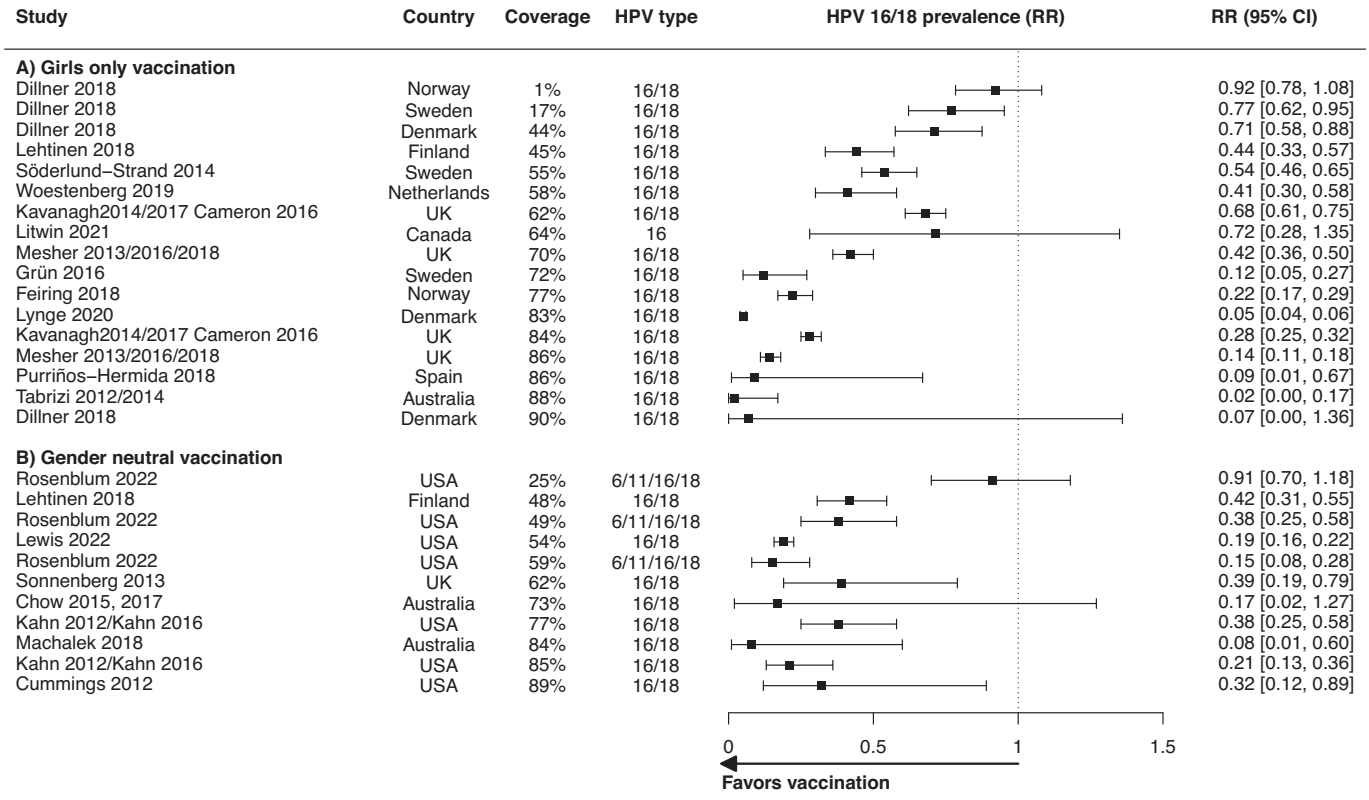

Fig. 3. The RR of genital HPV 16 and/or 18 infection in vaccinated versus unvaccinated populations by study, vaccination coverage, HPV type and years since vaccination. Fig. 3a shows the effect of vaccination when targeting girls only and Fig. 3b when targeting gender neutral. Studies were ordered by increasing vaccination coverage.

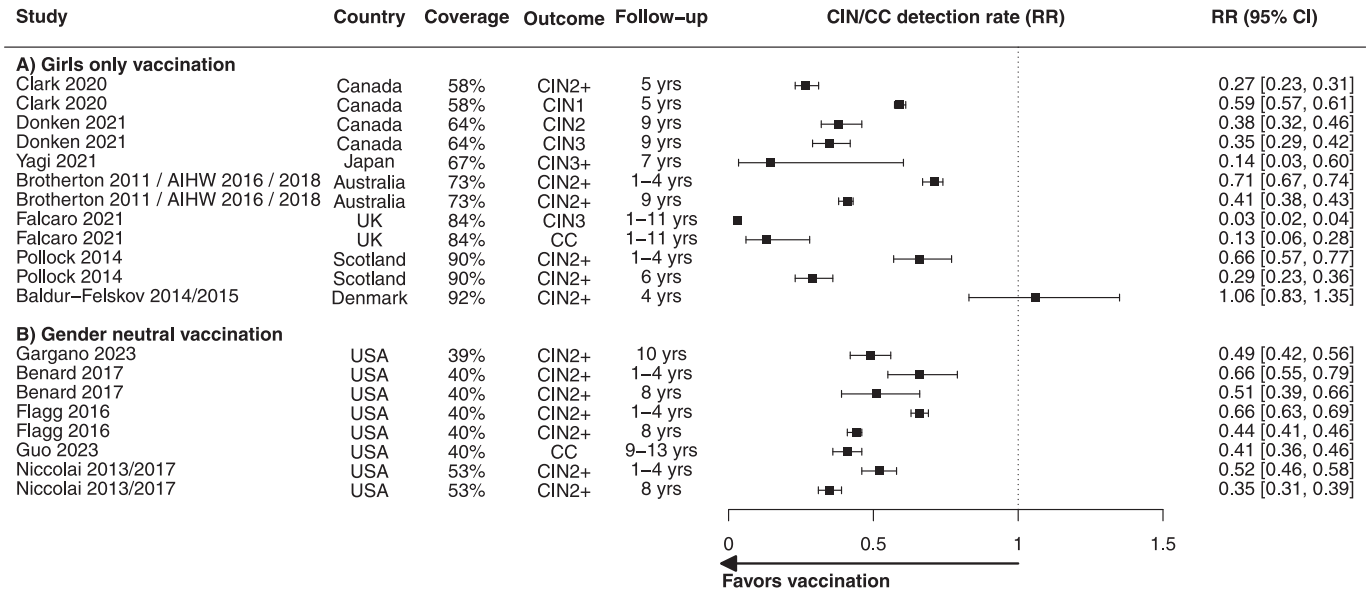

Fig. 4. The RR of CIN (CIN1/2/3, CIN2+, CIN3+ and cervical cancer) in vaccinated versus unvaccinated populations by study, country, vaccination coverage, and follow-up since vaccination. Fig. 4a shows the effect of vaccination when targeting girls only and Fig. 4b when targeting gender neutral. Studies are sorted by vaccination coverage.

and the data, especially with regard to data reported for shorter time periods (i.e. one to four years after vaccination).

4. Discussion

To our knowledge, this is the first systematic validation of modelling studies on the effect of HPV vaccination on HPV related disease against observational data. We identified a total of 32 observational studies covering 11 high-income countries (i.e. 20 for genital HPV infection, 13 for CIN1+ lesions), resulting in 48 data points (i.e. 28 for genital HPV infection and 20 for CIN1+ lesions) and 32 modelling studies covering 18 high-income countries (7 for HPV infection, 26 for CIN1+ lesions). A significant decrease was found of HPV diseases related outcomes in the post- versus pre-vaccination era, with 23 out of 28 data points and 19 out of 20 data points showing significant reductions in HPV prevalence and CIN2+ prevalence post vaccination respectively. This decrease was related to the vaccination coverage with negative regression coefficients in both outcomes and both subgroups, and significant coefficients for the HPV prevalence. This relationship seemed stronger for gender-neutral vaccination, but no clear difference was found compared to girls only vaccination. While the average time between start of vaccination and follow-up was equivalent between the girls-only and gender-neutral studies, boys vaccination was often later added to existing girls vaccination programs and its effects may not yet be fully visible in the data. Over 66 % (n/N = 12/18) of model predictions were more optimistic on HPV prevalence reductions compared to the 95 % CI of the meta-regression derived from observational studies. The main explanation for this would be the difference in time from vaccination to follow-up between the observational (around 5–10 years on average) and modelling (around 45 years on average) studies. While it is encouraging that 54 % (n/N = 29/54) of model predictions for CIN2+ outcomes fell within the 95 % CI, it is important to note that confidence intervals were relatively large due to fewer numbers of studies compared to HPV outcomes and that model predictions were more heterogeneous. Also, many of the optimistic modelling studies for CIN2+ focused on vaccine HPV type-specific outcomes and should not be directly compared to the observational studies that report reductions in CIN2+ of any HPV type.

Our systematic comparison of observational data and modelling studies provide further evidence as to the substantial impact HPV vaccination can have on cervical precancerous disease. Both observational data and model predictions agree that reaching the 90 % vaccination coverage, stated by the World Health Organization (WHO) cervical cancer elimination target, would reduce CIN2+ incidence by at least 50 %, but likely substantially more. The regression line of observational studies for gender-neutral vaccination estimates a RR for CIN2+ and CC of 0.08 at 90 % vaccination coverage based on only the first 11 years of follow-up after vaccination. This reduction alone would translate to reaching the age standardized rate or 4 per 100,000 women years WHO elimination target in almost all countries worldwide, except for the few highest-incidence countries with incidence rates of over 50 per 100,000 women years. Furthermore, these findings confirm an expected reduction in HPV positivity, CIN and cancer detection rates in cervical screening programs among vaccinated populations. This would mean a reduction in both benefits, through less detection and treatment of CIN lesions and early stage cancers, and harms, through less follow-up colposcopies and false-positive tests. However, these reductions are not necessarily directly proportional to each other. Cervical cancer screening in vaccinated cohorts will likely need to be adjusted to accommodate for this shift in the balance between harms and benefits as shown by previous modelling work [15,20]. Our analysis focused on high-income countries only, and it is unclear to what extent our findings are generalizable to low- or middle-income countries, especially those with higher disease burdens. None of the included observational studies reported on the nonavalent vaccine, most likely due to its more recent introduction and lack of sufficient follow-up time. As a consequence, the five modelling studies that did include the nonavalent vaccine could not directly be validated. However, this means any meta-regression estimates can be considered conservative if applied to settings where the nonavalent vaccine is implemented. Similarly, all included studies only concern three- or two-dose vaccination programs. While there is evidence supporting the efficacy of single-dose HPV vaccines and single-dose regimes are currently recommended by the WHO [86], there is no guarantee that the vaccination impacts found in our review would generalize to single-dose vaccination strategies.

The high heterogeneity in data studies, but especially in the modelling studies, makes a clear validation of the model predictions not straightforward. The heterogeneity in the model predicted impact of HPV vaccination is in line with the model comparison study by Brisson

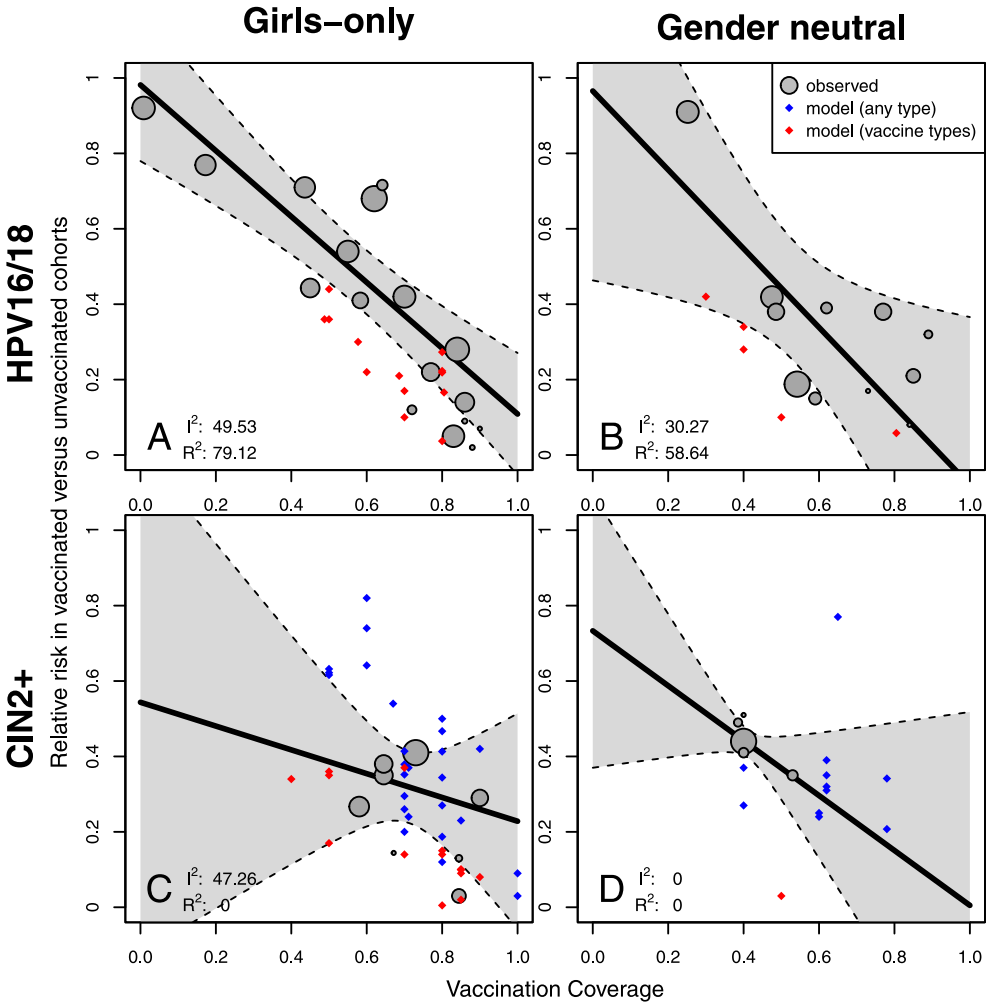

Fig. 5. Validation of model estimates against observed RR of the HPV infection (Fig. 5a) and CIN2+ lesions (Fig. 5c) in girls only vaccinated versus unvaccinated women, and in gender neutral vaccinated versus unvaccinated (Fig. 5b and d), depending on vaccination coverage. A weighted regression line is drawn for each subset of observational studies along with a 95 % CI. The size of the grey circles represents the study variance of the respective observational studies. Red diamonds represent modelling studies reporting on a decrease in vaccine-type-specific disease outcomes, whereas blue diamonds represent modelling studies reporting on a decrease in overall CIN2/3 and/or CC risk. The slope coefficients for the HPV regression line are −0.90 (*p*-value 0.000) and −1.03 (0.017) for girls only (Fig. 5a) and gender neutral vaccination (Fig. 5b) resepctively, and for the CIN2+ regression lines −0.92 (0.010) and −0.69 (0.120) for girls only (Fig. 5c) and gender neutral vaccination (Fig. 5d) respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al. [21], who showed that the predicted impact of vaccination on HPV infection varies widely across models, mostly driven by hard-to-measure underlying model structures concerning sexual network dynamics, immunity, and disease transmission and duration parameters. However, misalignment between model predictions and observational data could also be explained by reasons other than model specific characteristics. Firstly, modelling studies often report on impacts over a timeframe of several decades and rarely report short-term impacts. In contrast, the observational data identified in our review at most covers an impact time horizon of about twelve years, but more often much shorter. Supplementary fig. S1 compares some short term modelling outcomes for CIN2+, but only few studies reported short-term impacts. In addition, modelling studies were not necessarily from the same setting. Differences in epidemiological characteristics and vaccination implementation and uptake could explain heterogeneities in predicted versus observed impacts at similar coverage levels. While it is encouraging to see that, when stratifying our outcomes by country, we do find more agreement between models and observational data, more targeted validation efforts are clearly needed.

There are some potential reasons for the high levels of heterogeneity between the observational studies, especially for CIN2+ outcomes. First, it could be too early to see such an effect, as many studies report a time horizon of only a couple of years, while dwell times between HPV onset and CIN lesions and especially cervical cancer can be substantially longer [87]. Second, it is possible that the observed prevalence reductions are dependent on the pre-vaccination HPV prevalence, i.e. higher relative prevalence reductions can be achieved in countries with relatively high prevalence levels. Finally, sensitivity and specificity of the screening tests used might not be the same across the countries. More targeted validation exercises against existing or emerging observational data on vaccination impact, either through directly performing validation exercises or though standardized reporting of time- and age matched outcomes comparable to observational data, are highly needed to ensure that policy decisions are made on the best available estimates of vaccination impact. Simulation models should validate the predicted vaccination impact against setting-specific high-level data and ensure that this validation is done while matching model predictions to the age-groups and time since vaccine introduction in the data.

Our study has several additional limitations. Firstly, age-matching between modelling studies and data studies was impossible, as modelling studies never reported outcomes on specific age-groups reported in the observational studies. Secondly, the data studies did not all report on exactly the same age group, but we extracted the youngest age group reported to maintain as much consistency as possible. Next, the

limited amount of observational studies prevented us from including squared or cubed variants of vaccination coverage within our meta-regression models, and we were therefore not able to explore non-linearity between vaccination coverage and the outcome of interest while in theory this might be expected from potential herd-immunity dynamics. Also, we could not fully control for age at vaccination when assessing the impact across the different studies. If studies reported findings that predominantly reported on those vaccinated at older ages (e.g. through catch-up campaigns), the data may under- or overestimate the impact of vaccination, depending on how coverage was reported. Lastly, all of the results from the ecological studies in our review consider the aggregate effects of HPV vaccination in the full population, ignoring potential sub-population heterogeneities in vaccine impacts, for instance in high-risk populations.

In conclusion, we demonstrate that model predictions and observational data agree that HPV vaccination can have a substantial impact on HPV related outcomes on a population level. Despite substantial heterogeneities in observational data and modelling studies, it is particularly encouraging that model predictions on the impact of HPV vaccination on CIN2+ lesions align with observational studies. This helps expand trust for simulation models to help shape cervical screening strategies in vaccinated cohorts.

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CRediT authorship contribution statement

Daniël de Bondt: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Emi Naslazi:** Writing – original draft, Methodology, Investigation, Data curation. **Erik Jansen:** Writing – review & editing, Data curation. **Rachel Kupets:** Writing – review & editing, Conceptualization. **Bronwen McCurdy:** Writing – review & editing, Conceptualization. **Christine Stogios:** Writing – review & editing, Project administration, Conceptualization. **Inge de Kok:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Jan Hontelez:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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