# Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis

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## Summary

**Background** The extent of cross-protection is a key element in the choice of human papillomavirus (HPV) vaccine to use in vaccination programmes. We compared the cross-protective efficacy of the bivalent vaccine (HPV 16 and 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and quadrivalent vaccine (HPV 6, 11, 16, and 18; Gardasil, Merck, Whitehouse Station, NJ, USA) against non-vaccine type HPVs.

**Methods** We searched Medline and Embase databases, conference abstracts, and manufacturers' websites for randomised clinical trials assessing the efficacy of bivalent and quadrivalent vaccines against persistent infections (lasting ≥6 months) and cervical intraepithelial neoplasia (CIN) associated with the non-vaccine type HPVs (types 31, 33, 45, 52, and 58). We included studies of participants who were HPV DNA negative before vaccination for all HPV types assessed. We assessed heterogeneity in vaccine efficacy estimates between trials with $I^2$ and $\chi^2$ statistics.

**Findings** We identified two clinical trials (Females United to Unilaterally Reduce Endo/Ectocervical Disease [FUTURE] I and II) of the quadrivalent vaccine and three (Papilloma Trial Against Cancer In Young Adults [PATRICIA], HPV007, and HPV-023) of the bivalent vaccine. Analysis of the most comparable populations (pooled FUTURE I/II data *vs* PATRICIA) suggested that cross-protective vaccine efficacy estimates against infections and lesions associated with HPV 31, 33, and 45 were usually higher for the bivalent vaccine than the quadrivalent vaccine. Vaccine efficacy in the bivalent trial was higher than it was in the quadrivalent trial against persistent infections with HPV 31 (77·1% [95% CI 67·2 to 84·4] for bivalent vaccine *vs* 46·2% [15·3 to 66·4] for quadrivalent vaccine; p=0·003) and HPV 45 (79·0% [61·3 to 89·4] *vs* 7·8% [–67·0 to 49·3]; p=0·0003), and against CIN grade 2 or worse associated with HPV 33 (82·3% [53·4 to 94·7] *vs* 24·0% [–71·2 to 67·2]; p=0·02) and HPV 45 (100% [41·7 to 100] *vs* –51·9% [–1717·8 to 82·6]; p=0·04). We noted substantial heterogeneity between vaccine efficacy in bivalent trials against persistent infections with HPV 31 ($I^2$=69%, p=0·04) and HPV 45 ($I^2$=70%, p=0·04), with apparent reductions in cross-protective efficacy with increased follow-up.

**Interpretation** The bivalent vaccine seems more efficacious against non-vaccine HPV types 31, 33, and 45 than the quadrivalent vaccine, but the differences were not all significant and might be attributable to differences in trial design. Efficacy against persistent infections with types 31 and 45 seemed to decrease in bivalent trials with increased follow-up, suggesting a waning of cross-protection; more data are needed to establish duration of cross-protection.


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## Introduction

Infection with the human papillomavirus (HPV) is a key cause of cervical cancer,[1] and has been associated with other anogenital (vulvar, vaginal, penile, and anal) cancers[2,3] and head and neck cancers.[4] HPV types of high oncogenic risk, 16 and 18, are detected in about 70% of invasive cervical cancers[5] worldwide and in most anogenital and head and neck cancers that are positive for HPV.[2,4] The most common oncogenic HPV types worldwide—16, 18, 31, 33, 45, 52, and 58—contribute to about 90% of invasive cervical cancers.[5]

Two prophylactic vaccines have been licensed for use in many countries: the bivalent vaccine Cervarix (against HPV 16 and 18; GlaxoSmithKline Biologicals, Rixensart, Belgium) and the quadrivalent vaccine Gardasil (against HPV 6, 11, 16, and 18; Merck, Whitehouse Station, NJ, USA). Large clinical trials have shown almost 100% vaccine efficacy against pre-cancerous lesions associated with these vaccine HPV types.[6–8] Recent trials have also reported vaccine efficacy against non-vaccine type HPVs.[8–11]

Public health officials worldwide continue to assess which HPV vaccine should be used in their vaccination programmes. Cross-protection afforded by the HPV vaccines is a key factor of interest.[12,13] However, differences between characteristics of trial participants such as baseline prevalence and distribution of HPV infection complicate the comparison of cross-protection between bivalent and quadrivalent vaccines. Through a systematic review of published work, we aimed to summarise and compare evidence from clinical trials about the cross-protective efficacy of the bivalent and quadrivalent vaccines in HPV-naive populations (ie, individuals who are DNA negative for all tested oncogenic HPV types). We focused on vaccine efficacy in this population because such efficacy is least diluted by the presence of women who are infected or immune at baseline, which can vary between trials. Thus, trials in HPV-naive populations

provide improved estimates of the true prophylactic effect of vaccination.

## Methods

### Search strategy and selection criteria

We systematically reviewed published work and report it in accordance with the PRISMA guidelines.[14] We searched for randomised controlled trials assessing the efficacy of the bivalent or quadrivalent vaccines that included populations who were HPV negative for all tested oncogenic types. We included trials reporting efficacy against either cervical or genital infection or disease (cervical intraepithelial neoplasia [CIN] or cervical cancer) endpoints associated with non-vaccine type oncogenic HPVs and those reporting efficacy against individual non-vaccine type HPVs. We set no restrictions on population demographics.

We searched published work in three stages. First, we searched Medline and Embase databases to Jan 9, 2012, with the MeSH search terms and title and abstract text word search terms "HPV", "papillomaviridae", "papillomavirus vaccines", "efficacy", and "clinical trial". We identified eligible vaccine efficacy trials through scanning titles and abstracts. Second, we identified recent eligible studies by searching the abstracts of the major conferences on HPV (European Research Organisation on Genital Infection and Neoplasia Congress 2010 and 2011 and International Papillomavirus Conference 2009–11). Third, we searched the websites of the manufacturers of Cervarix and Gardasil up to Jan 27, 2012,[15,16] and contacted the manufacturers to obtain supplementary unpublished clinical trial results. Eligibility assessment for all reports was done by TM and MD and validated by MB.

See Online for appendix

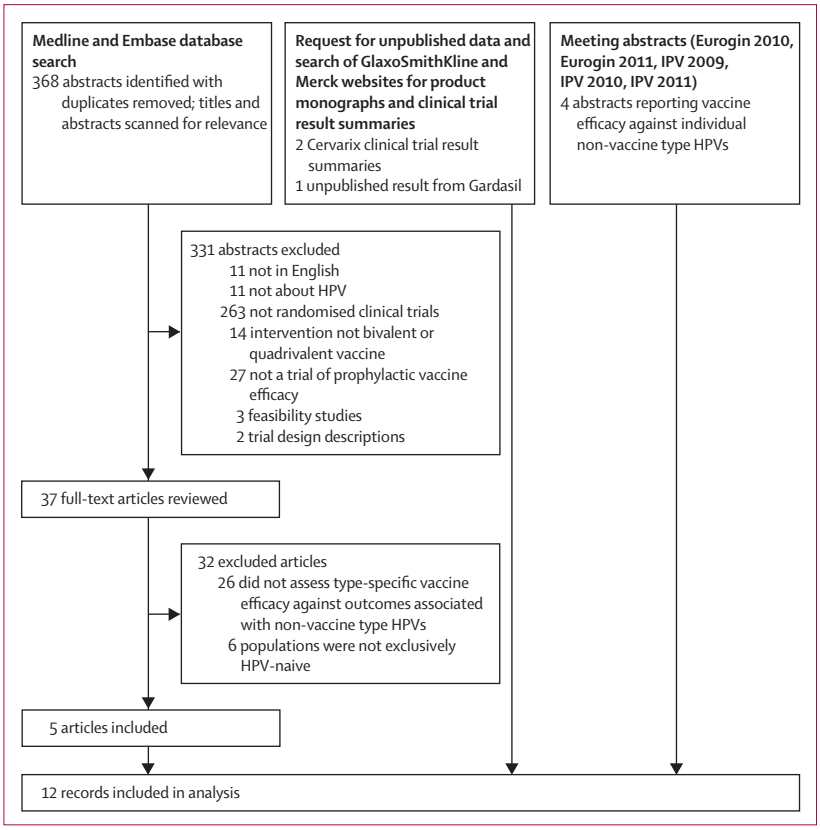


*Figure 1:* **Study selection**
HPV=human papillomavirus. EUROGIN=European Research Organisation on Genital Infection and Neoplasia. IPV=International Papillomavirus Conference and Clinical Workshop.

### Data extraction

Our primary outcome was type-specific efficacy of the quadrivalent and bivalent vaccines against persistent infections (lasting ≥6 months) and CIN grade 2 or worse (CIN2+) associated with HPV 31, 33, 45, 52, and 58. We chose these HPV types because they are the most prevalent types in cervical cancer after HPV 16 and 18,[1] and because of their phylogenetic similarity to the vaccine types.[17] Efficacy measures against CIN2+ are usually calculated in two ways—including or excluding lesions co-infected with HPV 16 or 18 (appendix)—and we report both here. Our secondary outcomes were efficacy against persistent infections (lasting ≥6 months) associated with HPV 16 and 18, and against CIN2+ associated with any non-vaccine type HPV. Results for these secondary outcomes are shown in the appendix.

We assessed the potential for bias within studies by reviewing concealment of the randomisation sequence, type of control vaccine, masking of treatment allocation from participants and research personnel, presence of stopping rules, loss to follow-up, exclusions after randomisation, HPV DNA tests, definition of endpoints, and attribution of lesion HPV types. TM assessed the eligibility of all reports, extracted the data, and assessed the methodological quality with standardised sheets. Two other investigators (MD and MB) independently reviewed the extracted data and quality assessment. If more than one analysis of the same trial were available, we used the analysis with the longest duration of follow-up.

### Statistical analysis

Because the main objective of our review was to compare vaccine efficacies against individual non-vaccine type HPVs between the bivalent and quadrivalent vaccines, we decided a priori not to pool the efficacies between HPV types and between vaccines. We first examined the heterogeneity between efficacy estimates of the different trials for each vaccine separately, with the $I^2$ and $\chi^2$ statistics, to examine whether the estimates could be pooled. $I^2$ quantifies the percentage of the variation across study estimates that is attributable to heterogeneity rather than chance alone,[18] whereas $\chi^2$ determines the statistical significance of heterogeneity. We calculated $I^2$ and $\chi^2$ with the Mantel-Haenszel random-effects method[19] on risk ratios comparing vaccine with control groups. We regarded $I^2$ values of less than 40% as low

heterogeneity, 50–75% as substantial heterogeneity, and more than 75% as considerable heterogeneity.[20] We did all heterogeneity analyses with Review Manager version 5.1.

## Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full

| | Quadrivalent vaccine trials | Bivalent vaccine trials | | |
|---|---|---|---|---|
| | FUTURE I/II | PATRICIA | HPV-007 | HPV-023 |
| Protocol identification number | 012, 013, and 015 | 580299/008 | 580299/007 (follow-up of 580299/001) | 109616 (follow-up of 580299/001 and 580299/007) |
| Publications reporting vaccine efficacy against non-vaccine type HPV | Brown et al (2009),[11] Malagon et al (2011),[24] and data on file with Merck | Wheeler et al (2012),[21] Naud (2010),[26] Romanowski (2010),[25] Schwarz (2011),[27] and Malagon et al (2011)[24] | Harper et al (2006)[9] interim analysis, GlaxoSmithKline Vaccine HPV-007 Study Group (2009),[22] and GlaxoSmithKline website[28] | De Carvalho et al (2010)[23] interim analysis and GlaxoSmithKline website[29] |
| HPV subpopulation* | RMITT2 | TVC naive | Per protocol, TVC* | Per protocol, TVC* |
| Participants | 2068 in infection analysis, 9296 in cervical disease analysis | 11 644 | 919 in the per-protocol analysis, 1113 in the TVC analysis† | 395 in the per-protocol analysis, 506 in the TVC analysis† |
| Locations | Australia, Austria, Brazil, Canada, Colombia, Czech Republic, Denmark, Finland, Germany, Hong Kong, Iceland, Italy, Mexico, New Zealand, Norway, Peru, Poland, Puerto Rico, Russia, Singapore, Sweden, Thailand, UK, USA | Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK, USA | Brazil, Canada, USA | Brazil |
| Funding | Merck | GlaxoSmithKline Biologicals | GlaxoSmithKline Biologicals | GlaxoSmithKline Biologicals |
| Eligibility criteria | Women aged 16–26 years, ≤4 lifetime sexual partners | Women aged 15–25 years, ≤6 lifetime sexual partners | Women aged 15–25 years, ≤6 lifetime sexual partners, and had received three doses of vaccine in initial study | Women aged 15–25 years, ≤6 lifetime sexual partners, and had received three doses of vaccine in initial study |
| Control group | Placebo vaccine | Hepatitis A vaccine | Placebo vaccine | Placebo vaccine |
| Cytology | Normal at baseline | Normal at baseline | Normal at screening; status at baseline not reported | Normal at screening; status at baseline not reported |
| Serostatus | Seronegative for HPV types 6, 11, 16, and 18 at baseline | Seronegative for HPV 16 and HPV 18 at baseline | Seronegative for HPV 16 and HPV 18 at screening; status at baseline not reported. | Seronegative for HPV 16 and HPV 18 at screening; status at baseline not reported. |
| HPV DNA status | Negative for 14 HPV types (4 vaccine and 10 non-vaccine) at baseline | Negative for 14 oncogenic types (2 vaccine and 12 non-vaccine) at baseline | Negative for 14 oncogenic types (2 vaccine and 12 non-vaccine) at screening; status at baseline not reported | Negative for 14 HPV types (2 vaccine and 12 non-vaccine) at screening; status at baseline not reported |
| Average age at entry, years (SD) | 19·8 (2·1) | 19·9 (3·1) | 20 (3) | 20 (3) |
| Received three doses, % | 97·2% of enrolled participants | 92% of enrolled participants | 100% in the per-protocol analysis, 93·1% in the TVC analysis (initial study)† | 100% in the per-protocol analysis, not reported in the TVC analysis† |
| Start of case counting | After first dose received | After first dose received | After third vaccination received in the per protocol group, after first dose received in the TVC analysis† | After third vaccination received in the per protocol group, after first dose received in the TVC analysis† |
| Endpoints | 6 month persistent infections, CIN1+, CIN2+, CIN2+ excluding co-infection with HPV 16 or HPV 18, CIN3+, CIN3+ excluding co-infections with HPV 16 or HPV 18 | 6 month persistent infections, CIN1+, CIN2+, CIN2+ excluding co-infection with HPV 16 or HPV 18, CIN3+, and CIN3+ excluding co-infections with HPV 16 or HPV 18 | Incident infections, 6 month persistent infections, CIN1+, and CIN2+ | Incident infections, 6 month persistent infections, 12 month persistent infections, CIN1+, and CIN2+ |
| Attribution of lesion HPV type | Detection of specific type HPV DNA in tissue biopsies was regarded as association with CIN lesion. CIN excluding co-infection with HPV 16 or HPV 18 was regarded as detection of specific HPV DNA in tissue biopsies, excluding those in which HPV 16 or HPV 18 was also detected | For CIN with or without co-infection with HPV 16 or HPV 18, detection of specific type HPV DNA in tissue biopsies was regarded as associated with CIN lesion. Detection of specific HPV DNA in tissue biopsies, excluding those in which HPV 16 or HPV 18 was also detected, was regarded as CIN excluding co-infection with HPV 16 or HPV 18 | Histopathologically confirmed CIN1+ or CIN2+ detected with HPV type in lesion | Histopathologically confirmed CIN1+ or CIN2+ detected with HPV type in lesion |
| Follow-up | Mean 3·6 years (up to 4 years) | Mean 3·7 years at end of study (up to 4 years) | Mean 5·9 years (SD 0·3) after start of initial study to final analysis (up to 6·4 years) | Up to 9 years at final analysis |

HPV=human papillomavirus. FUTURE=Females United to Unilaterally Reduce Endo/Ectocervical Disease. PATRICIA=Papilloma Trial Against Cancer In Young Adults. RMITT2=restricted modified intention to treat 2 (women without evidence of oncogenic HPV infection at baseline). TVC=total vaccinated cohort. TVC naive=women without evidence of oncogenic HPV infection at baseline. CIN1+=cervical intraepithelial neoplasia grade 1 or worse. CIN2+=cervical intraepithelial neoplasia grade 2 or worse. CIN3+=cervical intraepithelial neoplasia grade 3 or worse. *HPV-naive subpopulations. †Infection outcomes were assessed in the per-protocol populations, excluding protocol deviators; lesion outcomes were assessed in the TVC, including all individuals who received at least one dose of vaccine.

***Table:*** **Trials of vaccine efficacy against non-vaccine HPV types in HPV-naive subpopulations**

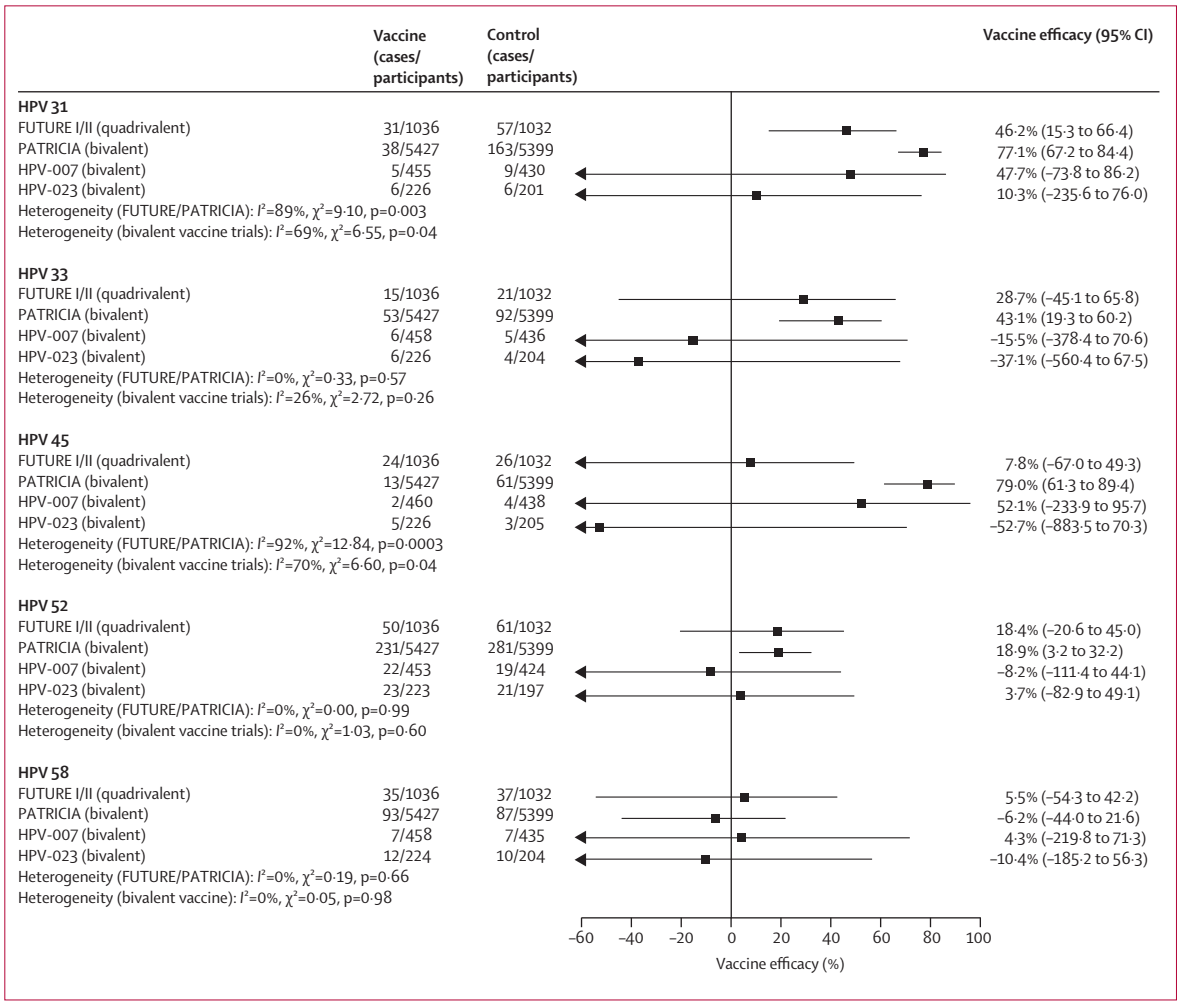


***Figure 2:*** **HPV vaccine efficacy against persistent infection (≥6 months) with individual non-vaccine type HPVs**
HPV=human papillomavirus. NA=not available, not reported, or not assessable.

access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Figure 1 shows the search strategy. We identified 12 reports, including results from five different trials (two for the quadrivalent vaccine and three for the bivalent vaccine; appendix).[9,11,21–29] The table summarises participant information and study characteristics and the appendix shows potential sources of bias. Populations from two trials of the quadrivalent vaccine (Females United to Unilaterally Reduce Endo/Ectocervical Disease [FUTURE] I and FUTURE II) were merged for vaccine efficacy against non-vaccine types in all publications and reports.[11]

All included studies assessed women aged 15–26 years. The most comparable trial populations were the restricted modified intention-to-treat population 2 in the quadrivalent FUTURE I/II trials and the total vaccinated cohort-naive (TVC naive; women without evidence of oncogenic HPV infection at baseline) in the bivalent Papilloma Trial Against Cancer In Young Adults (PATRICIA) trial. Both populations included participants in large international efficacy trials who were followed up for a mean of 3·6 years, restricted after randomisation to women who did not have 14 HPV types at baseline, were cytologically normal at baseline, serologically negative to the corresponding vaccine types, and who had received at least one vaccine dose (table). The main differences between FUTURE I/II and PATRICIA were the countries included in the trials and the HPV DNA assays used. Hereafter, we refer to FUTURE I/II or PATRICIA as the results in the HPV-naive subpopulation analyses of each trial. The other two trials (HPV-007 and HPV-023) were made up of participants who were HPV DNA negative for 14 oncogenic types, cytologically normal, and seronegative for HPV 16 and 18 at screening (before randomisation). Therefore, in the HPV-007 and HPV-023 trials some

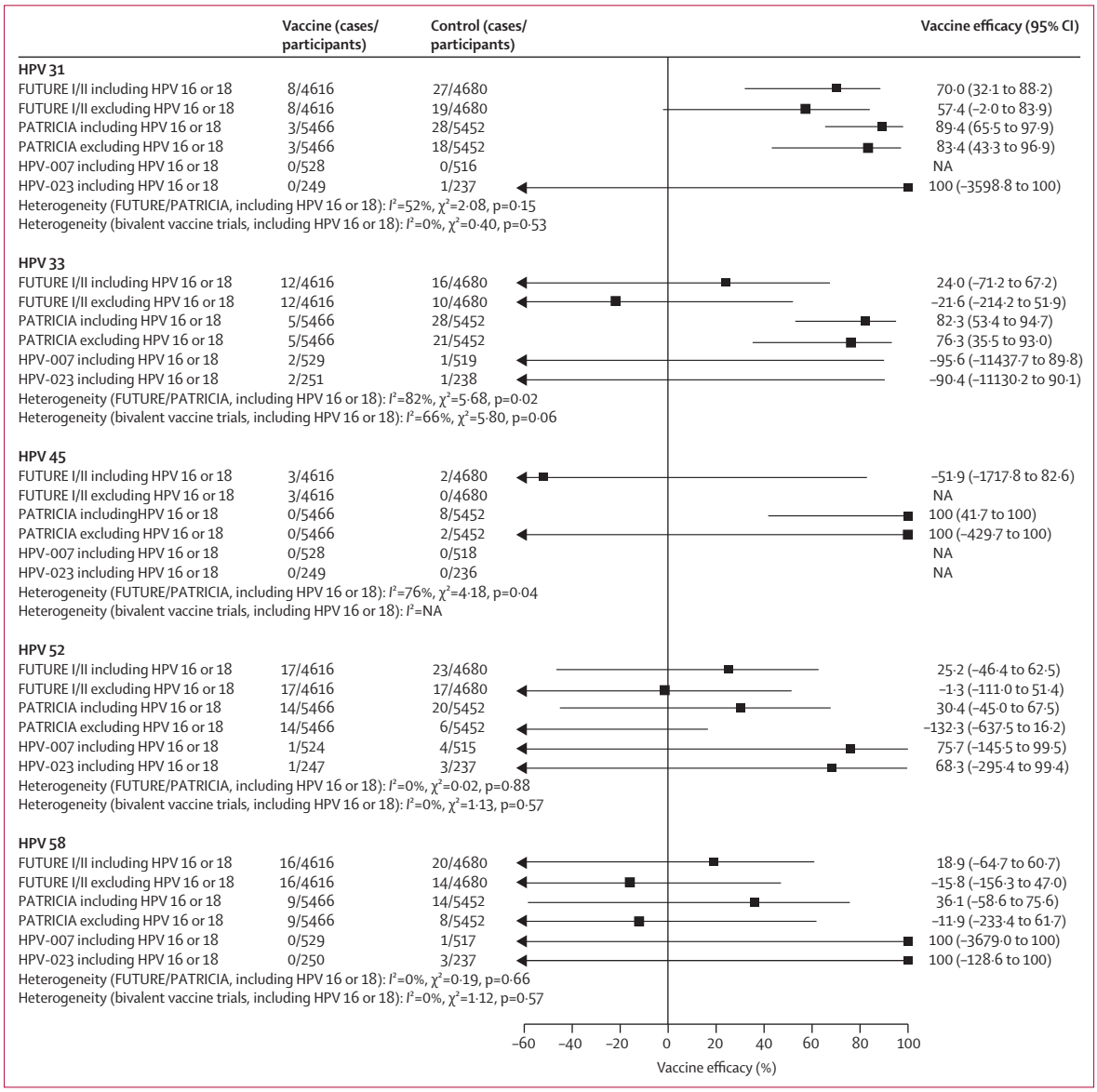


***Figure 3*: HPV vaccine efficacy against cervical intraepithelial neoplasia grade 2 or worse (CIN2+) detected with non-vaccine type HPVs, including and excluding lesions co-infected with HPV 16 or HPV 18**

Unpublished data for quadrivalent vaccine efficacy against CIN2+ (excluding lesions associated with HPV 16 or HPV 18) are on file with Merck. HPV=human papillomavirus. NA=not available, not reported, or not assessable.

individuals might have been infected between the first screening visit and vaccination (maximum 90 days). HPV-007 followed up participants for a mean of 5·9 years (SD 0·3). HPV-023 was a long-term follow-up of the Brazilian participants included in HPV-007 (up to 9 years).

Because the results of the FUTURE I/II trials were merged in all publications, heterogeneity could not be assessed between efficacy estimates of the quadrivalent vaccine. For the bivalent vaccine, we noted substantial heterogeneity between the three bivalent trials for efficacy against 6 month persistent infection with HPV 31 and 45 (figure 2). Estimates of efficacy seem to decline from the study with the shortest follow-up (PATRICIA) to those with longer follow-up (HPV-007 and HPV-023). For bivalent vaccine efficacy against CIN2+ lesions, heterogeneity results between the three trials suggest that variations in efficacy estimates against CIN2+ could be attributed to chance, apart from HPV 33 (figure 3). Because of the substantial heterogeneity noted between the bivalent trials, we did not pool results. The quadrivalent FUTURE I/II estimates were thus always compared with the bivalent PATRICIA estimates, because these studies had much the same length of follow-up (table).

Vaccine efficacy estimates against 6 month persistent HPV 31, 33, and 45 infections were higher in the bivalent PATRICIA trial than they were in the quadrivalent FUTURE I/II vaccine trial (figure 2) but there was substantial overlap of confidence intervals for HPV 33. In FUTURE I/II, quadrivalent vaccine had significant efficacy against persistent HPV 31 infections (figure 2). In the PATRICIA trial, bivalent vaccine had significant efficacy against HPV 31, 33, 45, and 52. Bivalent vaccine efficacy estimates reported in HPV-007 and HPV-023 against persistent infection for these HPV types were low and not significant (figure 2).

We noted substantial heterogeneity between the FUTURE I/II and PATRICIA trials for efficacy against 6 month persistent HPV 31 and 45 infection, but no heterogeneity for HPV 33, 52, and 58 infections.

As with previous analysis of persistent infection, the PATRICIA bivalent trial showed higher point estimates of efficacy against CIN2+ associated with HPV types 31, 33, and 45 than did the FUTURE I/II quadrivalent trial. Although all trials assessed efficacy against CIN2+ (figure 3), only FUTURE I/II and PATRICIA assessed efficacy against CIN2+ excluding lesions co-infected with HPV 16 or 18. Significant quadrivalent vaccine efficacy against CIN2+ associated with HPV 31 was noted when lesions co-infected with HPV 16 or 18 were included. This efficacy was reduced and became non-significant when lesions co-infected with HPV 16 or 18 were excluded. In PATRICIA, significant efficacy against CIN2+ associated with HPV 31, 33, and 45 was noted when lesions co-infected with HPV 16 or 18 were included. When these co-infected lesions were excluded, only efficacy against CIN2+ associated with HPV 31 and 33 remained significant. No significant efficacy against CIN2+ associated with non-vaccine types was noted in the HPV-007 or HPV-023 trials.

We noted substantial heterogeneity between FUTURE I/II and PATRICIA for vaccine efficacy against CIN2+ (including lesions co-infected with HPV 16 or 18) with HPV 33 and 45, but not with HPV 31, 52, and 58.

## Discussion

Quadrivalent and bivalent HPV vaccines offer cross-protection against some non-vaccine HPV types for individuals without previous infection. In our analysis, quadrivalent vaccine was efficacious against outcomes associated with HPV 31, and bivalent vaccine was efficacious against outcomes associated with HPV 31, 33, and 45. We noted differences in estimates between the vaccines, with the bivalent vaccine showing greater efficacy than the quadrivalent vaccine against HPV 31, 33, and 45 for persistent infection and CIN2+ disease, although the differences were not all significant. For both vaccines, there was very little evidence of cross-protection against HPV 52 and 58. Efficacy against persistent infections with HPV 31 and 45 seemed to decrease in bivalent trials with increased follow-up, suggesting waning of cross-protection.

Our findings of cross-protection are biologically plausible. The possibility of a cross-reactive immune response elicited by the vaccine types[30] is consistent with the phylogenetic similarities between L1 genes from vaccine and non-vaccine types (HPV 16 with HPV types 31, 33, 52, and 58 [A9 species] and HPV 18 with HPV 45 [A7 species]).[17] Furthermore, reported differences in cross-protection between vaccines might be attributable to different adjuvant systems. A head-to-head immunogenicity trial showed a significantly higher antibody response against HPV 16 and 18 and T-cell response against HPV 31 and 45 for the bivalent vaccine than the quadrivalent vaccine.[31,32] However, differences in mean antibody titres against HPV 31 and 45 were mostly non-significant.[31] Finally, antibody titres remain generally high for HPV 16 and 18,[32,33] but levels for HPV 31, 33, and 45 reach much lower titres after vaccination[31,34,35] and decline within 2 years to the levels seen with natural infection or lower than the limit of detection,[31] which suggests a potential for waning of cross-protection.

The increased efficacy estimates of the bivalent vaccine we noted against outcomes associated with HPV 31, 33, and 45 (figures 2, 3) might be because of true differences in cross-protection against these types, or might be because of differences between trials. Our systematic review compared type-specific vaccine efficacies in HPV-naive women with similar eligibility criteria and durations of follow-up to minimise bias due to possible differences in type distributions, baseline prevalences of infection, and demographic factors between the vaccine trials. At baseline, the FUTURE I/II and PATRICIA trial subpopulations were much the same in terms of age and lifetime number of sexual partners, and were cytologically normal, seronegative for HPV 16 or 18, and DNA negative against 14 HPV types. Furthermore, counting of events began after the first HPV vaccine or control vaccine dose, and mean follow-up was 3·6 years in both trials (table). However, differences did exist between FUTURE I/II and PATRICIA subpopulations. Incidence of infections was higher in the control group in FUTURE I/II than it was in the control group of PATRICIA, but type-specific incidence of CIN2+ was almost the same (appendix). Differences in rates of infection might be because, in FUTURE I/II, cervical and vulvar or perianal samples were tested for infection outcomes whereas cervical samples only were tested in PATRICIA, or because of differences in HPV DNA assay sensitivities and specificities. To what extent these differences affected the magnitude of the differences in cross-protection between the HPV vaccines is not known. However, residual variability in trial designs or study subpopulations that was not controlled for by our strict eligibility criteria would have to differentially affect vaccine efficacy measures for HPV types 31, 33, and 45, but not between the trials for outcomes associated with vaccine types HPV 16 and 18 in which no heterogeneity was reported (appendix).

Estimates of vaccine efficacy against persistent HPV 31, 33, and 45 infection seemed to decline in studies with increased follow-up (figure 2), whereas efficacy against persistent infection with HPV 16 or 18 remained stable (appendix). Despite the small sample sizes of the HPV-007 and HPV-023 trials, heterogeneity between vaccine efficacies of the different bivalent trials was sufficient to reach significance for HPV 31 and 45. Nevertheless, these results should be interpreted with caution and only viewed as suggestive of waning cross-protection because the trial subpopulations compared might have differed in terms of other characteristics and not just time. However, several findings suggest that the key measurable difference between these trial subpopulations was time of follow-up. First, women in all trials were previously uninfected with 14 HPV types at screening and adherence to vaccination was high (100% for one dose and 92–100% for all three doses in analysed bivalent trial populations). Second, PATRICIA included 8% of women who received fewer than the three vaccine doses in their analysis, compared with 0% for HPV-007 and HPV-023 (for analyses of persistent infection); these differences should increase efficacy in HPV-007 and HPV-023 compared with PATRICIA. Finally, efficacy against outcomes associated with vaccine types HPV 16 or 18 remained high across all bivalent trials (appendix). Notably, we did not identify any heterogeneity for cross-protective efficacy against CIN2+ lesions with HPV 31 and 45 (figure 3). However, if vaccine efficacy were to wane, infection outcomes would be the first to show the drop, with lesion outcomes following a few years later. More data than we have at present are needed, because waning of efficacy will be a key factor in decisions about the incremental benefit of cross-protection at the population level. Thus, information from trend analysis of PATRICIA and FUTURE I/II and other long-term efficacy trials is essential.

Substantial debate surrounds which outcome should be used to measure HPV vaccine efficacy. Infection outcomes are useful because they are associated with the development of cervical lesions and cancer,[36] are frequent and thus give precise estimates of efficacy, and are not subject to misclassification bias because of co-infections with other types of HPV.[37] However, persistent infection outcomes might underestimate efficacy against diseases because of undetected baseline infections or by trace contamination from an infected regular partner. Histopathological outcomes such as high-grade precancerous lesions (CIN2+) are closer surrogates for cancer, and are arguably a more clinically meaningful endpoint. However, they are susceptible to various biases. First, inclusion of HPV 16 and 18 co-infected lesions can inflate estimates of vaccine efficacy against lesions with non-vaccine type HPVs, because co-infected lesions will be more common in control groups than vaccine groups. For HPV types showing high and significant cross-protection against CIN2+ when HPV 16 and 18 co-infected lesions are included, exclusion of these lesions produces only a moderate decline (figure 3). Conversely, for HPV types showing non-significant or low cross-protection against CIN2+ when lesions co-infected with HPV 16 or 18 were included, exclusion of these lesions substantially reduces estimates of type-specific vaccine efficacy (figure 3). This finding suggests that, although part of the reported efficacy against non-vaccine types might be attributable to HPV 16 or 18, a cross-protective effect remains for some non-vaccine type HPVs (ie, 31, 33, and 45). Efficacy against all non-vaccine type HPVs combined also substantially declines when lesions co-infected with HPV 16 or 18 are excluded (appendix) because HPV types with significant cross-protection only form a small fraction of all non-vaccine types in CIN2+ lesions. Thus, efficacy against lesions with other non-vaccine types will mostly be attributable to efficacy against the HPV 16 or 18 co-infecting the lesion. Although efficacy against CIN2+ in participants with co-infection could also be subject to bias because of competing risks of other HPV types, it is very unlikely to have biased vaccine efficacy estimates because the risk of a non-vaccine type infection progressing to CIN2+ within the timeframe of the trials (3–4 years) is very low.[38,39] Infection and lesion outcomes would also be affected by the potential unmasking of types in the vaccine groups due to the removal of HPV 16 and 18. This unmasking effect is likely with the broad-spectrum amplification assays used in trials and would lead to underdetection of non-vaccine types in the control groups because presence of HPV 16 or 18 infections would overwhelm the assay readout and mask co-infections.[40] This characteristic would tend to underestimate vaccine efficacy, although the potential size of this bias is unknown.

By restricting our review to HPV-DNA negative populations, we minimised bias attributable to baseline infection and immunity, substantially improving comparability between studies. Assessment of efficacy by HPV type also increased comparability, because efficacy estimates were not affected by the different type distributions between trials. We integrated a substantial amount of unpublished data to obtain the most comparable results. Although the most comparable subpopulations were selected, we were unable to fully account for differences in subpopulation characteristics and study assays. Although there were few studies of cross-protection in individuals without previous HPV infections, and half the trials we identified were underpowered to show efficacy against non-vaccine types, we still reported substantial heterogeneity between vaccines and within bivalent vaccine trials. This finding suggests that the reported heterogeneity in results across trial subpopulations is not readily explained by chance alone.

Our results are of particular importance for clinicians, epidemiologists, modellers, and policy makers who compare vaccines and make recommendations on which HPV vaccine to use. HPV types 31, 33, and 45 are present

in a notable proportion of cervical cancers worldwide (4% for HPV 31 and 33 and 6% for HPV 45).[5] Thus, increased use of vaccines that are efficacious against these HPV types has the potential to further reduce cancer incidence. The public health effect of potentially increased cross-protection from the bivalent vaccine will have to be weighed against the quadrivalent vaccine's protection against genital warts. As for vaccine type HPVs,[41–43] the duration of protection against non-vaccine type HPVs will have an important effect on the population-level consequences of vaccination and the potential incremental benefits of cross-protection. Because HPV vaccines are mostly given to preadolescent girls, cross-protection would have very little effect at the population level if its duration is short (eg, 5–10 years). The bivalent vaccine might offer greater cross-protection than would the quadrivalent vaccine, but its efficacy seems to be associated with reduced estimates of cross-protection against infection with time, suggesting a potential waning of effect.

#### Contributors

TM, MD, and MB designed the study, did the search and analysis of published work, and wrote the first version of the report. M-CB, ELF, MJ, and JB interpreted the data and critically revised the report for scientific content. All authors approved the final version of the report.

#### Conflicts of interest

MB has consulted and received reimbursement for travel expenses from Merck Frosst and GlaxoSmithKline. ELF has served as an occasional consultant or advisory board member for Merck and GlaxoSmithKline. MD, M-CB, MJ, JB, and TM declare that they have no conflicts of interest.

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