SUMMARY OF EVIDENCE

Population-level impact and herd effects following papillomavirus immunization programmes: a systematic review and meta-analysis

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BACKGROUND

Since 2007, 65 out of 195 countries worldwide have implemented human papillomavirus vaccination (HPV)\(^1\). The population-level effect of HPV vaccination is expected to vary considerably between these countries, depending on 1) the vaccine used, 2) vaccination strategies and population targeted for vaccination, and 3) vaccination coverage achieved. The majority of high-income countries (HIC) are currently using the quadrivalent vaccine, while the picture is mixed for low- and middle-income countries (LMIC)\(^2\). The great majority of HPV vaccination programmes worldwide target pre-adolescent girls (also including catch-up programmes for older girls and women) and several countries have recently switched to gender-neutral HPV vaccination programmes (Australia, Austria, Italy, Switzerland, the USA, and Canada)\(^3\)-\(^11\). A systematic review of the “real-world” effects of HPV vaccination programmes is required to provide a base of evidence to guide HPV vaccine policy decisions worldwide.

OBJECTIVES

We performed a systematic review and meta-analysis of the most recent evidence about the population-level effect of HPV vaccination in girls and young women targeted for vaccination, and in boys, men, and older women. We focused on three HPV-related endpoints: HPV infection, anogenital warts, and high-grade cervical lesions (CIN2+). The specific objectives are to:

1. systematically identify published and unpublished time-trends studies that examined changes in HPV-related endpoints before and after the introduction of HPV vaccination
2. summarize existing evidence about the population-level effects of HPV vaccination for:
   a. Girls-only vaccination
   b. Gender-neutral vaccination
   c. Routine and catch-up vaccination (single and multiple age cohort immunization)

METHODS

In 2015, we published a systematic review and meta-analysis of the population-level impact and herd effects following HPV vaccination, including studies published between Jan 1, 2007 and Feb 28, 2014\(^12\). We updated this systematic review by searching Medline and Embase databases to identify additional studies published since our initial literature search (i.e., between February 1, 2014 and July 12, 2016). We used identical methods in both systematic reviews. Studies were eligible if they reported changes, between the pre- and post-vaccination periods, in the incidence or prevalence of at least one HPV-related endpoint: HPV infection, anogenital warts, or CIN2+. We assessed heterogeneity across studies using I\(^2\) and x\(^2\) and we performed trends analysis to examine dose-response association between each study effect measure and HPV vaccination coverage. We stratified all analyses by age and sex and used random-effects models to derive pooled relative risk (RR) estimates. Of note, the pooled estimates presented in this report are based on data collected in our initial systematic review and descriptive statistics are presented for articles identified in our updated review.
RESULTS
In our initial review, we identified 20 eligible article (HPV infection: 7, anogenital warts: 11, CIN2+: 2). In our updated review, we identified an additional 28 eligible articles: 15 on HPV infection (11 new studies\textsuperscript{13-23}; 4 updates\textsuperscript{24-27} of studies previously included in our review including more years post vaccination), 8 on anogenital warts (5 new studies\textsuperscript{28-32}; 3 updates\textsuperscript{33-35}), and 7 on CIN2+ (6 new studies\textsuperscript{20, 36-40}; 1 update\textsuperscript{41}). Overall the studies included in the initial and updated reviews were conducted in 12 high-income countries: the USA, Canada, England, Scotland, Sweden, Denmark, Germany, Norway, Greece, Belgium, New Zealand, and Australia. Although we did not identify any studies examining the impact of HPV vaccination in low- and middle-income countries, we identified several countries (e.g., Bangladesh, Bhutan, China, Rwanda) which published baseline data and/or described the surveillance system they will be using to document changes over time in HPV-related endpoints\textsuperscript{42-47}.

Girls-only immunization
Countries with high vaccination coverage of girls (≥ 50%)

- **Among girls aged 15-19 years old,** significant decreases between the pre- and post-vaccination periods were observed for HPV-16/18 infections (RR=0.32 [95% CI 0.19-0.52]), anogenital warts (RR=0.39 [95% CI 0.22-0.71]) and CIN2+ lesions (RR=0.69 [95% CI 0.66-0.73]) (Figure 1A). Significant reductions were also noted for HPV-31/33/45 (RR=0.72 [95% CI 0.54-0.96]), which suggest cross-protection. Of note, there was no significant difference for cross-protection between countries using the bivalent or quadrivalent vaccines. Recently published data from England suggest that the bivalent vaccine could confer protection against anogenital warts: significant decreases of anogenital warts were observed between 2009 and 2014 among girls aged 15-19 years old\textsuperscript{35}.

- **Among women aged 20-24 years old,** non-significant decreases in HPV16/18 were observed (RR=0.42 [95% CI 0.16-1.10]) whereas significant decreases in anogenital warts (RR=0.68 [95% CI 0.51-0.89]) were observed for women aged 20-39 years old (Figure 1A).

- **Among boys aged 15-19 years old,** anogenital warts decreased significantly (RR=0.66 [95% CI 0.47-0.91]) and new data from Australia showed non-significant decreases in HPV-16/18 (RR=0.37 [95% CI 0.12-1.10]) between the pre- and post-vaccination periods\textsuperscript{14}. Recent data from England also indicate that anogenital warts have decreased significantly among young boys following the implementation of girls-only bivalent vaccination\textsuperscript{35}. These observations suggest the presence of herd effects in countries with high vaccination coverage.

- **Among older men,** anogenital warts also decreased significantly (RR=0.82 [95% CI 0.72-0.92]) whereas non-significant decreases in HPV-16/18 were observed (RR=0.85 [95% CI 0.35-2.03]) (Figure 1A).

- The direct and herd effects of HPV vaccination from the initial review (Figure 1A) continue to be observed in the updated review. In addition, more data for CIN2+ outcomes are now available. Significant decreases in CIN2+ are observed for girls aged 15-19 years old\textsuperscript{36, 40, 41} whereas inconsistent results are observed for women aged 20-29 years old\textsuperscript{36, 41}.
Countries with low vaccination coverage of girls (<50%)

- Among girls aged 15-19 years old, significant decreases between the pre- and post-vaccination periods were observed for HPV-16/18 infections (RR=0.50 [95% CI 0.34-0.74]) and anogenital warts (RR=0.86 [95% CI 0.79-0.94]).
- Among older women and/or men, no significant herd effects are observed (Figure 2A).
- In the updated review, recent data from the USA indicate significant decreases in CIN2+ among girls up to 24 years old 38, 39.

Gender-neutral immunization

- Studies on the population-level impact of HPV vaccination are available for 3 countries having recently implemented gender-neutral programs (Australia, the USA and Canada). However, it is still too early to measure the additional impact of gender-neutral vaccination at the population-level, as the maximum follow-up available in the identified eligible articles is 1-2 years after the switch from girls-only to gender-neutral vaccination.

Routine and catch-up vaccination (single and multiple age cohort immunization)

- Many countries included catch-up vaccination in their HPV vaccination programs (Australia, Canada (British Columbia), Denmark, Greece, New-Zealand, Norway, Sweden, the UK and the USA).
- Most countries with high routine vaccination coverage also included a catch-up program (or campaign). There are thus too few countries with high routine vaccination coverage without catch-up vaccination to isolate the additional population-level impact of vaccinating multiple age cohorts (vs a single cohort).

IMPLICATIONS & CONCLUSION

Our findings strongly suggest that HPV vaccination is highly effective amongst vaccinated individuals and provides herd effects in settings with high vaccination coverage. Our results reinforce the need for high vaccination coverage to maximize the population-level impact and herd effects.
SUMMARY OF FINDINGS, Table 1. Population-level impact and herd effects of girls-only HPV vaccination in countries with A) high females vaccination coverage and B) low vaccination coverage.

### A) Countries with high vaccination coverage of females (≥ 50%)

<table>
<thead>
<tr>
<th>Outcomes (n of studies)</th>
<th>RR, 95% CI</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls 15-19 years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16/18 (n=5) *</td>
<td>0.32</td>
<td>[0.19; 0.52]</td>
</tr>
<tr>
<td>AGW (n=3)</td>
<td>0.39</td>
<td>[0.22; 0.71]</td>
</tr>
<tr>
<td>CIN2+ (n=1)</td>
<td>0.69</td>
<td>[0.66; 0.73]</td>
</tr>
<tr>
<td><strong>Women 20-39 years old</strong></td>
<td></td>
<td></td>
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<tr>
<td>HPV 16/18 (n=2) †</td>
<td>0.42</td>
<td>[0.16; 1.10]</td>
</tr>
<tr>
<td>AGW (n=3)</td>
<td>0.68</td>
<td>[0.51; 0.89]</td>
</tr>
<tr>
<td>CIN2+ (n=1)</td>
<td>1.11</td>
<td>[1.10; 1.12]</td>
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<tr>
<td><strong>Boys 15-19 years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16/18 (n=1)</td>
<td>0.37</td>
<td>[0.12; 1.10]</td>
</tr>
<tr>
<td>AGW (n=3)</td>
<td>0.66</td>
<td>[0.47; 0.91]</td>
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<tr>
<td><strong>Men 20-39 years old</strong></td>
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<tr>
<td>HPV 16/18 (n=1)</td>
<td>0.85</td>
<td>[0.35; 2.03]</td>
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<tr>
<td>AGW (n=3)</td>
<td>0.82</td>
<td>[0.72; 0.92]</td>
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### B) Countries with low vaccination coverage of females (< 50%)

<table>
<thead>
<tr>
<th>Outcomes (n of studies)</th>
<th>RR, 95% CI</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls 15-19 years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16/18 (n=1) *</td>
<td>0.50</td>
<td>[0.34; 0.74]</td>
</tr>
<tr>
<td>AGW (n=6)</td>
<td>0.86</td>
<td>[0.79; 0.94]</td>
</tr>
<tr>
<td>CIN2+ (n=0)</td>
<td>NA</td>
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<tr>
<td><strong>Women 20-39 years old</strong></td>
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<tr>
<td>HPV 16/18 (n=4) †</td>
<td>0.96</td>
<td>[0.77; 1.18]</td>
</tr>
<tr>
<td>AGW (n=6)</td>
<td>1.02</td>
<td>[0.90; 1.16]</td>
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<tr>
<td>CIN2+ (n=1)</td>
<td>0.97</td>
<td>[0.92; 1.02]</td>
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<td><strong>Boys 15-19 years old</strong></td>
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<tr>
<td>HPV 16/18 (n=0)</td>
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<tr>
<td>AGW (n=6)</td>
<td>1.07</td>
<td>[0.93; 1.22]</td>
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<tr>
<td>HPV 16/18 (n=0)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>AGW (n=6)</td>
<td>1.13</td>
<td>[0.95; 1.33]</td>
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* RR = prevalence ratio (post-vaccination prevalence / pre-vaccination prevalence)

* For HPV infections, the age group is 13-19 years old
† For HPV infections, the age group of older women is restricted to 20-24 years old
REFERENCES


