Supplementary Appendix

Supplement to:

**Estimating the direct effect of human papillomavirus vaccination on the lifetime risk of screen-detected cervical precancer**

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Mathematical formulas for estimating risks

Let $G_i$ be the set of all women with an HPV infection detected in screening round $i$ ($i=1,...,7$). Note that HPV infections in round 2,...,7 are incident infections preceded by a negative HPV test result in the previous round. For the $m$-th woman in the data, let $H_m$ be the set of all HPV types detected in the cervical smear. $H_m$ is equal to the empty set $\emptyset$ if the $m$-th woman is negative for all high-risk HPV types. The event that any type is detected in the $m$-th woman can be denoted by $\mathbf{1}_{H_m \neq \emptyset}$ using $\mathbf{1}_Z$ as indicator function for any event $Z$. For the $k$-th HPV type ($k = 1, ... , 14$) within the set [HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, HPV68], $\pi_k$ is the HPV type-specific risk of developing CIN3+ within 9 years.

By Assumptions III and IV in the Methods section, the risk of CIN3+ in HPV-positive women in Round 1 is

$$C_1 = \frac{\sum_{m \in G_1} \mathbf{1}_{H_m \neq \emptyset} \cdot \{1 - \prod_{k \in H_m} (1 - \pi_k)\}}{\sum_{m \in G_1} \mathbf{1}_{H_m \neq \emptyset}}.$$

Among women with an HPV infection detected in Rounds 2 to 7, the CIN3+ risk is equal to

$$C_2 = \frac{\sum_{m \in (G_2,...,G_7)} \mathbf{1}_{H_m \neq \emptyset} \cdot \{1 - \prod_{k \in H_m} (1 - \pi_k)\}}{\sum_{m \in (G_2,...,G_7)} \mathbf{1}_{H_m \neq \emptyset}}.$$

Risks $D_1$ and $Q_1$ are defined in a similar way as $C_1$, and risks $D_2$ and $Q_2$ are defined in a similar way as $C_2$. More specifically, for $D_1$ and $D_2$ the type-specific CIN3+ risk $\pi_k$ in $C_1$ and $C_2$ is replaced by the type-specific risk of both CIN3+ and abnormal cytology in women positive for the $k$-th HPV-type, and for $Q_1$ and $Q_2$ the type-specific risk $\pi_k$ is replaced by the type-specific risk of abnormal cytology in women positive for the $k$-th HPV-type.
Denote by $VE_k$ the vaccine efficacy of the $k$-th HPV genotype. Then, after vaccination, the probability of a positive HPV result in screening round $i$ ($i = 1, \ldots, 7$) becomes

$$P_i = \frac{\sum_{m \in G_i} 1_{H_m \neq \emptyset} \cdot \{1 - \prod_{k \in H_m} VE_k\}}{\sum_{m \in G_i} 1}.$$  

After vaccination, the risk of developing CIN3+ after a positive result in Round 1 becomes

$$C_1 = \frac{\sum_{m \in G_1} 1_{H_m \neq \emptyset} \cdot \{1 - \prod_{k \in H_m} (1 - (1 - VE_k) \cdot \pi_k)\}}{\sum_{m \in G_1} 1_{H_m \neq \emptyset} \{1 - \prod_{k \in H_m} VE_k\}}.$$  

and the CIN3+ risk after a positive result in Rounds 2 to 7 becomes

$$C_2 = \frac{\sum_{m \in (G_2, \ldots, G_7)} 1_{H_m \neq \emptyset} \{1 - \prod_{k \in H_m} (1 - (1 - VE_k) \cdot \pi_k)\}}{\sum_{m \in (G_2, \ldots, G_7)} 1_{H_m \neq \emptyset} \{1 - \prod_{k \in H_m} VE_k\}}.$$  

$D_1, D_2, Q_1$ and $Q_2$ were re-estimated in a similar way as shown for $C_1$ and $C_2$.  

**Supplementary Tables**

**Table S1:** Effect of vaccination on the lifetime risks of CIN3+ and CIN2+, with corresponding relative declines as compared to no vaccination.

| Scenario                                      | CIN3+ Risk (95% CI) | Relative decline (95% CI) | CIN2+ Risk (95% CI) | Relative decline (95% CI) |
|-----------------------------------------------|---------------------|---------------------------|---------------------|---------------------------|
| **Lifetime**                                  |                     |                           |                     |                           |
| no vaccination                                | 4.1 (3.5 to 4.9)    | ref                       | 6.5 (5.6 to 7.3)    | ref                       |
| 2/4vHPV                                       | 1.9 (1.4 to 2.4)    | 53.5 (43.7 to 62.2)      | 3.5 (2.8 to 4.1)    | 46.8 (38.9 to 54.8)       |
| 2vHPV + cross-protection                      | 1.2 (0.9 to 1.5)    | 70.5 (64.4 to 78.0)      | 2.3 (1.8 to 2.8)    | 64.3 (57.7 to 70.4)       |
| 9vHPV                                         | 0.5 (0.2 to 0.7)    | 88.5 (82.4 to 94.3)      | 1.1 (0.8 to 1.6)    | 82.7 (76.3 to 88.0)       |
| **Residual lifetime after an HPV-negative result in Round 1** |                     |                           |                     |                           |
| no vaccination                                | 1.4 (1.0 to 1.9)    | ref                       | 2.8 (2.2 to 3.4)    | ref                       |
| 2/4vHPV                                       | 0.8 (0.5 to 1.2)    | 42.5 (25.2 to 55.2)      | 1.9 (1.4 to 2.4)    | 32.9 (22.2 to 44.3)       |
| 2vHPV + cross-protection                      | 0.5 (0.3 to 0.7)    | 64.7 (51.7 to 75.1)      | 1.3 (0.9 to 1.7)    | 54.7 (45.2 to 64.8)       |
| 9vHPV                                         | 0.2 (0.1 to 0.4)    | 85.1 (71.4 to 94.8)      | 0.7 (0.4 to 1.0)    | 76.2 (65.4 to 86.0)       |
| **Lifetime with vaccine protection up to Round 1 at age 30** |                     |                           |                     |                           |
| no vaccination                                | 4.1 (3.5 to 4.9)    | ref                       | 6.5 (5.6 to 7.3)    | ref                       |
| 2/4vHPV                                       | 2.5 (1.9 to 3.1)    | 40.1 (31.4 to 49.2)      | 4.3 (3.6 to 5.1)    | 33.6 (26.6 to 40.4)       |
| 2vHPV + cross-protection                      | 2.1 (1.6 to 2.6)    | 49.7 (41.5 to 58.5)      | 3.8 (3.1 to 4.4)    | 42.0 (35.1 to 48.8)       |
| 9vHPV                                         | 1.6 (1.2 to 2.1)    | 60.6 (51.7 to 69.0)      | 3.2 (2.6 to 3.8)    | 50.9 (43.5 to 58.1)       |

**Table S2:** Effect of vaccination on the CIN3+ and CIN2+ risks in HPV-positive women, with corresponding relative declines as compared to no vaccination.

| Scenario                                      | CIN3+ Risk (95% CI) | Relative decline (95% CI) | CIN2+ Risk (95% CI) | Relative decline (95% CI) |
|-----------------------------------------------|---------------------|---------------------------|---------------------|---------------------------|
| **Round 1**                                   |                     |                           |                     |                           |
| no vaccination                                | 25.0 (20.3 to 29.1) | ref                       | 34.6 (29.9 to 39.7) | ref                       |
| 2/4vHPV                                       | 15.0 (9.5 to 19.8)  | 39.9 (25.6 to 57.8)      | 21.8 (16.2 to 28.0) | 36.9 (22.7 to 49.8)       |
| 2vHPV + cross-protection                      | 12.5 (7.4 to 16.4)  | 50.0 (36.8 to 68.1)      | 18.5 (13.2 to 24.9) | 46.4 (30.6 to 60.2)       |
| 9vHPV                                         | 6.8 (1.8 to 11.0)   | 72.9 (57.6 to 92.5)      | 11.9 (6.1 to 19.3)  | 65.5 (45.7 to 81.8)       |
| **Rounds 2 to 7**                             |                     |                           |                     |                           |
| no vaccination                                | 9.0 (6.6 to 11.9)   | ref                       | 17.9 (14.6 to 21.3) | ref                       |
| 2/4vHPV                                       | 6.8 (4.5 to 9.8)    | 24.9 (3.5 to 41.9)       | 15.7 (12.0 to 19.5) | 12.3 (~0.7 to 26.3)       |
| 2vHPV + cross-protection                      | 5.1 (3.2 to 7.7)    | 42.8 (21.2 to 59.5)      | 13.1 (9.5 to 16.7)  | 26.6 (12.2 to 42.7)       |
| 9vHPV                                         | 3.1 (1.1 to 6.1)    | 65.5 (34.9 to 87.9)      | 9.9 (5.8 to 14.6)   | 44.9 (20.4 to 66.6)       |
Table S3: Effect of vaccination on the CIN3+ and CIN2+ risks in HPV-positive women with abnormal adjunct cytology, with corresponding relative declines as compared to no vaccination.

| Scenario          | CIN3+               |       | CIN2+               |       |
|-------------------|---------------------|-------|---------------------|-------|
|                   | Risk                | Relative decline | Risk    | Relative decline   |
|                   | (95% CI)            | (95% CI)       | (95% CI) | (95% CI)           |
| Round 1           |                     |                  |         |                    |
| no vaccination    | 52.0 (40.6 to 61.1) | ref             | 65.9 (54.5 to 73.2) | ref |
| 2/4vHPV           | 41.4 (26.3 to 53.6) | 20.3 (3.4 to 42.2) | 54.8 (41.4 to 69.1) | 16.8 (~1.4 to 31.5) |
| 2vHPV + cross-protection | 40.1 (23.7 to 54.3) | 22.9 (1.9 to 47.2) | 53.8 (37.7 to 71.2) | 18.5 (~3.6 to 36.6) |
| 9vHPV             | 28.2 (6.6 to 50.8)  | 45.8 (5.4 to 86.3) | 35.6 (13.9 to 62.3) | 46.0 (6.1 to 77.2) |
| Rounds 2 to 7     |                     |                  |         |                    |
| no vaccination    | 20.3 (14.1 to 30.0) | ref             | 40.2 (32.0 to 50.9) | ref |
| 2/4vHPV           | 18.0 (10.0 to 29.3) | 11.5 (~18.7 to 40.4) | 40.3 (29.4 to 52.9) | ~0.2 (~20.4 to 20.9) |
| 2vHPV + cross-protection | 15.4 (8.0 to 25.9)  | 24.3 (~7.9 to 53.8) | 38.4 (26.0 to 52.8) | 4.3 (~22.1 to 29.5) |
| 9vHPV             | 13.9 (3.2 to 27.8)  | 31.8 (~25.4 to 82.9) | 34.2 (17.0 to 57.0) | 14.8 (~34.3 to 55.1) |
Supplementary Figures

Figure S1: Effect of vaccination on the probability of HPV infection.

The probabilities of HPV infection are estimates needed for the estimation of the lifetime risks of CIN3+ and CIN2+. The probability of a prevalent HPV infection in Round 1 is shown in blue and the probability of an incident HPV infection in Rounds 2 to 7 is shown in red. Separate estimates are presented for the no vaccination scenario and for the three scenarios bivalent/quadrivalent (2/4vHPV), bivalent with cross-protection (2vHPV + cross), and nonavalent (9vHPV) vaccination.
Figure S2: HPV type-specific risks of CIN3+ and CIN2+ among HPV type-positive women.

The HPV type-specific risks of CIN3+ (left) and CIN2+ (right) among HPV type-positive women are estimates needed for the estimation of the lifetime risks of CIN3+ and CIN2+. The HPV type-specific risks in Round 1 and in Rounds 2 to 7 are shown in blue and red respectively, for 14 high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).