Is viral status needed before vaccination?

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Summary Human Papillomavirus (HPV) testing prior to HPV vaccination is not recommended unless HPV tests are part of the established local routines for cervical cancer screening. The reasoning is based upon the very low frequency of women who, at the time of vaccination, would show markers of prior/current exposure (HPV DNA or serological tests) to the HPV types included in the vaccine. Thus at least one thousand women would need to be screened to find one that is HPV 16 and 18 DNA positive. The increase in cost and the other barriers afforded by a prior to vaccination test requirement would result in a lower coverage, the key indicator of a successful vaccination program.

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Rationale

It is widely accepted that the maximum benefit of Human Papillomavirus (HPV) vaccination will be achieved by vaccinating individuals prior to the onset of sexual activity. This is because the vaccines do not appear to have a measurable therapeutic effect and do not prevent either infection or lesions in females already infected with a given vaccine HPV type [1]. They also have been shown to not accelerate clearance of infections in women already infected with HPV 16 and 18 [2]. Therefore the principal target population for vaccination in most countries is adolescent females who have either not yet, or only recently, initiated sexual activity. The fact that the general population vaccine efficacy is higher when adolescent females are vaccinated does not indicate that the vaccine is failing to prevent incident infections with vaccine-targeted types of HPV in older women.

Instead it reflects the fact that the vaccine has no therapeutic effect in women already exposed to the vaccine-targeted types of HPV. Therefore it is likely that many sexually active women who have already initiated sexual activity will desire vaccination and in a few countries there are national recommendations for vaccinating these individuals [3]. Since the HPV vaccines are relatively expensive and the majority of women become infected with HPV within several years of initiating sexual activity [4,5], some clinicians are questioning whether viral status should be determined before vaccinating sexually active women.

Current evidence-based medicine

Impact of HPV status on vaccine efficacy

The results from Phase II and Phase III clinical trials of the two HPV vaccines indicate a lower efficacy in preventing either CIN lesions or vulvar/vaginal lesions associated with vaccine HPV types in individuals who have been previously exposed to vaccine-targeted HPV types at the time of vaccination [6–9]. A recent analysis of four large trials of either...
a HPV 16 monovalent vaccine or the quadrivalent HPV vaccine (6, 11, 16, 18) demonstrated a vaccine efficacy of 44% (95% CI 31—55%) for preventing HPV 16/18 associated CIN 2,3 or AIS in the ’’intent-to-treat’’ population (consisting of all women who were enrolled into the trial) after a mean follow-up of 3 years [10]. In contrast, the efficacy in the ’’per-protocol’’ (consisting of women who were naive to vaccine-targeted HPV types at baseline as determined by serology testing for the presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples for the presence of HPV DNA) was 99% (95% CI 93—100%). Although vaccine efficacy in the ’’intent-to-treat’’ population would be expected to increase over time as women in the placebo group continue to become infected with vaccine-targeted types of HPV and develop Cervical Intraepithelial Neoplasia (CIN) 2,3 lesions, vaccine effectiveness may be lower when sexually active women in the general population are vaccinated compared to the results obtained in the clinical trials to date. This is because the women enrolled in the Phase II and Phase III quadrivalent vaccine clinical trials were a relatively low-risk population for HPV infections based on age and sexual history. The average age of the 20,583 participants was 20 years, the mean age at first sexual intercourse was 16.7 years, and the median lifetime number of sexual partners in non-virginal enrollees was 2 [10]. Women with more than four lifetime sexual partners were not allowed to enroll in these trials.

**Prevalence of HPV infections in sexually active individuals**

Despite the relatively ‘‘low-risk’’ nature of the population enrolled into the pivotal vaccine trials, there was a relatively high prevalence of infection with vaccine types of HPV and cytological abnormalities found at entry into the study. The overall prevalence of positivity for HPV 16 or 18 by either PCR or serology in the four pivotal studies of the quadrivalent vaccine was 21% and 12% of the enrollees had an abnormal cervical cytology at entry [10]. A somewhat lower prevalence of infection with vaccine types of HPV was observed in the Phase III trial of the bivalent vaccine [9]. Based on PCR using the SPF10-LiPA primer-detection system, HPV 16 was identified in 5% of the enrollees at entry and HPV 18 in 2%. However, 17% of the women were seropositive for HPV 16 antibodies by enzyme linked immunosorbent assay (ELISA) and 12% were seropositive of HPV 18 antibodies. There have been two studies that have reported the prevalence of HPV DNA positivity in representative, population-based studies in the U.S. One used stored urine specimens collected from sexually active women aged 18—25 years of age which were tested for HPV using a PCR-based MYO9/MY11 with dot blot primer-detection system [11]. The prevalence of types 16 or 18 in this study was 7.8%. Another population-based study utilized women 14—59 years of age enrolled in NHANES, the Centers for Disease Control and Prevention’s National Health and Nutrition Examination Survey [12]. Self-collected vaginal swabs were tested for HPV DNA using PCR with a PGMY09/PGMY11 reverse line blot detection system. In this study the prevalence of HPV 16 and 18 was only 1.5% and 0.8%, respectively [12]. It is important to note, however, that both self-collected vaginal swabs and urine samples may underestimate the prevalence of HPV 16 and 18 compared to samples obtained directly from the cervix. Table 1 presents the prevalence of HPV 16 identified by either polymerase chain-reaction (PCR) DNA testing or serology in various recent studies. The HPV 16 DNA positivity rates range from 2% to 18% and the HPV 18 positivity rates range from 1% to 7%. It is important to recognize that these estimates are derived from cross-sectional surveys and do not provide an estimate of a woman’s cumulative lifetime exposure to HPV 16 or 18.

There are fewer serological studies of HPV 16 and 18 antibodies in women in the general population. Serology appears to underrepresent prior exposure to HPV since only approximately 60% of HPV DNA positive individuals develop a serological response [3]. In the recent bivalent vaccine study from Costa Rica, only two-thirds of the women who were HPV 16 or 18 DNA positive were seropositive for HPV 16 or 18 [2]. Unlike the prevalence of HPV DNA which declines

### Table 1: Estimates of prevalence of infection with HPV 16 and 18

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Median or mean age (years)</th>
<th>HPV 16 positivity (%)</th>
<th>HPV 18 positivity (%)</th>
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<tr>
<td></td>
<td></td>
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<td>DNA</td>
<td>Serology</td>
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<td>11</td>
<td>13</td>
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<tr>
<td>Wang et al. [19]</td>
<td>Costa Rica</td>
<td>38</td>
<td>4</td>
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<td>Naucler et al. [20]</td>
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<tr>
<td>Skjeldstad et al. [21]</td>
<td>Norway</td>
<td>21</td>
<td>16</td>
<td>16</td>
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<tr>
<td>FUTURE II [8]</td>
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<td>9</td>
<td>11</td>
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<td>Paavonen et al. [9]</td>
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<tr>
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<td>14—59</td>
<td>2</td>
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</tbody>
</table>

Modified from Refs. [1,2,6,8,9,11—13,18—21].

*a Restricted to women who are cytologically normal.*
with increasing age, seropositivity for antibodies against HPV 16 and 18 tends to remain stable with increasing age. In a representative sample of women 20–29 years of age in the U.S., 25% of individuals were seropositive for HPV 16 [13]. A population-based study of older women from Latvia has reported that the seropositivity rate for HPV 16 or 18 was 25% [14]. Although the cumulative lifetime exposure of women to HPV might be as high as 80%, the cumulative lifetime exposure to HPV 16 and/or 18 appears to be considerably lower. Table 1 also provides the prevalence of serological responses to HPV 16 or 18 in various recent studies. The prevalence of antibodies against HPV 16 ranges from 8% to 17% and from 3% to 15% for HPV 18. It is important to recognize that the prevalence of antibodies against a given HPV type probably underestimates cumulative exposure to that type of HPV since not all women exposed to HPV will seroconvert.

Limitations of current HPV detection methods

The HPV DNA detection methodologies such as Hybrid Capture II (Digene Diagnostics) or Amplicor (Roche Molecular Diagnostics) that are currently in clinical use are insufficiently sensitive to be used as a marker of infection. The detection methods that are currently being routinely utilized for clinical purposes have been specifically designed to identify a subset of HPV-infected women who are at greatest risk for developing high-grade cervical neoplasia or invasive cervical cancer [15,16]. Therefore these assays have been "detuned" in order to reduce their sensitivity for detecting low copy number HPV infections that are unlikely to be associated with high-grade neoplasia. For example, the sensitivity of Hybrid Capture II is approximately 5000 copies of high risk HPV DNA [16]. In contrast, the vaccine trials have utilized highly sensitive PCR assays that are designed to identify as many HPV-infected women as possible. The other issue is that HPV genotyping assays are not widely available for routine clinical use and the assays that are being occasionally used have not been validated in rigorous regulatory trials [15]. Therefore even if HPV DNA testing were to be routinely undertaken as a discriminate test prior to vaccination, it is unclear how valid the test results would be. There are similar issues with serological assays for HPV. Although research laboratories have developed highly reproducible two-step ELISA assays for HPV 16 and 18 antibodies that utilize L1 capsids as targets, these assays are not commercially available and they show considerable interlaboratory variation in estimated antibody levels [17]. An important step to developing validated commercially available serological assays for HPV 16 and 18 is the development of an International Standard for antibodies to HPV 16 and 18. This is currently being undertaken by the World Health Organization [17].

Safety of vaccinating women with prevalent vaccine-targeted HPV infections

A considerable number of women enrolled in the Phase II and Phase III trials had evidence of prevalent vaccine-targeted HPV infections at the time of vaccination. This data has been presented to the national regulatory bodies at the time of vaccine registration and has documented no increase in adverse events when women already infected with vaccine-targeted HPV infections are vaccinated. Based on this safety data, some countries have recommended vaccination of sexually active women, as well as women with a history of abnormal cervical cytology or who are high-risk HPV DNA positive, although it is clear that the vaccine will have no therapeutic effect in already infected with vaccine-targeted HPV infections and that efficacy will be lower in such women compared to women who have not previously initiated sexual activity [3].

Recommendations

Despite the fact that infection with or evidence of exposure to any single type of vaccine-targeted HPV type is relatively high in the vaccine trials as well as various population-based studies, evidence for infection with both HPV 16 and 18 is relatively uncommon. Infection with both HPV 16 and 18 was encountered in only approximately 1% of the women in these trials and only about 1 in 1000 had either serological or DNA evidence of exposure to all four types of HPV targeted by the quadrivalent HPV vaccine, HPV 6, 11, 16, and 18. This means that most women will receive some benefit from vaccination against HPV, although the level of benefit will decrease as the likelihood of prior exposure to HPV 16 increases [3]. Moreover, commercially available standardized tests for identifying HPV 16 and 18 DNA or antibodies against HPV 16 and 18 are currently not available for routine clinical use and there are currently no clinical indications for HPV serological testing other than research. Based on these considerations, HPV DNA testing or serology should not be used as a discriminate test prior to vaccinating sexually active women. However, sexually active women should be screened for cervical cancer at the time of vaccination in accordance with screening recommendations for a given country. Even though a woman has a history of cervical disease or an abnormal screening test result, they will can still benefit from vaccination.

Directions of future research

1. Continue cohort studies to better understand the incidence of HPV 16 and 18 over time in different populations.
2. Conduct clinical research to evaluate cervical cancer screening protocols for vaccinated women in different age groups.
3. Conduct additional studies to determine relationships between HPV 16 and 18 DNA status and serological status and response to vaccination in older, sexually active women.

Clinical perspectives

1. Although most sexually active women will have been exposed to HPV, very few will have been exposed to all of the vaccine target types of HPV and almost all will receive some benefit from vaccination.
2. Prevaccination testing for HPV (unless it is part of routine cervical cancer screening) is unnecessary and adds additional costs to the vaccination program.
3. Serological testing for HPV does not have any clinical application.
4. Vaccinating women who during routine screening are found to have either a high-risk HPV infection or CIN has not been associated with adverse events in the vaccine trials.

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Contributors: F.X.B’s research unit is involved in vaccine trials organized by GlaxoSmithKline and Merck/Sanofi Pasteur MSD. He is member of the Steering Committee of Merck/Sanofi Pasteur MSD, and external advisor of GlaxoSmithKline.

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