Naturally Acquired Immunity Against Human Papillomavirus (HPV): Why It Matters in the HPV Vaccine Era

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(See the major article by Castellsagué et al on pages 517–34.)

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Scientists do not know precisely which elements of the immune system are important in preventing or resolving human papillomavirus (HPV) infections in unvaccinated women. HPV has a battery of immune-evasion mechanisms that include hiding within the host mucosal cells, low-level production of late (L) proteins, and inhibition of innate immunity and cell-mediated response by early proteins [1].

HPV vaccine trials show that sufficiently high levels of neutralizing antibodies against viral capsid strongly protect women who are negative for vaccine types at baseline against homologous (same-type) HPV infection. The measurement of HPV antibodies is also important for identifying unvaccinated women who have mounted an antibody response following previous exposure to HPV infection and may, therefore, be naturally protected. However, only approximately half of women seroconvert within 18 months after HPV infection [2]. The interpretation of HPV serology is additionally complicated by substantial differences across assays used in different studies (eg, detection ranges, targeted HPV types, and epitopes) [3–5]. Despite these limitations, seroprevalence studies have been essential in understanding HPV exposure [6] and infection trends [7], and have more recently started providing prospective estimates of naturally acquired immunity after HPV infection [4].

In this issue of *The Journal of Infectious Diseases*, Castellsagué and colleagues [8] report on the association of HPV types 16 and 18 antibody levels and the development of new homologous HPV infections and cervical lesions in >8000 women (15–25 years of age) who comprised the control arm of a multinational randomized trial of the HPV-16/18 vaccine (PATRICIA). Findings are based on a virus-like particle (VLP)–based enzyme-linked immunosorbent assay (ELISA) that measures a broad spectrum of neutralizing and nonneutralizing antibodies directed against the L1 capsid protein. High titers of HPV-16 antibodies, but not of HPV-18 antibodies, were significantly associated with a lower risk of incident and persistent homologous type infection, and also with a lower risk of atypical squamous cells of undetermined significance (ASCUS) and cervical intraepithelial neoplasia (CIN) grades 1–3. Compared with HPV-16–seronegative women, new incident HPV-16 infections were reduced by 36% (95% confidence interval [CI], 22%–47%) in HPV-16–seropositive women (ie, 15% of unvaccinated women). Protection significantly increased with the increase in HPV-16 antibody titer; it was 66% (95% CI, 46%–79%) in the highest HPV-16 antibody quartile [8].

In the control arm of the Costa Rica Vaccine Trial, Safaeian et al [4] used the same VLP ELISA as Castellsagué et al [8] and reported the same seroprevalence (25%) at enrollment for HPV-16 and HPV-18. A significant reduction of new homologous type infections was observed in the highest tertile of HPV-16 and HPV-18 antibodies—protection of 50% and 64%, respectively.

Naturally acquired protection in older women was assessed in a population-based cohort study (median age, 37 years), also from Costa Rica [9], using a different VLP ELISA than the 2 vaccine trials [4, 8]. Seroprevalence at enrollment was 19% and 18% for HPV-16 and HPV-18, respectively. A significant protection (46%) from subsequent homologous infection was shown for HPV-16 but not HPV-18.

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A few studies [3, 9, 10], including that by Castellsagué et al [8], raised the possibility that serological response to HPV-16 and HPV-18 in women might not be the same. In fact, some studies showed similar seroprevalence of the 2 types in the general female population despite the consistently higher prevalence of HPV-16 DNA than HPV-18 DNA in vaginal samples [3, 10]. The evaluation of natural protection against HPV-18 is further complicated by the rarity of HPV-18–related clinical endpoints, including ASCUS and all grades of CIN [11].

Information on naturally acquired protection to HPV infection in males is much more limited than in females. HPV-16 incidence did not differ significantly by HPV-16 serostatus in a cohort of adult men [12] in whom the same VLP ELISA as in Wentzensen et al [9] was used. In fact, higher HPV seroprevalence has been consistently reported for different HPV types in women than men from the same source population [6, 13]. The observed difference by sex in immune response may be related to the tissues predominantly affected by HPV infection between the 2 sexes, that is, mucous membranes in the female genital tract vs keratinized epithelia in the male genital tract.

From a practical viewpoint, Castellsagué et al [8] contribute, together with some previous work, to fill a knowledge gap that hampers projections on the impact of HPV vaccination from dynamic transmission models. In the lack of sufficient data on naturally acquired protection, models published between 2002 and 2013 have assumed different patterns including complete lifelong immunity [14–19] and no natural immunity [17–24]. Partial immunity [19, 25–27] or waning of immunity [24, 28–32] has also been hypothesized, as well as boosting of immunity by repeated HPV infections [33] (Table 1).

The existence and the magnitude of naturally acquired protection against homologous HPV reinfection are crucial to assess the effectiveness of vaccinating sexually active young women [24, 34] and boys in addition to adolescent girls [18, 19, 25, 26]. If naturally acquired protection is absent or weak, vaccination of sexually active young women would be attractive because of the large fraction of them who may still be susceptible to HPV infection despite having been already infected and having cleared the infection in the past. Similarly, the existence of a large pool of susceptible men despite previous HPV infection would call for vaccination of boys in order to reduce the circulation of the virus in a population and eventually reach a desirable herd immunity threshold, that is, a fraction of protected individuals that can even prevent the infection from spreading to unvaccinated people [35].

In conclusion, the findings from Castellsagué et al [8] show that approximately 1 of 7 young unvaccinated women in the PATRICIA trial has some protection from HPV-16 infection because of naturally acquired antibodies. It is impossible, at the moment, to say if all HPV-16–seropositive women benefit from a partial protection from HPV-16 reinfection or if approximately one-third of them benefit from full naturally acquired immunity. This proportion may be different in older women; for example, it may be larger if they had had more time or chances to seroconvert or smaller if they tended to lose HPV antibodies. Naturally acquired immunity has not been demonstrated in men. Better understanding of these phenomena is crucial to model the effectiveness of different vaccination strategies.

Table 1. Human Papillomavirus Transmission Models by Assumptions on Pattern of Naturally Acquired Protection

Degree of Protection	Duration of Protection	No. of Models	References
Complete	Lifelong	6	[14–19]
	Waning	6	[24, 28–32]
Partial	Lifelong	4	[19, 25–27]
	Increasing with age	1	[33]
None	. . .	8	[17–24]

Notes

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