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Will HPV vaccines reduce oropharyngeal cancer burden?

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HPV vaccines were licensed and recommended more than a decade ago, in order to reduce individual- and population-prevalence of HPV, a cause of cancer at multiple anatomic sites.[1] These vaccines were initially tested and approved for the prevention of cervical precancer. HPV vaccine efficacy was later shown at non-cervical anogenital anatomic sites, including the vulva, vagina, penis and anus.[2-4] Currently, the World Health Organization (WHO) recommends vaccination of girls aged 9 to 14 years, the subset of the population with the greatest risk of HPV-induced cancer as well as the likelihood for benefit, and consequently, the most cost-effective strategy.[5] The US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices more expansively recommends routine HPV vaccination to females and males aged 9 to 26 and permissive vaccination based on shared clinical-decision making for individuals aged 27 to 45 (Table 1).[6] While the vast majority of countries are implementing female-only vaccination programs, 18% of the global HPV vaccine supply is currently utilized by males.[5] In 2020, the US FDA did expand the label of the nonavalent HPV vaccine to include prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine. Such approvals could further increase the proportion of countries moving towards gender-neutral HPV vaccination.

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Table 1

World Health Organization (WHO) and US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (US CDC ACIP) HPV vaccination recommendations

	US CDC ACIP	WHO
Routine and catch-up age groups	ACIP recommends routine HPV vaccination at age 11 or 12 years (as early as 9). ACIP also recommends catch-up vaccination for persons through age 26 years who are not adequately vaccinated.	Primary target group in most of the countries recommending HPV vaccination is adolescent girls, aged 9-14.
Permissive recommendation	ACIP recommends HPV vaccination based on shared clinical decision making for individuals aged 27 through 45 years who are not adequately vaccinated. HPV vaccines are not licensed for use in adults older than age 45 years.	Up to 18 (but no upper bound recommended)

Among men and women aged 18-33 years, the prevalence of oral HPV16/18/6/11 infections was 88% lower in recipients of at least one dose of the HPV vaccine, including a 100% reduction in fully vaccinated men.

Among HPV-naïve individuals, it is highly likely that HPV vaccination, which confers near-complete protection against cervical, vaginal, vulvar, penile and anal HPV infections and precancer, would be similarly efficacious against oral/oropharyngeal HPV infections that cause HPV-positive oropharyngeal cancer. Consistent with this expectation, studies show comparably high efficacy of HPV vaccines in preventing oral HPV. This protection against oral HPV infection arises from vaccine-induced robust systemic neutralizing antibodies, the likely effector mechanism against mucosal HPV infections.[7] Indeed, systemic IgG antibodies are the source for salivary IgG antibodies, with high observed correlation in the respective antibody levels.[8]

Vaccine-type (HPV16/18/6/11) oral HPV prevalence declined by 37% during 2009-2016 in unvaccinated US men aged 18-59 years, without a commensurate change in the prevalence of non-vaccine oral HPV infections.

The first evaluation of vaccine efficacy (VE) against oral HPV infection was conducted in a randomized clinical trial initially designed to evaluate efficacy of the bivalent HPV vaccine against persistent cervical HPV16/18 infection and precancerous lesions, the Costa Rica HPV Vaccine trial (CVT).[9] In this study among young women, a 93% reduction of prevalent oral HPV 16/18 infection was observed in the vaccine arm compared to the control arm approximately 4 years after vaccination.[9] Data from the US National Health and Nutrition Examination Survey (NHANES) confirm and expand the CVT observations in a population-representative setting.[10] Among young adults (ages 18-33 years), prevalence of vaccine-type oral HPV infections (HPV16/18/6/11) was 88% lower in men and women who self-reported receipt of at least one dose of the HPV vaccine, including a 100% reduction in vaccinated men.[10]

If a sufficient proportion of causally-relevant oral HPV infections are indeed acquired later in life in men, recommending bodies in countries with high OPC burden may consider expanding to gender-neutral vaccination and increasing the age range of vaccination (although cautiously, to not incentivize older age at vaccination).

In addition to direct benefit in vaccinated individuals, emerging evidence also suggests considerable herd protection against vaccine-type oral HPV infections (i.e. indirect benefit among unvaccinated individuals). For example, vaccine-type (HPV16/18/6/11) oral HPV prevalence declined by 37% during 2009-2016 in unvaccinated US men aged 18-59 years, without a commensurate change in the prevalence of non-vaccine oral HPV infections. These results suggest herd protection among unvaccinated men arising from increased vaccine uptake in females.[11]

Despite the high efficacy of the HPV vaccines against oral HPV infections, reductions in HPV-positive oropharyngeal cancers, whose incidence has increased dramatically in recent decades in numerous developed countries, are not anticipated for several decades. This is because it would take at least 20 to 30 years for the currently vaccinated individuals (in their teens and 20s) to attain ages of peak oropharyngeal cancer incidence (50s and 60s).[12]

Until HPV vaccine supply constraints have been adressed, expanded recommendations should be curtailed in order to prioritize the target population who will receive the most significant benefit, girls aged 9-14 years.

To address this, one may consider increasing the age at vaccination—yet, the optimal upper age-limit for catch-up vaccination for the prevention of HPV-positive oropharyngeal cancers remains uncertain. An important question when considering vaccinating older individuals is when the 'causal' HPV infection (in other words, the infections likely to cause cancer) is acquired. At the cervix, modeling studies suggest the majority of cervical HPV infections that lead to cervical cancer are acquired by 30 years of age.[13] Thus, vaccinating women over the age of 30 years is unlikely to avert a substantial proportion of the cervical cancer burden. Unlike cervical HPV infections, the prevalence/incidence of oral HPV infections does not decline with age.[14,15] While the natural history of oral HPV infections and HPV-positive oropharyngeal cancers remain largely unstudied, recent microsimulation modeling suggests that a low proportion of non-cervical cancers are attributable to infections acquired at older ages.[16]

If a sufficient proportion of causally-relevant oral HPV infections are indeed acquired later in life in men, recommending bodies in countries with high OPC burden may consider expanding to gender-neutral vaccination and increasing the age range of vaccination (although cautiously, to not incentivize older age at vaccination). However, this should only be considered once the current HPV vaccine supply constraints have been addressed.[17] Until that time, expanded recommendations should be curtailed in order to prioritize the target population who will receive the most significant benefit, girls aged 9-14 years.[5] ■

CONFLICT OF INTERESTS
The authors declare nothing to disclose.

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