EDITORIALS

HPV "Coverage"

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This issue of the *Journal* presents a milestone in expanding the coverage of cancers associated with the human papillomavirus (HPV). Joura and colleagues[1] report the results of a randomized, controlled trial of a new 9-valent HPV vaccine versus a quadrivalent HPV vaccine in more than 14,000 young women. The authors found that the new vaccine had an efficacy of nearly 97% against high-grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58. In the intention-to-treat analysis, the 9-valent vaccine was not found to be more beneficial than the quadrivalent vaccine, presumably because so many of the study participants, who were between 16 and 26 years of age, had already been infected with the five HPV types added to the new vaccine by the time of the study's onset. The rationale for vaccination at 11 to 12 years of age is to provide protection before exposure to HPV.

What HPV researchers talk about when they talk about "coverage" is the distribution of HPV types in cancers. Earlier vaccine formulations targeted the most common oncogenic types, 16 and 18, which are responsible for about 70% of cervical cancers. The 9-valent vaccine is expected to target an additional 15 to 20% of cervical cancers and an additional 5 to 20% of other HPV-related cancers.[2,3] While HPV-related cancer coverage can now expand, other types of coverage present ongoing challenges.

What many Americans talk about when they talk about "coverage" is health insurance. The HPV vaccine has been included in the Vaccines for Children (VFC) program since 2006.[4] The program entitles uninsured children through 18 years of age to free access to vaccines recommended by the Advisory Committee on Immunization Practices (ACIP). Since 2010, the Affordable Care Act (ACA) has required private health insurers to cover these vaccinations and has prohibited copayments or deductibles when the vaccines are delivered by an in-network provider. On paper, insurance coverage for HPV vaccines is now comprehensive. The limited availability of in-network providers in some rural jurisdictions and the persistence of some grandfathered plans not required to follow the ACA preventive care provisions represent the remaining barriers to access. HPV vaccines constitute the most expensive series currently included in the VFC program[5]; private-sector prices are even higher. The initial costs for clinicians to stock this product for privately insured patients while awaiting reimbursement as well as concerns regarding out-of-pocket expenses among patients without access to in-network providers may mean that insurance coverage constraints are inhibiting vaccination uptake in practice, if not statute.

What the immunization community talks about when we talk about "coverage" is the proportion of the targeted population that receives a vaccine. By any metric, HPV vaccine coverage in the United States is a problem. At 57%, coverage for the first dose of HPV vaccination among girls 13 to 17 years of age lags behind coverage for other vaccines recommended for children 11 to 12 years of age by approximately 20 to 25 percentage points.[6] If teenagers were offered and accepted HPV vaccination every time they received another vaccine, first-dose coverage for HPV would exceed 90%.[7] Even though private doctors' offices stock vaccines, and parents and teens visiting the offices accept other immunizations, 4 of 10 adolescent girls have not even begun HPV vaccination. Formative research suggests that parents hear mixed messages about HPV vaccination; pediatricians communicate less urgency and give weaker recommendations for this vaccine. When clinicians present HPV vaccine together with tetanus–diphtheria–acellular pertussis and meningococcal vaccines and make strong recommendations, there is greater acceptance.

It is possible that a three-dose series is daunting to parents of teens and their clinicians, whether because of the cost (even if borne by private insurance or the VFC program) or the difficulty of making three office visits during a stage when school and extracurricular activities can be all-consuming. Expanding in-network insurance coverage to pharmacies could present a convenient option for the completion of multidose series during the teenage years, but immunization data for these encounters should be made accessible to primary care physicians through immunization information systems. Regulatory authorities in several countries have approved two-dose series for young adolescents for both the quadrivalent and bivalent HPV vaccine based on the noninferior immunogenicity of two doses administered 6 months apart.[8] The ACIP has reviewed available data for two-dose schedules and will review forthcoming data on the immunogenicity of alternative schedules for the 9-valent vaccine.

Even with the availability of another HPV vaccine targeting additional cancer-causing virus types, vaccination of a much higher proportion of preteens is needed. Otherwise, decades from now oncologists will still be talking about HPV-associated cancers with thousands of new patients every year. Instead, I hope that in a few decades we will be able to tell a generation of adults who never had HPV-associated cancers or precancers that when they were teenagers, we had them covered.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Driving Pressure and Respiratory Mechanics in ARDS

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In this issue of the *Journal,* Amato et al.[1] use data from previously published trials to determine whether it is possible to predict outcomes in patients with the acute respiratory distress syndrome (ARDS) on the basis of the settings of their mechanical ventilators or parameters derived from monitoring the mechanics of the ventilation achieved. Previous articles published in the *Journal* had shown that a lung-protective strategy — that is, limiting the tidal volume (V_T) and plateau pressure while providing relatively high positive end-expiratory pressure (PEEP), can improve survival in ARDS,[2,3] thus demonstrating the importance of respiratory mechanics in determining outcomes in patients.[4] Lung-protective ventilation strategies maintain alveolar aeration, prevent overexpansion of the lung, and limit driving pressure (ΔP, which can be calculated as ventilator-measured plateau pressure minus applied PEEP) and thereby are thought to reduce ventilator-induced lung injury.

Amato et al. focus on ΔP as a predictor of outcome in ARDS. Because ΔP is the tidal increase in static transrespiratory pressure, it is proportional to V_T, with respiratory-system elastance (the inverse of compliance) being the constant of proportionality; elastance reflects the severity and extent of lung injury. Thus, ΔP is determined by variables known to predict or affect mortality in ARDS. The authors conducted a statistical mediation analysis of the aforementioned data, in which variations of V_T, PEEP, ΔP, and respiratory-system compliance were assessed to determine which of the operator-set or measured variables was most