

# Herd immunity or health equity? – extending HPV vaccination

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Of the 604,127 cases and 341,831 deaths attributable to cervical cancer in 2020, China accounted for an estimated 109,741 (18%) cases and 59,060 (17%) deaths.<sup>1</sup> Human papilloma virus (HPV), for which a vaccine has been available since 2006,<sup>2</sup> causes almost all cervical cancer.<sup>3</sup> Gao et al. examined the impact of delayed HPV vaccination uptake and HPV-based screening for cervical cancer in China, currently short of World Health Organization (WHO) targets.<sup>4</sup> Immediate introduction of both, using the nonavalent HPV (9vHPV) vaccine in girls in China was the most cost-effective strategy; initiating HPV-based screening, but not HPV vaccine, would result in up to 543,000 excess cases and 178,000 excess deaths, and USD4.4 billion in costs.<sup>4</sup> The greater cost effectiveness of 9vHPV has been confirmed in low-middle-income countries (LMICs) of Indonesia (incremental cost-effectiveness ratio [ICER] of USD830 per quality adjusted life year [QALY])<sup>5</sup> and South Africa (ICER of USD796<sup>c</sup>/QALY).<sup>6</sup>

In Asia, the age-standardised incidence rates (ASIR) per 100,000 woman-years in 2020 was greatest in Maldives (25/100,000) and Indonesia (24/100,000). The highest global ASIR was in southern and eastern Africa (36 and 40/100,000, respectively) with greater burdens in Malawi (68/100,000) and Zambia (66/100,000).<sup>1</sup> The HIV-attributable cervical cancer ASIR exceeds 20 per 100,000 in these regions: 64% and 27% of cervical cancer incidence in 2018 was in women living with HIV in southern and eastern Africa, respectively.<sup>7</sup> Vaccinating 9-year-old girls with 90% coverage globally from 2020 to 2029 with the 9vHPV vaccine could have averted 19 cases and 14 deaths per 1000 vaccinated.<sup>8</sup> By June 2020, 107 (55%) WHO Member States had introduced HPV vaccination.<sup>2</sup>

Globally, HPV is also associated with 17,000 (42%) and 18,000 (51%) anal cancers, and 30,200 (81%) and 7460 (20%) head and neck cancers in men and women respectively, and 13,000 (50%) penile cancers in men.<sup>3</sup> Increasing numbers of head and neck, penile and anal (particularly in men who have sex with men [MSM]) cancer, was described in people living with HIV in

South Africa.<sup>9</sup> In South-East Asia, MSM and transgender women who were HIV-infected were infected with significantly more anal high-risk HPV serotypes (76.6% vs 53.5%).<sup>10</sup>

Nonetheless, HPV vaccination, particularly in LMICs has been focussed on females. In 2019, 88% of high-income countries (HICs) had introduced HPV vaccination for females, compared with 44% which had additionally introduced vaccination for males. In LMICs, 40% of countries had introduced HPV vaccination for females and 5% for males.<sup>2</sup> Potential cost-benefits of vaccinating boys to enhance herd immunity and prevent HPV-associated cancers in men have been excluded from the current study,<sup>4</sup> thus the cost-benefit estimates the authors present may be an underestimate. In the Netherlands and Sweden, studies have shown that a more equitable programme of gender-neutral 2vHPV vaccination would be cost-effective in preventing HPV-associated cancers in men, while further enhancing the benefits of vaccination of girls to prevent HPV-associated cancers and precancerous lesions. For prevention of precancerous HPV and HPV-associated cancer, the ICER was USD8335<sup>c</sup>/QALY in the Netherlands in 2020,<sup>11</sup> and USD6,737<sup>c</sup>/QALY in Sweden, including additional prevention of genital warts, in 2018,<sup>12</sup> approximately nine-fold that of female-only vaccination campaigns in LMICs.<sup>5,6</sup> Many similar analyses exclude treatment costs of genital warts. In Sweden, prevention of genital warts increased the QALYs from 5600 to 6,010, further decreasing accumulated net costs from USD236 million<sup>c</sup> to USD 210 million<sup>c</sup>.<sup>12</sup> Although studies have shown that increasing vaccine coverage for girls impact HPV-associated cancers more, uptake has lagged. Reasons include the social acceptability of HPV vaccination, limited health access, concern over side effects, programme disruptions due to COVID-19, lack of knowledge of HPV-associated diseases, vaccine shortages globally and high HPV vaccination costs.<sup>2,11–14</sup>

Congenital rubella syndrome (CRS) follows rubella infection in pregnant women, and the WHO recommends rubella vaccination inclusion in national immunisation programmes, in association with measles immunisation. By December 2018, 168 countries had introduced rubella vaccine; global rubella case numbers decreased 97% from 2000 to 2018 (<https://www.who.int/news-room/fact-sheets/detail/rubella>), indicative of the advantages of gender-neutral vaccination campaigns to achieve herd immunity and ultimately eliminate disease. Costs can be mitigated. Gavi, the Vaccine

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<sup>c</sup>To make economic data comparable, average USD values were calculated for the year of publication.

Alliance has previously assisted eligible countries to receive HPV vaccination, and the Pan-American Health Organization has successfully negotiated reduced HPV vaccine costs.<sup>13</sup> WHO now recommends single dose schedules in HIV-uninfected females younger than 21 years ([https://cdn.who.int/media/docs/default-source/immunization/position\\_paper\\_documents/human-papillomavirus-\(hpv\)/hpv-background-document-report-march-2022.pdf](https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/human-papillomavirus-(hpv)/hpv-background-document-report-march-2022.pdf)), reducing campaign costs. Single dose trials with 9vHPV are underway (<https://clinicaltrials.gov/ct2/show/NCT03675256>; <https://clinicaltrials.gov/ct2/show/NCT03180034>).

Whether arguments are centred on herd immunity, gender neutrality or health equity, a wider target population for 9vHPV vaccination may encourage price reductions, decrease HPV-associated medical costs, enhance vaccine acceptance, promote vaccine equity, improve QALYs and augment healthcare in adolescents, a notoriously difficult group to assist. A comprehensive analysis of potential advantages for an inclusive 9vHPV vaccination strategy, including potential cost reductions, prevention of infectious, precancerous and cancerous lesions, and interactions with HIV and other STIs, is due.

#### Declaration of interests

The authors declare no conflict of interest.

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