

## EDITORIALS



## Who should be vaccinated against HPV?

As richer countries consider vaccinating males, the focus for lower income countries should remain on cervical cancer prevention

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Vaccination of girls against the human papillomavirus (HPV) has been implemented in most developed countries, driven by prevention of cervical cancer as a public health priority. Bivalent (Cervarix, GSK) and quadrivalent (Gardasil, Merck) vaccines protect against subsequent infection with oncogenic HPV16/18, and quadrivalent vaccine protects against HPV6/11, which cause anogenital warts. Although HPV vaccination effectively protects against external genital lesions and anal intraepithelial neoplasia in males, only a few jurisdictions have so far recommended universal vaccination of boys. These include Australia, Austria, two Canadian provinces, and the United States. In other countries, a cautious approach has been due, in part, to uncertainties around the population level impact and cost effectiveness of vaccination of boys.

In a linked article, Bogaards and colleagues (doi:10.1136/bmj.h2016) estimated the benefits to men of offering HPV vaccination to boys.<sup>1</sup> They used a dynamic simulation and a bayesian synthesis to integrate the evidence on HPV related cancers in men. The analysis takes account of indirect protection from female vaccination: heterosexual men will benefit from reduced HPV circulation in females, so if coverage in girls is high the incremental benefit of vaccinating boys is driven by prevention of the residual burden of anal cancer in men who have sex with men.

The findings reinforce those of prior analyses that found that adding boys to established vaccination programmes in girls becomes less cost effective as female coverage increases.<sup>2</sup> The cost effectiveness of vaccination of boys also depends on other local issues, especially vaccine type and vaccine and administration costs. A threshold total cost per vaccinated boy for cost effectiveness can be identified at any level of coverage in girls: such analyses can provide policy makers with the maximum rational vaccine price appropriate to the local environment. If vaccine coverage in girls is lower, however, the most effective use of resources is likely to involve increasing coverage in girls, if feasible.<sup>2,3</sup>

In some countries, vaccination of boys might not be cost effective, even at lower vaccine prices, due to higher administration costs.<sup>3</sup> Recent developments towards reduced dose schedules could help. In 2013 the European Medical

Agency recommended a two dose schedule for the bivalent vaccine in girls, in 2014 the United Kingdom switched to a two dose schedule, and the World Health Organization now recommends two doses for girls <15. Two dose schedules are the most cost effective option for girls provided protection lasts for  $\geq 20$  years<sup>4</sup> and reduced dose schedules in boys are also likely to increase cost effectiveness if adequate efficacy is maintained.

Bogaards and colleagues highlight the importance of vaccination for prevention of anal cancer in men who have sex with men. In part due to uncertainties in natural history, the effectiveness of anal cancer screening is not established.<sup>5</sup> Primary prevention with targeted vaccination of men who have sex with men is an attractive option and is potentially more cost effective than universal vaccination of boys. The US Advisory Committee on Immunization Practices already recommends vaccination of men who have sex with men up to the age of 26 years.<sup>6</sup> Older men who have sex with men could also potentially benefit. The UK's Joint Committee on Vaccination and Immunisation, as an interim position, recently stated that a programme to vaccinate men aged 16-40 who have sex with men with a quadrivalent vaccine should be considered, if cost effective.<sup>7</sup> Lower coverage rates expected with targeted versus universal male vaccination are an important consideration, and the two approaches are not mutually exclusive.

Several other new developments should be factored in to future policy decisions. A recent study showed that the bivalent vaccine is effective in women aged  $\geq 25$  without a history of HPV disease.<sup>8</sup> With a transition to primary HPV screening occurring in several countries, an interesting possibility to be evaluated involves "screen and vaccinate" strategies in older women—that is, offering HPV screening, followed by vaccination for HPV negative women with extended (or perhaps no) recall for this group. Secondly, a nonavalent vaccine (Gardasil9, Merck), which protects against an extra five HPV types,<sup>9</sup> has recently been recommended for use in the US.<sup>6</sup> In women, this will increase protection against cervical cancer in those who are fully vaccinated (from about 70% to about 90%)<sup>10</sup> but as most HPV cancers in men are attributed to types included in current vaccines,<sup>1</sup> tiered pricing structures for new generation vaccines based on differential incremental benefits (and thus differential

cost effectiveness thresholds) in girls versus boys could be considered.

All these policy decisions must consider burden of disease, safety, effectiveness, acceptability, equity, and cost effectiveness. Although the focus in developed countries has now, appropriately, shifted to considering these issues for boys, men who have sex with men, and older women, broader efforts to prevent cervical cancer should remain the priority in low and middle income countries. Of the 610 000 cancers annually attributable to HPV worldwide, 87% are cancers of the cervix, and three quarters of these occur in countries with a low or medium human development index.<sup>11</sup> Even if a substantial majority of young girls in such countries were vaccinated, hundreds of millions of older women would remain at risk—vaccination alone will not prevent an expected increase in cervical cancers in the next few decades, driven by population ageing. Here, the priority focus should be the development of integrated programmes for vaccinating young girls and screening older women. Based on experience in developed countries, this will also provide benefits for men through indirect vaccine protection.

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