Accelerating cervical cancer control and prevention

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Cervical cancer is probably the best understood and most preventable of all major human malignancies. The progressive steps of this disease—human papillomavirus (HPV) infection, progression to precancer, and invasion—are well described (figure).[1] Sexual transmission of causal HPV infections is ubiquitous but the rates of cervical cancer vary widely, inversely related to the effectiveness of prevention programmes. Almost 90% of deaths occur in low-income and middle-income countries. In high-income countries, cervical cancer has been relatively well controlled by expensive but effective prevention programmes based on cervical cytology screening.[2]

Discovery of HPV as the causative agent of most cervical cancers has led to two novel and highly efficacious prevention methods: prophylactic HPV vaccination to control the early peak of infections and sensitive HPV-based screening to detect and treat the secondary peak of precancers.[2] With current preventive methods, it is technically feasible to control cervical cancer globally. The speed and degree of control that is achieved depends on how vaccination and screening is implemented.

In *The Lancet Public Health*, Alejandra Castanon and colleagues[3] use a health decision model to estimate cervical cancer incidence in England, UK, under four different scenarios of implementation of vaccination and screening programmes. The authors developed a pragmatic model, combining age cohort modelling, observed individual level data, and microsimulation data for unobservable disease states to estimate future cancer incidence. The model addresses relatively minor modifications in the existing, high-quality prevention programme in England and projects slight changes in the already low cervical cancer burden in the coming decades, until vaccinated cohorts reach the age of cancer incidence.[3] Most importantly, Castanon and colleagues show that HPV screening leads to further reduction of cancer incidence compared with cytology, and that earlier introduction of HPV screening could prevent 1400 cases of cervical cancers. However, the model clearly shows that in places where the cumulative lifetime incidence is already less than 1%, additional substantial reductions are difficult.

Several findings from this study are important because they have implications for other settings. Firstly, vaccination of young girls has no short-term effect on cancer rates because of the 30–40 years' period from first HPV infection to invasive cervical cancer, the reduction of cervical cancer resulting from vaccination of girls aged 12–13 years will manifest only decades later. Secondly, as a direct consequence, screening will remain very important for decades. Lastly, the cancer burden will

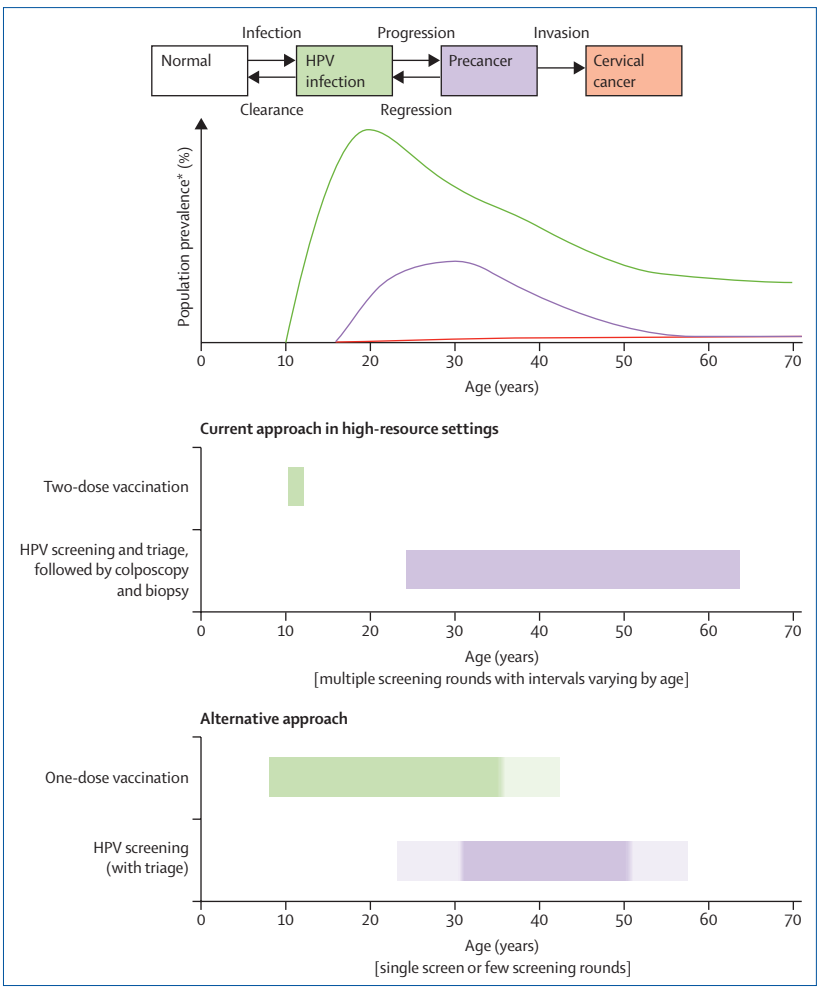

Figure: **Cervical cancer aetiology and prevention approaches**
Cervical cancer can arise from infection with one of a dozen carcinogenic HPV types. Infection is sexually acquired, with a peak transmission of causal infections in late adolescence and early adulthood (green). More than 90% of infections are suppressed within months to a few years by cell-mediated immunity; the small percentage of infections that persist lead to typically slow-growing cervical precancers whose incidence peaks from approximately ages 25–40 years (blue). A sizeable minority of precancers eventually acquires invasive potential, and cancers represent a third peak increasing about age 40 years and extended over the course of decades (red). Prevention in high-resource countries focuses on the strategies associated with individual-level protection. In the alternative approach, individual efficacy is not the objective; but rather reduced endemicity is the target, which can be achieved without demanding maximum long-term durability of immune response. At the same time, introduction of at least one or two highly sensitive screens using HPV testing is targeted to the ages of peak occurrence of cervical precancer, and before the typical ages of invasive cancer. HPV=human papillomavirus. *Curves are not to scale and so units are not shown.

shift to older women because the population is ageing and older birth cohorts do not receive vaccination.

The greatest burden of cervical cancer lies in low-resource settings that currently have neither vaccination nor screening programmes. The modelling presented by the authors shows that a very different strategy focused on cancer reduction is needed in high-risk, low-resource regions, where waiting decades to control cervical cancer incidences in women is not acceptable. Yet, efforts to introduce vaccination and screening in these settings have typically imitated approaches from high-resource settings. Vaccination programmes are emphasising maximal individual vaccine efficacy, which is achieved when vaccination is administered to young girls before onset of sexual activity. Screening is targeting all dozen carcinogenic HPV types, despite the strong variation in risk of individual types[4] and the paucity of infrastructure to manage all the women testing positive. Without actually focusing on low-resource settings, the model by Castanon and colleagues suggests that such an approach will not lead to a reduction of cervical cancer before decades, failing to address the immediate need and the predicted increase of cervical cancer incidences in countries most at need of control efforts.

An alternative approach has been proposed that can accelerate cancer control in low-resource regions.[5,6] It focuses on achieving high population coverage of vaccination to reduce HPV endemicity in adolescents and young adults, and introduction of HPV screening to detect and treat prevalent precancers in women. Herd immunity is emphasised and maximised by vaccination of a wider age range, during which most causal HPV infections are acquired, up to age 30 years or even older.[5,7] Importantly, herd immunity was not considered in the model by Castanon and colleagues, highlighting a need to adapt this decision model to low-resource settings. Despite lower individual efficacy, population effectiveness of vaccination by reduction of endemicity can achieve high coverage and herd immunity quickly. Importantly, recent data suggest that a single dose of the HPV vaccine might induce a sufficiently effective and durable immune response against HPV to break transmission networks and rapidly attack the hyperendemicity of HPV .[8]

This combined cancer control strategy abandons optimal individual-level protection in an HPV-endemic world to protecting individuals as part of the herd (ie, decreasing the chance that a sexual encounter will result in infection). On a global perspective, this strategy will probably save many more lives than introducing vaccination to young girls only or than further improving screening in high-resource settings such as England.

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We are employed by the National Cancer Institute, which has received cervical cancer screening assays in-kind or at reduced cost from Becton Dickinson, Cepheid, Hologic, and Roche for cervical cancer screening studies.

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