Eliminating HPV-related diseases as a public health problem: Let’s start with cervical cancer

The effectiveness of cervical cancer (CC) screening in reducing the morbidity and mortality of CC has been known for decades and is standard medical practice in high-resource countries. In the last decade, HPV vaccines, highly effective, safe, and cost effective tools to prevent the HPV infections that cause CC and other HPV-related diseases, have become available. The greater than expected vaccine immunogenicity, efficacy, and impact on HPV have given rise to global recommendations for its use. Discussions are beginning on whether it is time to move from a goal of controlling HPV-related diseases to a goal to eliminate HPV-related diseases as a public health problem. We and others believe that elimination of CC as a public health problem is feasible in countries with effective screening, treatment and immunisation (http://www.who.int/ncds/un-task-force/un-joint-action-cervical-cancer-leaflet.pdf). Demonstrating this is the logical first step towards the broader goal of elimination of HPV-related diseases in men and women worldwide.

The terms “control”, “elimination”, and “eradication” have specific meaning in the public health community (1). Control refers to the reduction of disease incidence, prevalence and mortality to acceptable levels, such as has been accomplished in several high-resource countries where CC incidence is now <10 cases/100,000 women. Elimination is the reduction of infection and disease to zero or near zero in a defined geographical area (e.g., state within a country, country), whereas eradication refers to the permanent extinction of the infectious agent worldwide. Only one human disease (smallpox) has ever been eradicated, allowing immunisation to end. HPV chronically infects billions worldwide with multiple virus types and does not produce lifetime immunity following natural infection; therefore, HPV is not a good candidate for eradication.

Nevertheless, CC does fulfil the conditions required for elimination. HPV vaccination probably confers long-lasting immunity against infection and disease. Today, there are multiple approaches available to both low- and high-resource countries to detect (e.g., cytology, HPV DNA testing, visual inspection with acetic acid) and treat (e.g., surgical, ablative methods) cervical pre-cancerous lesions (2). HPV transmission can be disrupted by vaccination, as demonstrated by the herd protection observed against genital wart prevalence in males when only females were vaccinated in Australia (3).

The great burden of cervical cancer occurs in low resource countries, where neither screening nor vaccination has achieved sufficient coverage to impact rates of disease.
Countries that include HPV vaccine in their National Immunisation programmes (NIPs) for females and males in 2016

At least 82 countries (42%) have introduced the HPV vaccine in their NIPs for females. Updated from ref. (7).
At least 13 countries (7%) have introduced the HPV vaccine in their NIPs for males. Updated from ref. (7).
The elimination strategy is, to varying degrees, being implemented in many high-resource countries. However, the great burden of CC occurs in low-resource countries, where to date neither screening nor prevention through vaccination has achieved sufficient coverage to impact rates of disease. Nevertheless, there is reason for optimism on several fronts.

First, HPV vaccine is more immunogenic and effective than originally predicted. The vaccine induces seroconversion and long lasting antibodies (> 15 years so far) in essentially 100% of vaccine recipients of all ages studied (4). Initially studied in a three-dose schedule, it is now recommended in a two-dose schedule for 9-14 year olds, and active research is underway to study the hypotheses that a single dose may suffice for long-term protection. Moreover, the protection against HPV infection and lesions caused by HPV types found in the vaccines (including cervical pre-cancerous lesions, and lesions of the anus, vulva, vagina and genital warts) is in the range of 90-100%. Studies of vaccine effectiveness have demonstrated dramatic reductions in genital wart cases (early indicator of vaccine effectiveness), strong evidence of herd protection and significant reductions in cervical pre-cancerous lesions caused by vaccine-related HPVs and in overall cervical lesions. Importantly, the vaccines have an excellent record of safety, with more than 200 million doses given and many studies showing the safety of these products. Unfortunately, anti-vaccine groups have damaged vaccine uptake in a number of countries despite the evidence of vaccine safety.

CC elimination requires development and implementation of strategies with clearly defined targets and resources, including infrastructure, budgets and milestones. Progress should be assessed by monitoring public health measures, such as percent of age-eligible cohorts vaccinated and screened, and epidemiological outcomes such as incidence of pre-cancerous lesions and cancer. This approach is being used for other vaccine-preventable diseases, for example, hepatitis B virus (HBV). WHO has called for the elimination of HBV as a public health problem, defining a prevalence of HBV carriers in children to be achieved by the year 2030. Similar to HPV, chronic HBV is a vaccine-preventable infection, primarily asymptomatic in childhood, which decades later causes death from cirrhosis and liver cancer. While the impact of HBV vaccination on cancer will be largely seen decades in the future, WHO has issued a call for the elimination effort now.

Elimination of HPV-related cancers will require a gender-neutral approach to vaccination

Elimination of HPV-related cancers, most of which are caused by HPV 16, will require a gender-neutral approach to vaccination (5). Even in high income countries the problems of elimination are compounded by a strategy of only giving the vaccine to girls and young women in most countries. This is still the official WHO SAGE recommendation, but gender-neutral vaccination is becoming recommended in an increasing number of countries (Figure 1). The weakness of female only vaccination is apparent when one considers that in most low-resource countries, where there is no CC screening programme, reduction of HPV-related disease will be entirely dependent on achieving high rates of uninterrupted vaccine coverage (Figure 2). In high-resource countries, with relatively good CC screening, the morbidity and mortality of non-cervical HPV-related diseases exceeds or equals that of cervical cancer. Many of
Figure 2
Estimated incidence of cervical cancer cases predicted and averted before age 75 in 118 million women targeted by HPV vaccination programmes by the end of 2014

The solid line shows the cumulative number of expected cervical cancer cases up to age 74 if targeted cohorts had not been vaccinated. The dashed line shows the cumulative number of expected cervical cancer cases up to age 74 in targeted cohorts considering 2014 HPV vaccination coverage. Modified from (7)
these diseases occur in men, as oropharyngeal and other cancers, and rates of HPV-related disease in men who have sex with men (MSM) exceed rates of CC in women before screening was available. Immunising women to protect men is not ethical, decreases resiliency of vaccine programmes and may lead to poor community protection when vaccine programmes are interrupted. Female-only programmes will not work for MSM. Finally, a female-only programme is not workable as an overall strategy if our goal is elimination of HPV infection and all HPV-related cancers, not just lowering rates of disease for the least possible cost. As usual, elimination is much more difficult in low-resource countries. While GAVI funding in the poorest countries makes HPV vaccination possible, the prior requirement for demonstration projects means that national-level programmes are just beginning (6). The PAHO Revolving Fund also negotiated low prices (~8.5 USD/dose) for its Latin American partners. A primary problem is that of middle-income countries not eligible for GAVI support. These countries have been unable to obtain affordable prices and are also interested in introducing Rotavirus, Pneumococcal and other vaccines. The Global Immunisation Community and the manufacturers must cooperate to help them acquire affordable vaccines.

Advocating for elimination will increase the awareness of this disease and galvanize political will

Screening and treatment of cervical lesions in low-resource countries has generally been unsuccessful, with less than 10% of women are screened. New strategies such as HPV-FASTER (8), and new technologies mentioned above will help, but lack of trained personnel, infrastructure and budgets to afford effective treatment will make many of these countries primarily reliant on HPV immunisation for preventing HPV-related cancers, delaying the goal of CC elimination for many years. Fortunately, even the poorest countries can deliver vaccines effectively if they can afford them. Ultimately, elimination of cervical cancer and other HPV-related diseases as a public health problem is both a political and public health issue. Advocating for elimination will increase the awareness of this disease and galvanise political will. We should endorse and embark on this strategy with enthusiasm and without delay. ■
REFERENCES:


