Implementation of HPV vaccination in South Africa

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The Millennium Development Goals (MDGs) identified maternal deaths as a priority and as a consequence of increased interventions the number of maternal deaths has fallen worldwide. In contrast the rates of cervical cancer deaths in low- and middle-income countries (LMIC) are rising. Currently more women globally and in South Africa (SA) die of cervical cancer than due to pregnancy-related complications. World Health organization (WHO) estimates for 2030 project a further increase in cervical cancer deaths (1). Cervical cancer prevention should be addressed as part of the aims of the Sustainable Development Goals (SDGs) for 2030 to 2035. Cervical cancer, like maternal mortality, is a striking example of global health inequity. Most of the global burden of cervical cancer falls on women of reproductive age in LMIC countries. In SA, cervical cancer is the second most common cancer among women, and the most frequent cancer among women between 15 and 44 years of age (2). More than 7,700 woman are diagnosed with cervical cancer in SA every year, of which more than half will ultimately die of the disease (2). This is in stark contrast to the five-year cervical cancer survival rate of almost 70% reported in the United States of America (USA) (3). Reasons for the high mortality rate in SA include the low screening coverage of 14% (2), late presentation of women at an advanced stage of disease combined with the compounding effect of the HIV epidemic. High risk human papilloma virus (hrHPV) persistence within the host cell is necessary for the progression to cervical cancer. HIV-infected women are more likely to be infected with HPV, are often infected with multiple HPV types, and are at an increased risk for viral persistence and progression to cervical cancer when compared with HIV negative women (4).

HPV vaccines and the HPV vaccination rollout

One of the most important recent advances in cervical cancer prevention is the prevention of hrHPV infection through vaccination. HPV vaccination programmes will have the most significant impact in countries like SA with a high HPV prevalence, low compliance to screening, high lost to follow up, and limited resources for management of women with HPV associated precancerous lesions or cancer. The Medicines Control Council (MCC) of South Africa approved two HPV vaccines in 2008, following the approval by the US Food and Drug Administration (FDA) in 2006 and 2007. These vaccines are only effective when used as prophylaxis when administered before exposure. HPV is mainly sexually transmitted and therefore the ideal age for vaccination is before the sexual debut. Both vaccines are approved to be administered to girls from 9 years of age. The bivalent vaccine, Cervarix® (GSK Aspen), contains viral like particles (VLPs) of HPV types 16 and 18 and the quadrivalent vaccine, Gardasil® (MSD), contains VLPs of HPV types 16, 18, 6 and 11. Cervarix® and Gardasil® protect against at least 70% of cervical cancers caused by HPV types 16 and 18, with possible cross-protection against similar types like HPV 31, 33 and 45 (5). Gardasil® also protects against the 90% of genital warts caused by HPV types 6 and 11 and is therefore also approved for boys 9 years and older (6). Both vaccines have been extensively evaluated in randomised control trails and are considered highly immunogenic and safe (5-8). Both vaccines were initially approved as a 3-dose series at 0, 1 or 2 and 6 months. Since the launch of the vaccines, some alternative and more flexible dosing schedules have been approved.

Reducing the number of doses of the HPV vaccine needed could improve adherence and increase coverage. In the initial studies the highest antibody responses were observed in the age group 9-14 years using 3 doses of vaccine. Subsequent studies showed that antibody responses to a 2-dose schedule in girls aged 9-14 years were immunological non-inferior to the 3-dose schedule in the 15-25 year age group in which efficacy was demonstrated initially (6). After WHO recommendations in 2014 a 2-dose schedule was approved for certain age groups in some countries (6). Gardasil® can be administered according to a 2-dose schedule (0 and 6+ months) for girls and boys aged 9-13 years and Cervarix® for girls aged 9-14 years as a 2-dose schedule (0 and 5-7 months) (6). These vaccines are endorsed by leading health organisations worldwide (8) with more than 175 million doses that have been distributed worldwide since their approval (7). These vaccines are approved in more than 170 countries, and are part of national immunisation programmes in at least 58 of these for girls and some also for boys (6). Both pharmaceutical companies have reduced the price of the HPV vaccine over the years, making it more affordable for the general public. The current cost in SA in the private sector is around R650 per dose for both vaccines.

Internationally, Cervarix® is approved up to the age of 45 years in females and Gardasil® up to the age of 26 years in men and 45 years in women. In SA there are about 16 million females aged 9 to 45 years and 11 million men aged 9 to 26 years (2). Unfortunately, the HPV vaccine uptake in SA was limited, with an estimation of around 50,000 individuals vaccinated from December 2009 to November 2014 in the private health sector (number of people vaccinated is based on the assumption that three doses sold equals a complete course for one person; data from Qlikview Total Private Market, IMS units data, Nov 2014). Reasons for the low coverage (0.2%) include limited vaccine-related awareness, knowledge and implementation by health care workers, limited knowledge and awareness among the general public, absence of public endorsement by the SA governments (prior to 2014) and the relatively high cost of the vaccines (5,9).

In April 2014 the South African National Department of Health implemented a school-based HPV vaccination program for all girls 9 years and older in grade 4 in public schools, targeting almost half a million girls. Private schools were not included in the rollout. Local health care specialists and HPV scientists supported this initiative with great optimism and enthusiasm (8). Eligible girls were offered a two dose vaccination series with Cervarix® which won the tender for their cervical cancer vaccine. Targeted coverage was set at vaccinating 70% of grade 4 girls (thus 35% of the population) to create herd immunity. Preliminary data shows excellent coverage of the targeted population, with 91% (412,617/454,652) and 93% (422,000/454,652) of targeted girls vaccinated in the first round and second round of vaccination, respectively (information from personal communication with GSK Aspen, unpublished data). However, there is still a big gap in the private schools where the HPV vaccine uptake through private health care is very low. Coverage for the total cohort of children born in 2004 (including boys and girls in private schools) in SA is estimated at around 39%. School-based vaccination programmes in Australia and the United Kingdom have achieved coverage rates of more than 70%, compared to the less than 35% coverage in the primary care-based programmes achieved in the US (5).

In December 2014 the FDA approved a 9-valent vaccine, Gardasil 9® (10). Mathematical modelling predict that the addition of VLPs of HPV types 31, 33, 45, 52 and 58 to the quadrivalent vaccine could potentially protect against 90% of all cervical cancers (11). Gardasil 9® will be submitted to the MCC for approval in South Africa in 2015.

Impact of HPV vaccination

Will the new national immunisation program against HPV associated disease contribute to the fulfilment of the MDG & new SDG?
Cervical cancer of a female caregiver or breadwinner also disrupts family structures, leading to poverty and cessation of education of affected children. Female grandparents or other elders may become the primary caregivers, who are also at risk of cervical cancer.

The HIV epidemic has changed the epidemiology of cervical cancer in South Africa. HIV uninfected women are mostly diagnosed with cervical cancer from the fourth and fifth decade of life, with a higher mortality rate as women get older. HIV-infected women generally present with cervical cancer and pre-cancer a decade earlier than HIV uninfected women, presenting from their late twenties to the third decade of life onwards (2). They also have more severe disease and a poorer prognosis (4). Cervical cancer affecting relatively younger women results in many more lost years of life in SA.

The implementation of the HPV vaccine is a step towards the SDG goal of reducing premature deaths. However, the maximum impact of 2014 HPV vaccine rollout in SA will only be seen in two to four decades, thus from 2034 onwards, when vaccination done in 2014 will prevent at least 70% of all cases of cervical cancers. Governments must envisage that the initial modest reduction in premature deaths by the 2030 SDG target date will be followed by substantial further reductions after 2030. Some health interventions should not be measured in increments of 15 years, as is done by the MDG & SDGs, but rather over three to four decades.

The HPV vaccine rollout also has some indirect shorter term benefits. Pubescent and adolescent health systems in SA were weak or non-existent before the launch of the HPV rollout. Knowledge about HPV and cervical cancer prevention among health care workers and the general public was insufficient (9). The development of a successful school-based vaccination programme opens the door to possible future interventions on that level e.g. rubella vaccination, guidance on life choice decision making and sexual health. If utilised, this education opportunity can ultimately help improve maternal health and result in healthier newborns as the vaccinated cohort becomes mothers. As consent forms are being sent home, female caregivers are simultaneously made aware and educated about cervical cancer and other cervical cancer prevention options, which may increase the uptake of cervical cancer screening.

The way forward

Cervical cancer prevention was not set as a priority or measurable goal in the MDGs due to many other competing health priorities, like the high maternal mortality fuelled by the HIV and TB co-epidemics. The progress and successes of the HIV treatment programme in SA supported the reduction of maternal and infant deaths, although the targets were not met. It is predicted that as the HIV/ART programme successfully keeps people alive for longer, other diseases, like cervical cancer, may become more prevalent if interventions are not targeted directly at these. Cervical cancer prevention programmes which combine pubescent vaccination with screening for women older than 30 years of age are thus crucial. Interventions like HPV vaccinations may only have the maximum impact in the post SDG era when today's vaccinated cohorts will be passing through the age where cervical cancer incidence is the highest.

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