EDITORIAL

Realities of alternative HPV vaccination schedules

The ability to generate human papillomavirus (HPV) virus like particles (VLPs) by the synthesis and self-assembly *in vitro* of the major virus capsid protein L1 has transformed our prospects for preventing benign and malignant disease caused by HPV particularly the most prevalent HPV caused malignancy – cervical cancer in women. HPV L1 VLPs are structures geometrically and antigenically almost identical to the native virion but lack DNA and are therefore non-infectious. Three HPV L1 VLP prophylactic vaccines have been developed and are commercially available (figure 1); Cervarix, a bivalent HPV16/18 product (2vHPV) from GlaxoSmithKline Biologicals Rixensart Belgium, and Gardasil also known as Silgard, a quadrivalent HPV16/18/6/11 product (4vHPV) from MSD Merck, Whitehouse Station, New Jersey USA have been licensed since 2006/7 in the USA and Europe, Gardasil9 HPV 6, 11, 16, 18, 31, 33, 45, 52, 58 a nonavalent product (9vHPV) licensed in 2014/15 in the USA and Europe.

In the randomised control trials (RCTs) that led to licensure of the current vaccines a classic prime, prime boost dosage regimen designed to generate high affinity, high avidity antibodies and a large B memory pool was used. This conservative approach was driven by the available knowledge (or lack of it) in the 1990's when these studies were being designed. There was not then, nor indeed is there now, an immune correlate of protection to guide clinical development and, since the vaccine would need to provide long term protection, the optimal immune response was desired if the developers were to maximise the likelihood of success.[1] Based on these considerations and the success of Hepatitis B immunisation (another sub unit particulate protein vaccine) the efficacy proof of principle studies carried out in 15-25 year old females for HPV vaccines used a 3 dose schedule of 0, 1, 6 months (Cervarix) or 0, 2, 6 months (Gardasil, Gardasil9).

The 2vHPV and 4vHPV HPV vaccines licensed first in 2006/2007 have been in some National Immunisation Programmes (NIPs) for 10 years. Their impact and effectiveness has been shown in high income countries that initially implemented a three-dose female-only vaccination program with >70% coverage (the threshold for optimal cost effectiveness) in 12–14 year-old girls with or without catch up programs of varying extent. Disease reductions have been reported for high grade cervical intra epithelial neoplasia (CIN, the surrogate endpoint for cervical cancer) and anogenital warts[2,3] together with dramatic falls in vaccine HPV-type prevalence in the vaccinated groups[4] and herd effects in unvaccinated men and women.[5,6] The impact and effectiveness of these vaccines is no longer in doubt but despite introduction in 71 NIPs[7] current estimates are that less than 4% of eligible women have been vaccinated gobally.[8] Furthermore most of these women come from high-income countries but the populations with the highest incidence and mortality of cervical cancer are in middle and low income countries (MIC,LIC) and they remain unprotected.[9]

HPV vaccines face many hurdles for implementation but recurring themes are cost and the operational challenges of delivering a multi dose vaccine to adolescents since in most countries there is no infrastructure outside the routine infant and early childhood schedules. Even in developed countries, with notable exceptions where school programmes have been implemented,[10] immunisation programmes do not deliver successfully the complete regimen and vaccination coverage varies hugely.[11] HPV vaccines are expensive to buy and expensive and complex to deliver. The realities for implementation faced by many health authorities are that rigid adherence to the dosage schedules is impractical and unaffordable. Flexibility in the dosing schedules is important for national vaccination policies particularly

	Cervarix Bivalent vaccine	Gardasil Quadrivalent vaccine	Gardasil9 Nonavalent vaccine
Manufacturer	Glaxo Smith Kline	Merck	Merck
Volume	Per dose 0.5ml	Per dose 0.5ml	Per dose 0.5ml
Adjuvant	ASO4: $Al(OH)_3$ 500mg MPL® 50mg	Amorphous Aluminium Hydroxyphosphate sulphate® 225mg	Amorphous Aluminium Hydroxyphosphate sulphate® 500mg
Antigens HPV VLPs 	L1 HPV16 20µg L1 HPV18 20µg	L1 HPV6 20µg L1 HPV11 40µg L1 HPV16 40µg L1 HPV18 20µg	L1 HPV6 30µg L1 HPV11 40µg L1 HPV16 60µg L1 HPV18 40µg L1 HPV31 20µg L1 HPV33 20µg L1 HPV45 20µg L1 HPV52 20µg L1 HPV58 20µg
Expression system	Hi-5 Baculovirus	Yeast: Saccharomyces cereviseae	Yeast Saccharomyces cereviseae
Licensed Schedule >15 years <15years	Intra muscular 0, 1, 6 months 0,6 to 12 months	Intra muscular 0,2,6 months 0,6 to 12 months	Intra muscular 0,2,6 months 0,,6 to 12 months
FDA licensed	2009	2006	2014
EMA LICENSED	2007	2007	2015

FIGURA 1. PROPHYLACTIC HPV VIRUS LIKE PARTICLE VACCINES

for low and middle income countries if the key objective of reaching enough vaccine coverage (>80%) for population impact is achieved in the target cohorts.

In 2008 the government of Quebec Province Canada on recommendation from the Quebec Immunisation Committee introduced an extended 3 dose school based schedule of 0, 6 60 months in 9-10 year old girls in the routine immunization programme. This step wise approach was based both on operational – better compliance in this age group, experience from the existing school based Hepatitis B programme- and immunological criteria.[12] Evidence from the immunobridging trials undertaken in 10-15 year olds showed that GMTs in these cohorts were twice those achieved in the 16-23 year old women in whom efficacy had been demonstrated in the RCTs.[13] Furthermore in these trials the seroconversion rates one month post a second dose given at 2 months in 10–15 year-old girls were similar to those reported one month post-third dose in 16–23 year-old women. After introduction of the 0-6-60-month extended schedule in Quebec, in 2008 a similar 0-6-60 schedule for girls under 14 years was initiated in Mexico, following recommendations by a group of experts coordinated by the National Institute of Public Health of Mexico (INSP). Universal HPV vaccination for girls between 10 and 11 years of age was introduced in Mexico in 2012 using an extended alternative vaccine schedule (0-6-60 months) as recommended by the INSP and based on the strength of the immune response to the VLP vaccines in 9–11 year-old girls. This strategy was implemented in Mexico as a vaccination policy to increase coverage at a time of financial constraint but also anticipating that scientific evidence would soon be available to give guidance as to the need for the 3rd dose booster.[14] In both Quebec and Mexico programmes were put in place for the monitoring and evaluation of new scientific data to inform the decision of the need for the third dose of vaccine at 60 months. An INSP-

implemented clinical trial in Mexico to evaluate the immunogenicity and non-inferiority of alternative HPV vaccination schedules found antibody titres generated by both the 2v and 4v vaccines were significantly higher after administration of two doses in 9–10-year-old girls than after three doses in 18–24-year-old women. Based on the available evidence both Quebec and Mexico in 2013/2014 adopted an alternative two-dose 0-6 vaccination schedule without intention for a third dose, a schedule that was proven to be not inferior to the traditional schedule in terms of immunogenicity.[15-17] In parallel with the off license programmes in young adolescents in Canada and Mexico the feasibility of changing from the 3 dose 'prime, prime, boost' to a 2 dose 'prime, boost' at 0 and 6 months only in the young adolescent cohort was being assessed in RCTs.[18,19] These studies showed that in 9-14 year old girls (and boys) given 2 doses at 0 and 6 months, antibody responses (titres and avidity) are non-inferior to those achieved after 3 doses in 16-26 year old women, the group in whom efficacy has been shown. After reviewing the evidence in 2014 the Strategic Advisory Group of Experts (SAGE) of WHO recommended "a 2-dose schedule for girls, if vaccination is initiated prior to 15 years of age. A 3-dose schedule remains necessary if immunization is initiated after the girls' 15th birthday. The recommended minimal interval between the 2 doses is 6 months. This interval may be extended to 12 months if this facilitates administration. A 3-dose schedule (i.e. at 0, 1-2, and 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected".[20]

However even with a 2 dose schedule, the effective delivery of these vaccines to the populations that most need them in MIC and LIC still faces programmatic and cost hurdles but what if the regimen could be reduced to 1 dose? This is a radical policy proposal but the reduction in programme costs achieved by implementing a one-dose schedule in terms of delivery costs and vaccine price would make it a very attractive option to public health authorities and governments. So is there data to support this? There is no data for immunogenicity and efficacy for 1 versus 2 or 3 doses from RCTs these trials are in progress. However immunogenicity and efficacy data from two studies, a post hoc analysis of the Guanacaste trial using the 2HPV vaccine[21,22] and an observational cohort study sponsored by IARC/WHO in India[23,24] using the 4vHPV vaccine show that 1 dose is as protective as 2 or 3 doses of vaccine against persistent infection with HPV 16 and 18 (a pre-requisite for the development of high grade CIN) up to 10 years after vaccination of girls and women aged 15-25 years (2VHPV) or 7 years for those 10-18 years (4vHPV).

A central issue for the 1 dose scenario is duration of protection. Protection will have to be maintained in women who are immunised at 12/13years of age for the following 2-4 decades. However there is no immune correlate of protection, no antibody threshold or other immune measurement has been defined that correlates with protection and even in individuals who apparently become seronegative post vaccination, protection against vaccine type HPV infection and disease is maintained. In all studies reported to date GMTs after 2 doses 0,6 or 0,12 months are non-inferior to the standard 3 dose schedule and the expectation is that, in view of this, protection will be equivalent to the standard 3 dose schedule. However GMTs after 1 dose in these studies are inferior to 2 or 3 doses but seroconversion rates do not differ between 1, 2 or 3 doses and the antibody kinetics are the same with antibody persisting above natural infection levels over time.[22,24] Importantly in the IARC/WHO Indian trial all the geometric mean avidity indices after fewer than three doses in any group were non-inferior to those after three doses of vaccine suggesting that antibody quality was as good as that achieved after 2 or 3 doses.[23] Could the stepwise extended schedule approach be applied to the one dose scenario with a single priming dose followed by a second dose if necessary and if so how long could the interval be between the first and second dose? A single dose of the 4HPV vaccine elicits high titres of somatically mutated, class switched neutralising antibody and potent B memory cells.[25] In a recent study from Fiji[26] a single dose of 4v vaccine elicited antibodies that persisted for 6 years and induced immune memory that was boosted by a single dose of 2v vaccine with neutralising antibody titres that did not differ from those generated after 2 or 3doses. This is a small study and should not be over interpreted but it does support an extended interval of years between doses should a flexible schedule be implemented.

The adoption of an alternative 1 dose or 1+1 regimen as opposed to standard dosage regimens in the absence of data from RCTs is a risk and the question then arises how much and how significant is the risk, what is the risk benefit balance? So far the evidence indicates sustained efficacy of 1 dose for 10 years but what if there is a loss of efficacy over time? How do we balance a possible loss in efficacy with the potential for a big increase in coverage and a herd effect? Public health authorities will address these questions in the context of their own disease burden, economic and social priorities. They will make risk assessments based on the evidence and devise risk management strategies for worst case scenarios. However it should be remembered that the worst case scenario in communities with a high burden

of cervical cancer, ineffective screening and low or no vaccine coverage is the status quo.

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