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Preventing cervical cancer and genital warts — How much protection is enough for HPV vaccines?

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Summary HPV associated disease is a global health problem: 5.2% of all cancers are HPV associated with HPV 16 and 18 accounting for 70% of cases of cervical cancer. Genital warts caused by HPV 6 and 11 have a lifetime risk of acquisition of 10%. HPV vaccines are subunit vaccines consisting of virus like particles comprised of the L1 major capsid protein. Two vaccines have been licenced since 2006/2007 and are in the National Immunisation programmes in 62 countries. Both vaccines include HPV 16 and 18 VLPs and one also includes HPV 6 and 11. The vaccines are highly immunogenic and well tolerated. Genital HPV is a sexually transmitted infection with peak incidence occurring just after the onset of sexual activity and the routine cohort for immunisation in almost all countries are adolescent girls 9—15 years of age with or without catch up for older adolescents and young women. Population effectiveness is now being demonstrated for these vaccines in countries with high vaccine coverage. HPV vaccines are highly immunogenic and effective and the original 3 dose schedules have already been reduced, for those 14 years and under, to 2 for both licenced vaccines. There is preliminary evidence that 1 dose of vaccine is as effective as 2 or 3 in preventing persistent HPV infection in the cervix in young women and further reductions in dosage may be possible if supported by appropriate virological, immunological and modelling studies.

Background

Human papillomaviruses (HPVs) are a large group of viruses that infect both cutaneous and mucosal squamous epithelia and have an exclusively intra-epithelial infectious cycle.[1] More than 170 HPVs have been isolated from clinical biopsies,[2] they are classified by DNA sequence and numbered in the sequence in which they were isolated eg. HPV 1, HPV 2 etc. About 30—40 HPV types regularly or sporadically infect the mucosal surfaces of the anogenital tract. A subset of these mucosal HPVs 16,18, 31, 33, 35, 52, 58, 39, 45, 59, 56, 66 and 51, are described as high risk or oncogenic HPV types since a rare, but

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important, consequence of infection with one of this subset is invasive cervical cancer in women, the third most common cancer in women worldwide.[3] Two types HPV 16 and HPV 18 cause more than 70% of carcinoma cervix with HPV 16 detected in more than 50% and HPV 18 in ≥12% of cases irrespective of the geographical location.[4] Although cervix cancer is the major consequence of oncogenic HPV infection, a proportion of cases of carcinoma of the penis, vulva, vagina, anus and oropharynx are attributed to HPV with HPV 16 the major player.[5] Overall 5.2% of all cancers are estimated to be HPV associated.[5] The disease burden of those mucosal HPVs rarely associated with cancers, the low risk HPVs — mainly types 6 and 11 the cause of genital warts is significant. Genital warts (GW) are the commonest viral sexually transmitted infection with a lifetime risk of acquisition of 10% and they constitute a huge disease burden for which there is inadequate treatment[6,7] HPV associated disease is a global health problem Fig. 1.

HPV type distribution in HPV associated cancers

Large international studies that employed robust, centralised methodologies for HPV testing and histopathology consistently show that HPV 16 and 18 are the major oncogenic types contributing to approximately 70% of invasive cervical cancers irrespective of geographical locale.[4,8] HPV 16 is the most prevalent detected in 50% or more of ICC followed by HPV 18 (≥12%). HPVs 31, 45 and 33 occupy positions 3—5 in all continents with the exception of Asia where HPVs 58, 33 and 52 were the commonest types after HPVs 16 and 18.[9] In non cervical associated cancers HPV 16 is the major player.

Licenced prophylactic HPV vaccines

HPV vaccines are sub-unit vaccines consisting of virus like particles (VLPs) made of only one protein — the major HPV coat or capsid protein L1. HPV VLPs are made using sophisticated recombinant technology in which the L1 gene is expressed in recombinant yeast or baculovirus vectors. The chemistry of the expressed protein is such that it spontaneously assembles into VLPs that are morphologically (and more importantly) immunologically similar to the native virus but lack DNA and are therefore non-infectious.

Three HPV VLP prophylactic vaccines have been licenced, Table 1. These are Cervarix®, a bivalent HPV 16/18 product (bHPV) from GlaxoSmithKline Biologicals FDA licenced in 2007, Gardasil® also known as Silgard, a quadrivalent HPV 16/18/6/11 product (qHPV) from MSD Merck, FDA licenced in 2006 and Gardasil9 a nine-valent (nHPV) 6,11,16,18,31,33,45,52,58 VLP vaccine from MSD licenced by the FDA in December 2014 for use in 9—26 year old females and 9—15 year old boys. All vaccines have undergone large, randomised, placebo controlled, double blind phase III trials (RCTs) in young women, 15—26 years old and have demonstrated remarkable efficacy >90% against disease and persistent infection in individuals naïve for the HPV types in the relevant vaccines at trial entry and at the completion of the 3 dose immunisation regimen.[10—13]

Implementation

Genital HPV is a sexually transmitted infection with peak incidence occurring just after the onset of sexual activity.[14] To achieve optimal vaccine effectiveness immunisation ideally should be completed before the start of sexual

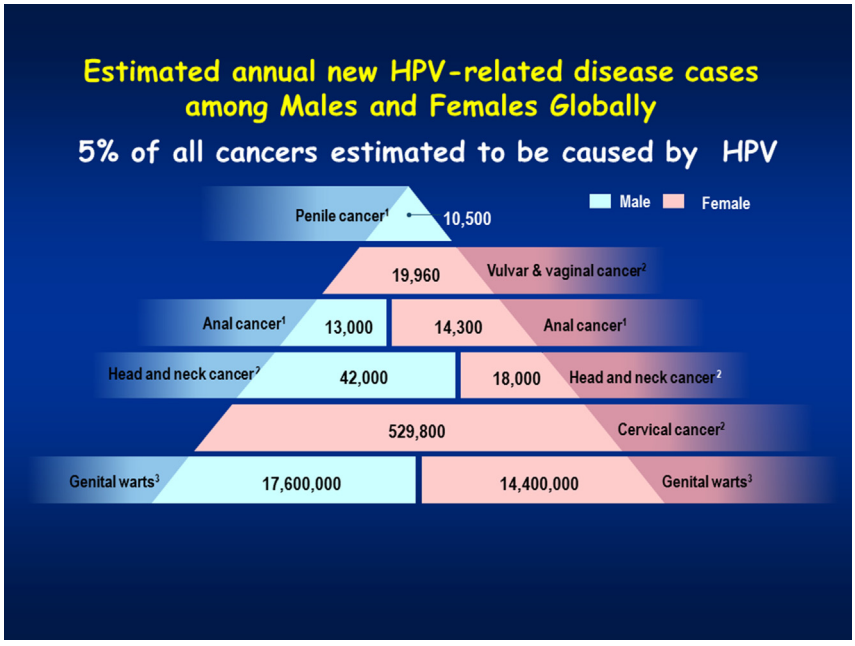

Figure 1 Estimated annual new HPV-related disease cases among males and females globally.