



ESGO Statement on Cervical Cancer Vaccination

August, 2007

In 2004, almost 31 000 women in the EU25 were diagnosed with cervical cancer and 14 000 died from the disease. Assuming that the proportion of uterine cancer of cervical origin in the 12 non-EEA countries was similar to that in the 10 new EU members states brings us to a rough estimate of 52 000 cases and 27 000 deaths for the whole European continent¹. Despite screening for early detection, cervical cancer remains the second most common cause of death from cancer (after breast cancer) among young women (aged 15-44) in EU countries².

It is currently estimated that systematic cytological screening of the cervix can reduce death rates from cervical cancer by 70%. Unfortunately, the benefits of screening have not been available to countries in the developing world, where 80% of cases and deaths from cervical cancer occur, due to lack of resources, and this has been disastrous for women in these countries. In Western Europe the coverage of cervical cancer screening ranges from 27% in Spain to 93% in Finland. Unfortunately, the high-risk group of patients is often not covered by the screening programs³.

By the end of the 1980s a substantial degree of knowledge on human papilloma virus (HPV) had accumulated⁴: the DNA of specific HPV types was consistently found in cervical cancer biopsies throughout the world; and it was established that these genes were essential for the maintenance of the malignant phenotype of cervical cancer cells. HPV infections are both extremely common and readily transmitted between sexually active adolescents and young adults. Prevalence studies in adolescent or college-aged women report that at any single point in time approximately 20-25% are HPV DNA positive⁵. After 2-3 years of follow-up the cumulative detection of HPV in the sexually active young women in the Western world is as high as 60 – 80%.

Today it is firmly established that the so-called high-risk infections cause almost all (99,7%) of cervical cancers, and that the association applies equally to both squamous cell and adenocarcinoma worldwide⁵. HPV 16 and 18 are the most common causing types, responsible for 71.5% of all cervical cancers in Europe⁶. The identification of these cancer provoking virus infections paved the way for preventive vaccines against primary high risk HPV infections, intended to act as a vaccine against cervical cancer. Vaccines using virus-like particles (VLP) were developed against HPV 16 and 18 and also against the HPV types 6 and 11 causing genital warts. Large scale trials in women proved the preventive potential of these vaccines against HPV 6, 11, 16 and 18 infections and the development of premalignant cervical disease caused by these viruses. Combined studies include more than 30,000 vaccinated children, adolescents and adults, all without serious adverse events⁷⁻⁸. While actual cancer events will not be measurable for several decades, HPV

August 28, 2007

infection and the development of precancerous cervical lesions are appropriate surrogate biologic endpoints.

The first cervical cancer vaccine was licensed in the US in June 2006 and in the European Union in September 2006. To date it is licensed in over 55 countries worldwide. Vaccination programs to prevent cervical cancer have so far been instigated and funded in the US, Canada, Australia and some EU countries.

Organizations such as the US Advisory Committee on Immunization Practices (ACIP), the Society of Gynecologic Oncologists (SGO) and the Canadian National Advisory Committee on Immunization (NACI) recommended the routine vaccination of 11 and 12 year old females and that the vaccination series can be started as young as age 9. They also recommended vaccination for females 13-26 years of age, ideally before the onset of sexual activity.

The European Society of Gynaecological Oncology (ESGO):

1. *Emphasizes* that the cytological cervical cancer screening programs in Europe remain pivotal in the prevention of cervical cancer, and that special efforts should be made to continue these programs and to develop them in regions where they are lacking, especially to reach those women with high-risk of developing cervical cancer. The vaccines do not protect against all oncogenic HPV types and therefore at present existing cervical screening recommendations should remain unchanged and should be followed regardless of vaccination status.
2. *Welcomes* the excellent research which has led to the production of two HPV vaccines and the extremely encouraging data about vaccine efficacy. ESGO views the history of progress in understanding cervical carcinogenesis, developing screening, identifying HPV and production of a vaccine as an example of collaboration between academia, health services and industry.
3. *Notes* that although the data about vaccine efficacy and safety are encouraging there are still complex issues about HPV type coverage, long term efficacy, value in women who are already sexually active and those who have HPV infection of cervical dysplasia and that there is still sensible caution about safety issues. All of these issues and others need further carefully conducted research or monitoring. ESGO also recognizes the financial/economic constraints around provision of the vaccine on a wide scale given the cost and other health care priorities which make it impossible to make the vaccine widely available in a short time scale.
4. Has a number of *comments* about clinical use of the vaccine:
 - (a) ESGO supports in principle the use of the vaccination in females between 9 and 13 years of age. While efficacy has not been definitively demonstrated in this age group the immunogenicity data implies that efficacy would be high and as this is before the usual onset of sexual intercourse efficacy should be greatest.
 - (b) The vaccine is not recommended for females below 9 years old as immunogenicity or efficacy is not established in this age group.
 - (c) Females between 14 and 26 years of age who are already sexually active are expected to benefit to a substantially smaller degree from HPV vaccination⁸.

Women between 14 and 26 years of age with previous cervical cytological abnormalities may not have had infection with the HPV type included in the vaccine and may benefit from the vaccine, but to what extent is currently unclear. Therefore, vaccination before the onset of sexual activity is preferable.

- (d) There is no indication that vaccination will have any effect on existing Pap test abnormalities or after treatment of already established dysplasia. These women should be advised that the vaccine has no known therapeutic effect.
 - (e) Development of recommendations for women over the age of 26 is important, as professionals are likely to be confronted with women of various ages requesting vaccination. In that respect the bivalent vaccine has shown to be immunogenic and well tolerated when administered in women 26 to 55 years of age. However, the clinical value of the vaccine in women aged over 26 years is unclear and additional data is required.
 - (f) Vaccination during pregnancy should be avoided if possible as specific studies in pregnant women were not conducted. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. If a pregnant woman is unknowingly vaccinated, the event should be reported. In the setting of any moderate to severe acute febrile illness, vaccination should be deferred until the illness subsides.
5. Finally and most importantly, the ESGO *perceives* the greatest opportunity and benefit for the vaccine being in areas of the world where cervical screening has not been available or feasible. The society urges national and international agencies and the companies who have developed the vaccines to give priority to their introduction in the areas of the world where they are most badly needed and have the potential to prevent suffering and save millions of lives.

References:

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