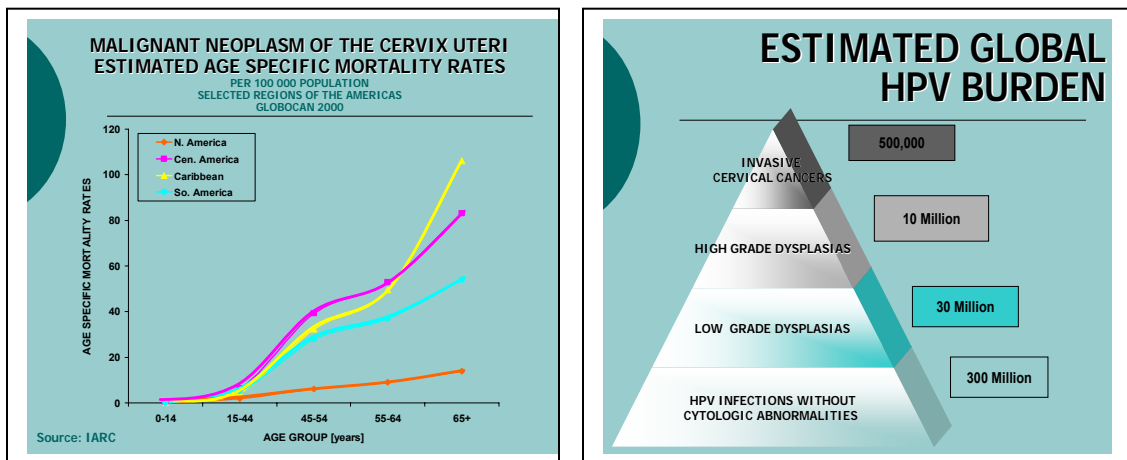




HUMAN PAPILOMAVIRUS VACCINES A NEW TOOL FOR CERVICAL CANCER PREVENTION

THE HEALTH PROBLEM

Cervical cancer is a major and devastating cause of morbidity and mortality worldwide, with an estimated global incidence of 470,606 new cases and 233,372 deaths, annually. Eighty percent of this estimated burden occurs among women residing in less developed countries. Every year, the Region of the Americas reports approximately 92,136 cases of cervical cancer and 37,640 deaths [TABLE 1]. Significant sub-regional disparities exist, however, as cervical cancer incidence and mortality rates in Latin America and the Caribbean [LAC] are roughly four to five times greater than those in North America. Cervical cancer is closely associated with poverty, poor access to health services, rural living, and low educational attainment, with the greatest burden occurring among middle-aged women.



Cervical cancer is caused by persistent infection with certain, high-risk, oncogenic types of Human Papilloma Viruses [HPVs], of which type 16 is the most prevalent. Virus types 18, 45, 33 and 31 have also been identified as dominant in Latin America. HPV types 16 and 18 account for 65-70 percent of

cervical cancers. The burden of cervical disease attributable to HPV infection is, however, not limited to cervical cancer, but includes an even greater proportion of pre-malignant cervical lesions. Additionally, low risk HPV types, such as 6 and 11 are responsible for 90 percent of the genital warts or condylomas.

CERVICAL CANCER PREVENTION- PROGRAMMATIC CHALLENGES

Secondary prevention programs for cervical cancer in Latin America and the Caribbean have not resulted in the profound reductions in morbidity and mortality observed in the industrialized countries of Europe and North America. The reasons for this lack of significant impact are multi-faceted and relate in part to: [a] under-recognition of cervical cancer as a preventable public health problem; [b] sub-optimal co-ordination and management of prevention and control programs; [c] inadequately sustained infra-structural resources to guarantee quality service; and [d] special socio-cultural challenges of women.

Traditional cervical cancer prevention and control programs based on screening, diagnosis and treatment have also been very costly. In 2001, Costa Rica reported cervical cancer program investments in excess of US\$86 million, while in the USA, cervical cancer treatment costs have been estimated at \$2 billion per annum. In addition to cervical cancer treatment costs, the USA spends more than \$6 billion annually on the evaluation and management of low grade lesions, the majority of which regress without intervention.

Against this background of high programmatic costs and issues of quality, an HPV vaccine would be a welcome primary preventive tool, significantly enhancing the prospects for comprehensive cervical cancer control. It must be emphasized, however, that even though HPV vaccines would potentially reduce the cervical cancer burden by about 70 percent, vaccination will not replace cervical cancer screening.

A PUBLIC HEALTH SOLUTION

The definitive identification of certain types of HPVs as the etiologic agents in cervical carcinogenesis, led to the rapid development of HPV vaccines, and their subsequent testing in human populations with excellent results.

To date, sub-unit monovalent [type 16], bivalent [types 16 & 18] and quadrivalent [types 6, 11, 16, 18] HPV vaccines have been developed and have undergone Phase I and II vaccine trials. All of these vaccines have been found to be highly immunogenic. They elicit significant humoral and robust cell mediated immune responses at levels higher than those observed in naturally acquired infections.

These vaccines are also highly efficacious in preventing persistent type-specific infections as well as associated cervical cytological abnormalities and pre-cancerous lesions. In addition, they have been safe and well tolerated in human subjects. Several Phase III trials are currently in progress at multiple international sites. It is estimated that these vaccines will become available in 2006.

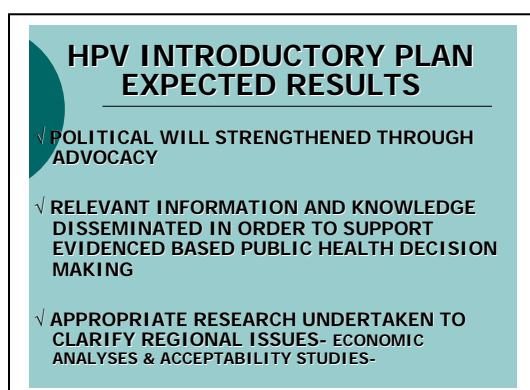
AN HPV VACCINE INTRODUCTION PLAN

In order to prepare Member States for the introduction of HPV vaccines, the Pan American Health Organization [PAHO] has embarked upon a series of activities which include:

- engaging both HPV vaccine suppliers in an ongoing technical dialogue;
- assembling all of the relevant internal stakeholders around the topic of HPV vaccine introduction and developing a joint work-plan;
- strengthening National Regulatory Authorities in order to ensure the quality of products;
- initiating advocacy efforts in order to heighten awareness about HPV vaccines through publications and oral presentations; and
- exploring avenues and mechanisms for building effective partnerships with external agencies and organizations.

THE REGIONAL PLAN

PAHO has developed an HPV vaccine introduction plan, the essential pillars of which include [1] building political will through advocacy using both top-down and bottom-up approaches; [2] disseminating relevant information and knowledge in order to support evidence-based decision making; [3] encouraging or conducting relevant research, such as economic analyses and acceptability studies in order to clarify specific regional issues; [4] designing surveillance systems and tools as appropriate; [5] mobilizing cross-sectional support through effective social



marketing and communication; and [6] mobilizing the essential financial and technical resources that will facilitate execution of these and other activities related to HPV vaccine introduction.

As with other vaccine-preventable diseases, PAHO's Immunization Unit will take the lead role with national health authorities for the introduction and implementation of new HPV vaccines. However, the Regional Immunization Program will work closely with other internal Units responsible for Non-communicable Diseases, Reproductive Health, Child and Adolescent Health, and Public Information in order to establish a unified and cohesive PAHO position, underpinned by best practice and public health principles.

PAHO is uniquely positioned to add value to the process of HPV vaccine introduction in Latin America and the Caribbean from a variety of perspectives. Firstly, PAHO, through its Immunization Unit has been providing technical cooperation and assistance to its Member States over the last thirty years in the areas of immunization program development, surveillance, demand forecasting, cold chain, and other strategic areas related to vaccines. Country efforts have resulted in an extensive umbrella of protection against poliomyelitis, measles, rubella, and tetanus in Latin America and the Caribbean. The opportunities are now available for PAHO to assist Member States in addressing important public health challenges such as cervical cancer.

Secondly, PAHO's Revolving Fund, which is the oldest international vaccine financing mechanism, has provided a tangible backbone of support to Member States in facilitating early procurement of and payment for vaccines and in promoting national self-sufficiency in relation to the purchase of routine vaccines. In this competitive arena of vaccine purchase and supply, PAHO plays a pivotal role in bringing countries together in a bulk purchasing arrangement with suppliers, with a consequent benefit of low vaccine prices. Thirdly, the national Immunization Program Managers in Latin America and the Caribbean also benefit from the advice, expertise and updates provided by the Technical Advisory Group [TAG] on Vaccine-preventable Diseases, which is convened, biennially, by PAHO. Fourthly, the existence of an Inter-Agency Cooperation Committee also contributes significantly to advancing the Immunization agenda in Latin America and the Caribbean as it provides a forum for collaboration and strategic discussion between partners, donors and stakeholders. It is anticipated that this inter-agency partnership will be expanded to include parties with an interest in HPV vaccine introduction.

OTHER SALIENT ISSUES

ESTIMATED REGIONAL VACCINE DEMAND

If the available prophylactic HPV vaccines are to be administered to females, aged 9-12 years, then the target population for immunization in Latin America and the Caribbean would be roughly 2.18 million girls [2007 estimates]. If, however, both girls and boys are considered, then the target population would be in the order of 44.5 million.

WHO PRE-QUALIFICATION

Prequalification by the World Health Organization is an essential requisite for any vaccine, which will be purchased by agencies of the United Nations, such as UNICEF and the PAHO Revolving Fund. This process allows for an independent appraisal of the quality of vaccines being offered for sale. In many instances, the WHO pre-qualification results are also utilized by individual countries to guide their decisions about vaccine purchase. It is anticipated that all of the HPV vaccines, which will be offered for commercial use, will be WHO pre-qualified. The process for a newly licensed product consists of review of the dossier, lot testing and a site visit to the manufacturing house, accompanied by the relevant NRA.



**TABLE 1. MALIGNANT NEOPLASM OF THE CERVIX UTERI IN THE AMERICAS
ESTIMATED INCIDENT CASES AND DEATHS BY COUNTRY WITH
AGE STANDARDIZED RATES PER 100,000 POPULATION, 2000**

COUNTRY	INCIDENT CASES	DEATHS	INCIDENCE RATE	MORTALITY RATE
ARGENTINA	2953	1585	14.2	7.6
BAHAMAS	31	13	22.1	9.3
BARBADOS	54	27	30.4	13.6
BELIZE	30	11	39.6	16.8
BOLIVIA	1807	661	58.1	22.2
BRAZIL	24445	8815	31.3	11.6
CANADA	1608	650	8.2	2.8
CHILE	2321	860	29.2	10.6
COLOMBIA	5901	2339	32.9	13.7
COSTA RICA	424	197	25.0	12.1
CUBA	1586	730	23.8	10.6
DOMINICAN REPUBLIC	1290	495	38.4	15.8
ECUADOR	2231	892	44.2	18.6
EL SALVADOR	1041	387	40.6	15.8
GUATEMALA	1432	566	39.6	16.8
GUYANA	184	69	51.1	20.6
HAITI	2428	1326	93.9	53.5
HONDURAS	833	329	39.6	16.8
JAMAICA	489	209	43.4	18.4
MEXICO	16448	6650	40.5	17.1
NICARAGUA	997	392	61.1	26.1
PANAMA	389	158	31.2	13.1
PARAGUAY	768	281	41.1	15.8
PERU	4101	1575	39.9	15.8
PUERTO RICO	252	114	10.3	4.3
SURINAME	77	31	43.8	18.2
TRINIDAD & TOBAGO	215	97	33.3	15.0
UNITED STATES OF AMERICA	13230	6417	7.8	3.3
URUGUAY	307	163	13.8	7.6
VENEZUELA	3904	1454	38.3	15.2

SOURCE: FERLAY ET AL: GLOBOCAN 2000, IARC

TABLE 2. CHARACTERISTICS OF HPV VACCINES

VACCINE CHARACTERISTICS	SUPPLIER-1	SUPPLIER - 2
CONSTITUENTS	6,11, 16,18	16,18
PRESENTATION	LIQUID	LIQUID
ADJUVANT	ALUMINIUM HYDROXYPHOSPHATE SULPHATE	ASO4 [ALUMINUM HYDROXIDE & MONOPHOSPHORYL LIPID A]
DOSING SCHEDULE	3 DOSES ADMINISTERED INTRA-MUSCULARLY AT 0, 1 AND 6 MONTHS	3 DOSES ADMINISTERED INTRA-MUSCULARLY AT 0, 1 AND 6 MONTHS
COLD CHAIN	2-8 °C	2-8 °C
PACKAGING	SINGLE DOSE PRE-FILLED SYRINGES	SINGLE DOSE VIALS PACKAGED X1 , X10, X100

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