HUMAN PAPILOMAVIRUS DISEASE BURDEN IN PORTUGAL

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INTRODUCTION

Human Papillomavirus (HPV) is a highly contagious virus responsible for the most common sexually transmitted infections. Around 70% of individuals will have contact with HPV throughout life. Although most HPV infections usually clear spontaneously within 2 years, persistent infections are associated with a wide spectrum of diseases that include benign lesions like genital warts or malignant disease such as pre-cancerous lesions and cancers. Cervical cancer is by far the most important consequence of HPV infection. But besides cervical cancer, HPV is responsible for a significant proportion of other anogenital cancer including vulvar, vaginal, penile and anal cancers and an increasing number of Head and Neck (oral cavity, tonsil, oropharynx, pharynx, larynx, etc) cancers. Additionally, HPV is also responsible for genital warts.
Despite screening programs, cervical cancer still represents a huge burden in female health and noteworthy, other HPV anogenital cancers are not screened.
According to the most recent National Oncological Registry (2005), 614 cervical, 81 vulvar, 28 vaginal, 83 anal and 76 penile new cancer cases were diagnosed in Portugal. This reality is clearly underestimated because of under reporting and the exclusion of some health services, for instance, the Azores islands and private units.

OBJECTIVES

The objective is to estimate the burden of HPV related diseases in males and females in Portugal, focusing in particular on HPV types 6, 11, 16 and 18, which are prevented by the quadrivalent vaccine.

METHODOLOGY

The HPV related burden of disease considers incidence and the total costs for the National Health System, as well as the total 2009 deaths per cancer.
To estimate the incidence of cancer cases, an iterative methodology was used based on DRGs (Diagnosis Related Groups) hospital data, the Disease Staging System application, and the Hospital Uniform Discharge Data Set (HUDDS). Although data used comes from official sources it is important to mention that there is evidence of underreporting and high proportion of unspecified cancer coding.
Due to the lack of official data, a mixed strategy combining international incidence data and Portuguese data from a set of health institutions was used to estimate the incidence of genital warts.
Directorate-General of Health (DGS) data on mortality was used for the year 2009.
Regarding financial burden, unit and average costs per procedure were obtained from national official tariffs, including DRGs. For HPV cancers and pre-cancerous lesions the estimation of total costs by disease (including diagnostic and treatment) was made for all hospitals and for 2009.
As some of the data is not available in the HUDDS (e.g., number of outpatient visits, number of emergency room visits, number of CT scan, and so on), data of a subset of hospitals was used.
Resource consumption and costs for the diagnosis and treatment of genital warts were estimated through expert panels.

Estimated cost per case of HPV disease, in Portugal, is shown in Table 1.

RESULTS

In Portugal, the estimated incidence of cervical, vulvar and vaginal cancer is, respectively, 18, 4 and 1 per 100,000. The estimated incidence of genital warts in women is 197 per 100,000.
For men, the estimated incidence of genital warts and penile cancer is, respectively, 269 and 2 per 100,000.
For men and women together, the estimated incidence of anal and Head & Neck cancers is, respectively, 6 and 19 per 100,000.
The summary of estimated burden of cancers which may be related with HPV all types and HPV types 6/11/16/18 is shown in Table 3. New cases and total related costs are estimated for all causes (including all HPV types) and for HPV types 6/11/16/18. It is important to mention that the incidence of both CIN1 and CIN2/3 is underestimated since only new cases treated in hospitals are considered.

METHODOLOGY

TABLE 1. ESTIMATED COSTS (IN EUROS) PER CASE OF HPV DISEASE

	Costs (per case)
Genital warts (males)	218.72
Genital warts (female)	595.75
CIN1	1,418.88
CIN2/3	1,947.33
Cervical cancer	8,996.09
Vulvar cancer	7,060.65
Vaginal cancer	4,641.06
Anal cancer	7,554.08
Penile cancer	4,878.64
Head & Neck cancers	19,217.43

Disease burden estimate is presented both for all causes (including all HPV types) and for HPV types 6/11/16/18.

Total yearly costs per disease take into account incidence (new cases) and average costs per case and, when justifiable, are adjusted for mortality occurring during the year, thereby correcting for costs not incurred.

Among the 40 HPV types known to affect genital mucosa, 15 types are classified as high risk and are a major risk factor for cancer development. The number of new cases of cancers due to HPV type 16/18, two of the 15 high risk HPV types, has been estimated in order to have an idea of the number of cancers that could be prevented by HPV vaccination (Table 2). This estimate used European HPV prevalence data, when available, and worldwide HPV prevalence data, when no data were available for Europe.

TABLE 2. PREVALENCE OF HPV (ALL TYPES), HPV 16 AND HPV 18 PER CANCER LOCATION

Cancer location (ICD 10)	**Prevalence of HPV per cancer location (%)**		
	HPV all types	**HPV 16**	**HPV 18**
Cervical (C53)	99.7	59.0	16.9
Vaginal (C52)	69.9	37.5	5.3
Vulvar (C51)	40.4	13.0	1.8
Anal (C21)	84.3	61.9	4.4
Penile (C60)	46.65	28.1	6.2
Oral cavity (C1-6)	16	10.9	5.5
Oropharynx (C9-14)	28.2	24.4	0.8
Larynx (C32)	21.3	14.7	3.6

Additionally, low risk HPV types 6 and 11 are responsible for 90% of genital warts.

RESULTS

TABLE 3. ESTIMATED DISEASE INCIDENCE AND RELATED COSTS (IN EUROS)

	All causes (including all HPV types)		HPV 6/11/16/18	
	Incidence	**Costs 2009**	**Incidence**	**Costs 2009**
Genital warts (males)	12,380	2,707,795	11,142	2,437,015
Genital warts (female)	9,785	5,829,696	8,807	5,246,726
CIN1	1,783	2,529,858	624	885,450
CIN2/3	1,784	3,474,037	1,053	2,049,682
Cervical cancer	987	8,402,344	752	6,711,775
Vulvar cancer	244	1,503,227	36	220,876
Vaginal cancer	52	214,523	22	91,653
Anal cancer	603	3,905,324	400	2,588,530
Penile cancer	118	499,718	41	173,281
Head & Neck cancers	1,998	16,733,685	243	3,809,090
TOTAL		45,800,207		24,214,078

TABLE 4. CANCER DEATHS (DGS, 2009)

Cancer location	
Cervical	271
Vaginal	12
Vulvar	63
Anal	32
Tongue	167
Penile	28
Mouth	145
Tonsil	45
Other Oropharynx	96
Hypopharynx	57
Pharynx Unspecified	102
Larynx	374

Diseases considered in Table 3. represent a total cost of 45 million Euros per year for the Healthcare system. Total HPV related costs considering the total costs and the percentages showned in Table 2. represent 31.3 million Euros per year.

Head & neck cancers, cervical cancer and genital warts are the diseases that represent the highest financial burden.
Total costs of HPV 6/11/16/18 related diseases are around 24.2 million Euros. From these, 6.7 come from cervical cancer, 7.6 from genital warts and 3.8 million Euros from Head & Neck cancers. Cervical cancer, CIN1/2/3 and female genital warts account for 61.5% of total costs.
HPV 6/11/16/18 related diseases represent 52.9% of total costs.

Table 4. shows 2009 mortality data due to cancers which may be HPV-related.
Mortality due to cervical cancer is by far the most representative of HPV disease burden, since this cancer is 99.7% HPV-related.
Due to the high prevalence of HPV in vaginal and anal cancer, and to a lesser extent, in vulvar and penile cancer, these cancers should also be emphasized as an important HPV disease mortality burden.
Head & Neck cancers also represent an important cause of death; when the proportion attributable to HPV 16/18 (circa 23%) is considered, the number of deaths (226), assuming lethality is the same for all cases, is similar to those caused by HPV 16/18 cervical cancer (206).

Some of these results should be analyzed with caution. Firstly, for all diseases but genital warts, only hospital costs are considered, which can underestimate the total costs, namely an important proportion of the disease burden for pre-cancerous lesions. Secondly, although official data is used, for some diseases, namely anal cancer, the lack of coding accuracy may introduce estimation bias. Thirdly, there are new data related with survival analysis by cancer, with treatment costs and with data on primary (number of women vaccinated) and secondary prevention (increased screening rate), that could change some of the health and financial gains estimated. This also requires further analysis, which could eventually show different values for vaccination impact.
Lastly, the recent evidence of vaccine efficacy against non-cervical cancers, as well as additional gains from cross-protection, highlights the need for new evidence based value of HPV primary prevention.
Taking into account these issues it is natural to expect an increase of the value for money of vaccination.

CONCLUSION

HPV related diseases represent an enormous burden in terms of morbidity and mortality in Portugal.
Diagnosis, management and treatment of HPV 6/11/16/18 related diseases lead to significant costs for the healthcare system and represents 24.2 million Euros, per year, in males and females together.
It is also worth highlighting that, although genital warts are not relevant in terms of mortality, its incidence and associated total costs (8.5 million Euros per year, 5.8 for women and 2.7 for men) are very important and are higher than total costs estimated in 2009 for cervical cancer treatment.
Other anogenital cancers, including vulvar, vaginal, penile, anal and Head & Neck cancers represent altogether an, at least, equal burden compared to cervical cancer.
In the near future, these other HPV related cancers should also be included in assessing the potential impact of HPV vaccination, since these are associated with high morbidity and financial burden and are not targeted by screening.
HPV vaccines may hold great promise in reducing the burden of HPV-associated cervical and non cervical cancers, in addition to genital warts burden reduction, for women and men.
The quadrivalent HPV vaccine is the only to have demonstrated efficacy against cervical cancer, cervical pre-cancerous lesions, vulvar, vaginal and anal pre-cancerous lesions (immediate cancer precursors), and genital warts, thanks to direct protection against four HPV types 6/11/16/18.