Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

# Economic burden associated with the management of cervical cancer, cervical dysplasia and genital warts in Belgium

Lieven Annemans, Vanessa Rémy, Emilie Lamure, Erik Spaepen, Mark Lamotte, Jean-Paul Muchada & Nathalie Largeron

**To cite this article:** Lieven Annemans, Vanessa Rémy, Emilie Lamure, Erik Spaepen, Mark Lamotte, Jean-Paul Muchada & Nathalie Largeron (2008) Economic burden associated with the management of cervical cancer, cervical dysplasia and genital warts in Belgium, Journal of Medical Economics, 11:1, 135-150, DOI: 10.3111/13696990801961611

**To link to this article:** https://doi.org/10.3111/13696990801961611

Published online: 19 Feb 2010.

**Original Research**

# Economic burden associated with the management of cervical cancer, cervical dysplasia and genital warts in Belgium

**Lieven Annemans[1], Vanessa Rémy[2], Emilie Lamure[3], Erik Spaepen[4], Mark Lamotte[4], Jean-Paul Muchada[5], Nathalie Largeron[2]**

## Abstract

***Objective***: Human papillomavirus (HPV) infections can lead to cervical intraepithelial neoplasia (CIN) lesions, cervical cancer (CC) and genital warts (GWs). This study intended to assess the annual cost of CC, CIN and GW management in Belgium.

***Method***: A retrospective study using a Belgian Hospital Disease Database (for yearly hospital cost of CC and GW patients) and a clinical expert survey were performed to assess the medical management of CC, CIN and GW patients. Belgian official sources were used to estimate the annual costs of management of CC, CIN and GW patients both from a healthcare payer perspectives (HCPP) and a societal perspective.

***Results***: Based on the 667 patients diagnosed annually in Belgium with CC and an annual cost per patient of €9,716, the total annual cost of CC is €6.5 million (HCPP). The 10,495 estimated CIN 1, 2 and 3 patients led to an annual cost of €1.97 million (HCPP). The 7,989 estimated annual number of diagnosed GW patients led to an estimated annual cost of €2.53 million (HCPP).

***Conclusion***: HPV-related diseases represent an important burden on Belgian society, especially when considering that the estimates in this study are probably underestimations, as the management costs of other HPV-related diseases (vulvar, vaginal, penile, oropharyngeal (pre-) cancers, recurrent respiratory papillomatosis etc.) are not included in this analysis.

*Keywords: human papillomavirus, cervical cancer, genital warts, cost, Belgium*

*Accepted for publication:* 18th January 2008

[1]Ghent University, Ghent, Belgium
[2]Sanofi Pasteur MSD, Lyon, France
[3]IMS HEOR, Paris, France
[4]IMS, Brussels, Belgium
[5]Sanofi Pasteur MSD, Brussels, Belgium

*Address for correspondence: Vanessa Rémy, Sanofi Pasteur MSD, 8 rue Jonas Salk, 69367 Lyon cedex 07, France. Tel: +33 4 37 28 41 78, fax: +33 4 37 28 44 43, e-mail: vremy@spmsd.com*

# Introduction

Throughout the 27 member states of the European Union, 34,300 women are diagnosed with cervical cancer (CC) annually, resulting in approximately 16,300 deaths[1], and another 688,000 patients* are diagnosed with genital warts (GWs)[2]. In Belgium, 667 new cases of invasive CC are diagnosed each year, and one-third of these cases will lead to death[3,4]. Infections with oncogenic human papilloma virus (HPV) are a necessary cause of CC, and certain non-oncogenic HPV cause GWs[5,6]. HPV is widespread and affects at least 70% of sexually active adults (male and female) during their lifetime[7].

Given the natural history of oncogenic HPV infection (which usually evolves from low-grade to high-grade lesions and then to cancer), it is possible to prevent cases of CC by detecting pre-cancerous lesions, also called cervical intraepithelial neoplasia (CIN), and treating them effectively. Thanks to the implementation of screening programmes, the incidence of CC in Europe has been declining over the past 30 years, leading to a decrease (ranging between 30 and 80%) in associated mortality[8,9]. In Belgium, screening is essentially opportunistic and often performed at yearly intervals. A scheme promoting the recommended one cervical smear every 3 years for women aged 25–64 years was set up in the Flemish Region alone[10]. However, according to Arbyn and Van Oyen[11], coverage of the Belgian female population is similar in all regions (i.e. 57% in Flanders, 61% in the Walloon Region and 58% in the Capital Region (Brussels)).

The incidence of GWs, which are clinically visible manifestations of certain non-oncogenic HPV types, most commonly with HPV types 6 and 11[5], is currently increasing throughout Europe[12] and it is estimated that 1% of the sexually active population in the US has clinically apparent GWs[13]. A recent published study on GW burden in four Nordic countries reported that 10% of women experience GWs before the age of 45, with an increasing occurrence in younger cohorts[14]. Current treatments for GWs are long and painful, and frequent relapses may occur[15,16].

CC screening and treatment of HPV-related diseases represent a high burden on public health and the healthcare budget. For example, screening activities and treatment of HPV-related diseases (including cervical dysplasia, CC and GWs) in the UK represent a cost of £208 million per year from the National Health Service (NHS) perspective[17], and an average €276 million per year from the healthcare payer perspective in France[18–20].

The prophylactic quadrivalent HPV vaccine (Gardasil®†) was licensed in Europe in September 2006. It is currently indicated for the prevention of CC, high-grade cervical dysplasia, high-grade vulvar dysplasia and external GWs caused

* Figure obtained by extrapolation of the UK genital wart incidence to the population of the 27 states of the European Union (Eurostat 2007).
† Gardasil® is a registered trademark of Merck & Co., Inc.

by HPV types 6, 11, 16 and 18. To estimate the potential benefits of a HPV vaccination programme, health authorities are interested in the economic burden associated with HPV-related diseases.

The cost of HPV screening in Belgium has already been calculated and reported by the Belgian Knowledge Centre for Healthcare (KCE)[3]. According to this report, screening activities in Belgium for the year 2005 represented a cost of €65 million. This cost includes consultations (with a gynaecologist in 90% of cases) and tests performed (including specimen handling and result analysis): 'Pap' smear tests (1.3 million), biopsies (19,507) and colposcopies (402,218).

The present study aimed to estimate the economic burden of HPV-related diseases in Belgium, focusing on CC, cervical dysplasia and GWs, both from the healthcare payers and the societal perspective.

# Methods

### Study sources

Two main sources were used to collect the data required for this study retrospectively.

The Intercontinental Marketing Services (IMS) Hospital Disease Database was used to provide information on resource use and costs associated with patients hospitalised for the treatment of CC and GWs, and a panel of experts was set up to collect data regarding outpatient medical care for cervical dysplasia and GWs.

The hospital database contained data from the Minimum Basic Data Set (MBDS, also known as MKG/RCM: 'Minimale Klinische Gegevens'/'Résumé Clinique Minimal') to which Belgian hospitals have contributed for each admitted patient since 1991. In the publicly funded Belgian healthcare system, MBDS reporting is a legal obligation for fulfilment of the reimbursement criteria established by the Belgian social security administration (the National Institute of Sickness and Disability Insurance (INAMI/RIZIV)) and to ensure adequate hospital funding by the federal public health authorities. Each patient carries a unique identification code throughout a given calendar year, which allows anonymous longitudinal case analysis over a well-defined and time-limited follow-up period, as patients cannot be traced beyond a 1-year period.

In this analysis, the 2004 full-year data (the most recent data available at the time of analysis) were used. In the database, case-mix data from 38 hospitals, representing approximately 11,908 beds (corresponding to 21.38% of the total number of hospital beds excluding psychiatric hospitals, 1-day admissions included, in Belgium in 2004) and 1,035,000 hospitalisations, were collected. The panel is representative with regards to type and size of hospital captured ('General <250 beds' 24.7% captured, 'General 250–500 beds' 36.6%, 'General >500 beds' 33.3% and 'University hospitals' 22% captured) and geographic distribution (65% Northern Belgium, 35% Southern Belgium). The MBDS includes in-hospital and day clinic admissions and contains the following

inpatient data for each individual: demographic information; all conditions diagnosed and all inpatient procedures performed (both reported using 9th Revision of the International Classification of Diseases, Clinical Modification (ICD-9-CM) codes[21]; and the All-Patients Refined–Diagnosis-Related Group)[22]. Mortality indices and the severity of the condition prompting hospitalisation are also recorded, together with the length of stay, drug use, diagnostic tests and procedures performed.

Simultaneously, a total of nine clinical experts (six from the Flemish Region and three from the Brussels and Walloon Regions) participated in a survey to collect information on the physicians' day-to-day management of HPV-related diseases (CIN and GWs). The expert survey was performed using a written questionnaire. Based on his/her clinical knowledge and expertise, each member of the expert panel was asked to provide their best estimate for the year 2006 for various figures requested related to treatment pathways following screening results, procedures and interventions.

## Study analysis

### *CC management*

Data on CC treatment were collected through the IMS Hospital Disease Database. CC patients were primarily selected on the basis of the ICD-9-CM code 180.xx ('malignant neoplasm of cervix uteri') as the primary diagnosis. Further classification into International Federation of Gynecology and Obstetrics (FIGO) stages was performed on the basis of additional ICD-9-CM co-diagnoses, indicating spread and metastases (stage I patients only had the 180.xx ICD-9-CM code, whereas stages II–IV had additional diagnostic codes to identify spread). Table 1 lists the codes that were used to classify the patients. It was impossible to distinguish between stages II and III using the ICD-9-CM codes alone, so these two stages were pooled for the purpose of the analysis. For all selected patients, the total pharmaceutical resource use and cost, together with procedures and surgery performed, length of stay (hotel cost) and other required variables such as in-hospital mortality, were extracted from the database.

### *CIN management*

The clinical expert survey investigated the proportion of patients treated according to their degree of dysplasia, treatment procedures performed during a 1-year follow-up period, the proportion of patients who took time off work during their treatment and the mean number of workdays lost by CIN grade (CIN 1, 2 and 3). It also provided the distribution of procedures performed at hospital or ambulatory level.

### *GW management*

Another part of the expert investigation was dedicated to analysis of the treatment pathway (number of visits, tests performed, treatment procedures etc.) for external GWs and for each line of treatment (first- to third-line). In addition, the proportion of hospitalised patients, not provided by the expert survey, was estimated from the IMS Hospital Disease Database, identifying GW patients with

 

**Table 1. ICD-9-CM codes for FIGO stage classification of cervical cancer patients.**

| *FIGO classification* | *ICD-9-CM* | *ICD-9-CM description* |
|---|---|---|
| Stage I | 180 | Malignant neoplasm of cervix uteri |
| | 180.0 | Malignant neoplasm of endocervix |
| | 180.1 | Malignant neoplasm of exocervix |
| | 180.8 | Malignant neoplasm of other specified sites of cervix |
| | 180.9 | Malignant neoplasm of cervix uteri, unspecified site |
| Stage II–IIIa | 182 | Malignant neoplasm of corpus uteri, except isthmus |
| | 182.1 | Malignant neoplasm of isthmus |
| | 182.8 | Malignant neoplasm of other specified sites of body of uterus |
| | 198.82 | Secondary malignant neoplasm of genital organs |
| Stage IIIb | 197.6 | Secondary malignant neoplasm of retroperitoneum and peritoneum |
| Stage IVa | 198.1 | Secondary malignant neoplasm of other urinary organs |
| Stage IVb | 197 | Secondary malignant neoplasm of respiratory and digestive systems |
| | 197.0 | Secondary malignant neoplasm of lung |
| | 197.1 | Secondary malignant neoplasm of mediastinum |
| | 197.2 | Secondary malignant neoplasm of pleura |
| | 197.3 | Secondary malignant neoplasm of other respiratory organs |
| | 197.4 | Secondary malignant neoplasm of small intestine includes duodenum |
| | 197.5 | Secondary malignant neoplasm of large intestine and rectum |
| | 197.7 | Malignant neoplasm of liver, secondary |
| | 197.8 | Secondary malignant neoplasm of other digestive organs and spleen |
| | 198 | Secondary malignant neoplasm of other specified sites |
| | 198.0 | Secondary malignant neoplasm of kidney |
| | 198.2 | Secondary malignant neoplasm of skin |
| | 198.3 | Secondary malignant neoplasm of brain and spinal cord |
| | 198.4 | Secondary malignant neoplasm of other parts of nervous system |
| | 198.5 | Secondary malignant neoplasm of bone and bone marrow |
| | 198.6 | Secondary malignant neoplasm of ovary |
| | 198.7 | Secondary malignant neoplasm of adrenal gland |
| | 198.8 | Secondary malignant neoplasm of other specified sites |
| | 198.81 | Secondary malignant neoplasm of breast |

ICD-9-CM, 9th Revision of the International Classification of Diseases Clinical Modification; FIGO, International Federation of Gynecology and Obstetrics.

ICD-9-CM code 078.11 'condyloma acuminatum' as the primary diagnosis. Combining both types of information, a global treatment pathway, including hospital and ambulatory treatments, was assessed.

## Cost evaluation

For all the analyses, two perspectives were considered, the public healthcare payer perspective (HCPP), including direct medical costs (i.e. hospital, procedures and physician visit costs) reimbursed by the healthcare payer, and the societal perspective (SP), including all direct medical patient costs and productivity-related costs. Costs were calculated for the year 2006.

### *CC management cost*

For patients with CC, a total annual hospital cost was calculated by summing all costs incurred for all hospital admissions within the calendar year. The hospital costs considered here were only calculated from the HCPP (the INAMI/RIZIV in Belgium) since real patient co-payment can only be calculated directly from the hospital invoice. Costs (mean and 95% confidence interval (CI)) are specified for the total population, per FIGO stage and for fatal disease. Calculation of the 95% CIs was based on the student's *T* distribution in order to accommodate for the sometimes low sample sizes ($N<30$). For fatal disease, all patients dying within the year of observation were considered, and their hospitalisation costs for the last 3 months before death were defined as the cost of fatal disease (i.e. the hospital costs for the last 3 months alive).

Ambulatory costs were not considered, but productivity loss has been estimated using the methodology published by the French National Cancer Institute[23]. Productivity loss was calculated on the basis of the national average monthly wage including social benefits (2004 data from the Belgian National Statistics Institute)[24]. Figures were updated to 2006 and a cost per workday (assuming 20 days per month) was calculated (€132.69)[24] and used to value lost workdays. Considering a mean number of workdays lost of 120 days per CC case (based on French published data[23] as no Belgian data were available) and based on the Belgian activity rate in women[25], the total number of workdays lost was estimated. Based on the unit cost by workday lost, total productivity-related costs were calculated.

### *CIN and GW management costs*

Average ambulatory costs associated with the treatment pathway for CIN and GWs were calculated by multiplying the mean resource use estimates (provided by the expert survey) with the unit cost for the corresponding item of resource use. Unit costs (extracted from the INAMI/RIZIV website[26] and presented in Table 2) are based on a health service nomenclature, which lists the services paid for by the healthcare system.

For CIN patients, the expert survey also provided data on the proportion of medical care given at hospital level. The hospital cost of conisation (ICD-9-CM procedure code 67.2 'conisation of cervix') and hysterectomy (procedure codes 68.3–68.9 for partial or total abdominal,

 

**Table 2. Unit costs (in Euros (€)).**

| *Parameter* | *INAMI (HCPP)* | *INAMI + patient (SP)* |
|---|---|---|
| Cost of GP visit* | 16.99 | 20.79 |
| Cost of gynaecologist visit* | 13.55 | 20.79 |
| Cost of dermatologist visit* | 15.23 | 24.97 |
| Cost of other consultation* | 13.55 | 20.79 |
| Cost of Pap smear* | 20.25 | 24.34 |
| Cost of colposcopy* | 11.06 | 11.06 |
| Cost of biopsy* | 112.76 | 121.44 |
| Cost of laser coagulation* | 32.77 | 32.77 |
| Cost of cryotherapy (cervix)* | 5.30 | 5.30 |
| Cost of conisation* | 162.5 | 171.44 |
| Cost of cervix amputation* | 189.20 | 189.20 |
| Cost of electrocoagulation* | 32.77 | 32.77 |
| Cost of surgical excision* | 52.44 | 52.44 |
| Cost of hysterectomy performed at hospital† | 2945.63 | 2945.63 |
| Cost of conisation performed at hospital† | 685.29 | 685.29 |
| Hotel cost of 1 hospitalisation day | 305.98 | 346.28 |
| Cost of 1 lost workday‡ | — | 132.69 |

INAMI, National Institute of Sickness and Disability Insurance; HCCP, healthcare payer perspective; SP, societal perspective; GP, general practitioner; IMS: Intercontinental Marketing Services.
* INAMI/RIZIV[26].
† IMS Hospital Disease Database: based on 1,252 admissions for conisation and 7,585 for hysterectomies.
‡ National Institute for Statistics[24].

laparoscopic or vaginal hysterectomies) was investigated with the IMS Hospital Disease Database (Table 2). Then, for the hospital-based procedures for which no IMS hospital data were available (laser, cryotherapy and cervix amputation), a 1-day hospitalisation cost (€305.98) and a patient hospitalisation fee (€40.33) was added to the procedure cost, the latter only for the SP (Table 2). Productivity loss was calculated based on work days lost for CIN management reported in the expert survey.

With regard to GW patients, a mean cost of hospitalisation was calculated based on the hospital cost extracted from the IMS database. Therefore, the total cost of GW management encompassed both the ambulatory treatment cost and the hospitalisation fees. Productivity loss was not reported for GW patients.

## Economic burden of disease

The annual economic burden was estimated by multiplying the total annual number of CC, CIN and GW patients with the respective mean cost of management. The number of CC and GW patients was retrieved from Belgian published sources[4,27,28]. As no data are available on the epidemiology of CIN in Belgium, a literature review of available European sources was performed to assess the number of CIN patients diagnosed annually in Belgium.

A sensitivity analysis was performed on CC costs using two other Belgian sources[29] to assess the annual number of CC cases and by applying a 10% variation around the number of workdays lost.

# Results

### Cervical cancer management and associated costs

From the 2004 Hospital Disease Database, it was possible to extract a total of 175 CC patients, comprising 112, 22 and 41 FIGO stages I, II+III and IV patients, respectively. 'Cost of fatal disease' was calculated on the 37 patients (7, 6 and 24 patients in FIGO stages I, II+III and IV, respectively) who died in hospital during the course of the year. Overall, the average annual hospital cost of a CC patient was estimated to be €9,716 (95% CI €8,062–11,369), whereas the split per FIGO stage demonstrated that higher FIGO stages were associated with higher annual costs (€6,777, 95% CI €5,335–8,218; €8,495, 95% CI €5,467–11,524; and €18,400, 95% CI €13,480–23,320 for FIGO stages I, II+III and IV, respectively). Of the total cost, the hotel cost proved to be the largest part (49% of total cost), followed by procedures cost (32% of total). Pharmaceutical product cost was the lowest contributor to the total cost (18% of total). The mean 'cost of fatal disease' was relatively high (€16,960, 95% CI €12,942–20,978). It was lowest for FIGO stage I patients (€8,879, 95% CI €2,309–15,450) and highest in FIGO stage II+III (€23,430, 95% CI €6,677–40,184) and stage IV (€17,699, €12,934–22,465).

Considering the 667 annual new CC cases[4,27] and the mean hospital cost of CC treatment, the annual population cost of CC treatment in Belgium has been estimated to be €6.5 million (95% CI €5.4 million–7.6 million) from the HCPP. Moreover, considering that 91% of active women[23] diagnosed with CC would stop working for an average of 120 days[23], the number of workdays lost has been estimated for each age class, resulting in a total productivity-related cost of €3.25 million (Table 3).

When taking into account a lower (595)[29] and higher estimate (818, extrapolated from the IMS Hospital Disease Database) for number of CC cases and applying a ± 10% variation on the number of workdays lost, the annual cost of CC management was estimated to be between €5.8 million and €7.9 million from the HCPP and between €8.4 million and €12.3 million from the SP.

### Cervical intraepithelial neoplasia management and associated costs

According to the expert survey, 19% of CIN 1 patients were given treatment, compared with an expected higher proportion of treated CIN 2 and CIN 3 patients (77% and 93%, respectively). Full results are presented in Table 4.

For CIN 1 patients, the two main procedures were conisation and laser therapy, each applied in approximately one-half of the treated patients. For CIN 2 and 3 patients, the most frequently prescribed treatment was conisation (80.3 and 93.7% of

 

**Table 3. Estimate of annual productivity-related costs of CC in the Belgian population.**

| *Age group (years)* | *Annual number of CC cases* | *% of active women*[25] | *Annual number of workdays lost** | *Total annual cost (€)*[†] |
|---|---|---|---|---|
| 15–24 | 4 | 32.7 | 114 | 15,161 |
| 25–29 | 20 | 82.5 | 1,295 | 171,883 |
| 30–34 | 53 | 82.1 | 3,365 | 446,522 |
| 35–39 | 77 | 79.7 | 4,796 | 636,367 |
| 40–44 | 82 | 76.4 | 4,867 | 645,800 |
| 45–49 | 76 | 71.3 | 4,231 | 561,431 |
| 50–54 | 64 | 56.2 | 2,793 | 370,539 |
| 55–59 | 56 | 32.4 | 1,414 | 187,660 |
| ≥60 | 234 | 9 (0% in the ≥65) | 1,641 | 217,692 |
| Total | 667[4] | | 24,516 | 3,253,055 |

CC, cervical cancer.
* Calculation based on an average of 120 days lost[23] per active women with CC who stops working multiplied by the proportion of women working full time or part time[30].
† Based on a mean cost of €132.69 per work day lost[24].

**Table 4. Treatment pathway for CIN.**

| | *CIN 1* | | *CIN 2* | | *CIN 3* | |
|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* |
| Follow-up | | | | | | |
| Mean number of physician visits after CIN diagnosis | 2.5 | 0.5 | 3.6 | 1.3 | 3.7 | 1.3 |
| Number of Pap smears over a 12-month period | 1.7 | 1.1 | 2.0 | 1.3 | 1.1 | 1.6 |
| Procedures performed (%) | | | | | | |
| Laser therapy (ambulatory) | 30.3 | 42.9 | 17.2 | 35.1 | 1.0 | 1.9 |
| Laser therapy (hospital) | 11.4 | 26.5 | 0.1 | 0.2 | 0.4 | 0.1 |
| Cryotherapy (ambulatory) | 5.6 | 16.7 | 0.6 | 1.8 | 0.2 | 0.7 |
| Conisation (ambulatory) | 49.8 | 41.0 | 75.5 | 32.4 | 88.2 | 6.4 |
| Conisation (hospital) | 3.0 | 4.9 | 4.8 | 5.5 | 5.5 | 5.4 |
| Cervix amputation (hospital) | 0 | 0.0 | 0.6 | 1.7 | 1.2 | 2.3 |
| Vaginal hysterectomy (hospital) | 0 | 0 | 1.2 | 3.7 | 3.8 | 3.6 |

CIN, cervical intraepithelial neoplasia; SD, standard deviation.

treated patients, respectively), mostly in an ambulatory care setting. Taking into account the proportion of hospital-based interventions and multiplying resource use with the mean cost per procedure (Table 2) led to estimated costs per CIN stage as shown in Table 5.

The mean number of workdays lost was 1, 1.9 and 2.4 days for CIN 1, CIN 2 and CIN 3 patients, respectively. The mean cost of productivity loss was included into the overall mean annual treatment cost for each CIN stage (for SP only). The most costly treatment was associated with CIN 3

**Table 5. Mean annual cost of CIN treatment by categories.**

| | *Mean cost (€)* | | | | | |
|---|---|---|---|---|---|---|
| | *CIN 1* | | *CIN 2* | | *CIN 3* | |
| | *HCPP* | *SP* | *HCPP* | *SP* | *HCPP* | *SP* |
| Total cost | 217.9 | 267.2 | 290.1 | 481.5 | 374.3 | 609.4 |
| Ambulatory cost | 158.7 | 188.1 | 218.0 | 259.2 | 217.2 | 256.9 |
| Hospital cost | 59.1 | 63.7 | 72.0 | 72.3 | 157.1 | 157.6 |
| Productivity loss cost | 0.0 | 15.3 | 0 | 150.0 | 0 | 194.9 |

CIN, cervical intraepithelial neoplasia; HCPP, healthcare payer perspective; SP, societal perspective.

(SP €609.4), followed by CIN 2 (SP €481.5) and CIN 1 (SP €267.2) (Table 5).

Three different sources were used to assess the number of CIN patients in Belgium. Considering the 19,507 biopsies performed in Belgium[3], a maximum of 19,507 CIN cases could be diagnosed annually in Belgium. An Italian publication[31] mentioned that 53.8% of biopsies led to a CIN diagnosis. Applied to Belgium, this would lead to approximately 10,495 CIN patients. Using the CIN distribution in biopsies reported in a recent French study[19], it was considered that 39% of CIN were CIN 1 and 61% were CIN 2/3, leading, respectively, to 4,093 CIN 1 and 6,402 CIN 2/3 patients annually in Belgium.

Considering the percentage of treated patients from the expert panel (19% of CIN 1 and 85% of CIN 2/3) and the mean cost estimates for CIN patients, the estimated total cost of CIN management in Belgium has been estimated at €173,353 (HCPP) and €212,591 (SP) for CIN 1 and €1.80 million (HCPP) and €2.95 million (SP) for CIN 2/3.

## Genital wart management and associated costs

On average, GWs were far more likely to be subject to first-line treatment (approximately 94%) than second- (25%) and third-line treatment (12.5%), as detailed in Table 6. Patients with GWs were more likely to consult gynaecologists than General Practitioners or dermatologists. The Pap smear was the most frequent first-line examination, whereas biopsy was the preferred second- and third-line test. Pharmacological treatment was the most common first-line treatment, whereas cryotherapy and laser therapy were the preferred second- and third-line treatments, respectively.

The mean ambulatory cost was estimated at €236.3 from a HCPP and €295.4 from a SP (detailed in Table 7).

The overall incidence rate of GWs is estimated at 76 per 100,000 person-years for the Belgian population as a whole (both male and female)[28], corresponding to a total number of 7,989 GW cases (3,909 males and 4,079 females) annually in Belgium.

Hospitalisations for GWs were reported in the IMS Hospital Disease Database in 77 male patients and 95 female patients. A mean cost per hospitalised GW patient was estimated at €1,083 for men and

**Table 6. Medical resource use for genital warts (mean frequencies).**

| | *First-line treatment* | *Second-line treatment* | *Third-line treatment* |
|---|---|---|---|
| % of patients treated | 94.4 | 25.4 | 12.5 |
| Consultations (mean number per patient per year) | | | |
| Visits to the GP | 1.2 | 0.6 | 0.3 |
| Visits to the dermatologist | 1.1 | 1.0 | 1.5 |
| Visits to the gynaecologist | 2.1 | 2.4 | 3.3 |
| Other (mixed visits) | 0.3 | 0.4 | 0.0 |
| Examinations (%) | | | |
| No examination | 3.0 | 15.0 | 16.0 |
| Pap smear | 70.7 | 16.7 | 13.3 |
| Biopsy | 5.2 | 51.7 | 50.7 |
| Other (colposcopy) | 15.6 | 20.0 | 20.0 |
| Treatments (%) | | | |
| Pharmacological treatment | 71.5 | 33.3 | 13.7 |
| Imiquimod | 91.6 | 76.5 | 53.3 |
| Podophyllotoxin | 8.4 | 23.5 | 3.3 |
| Electrocoagulation | 14.6 | 0.0 | 33.3 |
| Laser therapy | 11.4 | 24.2 | 27.2 |
| Cryotherapy | 2.6 | 45.4 | 39.2 |
| Surgical excision | 0.0 | 3.6 | 0.8 |

GP, general practitioner.

**Table 7. Mean ambulatory cost (in Euros (€)) of genital wart treatment.**

| | *Females* | | | *Males* | | |
|---|---|---|---|---|---|---|
| | *% of patients* | *HCPP cost (€)* | *SP cost (€)* | *% of patients* | *HCPP cost (€)* | *SP cost (€)* |
| Mean ambulatory cost | 89.1 | 236.3 | 295.4 | 90.8 | 236.3 | 295.4 |
| Mean hospital cost | 10.9 | 996 | 996 | 9.2 | 1,083 | 1,083 |
| Mean total cost | 100 | 319.05 | 371.7 | 100 | 314.2 | 367.9 |

HCPP, healthcare payer perspective; SP, societal perspective.

€996 for women. Since the database covered 21.38% of the total (11,908 beds captured out of 55,693 total hospital beds in Belgium), an extrapolation factor has been applied to obtain estimates for Belgium. Based on the 172 hospitalisations reported for GWs, an estimated number of 804 patients (360 males and 444 females) are hospitalised each year in Belgium due to GWs. The hospitalisation rate is therefore 9.2% for male GW patients and 10.9% for female GW patients.

A total mean cost of GW management was then estimated at €371.7 (SP) for female patients and €367.9 (SP) for male patients (Table 7).

**Table 8. Economic burden associated with management of CC, CIN and GWs in Belgium.**

| | *Annual number of cases* | *Annual cost (HCPP) (in million €)* | *Annual cost (SP) (in million €)* |
|---|---|---|---|
| CC | 667 | 6.48 | 9.73 |
| CIN | 10,495 | 1.97 | 3.17 |
| GWs, females | 4,079 | 1.30 | 1.51 |
| GWs, males | 3,909 | 1.23 | 1.44 |
| Total | – | 10.98 | 15.85 |

CC, cervical cancer; CIN, cervical intraepithelial neoplasia; GW, genital wart; HCPP, healthcare payer perspective; SP, societal perspective.

Considering the 7,989 GW cases in Belgium, the total treatment cost of GWs represented €2.53 million (HCPP) and €2.95 million (SP).

Overall, the annual economic burden of CC, cervical dysplasia and GW management in Belgium was therefore estimated at €10.98 million and €15.85 million from the HCPP and SP, respectively (Table 8).

# Conclusion and discussion

This study allowed an estimate of the annual cost of management of HPV-related diseases (i.e. CC, CIN and GW diseases) in addition to the €65 million spent for CC screening in Belgium[3]. Considering the 667[4] new patients diagnosed annually in Belgium, the total annual cost of CC was estimated at €9.7 million (SP). The estimated 10,495 CIN 1, 2 and 3 patients diagnosed each year led to an annual cost of €3.17 million (SP). Finally, the estimated annual number of GWs diagnosed was 7,989, leading to an annual cost of €2.95 million (SP).

Considering the scarce literature data currently available, this study provides significant insight into HPV-related diseases in Belgium. First, it provides relevant information on CC treatment and management of cervical dysplasia and GW patients. Second, a cost of disease management was calculated both from the HCPP and SP.

However, there are three limitations that need to be acknowledged regarding the present study.

The first limitation concerns the expert survey. The expert sample may not be representative of the country's overall physician population. The panel consisted of well-known practitioners in the HPV field in Belgium, therefore their practices may be different from those of other healthcare centres, leading to a bias. Moreover, the experts were not obliged to check their patient registries; they were only asked to formulate their responses on the basis of their clinical practices and experience. This factor could have introduced some bias (i.e. overestimate or underestimate) in their responses.

The second limitation is linked to hospitalisation associated with CIN and GW treatments. For certain procedures performed for CIN treatment (laser, cryotherapy and cervix amputation), only 1 day of hospitalisation was considered. This figure may be conservative and could lead to an underestimation of the real costs associated with hospital-based procedures. Furthermore, experts were not asked about hospitalisation and the length of stay for GW patients. To assess the hospital-based GW treatment costs, an estimation was made based on the number of hospitalised patients from the IMS database.

The third limitation concerns the estimation of productivity loss for patients with CC. A mean number of 120 workdays lost was considered for active women who stop working because of CC. This estimate was retrieved from a French published source and based on an international literature review. Although Belgian data would more accurately reflect the situation in Belgium, this information has yet to be published.

This study highlights the fact that the burden of HPV-related diseases, including CIN and GW management and CC treatment (€10.98 million from a HCPP for 10.5 million inhabitants[32]) in Belgium seems relatively low compared with other European countries. Indeed, in France HPV-related disease costs reached an amount of approximately €82.5 million (for approximately 60 million inhabitants) excluding treatment costs of male patients with GWs[18–20]. In the UK, this cost was estimated at £79 million (for approximately 60 million inhabitants)[17]. This difference may be explained by the potential underestimates of this study. First, in the base case only incident CC patients were considered for assessment of the annual CC burden although mean CC hospital costs were estimated among prevalent and incident cases, which are probably lower than treatment costs of incident cases only. Indeed, Wolstensholme and Whynes[33] reported that 80% of the costs were incurred during the first year following CC diagnosis. A sensitivity analysis was performed using the number of prevalent CC cases extrapolated from the hospital database, which led to an annual cost of CC treatment of €11.9 million annually (SP). With regards to CIN costs, a recent study published by the KCE[34] in Belgium reported a mean cost per CIN 2+ patient of €368.50 (HCPP), thus higher than the author's estimates (€282.40 when considering the proportion of CIN 2/3 treated).

Finally, other HPV-related diseases, such as vulval and vaginal cancers, were not considered in this study. Further analyses would be required to gain a complete picture of the burden of HPV-related diseases in Belgium.

These results are also of interest in light of results from recent clinical trials in young women with a quadrivalent HPV vaccine (HPV types 6, 11, 16 and 18), which showed up to 100% efficacy in preventing disease due to the targeted HPV-types in non-infected females[35,36]. Modelling studies have assessed the potential clinical benefits of the implementation of a quadrivalent HPV 6/11/16/18 vaccine alongside screening practices. In France, compared

with screening only, vaccinating 80% of a cohort of 14-year-old girls with the quadrivalent HPV vaccine would reduce the lifetime risk by 65% for CC, 47% for CIN 2/3, 21% for CIN 1 and 66% for GWs[37]. In the US, compared with current practice, vaccinating 70% of girls before the age of 12 years would reduce the incidence of GWs by 83% and CC by 78% due to HPV 6/11/16/18[38]. In Belgium, a recently published study reported that vaccination of 84% of 12-year-old girls with a HPV vaccine targeting HPV types 16/18 only could achieve a reduction of 49.3% of CC cases[34]. One can therefore expect a significant decrease in the burden associated with the management of CC, cervical dysplasia and GWs in Belgium with the implementation of a HPV vaccination programme alongside the current CC screening programme.

## Acknowledgements

***Declaration of interest***: This research was supported by an unrestricted research grant from Sanofi Pasteur MSD.

## References

1. Arbyn M, Autier P, Ferlay J. Burden of cervical cancer in the 27 member states of the European Union: estimates for 2004. *Annals of Oncology* 2007; **18**: 1425–1427.
2. The UK Collaborative Group for HIV and STI Surveillance. *Testing Times. HIV and Other Sexually Transmitted Infections in the United Kingdom: 2007*. London, UK: Health Protection Agency, Centre for Infections, 2007.
3. Hulstaert F, Arbyn M, Huybrechts M *et al*. *Dépistage du cancer du col de l'utérus et recherche du papillomavirus humain (HPV). Health Technology Assessment (HTA)*. KCE report 38B. Brussels, Belgium: Centre fédéral d'expertise des soins de santé (KCE), 2006.
4. Ferlay J, Bray F, Pisani P *et al*. *GLOBOCAN 2000. Cancer Incidence, Mortality and Prevalence Worldwide*. IARC CancerBase No. 5, version 2.0 Lyon, France: IARC Press, 2004.
5. Von Krogh G. Management of anogenital warts (condylomata acuminata). *European Journal of Dermatology* 2001; **11**: 598–603.
6. Walboomers JMM, Jacobs MV, Manos M *et al*. Human papillomavirus: a necessary cause of invasive cervical cancer world-wide. *Journal of Pathology* 1999; **189**: 12–19.
7. Munoz N, Bosch FX, de Sanjose S *et al*. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine* 2003; **348**: 518–527.
8. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987; **1**: 1247–1249.
9. International Agency for Research on Cancer. *Cervix Cancer Screening. IARC Handbooks of Cancer Prevention. Vol. 10*. Lyon, France: IARC Press, 2005.
10. Arbyn M, Van Oyen H. Cervical cancer screening in Belgium. *European Journal of Cancer* 2000; **36**: 2191–2197.
11. Arbyn M, Van Oyen H. *Analysis of individual health insurance data pertaining to pap smears, colposcopies, biopsies and surgery on the uterine cervix (Belgium, 1996–2000). Epidemiology, October 2004*. Brussels, Belgium: Scientific Institute of Public Health, SIPH/EPI Report N 2004–021.
12. Fenton KA, Lowndes CM. Recent trends in the epidemiology of sexually transmitted infections in the European Union. *Sexually Transmitted Infections* 2004; **80**: 255–263.

 

13. Koutsky L. Epidemiology of genital human papillomavirus infection. *American Journal of Medicine* 1997; **102**: 3–8.

14. Kjaer SK, Tran TN, Sparen P *et al*. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. *Journal of Infectious Diseases* 2007; **196**: 1447–1454.

15. McMillan A. The management of difficult anogenital warts. *Sexually Transmitted Diseases* 1999; **75**: 192–194.

16. Lacey CJN, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine* 2006; **24(Suppl 3)**: S35–S41.

17. Brown RE, Breugelmans JG, Theodoratou D *et al*. Costs of detection and treatment of cervical cancer, cervical dysplasia and genital warts in the UK. *Current Medical Research and Opinion* 2006; **22**: 663–670.

18. Arveux P, Benard S, Bouee S *et al*. Invasive cervical cancer treatment costs in France. *Bulletin du Cancer* 2007; **94**: 219–224.

19. Bergeron C, Breugelmans JG, Bouée S *et al*. [Cervical cancer screening and associated treatment costs in France.] *Gynécologie, Obstétrique & Fertilité* 2006; **34**: 1036–1042 [in French].

20. Monsonégo J, Breugelmans JG, Bouée S *et al*. [Anogenital warts incidence, medical management and costs in women consulting gynaecologists in France]. *Gynécologie, Obstétrique & Fertilité* 2007; **35**: 107–113 [in French].

21. National Center for Health Statistics. *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. Available at: http://www.cdc.gov/nchs/about/otheract/icd9/abticd9.htm [accessed July 2007].

22. Pirson M, Dramaix M, Leclercq P *et al*. Analysis of cost outliers within APR-DRGs in a Belgian general hospital: two complementary approaches. *Health Policy* 2006; **76**: 13–25.

23. Analyse économique des coûts du cancer en France: impact sur la qualité de vie, prévention, dépistage, soins, recherche. «Etudes et expertises» éditée par l'Institut National du Cancer. Mars 2007.

24. National Institute for Statistics. *Statistics Belgium*. Available at: http://www.statbel.fgov.be [accessed July 2007].

25. National Institute for Statistics. Available at: http://statbel.fgov.be/downloads/lfs1004-2004_fr.xls [accessed July 2007].

26. National Institute for Health Insurance (INAMI/RIZIV). Available at: http://www.riziv.be [accessed July 2007].

27. Castellsague X, De San José S, Aguado T *et al*. HPV and cervical cancer in the world, 2007 report. *Vaccine* 2007; **25**: C27–C219.

28. De Schrijver K. Epidemiologisch bulletin van de vlaamse gemeenschap, De epidemiologie van seksueel overdraagbare aandoeningen in belgië. NR 45 2003/3.

29. Belgian Cancer Registry Foundation. Available at: http://www.kankerregister.be/ [accessed December 2007].

30. Available at: http://www.onssrszlss.fgov.be/Onssrsz/FR/Statistics/Brochures/Green/xls/rrn_2007_1_fr.xls [accessed July 2007].

31. The National Centre for Screening Monitoring Fourth Report. Rivista dell'Associazione italiana di epidemiologia. Anno 30 (1) 2006 Supplemento 3.

32. Direction générale statistique et information économique. Population et ménages, Population totale et belge. 2004.

33. Wolstenholme JL, Whynes DK. Stage-specific treatment costs for cervical cancer in the United Kingdom. *European Journal of Cancer* 1998; **34**: 1889–1893.

34. Thiry N, Lambert ML, Cleemput I *et al*. *Vaccination HPV pour la prévention du cancer du col de l'utérus en Belgique: Health Technology Assessment*. KCE report 64B. Brussels, Belgium: Centre fédéral d'expertise des soins de santé (KCE), 2007.

 

35. Garland SM, Hernandez-Avila M, Wheeler CM *et al*. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine* 2007; **356**: 1928–1943.

36. The FUTURE. II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine* 2007; **356**: 1915–1927.

37. Bergeron C, Largeron N, McAllister R *et al*. Cost-effectiveness analysis of the introduction of a quadrivalent human papillomavirus vaccine in France *International Journal of Technology Assessment in Health Care* 2008; **24**: 10–19.

38. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies *Emerging Infectious Diseases* 2007; **13**: 28–41.

 