

A new approach to estimate Genital Warts incidence and prevalence in the Italian general female population

G. Vittori¹, A. Matteelli², F. Boselli³, L. Naldi⁴, L. Emberti Gialloreti⁵

¹Head of Gynaecology Unit, San Carlo di Nancy Hospital, Rome;

²Infectious and Tropical Disease Department, Spedali Civili, Brescia;

³Oncologic and Preventive Gynaecology Unit, University of Modena;

⁴GISED, Study Center, Bergamo;

⁵Department of Public Health and Cell Biology, University of Rome "Tor Vergata"

ABSTRACT

A new approach to estimate Genital Warts incidence and prevalence in the Italian general female population.

Genital warts (GW), known also as condyloma acuminata, are one clinical consequence of the infection with the Human Papillomavirus (HPV). Among the different genotypes, types 6 and 11 are responsible for about 90% of GW worldwide. Limited data on the incidence and prevalence of GW is available in the general female population in Italy. The objective of this study is to estimate the incidence and prevalence of GW in Italian female population aged 14-64 years.

Methods: A national retrospective, multicentre, observational study recruited 114 gynaecologists who were asked to provide aggregated data on the total number of women seen in 2005, and the number of new cases, early recurrent cases and late recurrent cases of GW diagnosed during that same year. From these figures, prevalence and incidence of GW in the female population visiting gynaecologists were estimated.

Results: The final sample of gynaecologists included 78 investigators, who saw in 2005, 98,605 women: 46.4% investigators were from Northern, 18.4% from Central, and 35.2% from Southern Italy. The incidence of GW in Italy was estimated to be 4.3 per 1,000 women for new cases, and 1.1 and 0.6 per 1,000 women for early recurrent and late recurrent cases, respectively. The resulted estimated overall prevalence was 6.0 per 1,000 women. The extrapolated expected number of prevalent cases of GW in 2005 in the general female population aged 14-64 was 118,160.

Conclusion: Genital warts represent an important burden in Italian female population consulting gynaecologists. Although the data should be considered with caution, they will be useful in the framework of the implementation of a HPV quadrivalent vaccination program, which is expected to strongly reduce the disease burden of GW.

Key words: genital warts, human papillomavirus, quadrivalent vaccine, prevalence, incidence.

SOMMARIO

Nuovo approccio per stimare l'incidenza e la prevalenza dei condilomi genitali nella popolazione femminile italiana.

I condilomi genitali sono una delle conseguenze cliniche dell'infezione con i Papillomavirus umani (HPV). Tra i differenti genotipi, i tipi di HPV 6 e 11 sono responsabili di circa il 90% dei condilomi genitali in tutto il mondo.

In Italia abbiamo dati limitati relativamente ad incidenza e prevalenza dei condilomi genitali nella popolazione femminile. L'obiettivo di questo studio è stato di stimare l'incidenza e la prevalenza dei condilomi genitali nella popolazione italiana femminile (età 14-64 anni).

Metodi: Studio retrospettivo, nazionale, multicentrico, osservazionale, che ha arruolato 114 ginecologi, a cui è stato richiesto di fornire dati aggregati relativamente al numero di donne visitate in totale nel 2005, sul numero di nuovi casi, o dei casi ricorrenti sia a breve che lungo termine diagnosticati nello stesso anno. A partire da questi dati, sono state stimate l'incidenza e la prevalenza dei condilomi genitali nella popolazione femminile afferente ai ginecologi.

Risultati: Il campione finale di ginecologi ha incluso 78 ginecologi, che hanno visitato nel 2005 98.605 donne: 46,4% ginecologi dal nord Italia, 18,4% dal centro e 35,2% dal sud. L'incidenza di condilomi genitali in Italia è stata stimata pari a 4,3 per 1.000 donne come nuovi casi, mentre 1,1 e 0,6 per 1.000 come casi ricorrenti rispettivamente a breve e lungo termine. La prevalenza complessivamente stimata è stata pari a 6,0 per 1000 donne. Il numero di casi di condilomi genitali prevalenti per il 2005 è quindi 118.160 per la popolazione femminile di età tra i 14 e 64 anni in Italia.

Conclusioni: I condilomi genitali hanno un notevole impatto nella popolazione italiana femminile che viene visitata dai ginecologi. Benchè tali dati vadano considerati con prudenza, sono comunque da considerare utili nel momento in cui si implementi una vaccinazione con vaccino quadrivalente anti HPV, dalla quale ci si attende una notevole riduzione di tale impatto.

Parole chiave: condilomi genitali, papilloma virus umano, vaccino quadrivalente, prevalenza, incidenza.

Correspondence: G. Vittori

© Copyright 2008, CIC Edizioni Internazionali, Roma

INTRODUCTION

Genital warts (GW), known also as *condyloma acuminata*, are due to the infection with Human Papillomaviruses (HPV) (1). HPV types that infect the genital area are classified as oncogenic low-risk (e.g., 6, 11, 42, 43, 44) or high-risk types (e.g., 16, 18, 31, 33), according to the associated lesions (2). Types 16 and 18 are most strongly linked to malignancies, particularly cervical cancer (3), whereas GW are usually caused by HPV types 6 and 11, which are responsible for more than 90% of all GW worldwide (4).

Diagnosis of GW (acuminate or flat) is primarily clinical. GW typically presents as flesh-colored, exophytic lesions, on the external genitalia, including the penis, vulva, scrotum, perineum, and perianal skin. The differential diagnosis includes *molluscum contagiosum*, fibroepitheliomas, *condyloma lata*, benign or malignant neoplasm, as well as flat-topped *condyloma* associated with secondary syphilis.

The primary treatment goal is the removal of symptomatic warts, the choice being guided by a number of considerations, including wart morphology, size, number and location. Switching to a new treatment is appropriate if there is no response after three treatment cycles. Biopsy and viral typing is usually not recommended for patients with typical lesions. Routine follow-up is recommended, in order to monitor response to therapy and to evaluate possible recurrences (5).

Treatment procedures can be chemical or ablative (6). Topical treatments are applied directly to the skin (Imiquimod, Podophylotoxin, Podofilox or Trichloroacetic acid). Surgery (cryotherapy, electrocautery, surgical excision, or laser) may be necessary to remove larger warts or warts not responding to medication. Treatment is often long, painful and unsatisfactory because of the relatively high number of recurrent and resistant cases requiring repeated visits with a noteworthy economic impact (7). The response to any treatment ranges from 60 to 90% (5) and the risk of recurrence from 5 to 65% (8).

GW are a benign condition, but extremely frequent with different local extension or volume and often accompanied by psychological distress (9-10). Sometimes, emotional di-

stress is higher than the medical consequences, with impact on sexual life and relationships and fear of developing cancer (11).

An international survey on perceptions in patients with GW showed that 61% are quite or very worried about having GW, due to the fear of transmissibility or recurrence; 40% of patients noted a change in their lifestyle, mostly at sexual level (9).

The prophylactic quadrivalent (types 6, 11, 16 and 18) HPV vaccine Gardasil® was licensed in Europe in September 2006 and is now marketed across Europe, including Italy. It is currently indicated for the prevention of cervical cancer, high grade cervical dysplasia, high grade vulvar dysplasia and external GW caused by the four vaccine VLP-HPV types. In order to estimate the potential benefits of a HPV vaccination programme, the Italian National Health Service (NHS) needs to know the epidemiological picture associated with HPV-related diseases, including GW. However, up to now, epidemiological data were lacking in Italy.

Historical data comes from the STD (Sexually Transmitted Diseases) Surveillance System. In Italy STD centres are public sites, mainly located in dermatological health structures, dedicated, as prescribed by the law, to the diagnosis and treatment of the "classical" venereal diseases such as syphilis, *lymphogranuloma venereum* or blenorrhagia (DG 837/56; DPR 2056/62). During the last decades many of these centres progressively closed, diminishing from 225 in 1965, to 133 in the '80s. Today only half of them perform specific activity on sexually transmitted diseases (12) and the female population attending these centres cannot be considered as representative of the general population. Unlike in the UK, where most cases of GW are treated at genito-urinary medicine clinics (13), in Italy GW cases in women are largely diagnosed and managed by gynaecologists.

The STD Surveillance System included 48 clinical sites (44 dermo-venereological departments but only four gynaecological departments) selected from urban and rural areas. Between 1991 and 1996, 44,438 cases of STD were recorded, GW being the most common (29.4%) (14).

In Italy, women generally go to gynaecologists for periodical visits. This practice is more frequent in the upper social class and the female population in the reproductive age. In Northern Italy, women go more often to gynaecologists in public centres, whereas in Southern Italy women more often use private centres. Official estimates on the percentage of women attending this periodical control annually are not available, but data from ISTAT indicates that, only considering the Gynecological visit for Pap testing, about 40% of Italian women repeated it annually (15).

Historical data from gynaecologist clinics show increasing estimates among the female population attending the clinic: the annual prevalence of GW rose from 1.9% in 1981 to 21% in 1990, with a peak in the under-25 age class (16).

In conclusion no data of incidence and prevalence of GW are present at the moment for general Italian female population aged 14-64 years.

MATERIAL AND METHODS

This national, multicentre, retrospective observational study was designed to assess the incidence and prevalence of newly diagnosed, late recurrent and early recurrent GW in the Italian female population visiting gynaecologists, and to estimate the corresponding number of expected cases in Italy.

Gynaecologists were recruited using lists provided by gynaecological scientific societies that represent extra-hospital, ambulatory or territorial gynaecologists. Gynaecologists were then stratified by geographical area (i.e., Northern, Central and Southern Italy) on the basis of the percentage of women aged 14-64 years living in that same area.

To select the final sample of investigators participating in the study, the following procedure was used:

- Two lists were combined to obtain one unique list; overlapping names were deleted. Potential biases were reduced by further stratifying by region: the list was divided into three sub lists based on geographical areas (North, Central, South and Islands).

- The number of investigators to be included within each area was based on the percentage of women aged 14-64 years living in that same area (Table 1):

Tab. 1 - Number of investigators per selected Regions.

	Women (%)	Gynaecologists (n)
Northern	44.61	67
Central	19.26	29
Southern and Islands	36.13	54
ITALY	100	150

So 150 gynaecologists were recruited randomly from this list.

In order to limit selection bias due to the presence in the sample of gynaecologists who treat mainly STD patients, the final sample of investigators was selected using the following assumptions, based on the Expert Board (that acted as the study Scientific Committee) advice:

- gynaecologists were excluded from the sample of investigators if one of the following criteria was met:
 - $\geq 35\%$ patients seen by the gynaecologist had been referred to him/her by other gynaecologists;
 - $\geq 40\%$ patients seen by the gynaecologist had STDs, and at least one of his/her patients had been referred to him by other gynaecologists;
 - $\geq 70\%$ of the patients seen by the gynaecologist had STDs, even if no one had been referred by other gynaecologists.

Data were collected for the year 2005, assuming that all women with GW visit a gynaecologist.

Each gynaecologist was requested to provide the following data:

- Total number of women aged 14-64 seen in 2005;
- Number of newly diagnosed cases of GW in 2005, defined as patients who

- never had GW before;
- Number of early recurrent cases of GW seen in 2005, defined as patients who had previous episodes of GW (regardless of location) in the last (\leq)12 months;
 - Number of late recurrent cases of GW seen in 2005, defined as patients who had had previous episodes of GW (regardless of location) but did not suffer from any recurrence in the last 12 months.

These definitions were developed by the Expert Board.

External Genital Warts were defined as flesh-colored, exophytic lesions (small bumps, flat, verrucous, peduncolated, raised papules, or dome-shaped lesions on keratinized skin) on the external genitalia, including vulva, perineum, and perianal skin.

Internal Genital Warts were defined as lesions, which affected the mucous membranes of the vagina, cervix, urethra, and/or anus.

Patients were not included if they met at least one of the following criteria:

- Patients with lesions linked to benign or malignant neoplasm, molluscum contagiosum, condyloma lata, and fibroepitheliomas.
- Patients participating in clinical trials in 2005, in order not to bias the resource use data (data not shown in this manuscript).
- Patients with "vestibular micropapillomatosis".
- Patients with other non HPV related warts (e.g. plana syphilitic *condyloma*).

STATISTICAL ANALYSIS

The study was based on a two-stage sampling design using gynaecologists as first stage of sampling, and the aggregated data of female patients as the second stage. All women who visited a gynaecologist were included (both those diagnosed and not diagnosed with GW).

We planned to recruit 150 gynaecologists, as this sample size guarantees an 80% power to estimate the incidence of GW in women with an upper bound of the 95%CI at around 2.0 per 1,000.

Data collected from investigators were analyzed with classical descriptive statistics and frequency tables, including stratification by geographical area and by private/public practice. Incidence and prevalence were calculated as follows:

1. Incidence and prevalence in women seen by gynaecologists

The incidence was calculated as the ratio between the total number of newly diagnosed GW cases (numerator) and the total number of person-years, obtained by multiplying the population at risk per 1 year (denominator). All women seen in 2005 were considered at risk.

Prevalence was calculated as the proportion between all reported GW (newly diagnosed, early and late recurrent) and the total number of women seen in 2005.

As some women diagnosed with GW were seen by more than one investigator in the same year, incidence and prevalence rates were reduced by 15%. The choice of this factor was based on the Expert Board advice, as no published data were available.

Ninety-five percent confidence intervals (95% CI) were calculated taking into account the clustering of subjects visiting the same gynaecologist (17).

2. Estimation of incidence and prevalence in the general Italian female population

To calculate the numerators we assumed that each Italian woman with GW was seen at least once during the year by a gynaecologist. In terms of denominators, 39.04% of women aged 14-64 were seen by a gynaecologist at least once in 2005 (ISTAT 2005). Thus, the denominators were divided by 2.56 (i.e., $1/0.39$). The same approach was used to correct the incidence and prevalence rates by geographical area.

Regarding the estimation of the number of GW cases in the Italian female population, we considered at risk the whole female population aged 14-64 years living in Italy in the year 2005; resident population data were retrieved from the National Institute of Statistics (ISTAT) web site (www.demo.istat.it).

RESULTS

Among 150 gynaecologists initially selected and who accepted to participate, 114

(76%) completed the questionnaire.

Out of the 36 who did not fill the questionnaire, 15 said they could not find time to retrieve their data, 12 did not trust their data and preferred not to provide incorrect numbers, and 9 provided no explanation.

The 114 investigators were contacted and asked to specify the proportion of referred patients and/or patients affected by STDs. As a consequence, 36 gynaecologists were excluded from the study sample.

The final sample of gynaecologists included 78 investigators who saw, in 2005, 98,605 women.

46.4% of the investigators were from the North, 18.4% from the Centre, and 35.2% from the South of Italy. This distribution was in line with the percentage of women aged 14-64 years living in these same geographical areas.

Out of the 98,605 women, 1,275 were diagnosed as new GW cases, 315 as early recurrent GW cases, and 189 as late recurrent GW cases. The corresponding crude incidence and prevalence are shown in Table 2.

During the year 2005, each gynaecologist saw, on average, 1,264 women. Out of these, each gynaecologist diagnosed, on average, 16 new (16.3), 4 early recurrent (4.0), and 2 late recurrent cases (2.4) of GWs.

The incidence and prevalence rates stratified by geographical area and the distribution stratified by private/public practice are shown in Table 3, 4 and 5.

The estimated incidence and prevalence of GW in the general Italian female population were calculated adjusting the crude data as described in Material and Methods.

Adjusted incidence and prevalence rates are shown in Table 6, where the adjusted differences among regional area are also reported. Adjusted incidence rates of new, early recurrent, and late recurrent GW cases in Italy were, respectively, 4.3, 1.1, and 0.6 per 1,000 person-years. Adjusted prevalence of GW in Italy was therefore 6.0 per 1,000 females aged 14-64 years.

The estimated incidence and prevalence, as well as the expected number of cases in the Italian female general population stratified by

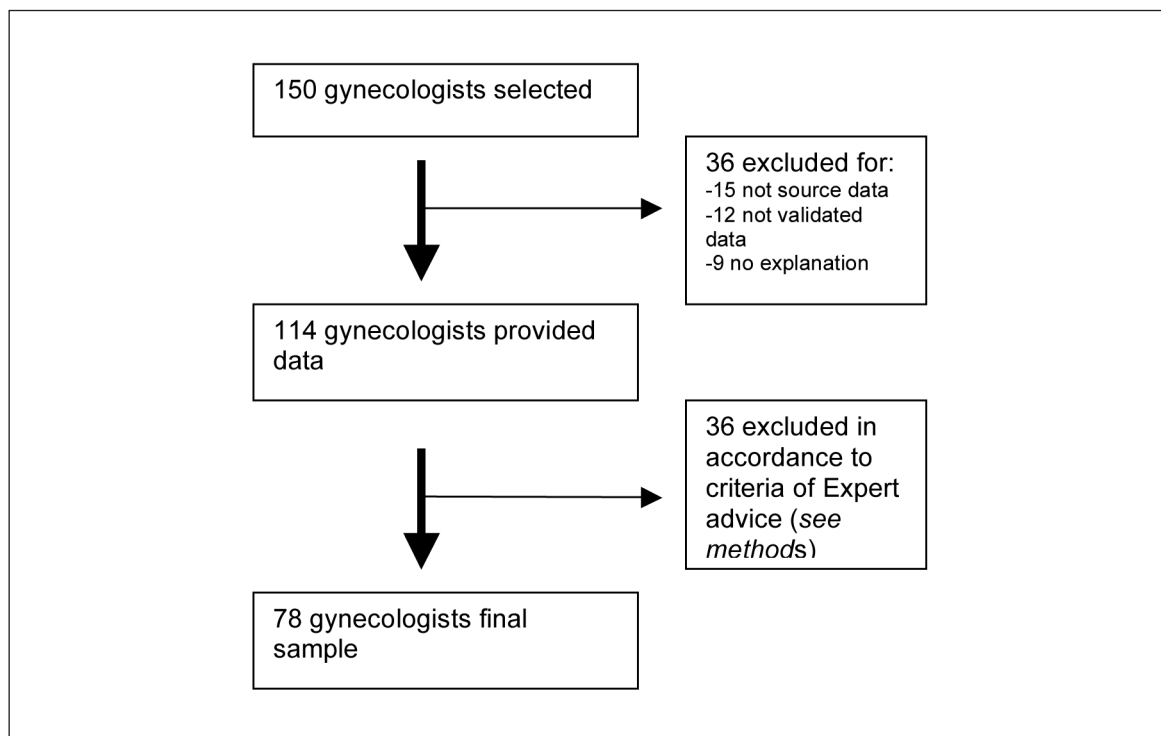


Figure 1. Selection of first-level gynaecologists.

Tab. 2 - Total number of women seen in 2005, newly diagnosed, early and late recurrent cases of GW; incidence and prevalence of GW with 95% CI.

Setting	Total (95% CI)	
Number of investigators	78	
Total number of women seen	98,605	
New GW cases	1,275	
Incidence of new GW cases (95% CI)	12.9	9.4-17.8
Early recurrent GW cases	315	
Incidence of early recurrent GW cases (95% CI)	3.2	2.1-4.9
Late recurrent GW cases	189	
Incidence of late recurrent GW cases (95% CI)	1.9	1.1-3.4
All cases	1,779	
Prevalence (95% CI)	18.0	12.8-25.5

Incidence and prevalence are expressed per 1,000 persons

Tab. 3 - Total number of women seen in 2005, newly diagnosed, early and late recurrent cases of GW; incidence and prevalence of GW with 95% CI, stratified by geographical area.

Setting	Northern		Central		Southern	
Number of Investigators	34		13		31	
Total number of women seen in 2005	45,722		18,166		34,717	
New GW cases	402		245		628	
Incidence of new GW cases (95% CI)	8.8	5.0-15.5	13.5	6.0-30.4	18.1	12.0-27.2
Early recurrent GW cases	90		72		153	
Incidence of early recurrent GW cases (95% CI)	2.0	1.0-3.8	4.0	1.4-11.3	4.4	2.4-8.0
Late recurrent GW cases	76		26		87	
Incidence of late recurrent GW cases (95% CI)	1.7	0.5-5.3	1.4	0.5-4.0	2.5	1.4-4.6
All cases	568		343		868	
Prevalence (95% CI)	12.4	6.5-23.8	18.9	8.0-44.6	25.0	16.3-38.4

Incidence and prevalence are expressed per 1,000 persons

type of GW (new, early and late recurrent) is shown in Table 7. The annual number of cases was estimated using the corrected incidence and prevalence rates (see Tab. 7) by the female population aged 14-64 years living in Italy in the year 2005.

DISCUSSION

This is the first study designed to provide an estimate of the incidence and prevalence of GW in the general Italian female population

at risk aged 14-64 years.

We estimated the incidence of GW in Italy to be 4.3 per 1,000 women for new cases, 1.1 and 0.6 per 1,000 women for early recurrent and late recurrent cases, respectively. The resulted estimated overall prevalence was 6.0 per 1,000 women.

These results extrapolate to 84,681 new cases of GW in Italy, in women aged 14-64 years, with 21,663 early recurrent and 11,816 late recurrent cases. Both incidence and pre-

Tab. 4 - Total number of women seen in 2005, newly diagnosed, early and late recurrent cases of GW; incidence and prevalence of GW with 95% CI, stratified by private/public practice.

Setting	Private		Public	
Number of Investigators	66		43	
Total number of women seen in 2005	48,583		50,022	
New GW cases	899		376	
Incidence of new GW cases (95% CI)	18.5	13.0-26.3	7.5	5.1-11.0
Early recurrent GW cases	226		89	
Incidence of early recurrent GW cases (95% CI)	4.7	3.0-7.3	1.8	1.0-3.0
Late recurrent GW cases	142		47	
Incidence of late recurrent GW cases (95% CI)	2.9	1.5-5.6	0.9	0.5-1.7
All cases	1,267		512	
Prevalence (95% CI)	26.1	17.9-38.0	10.2	6.8-15.4

Incidence and prevalence are expressed per 1,000 persons. The sum of private and public practices is larger than 78, as some gynaecologists provided data for both public, and private settings.

valence appear higher in Central and Southern Italy, as compared to Northern Italy.

When compared to other countries, our estimations appear higher. In the United States, approximately 1% of the sexually active population has clinically apparent GW, corresponding to about 1.4 million people (1). The highest infection rates have been consistently detected in sexually active women less than 25 of age (18), and the risk is strongly related to sexual behaviour (19). In an other US study, incidence ranged from 1.7 per 1,000 person-years overall, to a peak of 6.2 per 1,000 in women aged 20-24 years, and to 5 per 1,000 in 25-29 years old men (7).

Until today, in Europe, little information on the incidence and prevalence of GW in general population are available. Published data usually rely on reporting systems of Sexually Transmitted Diseases, case series or hospital discharge registries, but rarely on "true" general population samples (17, 20-23). In the United Kingdom, the number of all GW diagnoses (first episode, recurrent and re-registered cases) increased by 8 and 11 fold in men and women, respectively, between 1972 and 2004 (24). In the 2006 Report, the UK Health Protection Agency reports a rate of 767 per 100,000 women aged 16-19, and a range between 107 and 141 per 100,000 for new diagnosis of GW (25). In France, a recent pro-

spective observational study estimated an overall incidence of 228.9 x 100,000 in women 15-65 years (20).

In Sweden, the overall incidence in a middle-sized urban area was 2.4 per 1,000 (26). Another population based cross sectional study, showed that 11.3% of women aged 18-85 years had a history of clinically diagnosed GW (23). In the same study, women from Norway, Iceland and Denmark reported respectively in 9,5%, 12,0%, and 10,1% of the cases a history of clinical diagnosis of GW, and a range of 1.1-1.9% cases in the past 12 months (23). In Denmark, in a case control study 17% of the women aged 20-29 years reported GW (27).

In Southern Europe, a Spanish study (28), found that 16.9% of women aged 16-20 years visiting STD clinics were affected by GW. In Greece, a cross sectional study performed in STD clinics showed that 47% of the sample of 829 women had GW (21).

The incidence of new cases in women has been estimated to be 1.8/1,000 in France (20), and 1.3/1,000 in the UK (25). Nevertheless in the above mentioned recent large survey of 70,000 women from the general population in Denmark, Iceland, Norway and Sweden, 10.6% reported ever clinically diagnosed GW and 1.3% reported GW in the past 12 months (23).

Tab. 5 - Total number of women seen in 2005, newly diagnosed, early and late recurrent cases of GW; incidence and prevalence of GW with 95% CI, stratified by geographical area and by private/public practice.

Setting	Private					
	Northern		Central		Southern	
Number of Investigators	26		13		27	
Total number of women seen in 2005	20,088		7,926		20,569	
New GW cases	255		193		451	
Incidence of new GW cases (95% CI)	12.7	5.8-27.8	24.4	11.0-53.9	21.9	14.6-32.9
Early recurrent GW cases	57		64		105	
Incidence of early recurrent GW cases (95% CI)	2.8	1.1-7.2	8.1	3.3-19.9	5.1	2.8-9.3
Late recurrent GW cases	58		22		62	
Incidence of late recurrent GW cases (95% CI)	2.9	0.7-11.8	2.8	1.3-6.0	3.0	1.6-5.6
All cases	370		279		618	
Prevalence (95% CI)	18.4	7.5-45.0	35.2	15.9-77.8	30.0	19.7-45.9

Setting	Public					
	Northern		Central		Southern	
Number of Investigators	19		4		20	
Total number of women seen in 2005	25,634		10,240		14,148	
New GW cases	147		52		177	
Incidence of new GW cases (95% CI)	5.7	3.5-9.4	5.1	3.2-8.0	12.5	6.4-24.3
Early recurrent GW cases	33		8		48	
Incidence of early recurrent GW cases (95% CI)	1.3	0.7-2.3	0.8	0.3-2.4	3.4	1.5-7.5
Late recurrent GW cases	18		4		25	
Incidence of late recurrent GW cases (95% CI)	0.7	0.3-1.6	0.4	0.1-2.9	1.8	0.8-3.8
All cases	198		64		250	
Prevalence (95% CI)	7.7	4.7-12.8	6.3	3.4-11.6	17.7	9.2-34.1

Incidence and prevalence are expressed per 1,000 persons.

It has to be considered that the estimation of prevalence and incidence can vary dramatically across Countries and study designs, depending on both methodological and country-specific variables, such as the population under study (general or at risk), the healthcare settings, the type of investigator (STD specialist; general practitioner; gynaecologist), age and gender.

Since methodology varies across studies, it is difficult to compare these results.

Nevertheless, compared with other countries, our data could be considered as overestimated; an analysis of possible biases is therefore requested. Which might be explained by a number of limitations in the study design.

Firstly, since there is no official register in Italy the lists of investigators were provided by the Expert Board, and this could represent a selection bias.

Moreover, some gynaecologists are often specialized in treating GW and other STDs, and are therefore considered as "second-level". They usually operate in Public or University Hospitals where they have access to diagnostic and therapeutic tools generally not available to all (e.g. laser). Most of them work, also, in "private practice", and these "second level" gynaecologists often could visit patients already seen by other specialists and referred to them for GW. Thus, data collected via these "second-level" investigators

Tab. 6 - Adjusted incidence and prevalence of GW.

Incidence/prevalence of GW	Rates			
	Northern	Central	Southern	Total
<i>Incidence of new cases</i>	3.5	5.0	4.8	4.3
<i>Incidence of early recurrent cases</i>	0.8	1.5	1.2	1.1
<i>Incidence of late recurrent cases</i>	0.7	0.5	0.7	0.6
<i>Prevalence</i>	4.9	7.0	6.6	6.0

Incidence and prevalence are expressed per 1,000 persons

Tab. 7 - Estimates of the number of GW cases in the Italian female general population (14-64 years).

	Incidence x1000	Expected cases
Incidence of new GW cases	4.3	84,681
Incidence of early recurrent GW cases	1.1	21,663
Incidence of late recurrent GW cases	0.6	11,816
Prevalence of GW	6.0	118,160

The Italian female general population (14-64 years) in 2005 was 19, 693, 283.

could drive to an overestimation of the disease. Thus, for an incidence/prevalence study we need to rely only on "first-level" gynaecologists, that perform first diagnosis.

Although several methods (inclusion criteria, post-hoc exclusion) have been put in place to include data from first-level investigators only, it cannot be excluded that our study sample still includes second-level investigators.

In addition, gynaecologists may have underestimated the total number of women they have seen in 2005, leading therefore to an overestimation of the denominators and therefore of the incidence.

Uncertainties in the data could also arise from the fact that the study is based on investigators' rough estimates and not on patient records/databases.

The choice to collect data from gynaecologists in Italy in order to evaluate incidence and prevalence of genital warts in female general population is justified mainly by two factors:

1) as previously discussed the STD centres in Italy do not allow to collect data applicable

to a "true" general female population;

2) gynaecologists are physicians extremely skilled to diagnose and manage genital diseases and therefore the data collected are reliable from a clinical point of view.

Further studies, with a prospective design, could allow evaluating the weight of this bias on our results.

Further prospective studies are needed to evaluate if a change in lifestyle or sexual habits in Italian population (e.g earlier sexual debut) has occurred recently, as in other countries (23). Some of these factors can be related to the rates of genital HPV infection and their clinical consequences.

CONCLUSION

In conclusion, despite some limitations, this study is a first attempt to estimate the burden of GW in Italy. Our data are to be considered as pilot estimates, showing that GW represent a common disease giving rise to a considerable disease burden. Although these data should be considered with caution, they will be useful in the framework of the implementation of a HPV vaccine program, which is ex-

pected to reduce the disease burden of GW.

Acknowledgements

Sanofi Pasteur MSD Europe: Catherine Cohet, Laurence Serradell, Gabrielle Breugelmans, Nathalie Largeron.

Dr. F. Giorgino and AGEO.

REFERENCES

1. Koutski LA. Epidemiology of genital human papillomavirus infection. 1997;102(5A):3-8.
2. Bernard HU. The clinical importance of nomenclature, evolution and taxonomy of human papillomaviruses. *J Clin Virol* 2005;32(Suppl 1):S1-6.
3. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide. A meta analysis. *Br J Cancer* 2003;88(1):63-73.
4. von Krogh G. Management of anogenital warts (condylomata acuminata). *Eur J Dermatol* 2001;11:598-603.
5. CDC, Sexually Transmitted Disease Guidelines. *MMWR*, 4 Aug 2006;55:R11.
6. Kodner CM, Nasraty S. Management of genital warts. *Am Fam Physician*. 2004;70(12):2335-42.
7. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis*. 2003;36(11):1397-403.
8. French L, Nashelsky J. Clinical inquiries. What is the most effective treatment for external genital warts? *J Fam Pract*. 2002;51(4):313.
9. Maw RD, Reitano M, Roy M. An observational survey of patients with genital warts: perception regarding treatment and impact on lifestyle. *Int J STD AIDS*. 1998;9(10):571-8.
10. Voog E, Löwhagen GB. Follow-up of men with genital papilloma virus infection. Psychosexual aspects. *Acta Derm Venereol*. 1992;72(3):185-6.
11. Filiberti A, Tamburini M, Stefanon B, Merola M, Bandieramonte G, Ventafridda V, et al. Psychological aspects of genital human papillomavirus infection: a preliminary report. *J Psychosom Obstet Gynaecol*. 1993;14(2):145-52.
12. Giuliani M, et al. Il controllo delle malattie a trasmissione sessuale. *G Italiano Dermatol Venereol*, 1991;126:411-17.
13. Gilson RJ, Mindel A. Recent advances: Sexually transmitted infections. *BMJ*. 2001;322(7295):1160-4.
14. Giuliani M, Suligo B. The STD Surveillance Working Group, Sentinel Surveillance of sexually transmitted diseases in Italy. *Eurosurveillance*, 1998;3:55-58.
15. ISTAT, Indagine Multiscopo 2005.
16. Fallani MG, Penna C, Gordigiani R, Sonni L, Maggiorelli M, Marchionni M. Human papillomavirus infections in the lower genital tract of women. *Minerva Ginecol*. 1993;45(4):149-58.
17. Hardin J, Hilbe J. Generalized linear models and extension. Stata Press College Station 2001.
18. PHLS. *CDR Weekly* 2001;11(35).
19. Clifford GM, Gallus S, Herrero R, Muñoz N, Snijders PJ, Vaccarella S, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet*. 2005;366(9490):991-8.
20. Monsonégo J, Breugelmans JG, Bouée S, Lafuma A, Bénard S, Rémy V. Anogenital warts incidence, medical management and costs in women consulting gynaecologists in France. *Gynecol Obstet Fertil*. 2007;35(2):107-13.
21. Kyriakis KP, Hadjivassiliou M, Paparizos VA, Riga P, Katsambas A. Determinants of GW cases detection rates among STD clinics in Athens, Greece. *Int J Dermatol* 2005;44:650-3.
22. Brown RE, Breugelmans JG, Theodoratou D, Bénard S. Cost of detection and treatment of cervical cancer, cervical dysplasia and genital warts in UK. *Curr Med Res Opin* 2006; 22:663-70.
23. Kjaer SK, Tran TN, Sparen P, Tryggvadottir L, Munk C, Dasbach E, Liaw KL, Nygård J, Nygård M. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. *J Infect Dis*. 2007;196(10):1447-54.
24. Health Protection Agency, HIV and other Sexually Transmitted Infections in the United Kingdom in 2003 Annual Report, November 2004.
25. Health Protection Agency, A Complex Picture - HIV and other Sexually Transmitted Infections in the United Kingdom: 2006.
26. Persson G, Andersson K, Krantz I. Symptomatic genital papillomavirus infection in a community. Incidence and clinical picture. *Acta Obstet Gynecol Scand*. 1996;75(3):287-90.
27. Munk C, Svare EI, Poll P, Bock JE, Kjaer SK. History of genital warts in 10,838 women 20 to 29 years of age from the general population. Risk factors and association with papanicolau smear history. *Sex Transm Dis*. 1997;24(10):567-72.
28. Orduña Domingo A, Chu JJ, Eiros Bouza JM, Bratos Pérez MA, Gutiérrez Rodríguez MP, Almaraz Gómez A, et al. Age and sex distribution of sexually transmitted diseases in Valladolid. A study of 5076 cases. *Rev Sanid Hig Publica (Madrid)*. 1991;65(3):247-58.