

Trends and risk factors for syphilis infection in Piedmont Region, Italy, 2002-2008

Federica Vigna-Taglianti¹, Sergio Delmonte², Ivano Dal Conte³, Chiara Pasqualini⁴, and the Piedmont STD Network^a

¹Department of Clinical and Biological Sciences, University of Torino, Italy; ²Dermatologic Clinic, San Lazzaro Hospital, Torino, Italy; ³STI Clinic, Infectious Disease Department, Amedeo di Savoia Hospital, ASL TO 2, Torino, Italy; ⁴Regional Centre for Infectious Diseases Surveillance (SeREMI), ASLAL, Alessandria, Italy

Correspondence to: Federica Vigna-Taglianti, Department of Clinical and Biological Sciences, University of Torino, Regione Gonzole 10, 10043 Orbassano (TO), Italy. Email: federica.vignataglianti@unito.it

Abstract

Background: This work aims to analyze trends of syphilis infections in the Piedmont Region (Italy) between 2002 and 2008, and to evaluate risk factors for infection.

Methods: Syphilis trends were described according to socio-demographic characteristics, sexual behavior, condom use, number of partners and HIV infection. Independent risk factors for syphilis among men having sex with men (MSM), men having sex with women (MSW), and women were identified through logistic regression comparing cases with 12,773 negative patients.

Results: Between 2002 and 2008, 1,046 cases of syphilis were diagnosed, with peaks in 2004 and 2007. The risk of a syphilis diagnosis was independently associated with being older than 24, having a low education level, homosexual behavior, HIV self-reported infection (for MSM and MSW), number of partners (for MSW and women) and non- consistent condom use (for women).

Conclusions: Recent outbreaks suggest that the attention to syphilis can't be lowered. Screening, treatment of cases and notification of partners should be reinforced and integrated with sexual health education and counselling in high-risk environments. Surveillance data must be continuously collected.

Key words: syphilis, surveillance, trends, epidemic, HIV, risk factors

Introduction

Since late '90s, a series of syphilis outbreaks have been reported in US [1-8], Canada [9], Australia [10], and several European countries [11]: UK [12,13], Ireland [14], Spain [15], France [16], Italy [17,18], Germany [19], Belgium [20], Netherlands [21], Denmark [22], Norway [23], Sweden [24], and Czech Republic [25]. These outbreaks were mainly limited to men having sex with men (MSM).

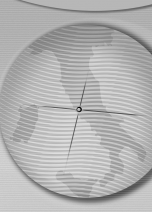
Syphilis outbreaks are a public health concern since syphilis is a preventable, treatable disease which can increase the likelihood of HIV transmission, thus impacting on HIV incidence [26-29]. Moreover,

it can be a worrying signal of changes in sexual behaviors towards unsafe sex [30].

In Piedmont, a Region of the North-West of Italy accounting for 4.5 million inhabitants, a network of Sexually Transmitted Diseases (STD) Centers was created in 2000 to survey, treat and prevent sexually transmitted diseases. The network is based on low-threshold public clinics, where medical consultation, testing and treatment are free of charge. Data are referred to the Regional Surveillance System (SeREMI, Alessandria) on a regular basis providing useful information to study trends and to identify epidemics in vulnerable groups.

The objective of this work was to analyze

^aThe Piedmont STD Network includes: Cesare Bolla, Maria Teresa Brusa, Angelo Casabianca (Infectious Disease Clinic, Cardinal Massaia Hospital, Asti); Lucio Dodaro (Dermatological Clinic, Infermi Hospital, Biella); Michele Bertero, Guido Raineri (Santa Croce e Carle Hospital, Cuneo); Pamela Farinelli (Dermatological Clinic, Maggiore della Carità Hospital, Novara); Ivano Dal Conte, Anna Lucchini, Monica Chiriotto (STI Clinic, Amedeo di Savoia Hospital, ASL TO2, Torino); Giacomo Audisio, Maria Vola (ASLTO3, Torino); Cecilia Tibaldi, Fulvia Albano, Maria Agnese Latino (Gynecology Clinic, Sant'Anna Hospital, Torino); Sergio Delmonte, Sabrina Rondoletti (Dermatological Clinic, San Lazzaro Hospital, Torino); Federica Poletti (Castelli Hospital, ASL VCO, Verbania); Maria Esposito (Sant'Andrea Hospital, Vercelli).



syphilis trends in the Piedmont Region between 2002 and 2008, and to evaluate risk factors for infection.

Methods

The network of Sexually Transmitted Diseases Centers is coordinated by SeREMI and includes 10 Sexually Transmitted Infections (STI) clinics located in the main hospitals of the region: Cardinal Massaia Hospital (Asti); Infermi Hospital (Biella); Santa Croce e Carle Hospital (Cuneo); Maggiore della Carità Hospital (Novara); Amedeo di Savoia Hospital (Torino); ASL TO3 (Torino); Sant'Anna Hospital (Torino); San Lazzaro Hospital (Torino); Castelli Hospital (Verbania); and Sant'Andrea Hospital (Vercelli). Personnel at STD Centers include dermatologists, gynecologists, infectious diseases specialists and nurses.

Data on sexually transmitted infections, diagnosed and treated in the STI clinics of the network, are collected, analyzed and published in regular bulletins by SeREMI (<http://epidem.aslal.it>). Case records include data on laboratory tests, socio-demographic characteristics and information on sexual orientation, condom use, number of sexual partners and HIV testing.

For the purpose of this study, the date of each syphilis case was defined as the date on which the patient accessed the clinical centre and was tested. Cases were defined as either primary (painless chancre or ulcer at the site of inoculation and regional lymphadenopathy), secondary (generalized muco-cutaneous rash and lymphadenopathy, systemic symptoms) or early latent syphilis (seroconversion in the last year, asymptomatic with history of infection or contact). Since primary and secondary syphilis cases were not distinguished in the referral system, the two forms were analyzed together in this study. Definite diagnosis of syphilis infection was confirmed by a positive result for venereal disease research laboratory test (VDRL) or rapid plasma reagin test (RPR), and a confirmatory positive treponemal test (TP-PA).

Trends in HIV co-infections were described using data from the same source.

Statistical analysis

Data were analyzed using Excel and the STATA statistical software package version 8.0 (Stata Corp., College Station, TX, USA).

R^2 was used to check whether any changes over time were significant.

To identify risk factors for syphilis, patients diagnosed with syphilis (cases: $n=1,046$) were compared to those accessing the STD centers in the

study period but testing negative to any sexually transmitted infections apart from HIV (controls: $n=12,773$). Odds Ratios and 95%CI of getting a syphilis diagnosis were calculated through univariate logistic regression. A multivariate model was built to identify independent risk factors for syphilis, including all factors significantly associated with syphilis diagnosis in the univariate analysis, plus condom use. With the same criteria, separate multivariate models were run to identify risk factors in the three subgroups of the study populations: MSM, men who have sex with women (MSW), and women. HIV infection, as self-reported when patients accessed the STI clinic, was assessed in the model as a risk factor for syphilis diagnosis.

In order to evaluate a possible underestimation of risk factors due to similarities between those associated with syphilis and HIV positive patients, a sensitivity analysis was conducted excluding HIV positive patients from the control group. Results of this analysis did not show any change in the significance of risk factors, apart from education level among MSM ($OR=0.75$, $p=0.052$ for 9-13 years old vs <9 years old).

Results

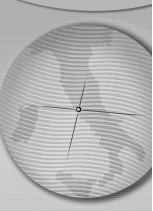
Between 2002 and 2008, a total of 1,046 cases of syphilis were diagnosed in the STD Centers of the Piedmont Region (Table 1). The number of cases almost doubled from 2003 to 2004 ($r^2=0.98$, statistically significant). Afterwards, a decrease was observed in 2005 and 2006, with a new increase in 2007 (Figure 1).

Demographic and behavioral characteristics of syphilis cases are shown in Table 1.

Early latent cases increased from about 20% in 2002-2004 to 30% in 2005-2008. The proportion of symptomatic cases was constantly higher than 75% in the observation period, with a small decrease to 73% in 2008.

The mean age of syphilis patients was 38.2 years ($SD=11.5$). A higher proportion of cases were 24-44 year olds, except in 2008 when the highest proportion were those 44 or older. The largest proportion of cases were Italian or from Western Europe (74-89%), followed by migrants from Eastern Europe (5-20%). Except for 2006 and 2007, the highest proportion of cases had a low education level (8 years), whilst the proportion of cases with a high level of education was stable around 8-12% during this period.

A large proportion of syphilis cases occurred among men (72-87%). When sexual orientation among men was considered, the proportion was generally higher among MSW.


Table 1. Main characteristics of syphilis cases, Piedmont Region, 2002-2008.

<i>Characteristic</i>	2002		2003		2004		2005		2006		2007		2008	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All cases	46	100	110	100	215	100	154	100	162	100	208	100	151	100
Stage of disease														
Primary/Secondary	38	82.6	90	81.8	172	80.0	108	70.1	114	70.4	138	66.3	109	72.2
Early latent	8	17.4	20	18.2	43	20.0	46	29.9	48	29.6	70	33.7	42	27.8
Symptoms														
yes	-	-	86	78.9	166	77.2	115	75.2	124	78.0	154	77.0	110	72.8
no	-	-	23	21.1	49	22.8	38	24.8	35	22.0	46	23.0	41	27.2
Age														
15-24	7	15.2	10	9.1	19	8.8	14	9.1	23	14.2	19	9.1	11	7.3
25-34	17	37.0	41	37.3	68	31.6	43	27.9	60	37.0	71	34.1	32	21.2
35-44	18	39.1	32	29.1	70	32.6	61	39.6	45	27.8	61	29.3	52	34.4
>44	4	8.7	27	24.6	58	27.0	36	23.4	34	21.0	57	27.4	56	37.1
Birthplace														
West Europe	34	73.9	86	78.9	191	88.8	131	85.1	122	75.3	180	87.4	124	82.1
East Europe	10	21.7	15	13.8	11	5.1	13	8.4	28	17.3	18	8.7	15	9.9
North/Centre Africa	1	2.2	7	6.4	8	3.7	9	5.8	7	4.3	3	1.5	5	3.3
Centre/South America/Asia	1	2.2	1	0.9	5	2.3	1	0.7	5	3.1	5	2.4	7	4.6
Education														
<6 years	-	-	7	6.4	18	8.4	7	4.6	17	10.5	15	7.2	9	6.0
6-8 years	-	-	45	40.9	86	40.0	65	42.2	56	34.6	68	32.7	84	55.6
9-13 years	-	-	45	40.9	80	37.2	60	39.0	66	40.7	88	42.3	37	24.5
>13 years	-	-	11	10.0	27	12.6	13	8.4	14	8.6	21	10.1	15	9.9
missing	-	-	2	1.8	4	1.8	9	5.8	9	5.6	16	7.7	6	4.0
Gender														
Men	39	84.8	96	87.3	173	80.5	123	79.9	117	72.2	175	84.1	129	85.4
Women	7	15.2	14	12.7	42	19.5	31	20.1	45	27.8	33	15.9	22	14.6
Sexual orientation among men														
MSW	17	43.6	55	57.3	79	45.7	68	55.3	68	58.1	93	53.1	62	50.4
MSM	22	56.4	41	42.7	94	54.3	55	44.7	49	41.9	82	46.9	61	49.6
HIV co-infection														
New positive	2	4.4	1	0.9	7	3.3	2	1.3	3	1.9	7	3.4	5	3.3
Old positive	3	6.5	10	9.1	30	13.9	14	9.1	14	8.6	31	14.9	24	15.9
Negative	39	84.8	96	87.3	172	80.0	134	87.0	135	83.3	167	80.3	117	77.5
Unknown	2	4.3	3	2.7	6	2.8	4	2.6	10	6.2	3	1.4	5	3.3
Condom use														
Regularly	5	10.9	9	8.2	34	15.8	23	14.9	23	14.2	43	20.7	14	9.3
Occasionally/rarely/never	39	84.8	94	85.4	157	73.0	99	64.3	106	65.4	133	63.9	115	76.1
missing	2	4.3	7	6.4	24	11.2	32	20.8	33	20.4	32	15.4	22	14.6
Stable partner														
Yes	25	54.4	56	50.9	131	60.9	105	68.2	98	60.5	-	-	-	-
No	18	39.1	35	31.8	49	22.8	32	20.8	30	18.5	-	-	-	-
missing	3	6.5	19	17.3	35	16.3	17	11.0	34	21.0	-	-	-	-
Number of partners in the last 6 months														
1	16	37.2	35	32.7	68	31.8	61	39.6	63	39.9	78	38.2	60	40.0
2-3	19	44.2	38	35.5	71	33.2	56	36.4	46	29.1	56	27.5	40	26.7
4-9	6	13.9	23	21.5	32	14.9	18	11.7	17	10.8	40	19.6	28	18.7
10-24	2	4.7	8	7.5	31	14.5	10	6.5	22	13.9	20	9.8	16	10.6
>24	0	0.0	3	2.8	12	5.6	9	5.8	10	6.3	10	4.9	6	4.0

Figure 1. Syphilis cases by year, gender and sexual orientation, Piedmont Region, 2002-2008.

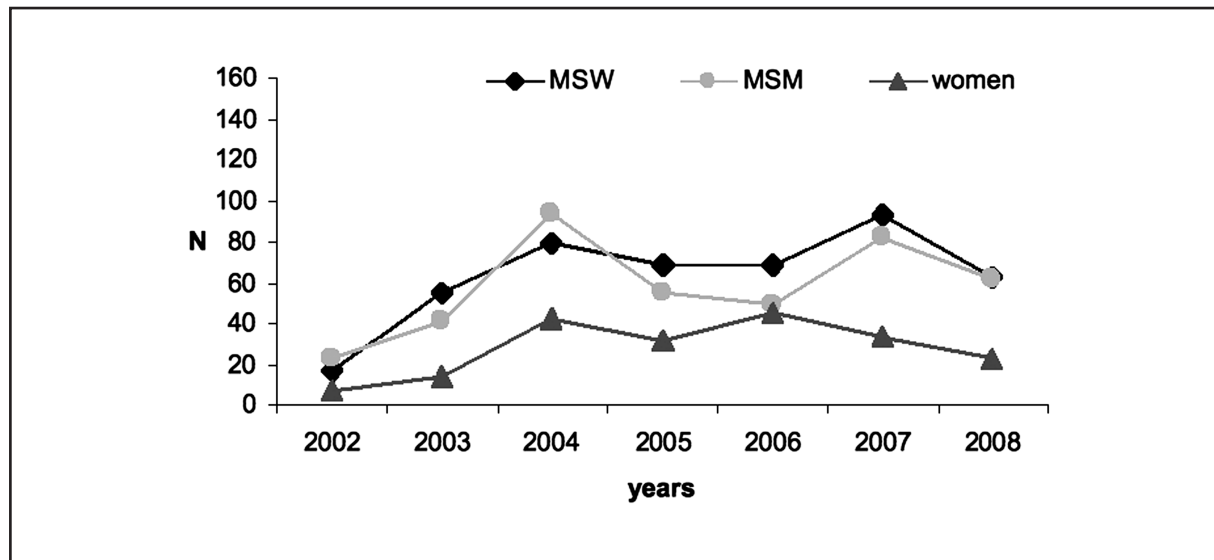


Figure 2. Syphilis cases and new HIV co-infections by year, Piedmont Region, 2002-2008.

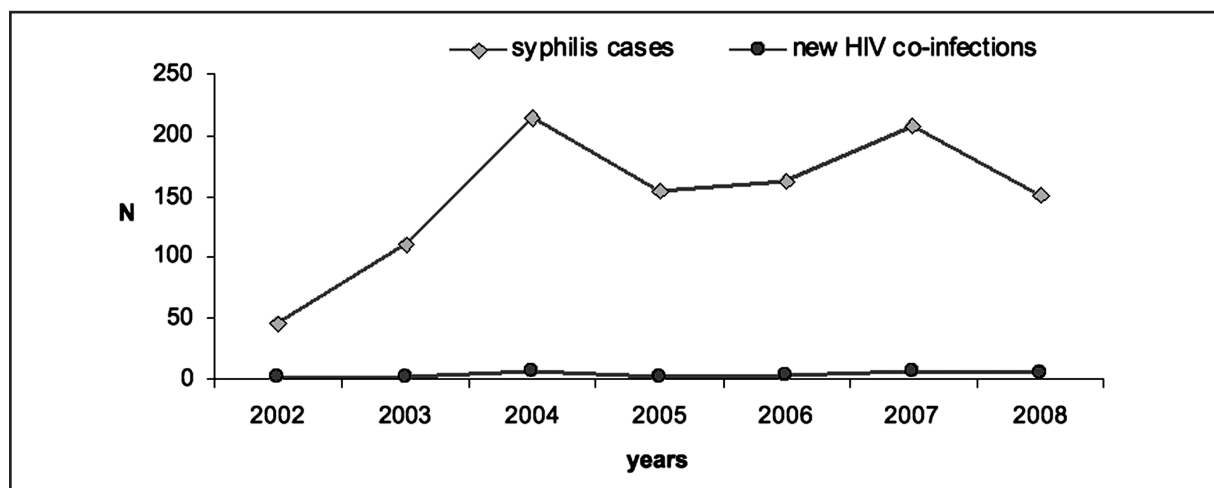
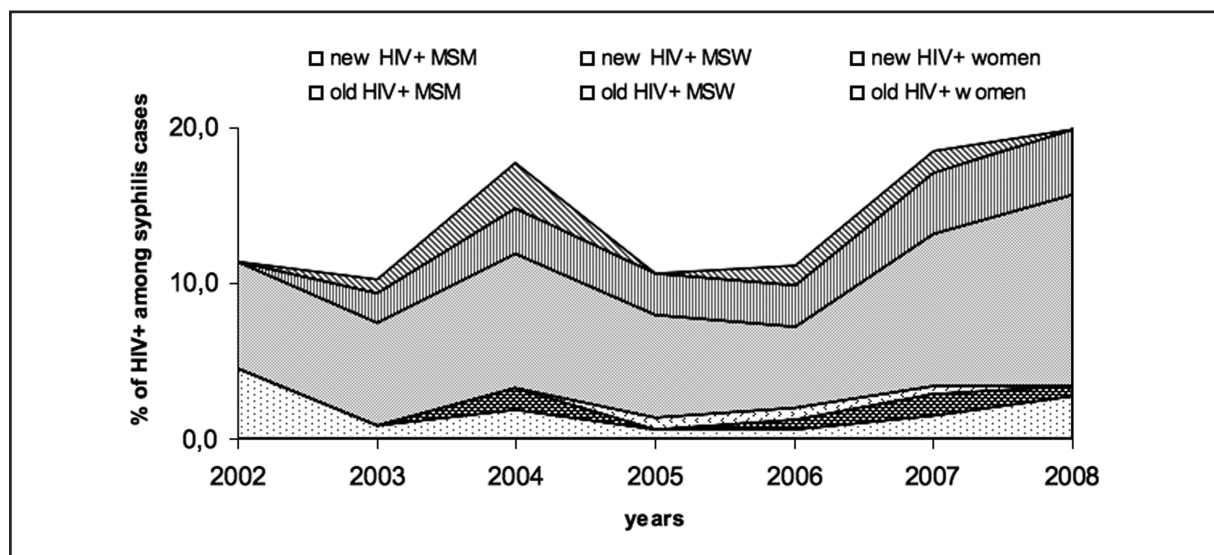
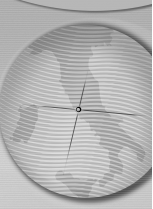


Figure 3. Proportions of new and old HIV+ among syphilis cases by year and sexual orientation, Piedmont Region, 2002-2008.





More than 50% of syphilis cases had a stable partner. Regular use of condoms varied from 8-10% of cases in 2002-2003 to 14-20% in 2004-2007 and dropped again to 9% in 2008 with some uncertainty due to the high number of missing values. Thirty-three to 40% of cases declared they had just one partner in the previous 6 months. The proportion of cases with 2-3 partners constantly decreased in the period, in favor of the category of 4-9 partners, whilst the proportion of cases with more than 24 partners was stable around 5%.

HIV co-infections increased from 10% in 2002-2003 to 17% in 2004, decreasing in 2005-2006 and increasing again to 18-19% in 2007-2008 (Table 1 and Figure 2). The increase in co-infections appeared to be related to the peaks in syphilis cases (Figure 2 and 3). In 2004 and 2007, when peaks of syphilis cases were observed, an increase in the proportion of old HIV positive cases was observed both in MSW (2.9% in 2004, 3.9% in 2007), in MSM (8.6% in 2004, 9.8% in 2007) and in women (2.9% in 2004, 1.5% in 2007). At the same time, an increase of new HIV positive cases was observed in MSW (1.4% in 2004, 1.5% in 2007), and MSM (1.9% in 2004, 1.5% in 2007). New female HIV positive cases did not appear to be related to syphilis peaks.

The risk of getting syphilis diagnosed according to various risk factors is described in Table 2. In the multivariate analysis, the risk of syphilis was independently associated with being over 24 years of age and particularly high for subjects older than 44 (adjOR=2.70, 95%CI: 2.09-3.49). Syphilis infection was more frequent among patients born in Italy or Europe, with a particularly low risk among patients from Africa (adjOR=0.46, 95%CI: 0.33-0.65). Higher education level significantly decreases the risk of infection (adjOR=0.33, 95%CI: 0.26-0.43 for people with more than 13 vs less than 9 years of education). The risk of a syphilis diagnosis is significantly associated with the sexual behavior: MSM have a higher risk vs MSW (adjOR=2.88, 95%CI: 2.41-3.44), whilst women have a lower risk (adjOR=0.34, 95%CI: 0.28-0.42). HIV self-reported status is a strong risk factor for syphilis (adjOR=2.73, 95%CI: 2.12-3.51). The risk shows a positive trend with the increase in the number of partners in the previous 6 months (adjOR=1.64, 95%CI: 1.16-2.33 for the category with more than 24 partners).

An older age is associated with a greater risk of syphilis both in MSW, MSM and women (Table 3). HIV self-reported infection and number of partners are significantly associated with the risk of syphilis among MSW, whilst high education level and African nationality are protective factors. Among

MSM, HIV self-reported infection appears to be the strongest risk factor, whilst number of partners is apparently not associated with the risk of syphilis. Among women, HIV self-reported infection is not significantly associated with syphilis whilst non-consistent condom use and number of partners appear to be the most important risk factors for syphilis infection in this group.

Discussion

Data from the surveillance of sexually transmitted infections in the Piedmont Region indicated a first peak of syphilis cases in 2004 and a second peak in 2007, mainly among MSW and MSM. The peaks are consistent with other outbreaks observed in Western countries [10,11,13,15,19-22,24].

In our study, risk factors for a syphilis diagnosis were slightly different in the MSW, MSM and women subgroups. Older age and low education level were independent risk factors for all subjects. However, HIV was associated with syphilis diagnosis only in MSW and MSM, whilst number of partners was a significant risk factor only in MSW and women. Non-consistent condom use was a risk factor only among women. These differences suggest the need for developing specific prevention strategies for the three populations. Among women, the risk seems to be related to the high number of partners or to the lack of regular condom use. If the very high number of partners is due the person being a professional sex worker, the risk of getting syphilis seems limited to those not using condoms regularly. On the other hand, migrants from Africa, South America and Asia show a lower risk of syphilis than East Europeans and Italians. This finding could be due to a different circulation of the infection in the countries of origin.

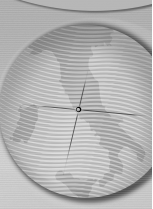
Since recent syphilis infection is an indicator of unsafe sex behaviors as well as a risk factor for HIV acquisition [28,31], concern for a resurgence of the HIV epidemic in correspondence to syphilis outbreaks has been expressed. However, according to the literature, evidence of the contribution of syphilis epidemics to increased HIV incidence appears to be limited, partly due to the high prevalence of HIV among syphilis affected MSM [5,30]. In our study, the proportion of HIV positive subjects among syphilis cases was quite high, especially among MSM (24.7% vs 7.7% of women, and 8.6% of MSW). These values are lower than those observed in other Western countries [6,7,10,13,16,20,32,33] but similar to other Italian studies [17,18]. Conversely, peaks of new HIV co-infections were observed in our set in 2002, 2004, 2007 and 2008, suggesting a

Table 2. Risk factors for syphilis diagnosis, Piedmont Region, 2002-2008, multivariate analysis.

Risk factors	Cases (n=1.022)		Controls (n=11.846)		Adjusted OR (95% CI)	P value
	n	%	n	%		
Age						
15-24	101	9.9	2.618	22.6	1.00	
25-34	323	31.6	4.733	39.9	1.52 (1.19-1.93)	0.001
35-44	330	32.3	3.030	25.5	1.97 (1.54-2.52)	<0.001
>44	268	26.2	1.465	12.0	2.70 (2.09-3.49)	<0.001
Birthplace						
West Europe	856	83.8	8.015	67.7	1.00	
East Europe	104	10.2	1.818	15.3	1.28 (1.01-1.62)	0.037
North/Centre Africa	39	3.8	1.377	11.6	0.46 (0.33-0.65)	<0.001
Centre/South America/Asia	23	2.2	636	5.4	0.68 (0.44-1.06)	0.089
Education						
<9 years	472	46.2	4.201	35.5	1.00	
9-13 years	371	36.3	4.994	42.2	0.59 (0.51-0.69)	<0.001
>13 years	98	9.6	1.796	15.2	0.33 (0.26-0.43)	<0.001
Unknown	81	7.9	855	7.2	0.61 (0.47-0.79)	<0.001
Gender/sexual orientation						
MSW	436	42.7	3.935	33.2	1.00	
MSM	398	38.9	1.280	10.8	2.88 (2.41-3.44)	<0.001
Women	188	18.4	6.631	56.0	0.34 (0.28-0.42)	<0.001
HIV self-reported infection						
Negative	563	55.1	6.729	56.8	1.00	
Positive	121	11.8	380	3.2	2.73 (2.12-3.51)	<0.001
Unknown	338	33.1	4.737	40.0	1.13 (0.96-1.32)	0.132
Condom use						
Regularly	148	14.5	1.622	13.7	1.00	
Occasionally/rarely/never	733	71.7	8.523	71.9	1.12 (0.92-1.36)	0.268
missing	141	13.8	1.701	14.4	0.87 (0.67-1.13)	0.290
Number of partners in the last 6 months						
0-1	377	36.9	7.401	62.5	1.00	
2-3	323	31.6	2.613	22.0	1.32 (1.11-1.58)	0.002
4-9	164	16.0	911	7.7	1.43 (1.15-1.80)	0.001
10-24	109	10.6	449	3.8	1.45 (1.11-1.91)	0.007
>24	50	4.9	472	4.0	1.64 (1.16-2.33)	0.005

possible increase in HIV diagnoses during peaks in syphilis cases. However, these data can't be clearly attributed to a concurrent HIV/syphilis transmission. In fact, the present referral system can't identify recent infections. Moreover, the proportion of missing data is different in each year of observation, and this can affect the reliability

of the proportion itself. Finally, data from the Surveillance System of HIV infections show a stability of recent infections in the observation period, with a constant rate of about 8 cases per 100,000 inhabitants [34]. From these data we can't conclude that there is a possible increase of new HIV infections in the Piedmont Region due

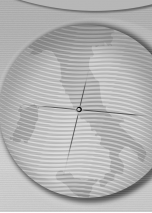

Table 3. Risk factors for syphilis diagnosis among MSW, MSM and women, Piedmont Region, 2002-2008, multivariate analysis.

Risk factors	MSW (n=4371)		MSM (n=1678)		Women (n=6819)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age						
15-24	1.00		1.00		1.00	
25-34	1.44 (0.97-2.15)	0.073	2.41 (1.45-3.98)	0.001	1.25 (0.84-1.88)	0.274
35-44	2.39 (1.60-3.57)	<0.001	2.42 (1.46-4.01)	0.001	1.60 (1.02-2.50)	0.039
>44	3.45 (2.32-5.13)	<0.001	2.39 (1.39-4.13)	0.002	2.75 (1.70-4.45)	<0.001
Birthplace						
West Europe	1.00		1.00		1.00	
East Europe	1.37 (0.97-1.92)	0.070	1.20 (0.40-3.58)	0.748	1.13 (0.78-1.64)	0.510
North/Centre Africa	0.65 (0.42-0.98)	0.043	1.73 (0.51-5.84)	0.377	0.15 (0.07-0.32)	<0.001
Centre/South America/Asia	0.28 (0.09-0.89)	0.031	1.05 (0.45-2.45)	0.907	0.76 (0.41-1.42)	0.397
Education						
<9 years	1.00		1.00		1.00	
9-13 years	0.67 (0.53-0.85)	0.001	0.82 (0.61-1.10)	0.177	0.39 (0.28-0.55)	<0.001
>13 years	0.35 (0.23-0.53)	<0.001	0.48 (0.33-0.69)	<0.001	0.13 (0.06-0.31)	<0.001
Unknown	0.59 (0.40-0.88)	0.009	0.69 (0.44-1.10)	0.118	0.80 (0.45-1.43)	0.450
HIV self-reported infection						
Negative	1.00		1.00		1.00	
Positive	3.15 (1.94-5.10)	<0.001	3.64 (2.55-5.20)	<0.001	1.56 (0.80-3.03)	0.192
Unknown	1.00 (0.80-1.24)	0.992	1.29 (0.94-1.78)	0.120	1.22 (0.89-1.68)	0.206
Condom use						
Regularly	1.00		1.00		1.00	
Occasionally/rarely/never	1.26 (0.94-1.68)	0.115	0.96 (0.70-1.32)	0.810	2.50 (1.30-4.81)	0.006
Missing	0.78 (0.52-1.16)	0.222	0.43 (0.28-0.67)	<0.001	4.24 (2.10-8.55)	<0.001
Number of partners in the last 6 months						
0-1	1.00		1.00		1.00	
2-3	1.08 (0.86-1.37)	0.505	1.11 (0.78-1.57)	0.554	1.99 (1.33-2.98)	0.001
4-9	1.31 (0.96-1.80)	0.091	1.04 (0.72-1.49)	0.842	1.96 (0.70-5.50)	0.202
10-24	1.60 (1.01-2.55)	0.046	0.96 (0.65-1.39)	0.819	4.97 (1.11-22.3)	0.036
>24	2.26 (1.02-4.99)	0.045	0.54 (0.29-1.00)	0.049	5.45 (3.18-9.32)	<0.001

to a syphilis epidemic. Ad hoc studies are needed to better investigate this relationship.

After the introduction of antiretroviral therapies for HIV infection, a resurgence in risky sexual behaviors has been observed especially among MSM. Improvements in HIV life expectancy following HAART therapy can, in fact, lower the perception of the risk of AIDS, with a consequent increase in sexual risk-taking [35-39]. Moreover, "safe sex" doesn't always protect against syphilis: a frequent sexual habit such as unprotected oral sex poses a relatively low risk of HIV transmission [40], but an increased risk of syphilis transmission [10,33,41].

This study had some limitations. Firstly, syphilis cases diagnosed at STD centers are probably underestimated compared to the real number of cases occurring in the population. However, since syphilis is not commonly treated by general practitioners and subjects are often directed to a specialized centre, the possible underestimation should be limited. Secondly, in order to investigate risk factors, we used subjects accessing STI clinics but testing negative to any sexual infection as the control population. This population is likely to be selected; consequently, the probability of identifying certain risk factors, such as number



of partners, is lowered. Thirdly, the extraction of data from a surveillance system prevents incidence estimation. However, since syphilis is generally treated by specialized centers in Italy, the indicator we used should be a proxy of the risk of infection, at least in the selected population accessing STD clinics.

The resurgence of a syphilis epidemic suggests that the attention to syphilis can't be lowered and that we are still far from the eradication of the disease, highly hoped by CDC in the late '90s [42,43]. Since the new epidemic appears to involve mostly men, and the MSM community, large primary prevention strategies should be planned for these risk groups. Secondary prevention measures, such as screening, rapid identification and treatment of cases, as well as notification of partners should be maintained and strengthened, and integrated with primary prevention activities, including sexual health promotion, counselling and safe sex education in high-risk environments.

On the other hand, the importance and the value of surveillance data for sexually transmitted diseases should be stressed. Efforts are needed to collect data of all patients accessing the clinics and to maintain high quality of data. A good surveillance system is precious to identify epidemics promptly, to study risk factors, and to suggest tailored preventive measures to be undertaken at the public health level.

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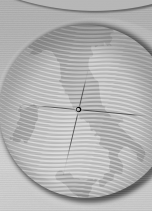
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Contributors

CP designed and coordinated the data collection. FVT and CP planned the analyses. FVT performed the analyses and drafted the paper. SD, IDC, and CP contributed in revising the paper. The personnel of STD Network collected the data.

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