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Estimated burden of *Chlamydia trachomatis* female infection and consequent severe pelvic inflammatory disease, Italy, 2005-2016

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Abstract

Chlamydia trachomatis (Ct) is the leading sexually transmitted infection (STI) across Europe. In Italy, Ct prevalence is low in general population, but predominance of asymptomatic infections, passive voluntary reporting, variable diagnostic criteria and coding practices can lead to considerable underestimation, preventing assessment of real burden of disease and health intervention. We analysed data on female genital Ct infection registered in STI sentinel surveillance systems in Italy from 2005 through 2016 and found 3305 women. Among them, those aged 20-24 years had the highest disability-adjusted life years (DALYs) estimation equal to 106.77 DALYs per 100 000-stratum specific population. Through the study period, incidence rate (IR) for female Ct infection increased significantly from 2.9 to 7.1 per 100 000 resident population. Besides, we analysed data on pelvic inflammatory disease (PID) reported from the National Hospital Information system (NHIS) in the same period. We found 287 women hospitalised with concurrent PID and Ct infection. We recommend targeted screening programmes in women aged 20-24, definition of nationwide active surveillance system, standardisation of diagnostic criteria and ICD-9CM coding practices.

Key words

- *Chlamydia trachomatis*
- sentinel surveillance
- hospitalisation
- pelvic inflammatory disease
- disability-adjusted life years (DALYs)

INTRODUCTION

Genital infection caused by *Chlamydia trachomatis* (Ct) is the most commonly reported sexually transmitted infection (STI) across Europe [1]. In 2012, the World Health Organization (WHO) estimated 131 million new annual infections among people aged 15-49 years [2].

Ct infection is curable by antibiotic treatment and long-term protective immunity is not induced [3]. Asymptomatic Ct genital infection is estimated in about 70% of women [2], therefore it is often undiagnosed or untreated, favouring a silent spread of infection. Otherwise, short-term acute symptoms of cervicitis arise. Infection can ascend to the upper reproductive tract and cause long-term sequelae as chronic pelvic pain, pelvic inflammatory disease (PID), tubal factor infertility (TFI) and ectopic pregnancy [2]. Recently, a systematic literature review conducted by the European Centre for Disease Prevention and Control (ECDC) estimated a 4-19% risk of developing PID after Ct infection. The risk for chronic pelvic pain after PID was estimated around 18-75%. Infertility was associated to 16% of the women with PID in reproductive age [4].

European (EU) population-based analyses reported that prevalence of female Ct infection ranged between 1.7% and 17% [5, 6]. In 2004, the burden of Ct infection and associated sequelae estimated in terms of disability-adjusted life years (DALYs) metric ranked third (0.2 million DALYs including both sexes) in the WHO EU Region behind tuberculosis and HIV/AIDS (1.7 and 1.2 million DALYs, respectively) [7].

In Italy, Ct infection notification is not mandatory, national epidemiological data in the general population are not available, and neither national guidelines on who should be tested nor Ct screening programmes exist. Different sources of epidemiological data have been used to describe the dynamics of Ct infection in Italy, including: a) the STI Sentinel Surveillance System (SSS) based on a network of clinics (SSS-STIClin) [8]; b) the STI-SSS based on a network of microbiology lab-

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oratories (SSS-STILab) [8]; c) local studies conducted among specific population groups (e.g., young women, pregnant women) [9-17]. Singly, these data-sources do not provide nationwide estimate on the number of Ct infections and associated sequelae. So far, lack of national burden on Ct genital infection has not allowed drawing specific health promotion policies or educational programmes for primary prevention.

The objective of the present study is to analyse the trend of Ct genital infection among women (outpatients or hospitalised cases) in Italy. The above data-sources are evaluated together for the first time to provide estimates on the national burden of female Ct genital infection and its sequelae in terms of DALYs.

MATERIALS AND METHODS

Study design

We performed a retrospective ecological study by analysing three data-sources (SSS-STIClin, SSS-STILab, and the National Hospital Information System – NHIS) to describe temporal trends of female Ct genital infection reported in Italy in the period 2005-2016 and to calculate its burden by DALYs metrics. We estimated the number of women who experienced severe Ct-associated sequela as those hospitalised with PID caused by Ct genital infection. As PID can have several causes, as a proxy, we identified the women hospitalised with PID and concurrent Ct infection. Due to country-specific issues on disease coding and consequent possible underestimation of data, we included Ct diagnosis at any body site among those hospitalised. For both Ct and PID cases, we considered women aged 15-70 years.

Data-sources and case definitions

- SSS-STIClin: the network is composed of 12 public STI clinics located in 11 cities (Gorizia, Trento, Brescia with two clinics, Milan, Turin, Genoa, Bologna, Florence, Rome, Bari, Cagliari) distributed in 10 out of 21 Italian regions and autonomous provinces. These specialised clinics provide diagnosis, treatment and care to symptomatic STI patients. Since 1991, this system collects anonymous individual sociodemographic, behavioural and clinical information on people with a confirmed STI. Only the first STI episode is reported. Since 2008, the diagnosis of Ct infection has been performed on endo-cervical swab and/or the first void urine by nucleic acid amplification test (NAAT). Previously, immune-enzymatic or immunofluorescence methods and swab samples were used. For the present analysis, we included women with Ct-related genital symptoms and laboratory-confirmed diagnosis of Ct registered in the SSS-STIClin from 2005 through 2016.
- SSS-STILab: the network is composed of 13 public microbiology laboratories located in 13 cities (Trieste, Pordenone, Trento, Legnano, Turin, Ivrea, Fano, Perugia, Rome, Galatina, Lecce, Catanzaro, Cosenza) distributed in nine out of 21 Italian regions and autonomous provinces. Since 2009, these laboratories collect anonymous individual sociodemographic, behavioural and clinical data on people (symptomatic and non-symptomatic) who undergo testing for Ct and/or *Neisseriae gonohorroeae* and/or *Trichomonas vaginalis*. For the diagnosis of Ct infection, laboratories perform NAAT on samples from endo-cervical swab and/or the first void urine. We considered women tested for Ct, regardless of the presence of Ct-related genital symptoms.
- NHIS: it has 100% national coverage including hospitalised cases and day-surgery interventions of symptomatic people admitted to hospital. Demographic and clinical data are reported in digital medical records and include up to five reasons for admission, which were used in the algorithms described below. For the present analysis, we defined a woman with Ct and PID by using two algorithms (one for Ct-positive women and one for PID cases). We based these algorithms on two sets of the International Classification of Diseases – 9th revision – Clinical Modification (ICD-9CM) codes specific for Ct infection or PID (13 and 32 codes, respectively; available online as *Supplementary Material 1*). Both algorithms were developed with the technical advice of gynaecologists qualified in Ct infection, and based on international literature. All data were anonymised.

We obtained approval from the Ministry of Health (MoH) to manage and analyse data.

Incidence rates

The incidence rate (IR) of Ct infection was obtained by dividing the number of women diagnosed with Ct infection reported in the SSS-STIClin by the number of women resident in the cities where the clinics are located.

We stratified the rough IR by four age groups (i.e. 15-24, 25-34, 35-44 and 45-70) and we calculated age-standardised IR in respect to the general Italian population. To estimate DALYs metrics, we used age groups by 4-year interval, according to the BCoDE model requirements (e.g. 15-19, 20-24, 25-29, and so on until 65-69).

The hospitalisation rates of women diagnosed with PID (hospPID rate) and of women diagnosed with concurrent PID and Ct infection (hospPIDCt rate) were obtained by dividing the number of women hospitalised with PID and that of women hospitalised with concurrent PID and Ct, respectively, by the number of women aged 15-70 years resident in Italy in the reference period.

Data were stored and managed according to the Italian privacy rules. Neither informed consent, nor ethical committee clearance were required for this retrospective study.

We performed descriptive statistical analysis using STATA version 12. Pearson – and Fisher exact tests were used to assess significance (p <0.05 level) in the trend analysis. We described the geographical distribution of cases in Northern, Central and Southern (including islands) areas according to ISTAT criteria [18].

DALYs estimate

We estimated the burden of Ct infection in Italy in terms of DALYs with 95% uncertainty intervals (UI) by using the ECDC-funded Burden of Communicable Diseases in Europe (BCoDE) toolkit [19, 20]. DALYs

metric included the number of years of life lost due to disability (YLD) and the number of years of life lost due to premature death (YLLs). We estimated the number of women diagnosed with Ct in the period 2009-2016 by multiplying the number (equal to 21 135 688) of Italian women aged 15-70 years in 2012 (central year in the reference period) with the Ct infection prevalence (2.6%) obtained from the SSS-STILab (data from the national AIDS unit – COA, unpublished data) between 2009 and 2016. Then, we calculated the number of symptomatic cases by multiplying our estimated number of women diagnosed with Ct with the BCoDE transition probability (equal to 20%, the percentage of Ct cases that develop symptomatic infection according to the BCoDE toolkit [19, 20]). We estimated the median annual number of symptomatic women by age group in Italy based on the age distribution of symptomatic women observed summing up data from the SSS-STILab and the SSS-STIClin. We ran the BCoDE model by performing 10 000 iterations and null time discount rate. We presented results as median values and 95% UI, per year and per 100 000 stratum specific population (age group or Ct acute infection or Ct-associated sequelae), in terms of aggregated (i.e. DALY) and disaggregated (i.e. YLDs and YLLs) analysis.

RESULTS

From 2005 through 2016, the SSS-STIClin reported 1301 symptomatic women diagnosed with genital Ct (*Figure 1A*), Almost half (45.9%) of them were aged 15-24 years (median age 25 years, interquartile range (IQR) 22-30 years) and over two thirds (70.1%) were Italian (data not showed). Based on these data, the number of women diagnosed with Ct doubled in the 12-years considered, from 76 cases in 2005 to 188 cases in 2016 (*Figure 1A*), accounting for 6.1% and 11.7% of women reported by the network with an STI, respectively. IR of female Ct infection increased significantly from 2.9 per 100 000 residents in 2005 to 7.1 per 100 000 residents in 2016 (p <0.0001). In particular, we showed a sharp increase starting from 2009 (IR 2.8 per 100 000 residents) to 2016 (IR 7.1 per 100 000 residents) (p <0.0001) (*Figure 1A*). Overall, the rough IR was 45.4 per 100 000 resident women. The standardised IR was 34.0 per 100 000 female population distributed among the four age-groups as follows: 14.9, 11.2, 2.3 and 5.6 among the age-groups 15-24, 25-34, 35-44, and 45-70 years, per 100 000 female population, respectively.

From 2009 through 2016, the SSS-STILab reported 2275 women diagnosed with genital Ct (63.6% were symptomatic, data not showed). Their median age was 27 years (IQR 22-34 years) and most of them (81.3%) were Italian. Prevalence of female Ct infection remained stable from 2.4% in 2009 to 2.6% in 2016, with a peak in 2014 (3.2%; p <0.05; data not showed).

In the period 2005-2016, we identified 329 880 (0.78%) women hospitalised with PID with or without Ct infection among those reported in NHIS. Among them, 287 (0.087%) were reported with ICD-9CM codes (available online as *Supplementary material 1*) identifying Ct infection (*Figure 1A*). The median age of women affected by PID and Ct was 32 years (IQR 23-38 years). The majority (72.5%) had Italian nationality (available online as *Supplementary Material 2*).

Based on the results obtained from the BCoDE toolkit, the annual DALYs per 100 000 stratum specific population stratified by age group (*Figure 1B*) shows the burden of Ct infection affecting mostly the women aged 20-24 years (106.77 DALYs per 100 000 stratum specific population).

In particular, the number of Ct women was estimated in 111 575 cases per year (*Table 1*). The median annual burden of Ct acute infection was estimated at 23.99 DALYs (95% UI: 21.28-26.92) per year corresponding to 0.08 DALYs per 100 000 stratum specific population (95% UI: 0.07-0.09). Regarding acute infection, DALYs were due entirely to YLDs (*Table 1*).

Overall, we estimated that over 99% of the national burden of Ct infection resulted from sequelae and amounted to 5978.85 DALYs per year corresponding to 19.10 DALYs per 100 000 stratum specific population (95% UI: 9.84-34.22; *Table 1*).

As for the Ct-associated PID cases, we observed a decreasing temporal trend from 27 average cases in 2005-2006 to 17 average cases in 2015-2016, although not significant in terms of hospPIDCt rate (0.093 in 2005 and 0.069 in 2016 per 100 000 residents; p >0.05). *Figure 2A* shows the Ct-associated PID cases stratified by year of notification and Italian and non-Italian nationality. *Figure 2B* shows that the highest hospPIDCt rate (0.24 per 100 000 residents) was among the women aged 15-24 years. During the 12-year period, most (41.8%) of the hospitalised foreign women diagnosed with concurrent PID and Ct were between 25 and 34 years old, while the majority of the Italian women (33.2%) were admitted to hospital with PID and Ct later in lifetime, at between 35 and 44 years old (*Figure 2B*). Mainly, hospitalised women diagnosed with concurrent PID and Ct were reported and resided in North Italy (66.6% and 63.8%, respectively) and had median hospital stay of five days (available online as *Supplementary material 2*). Almost half of them (43.6%) were admitted to the hospital under emergency conditions: 23.7% had a scheduled admission, 18.1% had a doctor's proposal and 1.4% were transferred from other public or private institutes; 13.2% had non-specified type of provenance (data not showed).

Based on the results obtained from the BCoDE toolkit, PID resulted as the main sequela of Ct infection, together with chronic pelvic pain syndrome (*Table 1*). Overall, the annual burden of Ct-associated sequelae was estimated at 5954.85 DALYs (95% UI: 3057.00-10 686.03). It was almost completely (99.8%) due to YLD and corresponded to 19.03 DALYs per 100 000 stratum specific population (95% UI: 9.77-34.14; *Table 1*).

DISCUSSION

Here we described cases due to Ct genital infection reported in Italy from 2005 through 2016 in SSS-STIClin and from 2009 through 2016 in SSS-STILab, and we estimated the national burden of female Ct infection in terms of DALYs metrics. Besides, we calculated the incidence of a severe sequela as Ct-associated PID

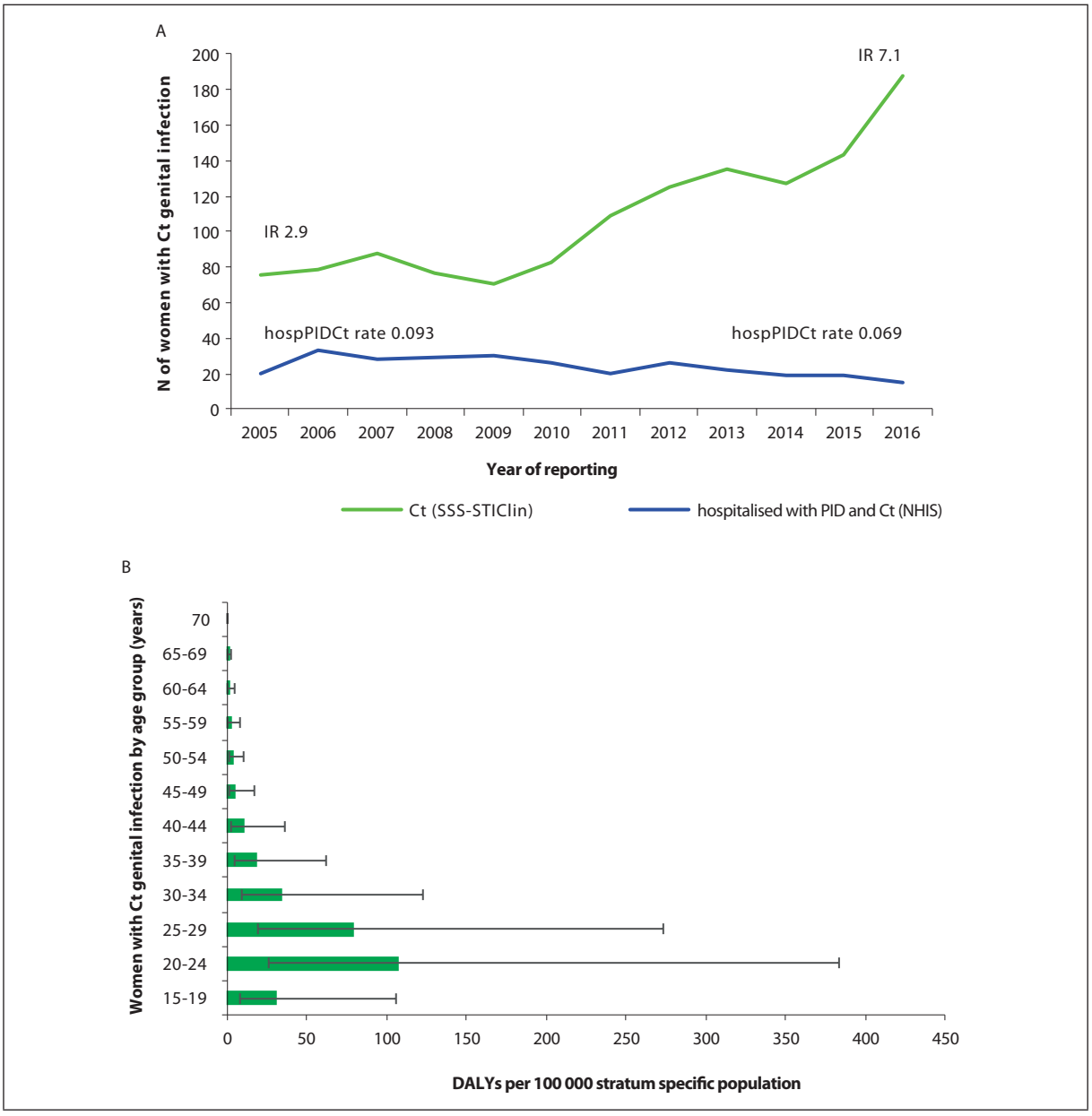

Figure 1
Temporal trends and rates of women affected by *Chlamydia trachomatis* (Ct) genital infection and pelvic inflammatory disease (PID) occurred in Italy, 2005-2016 (A), and burden of Ct (B) expressed in disability-adjusted life years (DALYs).

requiring hospitalisation registered in NHIS between 2005 and 2016. Although female Ct genital infections (adding up both SSS-STIClin and SSS-STILab data) significantly increased by 26% between 2009 and 2016, in this period the number of hospitalised women with PID and Ct infection has halved, even if not significantly. These diverse temporal trends might be explained by a range of events: I) rise in the number of Ct symptomatic cases; II) improved sensitivity in their notification among STI clinics, mostly due to increased sensitivity of NAAT testing after 2008; III) potential increase in testing rates; IV) earlier detection of genital Ct infection allowing timely treatment and prevention of sequelae [21]; V) shift in PID care from inpatient to outpatient settings based on comparable reproductive outcomes among women with mild-to-moderate PID to contain costs [22, 23]; VI) lack of standardised diagnostic criteria to define PID cases in hospital medical records leading to low accuracy in ICD-9CM coding and underestimation of Ct-associated PID cases. An overall decline in the hospitalisation rates for PID was reported also in other countries [1, 24].

The reliability of the information obtained from our data-sources, the national coverage of NHIS, the stable collection of data over time and the high diagnostic standards for Ct infection adopted in the clinics and microbiology laboratories participating in the sentinel systems make this study worthy. Underestimation of cases with Ct genital infection limited our analysis. In fact, Ct infection is not reported mandatorily in Italy,

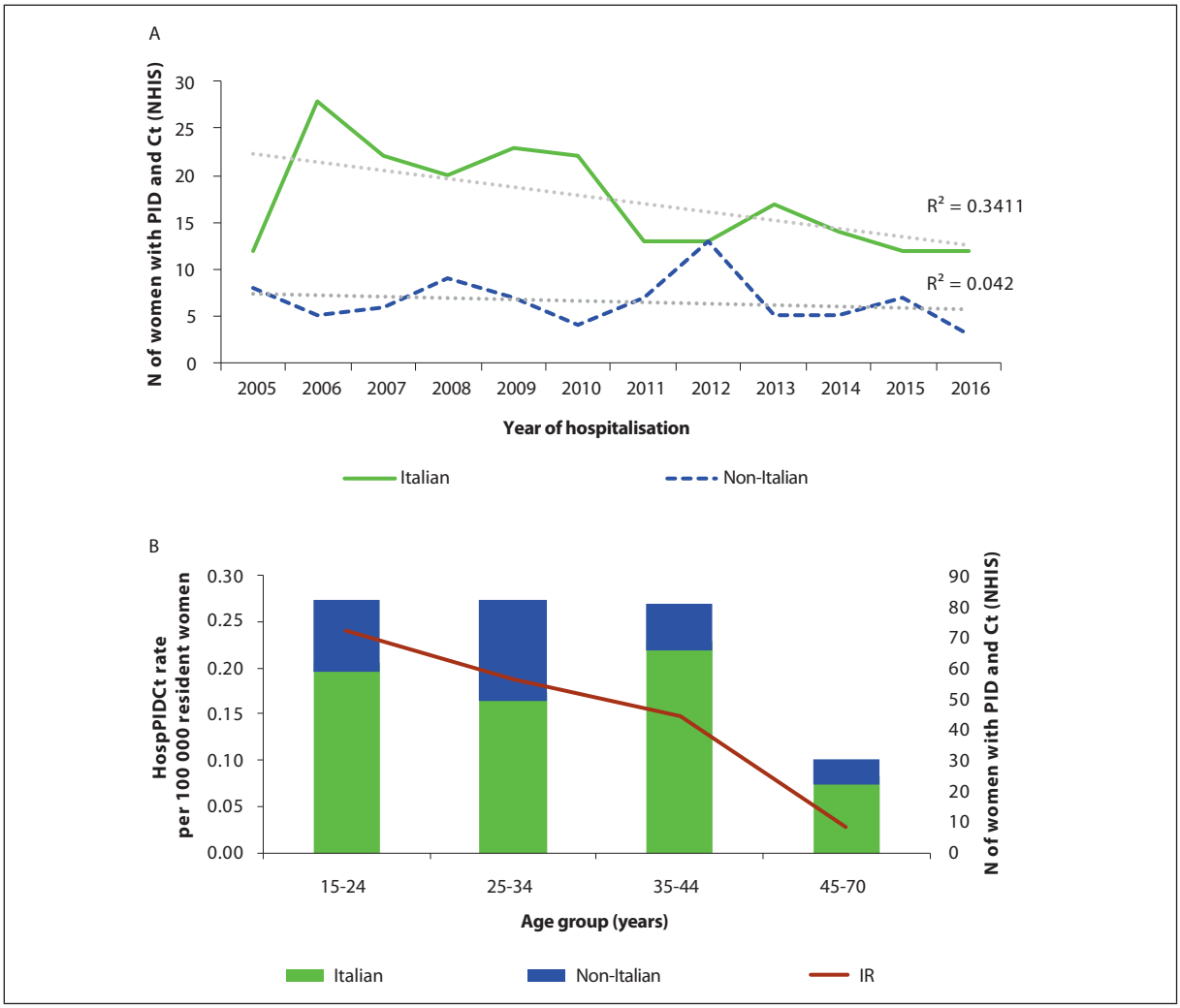

Figure 2
Distribution of women diagnosed with pelvic inflammatory disease and *Chlamydia trachomatis* notified to the NHIS by nationality and year of hospitalisation (A) or age group (B), with cumulative Incidence Rate, Italy 2005-2016.

Table 1
Annual estimated burden of *Chlamydia trachomatis* female infection and associated sequelae, Italy, 2009-2016 (time discounting was not applied). We obtained data from the Burden of Communicable Diseases in Europe (BCoDE) toolkit funded by the European Centre for Disease Prevention and Control (ECDC)

	Cases	per Year			DALY per case	per 100 000 Stratum specific population		
		YLD	YLL	DALY		YLD	YLL	DALY
Acute total	111 575.01	23.99	0	23.99	2.15E-04	0.08	0	0.08
Sequelae								
Pelvic inflammatory disease	60 234.11	395.30	0	395.30	3.54E-03	1.26	0	1.26
Tubal infertility	122.47	14.93	0	14.93	1.34E-04	0.05	0	0.05
Ectopic pregnancy	428.81[a]	10.61	8.79	19.40	1.74E-04	0.03	0.03	0.06
Chronic pelvic pain syndrome	27 919.23	5523.73	0	5523.73	0.05	17.65	0	17.65
Tubo-ovarian abscess	481.87	1.49	0	1.49	1.34E-05	4.77E-03	0	4.77E-03
Sequelae Total		5 946.07	8.79	5 954.85	0.05	19.00	0.03	19.03
All health outcomes Total		5 970.06	8.79	5 978.85	0.05	19.07	0.03	19.10

[a]Included 0.16 death. Abbreviations: DALYs, disability-adjusted life years; YLD, years lived with disability; YLL, years of life lost due to premature death. The toolkit is freely downloadable from https://ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys. Results are expressed in median values.

the SSS-STILab collected data by those laboratories participating in the network only and the SSS-STIClin reported symptomatic patients who attended these public clinics. We have no track of those tested at other public clinics and laboratories, or at private health care facilities. Besides, frequent absence of symptoms and/or lack of awareness to be infected by Ct lead to under-ascertainment of cases from the community. In addition, women diagnosed with PID approaching health care in Italy receive syndromic management and are not hospitalised. In case of persistence of symptoms only, after 48h they might be hospitalised with diagnosis of possible PID due to polymicrobial genital infection (without laboratory confirmation). Regional differences in ICD-9CM coding accuracy and ability for Ct diagnosis might explain different proportions of hospitalised cases in diverse Italian areas.

Taking into account that 9-15% of women diagnosed with PID are hospitalised [4] and based on the number of hospitalised PID cases observed in our 12-year analysis, about 2-3 million women with PID due to all causes were expected in Italy during 2005-2016. Considering that 4%-19% of PID cases are estimated to be associated with Ct infection [4], in the reference period about 88 000-700 000 PID cases due to Ct infection (up to about 60 000 cases per year) were expected. We found correspondence between this estimate on the number of PID cases caused by Ct and the results obtained with the BCoDE toolkit. Of them, based on the above-mentioned 9-15% PID hospitalization rate, 8000-100 000 women with PID due to Ct infection should have been hospitalised in the period 2005-2016. We identified 287 hospitalised women diagnosed with concurrent PID and Ct infection. This result suggests that in Italy under-reporting might play a relevant role in this discrepancy and at the same time that Ct-associated PID cases are hospitalised rarely and treated at home mostly, anyway increasing the rates of antibiotic consumption needed for the therapy, if not the costs of hospitalization.

Moreover, we showed that Ct infection affected mostly young women aged 15-24 years, and that the contribution of young non-Italian women in the spread of Ct infection is considerable (about one-third among the 15-24 age group), confirming data reported by the SSS-STILab [8, 17].

Under ascertainment, changes in testing practices and case definitions together with voluntary reporting suggested the need for improving and standardising the clinic-diagnostic path and data collection for Ct genital infections and associated sequelae. National prevention strategy for STI has been absent since 2012 [25]. As of January 14, 2019, as little as 68 dedicated public healthcare services for Ct diagnosis and case management exist throughout the country (over 60 million residents) [26]. A small number compared to other EU countries with similar population [25]. The diagnostic test for Ct is offered free of charge in some clinics only. Currently, sexual health and STI prevention are optional part of school education and specific Ct prevention campaigns have never be delivered.

CONCLUSIONS

We recommend the establishment of nationwide active surveillance system of laboratory-confirmed cases of Ct genital infection to monitoring the type of diagnostic tests used and evaluating assay-dependant differences of Ct incidence and prevalence in diverse settings and geographical areas through the country. Quality and focused epidemiological studies could better characterise risky sexual behaviours of the population most at risk to address targeted educational programmes for primary prevention. Promotion of condom use at the community level should be implemented. Overall, our national estimate for female Ct infection exceeded twice the EU burden (19.10 DALYs and 8.52 DALYs per 100 000 stratum specific population, respectively) [27], evidencing urgent need to starting preventive programmes to diagnose early and treat properly Ct infection, thus avoiding sequelae. Indeed, one single offer of Ct screening may reduce the incidence of PID at 1 year by 36% [4]. Our results pointed to young women between 20 and 24 years old as the population with the highest DALYs. Age targeted screening programmes with educational interventions would allow timely treatment by capturing adolescents usually reluctant to seek medical care, also identifying those asymptomatic who otherwise would not have been tested.

Authors' contributions

MS wrote the manuscript, selected the specific ICD-9 codes identifying Ct and PID cases and analysed data from NHIS; MCS managed and analysed data from the SSS; VR extracted data of the medical records from NHIS and supervised the statistical analysis; PP provided the 12-year medical records collected by the Ministry of Health, and supervised data extraction from NHIS and the statistical analysis; BS conceived and supervised the study project; all the authors contributed to the manuscript draft and revision.

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Conflicts of interest statement

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