EPIDEMIOLOGY OF SYPHILIS-RELATED HOSPITALISATIONS IN SPAIN BETWEEN 1997 AND 2006: A RETROSPECTIVE STUDY

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EPIDEMIOLOGY OF SYPHILIS-RELATED HOSPITALISATIONS IN SPAIN BETWEEN 1997 AND 2006: A RETROSPECTIVE STUDY.

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SUMMARY:

Objective: The goal of this study was to illustrate the important public health impact of syphilis, which is a preventable infection. We studied the epidemiology of syphilis-related hospitalisations in Spain over a 10-year period.

Methods: We conducted a retrospective study using the National Epidemiological Surveillance System for Hospital Data (Minimum Data Set, MDS). We analysed all the hospitalisations due to syphilis infection in any diagnostic position (ICD-9 CM 090-097) between 1997 and 2006, according to the Spanish version of the International Classification of Diseases, Ninth revision (ICD-9 CM).

Results: There were 9556 hospitalisations associated with syphilis in Spain. The hospitalisation rate was 2.33 per 100,000 population, the mortality rate was 0.07 per 100,000 population and the lethality was 3.17%. The hospitalisation rate increased significantly after 2000 and was higher in men.

Conclusion: Syphilis remains a major public health problem because of both potential complications and its close association with human immunodeficiency virus (HIV) infection. It is necessary to promote early diagnosis, ensure treatment in patients with syphilis and emphasise health promotion and prevention programs.

ARTICLE FOCUS

- To analyse the epidemiology of hospitalisations in patients with syphilis in Spain over a 10-year period (1997-2006)
- To compare this results with other notification systems existing in Spain.
- To illustrate the important public health impact of syphilis.

KEY MESSAGES

- The syphilis-related hospitalisation rate in Spain increased during the last ten years.
- Syphilis represents a re-emerging public health problem; epidemiological studies would allow to describe the causes of this new resurgence.
- The study contributes to fill an existent gap of information needed to develop and evaluate effective preventive and control measures.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study provides accurate information on the burden of syphilis.
- Due to the subclinical course of syphilis in most cases, hospitalised individuals represent only a small percentage of infected patients
- A unification of these monitoring systems for prevention would improve STI notification systems and, in turn, would allow a better comparison between countries

INTRODUCTION

Syphilis is a sexually transmitted infection (STI) of considerable public health importance due to both its global reach and its associated complications and sequelae. (1, 2)

A late syphilis diagnosis can lead to complications such as bone, cardiovascular and neurological lesions; in women, it can cause pregnancy loss (abortion and stillbirth), premature delivery and maternal transmission to the foetus, resulting in congenital syphilis or death. (1-3)

The World Health Organization (WHO) estimates that more than half a million children are born with congenital syphilis in the world every year (4) from infected pregnant women. A total of 25% of pregnancies to women infected with *Treponema pallidum* may end in stillbirth and 14% in neonatal death, representing an overall perinatal mortality of about 40% (3).

Moreover, syphilis is closely related to infection with human immunodeficiency virus (HIV). Ulcers caused by syphilis can increase the susceptibility and transmissibility of HIV, thereby increasing the risk of co-infection. (2)

The WHO estimates 340 million new cases of curable STIs annually among men and women aged 15-49 years (3) mostly in developing countries, although there has been an increase in the developed world. Recent epidemiological studies in Europe, the United States (US) and Australia have shown that the number of syphilis cases has been increasing (2, 5-7). After reaching its lowest rate in the 1990s, the incidence of syphilis has again increased significantly since 2001 (5,6).

Since 2000, epidemic outbreaks have been recorded throughout Europe, mainly due to changes in sexual behaviour and recreational drug use among men who have sexual relationships with other men (MSM) (8). An increase in syphilis rates has also been seen in

the US (5, 6), Asia (9) and Oceania (2). Similarly, the increased incidence rates of syphilis in Spain began in 2002 (1). Since that year, several studies showing increases in Barcelona (10) and Madrid (11) have been published. In 2008, a total of 2545 cases of syphilis were reported to the System of Diseases of Obligatory Declaration (EDO) in Spain (1), continuing the trend of an increasing incidence of this STI. This increase is also associated with outbreaks of syphilis among MSM. The practice of risky sexual behaviour associated with antiretroviral treatment could contribute to the greater number of syphilis infections in the HIV-positive population (2).

The purpose of this study was to describe syphilis-related hospitalisations in Spain between 1997 and 2006, using a population-based assessment. This study aims to illustrate the important public health impact of syphilis, which is a preventable infection and to compare this results with other notification systems existing in Spain.

MATERIALS AND METHODS

This retrospective study used the National Epidemiological Surveillance System for Hospital Data (Minimum Data Set, MDS), which includes data from 98% of public hospitals in Spain. It is estimated that the National Health System covers 99.5% of the Spanish population (12-14). This monitoring system uses the Spanish version of the International Classification of Diseases, Ninth revision (ICD-9-CM).

We analysed all hospital admissions due to syphilis infection (ICD-9 CM 090-097) in any diagnostic position for a period of 10 years (from January 1 1997 through December 31, 2006) in Spain. The MDS data included demographic information (age and gender) and clinical data including primary and secondary diagnosis.

Although the MDS does not record microbiological confirmation, the normal procedure for syphilis diagnosis in public hospitals in Spain involves microbial confirmation by laboratory tests.

We compared the hospitalisation data from the MDS with the information provided by the EDO and the mortality data with mortality rates obtained from the National Institute of Statistics (INE).

Statistical methods

We calculated the annual hospitalisation rate (per 100,000 population / year), average length of stay, mortality rates (per 100,000 population / year) and case fatality rates (% of deaths among hospitalised patients with syphilis). Population data were obtained from the municipal census for the years 1997-2006 in Madrid and were adjusted to the population covered by

hospitals included in the MDS. It is assumed that the age distribution of patients treated in public hospitals is the same as the age distribution in the general population.

To test for associations between continuous variables, we used either Pearson or Spearman correlations. The Student's t-test and ANOVA were used for comparison of means when parametric criteria were reached; for nonparametric distributions, we used the U-Mann Whitney and Kruskal-Wallis tests. Differences between proportions were evaluated by Chi-square tests. We used the Bonferroni correction to adjust for statistical significance for multiple comparisons. We calculated 95% confidence intervals (95% CIs), and p values < 0.05 were considered statistically significant throughout the analysis.

Statistical analysis of data was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0, Chicago, Illinois, USA).

RESULTS

During the study period, there were 9556 syphilis-related hospitalisations in Spain, 5988 in men and 3563 in women. A total of 29.1% of patients had syphilis as the primary diagnosis, and 56.7% had syphilis as a second diagnosis. When the diagnosis of syphilis was secondary, the most common primary diagnoses were HIV, pregnancy complications related to syphilis and cerebral infarction. The average age of patients was 47.55 years (standard deviation (SD) = 21.490), and the average length of stay was 14.32 days (SD = 19.382). Length of stay was significantly higher for men than women. (Table 1)

The most frequent comorbidities were HIV (13.05%), complications during pregnancy (syphilis during pregnancy) (3.12%), respiratory disease (pneumonia) (2.70%) and Hepatitis C (2.48%).

The hospitalisation rate during the study period was 2.33 per 100,000 population (95% CI: 2.29-2.38). In men, the hospitalisation rate was significantly higher ($p<0.05$), 2.98 per 100,000 population (95% CI: 2.90-3.05), which was almost twice the rate in women of 1.71 per 100,000 population (95% CI: 1.64-1.77) (Table 1).

Table 1: Hospitalisation, mortality, and case-fatality rates in patients with syphilis in Spain, by age group and gender. (1997-2006)

		N	Hospitalization rate (per 100,000) (95% CI)	Mortality rate (per 100,000) (95% CI)	Case-fatality rate (%) (95% CI)	Average length of stay (days) (SD)
General Analysis		9556	2.33 (2.29-2.38)	0.07 (0.07-0.08)	3.17 (2.82-3.52)	14.32 (19.382)
Gender	Men	5988	2.98 (2.90-3.05)	0.11 (0.10-0.13)	3.84 (3.35-4.33)	15.90 (21.129)
	Women	3563	1.71 (1.65-1.77)*	0.04 (0.03-0.04)*	2.05 (1.58-2.51)*	11.65 (15.662)*
Age	0-4	481	2.63 (2.40-2.87)	0.03 (0.01-0.06)	1.25 (0.26-2.24)	15.35 (17.230)
	5-9	55	0.28 (0.21-0.35)	0	0	4.35 (4.562)
	10-14	83	0.38 (0.30-0.47)	0.01 (-0.00-0.03)	3.61 (-0.40-7.63)	9.17 (13.025)
	15-19	174	0.68 (0.58-0.78)	0.02 (0.00-0.04)	3.45 (0.74-6.16)	9.17 (16.958)
	20-24	396	1.23 (1.13-1.38)	0.01 (0.00-0.02)	1.01 (0.03-1.99)	7.48 (9.961)
	25-29	629	1.81 (1.67-1.95)	0.03 (0.01-0.05)	1.91 (0.84-2.98)	8.76 (11.464)
	30-34	880	2.56 (2.39-2.73)	0.02 (0.00-0.03)	0.68 (0.14-1.23)	11.07 (13.253)
	35-39	909	2.77 (2.59-2.95)	0.03 (0.01-0.05)	1.21 (0.50-1.92)	12.34 (17.866)
	40-44	826	2.76 (2.57-2.95)	0.08 (0.05-0.11)	2.91 (1.76-4.05)	15.26 (16.674)
	45-49	736	2.77 (2.57-2.97)	0.08 (0.05-0.12)	2.99 (1.76-4.22)	17.90 (37.925)
	50-54	699	2.88 (2.67-3.09)	0.08 (0.05-0.12)	2.86 (1.63-4.10)	16.05 (15.359)
	55-59	675	3.10 (2.87-3.34)	0.1 (0.06-0.14)	3.11 (1.80-4.42)	16.96 (17.836)
	60-64	590	2.98 (2.74-3.22)	0.13 (0.08-0.18)	4.41 (2.75-6.06)	17.26 (24.346)
	65-69	597	2.99 (2.75-3.23)	0.1 (0.05-0.14)	3.18 (1.77-4.59)	16.55 (15.360)
	70-74	614	3.38 (3.11-3.64)	0.16 (0.10-0.22)	4.72 (3.05-6.40)	17.88 (22.855)
	75-79	608	4.33 (3.99-4.68)	0.29 (0.20-0.38)	6.74 (4.75-8.74)	14.82 (14.268)
	80-84	405	4.47 (4.04-4.91)	0.36 (0.24-0.49)	8.14 (5.48-10.81)	14.32 (14.453)
	>=85	199	2.73 (2.35-3.11)**	0.27 (0.15-0.39)**	10.05 (5.87-14.23)**	15.74 (13.432)**

*p< 0.05 Statistically significant difference by gender.
**p< 0.05 Statistically significant difference by age group.

There were 3563 syphilis-related hospitalisations in women, and 13.81% (492) of these women had syphilis or syphilis disorders associated with pregnancy. Over half of these women (53.25%, 262) had a diagnosis of syphilis in pregnancy, 27.03% (133) had premature rupture of membranes, 7.11% (35) had delivered prematurely and 5.08% (25) had a diagnosis of spontaneous abortion or risk of miscarriage.

The mortality rate was derived from the number of patients who died in the hospital due to syphilis infection. There were 303 deaths during the study period among hospitalised patients, representing a mortality rate of 0.07 per 100,000 population (95% CI: 0.07-0.08) and a case-fatality rate of 3.17% (95% CI: 2.82-3.52) (Table 1). Among patients who died, 29 had a primary diagnosis of syphilis (9.6%), and 24 had neurological damage caused by syphilis. We found HIV (15.18%), pneumonia (3.3%), stroke and cerebral haemorrhage (both 2.64%) as primary diagnoses for other patients who died.

Men had a mortality rate of 0.11 per 100,000 population (95% CI: 0.10-0.13) and a case-fatality rate of 3.84% (95% CI 3.35-4.33), both of which were significantly higher ($p<0.05$; $p<0.05$, respectively) than those in women, who had a mortality rate of 0.04 per 100,000 population (95% CI: 0.03-0.04) and a case-fatality rate of 2.05% (95% CI: 1.58-2.51).

Seventy-three of the women hospitalised with syphilis died, six with a diagnosis related to syphilis (syphilitic myelopathy, syphilitic general paresis, syphilitic myocarditis and syphilitic ruptured cerebral aneurysm) and the remainder due to HIV, cerebral haemorrhage, sepsis or a variety of malignancies. One of the women diagnosed with syphilis during pregnancy also died.

A total of 298 cases of congenital syphilis were recorded, with 2 deaths among them.

Figure 1 shows a statistically significant increase in both overall hospitalisation rates and hospitalisation rates by gender during the study period ($p<0.05$, $p<0.05$, $p<0.05$). Between 1997 and 2000, there was a decrease in hospitalisations, following the trend of the 1990s. After 2000, however, the hospitalisation rate started to increase, a trend that has persisted to the present. The highest hospitalisation rate was observed in 2006: 2.86 per 100,000 population (95% CI: 2.70-3.01).

The mortality and case-fatality rates did not show statistically significant changes ($p<0.05$, $p<0.05$) during the study period.

In stratified analyses by age group, there was a high hospitalisation rate in the age group 0-4 years of 2.63 per 100,000 population (95% CI: 2.40-2.87). There was also a significant increase in hospitalisation rates by age from 5 years. The highest rate of hospitalisation occurred in the age group of 80-84 years (4.47 per 100,000 population (95% CI: 4.04-4.91)) (Figure 2). The hospitalisation rate decreased in patients 85 years of age and older.

The mortality and case-fatality rates increased significantly with age ($p<0.05$), reaching the maximum rate at age 80 years.

Figure 3 shows the distribution of hospitalisation rates by region. The autonomous communities that had the highest hospitalisation rates were Ceuta and Melilla, with 6.78 and 11.52 per 100,000 population, respectively, and the lowest rates were found in Castilla La Mancha and the Basque Country, with 1.26 and 1.35 per 100,000 population, respectively.

DISCUSSION

The aim of this study was to analyse the epidemiology of hospitalisations in patients with syphilis in Spain over a 10-year period (1997-2006) and compare our results with the existent data reported to the System of Diseases of Obligatory Declaration (EDO) and the mortality data obtained from the National Institute of Statistics (INE).

Our results show the same upward trend in hospitalisation rates than the data collected by the EDO (763 cases in 1996 and 1711 in 2006) (1, 15). The syphilis-related hospitalisation rate in Spain increased significantly between 1997 and 2006, as demonstrated in previous studies (16). In the rest of Europe (17-21) and in the US (22, 23), the syphilis infection rate also started increasing in the year 2000 after years of steady decline.

There were significant differences by gender, with higher hospitalisation rates among men, a finding compatible with data published in the US (24), China (25) and various European countries (26) that show increased cases in men and particularly in MSM. We found a high rate of hospitalisation in children under the age of 5 years, which may be due to vertical transmission from mother to child that resulted in congenital syphilis, as the rate of hospitalisation in women also increased during the study period. Cases of congenital syphilis increased in Spain during the study period, with 298 new cases including two deaths. Therefore, improvement in the control and prevention of STI in pregnant women is necessary, as well as early treatment to prevent transmission of the disease. A recent French study showed that screening pregnant women in the first trimester of pregnancy improves diagnosis and prevents congenital syphilis cases (27).

Hospitalisation rates increased in people older than 65 years, which may be due to other chronic or acute age-related pathologies, such as respiratory disease (pneumonia), cerebrovascular disease and stroke or cerebral haemorrhage. Furthermore, we found higher rates of hospitalisation among children less than five years of age and young adults. These findings are similar to data from several other countries: Germany, where the average age of syphilis cases was 20-40 years (7); Ireland, where the average age was 20-44 years (20); and the US, where the average age was 35-39 years (28).

The mortality rate increased significantly with age and was highest after the age of 65 years. A high percentage of hospitalisations were due to complications associated with syphilis. When comparing our findings with the mortality rate data from the INE, we found a lower mortality rate in the INE data, from an annual 0.01 to 0.03 per 100.000 during the study period. This may be mainly due to the fact that hospital deaths may have been attributed to other diseases in these patients such as HIV, pneumonia and cerebrovascular diseases, which are common comorbidities with syphilis. (4, 20, 29).

Despite the heterogeneity of monitoring systems, diagnosis and control of STIs throughout the world, there has been a global trend of an increase in syphilis in recent years. Due to the subclinical course of syphilis in most cases, hospitalised individuals represent only a small percentage of infected patients. However, by including in the present study syphilis listed in any diagnostic position on the CMBD, we minimised this under-reporting due to limited information. A unification of these monitoring systems for prevention would improve STI notification systems and, in turn, would allow a better comparison between countries. Syphilis is a major public health problem because of the potential complications and its close association with HIV infection. Promoting early diagnosis in both men and women, ensuring

treatment in patients with syphilis and emphasizing prevention health programs should be essential goals to avoid pregnancy complications and to reduce and prevent complications caused by congenital syphilis (4, 30). These goals would also help decrease transmission among MSM.

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COMPETING INTERESTS

All the authors have seen and approved the final version. Authors have no conflicts of interest to declare.

COLLABORATIONS:

LGG participated in the data analysis, statistics and draft writing.

CAM contributed in the data analysis, statistics and draft writing.

AGE collaborated in the study design and draft review.

AAM collaborated in the data base design and data extraction.

AGM participated in the study design and draft approval.

RGP contributed in the study design; data analysis, statistics and draft review.

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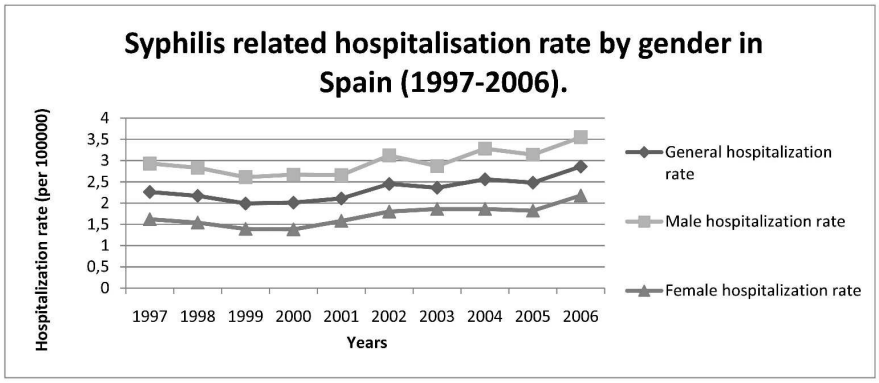
Figure 1: Syphilis related hospitalisation rate by gender in Spain (1997-2006).

Figure 2: Hospitalization, mortality and case-fatality rates related to syphilis by age group in Spain (1997-2006).

Figure 3: Syphilis related hospitalisation rate by region in Spain (1997-2006).



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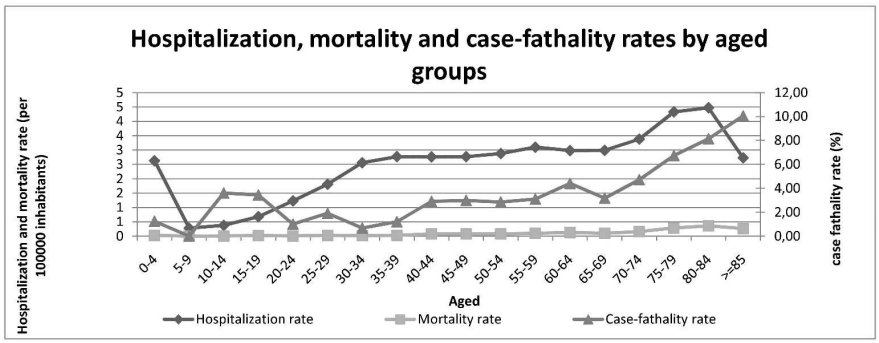

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3,5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	-
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

EPIDEMIOLOGY OF SYPHILIS-RELATED HOSPITALISATIONS IN SPAIN BETWEEN 1997 AND 2006: A RETROSPECTIVE STUDY

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EPIDEMIOLOGY OF SYPHILIS-RELATED HOSPITALISATIONS IN SPAIN BETWEEN 1997 AND 2006: A RETROSPECTIVE STUDY.

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Keywords: Hospitalisation, Sexually Transmitted Infection, Syphilis.

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SUMMARY:

Objective: The goal of this study was to illustrate the important public health impact of syphilis, which is a preventable infection. We studied the epidemiology of syphilis-related hospitalisations in Spain over a 10-year period.

Methods: We conducted a retrospective study using the National Epidemiological Surveillance System for Hospital Data (Minimum Data Set, MDS). We analysed all the hospitalisations due to syphilis infection in any diagnostic position (ICD-9 CM 090-097) between 1997 and 2006, according to the Spanish version of the International Classification of Diseases, Ninth revision (ICD-9 CM).

Results: There were 9556 hospitalisations associated with syphilis in Spain. The hospitalisation rate was 2.33 per 100,000 population, the mortality rate was 0.07 per 100,000 population and the lethality was 3.17%. The hospitalisation rate increased significantly after 2000 and was higher in men.

Conclusion: Syphilis remains a major public health problem because of both potential complications and its close association with human immunodeficiency virus (HIV) infection. It is necessary to promote early diagnosis, ensure treatment in patients with syphilis and emphasise health promotion and prevention programs.

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ARTICLE FOCUS

- To analyse the epidemiology of hospitalisations in patients with syphilis in Spain over a 10-year period (1997-2006)
- To compare this results with other notification systems existing in Spain
- To show that current policies of control and prevention of syphilis infections in Spain can be improved.

KEY MESSAGES

- Syphilis is a common infection in Spain and has increased during the last decade.
- Promoting early diagnosis in both men and women, ensuring treatment in patients with syphilis and emphasizing prevention health programs should be essential goals to avoid pregnancy complications and congenital syphilis.
- Unification of surveillance systems would improve the knowledge of syphilis epidemiology and comparison between countries

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study provides accurate information on the burden of syphilis.
- Due to the subclinical course of syphilis in most cases, hospitalised individuals represent only a small percentage of infected patients
- A unification of these monitoring systems for prevention would improve STI notification systems and, in turn, would allow a better comparison between countries

INTRODUCTION

Syphilis is a sexually transmitted infection (STI) of considerable public health importance due to both its global reach and its associated complications and sequelae. (1, 2)

A late syphilis diagnosis can lead to complications such as bone, cardiovascular and neurological lesions; in women, it can cause pregnancy loss (abortion and stillbirth), premature delivery and maternal transmission to the foetus, resulting in congenital syphilis or death. (1-3)

The World Health Organization (WHO) estimates that more than half a million children are born with congenital syphilis in the world every year (4) from infected pregnant women. A total of 25% of pregnancies to women infected with *Treponema pallidum* may end in stillbirth and 14% in neonatal death, representing an overall perinatal mortality of about 40% (3).

Moreover, syphilis is closely related to infection with human immunodeficiency virus (HIV). Ulcers caused by syphilis can increase the susceptibility and transmissibility of HIV, thereby increasing the risk of co-infection. (2)

The WHO estimates 340 million new cases of curable STIs annually among men and women aged 15-49 years (3) mostly in developing countries, although there has been an increase in the developed world. Recent epidemiological studies in Europe, the United States (US) and Australia have shown that the number of syphilis cases has been increasing (2, 5-7). After reaching its lowest rate in the 1990s, the incidence of syphilis has again increased significantly since 2001 (5, 6).

Since 2000, epidemic outbreaks have been recorded throughout Europe, mainly due to changes in sexual behaviour and recreational drug use among men who have sexual relationships with other men (MSM) (8). An increase in syphilis rates has also been seen in

the US (5, 6), Asia (9) and Oceania (2). Similarly, the increased incidence rates of syphilis in Spain began in 2002 (1). Since that year, several studies showing increases in Barcelona (10) and Madrid (11) have been published. In 2008, a total of 2545 cases of syphilis were reported to the System of Diseases of Obligatory Declaration (EDO) in Spain (1), continuing the trend of an increasing incidence of this STI. This increase is also associated with outbreaks of syphilis among MSM. The practice of risky sexual behaviour associated with antiretroviral treatment could contribute to the greater number of syphilis infections in the HIV-positive population (2).

The purpose of this study was to describe syphilis-related hospitalisations in Spain between 1997 and 2006, using a population-based assessment. This study aims to illustrate the important public health impact of syphilis, which is a preventable infection and to compare this results with other notification systems existing in Spain.

MATERIALS AND METHODS

This retrospective study used the National Epidemiological Surveillance System for Hospital Data (Minimum Data Set, MDS), which includes data from 98% of public hospitals in Spain. It is estimated that the National Health System covers 99.5% of the Spanish population (12-14). This monitoring system uses the Spanish version of the International Classification of Diseases, Ninth revision (ICD-9-CM).

We analysed all hospital admissions due to syphilis infection (ICD-9 CM 090-097) in any diagnostic position for a period of 10 years (from January 1 1997 through December 31, 2006) in Spain. The MDS data included demographic information (age and gender) and clinical data including primary and secondary diagnosis.

Although the MDS does not record microbiological confirmation, the normal procedure for syphilis diagnosis in public hospitals in Spain involves microbial confirmation by laboratory tests.

We compared the hospitalisation data from the MDS with the information provided by the Notifiable Disease System (EDO) and the mortality data with mortality rates obtained from the National Institute of Statistics (INE).

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Statistical methods

We calculated the annual hospitalisation rate (per 100,000 populations / year), average length of stay, mortality rates (per 100,000 populations / year) and case fatality rates (% of deaths among hospitalised patients with syphilis). Population data were obtained from the municipal census for the years 1997-2006 in Madrid and were adjusted to the population covered by

hospitals included in the MDS. It is assumed that the age distribution of patients treated in public hospitals is the same as the age distribution in the general population.

To test for associations between continuous variables, we used either Pearson or Spearman correlations. The Student's t-test and ANOVA were used for comparison of means when parametric criteria were reached; for nonparametric distributions, we used the U-Mann Whitney and Kruskal-Wallis tests. Differences between proportions were evaluated by Chi-square tests. We used the Bonferroni correction to adjust for statistical significance for multiple comparisons. We calculated 95% confidence intervals (95% CIs), and p values < 0.05 were considered statistically significant throughout the analysis.

Statistical analysis of data was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0, Chicago, Illinois, USA).

RESULTS

During the study period, there were 9556 syphilis-related hospitalisations in Spain, 5988 in men and 3563 in women. A total of 29.1% of patients had syphilis as the primary diagnosis, and 56.7% had syphilis as a second diagnosis. When the diagnosis of syphilis was secondary, the most common primary diagnoses were HIV, pregnancy complications related to syphilis and cerebral infarction. The average age of patients was 47.55 years (standard deviation (SD) = 21.490), and the average length of stay was 14.32 days (SD = 19.382). Length of stay was significantly higher for men than women. (Table 1)

The most frequent comorbidities were HIV (13.05%), complications during pregnancy (syphilis during pregnancy) (3.12%), respiratory disease (pneumonia) (2.70%) and Hepatitis C (2.48%).

The hospitalisation rate during the study period was 2.33 per 100,000 populations (95% CI: 2.29-2.38). In men, the hospitalisation rate was significantly higher ($p<0.05$), 2.98 per 100,000 population (95% CI: 2.90-3.05), which was almost twice the rate in women of 1.71 per 100,000 population (95% CI: 1.64-1.77) (Table 1).

Table 1: Hospitalisation, mortality, and case-fatality rates in patients with syphilis in Spain, by age group and gender. (1997-2006)

		N	Hospitalisation rate (per 100,000) (95% CI)	Mortality rate (per 100,000) (95% CI)	Case-fatality rate (%) (95% CI)	Average length of stay (days) (SD)
General Analysis		9556	2.33 (2.29-2.38)	0.07 (0.07-0.08)	3.17 (2.82-3.52)	14.32 (19.382)
Gender	Men	5988	2.98 (2.90-3.05)	0.11 (0.10-0.13)	3.84 (3.35-4.33)	15.90 (21.129)
	Women	3563	1.71 (1.65-1.77)*	0.04 (0.03-0.04)*	2.05 (1.58-2.51)*	11.65 (15.662)*
Age	0-4	481	2.63 (2.40-2.87)	0.03 (0.01-0.06)	1.25 (0.26-2.24)	15.35 (17.230)
	5-9	55	0.28 (0.21-0.35)	0	0	4.35 (4.562)
	10-14	83	0.38 (0.30-0.47)	0.01 (-0.00-0.03)	3.61 (-0.40-7.63)	9.17 (13.025)
	15-19	174	0.68 (0.58-0.78)	0.02 (0.00-0.04)	3.45 (0.74-6.16)	9.17 (16.958)
	20-24	396	1.23 (1.13-1.38)	0.01 (0.00-0.02)	1.01 (0.03-1.99)	7.48 (9.961)
	25-29	629	1.81 (1.67-1.95)	0.03 (0.01-0.05)	1.91 (0.84-2.98)	8.76 (11.464)
	30-34	880	2.56 (2.39-2.73)	0.02 (0.00-0.03)	0.68 (0.14-1.23)	11.07 (13.253)
	35-39	909	2.77 (2.59-2.95)	0.03 (0.01-0.05)	1.21 (0.50-1.92)	12.34 (17.866)
	40-44	826	2.76 (2.57-2.95)	0.08 (0.05-0.11)	2.91 (1.76-4.05)	15.26 (16.674)
	45-49	736	2.77 (2.57-2.97)	0.08 (0.05-0.12)	2.99 (1.76-4.22)	17.90 (37.925)
	50-54	699	2.88 (2.67-3.09)	0.08 (0.05-0.12)	2.86 (1.63-4.10)	16.05 (15.359)
	55-59	675	3.10 (2.87-3.34)	0.1 (0.06-0.14)	3.11 (1.80-4.42)	16.96 (17.836)
	60-64	590	2.98 (2.74-3.22)	0.13 (0.08-0.18)	4.41 (2.75-6.06)	17.26 (24.346)
	65-69	597	2.99 (2.75-3.23)	0.1 (0.05-0.14)	3.18 (1.77-4.59)	16.55 (15.360)
	70-74	614	3.38 (3.11-3.64)	0.16 (0.10-0.22)	4.72 (3.05-6.40)	17.88 (22.855)
	75-79	608	4.33 (3.99-4.68)	0.29 (0.20-0.38)	6.74 (4.75-8.74)	14.82 (14.268)
	80-84	405	4.47 (4.04-4.91)	0.36 (0.24-0.49)	8.14 (5.48-10.81)	14.32 (14.453)
	>=85	199	2.73 (2.35-3.11)**	0.27 (0.15-0.39)**	10.05 (5.87-14.23)**	15.74 (13.432)**

*p< 0.05 statistically significant difference by gender.
**p< 0.05 statistically significant difference by age group.

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There were 3563 syphilis-related hospitalisations in women, and 13.81% (492) of these women had syphilis or syphilis disorders associated with pregnancy. Over half of these women (53.25%, 262) had a diagnosis of syphilis in pregnancy, 27.03% (133) had premature rupture of membranes, 7.11% (35) had delivered prematurely and 5.08% (25) had a diagnosis of spontaneous abortion or risk of miscarriage.

The mortality rate was derived from the number of patients who died in the hospital due to syphilis infection. There were 303 deaths during the study period among hospitalised patients, representing a mortality rate of 0.07 per 100,000 population (95% CI: 0.07-0.08) and a case-fatality rate of 3.17% (95% CI: 2.82-3.52) (Table 1). Among patients who died, 29 had a primary diagnosis of syphilis (9.6%), and 24 had neurological damage caused by syphilis. We found HIV (15.18%), pneumonia (3.3%), stroke and cerebral haemorrhage (both 2.64%) as primary diagnoses for other patients who died.

Men had a mortality rate of 0.11 per 100,000 population (95% CI: 0.10-0.13) and a case-fatality rate of 3.84% (95% CI 3.35-4.33), both of which were significantly higher ($p<0.05$; $p<0.05$, respectively) than those in women, who had a mortality rate of 0.04 per 100,000 population (95% CI: 0.03-0.04) and a case-fatality rate of 2.05% (95% CI: 1.58-2.51).

Seventy-three of the women hospitalised with syphilis died, six with a diagnosis related to syphilis (syphilitic myelopathy, syphilitic general paresis, syphilitic myocarditis and syphilitic ruptured cerebral aneurysm) and the remainder due to HIV, cerebral haemorrhage, sepsis or a variety of malignancies. One of the women diagnosed with syphilis during pregnancy also died.

A total of 298 cases of congenital syphilis, defined as syphilis in the newborn due to maternal-fetal transmission in utero (15), were recorded, with 2 deaths among them.

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Figure 1 shows a statistically significant increase in both overall hospitalisation rates and hospitalisation rates by gender during the study period ($p<0.05$, $p<0.05$, $p<0.05$). Between 1997 and 2000, there was a decrease in hospitalisations, following the trend of the 1990s. After 2000, however, the hospitalisation rate started to increase, a trend that has persisted to the present. The highest hospitalisation rate was observed in 2006: 2.86 per 100,000 populations (95% CI: 2.70-3.01).

The mortality and case-fatality rates did not show statistically significant changes ($p<0.05$, $p<0.05$) during the study period.

In stratified analyses by age group, there was a high hospitalisation rate in the age group 0-4 years of 2.63 per 100,000 populations (95% CI: 2.40-2.87). There was also a significant increase in hospitalisation rates by age from 5 years. The highest rate of hospitalisation occurred in the age group of 80-84 years (4.47 per 100,000 population (95% CI: 4.04-4.91)) (Figure 2). The hospitalisation rate decreased in patients 85 years of age and older.

The mortality and case-fatality rates increased significantly with age ($p<0.05$), reaching the maximum rate at age 80 years.

Figure 3 shows the distribution of hospitalisation rates by region. The autonomous communities that had the highest hospitalisation rates were Ceuta and Melilla, with 6.78 and 11.52 per 100,000 populations, respectively, and the lowest rates were found in Castilla La Mancha and the Basque Country, with 1.26 and 1.35 per 100,000 populations, respectively.

DISCUSSION

Syphilis infections are of mandatory notification in Spain through the Notifiable Disease System (EDO). All new cases are recorded on a weekly basis at both the Primary Care and Hospital level. There are also ITS regional centers, where patients with ITSs are treated and followed. Hospitalisations occur in the most severe cases, latent and tertiary syphilis or comorbidities. The aim of this study was to analyse the epidemiology of hospitalisations in patients with syphilis in Spain over a 10-year period (1997-2006) and compare our results with the existent data reported to the Notifiable Disease System (EDO) and the mortality data obtained from the National Institute of Statistics (INE). Our results do not show the real incidence of syphilis infection, as primary and secondary infections are mainly treated in Primary Care centers. That is the reason why we don't talk about incidence, but about hospitalisation rates throughout the paper.

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Our results show the same upward trend in hospitalisation rates than the data collected by the EDO (763 cases in 1996 and 1711 in 2006) (1, 16). The syphilis-related hospitalisation rate in Spain increased significantly between 1997 and 2006, as demonstrated in previous studies (17). In the rest of Europe (18-22) and in the US (23, 24), the syphilis infection rate also started increasing in the year 2000 after years of steady decline.

By comparing the figures obtained in the present study with the total of cases reported to the EDO (1), we can estimate a 42% of the syphilis infections needing hospitalisation. Both hospitalisation rates and incident estimates obtained in this study are higher than those published for other European countries (19). Possible explanations for these figures could be

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different sexual behaviours and the increasing immigrant population since 2000 coming from different regions with higher syphilis incidences.

There were significant differences by gender, with higher hospitalisation rates among men, a finding compatible with data published in the US (25), China (26) and various European countries (27) that show increased cases in men and particularly in MSM. This could be due to the behavioural changes of this population group, with a decrease in the preventive measurements and the increase of risky sexual practices that favour the infection (28).

We found a high rate of hospitalisation in children under the age of 5 years, which may be due to vertical transmission from mother to child that resulted in congenital syphilis, as the rate of hospitalisation in women also increased during the study period. Cases of congenital syphilis increased in Spain during the study period, with 298 new cases including two deaths. Pregnant women are tested twice for syphilis infection during the routine pregnancy controls in the National Health System in Spain, a first serology in the first antenatal consultation and a second one in the third trimester. Treatment is given both to the woman or her couple when needed. If woman is positive to the infection, a second serology will be done during delivery, both to the mother and the newborn to check its serological status (3, 4). The increase of congenital syphilis during de study period reflects an increase in the primary and secondary syphilis cases among women in Spain. It could be due to the increasing immigrant population from countries where syphilis incidence is higher. These women can have a lower adherence to the health system and less access to prenatal consultation and can be at a higher risk of syphilis and HIV transmission. Universal screening, and treatment of women positive for syphilis offer immediate benefits to mother and to locate and treat potentially infected couples. It also prevents the transmission of syphilis and HIV and prevents the development of complications in newborns and in mothers and their partners (4).

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Therefore, improvement in the control and prevention of STI in pregnant women is necessary, as well as early treatment to prevent transmission of the disease. A recent French study showed that screening pregnant women in the first trimester of pregnancy improves diagnosis and prevents congenital syphilis cases (29).

Hospitalisation rates increased in people older than 65 years, which may be due to other chronic or acute age-related pathologies, such as respiratory disease (pneumonia), cerebrovascular disease and stroke or cerebral haemorrhage. Furthermore, we found higher rates of hospitalisation among young adults. These findings are similar to data from several other countries: Germany, where the average age of syphilis cases was 20-40 years (7); Ireland, where the average age was 20-44 years (21); and the US, where the average age was 35-39 years (30).

The mortality rate increased significantly with age and was highest after the age of 65 years. A high percentage of hospitalisations were due to complications associated with syphilis. When comparing our findings with the mortality rate data from the INE, we found a lower mortality rate in the INE data, from an annual 0.01 to 0.03 per 100.000 during the study period. This may be mainly due to the fact that hospital deaths may have been attributed to other diseases in these patients such as HIV, pneumonia and cerebrovascular diseases, which are common comorbidities with syphilis. (4, 21, 31).

Despite the heterogeneity of monitoring systems, diagnosis and control of STIs throughout the world, there has been a global trend of an increase in syphilis in recent years. Due to the subclinical course of syphilis in most cases, hospitalised individuals represent only a small percentage of infected patients. However, by including in the present study syphilis listed in

any diagnostic position in the CMBD, we minimised this under-reporting due to limited information. A unification of these monitoring systems for prevention would improve STI notification systems and, in turn, would allow a better comparison between countries. Syphilis is a major public health problem because of the potential complications and its close association with HIV infection. Promoting early diagnosis in both men and women, ensuring treatment in patients with syphilis and emphasizing prevention health programs should be essential goals to avoid pregnancy complications and to reduce and prevent complications caused by congenital syphilis (4, 32). These goals would also help decrease transmission among MSM.

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COMPETING INTERESTS

Authors have no conflicts of interest to declare.

COLLABORATIONS:

LGG participated in the data analysis, statistics and draft writing.

CAM contributed in the data analysis, statistics and draft writing.

AGE collaborated in the study design and draft review.

AAM collaborated in the data base design, data extraction and draft writing.

AGM participated in the study design and draft approval.

RGP contributed in the study design; data analysis, statistics and draft review.

All the authors have seen and approved the final version.

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Figure 1: Syphilis related hospitalisation rate by gender in Spain (1997-2006).

Figure 2: Hospitalisation, mortality and case-fatality rates related to syphilis by age group in Spain (1997-2006).

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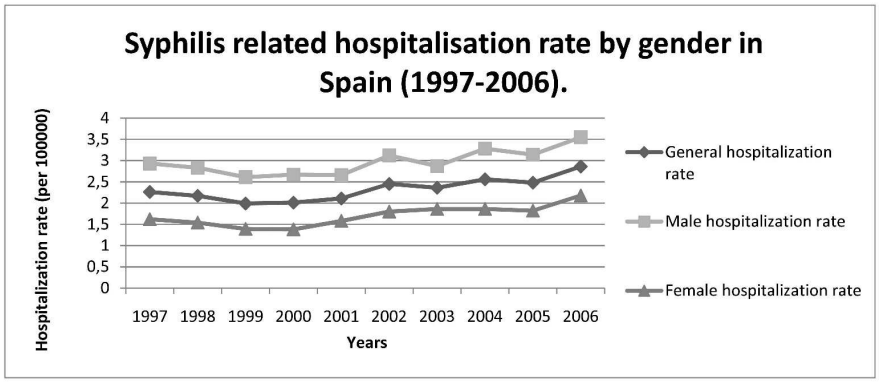
Figure 3: Syphilis related hospitalisation rate by region in Spain (1997-2006).



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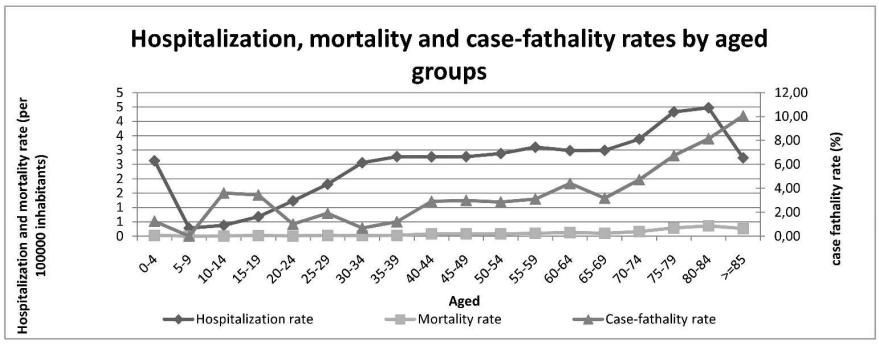

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3,5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	-
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	-

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.