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Sexually transmitted infections in Portugal: mapping and spatial analysis

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ABBREVIATIONS LIST

CDC - Centers for Disease Control and Prevention

CrI - Credible Interval

ECDC - European Centre for Disease Prevention and Control

EDI - European Deprivation Index

EIDs - Emerging Infectious Diseases

EU - European Union

GIS - Geographic Information System

HIV - Human Immunodeficiency Virus

INE – Instituto Nacional de Estatística (Statistics Portugal)

ISPUP - Instituto de Saúde Pública da Universidade do Porto

LGV - Lymphogranuloma Venereum

MSM - Men Who Have Sex With Men

PPH - Precision Public Health

RR - Relative Risk

SINAVE - Sistema Nacional de Vigilância Epidemiológica

STIs - Sexually Transmitted Infections

US - United States

WHO - World Health Organisation

ABSTRACT

Background: Over the last few years there has been an increase in the number of sexually transmitted infections (STIs) worldwide. The most common STIs around the globe include chlamydia, gonorrhoea, and syphilis. The re-emergence of these infections among populations represents a serious public health threat due to severe complications on the reproductive and neonatal health. Spatial differences in STIs occurrence have been commonly seen between countries and regions. Using finer scales to monitor disease variation and to identify high-risk communities is a critical aspect to develop targeted interventions towards the reduction of the burden of STIs.

Objective: This study aimed to map the spatial patterns of chlamydia, gonorrhoea, and syphilis, identify high-risk areas across Portuguese municipalities and determine the association of these STIs with socioeconomic deprivation, urbanity level, and population density.

Methods: STIs notifications at municipality level for the period 2015-2017 were obtained from Portugal's Epidemiologic Surveillance System (SINAVE). Spatial Bayesian models were used to calculate smoothed standardised notification rates, identify high- and low-risk areas and estimate associations (Relative Risk, RR, 95% Credible Intervals, 95%CrI).

Results: There were 4819 reported cases of chlamydia, gonorrhoea and syphilis accounting for 15.3%, 33.2%, and 51.5% of the notifications, respectively. From 2015 to 2017, there was an increase in the number of cases of STIs (1432, 1448, and 1939 cases). The highest increase (110%) was observed in chlamydia infections with 173, 201, and 363 cases. A 40% rise in gonorrhoea (468, 474, 656) and an increase of 16% in syphilis (791, 773, 920) was also registered. STIs notification rates were substantially higher in Porto and Lisbon Metropolitan Areas and concentrically disperse around those. Notification rates of the three STIs were strongly correlated (r>0.8). Rates of gonorrhoea and syphilis were associated with population density (Q1-lowest density vs. Q5-highest RR=2.10 95%CrI 1.08-4.25 and RR=3.16 95%CrI 2.00-5.13, respectively). Notifications of chlamydia and syphilis increased with urbanity level (Q1-least urban vs. Q5-most RR=9.64, 95%CrI 1.73-93.59 and RR=1.92, 95%CrI 1.30-2.88, respectively). We also found that notification rates of gonorrhoea were associated with socioeconomic deprivation (Q1-least vs. Q5-most deprived RR=1.75, 95%CrI 1.07-2.88).

Conclusions: These findings indicate that, in Portugal, there are wide spatial inequalities in STIs notification rates, which were predominantly concentrated in the two metropolitan areas of the country. Different contextual factors influence the occurrence of STIs in the population. Our findings can help guide more targeted interventions to reduce STIs incidence.

Key-words: Gonorrhoea; chlamydia; syphilis; epidemiology; spatial analysis; geographical health inequalities; precision public health.

Resumo

Introdução: A nível mundial tem-se verificado um aumento no número de infeções sexualmente transmissíveis (ISTs), nos últimos anos. Globalmente, as ISTs mais comuns são a clamídia, a gonorreia e a sífilis. O reaparecimento destas infeções representa um importante problema de saúde pública devido às graves consequências na saúde neonatal e reprodutiva. Têm sido observadas diferenças espaciais na ocorrência das ISTs entre países e regiões. A utilização de escalas geográficas mais finas para a monitorização destas infeções e para a identificação de comunidades de maior risco é um aspeto crítico para o desenvolvimento de acções mais direcionadas para reduzir a carga das ISTs nas populações.

Objetivos: Este estudo teve como objetivo mapear os padrões espaciais das infeções de clamídia, gonorreia e sífilis, identificar as áreas de risco nos municípios portugueses, e determinar a associação entre as ISTs com a privação socioeconómica, o nível de urbanidade e a densidade populacional.

Métodos: Foram obtidas as notificações das ISTs, a nível do município, através do Sistema Nacional de Vigilância Epidemiológica (SINAVE) durante o período de 2015-2017. Foram utilizados modelos espaciais bayesianos para calcular e suavizar as taxas de notificação padronizadas, identificar as áreas de alto e baixo risco e estimar associações (Risco Relativo, RR, Intervalo de credibilidade a 95%, 95%ICr).

Resultados: Durante o período de estudo, foram reportados 4819 casos de clamídia (15.3%), gonorreia (33.2%), e sífilis (51.5%), em Portugal. Entre 2015 a 2017, ocorreu um aumento no número de casos de ISTs (1432, 1448, e 1939 casos). O maior aumento (110%) foi observado nas infeções por clamídia com 173, 201, e 363 casos. Mas também foi registado um aumento de 40% nas notificações de gonorreia (468, 474, 656) e um aumento de 16% nas notificações de sífilis (791, 773, 920). As taxas de notificação de ISTs foram substancialmente superiores nas áreas metropolitanas do Porto e Lisboa, dispersando concentricamente a partir destas zonas. As taxas de notificação das três ISTs apresentaram-se fortemente correlacionadas ($r>0.8$). As taxas de gonorreia e sífilis encontraram-se associadas com a densidade populacional (Q1- baixa vs. Q5-alta densidade RR=2.10 95%ICr 1.08-4.25 and RR=3.16 95%ICr 2.00-5.13, respetivamente). As notificações de clamídia e sífilis aumentaram com o nível de urbanidade (Q1-menor vs. Q5-maior urbanização RR=9.64, 95%ICr 1.73-93.59 and RR=1.92, 95%ICr 1.30-2.88, respetivamente). Por fim, as taxas de notificação de gonorreia mostraram-se associadas com a privação socioeconómica (Q1-menor vs. Q5-maior privação RR=1.75, 95%ICr 1.07-2.88).

Conclusões: Em Portugal, existem grandes desigualdades espaciais nas taxas de notificação de ISTs, estando estas predominantemente concentradas nas duas áreas metropolitanas do país. Verificamos também que diferentes fatores contextuais influenciam a ocorrência das ISTs na população. Os nossos resultados poderão ajudar a orientar a implementação de medidas mais direcionadas de forma a reduzir a incidência das ISTs.

Palavras-chave: Gonorreia; clamídia; sífilis; epidemiologia; análise espacial; desigualdades geográficas em saúde; saúde pública de precisão.

INTRODUCTION

1. FUNDAMENTAL PRINCIPLES OF INFECTIOUS DISEASES

1.1. Human-Microbe Interactions

There is an inevitable relation between humans and microorganisms. In fact, human beings have their own indigenous microbiota initially acquired during birth (1). The human-microbe interactions shape a symbiotic association, which can either be a mutualism (both agent[1] and host[2] benefit from the interaction), a commensalism (one benefits and the other is not positively or negatively affected), a parasitism (the agent benefits nonetheless the host does not) or an antagonism relationship (neither the agent nor the host benefits from the interaction) (4).

The presence of these microorganisms does not, normally, cause harm to the host. As a matter of fact, these microbes help the host's physiology by acquiring certain compounds through metabolic activities, avoiding colonisation of other pathogenic microorganisms and modulating epithelial and systemic responses (5). However, if the host's state of health is altered, for instance, immunocompromised or affected by an underlying chronic disease; if the host's microbiota expands to a site where it does not naturally exist; or if its normal microbial communities change, for example, due to use of antibiotics, it might generate an imbalance and, as a result, these harmless microbes become opportunistic pathogens (4). Nonetheless, most human infections are not caused by opportunistic pathogens, but by several microbes inhabiting outside the human body (6).

1.2. Microbial Reservoirs of Infection and Entry into the Host

We are all surrounded by a countless number of microscopic organisms. These pathogens lodge in diverse reservoirs, such as animals, plants and other human beings (4). In order to reach a susceptible host, infectious agents must be transmitted from a source, which may or may not be the same as their natural reservoirs. When referring

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[1] Agents (virus, bacterium, parasite, fungus or prions) are potential infectious pathogens that can cause the onset of infection or disease. 2. Gange SJ, Golub ET. Study Design. Infectious Disease Epidemiology: Theory and Practice. 3rd edition ed: Jones & Bartlett Learning; 2014. p. 45-76.

[2] A host is any person or animal who can shelter or provide the necessary conditions for an infectious agent. 3. A Dictionary of Epidemiology. 6th ed: Oxford University Press; 2014.

to pathogens inhabiting in human reservoirs, infectious agents may exit the human body via body secretions and fluids through a suitable portal of exit, which is normally associated with the site where they were established (figure 1) (7).

Skin/mucous membrane	Respiratory Tract	Gastrointestinal Tract	Urogenital Tract	Other means
• Wounds	• Coughing • Sneezing • Talking	• Saliva • Sputum • Fecal material	• Semen • Vaginal secretions • Urine	• Blood • Breast milk • Placenta • Ear wax • Tears

Figure 1: Microorganisms potential portals of exit from human reservoirs. Adapted from (7)

When leaving the reservoir/source, the agent may be spread through different means of transmission either by direct or indirect mechanisms displayed in figure 2 (8). It is noteworthy that some pathogens have multiple modes of transmission instead of an exclusive one. From a public health perspective, knowing the reservoir and its route of transmission is crucial for implementing effective control measures and, in this way, avoid potential outbreaks (9).

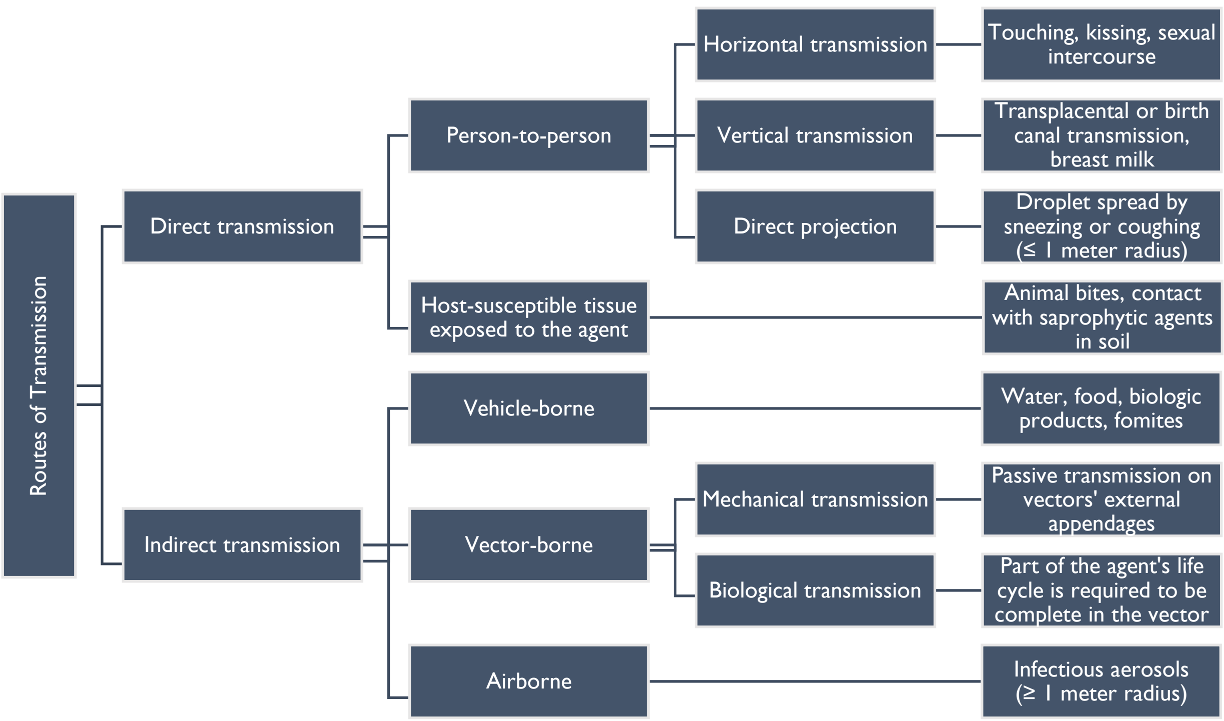

Figure 2: Distinct routes of transmission of infectious diseases. Direct transmission occurs when the infectious agent is transmitted from a reservoir to a susceptible host without any type of intermediary as in indirect transmission (4, 8).

As previously mentioned, human beings are consistently exposed to countless microbes. However, humans do not become persistently ill as a result of innate and adaptative immunity. Innate immunity provides immediate undifferentiated barriers against any type of microorganism whereas adaptive immunity recognises the pathogen attempting to invade the organism and, therefore, produces a specific immune response. Hence, the pathogen or their toxic products must firstly surpass the primary innate mechanisms in order to gain access to the human body (10). This task may be accomplished by entering humans' natural mechanic barriers through disruption on skin surfaces due to accidental or surgical wounds, injections, bites, burns or via mucous membranes by penetration, direct contact, ingestion or inhalation as shown in figure 3.

Skin	Respiratory System	Digestive System	Urogenital system	Other means
• Ducts of sweat glands • Mammary glands • Hair follicles	• Inhaled air • Dust particles • Airborne droplets	• Food • Water • Hands	• Sexual intercourse • Microbes entering from skin surfaces	• Ears • Nose • Mouth • Eyes • Placenta

Figure 3: Microorganism's potential portals of entry through penetration, direct contact, ingestion or inhalation. Adapted from (4).

Access to the host' organism may be achieved by only one exclusive portal of entry or by multiple ones, depending on the pathogen characteristics. The portal of entry, usually, is directly related to the type of disease produced and can influence the agent pathogenicity, that is, the agent's ability to induce disease (4, 11). However, if the microbial pathogen enters, for example, in the bloodstream, it can potentially spread to diverse parts of the body and damage other tissues that are not whatsoever related with the initial entry site (12, 13).

1.3. Infection versus Disease

It is essential to distinguish infection from disease. Infection emerges upon the invasion of an infectious agent and its multiplication on or within a susceptible host (6, 12). Infectious agents or even its toxins can trigger a bacterial, a viral, a fungal, a parasitic or a prion infection, depending on the etiologic agent, which might lead to the development of an infectious disease (3). Hence, disease happens when the function of a tissue or an organ is compromised, and its normal function is affected. Usually, the malfunction causes clinical signs and symptoms in the host (1, 4). However, it should be noted that despite being infected with a pathogen, it is not certain that the disease will emerge (12). For instance, the host's response may vary depending on previous immunisations. Therefore, there are different possible outcomes upon contact with an infectious agent with might be colonization without infection, infection or ultimately the manifestation of the disease (9).

1.4. Factors that Influence the Occurrence of Infection and Disease

As previously mentioned, innate and adaptive immunity and route of exposure contribute to the development of clinical infection. Nevertheless, there are many other factors that contribute to the onset of infection. The characteristics of the agent, the host, and the environment have a fundamental role in the chain of infection as shown in figure 4 (2, 9).

Agent Factors	Host Factors	Environmental Factors
- Infectivity - Infective dose - Pathogenicity - Virulence factors - Antigenicity or immunogenicity - Evasiveness - Environmental stability (e.g. survival in different pH)	**Intrinsic Factors** - Age - Sex - Race/Ethnicity - Genetic profile - Immune responsiveness **Behaviour/Extrinsic Factors** - Lifestyle (e.g. smoking) - Sexual behaviour - Occupation - Recreational activities - Immune status due to chemotherapy, immunization and immunosuppresive medications	**Physical Environment** - Climate - Vector presence - Urbanity level - Remoteness **Social Environment** - Sexual network - Crowding - Medical availability - Education - Public health resources (e.g. universal access to contraception)

Figure 4: Agent, host, and environment factors contributing to increased risk of infectious disease onset. Adapted from (4, 9).

1.5. Epidemiologic Concepts of Infectious Disease

Some factors that influence the development of infection also determine the latency and incubation period as well as the period of infectivity of an infectious disease (9).

The latency period is the time between infection and the onset of infectiousness while the incubation period is the time from infection to the development of signs and symptoms (11). The incubation period can range from just a couple of hours to days, months or even years depending on the inoculum of the pathogen, its route and its rate of replication. Nevertheless, it is important to note that even when people contact with the same agent, in the same circumstances, they can have slightly different incubation periods due to individual characteristics (11). The estimation of these periods can be quite challenging since the detection of the beginning of infection and infectiousness are not evident and, therefore, relatively difficult to assess. Moreover, when a pathogen has a short latency period but a very long incubation period, such as human immunodeficiency virus (HIV), people will transmit the infectious agent without knowing they are infectious. This situation can be quite challenging for public health since symptoms have not been experienced yet and, perhaps, a medical diagnosis has not been sought which might perpetuate the spread of disease (14).

The period of infectivity is the duration of time from which individuals are infectious. This time period is vital to control the spread of disease. For instance, people can remain infectious even though they have already recovered from the disease (carrier state). This peculiar condition can lead to dreadful outbreaks especially in infectious diseases transmitted from person-to-person. An interesting example is the case of cook Mary Mallon who was responsible for raising more than 200 cases of typhoid fever (11). Moreover, when the incubation period is longer than the latent period, people will become infectious without any symptoms. Thus, isolation of infected persons will not be as effective in preventing the occurrence of new cases since the infectious period has already begun before the onset of symptoms (15). This situation can be also verified for clinically inapparent infections.

The basic reproduction number (R_0) is another epidemiologic concept that helps to interpret how infectious a disease is. R_0 represents the mean number of secondary infections that one person can transmit (during the infectious period) in a fully susceptible population, that is, all members of a population can develop the infection if infected (3, 14). R_0 does not consider cases derived from secondary cases (14), the presence of any immune individuals nor any public health measures already implemented to control transmission (16). R_0 is a measure that is influenced by the contact rate among infected and non-infected people, the transmission probability per contact, and the duration of infectiousness (14, 17). When the R_0 value is less than one, the infectious disease being studied is not an imminent threat since the number of persons being infected is below the required minimums to continue disease transmission. Therefore, if this tendency continues, the number of new cases decreases until it is no longer being propagated throughout the population. If the R_0 value is equal to one, the disease is maintained in the population (endemic) until effective measures are implemented, and in this case, the number of cases will decline in the target population. However, if a factor that contributes to the increase of an infectious disease is triggered, the R_0 value might exceed one. This scenario leads to the beginning of an outbreak or epidemic. Furthermore, the R_0 value is also dependent on the agent, host and environment factors. Consequently, R_0 is not a fixed number for a certain infectious disease. R_0 can fluctuate in different communities, for example, according to the population density and the way people interact with each other. Thus, the R_0 value represents the transmission potential of microbes within a specific time and population. However, the R_0 value assumptions do not translate exactly into reality. In fact, some individuals are already immune to certain pathogens. Thus, the expected number of cases produced by an index case (the first case being identified) will be less than the predicted R_0. When considering immune individuals in the population, we then refer to the effective reproductive number (R_e) (14).

All these epidemiologic concepts are essential to understand infectious disease dynamics which helps public health practitioners to comprehend the type of pathogen causing the infection, its characteristics, and transmission and, therefore, apply appropriate control measures necessary to protect people's health.

1.6. (Re)Emergence of Infectious Diseases

Infectious diseases have been historically present over centuries resulting in dreadful epidemics of plague, smallpox, and syphilis, for example (18). Continuous advances in scientific knowledge and technology contributed to understand the complex mechanisms used by microorganisms to successfully cause disease and also grant the development of efficient preventive measures and treatment for controlling infectious diseases (18, 19).

During the 20th century, infectious diseases morbidity and mortality declined due to improvements in sanitation and hygiene, implementation of vaccination programmes, the discovery of antibiotics and other antimicrobial medicines as well as the adoption of serologic testing, viral isolation, tissue culture and molecular techniques. Otherwise thought to be close to being extinguished, in part due to the effectiveness of using vaccines and antibiotics, infectious diseases still constitute an enormous impact in communities (6, 18). From 1940 onwards the incidence of emerging infectious diseases has increased reaching its highest in the 1980s associated with the emerge of HIV/AIDS pandemic (20).

Emerging infectious diseases (EIDs) have become a global problem. EIDs have increased as a result of diverse factors such as microbial adaptation and change. For example, the adaptation of microbes has allowed some pathogens to recently enter human populations (severe acute respiratory syndrome (SARS), H1N1 and H5N1 influenza virus) (21). The continued overuse and misuse of antibiotics aggravated the battle with multi-drug-resistant strains. The scarceness of new effective antibiotics and vaccines is intensifying the problem of EIDs (22). Unfortunately, there is also a re-emerge of vaccine-preventable diseases. The most recent cases of measles are quite worrying. The number continues to rise in a tremendous way. In Europe, there were 5,273, 25,869, 83,540 cases in 2016, 2017 and 2018, respectively (23). Not only do low-income countries suffer from their low immunisation coverage but also countries with stronger health care systems due to the growing movements of anti-vaccination groups which are fearful threats to public health (22). Moreover, the increasing world population growth, the demographic change in society and its changed behaviours have also influenced the resurgence of infections. Urbanisation, globalisation, expansion and changes in land use, relocation of animals, global climate change, and lack of political will are some of the factors that contribute to the occurrence of these infections (24, 25). The shift to a more urbanised environment leads to changes in human interactions and consequently shapes disease transmission and persistence. In addition, urban slums with poor living conditions provide propitious settings for infectious diseases (26).

All these changes have facilitated the spread of pathogenic agents allowing them to access new areas and populations, which in turn modifies the spatial diffusion processes of infectious diseases. Further, the ease of travelling in a shorter amount of time and to longer distances has led to the different spatial distribution of infectious diseases. Currently, infectious diseases are not confined to closed populations where disease spread progressively to adjacent areas (contagious diffusion). Stronger transportation connections allowed greater mobility which enabled hierarchical diffusion to occur, where the disease spreads from large cities to small towns and also enabled network diffusion, which reflects new social interactions (27). Understanding the dynamic of these processes allows better opportunities for control and stop outbreaks.

Although sexually transmitted infections (STIs) have been around for a long time, there has been an increase in STIs in the last few years (28, 29). The re-emergence of these diseases represent a serious public health threat and more scientific evidence is needed to understand the underlying reasons for the current trend and provide guidance on public health interventions.

2. Sexually Transmitted Infections (STIs)

2.1. STIs current trends

Sexually transmitted infections are contagious infections caused by bacteria, viruses or parasites typically diffused by sexual contact. These infections can also be spread via non-sexual means (blood or blood products) or transmitted from mother to child during pregnancy and childbirth (30). Some common consequences of these infections are infertility, ectopic pregnancies, pelvic inflammatory disease, miscarriage, foetal death, congenital infections, facilitation of transmission of STIs, which overall translates into a massive public health problem (28, 30, 31).

Sexually transmitted infections are currently increasing every year. This scenario is being verified worldwide as the World Health Organisation (WHO) estimated that more than one million STIs are acquired daily being a substantial public health issue (30). The most common STIs around the globe include chlamydia, gonorrhoea, and syphilis with an estimate of 127, 87 and 6 million new cases, in 2016, respectively (28). These worrying data motivated WHO to include gonorrhoea and syphilis on their prioritising list on the WHO Global Health Sector Strategy on Sexually Transmitted Infections, 2016–2021 (32). According to the Centers for Disease Control and Prevention (CDC) report, 'Sexually Transmitted Disease Surveillance 2016', there are an estimated 20 million new STIs cases every year in the United States (US), with half of those cases emerging between the ages of 15 to 24. This tendency is verified in chlamydia, primary and secondary syphilis (33), gonorrhoea and congenital syphilis, with a 4.7%, 17.6%, 18.5% and 27.6% rate increase since 2015, respectively (31). The 2017 CDC report on STIs continued to find this trend, revealing a 6.9% increase in chlamydia compared to the 2016 rate (29). There is also a large economic burden associated with STIs. Around $16 billion dollars are spent in direct medical cost, and, annually, the US healthcare system has a $742 million dollars expenditure on curable STIs (34).

In Europe, the European Centre for Disease Prevention and Control (ECDC) releases the annual epidemiological report of some diseases that are under surveillance in the

European Union (EU). Latest results showed that for gonorrhoea the number of reported cases had increased by 14%, in 2015, when compared with 2014, stabilised in 2016, but increased again by 17%, in 2017 (35, 36). Regarding chlamydia infection, the number of cases appears stable even though there are slight differences between countries (37, 38). For syphilis, the number of cases increased since 2011, namely among men, predominantly men who have sex with men (MSM) (39, 40).

Portugal is not an exception. The latest data collected through the national serological survey 2015/2016 estimated, among other purposes, the prevalence of STIs in individuals aged 18 or over. The results indicated that about 2.7% of Portuguese people were infected with Chlamydia trachomatis and 2.4% with Treponema pallidum (mostly people above 56 years old which is explained by Portugal's high prevalence of syphilis in the '60s and '70s) (41). The results obtained from this survey also showed a slight increase when compared with previous years. This phenomenon was already clear in the 2011/2014 report of the notifiable diseases, where there was a substantial increase in the number of cases being notified. In fact, two of the most commonly reported notifiable diseases were syphilis and gonorrhoea (42).

2.2. *Chlamydia trachomatis* infections

2.2.1. Biological and clinical characteristics of *Chlamydia trachomatis*

Chlamydia trachomatis is a nonmotile gram-negative bacteria that can be classified into two distinct biovars: i) trachoma and ii) lymphogranuloma venereum (LGV). The trachoma biovar is associated with ocular and genital tract infections whereas LGV biovar is related to lymphatic system infections. This species features an array of serovars due to variations in its major outer membrane protein (MOMP). These variations are associated with different pathological outcomes (43-45).

This bacterium is an obligate intracellular bacterium that has an exclusive natural host, the human being (46). It gains access to other individuals primarily through sexual contact either by anal, oral or vaginal sex. However, this bacterium can also be transmitted by hand to eye contact resulting in cases of inclusion conjunctivitis. Likewise, mothers can transmit to their offspring, during pregnancy or during birth, which culminates in cases of conjunctivitis and pneumonia as *C. trachomatis* can target columnar cells of the respiratory tract (47).

The trachoma biovar infects the columnar epithelium of human's genital and respiratory tracts as well as the conjunctiva (43). This spherical bacterium can replicate in epithelial cells of the conjunctiva, urethra and rectum. In addition, due to anatomical differences, the trachoma biovar targets epithelial cells of the endocervix and the upper genital tract, in women, and epithelial cells of the epididymis and prostate, in men. Thus, the clinical consequences include: i) chlamydial urethritis and proctitis, in both sexes; ii) epididymitis in men and iii) cervicitis, endometritis, salpingitis as well as pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, infertility, and pregnancy complications, in women (43, 47).

Although epithelium cells are the main target of *C. trachomatis*, this bacteria can also infect fibroblasts (48) and cells of the immune system, such as monocytes and macrophages. For instance, when macrophages that do not complete intracellular elimination are directed to regional lymph nodes, *C. trachomatis*, namely LGV biovar, can potentially diffuse to other parts of the body and cause a systemic infection (44). LGV biovar clinical outcomes are slightly different from trachoma biovar. The clinical manifestation starts with a primary lesion at the site of infection, which quickly disappears. The LGV strain is then drained from the infected location to surrounding lymph nodes inducing lymphadenopathy. Systemic symptoms appear days or weeks after the lesion healing process. The inflammation process will be prompt, creating an inflammatory mass and ultimately fibrosis. If this pathological process continues, elephantiasis of genitalia occurs due to lymphatic obstruction. Other possible clinical outcomes are proctitis and proctocolotis, namely in MSM (47).

The incubation period for *C. trachomatis* is around one to three weeks (43), however, LGV biovar primarily lesions appear 7 to 12 days after infection (49). More than 50% of men and 80% to 90% of women are asymptomatic (43). As most cases of infection with *C. trachomatis* do not present symptoms, diagnosis and appropriate treatment of infection are hindered. The ongoing infection without natural resolution or treatment might aggravate the clinical manifestation of the disease since the chances of *C.*

trachomatis migrating to other sites and establishing a chronic infection increases (46). In addition, the long-lasting chlamydia infections contribute to maintaining the infectious agent in the population (43). It is not clearly known the average duration of untreated chlamydia infection. However, studies have estimated values based on the duration of infection until treatment. In women, the average duration of chlamydia infection without treatment is around 1.35 years (50, 51). In men, it has been estimated a mean duration of 2.84 years. Although men present a slower clearing rate than women, Lewis *et al.* verified that men are less likely to establish infection. The duration of asymptomatic infection is then an important factor to provide evidence for improving public health practise, namely, creating routine screening programmes in sexually active individuals as well as understanding the transmission probability to prevent reinfection or new cases of chlamydia infections and its clinical complications (50).

2.2.2. Epidemiologic characteristics and geographic disparities

Chlamydia infections are the most common bacterial STI in the world (47). However, these infections are not evenly distributed across the globe. Estimates from 2012 showed that the Western Pacific Region had the highest estimated prevalence rates, in both sexes, and the Region of the Americas had the highest estimates in women. Comparatively, the African region displayed low rates of chlamydia infections (52). According to the WHO, there were 127 million new cases of chlamydia in people aged 15-49, in 2016 (53). In Europe, the most notified STI is chlamydia. Chlamydia rates among European countries differ, but the overall crude notification rate is about 146 per 100,000 inhabitants. In 2017, Bulgaria, Croatia, Cyprus, Hungary, Luxembourg, Poland, Portugal, and Romania showed notifications rates below 10 per 100,000 inhabitants whereas Iceland, Denmark, Norway, the United Kingdom, Sweden, and Finland had higher reporting cases (200 cases per 100,000 population). The differences observed in chlamydia estimates are the result of the effort of certain countries public health programmes to detect these infections rather than a relevant prevalence difference between countries (38). Furthermore, chlamydia infections are observed mostly among women reflecting more directed testing towards women, except in a few countries, such as Portugal. More than half the cases reported were observed in the 15-24 years age group, where the 20-24 years age group accounted for most cases.

The most common transmission mode was heterosexual contact (86%), followed by MSM (10%). Although there was a 3.7% increase in the overall chlamydia notification rate, in countries who systematically report chlamydia infections from 2008 to 2017, the notifications appear to be stable but high (38). A similar scenario is observed in the US were chlamydia infections are the most common notifiable disease (529 cases per 100,000 population). Since 2014, there has been a slight increase in reported cases. Once more, most reported cases occur in the 15-24 years old group, especially in the 20-24 years old group. Even though women have almost twice the men's rate, there has been a substantial increase in the number of cases in males. These numbers can be explained either by the increased diagnoses in gay, bisexual and other MSM or by a real notification increase (29).

Lymphogranuloma venereum is a rarer form of *C. trachomatis* infection. It is endemic in some areas such as Africa, India, Southeast Asia, South America, and the Caribbean (47). However, recently some outbreaks have been reported, namely among MSM, in European countries, such as in the Netherlands (54), Spain (55), Malta (56), as well as North America and Australia (47). In 2017, the ECDC epidemiological report noticed a slight decline in the number of reported cases of LGV, but this reduction is most likely related to ending outbreaks or changes in testing practices (57). Nonetheless, some countries verified a rise in the number of reported cases of LGV. Among them, Portugal was the country where it was verified the highest increase (300% between 2016 and 2017). In general, most cases of LGV were observed in MSM and people aged 25 and over (57).

The risk of contracting genital chlamydia infection is commonly associated with young age, especially among female adolescents. The physiologic changes from this transitional stage and differences in sexual behaviours make these age groups more susceptible to infection (58). However, LGV is commonly observed in men, namely in MSM (47). Having new or multiple sexual partners, inconsistent or non-use of barrier contraception and poor sexual health literacy also contribute to a higher risk of chlamydia transmission (59, 60). In the US, race/ethnicity seems to play an important part in chlamydia acquisition (61, 62). Furthermore, infection rates are higher in people with a lower socioeconomic position, lower educational attainment, lower occupational class or unemployment and greater area deprivation (63).

In 2017, the US exhibited more than 50% of the reported chlamydia cases in the metropolitan statistical areas. In addition, during 2016-2017 there was an increase of 8.3% of notified cases in these areas (29). Higher chlamydia rates have been frequently associated with urban areas (64, 65), although recent studies in the Netherlands noticed more chlamydia infections in less urbanised regions, and in Pennsylvania (US) a shift in the case rate from urban to rural populations was detected (66, 67).

2.3. Syphilis infections

2.3.1. Biological and clinical characteristics of *Treponema pallidum*

Treponema pallidum subspecies *pallidum* is a spiral organism that causes venereal syphilis in humans, its only natural host (68). This gram-negative bacteria enters a new host through direct penetration of mucous membranes, abrasions or lesions on the skin during sexual contact (69). During pregnancy, or more rarely during birth, this fastidious pathogen can be transmitted from mother to foetus resulting in cases of abortion, stillbirth, preterm birth or infants with congenital syphilis (68). *T. pallidum* is also possibly transmitted through contaminated bodily fluids, blood transfusion or via organ donation (70, 71). Syphilis appearance is related to the number of sexual partners, population mobility, social disruption and collapse of medical services (72).

If left untreated, acquired syphilis may evolve into different clinical stages and potentially become systemic. T. pallidum replicates very slowly, with a division time of approximately 30-33 hours (73, 74). This slow growth generates a long incubation period which varies between 10 to 90 days which is also influenced by the inoculum (33, 69, 75). Firstly, a chancre appears in the site of infection either on the rectum, anal canal, oral cavity, penis (men), labia or cervix (women), or other body parts that might be exposed, such as hands (68, 75). Usually, the chancre is painless, indurated, non-exudative and might be imperceptible which contributes to a later diagnose and progression of the infection, especially in women and MSM, due to internal vaginal or anogenital lesions (75). Regional lymphadenopathy is another possible clinical manifestation of the primary stage, once T. pallidum reaches nearby lymph nodes. Without leaving any scars, the chancre will cease up on its own after 3-6 weeks whereas the lymphadenopathy might remain unresolved (75).

Secondary syphilis is the result of the continuous spread of *T. pallidum*, by the bloodstream, to different tissues throughout the body (68, 75). Hence, the bacteria can target any anatomic site and produce a panoply of symptoms, such as low-grade fever, malaise, pharyngitis, anorexia, weight loss, arthralgias, and myalgias. The immense variety of symptomatology might delay appropriate diagnose and treatment since it can be confused with some other pathologies (69). Usually, after 4 to 10 weeks after the initial manifestation of the chancre, or even during primary syphilis, small mucocutaneous rashes start to appear on the trunk and proximal extremities (68, 69). Usually, the manifestations are not confined to a single location. As *T. pallidum* spirochetes reach other parts of the body through lymphatic and blood vessels, lesions on the palms and soles start to develop, as well as, on other mucosal areas such as the oral cavity and genitalia. These cutaneous lesions can be macular, papular, papulosquamous, annular or pustular or variations of these type of rashes, which might be confused with other skin conditions (75). Furthermore, patients might develop condylomata lata, alopecia and generalised lymphadenopathy (69). The pathological outcomes of secondary syphilis can naturally heal within 3 months and the infection may enter an asymptomatic phase - the latent syphilis stage (68).

Infections lasting less than one year are designated as early latent syphilis. During this stage, spirochetes might still circulate in blood vessels which might result in patients presenting, once again, secondary syphilis symptoms (68, 69). After one year of infection, this highly invasive agent is typically confined to a certain area and the infection is denominated as late latent syphilis (69). As seen, symptoms can come and go and in the later stages becomes asymptomatic. Unaware patients who do not take appropriate attention to existing signs and symptoms might complicate their current disease stage and contribute to syphilis evolution. Lastly, the ongoing infection can last 5 to 30 or more years, ultimately producing gummatous, cardiovascular syphilis, and neurosyphilis, however, the central nervous system can be targeted in early phases of syphilis (69). In addition, in tertiary syphilis, the liver (76), joints (77) and testes (78) can be also affected. This final stage is uncommonly seen since the antibiotic era, as syphilis can be easily treated with penicillin (79).

The most infectious stages of syphilis are during the primary and secondary syphilis (including early latent syphilis) since lesions are moist and prone to infection with a generation time of 30 hours (68, 69). Syphilis genital ulcers contribute to the acquisition of human immunodeficiency virus (HIV). The lesions act as a portal of entry for the virus and the common presentation of lymphadenopathy provide the optimal cells target for HIV (75, 80), making syphilis-infected individuals more susceptible to contract HIV (68, 81).

2.3.2. Epidemiologic characteristics and geographic disparities

Newman *et al.* verified a higher syphilis estimated prevalence rate in the African Region in women and men. In addition, the study also verified that women in lower-income countries had a higher prevalence of syphilis (52). In 2016, there were 6 million new cases of chlamydia in people aged 15-49, worldwide (53).

In Europe, as with chlamydia, there are slight differences in syphilis notifications rates between countries. Iceland, Malta, United Kingdom and Spain presented the highest rates, while Croatia, Cyprus, Estonia, Italy, Portugal and Slovenia have lower rates, below 3 cases per 100,000 population, in 2017. Among the countries considered, a crude notification rate of 7.1 cases per 100,000 population was obtained. Unfortunately, rates of syphilis continue to rise in both sexes. Although males are most affected by syphilis infections, the male-to-female ratio varies between 15:1 and 2:1 among European countries. Unlike chlamydia, the highest rates were observed in older age groups, namely between the ages of 25 and 34. The most common transmission mode was among MSM (67%), followed by heterosexual transmission (20%). In addition, 26% of infected individuals were co-infected with HIV, of which 39% were MSM. Regarding the clinical stage of syphilis, latent syphilis, namely early latent syphilis, was the most common reported stage, especially in Iceland, Lithuania and Malta. From 2011 onwards, the trend on syphilis notifications has been on the rise, particularly in western Europe (40). The increased number of cases has been more pronounced in men than women, due to a sharp increase in cases among MSM (40).

In the US, the notifications of syphilis have been rising since the year 2000, currently recording the highest value since 1993. In 2017, primary and secondary syphilis presented a rate of 9.5 cases per 100,000 population, where the majority of cases occurred in men (87.7%) and in individuals aged 25-29 years old. From all cases, MSM accounted for 57.9% of syphilis cases and this particular group also showed the highest share of HIV co-infection (45.5%). However, increases in the number of cases in women are also observed, which requires special attention since it may boost the number of cases of congenital syphilis. Syphilis cases had an impressive increase of 72.7% from 2013 to 2017. A 17.6% increase was observed in the number of cases of early latent syphilis and a 17.3% increase in the late and late latent syphilis (29). Japan has also registered an increase in syphilis notifications (82). Public health practitioners should have a comprehensive monitorisation to understand how syphilis is spreading in the population and implement appropriate actions.

Syphilis infections are not equally distributed in all race/ethnicities. Blacks had 4.5 times the rate observed among Whites and if we only consider women the disparity was even higher (5.2). When compared to Whites, Native Hawaiians/other pacific islanders (2.6), Hispanics (2.2), and American Indians/Alaska natives (2.1) had a higher rate of reported primary and secondary syphilis. Overall, across the US, the most reported cases were observed in black male aged 25-29 years. Furthermore, the most populous metropolitan areas account for 70.4% of primary and secondary syphilis (29). On the other hand, in Guangdong Province, South China, notifications rates were clustered across rural areas, due to older people cases, but also across cities (83).

Other factors disclose health disparities among communities. For example, in Massachusetts, syphilis rates were highest across the poorest census tracts, namely in 25-44 years old non-Hispanic black and Hispanic men (84). In Baltimore, poverty, low education attainment, lack of sexual health information contributed to a higher incidence of syphilis in inner-city dwellers (85). Although most core areas occur in urban settings, syphilis infections are still high in rural areas of North Carolina, in the US, probably determined by a rural core group connection to high rate core areas (86).

2.4. Gonorrhoea infections

2.4.1. Biological and clinical characteristics of *Neisseria gonorrhoeae*

Gonorrhoea is a bacterial infection with *Neisseria gonorrhoeae*, a non-spore-forming bacterium whose only natural host are humans (87). This gram-negative diplococcus may contain in its outer membrane type IV pili which allows its movement through "twitching", promotes the ability to attach to susceptible host cells, and escape immune responses through its antigenic variation (88). In addition, *N. gonorrhoeae* contains in its outer membrane other elements that influence its virulence and the host response to infection, such as porins (Por), opacity (Opa) proteins, reduction-modifiable protein (Rmp) and gonococcal lipo-oligosaccharide (LOS) (89).

N. gonorrhoeae is transmitted to new hosts via vaginal, oral or anal sex or from mother-to-child. Sexual transmission of gonorrhoea is not identical between sexes. Females are more prone to get a gonococcal infection from their male sexual partner than men from their female sexual partner (89, 90). In addition, the acquisition of infection is highly dependent on the number of partners, the number of exposures and the anatomic site (91, 92). For instance, in men who have sex with women, a higher number of exposures is related to contracting gonococcal urethritis (93) and, in MSM, there is a higher risk of transmitting gonorrhoea from the rectum to the urethra than from the pharynx (94).

This fastidious bacterium infects the mucosal epithelium of the urethra, cervix, rectum, oropharynx and conjunctiva. Therefore, the clinical consequences of *N. gonorrhoeae* include: i) gonococcal urethritis, proctitis and oral-pharyngeal infections, in both sexes; ii) acute epididymitis and periurethritis, in men, and iii) cervicitis, endometritis, salpingitis, tuboovarian abscess, bartholinitis, as well as pelvic inflammatory disease, ectopic pregnancy and pregnancy complications, in women. Other possible pathologies, when gonococcemia occurs, include attendant conjunctivitis, in new-born babies, peritonitis and perihepatitis, in women, and ophthalmitis, arthritis, tenosynovitis, dermatitis, endocarditis and meningitis (87, 89, 95). The incubation period of *N. gonorrhoeae* is 2 to 7 days (87). MSM, who exhibit pharyngeal or rectal gonococcal infections, are typically asymptomatic, whereas heterosexual men usually have urethra symptomatic manifestations. This might explain the increasing gonorrhoea infections rate, in MSM, as people will continue to transmit the infectious agent without even knowing it. (96, 97). In women, gonococcal infections symptoms are very mild or non-existent, resulting in later diagnose and treatment which overall leads to serious disease complications (98). Estimates of the duration of infection for *N. gonorrhoeae* are between 3 to 8 months (99), and the site of infection seems to also play an important part in the duration of infection. Among MSM, the average duration of pharyngeal gonorrhoea is about 3 to 4 months whereas rectal gonorrhoea can even last up to 12 months (100).

2.4.2. Epidemiologic characteristics and geographic disparities

Gonorrhoea infections are highly prevalent in the African Region, among women, and in the Western Pacific Region, among men (52). In 2016, there were 87 million new cases of chlamydia in people aged 15-49, worldwide (53).

Data from 2017 showed that northern European countries such as the United Kingdom, Ireland, Denmark, Iceland, Norway and Sweden presented the highest gonorrhoea rates, while Bulgaria, Croatia, Cyprus and Romania obtained the lowest rates. Overall, a crude notification rate of 22.2 per 100,000 inhabitants was observed, in Europe. Younger people aged 20-24 years were the most affected age group as well as men. The most common mode of transmission is MSM (47%) followed by heterosexual contact (45%) (36). Among European countries, 14% of gonococcal infections were HIV-positive, and 22% of MSM who had gonorrhoea were also HIV-positive. In addition, the incidence of gonorrhoea has been increasing with slight variations between European countries, making gonorrhoea the second most notified STI. France, Portugal, Denmark and Ireland presented the largest increases from 2008-2017. This trend is a major public health concern since *N. gonorrhoeae* has been developing resistance to currently recommended treatment, such as third-generation azithromycin and cephalosporins, which ultimately may lead to untreatable gonorrhoea (101-104).

As in Europe, gonorrhoea is the second most reported STI in the US. Since 2009, a 75.2% increase in reported gonorrhoea cases was observed. In 2017, gonococcal infections exhibit a rate of 171.9 cases per 100,000 population, where the majority of cases occurred in men and in individuals aged 20-24 years old. There are also differences in reported cases of gonorrhoea according to race/ethnicity which emphasises health discrepancies. American Indians/Alaska Natives, Native Hawaiians/Other Pacific Islanders, Hispanics, Asians showed rates 4.5, 2.8, 1.7 and 1.2 times higher than white people, respectively (29). The highest rates of gonococcal infections were registered in black people (8.3 times higher than white people).

As in other STIs, gonorrhoea incidence is also influenced by several determinants. The level of education, number of partners, neighbourhood SES are some variables associated with higher gonorrhoea rates (66, 105). Gonorrhoea has also been correlated with not being married and moderately correlated with population density (106), as well as living in urban settings (64, 107). In fact, in the US, 61.3% of cases were seen in metropolitan statistical areas (29). In the US, from 2005 to 2009, metropolitan areas with high levels of racial residential segregation exhibited higher gonorrhoea rates, especially among black individuals (108). Gonococcal infections were high in rural areas, in North Carolina, although core areas are in urban settings and, in Pennsylvania, a rural tendency was also observed as previously seen with syphilis infections (67, 86).

3. PRECISION PUBLIC HEALTH

Through the use of current technologies, community data can be used to effectively detect the people, the place and the time of occurrence of a specific outcome and ensure prompt interventions. This is the foundation of precision public health (PPH). Although this term is quite recent and academics are still debating its meaning (109-111), PPH can be defined as improving the ability to prevent disease, promote health, and reduce health disparities in populations by: 1) applying emerging methods and technologies for measuring disease, pathogens, exposures, behaviours, and susceptibility in populations; and 2) developing policies and targeted public health programs to improve health (112, 113).

Adaptation of targets and interventions to local context is pivotal to effective country response to tackle STIs occurrence. Although national estimates facilitate international comparisons, these cannot solve heterogeneity at the geographical level where public health actions usually take place. For that, it is important to monitor disease variation using finer scales to identify clusters of cases and inequalities, which is a critical aspect in precision public health and in efficient resource allocation (114). As mentioned by Bill & Melinda Gates Foundation, PPH "requires robust primary surveillance data, rapid application of sophisticated analytics to track the geographical distribution of disease, and the capacity to act on such information" (115).

Effective analyses can provide useful information on the communities that could benefit most from the intervention, highlight the underlying causes of the disease and, therefore, achieve better health outcomes in a heterogeneous population. Hence, PPH reduces areas of interventions without alarming people who are not at risk and enables better allocation of resources (112).

It should be noted that managing this type of information requires proper public disclosure since the data is quite sensible. Imprudent handling of data might jeopardise people's confidentiality and lead to unwanted results, such as stigmatisation and reduced trust in institutions (112). As interventions will be more targeted towards specific groups of the community, special attention should be given to the way interventions are implemented in order to ensure that stigmatisation or discrimination will not occur (116). Historically, society has developed negative connotations towards individuals who contract STIs typically associating it with irresponsible sexual behaviour (117). Embarrassment and shade related to STIs acquisition have a significant role in people's willingness to be tested, self-notifying their sexual partners and seeking treatment (118, 119).

Other relevant risks arise with PPH. When directed interventions are targeted towards high-risk groups, disease transmission patterns might be maintained in borderline cases. Moreover, the interventions might only target wealthier communities who regularly have their health data collected, and also the abundance of data generated requires higher efforts to maintain data quality which might slow down scientific progress (112).

4. Geographic Information Systems, Spatial Analysis, and Public Health

A geographic information system (GIS) is a "framework for gathering, managing, and analyzing spatial data. Rooted in the science of geography, GIS integrates many types of data. It analyzes spatial location and organizes layers of information into visualizations using maps and 3D scenes. With this unique capability, GIS reveals deeper insights into data, such as patterns, relationships, and situations helping users make smarter decisions"(120).

The key characteristic (and advantage) of GIS is the ability to link the building blocks of epidemiology: place, time and people (121). Through the use of current technologies, GIS are able to integrate and analyse geographic data of diverse spheres, such as the health field (122). Indeed, health geography and spatial epidemiology are subfields of medical research that use geographic techniques, such as mapping, spatial statistics and GIS, to investigate geographical inequalities and the impact of a person's context on their health.

Geographic information systems and spatial analytical techniques can provide health researchers with a geographic foundation for mapping health information, analysing the risks, the spread and clustering of health events and offer a privileged understanding of health for policymakers (122).

The ability to integrate different sources of information that shape the occurrence of disease, for instance, environmental, genomic, social and demographic data, allows for a multilevel approach and helps to understand the underlying forces that shape disease patterns in the population (123). Studying the individual, social and environmental characteristics of communities is essential to recognise individual risk behaviours and social conditions, that differ from place to place, and helps to explain the uneven distribution of disease in the population (124).

Disease mapping is a key component of spatial analysis. Although numerous other techniques exist (125, 126), Bayesian spatial models have become a standard approach to disease mapping in recent decades. Bayesian spatial models borrow information from neighbouring areas resulting in the smoothing or shrinking of extreme values, which are common in small area-studies that deal with small population sizes. Besides, these models take into account the spatial autocorrelation controlling for residual spatial confounding which occurs when an important spatially correlated covariate is either unmeasured or unknown (127).

For all these reasons, GIS and spatial analysis can be useful tools to handle different public health questions and offer opportunities to enhance prevention and control of health-related problems, such as STIs.

OBJECTIVES

The main aim of the project is to describe the spatial epidemiology of the most common STIs in Portugal, namely chlamydia, gonorrhoea, and syphilis, between 2015 and 2017.

This broad objective is then divided into three specific objectives:

1. Estimate and map the spatial distribution of the notifications rates of chlamydia, gonorrhoea, and syphilis, at the municipality level, and assess if there is a spatial overlap among the studied STIs;
2. Delimitate high-risk and low-risk areas of STIs notification rates, at the municipality level;
3. Investigate the association between STIs notification rates, at the municipality level, and contextual characteristics, namely socioeconomic deprivation, urbanity level, and population density.

SCIENTIFIC PAPER

Mapping geographical patterns and high-risk areas for sexually transmitted infections in Portugal – a retrospective study based on the National Epidemiological Surveillance System.

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ABSTRACT

Objective: Monitoring disease variation using finer scales to identify high-risk communities is a critical aspect for precision public health and for efficient resource allocation. This study aimed to map the spatial patterns of chlamydia, gonorrhoea and syphilis, identify at-risk areas across Portuguese municipalities and determine the association of these sexually transmitted infections (STIs) with socioeconomic deprivation, urbanity level, and population density.

Methods: STIs notifications at municipality-level for the period 2015-2017 were obtained from Portugal's Epidemiologic Surveillance System (SINAVE). Spatial Bayesian models were used to calculate smoothed standardised notification rates, identify high- and low-risk areas and estimate associations (Relative Risk, RR, 95% Credible Intervals, 95%CrI).

Results: 4819 cases of chlamydia, gonorrhoea and syphilis were reported, accounting for 15.3%, 33.2%, and 51.5% of the notifications, respectively. STIs notification rates were substantially higher in Porto and Lisbon Metropolitan Areas and concentrically disperse around those. Notification rates of the three STIs were strongly correlated (r>0.8). Rates of gonorrhoea and syphilis were associated with population density (Q1-lowest density vs. Q5-highest RR=2.10 95%CrI 1.08-4.25 and RR=3.16 95%CrI 2.00-5.13). Notifications of chlamydia and syphilis increased with urbanity level (Q1-least urban vs. Q5-most RR=9.64, 95%CrI 1.73-93.59 and RR=1.92, 95%CrI 1.30-2.88). We also found that notification rates of gonorrhoea were associated with socioeconomic deprivation (Q1-least vs. Q5-most deprived RR=1.75, 95%CrI 1.07-2.88).

Conclusions: Wide spatial inequalities in STIs notification rates were observed, which were predominantly concentrated in the two metropolitan areas of the country. Our findings can help guide more targeted interventions to reduce STIs incidence.

Key-words: Gonorrhoea; chlamydia; syphilis; epidemiology; spatial analysis; geographical health inequalities; precision public health.

INTRODUCTION

Globally, sexually transmitted infections (STIs) are increasing and represent a threat to international public health. In 2016, 220.4 million new cases of curable bacterial STIs were estimated to occur annually among 15-49-year-olds worldwide. Chlamydia infections had the highest incidence (127.2 million), followed by gonorrhoea (86.9 million) and syphilis (6.3 million).[1] No signs of reduction were observed since 2012[2] which highlights the ubiquitous lack of progress in STIs management.

Usually, these STIs are asymptomatic and if left untreated may lead to severe complications on the reproductive and neonatal health or even become systemic. Long-term consequences, namely in women, might include ectopic pregnancies, infertility, and pregnancy complications. Untreated maternal infections promote mother-to-child transmission which leads to spontaneous abortion, stillbirth, prematurity, low birth-weight and congenital diseases.[3] Other well-recognised consequences are the increased risk of transmission and susceptibility to HIV[4], stigmatisation[5] and the economic impact of direct medical expenditures along with costs of lost productivity.[6]

Although the aforementioned STIs have effective treatment, their global burden remains high.[1] Thus, without belittling the importance of chlamydia infections, the World Health Organisation (WHO) included gonorrhoea and syphilis on their prioritising list to halt STIs epidemics.[7] Under the 2030 Agenda for Sustainable Development, the WHO's Global STIs Strategy established the goal of reducing by 90% the incidence of syphilis and gonorrhoea until 2030.[7] To ensure that this goal is met a collective effort from different nations is vital to understand STIs dynamics and establish targeted interventions to avert new infections.

Adaptation of targets and interventions to the local context is pivotal to effective country response to tackle STI occurrence. Although national estimates facilitate international comparisons, these cannot solve heterogeneity at the geographical level where public health actions usually take place. It is important to monitor disease variation using finer scales to identify clusters of cases and inequalities, which is a critical aspect for precision public health and for efficient resource allocation.[8] Indeed, spatial differences in STIs occurrence have been commonly seen between countries and regions worldwide.[1] And, even within countries, many studies identified clusters of STIs and a concentration of cases in socioeconomically deprived and highly populated areas, especially in urban settings.[9-12] Such evidence supports the need for bringing the geographical dimension to STIs epidemiological research.

In Portugal, recent official reports documented a substantial increase in the number of STIs cases being notified.[13] Despite this upsurge, there is a limited number of studies evaluating the epidemiology of these STIs and to our knowledge, none have investigated the spatial distribution and geographical determinants of these infections.

Therefore, the aim of the present investigation was to map the spatial distribution of the notification rates of the most common STIs in Portugal between 2015 and 2017, identify high-risk areas, and investigate the association between STIs notification rates and socioeconomic deprivation, urbanity level, and population density.

METHODS

Notifications of sexually transmitted infections

This retrospective study included data from Portugal's National Epidemiological Surveillance System, SINAVE (Sistema Nacional de Vigilância Epidemiológica), from 2015-2017. SINAVE is a real-time electronic platform used by public, private and social healthcare institutions in Portugal to collect data on communicable diseases and other public health risks.[14] Since 2015, Portugal's mandatory reporting of communicable diseases is required to be notified via SINAVE. As chlamydia, gonorrhoea, and syphilis infections are listed in Portugal's mandatory notifications, all cases notified from 1st January 2015 to 31st December 2017 were included in this study along with patients' sociodemographic, sexual behaviour, geographical and clinical variables. This 3-year period was selected because the prior form of notification (paper form) was based on a sluggish mail reporting system that could possibly lead to duplicated cases and overall lower data consistency.[15]

We analysed *Chlamydia trachomatis* infections by combining genital trachoma and lymphogranuloma venereum (LGV) biovars notifications since the number of LGV notifications were relatively low for separate analysis.

All notifications were geocoded according to the municipality of occurrence of the infection. In Portugal, in 2015, there were 308 municipalities in Portugal with an average population of 33575 (range 459–504471).

Covariates

To characterise the context of the STIs place of occurrence, the municipalities' socioeconomic deprivation, urbanity level and population density were used. Population density at the municipality level (inhabitants per squared kilometre) was obtained from the Portuguese National Institute of Statistics (INE). The population density was then categorised into quintiles, from quintile 1 (Q1) (least) to quintile 5 (Q5) (most populated).

Urbanity level was determined according to the classification of the urban areas, published by Statistics Portugal in 2014. This classification groups the Portuguese parishes (a smaller administrative unit than municipalities) into three classes: predominantly urban areas (PUA), moderately urban areas (MUA) and predominantly rural areas (PRA). As our unit of analysis was the municipality, we calculated the urbanity index (U.I.) of each municipality (i), as follows (equation 1).

$$U.I._{i} = \frac{1 \times \text{PUA population} + 0{,}5 \times \text{MUA population} + 0 \times \text{PRA population}}{\text{Total population}} \quad \text{(equation 1)}$$

where $U.I._i$ is the urbanity index of each municipality, where 1, 0.5 and 0 are weights, PUA population is the number of inhabitants of the municipality living in predominantly urban parishes, MUA population is the number of inhabitants living in moderately urban parishes, PRA population is the number of inhabitants living in predominantly rural parishes and Total population is the total number of inhabitants of the municipality. The urbanity index was then categorised into quintiles, from Q1 (least) to Q5 (most urban).

The European deprivation index (EDI) was used to classify the municipalities according to their level of socioeconomic deprivation. The EDI was constructed in three steps previously detailed.[16] In Portugal, the 2011 EDI resulted from the weighted sum of the following standardised variables: percentage of non-owned households; households without indoor flushing; households with five rooms or less (pantries, kitchens, corridors, bathrooms and balconies excluded); individuals with blue-collar (manual) occupations; individuals with low education level (≤6th grade); non-employers; unemployed looking for a job; and foreign residents. The index was categorised into quintiles, from Q1 (least) to Q5 (most deprived).

Statistical analysis

We used hierarchical Bayesian spatial models to estimate age-standardised notification rates at area-level, to delimitate high-risk and low-risk areas and to estimate associations with the covariates of interest. Hierarchical Bayesian spatial models borrow information from neighbouring areas resulting in the smoothing or shrinking of extreme values, which are common in small area-studies that deal with small population sizes. Besides, these models take into account the spatial autocorrelation controlling for residual spatial confounding which occurs when an important spatially correlated covariate is either unmeasured or unknown.

To guarantee that the geographic patterns and associations assessed were not driven by the different age and sex structures of Portuguese municipalities, notification rates were age-sex-standardised.

We assumed that the response variable, cases of STIs (O_i) in each ith municipality, follows a Poisson distribution where E_i is the expected number of cases and θ_i is the Standardised Notification Ratio (equation 2). We used the Portuguese STIs notification rates by sex and age as a reference to compute the expected number of cases, E_i.

$O_i \sim \text{Poisson}(E_i, \theta_i)$ (equation 2)

$\log(\theta_i) = \alpha + s_i$ (equation 3.1)

Here α is an intercept quantifying the average number of STIs cases in the 308 municipalities. The area-specific effect s_i was modelled considering a BYM model[17] with a parameterization suggested by Dean and colleagues[18] (equation 3.2.).

$s_i = \tau(\sqrt{\phi} * u_i + \sqrt{1-\phi} * v_i)$ (equation 3.2)

where u_i is the structured effect and v_i is the unstructured effect. The u_i effect was scaled in order to make the model more intuitive and interpretable,[19] so that ϕ expresses the proportion of the spatial effect due to the structured part and $1/\tau$ is the marginal variance of s_i.

Posterior distributions were obtained using the Integrated Nested Laplace Approximation (INLA), which was implemented in the R INLA library.[20]

Additionally, we used the function 'excursions' to delimitate high- and low-risk municipalities.[21-23] This method uses the posterior joint distribution computed from INLA and takes into account the dependence structure, allowing to accurately identify areas where the notification ratio is greater/smaller than 1 (i.e. greater/smaller than the national average).

To facilitate interpretation, standardised notification ratios were converted into rates per 100,000 inhabitants by multiplying the standardised notification ratios by the crude national notification rates.

Finally, the associations between STIs notifications and urbanity level, population density and socioeconomic deprivation, were estimated by extending the previous model, as follows (equation 3.3)

$$\log(\theta_i)=\alpha+ \beta x_i + s_i \qquad \text{(equation 3.3)}$$

Where βx_i is the effect of each covariate. Associations were expressed in relative risk (RR), which is the ratio between the STIs' risk of the covariate class and the risk of the reference class. For example, an RR of 1.10 in a certain covariate class means that the STIs' risk for that class was 10% higher than the risk in the reference class. An RR would be considered significantly higher or lower if its 95%CrIs did not include the value 1.

RESULTS

Table I presents the characteristics of patients. During the three years study period, a total of 4819 cases of chlamydia, gonorrhoea and syphilis were reported, accounting for 15.3%, 33.2%, and 51.5% of the notifications, respectively. From 2015 to 2017, there was an increase in the number of cases of STIs (1432, 1448, and 1939 cases). The highest increase (110%) was observed in chlamydia infections with 173, 201, and 363 cases during this time period. A 40% rise in gonorrhoea (468, 474, 656) and an increase of 16% in syphilis (791, 773, 920) was also registered.

For chlamydia, gonorrhoea and syphilis, most cases were seen in men – 66.1%, 88.8%, 75.1% – in Portuguese people – 85.2%, 85.9%, 89.3% - and were geographically concentrated in the Lisbon Metropolitan Area – 70.4%, 57.3%, 47.4%, respectively. The largest proportion of cases were among 25-34-year-olds for chlamydia, 15-24-year-olds for gonorrhoea and 45-64-year-olds for syphilis. The most common form of STI acquisition was by heterosexual contact. A 162% increase in chlamydia (50, 63, 131) notifications among homo/bisexual vs. a 94% increase (113, 122, 219) in heterosexual populations; 88% increase in gonorrhoea (137, 125, 257) vs. 15% increase (285, 299, 329); and a 27% increase in syphilis (294, 255, 373) vs. 16% increase (333, 336, 385) was observed. Only 2 and 4 homo/bisexual women with syphilis were identified in 2016 and 2017, respectively.

Nationwide crude notification rates were 2.4, 5.2 and 8.0/100,000 inhabitants for chlamydia, gonorrhoea and syphilis, respectively. Yet, substantial geographical differences were observed.

Figure 1 shows the spatial distribution of the age-standardised notification rates of each studied STI and the delimitation of the high and low-risk municipalities. The standardised chlamydia rates ranged from 2.10 to 201.16 notifications/100,000 inhabitants (Figure 1-A). The highest notifications rates were mainly observed in highly populated areas and surrounding neighbourhoods around Lisbon and Porto Metropolitan Areas and concentrically dispersed around those. There were 263 municipalities with rates below the national average (low-risk municipalities) and 9 above the national average (high-risk municipalities) – 3 located in Porto Metropolitan area and 6 in Lisbon Metropolitan area.

For gonorrhoea, rates ranged from 6.19 to 299.66 notifications/100,000 inhabitants (Figure 1-B). There were 3 municipalities with rates above the national average (high-risk areas) in Porto Metropolitan area and 7 in Lisbon Metropolitan Area. Nevertheless, most municipalities (n=233) were in low-risk areas.

Syphilis rates varied between 14.81 and 337.14 notifications/100,000 inhabitants (Figure 1-C). The highest notification rates were mainly concentrated along mainland Portugal's coast and metropolitan areas. There were 7 municipalities with rates above the national average (2 in the North region, including 1 located in Porto Metropolitan Area, and 6 in Lisbon Metropolitan Area), while 203 were low-risk municipalities.

The spatial patterns of the three STIs were significantly correlated. Standardized rates of chlamydia and gonorrhoea displayed a very strong relationship ($r=0.893$, $p<0.001$), followed by gonorrhoea and syphilis ($r=0.870$, $p<0.001$) and chlamydia and syphilis ($r=0.825$, $p<0.001$). Therefore, the high-risk areas overlapped among STIs.

Table 2 shows the relative risks (RR) for STIs notification according to quintiles of socioeconomic deprivation, urbanity, and population density. The notification rates of chlamydia and gonorrhoea appear to gradually increase with socioeconomic deprivation. However, a significant association was only observed for gonorrhoea: compared to the least deprived municipalities, notification rates of gonorrhoea were 75% higher in the most deprived municipalities (RR 1.75, 95%CrI 1.07-2.88).

The risk of chlamydia and syphilis infections seemed to monotonically increase with urbanity level. A significant association between urbanity and chlamydia infection was observed when comparing the least urban municipalities and those in the third (RR 6.65 95%CrI 1.18-65.47) and fifth quintiles of urbanity (RR 9.64, 95%CrI 1.73-93.59). For syphilis, compared to the least urban municipalities, the most urban areas presented a 92% higher notification rate (RR 1.92, 95%CrI 1.30-2.88).

Finally, notification rates of gonorrhoea and syphilis also increased with population density. The rates of syphilis increased linearly with population density (Q1-lowest density vs. Q2 RR 1.77 95%CrI 1.10-2.89; Q3 RR 1.91 95%CrI 1.21-3.10; Q4 RR 2.43 95%CrI 1.56-3.90; Q5-highest density 3.16 95%CrI 2.00-5.13). For gonorrhoea, a statistically significant association was only observed when comparing the extreme classes of population density: compared to the least dense areas, notification rates of gonorrhoea were 2.10 times higher (95%CrI: 1.08-4.25) in the municipalities with the highest population density.

DISCUSSION

In this study, we observed wide spatial inequalities in STIs notification rates across Portugal, which were predominantly concentrated in the two metropolitan areas of the country. Besides, contextual factors like socioeconomic deprivation, urbanity and, especially, population density, were associated with STIs notification rates.

Mapped notification rates showed a clear uneven distribution of STIs, which were especially concentrated in the Portuguese metropolitan areas and (to a lesser degree) along the coast. This is in accordance with studies conducted in other countries.[10 12 24] The spatial clustering of STIs in large urban settings results from complex human spatial interactions. Individual's sexual behaviours aligned with urban centres' physical and social environments can influence the occurrence of infection by modulating sexual partnerships.[25] Urban areas tend to be densely populated which promotes higher interactions between people and potentially increase the number of sexual partners in those networks. The establishment of core groups can potentially spread STIs through sexual bridges and easily reach groups outside the core areas.[26] Therefore, highly located patterns in large cities require special attention since they can act as reservoirs of disease.

The strong and consistent spatial overlap of high-risk areas among STIs indicates that common socio-geographic locations highly influence the risk of STIs acquisition, pinpointing vulnerability to local intervention and prevention strategies. It should be acknowledged that the absence of clusters in some municipalities should not be overlooked. This might have occurred due to underreporting of cases in those areas or due to mobile populations since geocoding was based on the place of acquired infection instead of the residential place.

Although the notification rates of these STIs were strongly correlated, we observed distinct associations according to specific contextual factors. The different biological characteristics of the STIs, namely their infectiousness, infectivity, duration of infection, and symptomatic nature might partially explain why associations varied among them.[12]

Patterson-Lomba *et al.* found a strong association for all three bacterial STIs and population density. STIs displayed increased incidence patterns in high population density in metropolitan areas with the largest increases observed in gonorrhoea and syphilis.[12] This is in line with our results since population density was strongly associated with syphilis' notification rates and also (although not so consistently) with gonorrhoea. The strong effect of population density in syphilis might be explained by its transmissible nature. Since syphilis's infectivity is lower compared to chlamydia and gonorrhoea, larger sexual networks might benefit to a higher extent syphilis occurrence.[12]

Similarly, we also observed a trend of increasing STIs notifications with increasing levels of urbanity, especially for chlamydia and syphilis. Research in the United Kingdom observed higher STIs concentration in urban settings.[10 11] In the Netherlands the degree of urbanisation was also found to be an important factor for chlamydia prevalence where highly urbanised areas presented higher prevalence compared to rural areas.[27] In our study, the differences observed might be related to increased screening opportunities in urban settings and rural-to-urban movement. Demographic and socioeconomic disparities among urban populations may also influence sexual behavioural risk factors.[28]

Regarding socioeconomic deprivation, most associations with STIs were weak or absent, in agreement with findings from other analyses.[9 29] Usually, socioeconomic disparities are highly correlated with racial/ethnic minorities, and after adjusting for socioeconomic factors the variations in STIs rates are attenuated suggesting that these groups require further attention.[9 11]

It is important to refer that there was an increase of 110%, 40% and 16% in chlamydia, gonorrhoea and syphilis notifications, respectively, during 2015-2017. The resurgence of STIs is concordant with reported trends in high-income countries.[30] The growing number of cases observed in Portugal could possibly be explained by the launch of the electronic support of SINAVE, in 2015, which improved Portugal's reporting system, along with same-sex sexual behaviour changes, namely among men. This raise might also be related to screening programmes targeting these subpopulations.

In this panorama of the increasing number of STIs cases, the present study contributes to better understand Portugal's geographical trends of STIs. Since this study included all individuals who have been notified in the Portuguese epidemiological surveillance system, a national picture of these infections was obtained. Although it might not include every person infected, the results allow the characterisation of Portuguese epidemiologic trends during 2015-2017. Additionally, this study contributed to establishing specific risk factors that might assist to explain differences in the studied STIs and target appropriate programmes towards certain sociodemographic groups and geographic areas.

Although this study brings novel information, some caveats must be discussed. It should be noted that Portugal does not have a routine screening activity implemented for curable bacterial STIs. Cases might not be included in the reporting system if people are reluctant to seek medical care or have difficulties obtaining healthcare provision, if individuals are asymptomatic or if healthcare is obtained outside the country. Therefore, the proportion of reported cases might be underestimated and the real STIs' incidence might be masked. Furthermore, it remains the possibility that the spatial discrepancies, namely in Azores and Madeira Islands, might be in part related to underreporting.[15] This might be clearer within the next few years since spatial-temporal tendencies cannot be assessed only based on three years.

Despite these limitations, we strongly believe that this work has noteworthy public health implications since the identification of high-risk geographical areas and vulnerable groups provides data about where prevention and control measures should be strengthened.

KEY MESSAGES

- STIs are mainly clustered in metropolitan areas.
- Geographical patterns of different STIs were strongly correlated.
- Associations of urbanity, deprivation and population density with STIs were observed.

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Ethics approval: This study was approved by the Ethics Committee of Instituto de Saúde Pública da Universidade do Porto [approval number (CE18103)].

Contributions: AIR and BG conceptualised the study. AIR and CJS managed the spatial data. AIR and CJS conducted the statistical analysis. CJS wrote the first draft of the manuscript. AIR and BG supervised the study and reviewed and edited the final version of the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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Table 1 – Demographic, social, clinical and behavioural characteristics of patients according to sexually transmitted infection (2015-2017, Portugal)

	Chlamydia		Gonorrhoea		Syphilis		
	n	%	n	%	n	%	p-value*
Sex							
Male	487	66.1	1419	88.8	1866	75.1	<0.001
Female	250	33.9	179	11.2	618	24.9	
Age group							
0-14	17	2.3	19	1.2	0	0.0	<0.001
15-19	74	10.0	209	13.1	92	3.7	
20-24	145	19.7	383	24.0	320	12.9	
25-34	293	39.8	544	34.0	617	24.8	
35-44	131	17.8	260	16.3	510	20.5	
45-64	74	10.0	157	9.8	702	28.3	
≥65	3	0.4	26	1.6	243	9.8	
Nationality							
Portuguese	628	85.2	1372	85.9	2217	89.3	0.001
Foreign	109	14.8	226	14.1	267	10.7	
Place of occurrence							
Porto Metropolitan Area (AMP)	127	17.2	314	19.6	462	18.6	<0.001
North (expect AMP)	24	3.3	126	7.9	289	11.6	
Centre	43	5.8	128	8.0	314	12.6	
Lisbon Metropolitan Area	519	70.4	915	57.3	1177	47.4	
Alentejo	12	1.6	55	3.4	75	3.0	
Algarve	7	0.9	49	3.1	71	2.9	
Azores	3	0.4	7	0.4	42	1.7	
Madeira	2	0.3	4	0.3	54	2.2	
Case							
Confirmed	694	94.2	1046	65.5	200	8.1	<0.001
Probable	6	0.8	65	4.1	2095	84.3	
Unknown	37	5.0	487	30.5	189	7.6	
Form of transmission							
Heterosexual	454	61.6	913	57.1	1050	42.4	<0.001
Homosexual/bisexual	244	33.1	519	32.5	922	37.1	
Vertical or Other	14	1.9	15	0.9	11	0.4	
Unknown	24	3.3	150	9.4	496	20.0	
Missing Values	1	0.1	1	0.1	3	0.1	
Contact with a sex worker?							
Yes	0	0.0	26	1.6	77	3.1	<0.001
No	14	1.9	500	31.3	646	26.0	
Unknown	9	1.2	583	36.5	910	36.6	
Missing Values	714	96.9	489	30.6	851	34.3	
Epidemiological link with a probable or confirmed case?							
Yes	163	22.1	258	16.1	419	16.9	0.003
No	105	14.2	254	15.9	381	15.3	
Unknown	466	63.2	1084	67.8	1683	67.8	
Missing Values	3	0.4	2	0.1	1	0.0	

Has the patient been informed about the risks of transmission of the disease and the possibility of having partners (or partners) infected?							
Yes	685	92.9	1464	91.6	2212	89.0	0.002
No	8	1.1	37	2.3	52	2.1	
Unknown	12	1.6	24	1.5	73	2.9	
Missing Values	32	4.3	73	4.6	147	5.9	
Does the patient take responsibility for contacting the partner and for a referral to medical consultation for screening?							
Yes	638	86.6	1250	78.2	1789	72.0	<0.001
No	25	3.4	104	6.5	179	7.2	
Unknown	39	5.3	166	10.4	353	14.2	
Missing Values	35	4.7	78	4.9	163	6.6	
The contacts (partners) were identified by the service?							
Yes	171	23.2	260	16.3	557	22.4	<0.001
No	233	31.6	852	53.3	1161	46.7	
Unknown	291	39.5	405	25.3	595	24.0	
Missing Values	42	5.7	81	5.1	171	6.9	
Contacts were forwarded to a medical appointment?							
Yes	149	20.2	184	11.5	472	19.0	<0.001
No	15	2.0	28	1.8	32	1.3	
Unknown	5	0.7	32	2.0	28	1.1	
Missing Values	568	77.1	1354	84.7	1952	78.6	
Does the patient consent to be contacted by the local health authorities for the tracing of contacts (partners)?							
Yes	64	8.7	325	20.3	560	22.5	<0.001
No	432	58.6	603	37.7	837	33.7	
Unknown	209	28.4	582	36.4	901	36.3	
Missing Values	32	4.3	88	5.5	186	7.5	

*Chi-square test

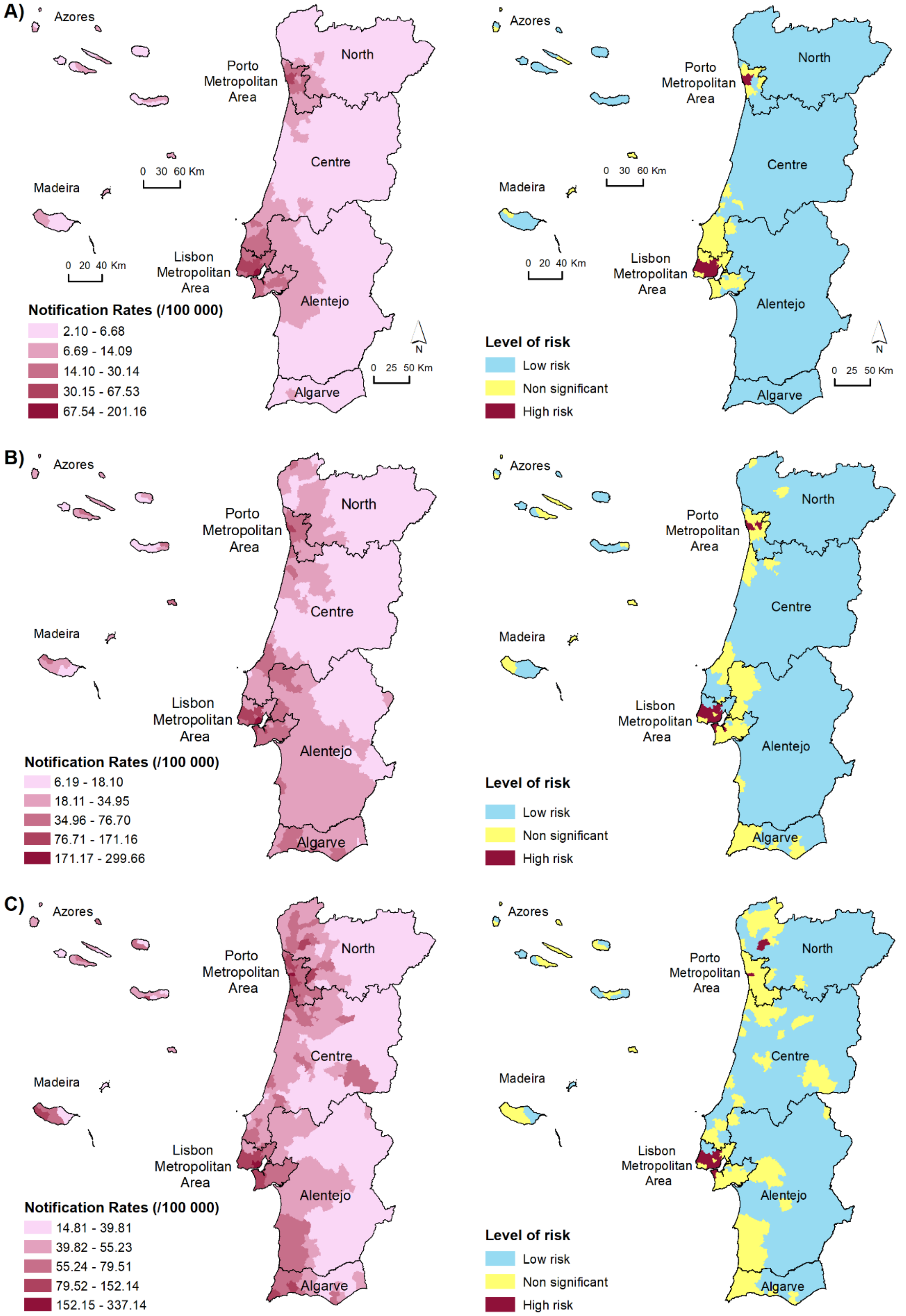

Figure 1 – Spatial distribution of the age-sex standardized notification rates (/100,000 inhabitants) and identification of high-risk municipalities for (A) chlamydia, (B) gonorrhoea and (C) syphilis (2015-2017, Portugal).

Table 2 – Associations (Relative Risk an 95% Credible Intervals) between notifications of sexually transmitted infection, socioeconomic deprivation, urbanity and population density (2015-2017, Portugal)

	Chlamydia	**Gonorrhoea**	**Syphilis**
Socioeconomic deprivation			
Q1-Least deprived	Ref	Ref	Ref
Q2	1.01 (0.49-2.07)	1.26 (0.82-1.94)	1.19 (0.90-1.57)
Q3	1.39 (0.68-2.85)	1.37 (0.88-2.16)	1.14 (0.85-1.54)
Q4	1.54 (0.76-3.18)	1.58 (1.00-2.51)	1.25 (0.92-1.70)
Q5-Most deprived	1.86 (0.88-3.97)	1.75 (1.07-2.88)	1.10 (0.78-1.54)
Urbanity			
Q1-Least urban	Ref	Ref	Ref
Q2	3.32 (0.50-37.40)	0.71 (0.36-1.42)	1.14 (0.74-1.77)
Q3	6.65 (1.18-65.47)	0.99 (0.56-1.81)	1.23 (0.83-1.84)
Q4	5.32 (0.96-51.56)	1.12 (0.65-1.99)	1.38 (0.95-2.04)
Q5- Most urban	9.64 (1.73-93.59)	1.65 (0.94-3.00)	1.92 (1.30-2.88)
Population density (inhabitants/km^2)			
Q1-Lowest density	Ref	Ref	Ref
Q2	0.43 (0.09-1.75)	1.24 (0.62-2.53)	1.77 (1.10-2.89)
Q3	0.68 (0.22-2.32)	1.44 (0.75-2.87)	1.91 (1.21-3.10)
Q4	1.46 (0.54-4.51)	1.60 (0.85-3.16)	2.43 (1.56-3.90)
Q5-Highest density	2.18 (0.79-6.83)	2.10 (1.08-4.25)	3.16 (2.00-5.13)

Discussion / Conclusion

The present study sought to map and characterise the spatial distribution of STIs, namely chlamydia, gonorrhoea, and syphilis, in Portugal, as well as evaluate the association of these infections with socioeconomic deprivation, urbanity level, and population density.

Research papers and reports suggest that STIs are not equally distributed in space (29, 128, 129). Likewise, our study found wide spatial inequalities in STIs notifications rates. The studied STIs were mainly concentrated in Lisbon and Porto Metropolitan Areas. In the US, high-rate clusters of chlamydia and gonorrhoea were also located in metropolitan counties (62). Moreover, studies conducted in the US, Canada and England, have also shown that STIs are concentrated in highly populated areas especially in urban settings (130-132). The establishment of geographical clusters of STIs (also known as core areas) arises because people tend to select sexual partners that are geographically closer to them (133). Therefore, densely populated urban areas might give appropriated settings for intertwined sexual networks. STIs' clusters may serve as reservoirs of disease and maintain these infections within communities which may eventually lead to the start of an epidemic (128, 134, 135). Hence, highly located patterns in large urban cities should be carefully analysed and target interventions should be implemented in order to reduce STIs morbidity.

However, there are some exceptions. In South China, South Africa, and in the US (Pennsylvania), rural areas were the most affected locations (67, 83, 130). Thus, the geographic distribution of STIs in Portuguese rural areas should not just be ignored. The absence of clusters in some municipalities might be due to underreporting of cases in those areas or due to mobile populations since geocoding was based on the place of acquired infection instead of the residential place. The presence of geographical heterogeneity in STIs incidence emphasises the importance of having geographical references in STIs surveillance system in order to plan and evaluate sexual health services (128, 133).

Furthermore, the strong spatial overlap of high-risk areas among STIs suggests that shared socio-geographic factors affect the spread of STIs. Therefore, intervention and prevention strategies may be combined to target multiple STIs effectively and make better use of financial resources. Some valuable approaches that could improve STIs morbidity patterns include: strengthening surveillance among subpopulations who are especially at risk of acquiring STIs, namely in the metropolitan areas; improve people's knowledge about their sexual health through education and counseling in healthcare services and schools; and promote safe sexual health behaviours, treatment and screening programmes, including the distribution of barrier contraceptives (136). These measures could possibly fight low levels of awareness of STIs within populations, reduce the associated stigma and, therefore, avoid long-term complications on the reproductive and neonatal health.

Our study also observed some differences in the association of STIs with distinct contextual factors, namely socioeconomic deprivation, urbanity level, and population density. The spread of STIs is prompted by inherent biological factors of each infectious pathogen and by individuals' sexual behaviours which are modulated by social, demographic, economic and cultural context (137). According to Geoff P. Garnett "The pattern of sexual contacts within the population is the same for each STI, but the ability of the infection to exploit these contacts will determine its distribution and depends upon its own biology." (137). Thus, it would be expected some differences between the association of contextual factors and the risk of acquiring a specific STI.

In our study, the population density was strongly associated with syphilis notification rates and also (although not so consistently) with gonorrhoea. This might be related to syphilis lower infectivity compared to the other bacterial STIs since larger sexual networks might benefit to a higher extent syphilis occurrence by increasing the rate of exposure to this infection (132). Densely populated urban areas along with economically driven migration from rural-to-urban settings and increased screening opportunities in urban areas might explain a trend of increasing STIs notifications with increasing levels of urbanity, especially for chlamydia and syphilis. In addition, demographic and socioeconomic disparities among urban populations may influence riskier sexual behaviours among urban core groups.

Finally, socioeconomic deprivation was not associated or was weakly associated with the STIs analysed. Usually, socioeconomic deprivation is highly correlated with racial/ethnic minorities (138, 139). Studies that adjusted for socioeconomic factors saw that the variations in STIs rates are attenuated suggesting that these groups require further attention (138, 140). For instance, reported gonorrhoea in the US affects more black Americans, American Indians, Alaska Natives, Native Hawaiians and other Pacific Islanders and Hispanic Americans (83). In Europe, the burden of STIs is also larger among foreign (and possible non-Caucasian) individuals (141). In Portugal, the proportion of ethnic minorities is relatively small and the distribution of relative socioeconomic deprivation levels are geographically homogeneous. These factors could possibly have attenuated the impact of socioeconomic deprivation in STIs occurrence.

The growing number of STIs cases observed in Portugal could also be explained by the launch of the digital support of the National Epidemiologic Surveillance System, SINAVE, in 2015. One-year after SINAVE's platform implementation, gonorrhoea and syphilis notifications had increased by 127% and 116%, respectively. However, the percentage change was deeply attenuated from 2015 to 2016, where there was a 1% increase in gonorrhoea and a 2% decrease in syphilis. Therefore, the sudden rise observed in 2015 might reflect the improved STIs case reporting instead of a real STIs aggravation. Nevertheless, between 2016 and 2017, the number of cases of gonorrhoea and syphilis increased again by 38% and 19%, respectively. This abrupt change is plausibly related with the integration of public and private laboratories in the electronic notification platform (SINAVE lab), from 1st January 2017, which meant that laboratories were also required to report communicable diseases. These results highlight the importance of improving countries surveillance system's structure in order to have a strong surveillance system and, therefore, have high-quality data that can mirror the country's context and evidence to act accordingly.

From 2015 to 2017, the rise of notifications per STI was distinct. Chlamydia infections had the highest increase (110%) followed by gonorrhoea (40%) and syphilis (16%). These discrepancies, namely in chlamydia, may reflect the period of time when these infections became mandatorily notified. Chlamydia notifications were not mandatory until 2015, which could possibly explain chlamydia sharpest increase compared to gonorrhoea and syphilis.

STIs notifications are influenced by a variety of factors such as public health funds and priorities, testing policies, reporting practices, and social awareness of STIs (38, 41). Furthermore, notifications patterns might be also influenced by differential access to healthcare provision and healthcare-seeking behaviours and even by the asymptomatic nature of STIs. In Portugal, there is no routine screening activity implemented for the STIs analysed. Therefore, the proportion of reported cases might be underestimated and the real STIs' incidence in the country might be masked.

In Portugal, surveillance data revealed that syphilis was the most common notified STI during the triennium. Lately, analyses conducted in Europe (142) and the US (29) have been observing increases in syphilis cases, especially among MSM. However, syphilis is not reported as the most notified STI within countries. Portugal's high number of syphilis might be possibly explained by other implemented screening programmes, namely HIV screening activities, that might detect these infections through combined screening (143) and also by overestimation in syphilis cases in older individuals (41). During syphilis's primary stage, the body produces specific antibodies against the *Treponema pallidum* bacteria. The serum concentration of treponemal antibodies remains high for a lifetime. Thus, one might expect to find more cases in older individuals especially if case finding relies on treponemal antibodies diagnoses. The observed number of reported syphilis tended to increase with age and cases were mainly diagnosed as probable. Portugal's known history of a high incidence of syphilis in the '60s and '70s explains the superior number of notifications in the 45-64 age group (41, 144). Furthermore, in Portugal, syphilis was mainly observed in men. In Europe and in the US, syphilis is mainly observed in MSM (29, 40). This group has been particularly studied since it has been verified an increasing diagnosis of STIs, compared with women and men who have sex with women only (31). Some of the reasons that might explain this trend are higher numbers of sexual partners, shorter gaps between partner change, and unsafe sexual behaviour possibly related with perceived low-risk among HIV seroconcordant men (31, 131, 141, 145). However, in Portugal, heterosexual men were still the group that presented most notifications of syphilis.

This might reflect different testing and reporting practices as well as distinct surveillance systems structures implemented in other countries (40).

Unlike the US (29) and Northern Europe countries, namely the United Kingdom (40), Portugal has the least reported notifications of chlamydia compared to the other STIs analysed. This might be explained by not systematic screening of infection. In addition, reported chlamydia infections were consistently higher among men than among women. However, most reported cases around Europe (38) typically display a higher proportion of women affected by this infection. This is probably explained by the asymptomatic nature of the infection, namely among women, and the consequent underreporting cases in Portugal along with differences in countries' screening recommendations towards women (38). In this study, the 25-34-year-old group showed the highest number of reported cases. Adolescents and young adults between 15-24 years are typically most affected by these infections (29, 38). Perceived stigma and possibly lower levels of sexual health education may act as a deterrent to further diagnosis of chlamydia infections in younger people in Portugal. Therefore, Portugal would greatly benefit from the implementation of more pronounced screening and educational programmes, especially among young people, since these infections are highly asymptomatic.

Gonorrhoea was especially prevalent in men and the most affected age-groups were consistent with reported notifications observed in European countries (36). The most common mode of transmission of gonorrhoea, in Portugal, was by heterosexual contact. However, MSM were particularly more affected by this infection in other European countries. These discrepancies might be related to different screening activities and testing practices, distinct access to medical care, different reporting practices and surveillance systems structures (36). A special concern with multi-drug resistant strains of gonorrhoea makes this infection a priority. This fairly easy treatable infection can become no longer curable if it continues to demonstrate high levels of resistance to the currently available treatment (146). Therefore, countries should monitor attentively the patterns of this infection.

Overall, STIs were found to be disproportionally concentrated among certain population groups. Those groups included men and typically younger adults. The increased number of cases of STIs, in men, can be possibly explained by increased transmission patterns, changes in reporting practices, improved screening case identification in men (31) or by the increased asymptomatic nature of STIs in women than in men. Although STIs can affect individuals of all ages, they are particularly more prevalent in adolescents and young adults for behavioural, biological, and cultural reasons. For instance, in the US, 63% of all reported chlamydia cases occurred in young people aged 15-24 years old. Moreover, half of the 20 million new STIs registered annually in the US were found in the same age group (31). Likewise, in Alberta (Canada), higher rates of reportable STIs are found in the 15-24 years old age group (147).

In this study, most people took the responsibility of contacting their partners and give them a referral to medical consultation. However, only a few people were in fact forwarded to a medical appointment which might contribute to the continuous spread of STIs in the community. In addition, people do not tend to agree with being contacted by the local authorities for tracing their partners. Epidemiologic investigation of these people's connections could be a useful tool for reducing repeated infections and, therefore, control STI dissemination as these curable STIs do not confer the host immunity to infection. Thus, if the transmission patterns within the sexual network are not broken down, reinfection with the infectious pathogen is probable and this may contribute to the persistence of infection within the population. For public health purposes, contact tracing should be encouraged in order to provide means for the identification of sexual networks and, in this way, detect the presence of core groups and provide appropriate diagnosis and treatment. Nevertheless, this approach gives rise to some controversy over the protection of individual's privacy and rights and the fundamental protection of public health interests.

In conclusion, this study revealed an uneven distribution of STIs notification rates across all 308 municipalities of Portugal. STIs were mainly clustered in metropolitan areas and were strongly correlated with each other. In addition, different associations between contextual factors and STIs were observed, probably determined by the social structure of sexual networks and the biology of the infectious pathogen. Future research should include additional individual-level risk factors including drug and alcohol consumption, race/ethnicity, previously diagnosed STIs and the connections between sexual networks.

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