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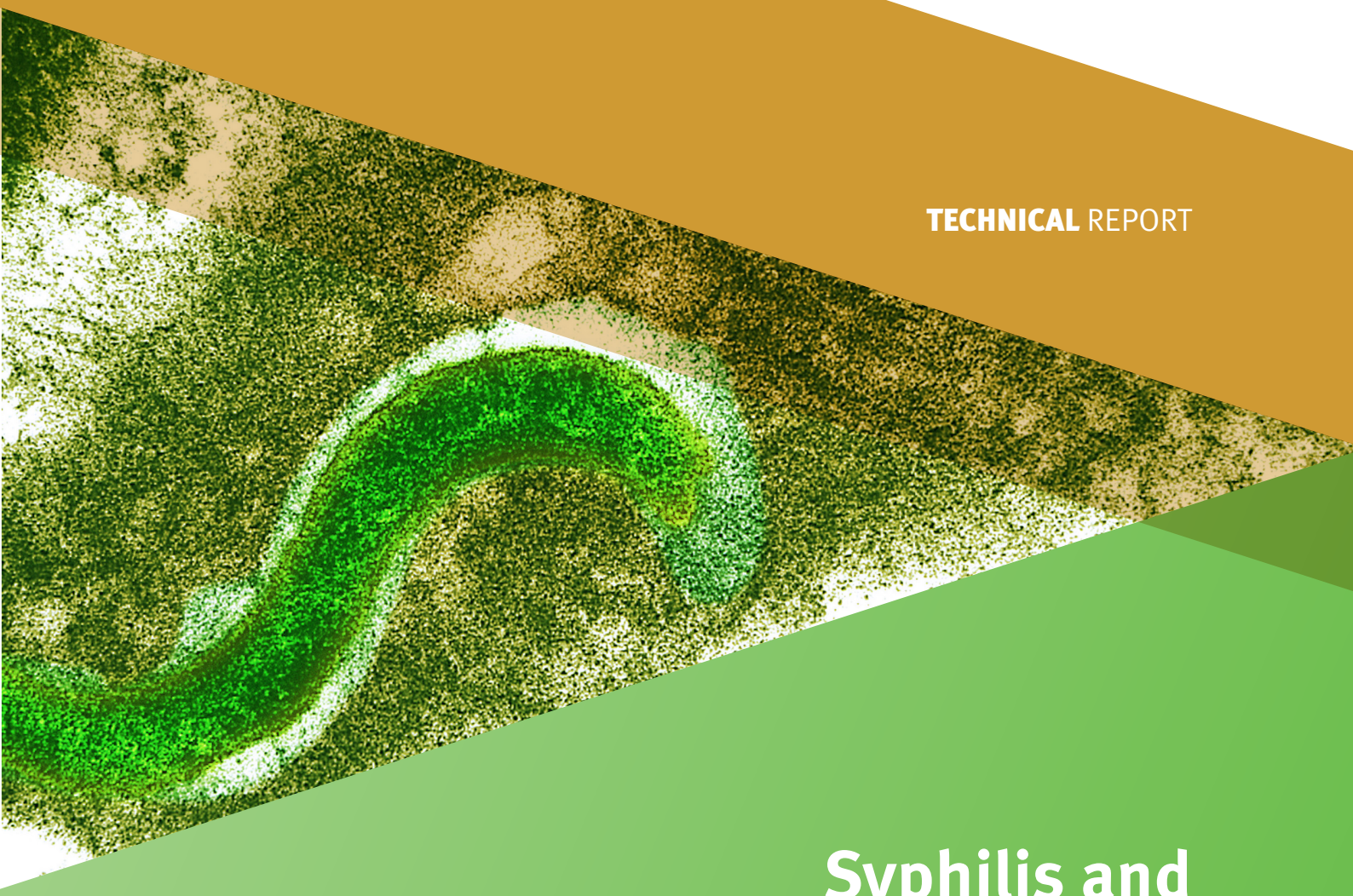

Syphilis and congenital syphilis in Europe

A review of epidemiological trends (2007–2018) and options for response

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A review of epidemiological trends (2007–2018) and options for response

This report was produced by Aitana Morano Vazquez, Otilia Mårdh, Gianfranco Spiteri and Andrew J Amato Gauci, of the European Centre for Disease Prevention and Control (ECDC).

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Abbreviations

IUSTI	International Union against Sexually Transmitted Infections
MSM	Men who have sex with men
PCR	Polymerase chain reaction
PICO	Population, intervention, comparator, outcome
PLWH	People living with HIV
PrEP	Pre-exposure prophylaxis for HIV
PMTCT	Prevention of mother-to-child transmission
PWID	People who inject drugs
NTT	Non-treponemal tests
LGBTQ	Lesbian, gay, bisexual, transgender and queer
TT	Treponemal tests
TESSy	The European Surveillance System
STI	Sexually transmitted infections
VDRL	Venereal Diseases Research Laboratory
TPHA	*Treponema pallidum* haemagglutination
TPPA	*Treponema pallidum* passive particle agglutination

Executive summary

Background and objectives

Since 2010, syphilis notification rates in the EU/EAA have been on the increase, but in recent years this trend seems to accelerate, predominantly among men having sex with men (MSM). Similar trends have been observed in high-income countries outside the EU/EAA. While the overall trend remained relatively stable, outbreaks or clusters of syphilis cases have also been reported among heterosexual populations in the EU/EEA. In several high-income countries (e.g. USA, Japan), increases in congenital syphilis occurred in connection with increases in syphilis notifications among women.

The diagnosis and treatment of syphilis are both accessible and cost effective. Left untreated, syphilis infection can cause severe health outcomes and facilitate transmission of HIV infection. Untreated syphilis infection during pregnancy can severely compromise pregnancy outcomes (foetal loss, stillbirth) and lead to congenital syphilis in the newborn.

In September 2018, the ECDC STI (sexually transmitted infections) coordination committee raised concerns about the increase of syphilis in the EU/EEA and asked ECDC to prepare an update on syphilis epidemiology, assess the current risk level, and indicate options for response.

Methods

A non-systematic literature review of several databases (PubMed, Embase and Scopus) for the period 2007–2018 was conducted to identify trends, describe recent outbreaks, and better understand the drivers of the rising syphilis epidemic. The review also aimed to describe case characteristics in the EU/EEA and other countries/settings relevant for the EU/EEA (candidate countries, high-income countries: Australia, Canada, Japan, New Zealand and the USA). This was combined with an analysis of EU/EEA surveillance data (2007–2017) on syphilis and congenital syphilis and a 2019 EU/EEA Member States survey about recent syphilis trends and changes in surveillance. The overall goal was to comprehensively describe the EU/EEA syphilis epidemiology.

In addition, a systematic literature review covering the same period and geographical area was performed to collect an evidence base that could inform options for response for syphilis outbreaks and increasing notification trends. The search was conducted in PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews and supplemented by Google and hand searches. A total of 189 studies identified through the non-systematic search on syphilis and congenital syphilis epidemiology and 78 studies reporting response interventions with a documented impact were used to inform this risk assessment. Responses to the ECDC survey were received from 28/31 Member States.

Results

Epidemiology

Over the last decade, EU/EEA and several other high-income countries observed by an increasing syphilis trend. MSM are the most affected population in the EU/EEA and account for an increasing proportion of cases. Lower case numbers were reported among heterosexual men and women, but in some countries, rates among heterosexual populations are on the increase. The increases in syphilis diagnoses among pregnant women that were reported in high-income settings outside of the EU/EEA, led to increases in congenital syphilis infections. Several syphilis outbreaks (n=25) and clusters of cases (n=4) – with a range of between 5 and more than 1000 cases – were reported in high-income countries over the last ten years. Most of these cases occurred in an urban environment and predominantly affected MSM.

The increases in syphilis infection among MSM have been associated with high rates of condomless sex, serosorting among HIV-positive MSM, a general increase in the number of sex partners in HIV-negative MSM, and the impact of pre-exposure prophylaxis (PrEP) for HIV on risk compensation. The use of social networking sites or mobile device applications to find sex partners were cited among the determining factors of outbreaks among MSM.

Factors reported in association with syphilis among various groups of heterosexual populations were: unprotected sex, multiple sex partners, substance use (drug or alcohol), history of incarceration, sex work, previous STI and several social vulnerabilities such as poverty, homelessness, ethnic minority, migrant or refugee status.

Factors associated with congenital syphilis were risk factors of the mother: high-risk sexual behaviour and/or drug use, history of incarceration, low income and younger age, east-European ethnicity, and factors related to the healthcare system capacity to identify and treat syphilis infection during pregnancy: no testing for syphilis during

antenatal care visits, inadequate or no treatment for positive pregnancies, and syphilis infection acquired after a first negative screening test.

Options for public health response

Any type of public health response directed at increases in syphilis infections and outbreaks needs to be informed by sound epidemiology data. In addition, response measures should be targeted to the affected population groups and take into account the main determinants of transmission.

Responses to syphilis outbreaks should be coordinated by a multi-disciplinary outbreak control team that may involve public health authorities, sexual health/STI clinicians, primary care services, antenatal services and teenage pregnancy and contraceptive services – depending on outbreak characteristics, allowing for combination interventions to be implemented. The involvement of community organisations, such as organisations offering sexual health services to MSM during outbreaks, will facilitate access to 'hard-to-reach' individuals and implementation of targeted responses. Interventions should be tailored to the phase of the outbreak/epidemic and the population affected.

In general, all activities considered in response to an outbreak or as part of a programmatic approach should include a combination of case management (where appropriate treatment is being given following the diagnosis), case finding and education. Further on, case finding includes, for example, screening of populations at risk, partner notifications and surveillance activities. Educational activities are directed at the general population, at populations at risk, and at healthcare providers.

If disease trends are on the increase or an outbreak was reported, the following interventions may be considered:

- Enhanced screening of populations at risk in order to increase detection of early asymptomatic syphilis infections: inclusion of syphilis testing in the routine HIV clinical monitoring for HIV-positive MSM, quarterly testing of the HIV-negative MSM engaging in high risk sexual practices (i.e. MSM under PrEP, MSM with a high number of sex partners, MSM with prior syphilis diagnosis), routine testing of STI clinic attendees. Testing of other risk groups (e.g. ethnic minorities, marginalised populations, sex workers, people who inject drugs (PWID)) should be informed by local syphilis epidemiology.
- Expanded testing in outreach venues in order to increase syphilis detection among populations at risk that do not regularly attend traditional healthcare settings. Testing of MSM in venues where they meet for sex can be considered, especially during outbreaks. Links to healthcare services for the verification of positive screening tests, reporting, treatment, and follow-up is important.
- Appropriate and effective partner management services in settings that see a high number of cases; notifying and locating contacts could be supported with alternative tools for (e.g. internet-location services, online tools, smartphone applications, Facebook).
- Educational, health-promotion and awareness-raising activities directed at the general population and/or subpopulations at high risk, depending on the local epidemiology. Social media platforms (e.g. Facebook, Twitter, YouTube, Instagram and dating apps) may be effective in reaching adolescents, young adults and MSM in order to improve knowledge of syphilis testing and thus increase testing uptake. Evaluation of education campaigns outcomes is recommended because of mixed impact reported.
- Education of healthcare providers is important to maintain a suitable level of knowledge and awareness that will facilitate early recognition of symptoms and atypical presentations; this should have a positive impact on syphilis testing and case detection.

Based on public health practice in those EU/EEA Member States that responded to the ECDC syphilis survey, several other interventions may be considered in response to the growing number of syphilis infections and outbreaks:

- Implementation of a national STI strategy, either stand-alone or as part of a larger sexual health or HIV/STI strategy. Such a strategy is an important element as it will ensure the commitment of various stakeholders and the allocation of resources (trained staff, contingency budget for outbreak activities).
- Development of national syphilis action plans and enhanced surveillance activities.
- Increased emphasis on sexual education in schools, shifting the focus from HIV to *HIV and STI*.
- Increasing the number of 'checkpoints' for low-threshold testing in major cities, mostly targeting MSM.
- Communication on increases in syphilis infections in epidemiological bulletins.

Congenital syphilis levels in the EU/EEA have been consistently low. In order to sustain these low rates, effective national antenatal screening programmes are needed, together with interventions to control syphilis transmission among heterosexual populations. The main instruments for prevention of vertical transmission of syphilis include the following measures:

- Universal offer of early prenatal syphilis screening (during the first trimester of pregnancy) together with treatment appropriate to the stage of maternal infection before 28 weeks of gestation

- Re-testing of pregnant women at high risk of acquiring syphilis infection during the third trimester of pregnancy (between 28–32 weeks gestation); countries should identify nationally relevant high-risk groups based on local epidemiology.
- Testing of all women at delivery if they have not been tested before.
- Collecting surveillance data that link syphilis-infected pregnant women to their birth outcomes can identify gaps in prevention and inform targeted interventions.
- Congenital syphilis prevention interventions may include: public education campaigns, healthcare provider education/training on screening and treatment recommendations, ensuring availability of benzathine penicillin G for treatment of pregnant women, etc.
- Increased harmonisation of case definitions across the EU/EEA Member States and inclusion of adverse pregnancy outcomes would allow for a more complete estimation of the disease burden with regard to the mother-to-child transmission of syphilis.

Background

1.1 Background

Since 2010, the rates of syphilis infection in the EU/EEA have increased substantially [1]. This increase has mainly been driven by cases reported among men, specifically among men who have sex with men (MSM). Trends among heterosexual men and women, on the other hand, appear stable although there was a slight increase in the number of reported cases among both groups in 2016. In addition, outbreaks of syphilis infections have been reported in several European countries, affecting both MSM and heterosexuals [2-4]. Similar outbreaks have been reported in recent years from other high-income countries worldwide [5-8].

Congenital syphilis rates in the EU/EEA have been decreasing since 2005 [9]. During this time, rates of syphilis among women have decreased consistently in the EU/EEA, particularly in eastern Europe, contributing to the reduction of the risk of mother-to-child transmission of syphilis. Despite this, underreporting of congenital syphilis is likely in several Member States of the EU/EEA and syphilis rates among women have been increasing in some western EU/EEA countries [10]. According to a 2013 ECDC survey, the majority of EU/EEA countries implement antenatal syphilis screening, including testing for syphilis during the first trimester of pregnancy [11]. The most common antenatal screening strategy for syphilis was an opt-out strategy, followed by universal screening. Survey respondents identified a remaining risk of vertical transmission of syphilis among some vulnerable populations (e.g. women presenting late for antenatal care, migrant women, women engaging in high-risk sexual behaviours or with partners at risk for sexually transmitted infections (STI).

At the ECDC STI Disease Network Coordination Committee meeting held on 5 September 2018, several Committee members and the observers from WHO, CDC and International Union against Sexually Transmitted Infections (IUSTI)-Europe raised their concerns regarding the increasing problem of syphilis in the EU/EEA. ECDC was asked, as a first step, to prepare a risk assessment before considering further actions.

The objective of this report is to describe the epidemiology (including recent disease trends) of syphilis and congenital syphilis in EU/EEA countries from 2007 to 2018 and to formulate options for a suitable response.

1.2. Disease background

Syphilis is a systemic human disease caused by the spirochaete *Treponema pallidum* subspecies *pallidum* [12,13]. This disease is usually acquired by sexual contact, with the exception of congenital syphilis, where the infant acquires the infection by transplacental transmission. Transmission via blood products and organ donation has been also reported [13].

Syphilis infection evolves through stages termed primary, secondary, and tertiary. Primary infection is characterised by a lesion, the chancre, at the original site of infection, which and can occur 10 to 90 days after exposure (usually by sexual contact). Primary syphilitic chancres most frequently occur in genital areas, but other parts of the body may also be affected (e.g. rectum, tongue, pharynx, breast, etc.). Often, chancres may go unnoticed if not visible, for example in women or among MSM with rectal lesions. Two to three months after the onset of chancre, the untreated infection will progress to the secondary stage with multisystem involvement due to bacteriaemia. A non-itching skin rash (involving palms and soles) and/or mucocutaneous lesions will be present in 90% of cases. In some cases, other dermatologic manifestations (annular lesions, alopecia, mucosal lesions) may occur. Systemic symptoms (fever, malaise, swollen lymph nodes) may also be observed in the secondary stage. A period of latency, with absence of clinical symptoms but with serological evidence of treponemal infection will follow in the untreated persons. When the duration of infection is less than one year, this is termed early latent syphilis and late latent syphilis when disease duration is more than one year. Late manifestations of syphilis, or tertiary syphilis can occur 10 to 30 years after the initial onset and can include variable clinical syndromes grouped as: neurosyphilis, cardiovascular syphilis, and late benign syphilis. In pre-antibiotic era, tertiary syphilis occurred in about 30% of the untreated infections. HIV infection does not lead to more severe early syphilis symptoms [14] although atypical presentations are more frequent and serological markers decline more slowly following treatment [15,16].

Transmission of syphilis by sexual contact is most likely to occur within the first year or two of infection, with the highest risk of transmission in primary and secondary syphilis and lower risk during early latent syphilis [13].

T. pallidum can be transmitted from the bloodstream of an infected woman to her foetus at any time during pregnancy, although the risk of foetal infection is much higher during early maternal syphilis (the first year of infection) than during later stages [17]. Antibiotic treatment of the mother during the first two trimesters is usually sufficient to prevent negative outcomes, while later treatment or lack of treatment may result in foetal death, foetal morbidity, or birth of infected infant [18]. Congenital syphilis can present with early manifestations in the first two years of life as well as late manifestations appearing after two years, and residual stigmata [19].

European guidelines recommend that diagnostic testing for syphilis should be performed for all pregnant women (regardless of perceived risk) and people donating blood, blood products, or solid organs. Testing should be offered to specific groups at higher risk of syphilis such as all patients newly diagnosed with STI, persons with HIV, patients with hepatitis B or C, patients with suspected early neurosyphilis and patients who engage in sexual behaviour that places them at higher risk (e.g. MSM, sex workers and all those individuals at higher risk of acquiring STIs). Screening tests should also be offered to all attendees at dermato-venereology/genitourinary medicine clinics [14].

Diagnosis of syphilis can be made directly, for example through polymerase chain reaction (PCR) testing of primary lesions or using dark field microscopy, or indirectly, through serologic testing [14,20,21]. There are two types of serologic tests for syphilis: non-treponemal tests (e.g. Venereal Diseases Research Laboratory test (VDRL)) and treponemal tests (e.g. *T. pallidum* haemagglutination test (TPHA), *T. pallidum* passive particle agglutination test (TPPA)). Non-treponemal tests have a high sensitivity in the secondary and early latent stages, become positive 10–15 days after the appearance of the primary chancre (so have low sensitivity early in primary syphilis), and in the absence of treatment reach a peak after 1–2 years and remain positive at low titres in late stage disease and therefore have lower sensitivity for late syphilis. Non-treponemal tests can become negative after successful treatment and are used to monitor effectiveness of treatment. Treponemal tests become positive 1–2 weeks after appearance of the chancre and vary in their sensitivity in early primary syphilis. They have high sensitivity in secondary, early latent and late latent stages and remain positive for life in most patients. They are thus not useful for monitoring effectiveness of treatment or disease activity. Diagnosis is usually through the use of different combinations of treponemal and non-treponemal tests as screening and confirmatory tests [14,22]. A variety of rapid point-of-care serologic tests for syphilis have been developed which allow for greater access to syphilis screening; the European syphilis guideline, however, does not currently recommend their use in Europe when laboratory diagnostics are available [14,23-26].

Benzathine penicillin is the first line recommended treatment for syphilis. During 2014–2016, over 40 countries globally reported shortages in benzathine penicillin. Among countries surveyed, shortages were reported in a number of EU and other high-income countries, including Australia, Canada, Croatia, Germany, Greece, the Netherlands, Switzerland and the United States [27]. The recommended first line treatment for early syphilis (including primary, secondary, and early latent syphilis), is benzathine penicillin G 2.4 million units once intramuscularly [14,28,29]. For late latent syphilis (i.e. acquired >1 year previously or of unknown duration), cardiovascular, and gummatous syphilis the recommended first line therapy is benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks; for neurosyphilis, ocular and auricular syphilis, benzyl penicillin 18–24 million units IV daily, as 3–4 million units every 4 hours, for 10 to 14 days is recommended [14,28,29]. Pregnant women should be treated with the first-line therapy option appropriate for the stage of syphilis. Second line therapy options and treatment of persons with penicillin allergy are described in treatment guidelines [14,28,29]. Treatment regimens are identical for HIV-positive individuals. No vaccine is available against syphilis infection.

1. Methods

The epidemiology of syphilis infections in the EU/EEA was described through an analysis of EU/EEA syphilis surveillance data supplemented by a literature review of syphilis epidemiology in EU/EEA and other high-income countries. In addition, options for response to increasing trends and outbreaks were identified through a systematic literature review. A survey in EU/EEA Member States helped to identify models of practice and fill in a number of knowledge gaps.

1.1 Surveillance data

This analysis was based on surveillance data from 2007 to 2017, retrieved from The European Surveillance System (TESSy) in March 2019. TESSy is the official EU system for the collection, analysis and dissemination of data on communicable diseases and is described elsewhere [1].

Twenty-eight countries reported syphilis data for 2017 to TESSy. The majority (18) reported data using the standard EU case definitions [30], five countries reported using national case definitions, and five countries did not state which case definition was used. Most countries (25) have comprehensive surveillance systems. Three (Belgium, France and the Netherlands) have sentinel systems that only capture syphilis diagnoses from a selection of healthcare providers. Reporting of syphilis infection is compulsory in 24 countries, voluntary in three (all with sentinel systems); syphilis-reporting requirements in the United Kingdom are categorised as 'other'.

For congenital syphilis, the majority of countries (18) reported data using the standard EU case definition [30]. The remaining five countries reported either using national case definitions or did not specify the used case definition. The EU congenital syphilis case definition refers to infants under two years of age and defines confirmed cases as those meeting laboratory criteria for confirmation and probable cases as those with clinical features and either an epidemiological link or having laboratory criteria for probable cases. The case definition does not include other adverse pregnancy outcomes (such as abortion, stillbirth, foetal death). All reporting countries have comprehensive surveillance systems. Reporting of congenital syphilis infection is compulsory in all countries except for the United Kingdom [31].

In the analysis, data from sentinel systems were not included in the calculation of national or overall rates because their population coverage was not always well defined and their denominators were therefore not available. Although the EU/EEA syphilis case definition specifies that cases of late latent syphilis are not under surveillance, some countries report cases of late latent syphilis infection. All reported cases of syphilis are included in the analysis below, which for some countries might therefore also include cases of non-infectious syphilis. It was not possible to exclude cases of late latent syphilis for some countries because they did not provide information on the stage of infection.

Available surveillance data in the European Surveillance System for EU/EEA countries were analysed to determine trends of syphilis by country, gender, age (age groups 0–14, 15–19, 20–24, 25–34, and ≥ 35 years), sexual orientation, syphilis stage and HIV status. Reporting rates of syphilis were calculated per 100 000 persons for countries with comprehensive surveillance systems and that consistently reported data. Reporting rates for congenital syphilis were calculated per 100 000 live births. Population data were retrieved from official Eurostat statistics.

A descriptive analysis of trends was conducted for countries with longitudinal data, including countries with both comprehensive and sentinel surveillance systems. Due to variations in the case definitions, data coverage, completeness and representativeness, comparisons between countries should be made with caution.

1.2 Literature review

To obtain a better understanding of the epidemiology and dynamics of the observed trends in syphilis diagnoses and possible options for response, two literature searches were conducted; four research questions were formulated (see below). The first review focused on the epidemiology of syphilis in EU/EEA countries and countries/settings relevant for the EU/EEA (candidate countries, high-income countries: Australia, Canada, Japan, New Zealand and USA) (e.g. number of cases, rates, trends and main characteristics of cases); the second review was a systematic review focusing on options for syphilis control (e.g. interventions conducted by countries, optimal interventions in risk groups, interventions to strengthen antenatal screening programmes). Identifying treatment options was outside the scope of this review as evidence-based clinical guidelines already exist.

1.2.1 Literature review on syphilis epidemiology

A non-systematic literature review [32] was conducted to help to identify trends, describe recent outbreaks and better understand the rising syphilis epidemic in European and other countries/settings that are relevant for the

EU/EEA (e.g. candidate countries, high-income countries: Australia, Canada, Japan, New Zealand and USA).
A medical librarian, with input from the authors developed a search strategy using the thesaurus search terms (i.e. syphilis, syphilis congenital), synonyms and equivalent text words. Broader topics were mapped out using prior references in the existing literature and other equivalent medical terms.

Excluding studies from the literature search results

Searches were not restricted by study design, population, language, location or publication status. Three electronic resources were searched from 1 January 2007 to 31 October 2018, including PubMed, Embase and Scopus.

The submitted search strategies combined the concepts of syphilis and congenital syphilis with surveillance and outbreak. Controlled vocabulary (i.e. MeSH and Emtree terms) and natural vocabulary (i.e. keywords) in multiple field search combinations were used to represent the concepts in the search strategies. Search strategies are available in Annex 2.

The results of each applied filter can also be consulted in Annex 2.

The literature search in PubMed, Scopus and Embase produced 14 941 results. Results included a large number of overlapping citations so one of the authors removed all duplicates and merged the retrieved studies into a combined database of 8 299 studies.

Study pre-selection based on geographical settings

A geographical filter was applied to the 8 299 remaining studies. The following geographical criteria were applied:

- All 28 EU Member States, EEA/EFTA (Norway, Iceland, Liechtenstein and Switzerland) and candidate countries (Albania, Montenegro, Serbia, former Yugoslav Republic of Macedonia, and Turkey).
- Canada, USA, Japan, Australia, and New Zealand
- Capital cities, regions, capital regions and cities >15 000 habitants of the countries mentioned above

A first exclusion round was done by review of the title and a second exclusion round by reading the abstract. Titles or abstracts that were not relevant to the objective or that did not fit in the inclusive geographical criteria were excluded. Following the application of this geographical criteria, 3 609 studies were excluded, leaving 4 690 studies.

Content selection criteria

The following exclusion criteria were applied to the remaining 4 690 reports, according to the appropriateness of the subject and content:

- Reports or articles related to non-humans
- Case report articles
- Reports focussing solely on the clinical aspects of syphilis (signs and symptoms)
- Reports focused on laboratory settings and tests (diagnostic techniques, new methodologies, technical advances, etc.)
- Historical articles or articles related to the history of syphilis prior to 2007 (including paleopathology publications)
- Outbreak reports or study results prior to 2007
- Studies related to social determinants without referring to syphilis increases or outbreaks
- Reports focused on other diseases as the main subject
- Reports based on cost-effectiveness analysis as the main subject
- Reports based on screening programme implementation without quantitative results

A first exclusion round was done by reviewing the title and a second exclusion round by reading the abstract. Following the application of these subject content criteria, 4 425 studies were eliminated, leaving 265 studies for full text review. A separate EndNote library was built for studies on social determinants; these nine studies were included in the results chapter.

Of the 265 studies selected for full text review, articles which were not in English, Spanish, Italian, Portuguese or French were excluded. Full-text articles were not available for 19 studies. After applying the subject content inclusion criteria, a further 57 articles were excluded. In total, 76 studies were excluded, leaving 189 studies for in-depth review by two of the authors.

1.2.2 Systematic review on options for response

A systematic literature review was conducted to identify interventions that were used to respond to outbreaks or increases in syphilis notifications in EU/EEA Member States or in countries/settings relevant for the EU/EEA (e.g. candidate countries, high-income countries: Australia, Canada, Japan, New Zealand and the USA). Two research questions (see below) were developed based on the PICO model.

Table 1. Population, intervention, comparison and outcome (PICO) for responses to outbreaks or increases in syphilis and congenital syphilis cases

PICO – Responses to outbreaks or increases in syphilis and congenital syphilis cases	
Population	All populations
Intervention	• National/regional responses to increases in syphilis notifications (defined as outbreak, cluster, epidemic, resurgence, re-emergence) • National/regional responses to reports of congenital syphilis
Comparator	No interventions or baseline prevention
Outcomes	• End of an outbreak or control of transmission or reduction of cases or other reported indicators • Prevention of congenital syphilis/vertical transmission

The search strategy was developed by a medical librarian, with input from the authors and combined the concepts of syphilis, outbreaks, trends, and interventions. Controlled vocabulary (i.e. MeSH and Emtree terms) and natural vocabulary (i.e. keywords) in multiple field search combinations were used to represent the concepts in the search strategies. Search strategies were developed for PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews (CDSR) (see Annex 2). Supplementary Google searches were conducted to retrieve public health and clinical guidelines and recommendations. No language restrictions were applied; the literature was retrieved from January 2007 onwards.

A total of 6 217 citations were retrieved from electronic databases, with an additional 30 references through Google and hand searches on 10 December and 14 December 2018 and transferred into an EndNote library. On 14 December, automatic email updates were set up in all these databases to continue receiving new results from the designed searches. These alerts were monitored until 28 February 2019 and led to the identification of 125 additional citations. After removal of duplicates, 3 936 original research articles were retained for title and abstract screening.

1.2.3 Study selection strategy

The title and abstract screening was performed by two authors; discrepancies were solved through discussion.

The following inclusion criteria were applied:

- Studies reporting on interventions to respond to outbreaks or increased case numbers of syphilis
- Studies reporting on interventions to respond to outbreaks or increased case numbers of STIs in general (if relevant for syphilis, e.g. bacterial STIs)
- Studies reporting on interventions to respond to increases in congenital syphilis cases
- Studies from EU/EEA Member States or other settings relevant for the EU/EEA such as the USA, Australia, Canada, New Zeeland, Japan. Exception: studies focussing on subpopulations (e.g. indigenous populations) not relevant for the EU/EEA.

Studies were excluded if:

- the intervention was only mentioned in the authors recommendations;
- the impact of interventions was not sufficiently described;
- the epidemiological context was not relevant (neither outbreak nor increases in case numbers);
- the study design was not relevant: case studies/clinical reports, audits of practice, or evaluation of guidelines.

Conference abstracts were included if the interventions and their outcomes were comprehensively reported.

Following the application of these criteria, 159 studies were retained for full-text review (conducted by one author), and 78 were accepted for data extraction and synthesis for both syphilis and congenital syphilis responses. The following variables were extracted and saved in an Excel worksheet:

1. Reference
2. Year of publication
3. Journal
4. Type of publication
5. Title
6. Country
7. Background event (outbreak/increasing trend/re-emergence/resurgence, other)
8. Intervention
9. Population targeted
10. Aim of intervention

11. Outcome
12. Services involved
13. Impact indicators
14. Type of study

Summary tables were created separately for congenital syphilis and for syphilis among adults. The latter were further separated in: 1) studies reporting on single interventions and 2) outbreak management studies reporting outcomes of multiple interventions. Single interventions studies were grouped in several categories by type of intervention: screening, outreach testing, partner notification, education, interventions using social media tools, and biomedical interventions. Public health and clinical guidelines from international organisations (e.g. WHO, ECDC, IUSTI) or national authorities identified through the search (and available in English) were presented for each intervention category. The most recent edition of a guidance document was considered and cited if the search identified several versions that were published during the specified search period. The final guidance document was preferred when both the guidance and the evidence review that informed the guidance were available.

References cited in narrative reviews or systematic literature reviews were checked to identify original studies not retrieved by this search.

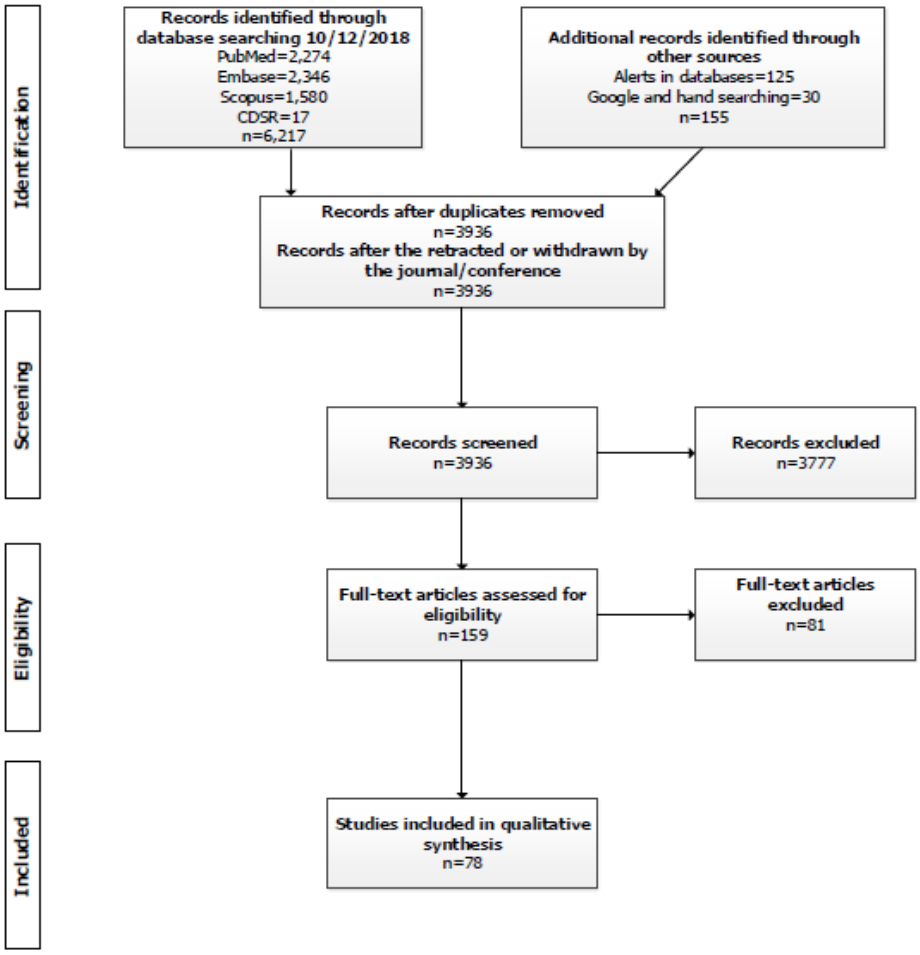
The quality of the evidence of individual studies was graded based on study design and availability of full-text article (as opposed to a conference abstract) as follows:

- High: randomised controlled trial (RCT), article in full text
- Moderate: non-randomised controlled trial (quasi-experimental), cohort studies, case-control studies, cross-sectional studies with comparison pre- vs. post-intervention; article in full text
- Low: surveillance studies, outbreak management studies if reported in full-text article; any of the study designs if reported in a conference abstract.

For guidelines, the quality of evidence and the strength of recommendation was presented as assessed by the authors/publishing organisation.

Due to the heterogeneous nature of the interventions, differences in aims, and diversity in impact measurements, data were not pooled. A narrative synthesis of the studies was produced by category of intervention.

Figure 1. Flowchart of papers included in the review of options for response to outbreaks or increases in syphilis, in Europe (cumulative for Q1 and Q2)



1.3 Surveys among Member State experts

A brief survey of STI experts from each of the EU/EEA Member States that make up the ECDC STI disease network was carried out between 14 November 2018 and 31 December 2018. The main aim of the survey was to investigate if there were increases in syphilis and congenital syphilis reports in EU/EEA Member States in 2018, collect information on any changes in syphilis surveillance in Member States which might affect reported rates of infection in recent years, and to collect information on planned or implemented measures in response to the syphilis epidemic. The questionnaire is available in Annex 3.

2 Results

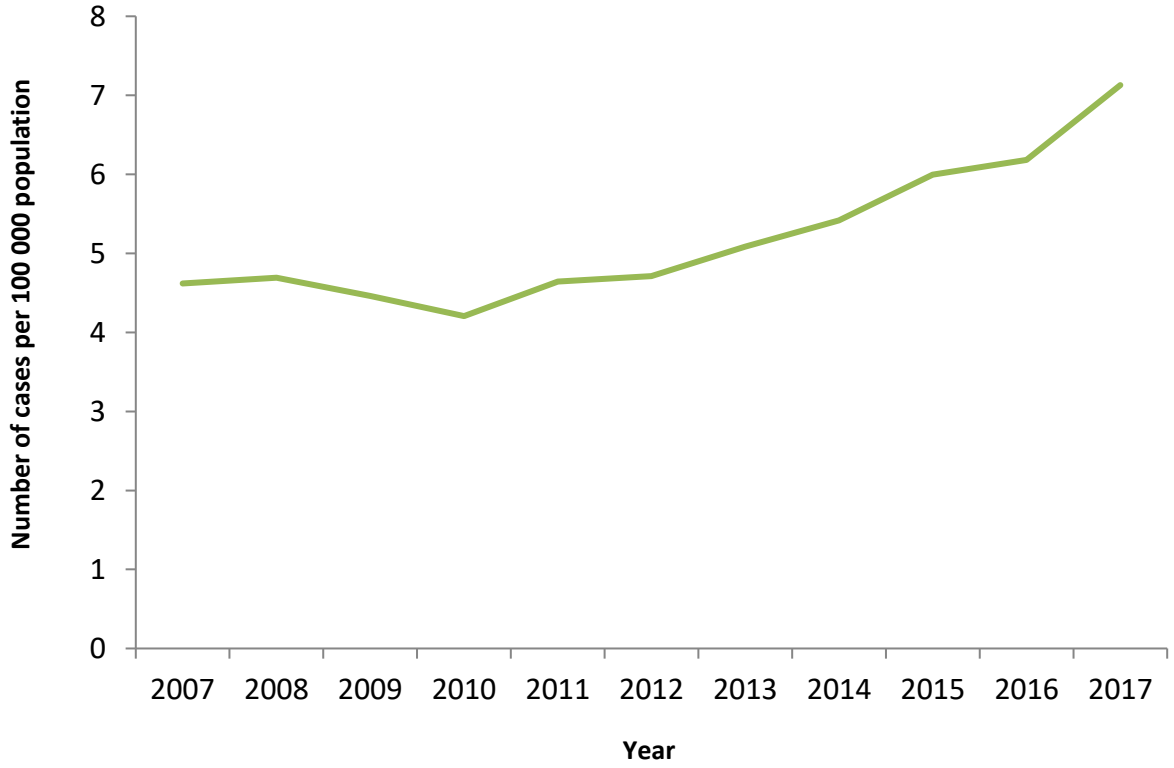
2.1 Surveillance data analysis

During the period 2007–2017, 260 505 confirmed syphilis cases were reported from 30 EU/EEA countries. Liechtenstein did not report syphilis data during this time, Austria reported data until 2013, Croatia reported data from 2012, whereas Greece reported data for all years except 2017. The number of reported cases decreased from 19 898 cases in 2007 to a low of 18 829 cases in 2010, before increasing continuously to 33 193 cases in 2017.

Among 23 countries with comprehensive surveillance systems reporting consistently between 2007 and 2017, the syphilis notification rate in the EU/EEA was stable in 2007 (4.6) and 2008 (4.7) before decreasing to a minimum of 4.2 per 100 000 persons in 2010. Since then there has been a major increase in the overall EU/EEA notification rate, reaching a peak of 7.1 per 100 000 population in 2017 – an increase of 70% over the notification rate in 2010 (Figure 2).

Between 2010 and 2017, 15 countries reported an increase in the notification rate of more than 15%. This increase varied among countries: rates more than doubled in Iceland (876%), Ireland (224%), the United Kingdom (153%), Germany (144%) and Malta (123%). During this time, decreasing rates were reported in six countries, with decreases of 50% or more in Estonia (-50%) and Romania (-53%).

Figure 2. Number of reported syphilis infections per 100 000 population by year of notification, EU/EEA countries, 2007–2017



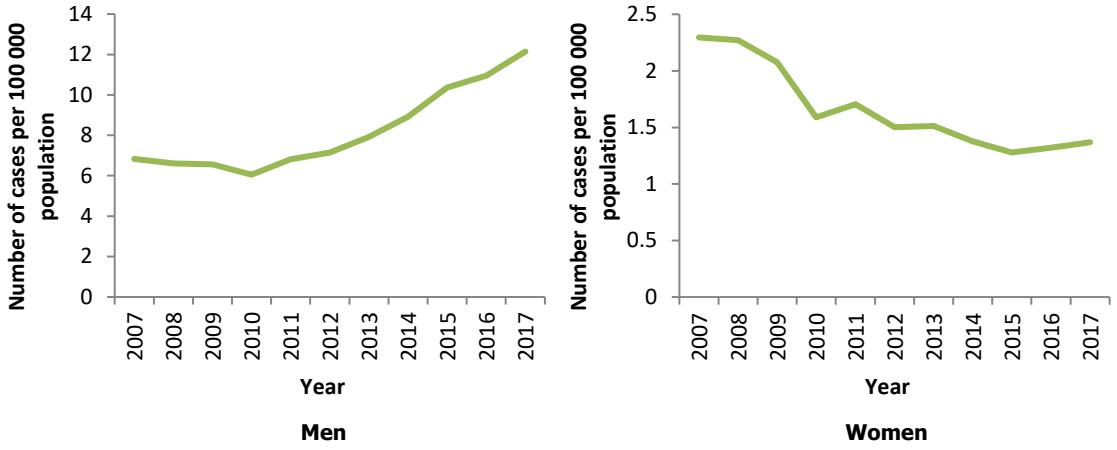
Source: Country reports from Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Germany, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

2.1.1 Gender

Notification rates were consistently higher among men between 2007 and 2017. Notification rates among men decreased from 6.8 cases per 100 000 population in 2007 to 6.1 in 2010 and since then increased to 12.1 in 2017. Rates among women were highest in 2007 (2.3 per 100 000) and decreased to a minimum of 1.3 per 100 000 in 2015, before increasing slightly to 1.4 in 2017. In 2017, the highest rates among men (above 15 cases per 100 000 population) were observed in Iceland (25), the United Kingdom (22), Malta (22), Germany (17) and Ireland (16), while rates among women were highest (above 3 cases per 100 000 population) in Iceland (6.0), Bulgaria (5.4), Latvia (4.8) and Lithuania (4.8).

When compared with 2010, the gender-specific notification rate in 2017 doubled among men and decreased among women by 14% (Figure 3). Similar trends are observed in the majority of EU/EEA countries when compared with 2010. Notification rates among men more than doubled between 2010 and 2017 in Germany, Ireland, Malta, Poland, Sweden and the United Kingdom. Among women, notification rates increased in Bulgaria, Germany, Ireland, Latvia, Luxembourg, Malta, Norway and the United Kingdom, with rates more than doubling in Luxembourg, Germany and Norway, although notification rates in these countries in 2017 remained low.

Figure 3. Number of reported syphilis cases per 100 000 persons by gender



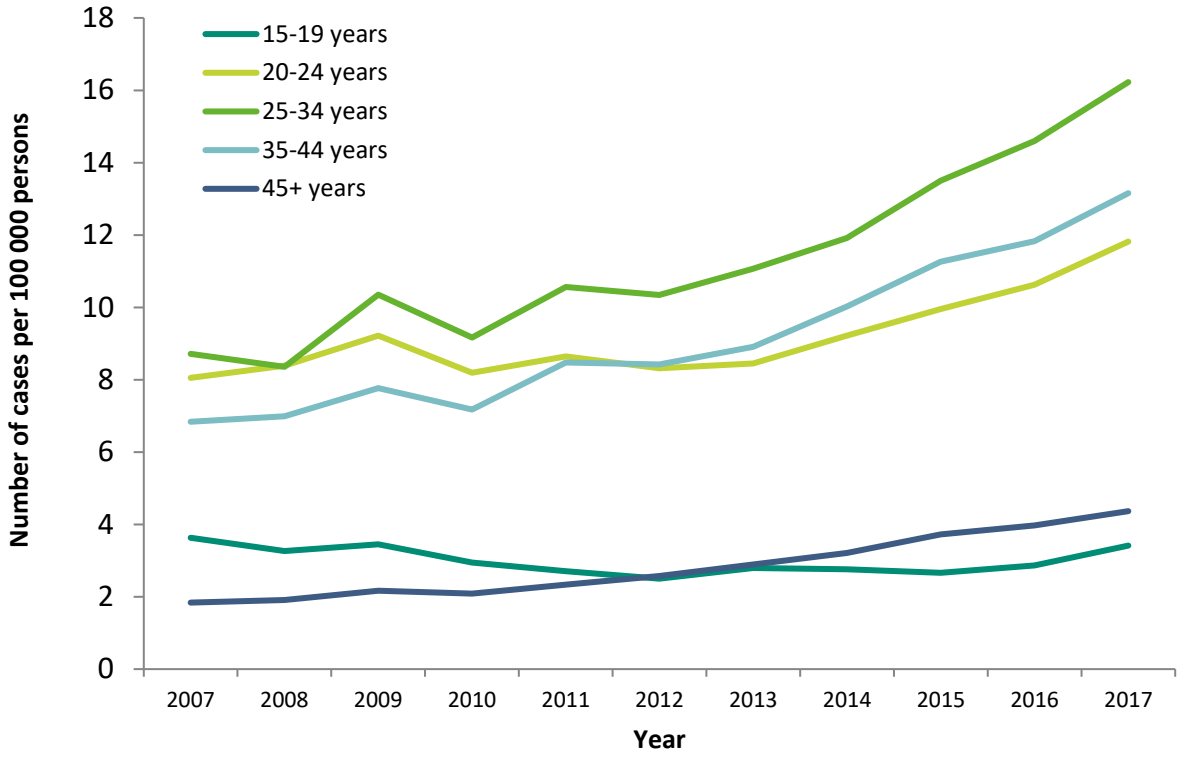
Source: Country reports from Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Germany, Ireland, Italy, Latvia, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom

2.1.2 Age

Information on age was available for 23 countries between 2007 and 2017. Data on age were not available for Austria, Belgium, Bulgaria, Croatia, Poland and Spain; these six countries together accounted for 25% of all cases during this time.

In 2017, the largest proportion of cases was reported in age groups above 24 years of age: 25–34 years (30%), 35–44 years (26%) and 45 years and over (31%). Notification rates in 2017 were highest among 25–34-year-olds (16 per 100 000 persons) and 35–44-year-olds (13 per 100 000 persons). Between 2007 and 2017, notification rates among those aged 25 years and over increased consistently. By contrast, rates among 20–24-year-olds fluctuated between 2007 and 2013, but have since increased rapidly. Rates among 15–19-year-olds decreased between 2007 and 2012 and were stable until 2015 but have since increased as well (Figure 4).

Figure 4. Number of reported confirmed syphilis cases per 100 000 population by age group, EU/EEA countries, 2007–2017



Source: Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom

Age and gender-specific rates were higher among men in all age groups between 2012 and 2017. By contrast, between 2007 and 2011, rates were higher among women between 15 and 19 years of age. Notification rates were highest among men aged 25–34 years for all years between 2007 and 2017 except for 2008 when rates were slightly higher among 35–44-year-old men. The highest age- and gender-specific rate observed during this time was among 25–34-year-old men in 2017 (28 cases per 100 000 population).

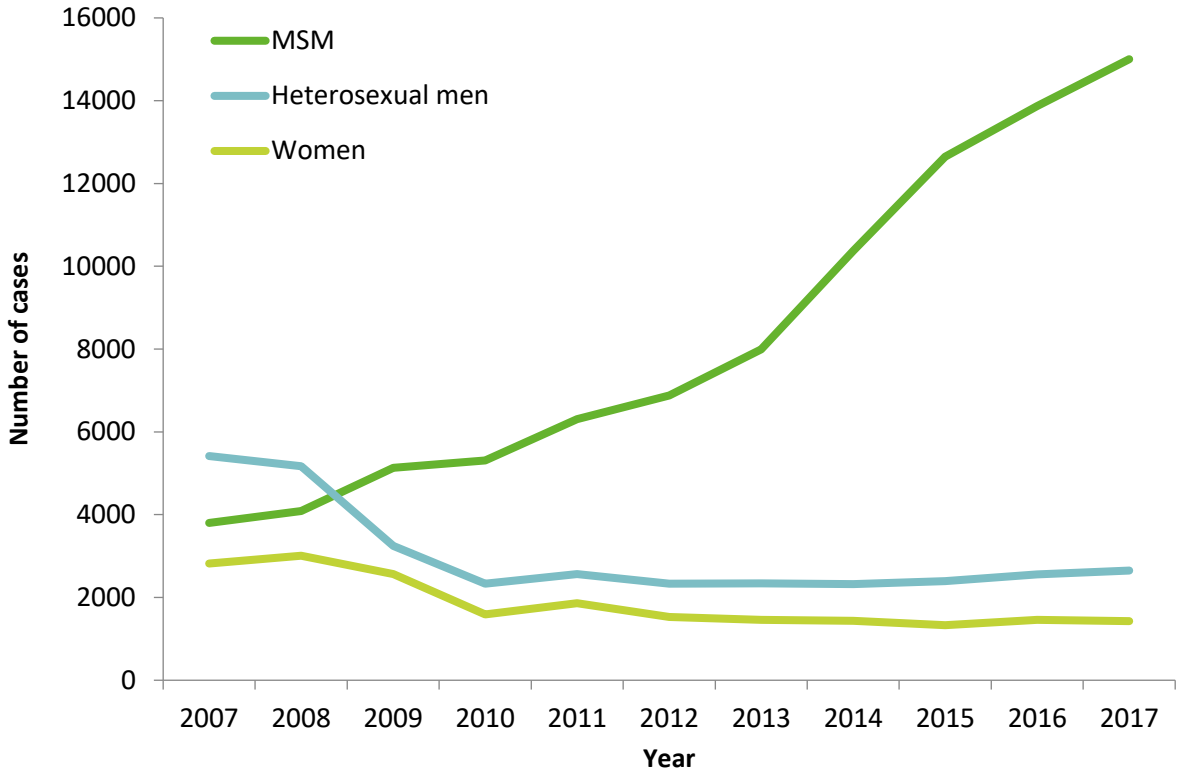
2.1.3 Transmission, HIV status and syphilis stage

Between 2007 and 2017, the mode of transmission of cases was reported for 152 233 cases (58% of all cases). Of these, 94 015 were reported to be MSM (62%), 35 633 were heterosexual men (23%) and 22 242 were heterosexual women (15%). In 2017, 77% of cases were reported to be among MSM, 15% among heterosexual men, and 8% among heterosexual women. The proportion of cases diagnosed among MSM ranged from below 20% in Latvia, Lithuania and Romania to more than 80% in France, Germany, Ireland, the Netherlands, Sweden and the United Kingdom.

MSM accounted for the majority of cases in 2017 among all age groups, with the proportion of MSM increasing with age from 53% among 15–19-year-olds to 82% among 35–44-year-olds and those aged 45 years or over. The proportion of heterosexual women decreased with age, from 29% among 15–19-year-olds to 4% among those aged 45 years or over. The proportion of heterosexual men ranged between 13 and 17%, with the highest proportions among those aged 15–19 and 20–24 years of age.

Among countries which reported data on the route of transmission between 2007 and 2017 there was a sharp increase in cases reported among MSM particularly since 2013 (Figure 5); cases among heterosexuals appear to be stable in recent years.

Figure 5. Number of syphilis infections by route of transmission and year of report, EU/EEA countries, 2007–2017



Source: Cyprus, the Czech Republic, Denmark, France, Germany, Iceland, Ireland, Latvia, Lithuania, Malta, the Netherlands, Norway, Romania, Slovenia, Sweden and the United Kingdom.

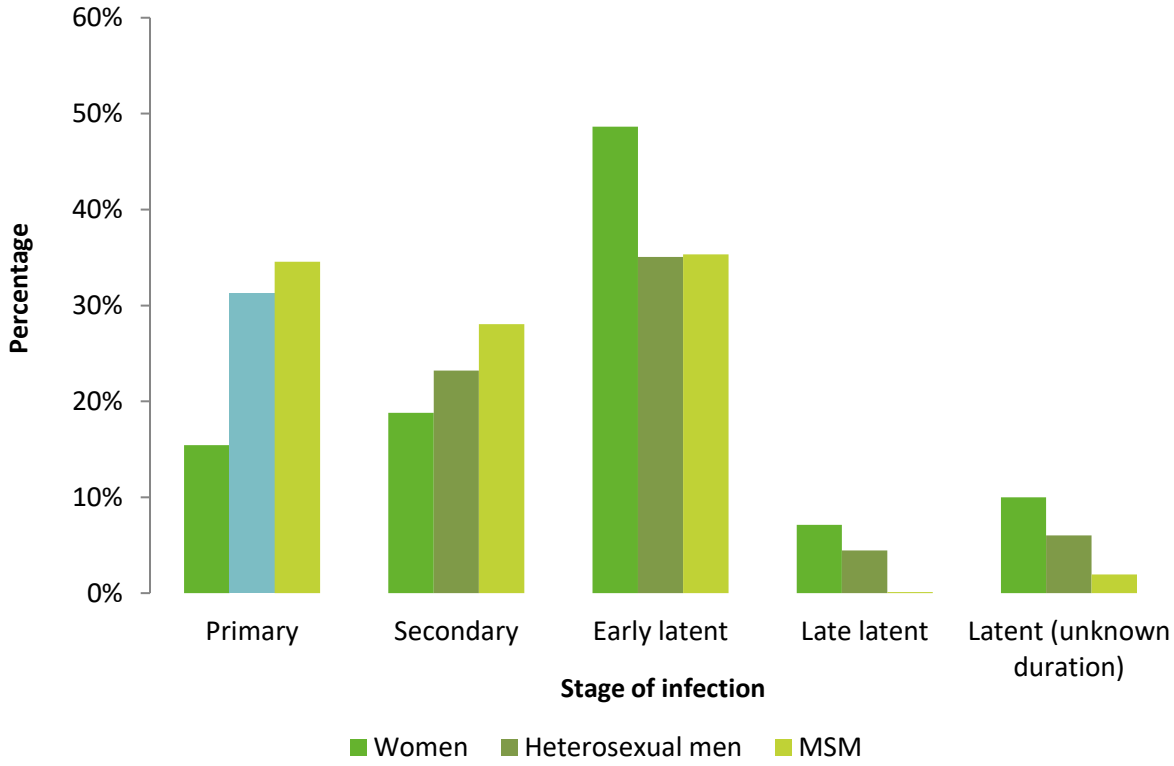
Data on HIV coinfection were reported for only 11% of cases between 2007 and 2013. Between 2014 and 2017, however, completeness increased to 36%. Of those with known HIV status between 2014 and 2017 (data reported by Cyprus, the Czech Republic, Denmark, Estonia, France, Hungary, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, the United Kingdom), 42% were reported as HIV positive (either known or newly diagnosed); 95% of HIV-positive cases were among MSM. Among MSM, the proportion of HIV-positive cases was stable in 2014 and 2015 but decreased in 2016 and 2017 (2015: 45%; 2017: 39%). Among heterosexuals, the proportion of cases that were HIV positive was 11% among men and 2.3% among women, with no clear trends. Although the proportion of cases among MSM that were HIV positive decreased, the number of syphilis cases among HIV-positive persons increased during this time by 37%. However, the increase among HIV-negative persons was higher (74%). Cases among HIV-negative heterosexual men and women also increased during this time (by 37% and 30%, respectively). Among MSM, the proportion of cases that were HIV positive increased with age, from 7.1% among 15–19-year-olds to 53% among those aged 45 years or over. Among heterosexual men and women, the proportion of cases that were HIV positive also increased with age but peaked among 35–44-year-olds among both men and women (14% and 4%, respectively) before decreasing among older women or remaining stable among older men.

Details on the stage of syphilis infection were reported for 29% of cases between 2007 and 2017. Between 2014 and 2017, there were increases in the number of reported cases for all stages with the exception of latent infections of unknown duration (-8%), with the largest increases reported for primary syphilis (52%) and early latent syphilis infections (44%).

The most frequent stage reported for all routes of transmission was early latent infection (MSM: 35%; heterosexual men: 35%; women: 49%); however, among MSM there was an equal proportion of primary syphilis cases (35%).

Only 15% of cases among women were diagnosed at the primary stage whereas 31% of cases among heterosexual men were diagnosed at the primary stage (Figure 6).

Figure 6. Distribution of reported syphilis infection stages by gender/sexual orientation, EU/EEA, 2014–2017

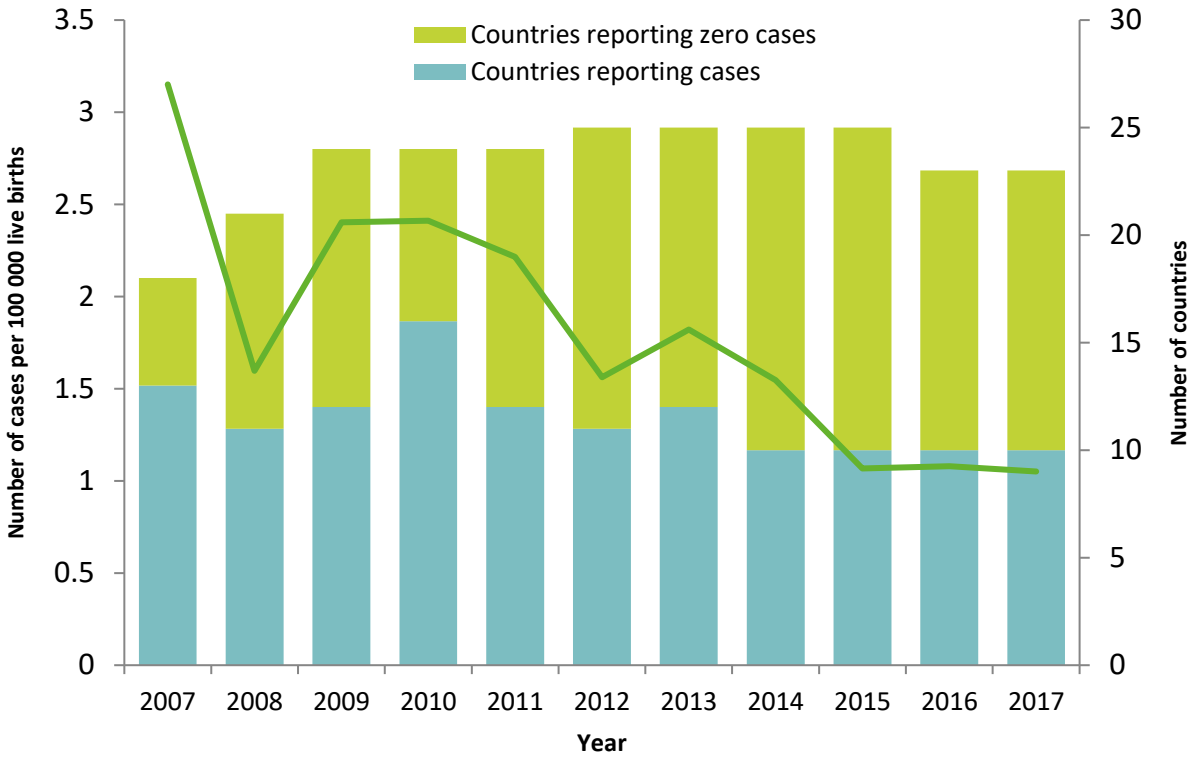


Source: the Czech Republic, France, Hungary, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Sweden, the United Kingdom

Congenital syphilis

In the period 2007–2017, 787 confirmed cases of congenital syphilis were reported in 25 EU/EEA countries. Bulgaria reported the largest number of cases during this time (n=279; 35% of all cases), followed by Portugal (98, 12%), Romania (89, 11%) and Poland (84, 11%). The number of reported congenital syphilis cases decreased from 122 in 2007 to 36 in 2017. During this time, the largest number of cases were reported each year by Bulgaria (low: 10 cases in 2015; high: 38 cases in 2011). The trend in all countries reporting cases was generally decreasing or stable.

Figure 7. Number of reported confirmed congenital syphilis cases per 100 000 live births, EU/EEA countries, 2007–2017



Sources: Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom

The crude rate of reported congenital syphilis infection in the EU/EEA was 3.1 per 100 000 live births in 2007 and decreased to 1.1 cases per 100 000 live births in 2017 (Figure 7). The highest rates were observed in Bulgaria throughout the period under observation.

2.2 Epidemiological review: outbreaks and trends

Peer-reviewed publications identified through the literature review are presented in the evidence tables in Annex 4, Tables 4.1 to 4.12

2.2.1 Outbreaks and epidemics

A total of 29 peer-reviewed publications were reviewed describing 25 outbreaks and 4 clusters of syphilis in high-income countries between 2007 and 2018 [2-4,33-57]; all are recorded in Table A4.1. Outbreaks were mostly reported from the UK, the USA and Australia, with a few also from Canada, Greece and Serbia, suggesting that there may be a great deal of underascertainment of these outbreaks in many countries. The size of reported clusters and outbreaks ranged from 5 to more than 1 000 cases. The largest outbreaks were reported in Florida, US (n=1357, 2016), the Netherlands (n=1123, 2011–2015), Australia (n=790, 2011–2015), London, UK (n=778, 2001–2010) and far north Queensland, Australia (n=633, 2015–2016). Geographically, most of the outbreaks were in urban environments, although outbreaks in remote or rural areas were also reported [37,40,41,52].

MSM were the most commonly affected group and the main risk group in 10 studies [35,46,58]. One feature of the MSM outbreaks cited to be important was the use of social networking sites or mobile device applications to find sex partners [3]. Regarding HIV status, seropositivity prevalence varied from 0% to 87.5% [3,4]. MSM reporting a previous history of STI [4] and high rates of unprotected sex suggest an increasing prevalence of unsafe sexual practices [56].

Although most outbreaks were reported mainly in men [35,41,42,44], concerns around syphilis outbreaks involving young women are growing. Nine outbreaks were reported affecting mainly female groups [33,34,36-38,43,45,51,57], and the majority of cases were in reproductive age females, leading to at least seven cases of congenital syphilis [38,39]. Additional risk factors associated with these outbreaks (apart from MSM) included substance use (drugs or alcohol), incarceration, chemsex, multiple sex partners, gang affiliation, unprotected sex, or trade sex for drug or money [38,39,43,56].

2.2.2 Rising trends

More than 60 studies reporting on rising syphilis trends were reviewed (Table A4.2). In high-income countries, rising trends of syphilis cases have been described since the early 2000s. These rising trends are reflected in syphilis notification data in many European countries, particularly over the last few years. The highest increases have been reported in males [59]. In almost all studies, the majority of cases (>60%) were reported among men [60,61], with the proportion exceeding 90% in some cases [62]. Despite the general decreasing trend in women [63,64], several studies reported an increase in the number of female cases [65-68].

The average age of the cases in these studies was between 35-39 years [61,65,66,69], with most of the cases concentrated in 25-44 age group [59,70]. However, there are differences in the syphilis epidemics described in different locations and countries regarding gender, age or ethnicity [71-73].

Most of the increases described were in MSM [74,75], and some studies focused exclusively on this risk group [63,76,77]. Pinto et al. reported an observed increase from 8.6 cases per 1000 MSM to 25.9 per 1000 MSM in one year (2013–14) in Brighton, UK [78]. MSM living with HIV in Malaga, Spain, were reported to have the highest increase in infections [79], with other studies reporting the rates of coinfection with HIV varying between 28.5 to 44.3% [35,63,69]. However, the acquisition of syphilis by heterosexual contact remains significant, and one study reported that 20% of new cases in Switzerland were women [65].

In studies where the country of origin was analysed, the majority of syphilis cases were detected among locals or natives [59,63,80]. The proportion of cases in foreign-born patients varied depending on the location; two studies from Prague and Dublin estimated this proportion to vary from 20% to 40% [70,81].

There was just one study from Romania that appeared to show a decreasing trend in syphilis cases, however this is likely due to a change in the definition of 'syphilis case' [82].

Studies from the USA and Canada have reported a resurgence of syphilis in recent years, especially since 2010 [83]. Annual increases were between 11% to 40% [84,85]. The majority of cases have been reported in males [7,86] aged 20–39 years [7,87]. Increases were observed among men of all ages and races/ethnicities, but some race/ethnicity shifts were reported to have occurred in the USA more recently [88]. The highest rates were among black non-Hispanic men. However, when compared to blacks, the greatest percentage increases in cases occurred among Hispanics and whites [7,89-92].

Similar to the syphilis trends observed in Europe, the largest increases in the US and Canada occurred among MSM [93,94]. HIV coinfection prevalence is also reported as high in this risk group, especially among those with repeat infection and was reported to have reached levels of up to 86% in certain cities [95,96]. Increases in heterosexual male and women have been also reported. In Florida, there was a 42% increase in non-MSM individuals between 2012 and 2014. In contrast to the European trend, syphilis cases among women in the US decreased until 2012 [97] but started to increase from then onwards. In Mississippi, over the ten year period 2007–2016, there was an increase in syphilis cases by 34% among non-MSM males and 48% in females [98].

There was a reported decrease in the proportion of HIV-positive MSM syphilis cases in four US cities, from approximately 60% to 40%. This coincided with an increase in syphilis cases among HIV-negative MSM. These trends were attributed to a decrease in condom use and serosorting among HIV-seropositive MSM and an increase in the number of sex partners in HIV-seronegative MSM [86]. Most cases occurred in young men, belonging to a minority ethnicity and living or getting infected in metropolitan areas [83,91].

Studies from Australia and New Zealand also report rising trends of syphilis cases [99]. Traditionally, the highest rate of infections was seen among aboriginal populations, but this pattern has changed in recent years, with an increase in males residing in urban and outer regional areas [100-102]. The majority (83% in one study) of these males were reported to be gay or bisexual men [103]. While the overall number of heterosexual cases was small, there was a 3.8-fold increase in 2016 compared with 2014. Most heterosexual infections are reported to have occurred overseas, among people of non-European, non-Maori ethnicity [102]. Despite the number of female cases diagnosed each year, it is of some concern that the majority of these cases are detected through screening of asymptomatic patients [101].

Reports from Japan, also indicate an increase in cases every year, with the annual rate of increase greatest for primary and secondary syphilis cases. The majority of these cases were in heterosexual males (MSW), followed by MSM and females that have sex with men (WSM) cases. The men were reported to be older than women (37 years, IQR: 28-46y vs. 26 years, IQR: 28-46y). Among women, 20–24-year-olds consistently had the highest reported rate. The number of cases among women who were either 'pregnant' or 'found through pregnancy screening' has increased over time. The largest annual increase in reports in MSM occurred in 2013, whereas MSW and WSM experienced a greater rate of increase in the most recent years [104].

2.2.3 Syphilis in specific risk groups MSM and bisexual men

The current syphilis epidemic in high-income countries affects mainly MSM [105,106], see Table A4.3. A large proportion of syphilis cases in this group are among HIV-positive MSM [106-109]. HIV-positive MSM had an increased risk of infection compared to MSM who were either HIV-negative or with unknown HIV status in 2009 and 2013 [105]. Overall, the risk of syphilis infection was found to increase with age [110] with HIV coinfected patients found to be older than the HIV negative patients [106]. In addition, other risk factors were associated with age, for example younger MSM involved in commercial sex work were at higher risk of syphilis infection but not the older MSM. An increase in the number of sex partners was found not to be associated with the risk of infection either in younger or older MSM [110]. The risks associated with ethnicity differed between study populations. In the US studies, non-Hispanic whites or black-MSM made up the highest proportion of cases [106,111], while in the Netherlands for the period 2006-12, those at highest risk were young MSM (15–24 years of age) – especially those originating from Latin America – and in those involved in commercial sex work [110].

Most of the studies in this risk group reported on primary and secondary syphilis cases [107,111] or did not give information on the stage of disease [112], making it difficult to estimate the predominant stage of infection at diagnosis in the MSM population. However, one study from 16 states and Washington DC in the US reported that of the early syphilis infections diagnosed in MSM in 2012, 15% were primary, 39% secondary and 46% early latent infections. The proportion of MSM with HIV coinfection increased from 42% among primary syphilis cases to 59% among cases with secondary syphilis and 66% among those with early latent syphilis infection [113]. In this study, the distribution by stage of infection and the percentage of HIV coinfection remained stable during 2009 and 2012. By contrast, a clinic in Brighton, UK, reported significantly fewer MSM presenting with symptomatic syphilis (primary and secondary) in 2017 compared with 2014, as well as an increase in extra genital lesions in MSM [114].

Two studies from Europe also reported encouraging developments. A Dutch study reported a decrease in syphilis positivity rates over time in young MSM attending STI clinics, while a Swedish study reported a very minor decrease, but no clear trend in 2007–2011 [115,116].

Prisoners

Only two studies on prisoners met the inclusion criteria (Table A4.4). Syphilis prevalence remained stable over the period under study but it was still higher than in the general population [117,118]. The majority of syphilis cases was reported in males and among migrants. The most common transmission route was unprotected heterosexual contact (83.0%). Factors such as being a client of a sex worker, having casual sex, or having condomless sex were associated with a syphilis diagnosis [117,118]. Early syphilis was the most frequent stage of disease detected in this risk group.

Persons who inject drugs (PWID)

The search retrieved only one study on PWID (Table A4.5). The use of five specific substances was evaluated among primary and secondary syphilis cases in the USA, including injectable drugs. An increase in the number of cases has been reported across all categories. The percentage of cases using drugs remained stable in MSM but increases of between 8–16% were observed in heterosexual males and females. According to the study, MSM reported substance use more frequently than other risk groups [119].

People living with HIV (PLHIV)

Nineteen studies on syphilis in HIV-positive patients were reviewed (Table A4.6). In cohorts of PLHIV, the number of syphilis cases has increased over the last years [96,120-123], as has the prevalence of other STIs [124,125]. Studies from Canada show that syphilis rates were generally higher in HIV-positive persons than in HIV-negative people [126]; in addition, PLHIV more frequently reported a history of STI [126]. Syphilis prevalence among PLHIV varied, with rates of 2% to 16% reported in these studies [127-129]. Coinfection among MSM was found to increase with age in a US study [130]. Condomless sex, ethnicity, drug or alcohol use, higher numbers of male sex partners, engaging in oral or anal intercourse, HPV coinfection and use of social media to seek partners were all associated with a higher risk of syphilis in PLHIV [93,121,126,131,132]. The MSM and bisexual male HIV-positive population was most affected by syphilis [121,125,131,133], especially white MSM [121,123], although other studies indicated Latino MSM as a risk group for coinfection [122]. Studies in the MSM population also found a high proportion of asymptomatic cases [79,124,134]. A case series of patients attending the Southern Alberta and Calgary STI Clinics showed that 80% of those with coinfection were on ART, and 64% were fully virally suppressed at the time of syphilis coinfection [123,125]

Heterosexuals, adolescents and older adults

Six studies among heterosexuals are presented in Table A4.7. A study of 319 women with syphilis in Phoenix, USA, reported that 30 per cent were pregnant or had an unknown pregnancy status; the study found several high-risk behaviours, e.g. methamphetamine use, incarceration within the previous 12 months, sex with anonymous partners, or previous history of sexually transmitted diseases [135]. One review of Florida's sexually transmitted disease surveillance system reported that the number of heterosexual male cases increased by 14% between 2012 to 2014; during the same time period, a 23% increase was recorded among women [136].

A US study among high-risk adolescents (15–24 years old, homeless, LGBTQ) found that treponemal antibody prevalence was below 2% among 15–19-year-old women and men and among 20–24-year-old women; the percentage increased to 7% in 20–24-year-old males recruited from these settings [137]. Prevalence of active syphilis was 0.7% among 18–34-year-old men with unrecorded sexual orientation attending for emergency care in another US study [138]. A 2014 US study found that 17.7% of young (13–24 years of age) individuals newly diagnosed with HIV had positive syphilis serology (RPR titres ≥ 1:8) at HIV diagnosis, with the subjects being predominately African-Americans (84.6%) and MSM (84%) [139]. The studies conveyed only few details on the syphilis stages in heterosexual cases. In one study among women in Phoenix, USA, 3% of women were diagnosed in the primary stage, 16% were in the secondary stage, 16% had early latent syphilis, and 65% had late latent infection (2013 and 2014) [135].

Migrants and refugees

Migrants and refugees are an important risk group regarding the burden of syphilis (Table A4.8). Some studies have shown a higher prevalence in the identified foreign-born population [140,141]. Studies in this risk group reported a varying prevalence of syphilis from 1.5% to 4.8% in migrants [142-144], with one study from Spain finding positivity rates up to three times higher in migrants than in natives [141]. When investigating especially vulnerable populations, such as Roma, additional risk factors such as a higher proportion of sex workers (>30%) was found [140].

More cases were described in male migrants [140-142], never married, with a low level of education [140]. The relationship with age was less clear, with one study from Spain finding migrants with syphilis to be younger than natives [141], but the study on Roma in Belgrade found a higher proportion of cases in the older age groups [140]; several studies found the most affected population to be of African origin [141,143,144].

Pregnant women

Due to the association with congenital syphilis, pregnant women are an extremely important population group (Table A4.9). Data from various US studies show an increase in the number of syphilis cases in pregnant women (and in congenital syphilis cases) from 2012 onwards [145-154], which in 2017 resulted in the highest number of babies born with syphilis in the USA in twenty years [155]. Similar increasing trends have been observed in other high-income countries such as Australia (especially in aboriginal populations) and Japan [147]. A high proportion (>20%) of female syphilis cases are pregnant women [156,157]. In Spain, a positive test result was twice as common among pregnant women as in the general population [158]; in Ireland, positive results in pregnant women were four times higher than in the rest of the population [159], most likely because of increased detection through antenatal screening. Despite the high levels of antenatal care attendance [152], not all pregnant women were tested for syphilis or received adequate pre-natal care or treatment [148-150,155,160].

Several US studies showed that syphilis diagnosis at delivery was greater among women who were black or Hispanic [148,151,152], had the lowest annual household income, came from a high-morbidity neighbourhood or resided in a high poverty neighbourhood [148] or had a history of incarceration [161]. However, large increases have also been described in white women and women in the highest annual household income quartiles [148]. In many of the studies, there was a high proportion of cases in migrants [148,157,162,163]. Compared with non-pregnant women, the pregnant females found to have syphilis were younger, almost all were married or in a steady long-standing relationship, but had more lifetime sexual contacts [147,151,164]. The social circumstances of mothers varied and included drug use, sex work, or a history of incarceration [150,156,164].

Other risk groups

Although the most important risk groups are listed above, other groups were occasionally cited (Table A4.10).

- **Sex workers.** Only one study in sex workers was retrieved by the literature search. In this study on female sex workers working in Tirana, the syphilis prevalence was found to be 6.5%. General knowledge on HIV/STI and condom use was high, but this was not translated into self-reported lower risk behaviour [165].
- **Military.** Military health services have their own surveillance system, and syphilis was an important priority in the 20th century. Syphilis cases in the US military, as in civil society, are also on the rise [166,167], with annual rates of syphilis increasing by 3–19% [168]. Increases in incidence rates have been reported for each year since 2011, especially in individuals aged 20–29 years [168]. Males contributed for the greatest proportion of cases and reported the highest increase, especially black, non-Hispanic males [166-168]. The annual incidence rates among women in the US military decreased to rates below those among men in 2010 and have remained stable since then [168]. One study among beneficiaries of the US military health system, found that crude incidence rates increased from 30.9 cases per 100 000 person-years in 2010 to 47.4 cases per 100 000 person-years in 2015 (mostly males), and 24.4% were diagnosed as HIV coinfected [166].
- **Blood donors.** Syphilis screening in blood donors is widely implemented in high-income countries as a fundamental blood safety measure. Results from screening the blood donor population revealed that syphilis antibody prevalence varied from 0.02 to 0.15% [169-171], and increases in the number of infections in

donors have been reported [171,172]. The prevalence was higher among males in most of the studies [169,173], but the peak age groups differed [169,173]. Some risk factors were identified, such as the country of origin being from eastern Europe, previous history of intravenous drugs, having tattoos or piercings and being MSM [170,172,173]. Secondary syphilis was the most frequent stage of disease reported in this group [173].

2.2.4 Other issues related to syphilis

In recent years, ocular syphilis and reinfection with syphilis have emerged as important issues. In addition, studies focused on the use of pre-exposure prophylaxis (PrEP) to prevent HIV and whether PrEP has a detectable impact on syphilis infection (Table A4.11).

- **Ocular syphilis.** Syphilitic uveitis is a preventable cause of ocular and neurologic morbidity and has been on the rise since 2014 [174-178]. Most of the cases were reported in males, especially in MSM [174,178-183]. Some studies established an association between ocular syphilis (OS) and HIV-positive status. A higher prevalence of OS has been observed in HIV-infected patients with a higher viral load, lower CD4 count, and older age [179]. The most severe disease cases were reported in PLHIV [179,181]. The majority of OS cases were in early syphilis stages [182,183], but the stage of disease was not associated with any specific symptoms, diagnosis, or extent of eye involvement [178]. Treatment improved the symptoms in all cases [174,181,183] but important long-term sequelae were still reported [182].
- **Reinfection.** Syphilis reinfection is rising [184], with annual increases reported to be ranging between 1.7% and 31% [177,185]. Recurrent syphilis infections are more common in certain risk groups, such as MSM, especially black MSM [185]. Reinfection was reported more often among older individuals [81]; there is also an increased risk of reinfection in PLHIV [177,184-186]. In one study from the US city of Baltimore, repeated syphilis infections were reported in 20% of MSM cases [95]. The number of recurrent syphilis infections per individual ranged from one to more than four [177,185]. According to one study, the median time between the two most recent syphilis diagnoses was approximately 18 months [95].
- **PrEP.** Concerns over the potential for an increase in STIs following PrEP initiation persists. In the studies listed in Table A4.11, an increase in syphilis cases during PrEP use has been reported. One study observed an increase of syphilis prevalence from 1.5% before PrEP introduction to 3.5% afterwards [187]. Another study compared syphilis cases in HIV-infected and uninfected patients: an increase of syphilis cases in HIV-uninfected MSM on PrEP was described [188]. Some studies see PrEP as an opportunity to decrease the HIV risk of infection in MSM that were recently diagnosed with syphilis or other STIs [189]. However, a study from Chicago cited a number of behavioural risk factors in newly infected individuals on PrEP, for example multiple sex partners, high rates of receptive anal intercourse, condomless sex and drug use during sex [190].

2.2.5 Congenital syphilis

Overall, congenital syphilis (CS) rates in the EU/EEA countries have decreased steadily since 2005 [9]. Recent studies show that the reduction in cases continues [164], despite some heterosexual syphilis outbreaks [34]. However, rates of CS vary across countries, with rates ranging from 0.1 to 39.8 cases per 100 000 live births [191]. By contrast, increases in CS diagnoses have been reported throughout the United States since 2012 [155,176], with increasing rates of primary and secondary [51,145] or early latent [146] syphilis among women of reproductive age. Concerns have also been expressed in Japan where the ongoing heterosexual outbreak is disproportionately affecting young women. An increase in diagnosed infections in pregnant women was observed, which is linked to an increase in CS infections [104,147].

Antenatal care programmes in high-income countries include syphilis screening once or twice during pregnancy. A frequently observed risk factor in mothers of CS cases is the absence of timely prenatal care [145,148,149] or infection after the initial test [145,148,155]. Other determining factors were the lack of syphilis treatment during pregnancy (or inadequate treatment) in spite of at least one prenatal visit [162]. Occasionally, some of the cases were not tested for syphilis during prenatal visits [145].

Other risk factors identified in pregnant women with a positive syphilis test include history of incarceration, high sexual risk behaviour, or drug use [150]. Regarding socio-economic status, low-income individuals have a higher risk of CS [159]. In addition, younger age has been associated with CS [151,159].

Non-Hispanic blacks are the most affected ethnic group in the majority of the US studies [148,151,152]; however, other studies could find any significant difference between the risk of infected babies born to black or Caucasian mothers [151]. Even where decreasing trends are observed, most of the US cases of CS continue to be among infants whose mothers where black [145]. In Europe, most of the cases are in mothers from east European countries [160,162-164].

2.2.6 Social determinants

Certain social determinants combine with behavioural risk factors and environmental conditions to facilitate the spread of infectious disease. Interactions between the individual pathogen's characteristics and societal norms and patterns of behaviour can influence the epidemiology of infectious disease [192].

Several determinants are known to be associated with the spread of syphilis; these include poverty, young age, scarcity of men or low status of women [192]. In several studies, the highest rates of syphilis infection were observed among ethnic minorities [193-195], likely due to community-level differences and segregation. Migration, under certain circumstances, also involves segregation-based clustering and bridging. Ethnic minorities and other high-risk groups like migrants or refugees often do not have access to appropriate healthcare – an essential factor for the prevention of STI transmission [196]. Improvements in service accessibility and choice and the provision of sexual health services offer further opportunities for STI control [197].

Another important social determinant is socioeconomic status. Lack of resources and inequality of resource distribution have been associated with risky sexual behaviour, lack of care about consequences, and a rising number of STI [82,198]. This is particularly obvious for syphilis, where lower income is associated with increased prevalence [199].

2.3 Survey among Member States

2.3.1 Overall

ECDC received 29 responses to the survey, including two from Poland (which were merged). As a result, 28 Member State questionnaires could be analysed. With 31 EU/EEA Member States, the response rate was 90%.

2.3.2 Syphilis surveillance

Of the 27 Member States that provided information on their surveillance system, 24 confirmed having a comprehensive syphilis surveillance system, while three have sentinel surveillance systems. Of the Member States with comprehensive surveillance systems, 16 reported that their system captured all syphilis diagnoses in the country, whereas seven reported that their system did not capture all diagnoses in the country; one country did not respond to the question. Estimates of surveillance system coverage for these seven countries ranged from 50–90%; four countries where unable to estimate the true surveillance system coverage. Of the three countries having sentinel surveillance systems for syphilis, the estimated coverage of all syphilis diagnoses in the country was 17%, 70% and 80%. Most countries (17) confirmed using EU case definitions (EU-2008 [200] or EU-2012 [201]: 15 countries; EU-2018: 2 countries [30]), whereas five countries reported using national case definitions; four countries did not report the case definition in use. (Please note that the EU 2008 and 2012 case definitions are identical.)

Fourteen of 27 countries (52%) reported changes in the syphilis surveillance system between 2010 and 2017. The changes included changes in reporting methodology (nine countries), increase in the number of reporting sites (four), and other reasons (three). Changes in the methodology (some countries reported more than one change) included reduced testing of low-prevalence populations (one country), implementation of case-based reporting systems (four countries), implementation of electronic reporting (four countries), changes to case definitions (two countries) and measures to reduce duplicate reporting. Countries with increases in the number of reporting sites reported inclusion of data from non-specialist services (generally covering populations with lower prevalence rates) or additional laboratories or institutions with varying contributions of cases. The full impact of these changes was not assessed in the survey.

Preliminary data for 2018 were available from 18 countries (64%). Of these, four countries reported increases compared to 2017 (Belgium, Cyprus, Ireland and Malta). Among the 11 countries that answered the question, two reported some changes in the epidemiology of syphilis cases in 2018 compared to previous years: Denmark reported a slight increase in the number of cases among heterosexuals, whereas the Netherlands reported increases among MSM; testing rates, however, have increased and positivity rates are stable. Among countries not having preliminary 2018 data (10), two (Sweden and the United Kingdom) have received informal reports of increases in syphilis cases. Both countries have also received reports of syphilis outbreaks, some of which have been ongoing since 2016.

2.3.3 Congenital syphilis surveillance

In the 19 countries reporting congenital syphilis data, congenital syphilis surveillance systems are comprehensive. In addition, France is currently setting up a congenital syphilis surveillance system.

Of the 19 reporting Member States, 16 said that their surveillance system covers all congenital syphilis diagnoses in the country. Slovakia and Poland reported a coverage of 80% and 90%, respectively. The United Kingdom does currently not have a specific surveillance system for congenital syphilis.

Of the 19 countries, 14 reported using the EU case definition, which has not changed since 2008 [30]. Three countries reported using national case definitions; two countries did not report the case definition in use.

Changes in the congenital syphilis surveillance systems between 2010 and 2017 were reported by eight out of 28 countries. Changes included more specific descriptions of laboratory tests to allow for verification, implementation of electronic reporting, the introduction of enhanced surveillance, measures for deduplication of cases, and implementation of case-based reporting.

Preliminary data on cases of congenital syphilis for 2018 were available for 15 out of 28 countries. Of two of these fifteen countries report increases compared to 2017: Poland reports 14 cases still under verification (although it is likely that many will be discarded following verification), and Slovakia reported two confirmed and two possible cases. None of the respondents reported changes in the epidemiology of congenital syphilis infections. Among the countries that do not have preliminary congenital syphilis surveillance data for 2018, none reported receiving informal reports of increases in cases.

2.3.4 Response activities

Thirteen countries reported the implementation of specific response measures to counter increases in syphilis/congenital syphilis infections between 2010 and 2018. These included:

- Implementation of national STI and/or integrated strategies to combat HIV/STI and hepatitis with increased emphasis on sexual education in schools, shifting from an HIV focus to HIV and STI.
- Introduction of national outbreak response groups to respond to the increases in syphilis and other STI.
- Increase in the number of community-based HIV and STI low-threshold testing sites ('checkpoints') in major cities, mostly targeting MSM.
- Campaigns targeting MSM, either directly from public health institutions or through community organisations, have been implemented to increase regular testing in those with high risk behaviour.
- Courses for clinicians to increase their knowledge and awareness.
- Communication on increases in syphilis in epidemiological bulletins.
- Contribution to reports in the press on increases in syphilis, resulting in an increasing awareness in general population and risk groups.

In addition, some countries are planning similar or additional activities, including development of national syphilis action plans and enhanced surveillance activities. A Syphilis Action Plan has been launched by PHE, UK on 4 June 2019 [202].

2.4 Systematic literature review on public health response

Seventy-eight publications: studies (66); guidelines (10); and other types of technical documents (2); retrieved from databases or through Google and hand searches met the eligibility criteria and were included in the evidence review.

Of the 66 studies published in peer-reviewed journals reporting on responses to increases in syphilis notifications and/or to syphilis outbreaks, 59 reported outcomes of interventions implemented among the adult populations and seven reported outcomes of interventions addressing increases in congenital syphilis cases (Annex 5). Of the studies reporting outcomes of interventions among the adults, 50 reported results of single interventions (Annex 5, Table A5.1) and nine were studies reporting outcomes of multiple interventions (reports of comprehensive responses to outbreaks of syphilis) (Annex 5, Table A5.2). Recommendations from ten evidence-based public health or clinical guidelines were considered informative for responses to increases in syphilis among the adults (5) and to congenital syphilis cases (5) and were also summarised (Annex 5, Table A5.4). The contents of two operational guidelines on syphilis outbreak management from European national authorities (Ireland and the UK) are presented in addition to the outcomes reported from the nine outbreak management studies.

2.4.1 Response to outbreaks or increases in syphilis among adults

In general, public health responses to increases in syphilis infections may aim to quickly identify and treat syphilis cases and prevent new infections. This may be achieved through *case finding*, involving screening of the general population or of populations at risk, partner notification and management services and surveillance activities; through *case management*, including appropriate treatment of diagnosed infections and risk reduction counselling; and through *education* of the general population, of populations at higher risk, and education of healthcare providers (adapted from [203]). In line with this, the 50 studies reporting interventions among adult populations were categorised and presented separately as: screening (n=15), outreach venue testing (n=5), partner

notification (n=6), education and awareness (n=15), interventions using social media (n=6) and biomedical interventions (n=3).

Screening

Fifteen studies reported on screening for syphilis, where screening was defined as 'routine', 'regular' or 'frequent' syphilis testing offered to certain populations (Table A5.1). The declared aim of screening interventions was to detect early (asymptomatic, infectious) syphilis infections, reduce incidence or, to only increase syphilis testing coverage and/or increase testing frequency. Most (11/15) studies reported interventions among MSM (of which 7/11 among the HIV-positive MSM), one among men (regardless of their sexual orientation) during an outbreak of syphilis among MSM [138] and three referred to populations at high risk in general [204-206]. Also included in this section is one study that aimed to reduce the time between a positive test result and treatment [204].

Including testing for syphilis serology in the clinical monitoring of HIV-positive MSM attending HIV clinical care facilities increased the detection of early asymptomatic infections or re-infections. An increase in asymptomatic syphilis infections diagnosed from 21% to 85% with 6-monthly syphilis screening in a sexual health clinic in Melbourne/Australia [207] and from 6.6% to 15.5% with syphilis testing every 3 to 6 months in a community based clinic offering laboratory monitoring to HIV-positive MSM in Georgia/US [208] were observed. When routine syphilis serology was introduced in an outpatient clinic for HIV-positive MSM in Netherlands [209], 33% of infections that were asymptomatic and would otherwise have been missed were detected. Introduction of an opt-out strategy for offering syphilis testing during HIV monitoring in a primary care practice with high numbers of MSM patients in Sydney, Australia (in 2016) increased the mean number of tests per patient from 1.1 in 2005 to 2.3 in 2007 ($p<0.001$) and decreased the proportion of men who had no syphilis tests in a 12-month period from 27% to 3% ($p<0.001$) during the same period [210]. Also in Australia, in a study involving a larger range of clinical practices implementing quarterly syphilis testing of sexually active HIV-positive MSM, from primary care to hospital outpatient clinics, syphilis testing was 5 to 6 times higher in settings with opt-out or opt-in strategies as compared to risk-based syphilis testing that offered same-day syphilis and viral load testing [211]. When STI self-testing was offered to HIV-positive MSM attending for routine HIV care in a large urban clinic in US, testing uptake increased for *Chlamydia trachomatis* (CT)/*Neisseria gonorrhoeae (NG)* (pharynx and rectal self-sampling in facilities close to waiting area) but not for syphilis [212]. According to the authors, this was likely because while CT/NG testing kits and urine collection cups were readily available in the self-sampling/testing room located in the waiting room area, a visit to the clinic's laboratory was needed for venepuncture for syphilis testing. By contrast, offering syphilis point of care (POC) testing (rapid finger-prick Syphilis Heath Check treponemal test), followed by empirical treatment if positive, to all men attending for emergency care in a US city during a syphilis outbreak among MSM, detected active syphilis infections in 0.7% (6/871) of the patients tested [138].

In a US study among HIV-negative MSM engaging in high risk sexual practices and taking PrEP, quarterly testing for syphilis detected 20.4% more infections than 6-monthly only or symptom-based testing [213].

In a study from Australia, the offering of routine syphilis serology testing with enhanced frequency to MSM attending high caseload sexual health clinics in Melbourne during 2007-2010 was associated with increased syphilis test uptake, by 7% per year among the HIV-positive and by 12% per year among the HIV-negative MSM [214]. There was a subsequent decline in infectious syphilis incidence, by 21% in HIV-positive and 29% in HIV-negative MSM. The most substantial reduction was in the high risk HIV-negative MSM (>10 partners in the previous 6 months and inconsistent condom use). A modelling study considering Canadian settings and examining the effect of increased frequency versus increased coverage of syphilis screening of high-risk MSM concluded that screening every three months was the most effective strategy in reducing reported and incident syphilis infections and that increasing testing coverage without increasing test frequency resulted in a smaller decline in incidence [215].

Acceptability among MSM with repeat syphilis infections, of interventions to increase syphilis testing was best for automatic reminders sent by a Web site (every 3 months) and for home test kit [216]. Most participants in this qualitative survey were open to be tested more frequently. Targeting MSM with prior syphilis infection for enhanced screening may efficiently reduce transmission, especially when identification of high-risk MSM via self-reported number of partners is difficult in practice [217].

In a study not specifically referring to MSM but more generally to populations with high burden of syphilis and HIV coinfections, when syphilis testing was integrated in an existing HIV POC testing program ('tandem' HIV and syphilis testing) for populations at high risk for STI in Virginia, the US, 15% (62/420) of attendees of several community based settings were detected with syphilis [206]. Also when referring more largely to people at high risk for STI/HIV that require frequent testing, sending SMS text reminders significantly increased re-attendance for STI testing in a genito-urinary clinic in the UK (by 41% in the intervention group vs. 28% in the control group – patients attending before SMS reminders implemented, $p<0.001$) [205]. Other (non-SMS, details not reported) reminders for quarterly STI testing were preferred by HIV-negative MSM at high risk in a study from US [218]. Notifying clients about their STI test results by SMS vs. traditional methods (phone or follow-up clinic visit) ensured that more of those with positive test results received treatment within the first four days (52% vs 42%) in a clinic in Florida, 2016 [204].

In line with these results, a literature review of interventions aiming to improve STI screening in clinical settings, identified that changing the clinic flow to routinely collect specimens for testing, using electronic reminders to healthcare staff to screen patients, and reminding patients to get screened or rescreened (via text, telephone, and postcards) can increase the number of patients screened from 5% to 20% [219].

Published in 2016, the US Preventive Services Task Force guideline for 'Screening for Syphilis Infection in Non-pregnant Adults and Adolescents' recommends syphilis screening of asymptomatic persons at increased risk for infection (MSM, PLWH and other US specific risk groups) - Grade A recommendation [220]. More specific to MSM, the 2016 United Kingdom national guideline on the sexual healthcare of MSM recommends all asymptomatic MSM to be tested for syphilis as part of sexual health screening: annually if at low risk and 3-monthly if at risk [221]. The IUSTI 2014 European Guideline on the Management of Syphilis recommends syphilis testing for case finding in groups at higher risk such as patients newly diagnosed with STIs, persons with HIV, HBV, HCV, patients suspected of early neurosyphilis, persons who engage in high risk sexual behaviour that puts them at risk (e.g. MSM, sex-workers and all those individuals at higher risk of acquiring STIs) and to all GUM/STI clinic attendees [14]. The same guidance indicates routine syphilis testing of all pregnant women, people donating blood, blood products or solid organs.

Outreach venue testing

Four studies reported syphilis testing in outreach venues (Table A5.1). These aimed at detecting infections among populations at risk that do not usually attend traditional testing venues. One additional study reported on modernising an MSM clinical venue to facilitate access to testing and treatment of a high risk MSM cohort [222].

Screening MSM attending a sauna in a city in UK during a syphilis outbreak contributed to a decline in MSM cases, while the number of heterosexual cases continued to increase [223]. Offering STI/HIV testing to men attending two saunas in Newcastle, UK, in 2013, reached individuals that had never been screened for syphilis before (28% of clients screened, no infectious syphilis cases detected) [224]. In a study from the US, offering free testing twice a month to MSM at commercial sex venues in Maricopa County during two consecutive periods (December 2013 to November 2014 and December 2014 to November 2015) led to increasing numbers of syphilis cases detected [225]. The same study reported fewer commercial sex venues participating during the second period and attributed this decrease to MSM being less inclined to seek STI testing at venues they attend for sex.

Two large-scale adult lifestyle events in London, UK (Erotica, 2013; Sexpo, 2015) were used to offer outreach-based STI/HIV screening (blood testing for syphilis included) and sexual health advice to about 20,000 attendees (sexual orientation not specified) [226]. Of the 381 participants screened (56% men), 31% had never tested before for HIV, 3 (0.8%) were diagnosed with syphilis.

A doubling of the syphilis diagnoses rate (from 4% to 8%) among a cohort of high risk MSM was achieved after an MSM clinic in Brighton, UK was modernised to offer a walk-in system, possibility of self-taken swabs, POC tests/HIV and introduced a dedicated clinic team for patient continuity [222]. Increased attendance by high risk MSM explained the increased diagnostic rate.

The search did not identify studies reporting on syphilis related interventions in prisons settings relevant to the EU/EEA. This is consistent with the outcome of the evidence review that informed the ECDC/EMCDDA guidance on active case-finding of communicable diseases in prison settings, that indicated very limited evidence of effectiveness of STI testing [227] [228].

Partner notification

Six studies reported outcomes of interventions related to partner notification of syphilis cases (Table A5.1). In two studies the aim was to offer partner notification services in settings that do not usually perform partner notification but are seeing high numbers of syphilis cases [229,230]. Two other studies looked into how to more effectively reach the anonymous sex partners, frequently the case among MSM with syphilis [231,232]. One further study reported the impact of offering incentives to syphilis cases in order to increase the number of identified contacts [233]. Options to optimise partner services by targeting early syphilis cases are reported in one other study [234]. While most interventions were among syphilis cases and their contacts, two studies were specific to HIV-positive syphilis cases and their contacts [229,230].

In response to high numbers of syphilis infections among contacts of HIV-positive patients attending HIV-care clinics in Arizona State, US, partner services in several clinics were reinforced by allocating extra staff specialised in providing partner services, part-time every week, over the course of several years [229,230]. There was a decrease in the duration of time-to-treatment and time-to-interview [229,230] and an increase in number of partner elicitation interviews and number of locatable partners in the participating clinics [229].

Two US studies, reported on the use of Internet-based Partner Notification (IPN), a program designed to notify contacts of HIV/syphilis cases by using internet-locating information (email, website screen name) when traditional locating data (name, address, phone) were missing [231,232]. The use of IPN led to 83% more sex partners notified about exposure and 26% more partners medically examined in one study [231] and to 63% contacts successfully notified through IPN in the second study [232].

Also in the US, one study aimed to encourage syphilis patients to name partners and offer valid contact information during partner elicitation interview by using incentives offered progressively with the number of partners named [233]. A higher ratio of partners with information that allowed their follow-up (0.39 vs. 0.25, $p<0.05$) was observed after implementation of this intervention.

In order to adapt to limited resources, in NYC, US, partner services were restricted to syphilis cases ≤ 45 years-old and the interviews of late latent or latent of unknown duration syphilis cases were stopped [234]. This lead to the expected decrease in the number of syphilis interviews but also to better results for primary, secondary and early latent syphilis cases (more likely to be interviewed within 14 days of specimen collection, $p\leq0.001$).

The IUSTI European guidelines for the management of partners of persons with sexually transmitted infections published in 2015, recommend notification of all contacts of syphilis cases about the possibility of infection [235]. The look back period is 3 months for primary syphilis, 6 months for secondary syphilis and 2 years for early latent syphilis. Practitioners may consider epidemiological treatment (therapy given in advance of laboratory confirmation) for the contacts of infectious syphilis cases.

Education and awareness

Eleven studies reported outcomes of interventions that aimed at increasing awareness of the population on ongoing syphilis epidemics, increasing knowledge on syphilis infection and enabling early recognition of symptoms, advising on importance of testing and providing information on testing sites (Table A5.1). Ten interventions were among MSM, and one targeted an ethnic community [236]. Three studies were from Australia [237-239] and eight from the US [240-246].

Three other publications reported interventions that aimed at reducing STI incidence, two among adolescents [247,248] and one among STI clinic attendees [249]. One further study reported outcomes of syphilis testing after education intervention among healthcare workers [250].

Most interventions addressing MSM were social marketing campaigns including health promotion materials (posters, small-media), advertisements in newspapers, magazines, radio/TV, public transportation, gay press, syphilis alert banners on relevant websites, alerts on gay social media, mobile applications, etc. Three of these campaigns reported positive outcomes: 'Stop the sores' (Los Angeles, US, 2002) increased coverage of syphilis testing among the men targeted [242,244]; 'Check Yourself' (Los Angeles, US, 2007) increased frequency of recent testing [243] and 'Syphilis is Up' (Denver, US, 2013) increased syphilis testing by 22% and syphilis diagnoses by 78% [241]. Results were however inconclusive in the other studies. Two campaigns in Australia, 'Check-it-out' (Victoria, 2004) [238] and 'Drama Down Under' (Melbourne, 2008-2013) [237-239], did not result in improvements in the time-to-test or time-to-treat, or any significant increases in syphilis testing rates among MSM. Similarly, a social marketing campaign in Florida, 2004 [240] had no impact after six months, on risky sexual practices and did not increase clinic visits, or testing or treatment for syphilis, despite increasing exposure to the campaign.

With less resources required, an educational video 'Syphilis and Men' projected in an emergency room in a hospital in Bronx, US, in 2006, significantly ($p<0.001$) improved knowledge on syphilis symptoms, transmission, risk reduction strategies and treatment, among the men exposed [245].

In response to a high syphilis morbidity in the Hispanic community in Baltimore City, US, a culturally appropriate health promotion campaign - 'Syphilis Elimination Project' in 2014, significantly increased knowledge about syphilis ($p=0.009$), prevention and transmission ($p=0.033$) and testing behaviour after ten weeks of street and business outreach [236].

A RCT among STI clinic patients that investigated the impact on STI incidence (including syphilis) of a combination of brief patient-centred risk-reduction counselling and rapid HIV test (intervention) compared to rapid HIV test with information only (control) identified no significant difference in STI incidence six months later (aRR, 1.12; 95% CI, 0.94-1.33) [251].

While not being specific to syphilis, two meta-analyses reported on the impact of education interventions in reducing STI incidence among adolescents in the US [247,248]. Group-based comprehensive risk reduction interventions were effective in reducing STI (OR 0.65) but also the frequency of sexual activity (OR 0.81), unprotected sexual activity (OR 0.70) and number of sex partners (OR 0.83) but results were inconclusive for abstinence-promoting education interventions [247]. Similarly, in the second publication, comprehensive interventions programmes aimed at improving skills and promoting safe sex practice among adolescents proved to reduce the risk of STI (23% relative risk reduction) while abstinence-promoting education did not [248].

One study reported outcomes of interventions targeted to healthcare workers in primary care and sexual health/STI clinics [250]. A two-days course that aimed at building basic knowledge, skills and attitudes for effective STI patient management among doctors, nurses or any type of clinician that are routinely seeing patients with (or at risk of STIs in Ireland, found a low syphilis awareness before the course but induced a 12.7% increase in syphilis testing after the training.

Details on utilising social media for HIV/STI prevention programmes among young people can be found in the ECDC 2017 handbook [252] and a series of resources for effective use of digital platform for STI/HIV prevention among MSM at ECDC website [253].

Interventions using social media

Six studies reported on interventions using social media tools in response to syphilis clusters, outbreaks or, more generally, to increases in syphilis/STIs (Table A5.1). They targeted men/MSM [254-256], young people (adolescents or young adults) [257,258] or more largely, high risk individuals either young people or MSM [259], aiming to increase knowledge on and improve testing and diagnosis of syphilis and other STI [257-259], optimise syphilis case management [254] and partner services [256].

A Facebook page providing information on syphilis and where to get tested, created in response to an outbreak among MSM in Christchurch, New Zealand in 2012, is believed to have contributed to the decrease in infectious syphilis cases, in combination with other interventions [255]. A Facebook account created and used by public health services during a syphilis outbreak among young black MSM in Milwaukee, US, helped to identify 2 out of 55 syphilis cases and notify five partners that otherwise might not have been reached [256].

An online patient engagement platform and smartphone app ('Healthvana') was used to notify clients of a sexual health clinics network in the US on their STI test results, and was found to significantly reduce the time between STI test and notification (9 to 7 days, $p<0.001$) and between STI test and treatment (13 to 11 days, $p=0.022$) [254].

An internet-based STI testing service (e-STI testing) offering self-sampling kits for chlamydia, gonorrhoea, HIV and syphilis (details on the test not provided) to young sexually active adults in London, significantly increased testing uptake (RR 1.87, $p<0.0001$) in comparison to a website signposting the availability of testing at local clinics [258]. A large increase in testing for syphilis and an increase in syphilis detection were obtained by a social media-based youth driven campaign of twelve months (involving Facebook, Twitter, YouTube, Instagram) in Philadelphia, US that aimed to improve knowledge about and testing for STI/HIV [257]. The number of syphilis tests increased from 410 to 1150, and the number of positive test from 3 to 5, post-campaign.

A state-wide STD prevention and testing campaign in Rhode Island, US, using social media platforms identified through a social media-use survey among STD clinic attendees, doubled the percentage of MSM presenting to STD clinics [259].

Biomedical interventions

Two studies (RCT) reported on the use of doxycycline as pre-exposure prophylaxis [260] and post-exposure prophylaxis for syphilis (and other STIs) [261] among MSM engaging in high risk sexual practices, both aiming at reducing syphilis/STI incidence. One modelling study investigated the impact of the prophylactic use of doxycycline on syphilis incidence among MSM [262]. See Table A5.1.

Daily use of doxycycline (100 mg) by HIV-positive MSM engaging in high risk sexual practices (≥2 episodes of syphilis since their HIV diagnosis) and followed-up for a duration of 48 weeks, significantly reduced the composite STI incidence (chlamydia, gonorrhoea and syphilis together) (OR=0.27, 95% CI 0.09-0.83, $p=0.02$) as compared with contingency care, in a RCT pilot in US [260]. Two cases of syphilis occurred in the intervention group and six in the control group. When doxycycline (200 mg, single dose) was taken within the first 24 hours after condomless sex by HIV-negative MSM taking PrEP for HIV, during a 10-month follow-up period in a RCT in France, the occurrence of syphilis was significantly reduced (HR=0.27; 95% CI 0.07-0.98, $p=0.047$) as compared to no prophylaxis [261].

A modelling study in Australia, indicated that the prophylactic use of doxycycline (100 mg, daily, with 70% real-life effectiveness that considers imperfect adherence of users) could reduce syphilis incidence by 49% within one year and by 85% within 10 years, if taken consistently by 50% of MSM with a high risk sexual profile [262]. The authors indicated coverage, usage (adherence) and drug efficacy as main factors to influence effectiveness of doxycycline chemoprophylaxis as public health intervention.

Outbreak management studies

Nine studies reported on comprehensive responses involving multiple interventions to outbreaks (Table A5.2). Five outbreaks were mainly among heterosexuals (4 UK, 1 US), one among MSM (UK), one among MSM and bisexual men (New Zeeland) and two outbreaks affected both MSM and heterosexual populations (both in the UK). Congenital syphilis cases were reported in 3 out of 6 outbreaks involving heterosexual populations (2 UK, 1 US). Two reviews synthesised some of the lessons learned from public health responses to syphilis outbreaks in the UK [3,263].

In all the studies reviewed, the response activities were implemented through the coordination of multi-agency, multi-disciplinary outbreak control teams that involved public health authorities, sexual health/STI clinicians, primary care services, antenatal services and teenage pregnancy and contraceptive services, allowing for combination interventions to be implemented. Moreover, when the outbreak involved MSM and bisexual men,

community organisations offering sexual health services to MSM were engaged for facilitating access to 'hard-to-reach' individuals and for implementing MSM targeted responses [255,264,265]. Involving a tribal health agency and local Native American health services was pivotal for the response to a syphilis outbreak affecting American-Indian communities in the US [36].

Activities to raise public awareness and deliver health promotion information were described by eight studies [34,49,50,255,264-266]. The general public was informed about the outbreak, syphilis symptoms, importance of testing and about location of testing sites through local media campaigns (radio, newspapers, newsletters), posters, leaflets in public spaces or through social media. The gay press, social networking apps and Facebook pages were used for MSM-targeted health promotion and awareness raising campaigns [255,264,265].

Seven studies reported on increasing healthcare professionals' awareness of the outbreak, reminding them of syphilis symptoms and promoting testing and/or referral to specialised services [34,36,49,50,255,264,267]. Information was sent through letters, bulletins, newsletters, and public health agencies' websites and covered a wide range of healthcare practitioners (general practitioners, dentists, community pharmacists, sexual health clinics, acute clinical services, antenatal services, National Chlamydia Screening Programme (UK), etc.). In one study, a prompt appearing on electronic medical records screens in healthcare facilities was used to remind clinicians to offer syphilis screening [36].

Eight studies mentioned syphilis screening activities in response to outbreaks [33,34,36,49,50,255,266,267]. In particular, syphilis testing was extended to additional sites that do not routinely offer syphilis testing, such as National Chlamydia Screening Programme and sites offering contraceptives in the UK, during an outbreak involving heterosexuals [49]; to prisons during an outbreak involving the Native-American community in US [36]; and to an MSM sauna [267]. Enhanced antenatal screening with syphilis testing, repeated during the third trimester of pregnancy, was implemented during outbreaks involving heterosexuals [36,49,50]. Routine screening programmes, such as antenatal screening and blood donor screening, contributed to the detection of two cases in a UK outbreak [33] and of one case in an outbreak in New Zealand [255].

Partner services were attributed to have had successfully prevented the further spread of the outbreak when all cases managed to inform their contacts during an outbreak among heterosexuals in UK [33] or when most (78%) of the identified contacts attended partner services in a small syphilis outbreak among MSM and heterosexual students also in UK [266]. By contrast, in a prolonged outbreak (started in 2006 and still ongoing in 2010) among young heterosexuals in UK, only 50% of contacts could be traced [34]. Partner notification proved, however, most challenging for MSM in a New Zealand study, due to the large numbers of anonymous sexual contacts and use of geo-spatial networking apps [255].

A review of lessons learned from ten STIs outbreaks in UK [263] found that outbreak management teams benefited from using clinical staff knowledgeable about the local population. Informing and increasing the awareness of the outbreak of other professionals (in addition to the sexual health staff) can maximise case finding from settings other than sexual health clinics. While still relatively effective during heterosexual outbreaks, traditional partner notification approaches (by healthcare providers) have been challenged during MSM outbreaks especially due to the use of online apps leading to recruitment of anonymous partners. New approaches for partner notification of cases with anonymous sex partners were indicated as needed.

Outbreak management guidelines

Public Health England (PHE) (in 2017), and the Health Protection Surveillance Centre (HPSC), Ireland (in 2016), published operational guidance for managing outbreaks of STIs [268,269]. Both documents describe activities to be undertaken during an outbreak (control phase) but also before the outbreak (planning phase) and after the outbreak (evaluation phase) (Table 1).

Table 2. Management of local STI outbreaks

Phase, aim	Activities
Planning (preparedness) Aim: To ensure capacity to respond to outbreaks	
-	Develop outbreak investigation plans
	Identify and secure resources (including contingency funds)
	Create multidisciplinary teams. Maintain regular contact among members. (e.g. STI/sexual health clinicians, HIV and/or ID clinicians, epidemiologists, microbiologists, third sector (NGOs), communication experts, environmental officers, etc.)
	Ensure systems for identifying an outbreak (e.g. observations by clinicians or public health structures, exceedance reporting tools, automated spatiotemporal detection tool (developed based on SaTScan [270] and R [271]))
Preliminary investigation Aim: To confirm the outbreak	

Phase, aim	Activities
-	Review surveillance data, compare with expected level; descriptive epidemiology (e.g. epidemic curve); analytical epidemiology if justified
	Confirm increase
	Convene OCT, communicate, alert stakeholders
Control phase Aim: To interrupt onwards transmission to prevent further cases and recurrences	
-	Characterise the outbreak and select appropriate interventions (e.g. enhanced surveillance in STI clinics if justified (questionnaire); focused investigation and in-depth interviews with cases; case-control studies if needed)
	Primary prevention activities (to modify sexual risk taking behaviour)
	• outreach targeting key venues
	• sexual health promotion campaigns through media and social media (e.g. messages on local press or radio, social media, public transport). Involve community.
	• messages on sexual and social networking apps, Twitter, Facebook targeted to sexual networks, healthcare professionals
	Secondary prevention (to find and treat additional cases)
	• partner notification
	• case finding and venue based screening (e.g. expand testing through pre-existing sexual health programmes, screening in social venues for specific target groups)
Evaluation Aim: to determine effectiveness of the process and control interventions	
-	Process and outcome evaluation of outbreak response
	Audit interventions
	Produce outbreak report

Adapted after Public Health England, The United Kingdom and Health Protection Surveillance Centre, Ireland [268,269]

According to the PHE guidance, control activities should be infection specific, tailored to the phase of the outbreak/epidemic and the population affected. Information collected through enhanced surveillance in STI clinics (questionnaires, in-depth interviews with cases), discussions with members of the affected community and analytical epidemiology tools, may serve to characterise the outbreak, formulate hypotheses on risk factors and drivers of transmission and, orient the selection of response activities by the outbreak control team. Examples of primary and secondary prevention interventions suggested by PHE are presented in Table 1. PHE also provides a supplementary list of questions and answer options that can be used in outbreak investigations by public health professionals (access limited to PHE).

Information on stage of infection (primary, secondary and early latent syphilis) is important and it will provide insight into the development of the outbreak and effectiveness of control efforts. It may take several months or longer to control an STI outbreak, with the timeframe highly influenced by how early the outbreak was detected (PHE). Two publications describe in details the use of Kulldorff's scan statistics (SaTScan) to distinguish endemic and temporary clusters in syphilis diagnoses among men [4,270]. Investigating the diversity of local epidemics (i.e. sexual orientation, demographic factors, stage of syphilis infection and HIV serostatus) can predict outbreak structure, help the planning and evaluation of sexual health services and guide public health investigations [270].

2.4.2 Responses to increases in congenital syphilis infections

Six individual intervention studies and one systematic literature review reported on interventions related to increases in CS during the search period (Table A5.3).

Early prenatal syphilis screening (during the first or second trimester of pregnancy) together with treatment of maternal infection before 28 weeks of gestational age are the main instruments for prevention of CS. In a US CDC analysis reporting on effectiveness of prenatal screening to prevent CS in two US states with increasing rates of CS during 2013-2014, early screening averted 92% of potential CS cases (470/513 syphilis positive pregnant women delivered healthy babies) whereas screening during the third trimester averted 78% of potential CS cases (85/109 syphilis positive pregnant women delivered babies without CS) [272]. Factors associated with antenatal screening failing to prevent CS during the first or second trimester of pregnancy were: pregnant women refusing treatment, treatment insufficient for late or unknown duration of syphilis, women re-infected during pregnancy. For the third trimester of pregnancy the risk factors were: women seroconverting around delivery after testing negative earlier in pregnancy and pregnant women not being treated at least 30 days before delivery. Nine treatment failures in the same study were among women that were appropriately treated and who still delivered infected babies, with

elevated maternal titres and late gestational age identified as contributors. The authors concluded that prevention of all CS cases will require zero syphilis cases among women [272].

A review of evidence-base for other public health interventions to prevent CS in high/upper middle income countries was published by Plotzker et al 2018 [273]. The authors concluded that treatment of maternal syphilis infection with benzathine penicillin G (2.4 million units i.m. single dose for primary, secondary and early latent syphilis, and once a week for three weeks for late latent/unknown duration syphilis) is highly effective (close to 100%) if given before the 28th week of gestational age, and 90-98% effective at any gestational age [273]. Re-testing during the third trimester and at delivery of women at high risk of acquiring syphilis infection can identify infections among women that tested negative at a first screening test. Re-testing of high risk pregnancies detected 5% of prenatal syphilis diagnoses in two high morbidity states in the US during 2012-2014 and led to treatment and prevention of 30 CS cases [273]. Definition of high-risk groups that need to be targeted for repeat testing should be considered based on the local epidemiological profile. The evidence-base for the effectiveness of public health interventions such as partner notification and prenatal screening laws was limited. While there is some biological plausibility for identification and treatment of sexual contacts of positive pregnancies, no study clearly demonstrated that partner notification reduced CS incidence. Introduction of a universal antenatal screening policy in the US was associated with a reduction in neonatal mortality due to syphilis and it proved cost-effective. Finally, the authors indicate the importance of using surveillance data to identify gaps in CS prevention and guide clinical and public health responses.

Table 3. Considerations for follow-up interventions

Missed opportunity category	Potential follow-up interventions
Lack of prenatal care	• Congenital syphilis public education campaign • Partner with community-based organisations to conduct outreach to vulnerable populations • Partner with providers to reduce barriers to prenatal care • Partner with internal local health department staff, including staff from maternal, child, and adolescent health divisions to reduce barriers to prenatal care
Missed syphilis diagnosis	• Provide visitation and training on syphilis diagnosis and local syphilis epidemiologic data • Grand rounds for providers at healthcare facilities
Missed screening opportunity	• Provider visitation and training on screening recommendations and local syphilis epidemiologic data • Work with corrections to facilitate screening in jails
Missed treatment opportunity	• Ensure availability of benzathine penicillin G • Provider education on recommended treatment and importance of timely treatment • Partner with providers to ensure that pregnant women with syphilis are brought to treatment after positive lab result
Health department follow-up	• Syphilis reactor prioritisation evaluation • Ensure timeliness of syphilis case follow-up • Consider local systems and procedures that can improve prevention efforts

Note that this list highlights some potential follow-up interventions but is not comprehensive or targeted for any particular case or jurisdiction.
Adapted from: California Department of Public Health. The Congenital Syphilis Morbidity & Mortality Review Toolkit. A Prevention Tool for Local STD Programs (available from: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH Document Library/CDPH-CS-MM-Toolkit-PPT.pptx)

In line with this, two US studies used surveillance data to link pregnant women with syphilis to their birth outcomes in order to build CS prevention cascades [153,274]. Several indicators, all measured ≥30 days prior to delivery, such as % first prenatal care visit documented, % tested for syphilis, % initiated treatment, % treated according to stage were used to identify gaps in care and prevention needs. 2016 data for the US overall indicate that from the pregnant women reported with syphilis and at least 30 days before delivery, 88.0% received prenatal care, 89.4% were tested and 76.9% received adequate treatment, leading to a CS prevention ratio of 75% [274].

A case review board was established in Louisiana, the US state with the highest rate of CS in 2016, to study the CS cases files, identify gaps in practice and propose interventions [275]. Of the 79 CS cases recorded between January 2016 and July 2017, 60% could have been prevented and were associated with inadequate screening, treatment and reporting. Following the review board findings, many healthcare providers changed their practice.

Documenting pregnancy status of women of reproductive age with reactive syphilis laboratory results can offer further opportunities for CS prevention such as linkage to care and timely treatment. When implemented in Florida, US, an automated email alert system that requested/reminded healthcare staff to ascertain pregnancy status for all the 15-44 years old women with syphilis reactive laboratory results helped reducing the unknown pregnancy status by 70% [276]. Placing a clinical management algorithm of infants exposed to syphilis in the patient files in a tertiary maternity clinic in Ireland helped clinicians to comply with the evidence-based clinical guidance for investigation and treatment of such infants [277].

A CS prevention toolkit has been developed by California Department of Public Health, the STD control branch for use by local health authorities to conduct in-depth review of congenital syphilis cases to identify gaps in CS prevention and identify interventions to prevent future cases [278]. For each of the missed opportunities the document suggests some potential follow-up interventions (see Table 3 above).

The ECDC guidance on antenatal screening for infections published in 2017 recommends that all pregnant women should be tested for syphilis (universal, voluntary, opt-out strategy) during the first trimester of pregnancy or at the first antenatal care visit [279]. The testing offer should be repeated during the third trimester (ideally weeks 28–32) for women at increased risk of infection and for those who refused testing before. Countries should identify nationally relevant groups of pregnant women at increased risk of syphilis for targeted interventions.

Antenatal screening recommendations from several other organisations were identified through the search. Screening of all pregnant women very early in pregnancy, during the first antenatal care visit is also recommended by the WHO Guideline on Syphilis Screening and Treatment for Pregnant Women, 2017 [280], the British Association for Sexual Health and HIV (BASHH) UK national guidelines on the management of syphilis, 2015 [281] and the US Preventive Services Task Force recommendation for screening for syphilis infection in pregnant women, 2018 [282]. Repeat screening later in pregnancy and again at delivery in high risk women is recommended by the BASHH UK national guidelines on the management of syphilis, 2015 [281], the US CDC Sexually Transmitted Diseases Treatment Guidelines, 2015 [283] and American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) guidelines for perinatal care, 2017 [284]. The AAP and ACOG also recommend repeat screening after exposure to infected partner [284].

3 Conclusions and options for public health response

Epidemiology review

Over the last decade, syphilis trends have continued to increase in the EU/EEA Member States and several other high-income countries. The most affected population are urban men, with MSM accounting for an increasing proportion of cases. The numbers of reported cases among heterosexual men and women are lower than among MSM, but in some countries, their rates are increasing. Increases in syphilis among pregnant women in some high-income countries outside of the EU/EEA is a cause for concern as this has led to increases in congenital syphilis infections. Several syphilis outbreaks and clusters of cases have been reported in high-income countries over the last ten years.

There is a direct relation between sexual risk behaviour and the risk of syphilis or other STIs. The increases in syphilis infection are associated with high rates of unprotected/condomless sex, drug use, history of incarceration or previous STI [135,285,286]. The use of social networking sites or mobile device applications to find sex partners were cited among the determining factors during some outbreak investigations. Other factors cited included serosorting among HIV-seropositive MSM, a general increase in the number of sex partners in HIV-seronegative MSM and the impact of PrEP on risk compensation. These findings suggest a low awareness of the risk of syphilis that is resulting not only in rising trends of syphilis cases but also in high rates of coinfections and reinfections [285]. The reduction of condom use is due in part to increases in sero-adaptive behaviours among MSM and possibly the increasing reliance on PrEP for HIV prevention [286-289]. Syphilis rates are also higher in HIV-positive persons and in many cases in the foreign-born population.

The epidemiological impact of the social determinants known to be associated with the spread of syphilis such as poverty, migration or low status of women is magnified by prevalent patterns of sexual mixing, particularly race/ethnicity-assortative sex. Thus, the social context creates potential sex partner pools of individuals with high-risk sexual behaviours and high syphilis prevalence; this leads to a higher probability of exposure to infection for each sex act. This is especially so for those at higher risk in the lower social economic classes and ethnic minorities. Ethnic minorities and other groups like migrants or refugees often do not have the access to appropriate healthcare and this is essential for early diagnosis and treatment and therefore to prevent further STI transmission. Improvements in service accessibility and choice and the provision of sexual health services provide further opportunities for STI control [197].

Although congenital syphilis rates remain low in the EU/EEA, they have increased in other high-income countries. In order to ensure that congenital syphilis rates remain low, effective syphilis control particularly among heterosexuals, needs to be sustained together with implementation of national antenatal screening programmes with testing offered early during pregnancy to all women. Repeat testing of women at risk of re-infection in the third trimester and testing at delivery of all women who were not tested before, should also be ensured in order to reduce the risk of vertical transmission. In the United States, increases in congenital syphilis notifications followed the increases in syphilis rates among women. Collecting and analysing data on congenital syphilis cases and their mothers should identify gaps in prevention of mother-to-child transmission and inform future targeted interventions. Increased harmonisation of case definitions across the EU/EEA Member States and inclusion of adverse pregnancy outcomes would allow for a more complete estimation of the burden on mother-to-child transmission of syphilis.

Options for public health response

Public health response to increases in syphilis infections and to outbreaks may include a combination of *case finding* through screening of the general population or of populations at risk, partner notification/management and surveillance activities; *case management*, including appropriate treatment of diagnosed infections and risk reduction counselling; and *education* of the general population, of populations at higher risk, and education of healthcare providers. The response activities have to be adapted to the national or local settings, population group affected and determinants of transmission. Based on the epidemiology review findings and EU/EEA surveillance data the populations at highest risk for syphilis in EU/EEA include: HIV-positive MSM, HIV-negative MSM engaging in high risk sexual practices. Other groups at risk at national/local level can be identified based on local syphilis epidemiology.

A list of effective interventions as identified through the literature review on responses is presented below.

Enhanced screening of populations at risk

- Inclusion of syphilis testing in the routine HIV clinical monitoring (3 or 6-monthly, opt-out vs. risk based strategy) would increase detection of early asymptomatic infections among HIV-positive MSM.
- Quarterly vs. bi-annual or symptom-based testing would increase syphilis detection among the HIV-negative MSM engaging in high-risk sexual practices. A high number of sex partners and prior syphilis infection may be considered as indicative for enhanced screening. The link between PrEP users and high syphilis rates suggests that PrEP users should be one of the groups with increased frequency of syphilis testing.
- Setting reminders for clinicians to include syphilis in routine STI testing (e.g. system generated alerts) and sending reminders to patients to get screened or rescreened (e.g. SMS text, telephone) would optimise screening rates for syphilis and increase testing frequency among STI clinics attendees.
- In addition to MSM and STI clinics patients, other risk groups identified based on local syphilis epidemiology or as indicated by evidence-based guidelines, should be targeted for testing.
- Details on groups at risk to be targeted for testing for case finding are available from the IUSTI 2014, European guidelines on the management of syphilis [14] (currently under revision).

Screening in outreach settings

- Expanding testing outside of traditional settings should increase syphilis detection among populations at risk that otherwise would not be reached. Testing in venues where MSM meet for sex would help case detection in an outbreak context.
- Populations with inadequate access to healthcare (for example ethnic minority or marginalised populations) can also be targeted through outreach testing.
- People with positive screening tests (i.e. rapid POC tests) should be linked to health service for appropriate verification of results and reporting, treatment and follow up (including partner services).
- ECDC and EMCDDA guidance on communicable diseases case finding in prison settings recommends STI testing based on risk profile, age-based and/or universal testing approaches [228]. The evidence for effectiveness for the EU/EEA settings was considered very limited.

Partner notification

- Placing staff trained in partner management in settings seeing high numbers of syphilis cases where they do not usually undertake such activities (e.g. community based clinics) or improving partner management skills of existing staff would improve performance of partner identification and management.
- Setting quality standards and indicators such as number of partners elicited per index patients, number of partner tested per index patients, number of partners treated will help to measure performance of partner services [235,290].
- Using alternative tools for notifying and locating contacts (i.e. internet-locating information) would be useful when traditional contact information is missing.
- Details on the management of contacts of syphilis cases are provided by the European guidelines for management of partners of persons with sexually transmitted infections, IUSTI 2015 [235] and the 2014 European Guideline on the Management of Syphilis [14].

Education

- Depending on local epidemiology, educational, health promotion and awareness raising should be directed at the general population and/or targeted at sub-populations at higher risk.
- Education campaigns among MSM may help increase knowledge on syphilis and its transmission, awareness of ongoing outbreaks, increase testing and detect early syphilis infections. Evaluations of education campaigns outcomes are recommended because of mixed impact reported.
- Education interventions among adolescents improving skills and promoting safer sex practice proved effective in reducing STI occurrence.
- Education of healthcare providers is important to maintain a suitable level of knowledge and awareness that will facilitate early recognition of symptoms and of atypical presentations and will increase syphilis testing and case detection.

Using social media

- The use of social media platforms such as Facebook, Twitter, YouTube and Instagram appears to be an effective way to reach adolescents, young adults and MSM in order to improve knowledge on and increase testing syphilis.
- Internet-based testing services, online and smart-phone applications (dating apps) or Facebook may offer alternatives to traditional patient care pathways and partner services.

- Details on utilising social media for HIV/STI prevention programmes among young people can be found in ECDC 2017 handbook [252] and a series of resources for effective use of digital platform for STI/HIV prevention among MSM at ECDC website [253].

Biomedical interventions

- Doxycycline chemoprophylaxis, either as pre- or post-exposure prophylaxis, appears to be effective for syphilis prevention among MSM. More evidence is needed on the long-term consequences of this strategy for syphilis and other infections before considering widespread implementation [291].

Case management (treatment)

- While not in the scope of this review, details on the recommended treatment regimens are available in the 2014 IUSTI Guidelines on the management of syphilis [14]. Benzathine penicillin G (2.4 million units intramuscularly, one day) is recommended as the first line therapy option for early syphilis cases and procaine penicillin (600,000 units, intramuscularly, daily for 10-14 days) as a second option if benzathine penicillin G is not available. Details on the clinical and serology follow-up of early syphilis cases are provided [214].
- Syphilis cases usually become non-infectious with within five days after one dose of benzathine penicillin G [292]. Patients need to be informed that completion of a treatment course does not confer immunity and re-infection may occur [293]. Immediate epidemiologic treatment is advised for sexual contacts, particularly if the contact is a pregnant woman [14].

Establishing comprehensive outbreak response

- Responses to syphilis outbreaks should be coordinated by a multi-disciplinary outbreak control team that may involve public health authorities, sexual health/STI clinicians, primary care services, antenatal services and teenage pregnancy and contraceptive services – depending on outbreak characteristics, allowing for combination interventions to be implemented.
- Involving community organisations, such as organisations offering sexual health services to MSM during outbreak involving MSM and bisexual men for example, will facilitate access to 'hard-to-reach' individuals and implementation of targeted responses.
- Interventions should be tailored to the phase of the outbreak/epidemic and the population affected.
- Details on outbreaks management guidelines were presented in chapter 3.4.1 and examples of interventions in Table 1.

Based on public health practice of the EU/EEA Member States that responded to the ECDC syphilis survey, several other interventions may be considered in response to current increases and outbreaks of syphilis. These include:

- Implementation of a national STI strategy either as a stand-alone strategy or integrated in a larger sexual health or HIV/STI strategy. An STI strategy is an important element that will ensure commitment of various stakeholders and allocation of resources (trained staff, contingency budget for outbreak activities).
- Development of national syphilis action plans and enhanced surveillance activities.
- Increased emphasis on sexual education in schools, shifting from an HIV focus to HIV and STI.
- Increasing the number of 'checkpoints' for low-threshold testing in major cities, mostly targeting MSM.
- Communication on increases in syphilis infections in epidemiological bulletins.

Prevention of congenital syphilis

- Universal offer of early prenatal syphilis screening (during the first trimester of pregnancy), together with treatment of maternal infection before 28 weeks of gestation and appropriate to the stage of the infection – these are the main instruments for the prevention of congenital syphilis.
- Re-testing during the third trimester (before 32 weeks gestation to allow enough time for effective treatment) is recommended for women at high risk of syphilis. Countries should identify nationally relevant high-risk groups based on the local epidemiological profile. All women should be tested at delivery – if not already tested during pregnancy.
- Collecting surveillance data that link syphilis-infected pregnant women to their birth outcomes can identify gaps in prevention in order to prevent mother-to-child transmission and inform targeted interventions.
- Examples of interventions should include: public education campaigns on congenital syphilis, healthcare provider education/training on screening and treatment recommendations, and ensuring availability of benzathine penicillin G for the treatment of pregnant women.
- Details on screening recommendations and interventions for improving antenatal screening for syphilis (and HIV and hepatitis B) among vulnerable groups are provided in ECDC's 2017 antenatal screening guidance [279].

- Increased harmonisation of case definitions across EU/EEA Member States and inclusion of adverse pregnancy outcomes would allow for a more complete estimation of the disease burden with regard to the mother-to-child transmission of syphilis.

Strengths and limitations of this report

The main strength of this report lies in the use of a comprehensive and transparent methodological approach to document increases in the number of syphilis infections in the EU/EEA and other high-income countries. In addition, the report identifies the main drivers of transmission and the affected populations groups. This is achieved by a literature review of the syphilis epidemiology, an analysis of the EU/EEA surveillance data, and a survey among experts in the Member States.

An evidence-based approach was used to identify options for response, again relying on a systematic literature review and a survey among Member States. Both literature reviews involved comprehensive searches in several databases and a search of grey literature, covering the period 2007–2018.

Most of the data used to describe disease trends are notification data. Disease surveillance data suffer from a number of limitations, including, as described above, under-ascertainment and underreporting. In addition, some countries report data from sentinel surveillance systems which, by definition, collect only a proportion of the total number of diagnoses. Access to diagnostic services may also vary across Europe. A number of countries reported changes in the syphilis surveillance systems between 2010 and 2017, which include modifications in the reporting methodology (nine countries), an increase in the number of reporting sites (four), and a number of other changes (three).

Case definitions used for reporting syphilis data vary across the EU/EEA and varied over the period under observation. This may have had an impact on cases included in surveillance at the EU/EEA level. A number of countries do not report the stage of syphilis infection, which means that the interpretation of data on infectious syphilis is difficult and that comparisons should be made with caution.

For congenital syphilis, the current case definition at the EU/EEA level does not include stillbirths, possibly leading to some case of congenital syphilis transmission that are not captured by the surveillance system. An updated European congenital syphilis case definition has been agreed upon by the European surveillance network [31]. A number of countries have national case definitions for both syphilis and congenital syphilis. It is not known how much these deviate from the EU case definition and how they impact disease surveillance. These challenges will be addressed in cooperation with the European STI disease network.

The limitations of the systematic review are linked to limitations of the literature found. A large number of the publications included descriptions of interventions without a proper documentation of outcomes and public health impact. Some of the citations were conference abstracts, limiting the amount of information about study background. Very few studies were of high quality; the majority of included studies were pre- and post-intervention comparisons. The heterogeneous nature of the interventions, differences in aims, and a large variation in measurements of the impact did not allow the pooling of data and the grading of evidence. Although the research team did not apply language filters, most studies were from English-speaking countries such as the USA and Australia, with European countries other than the UK and Ireland poorly or not at all represented (except for the Netherlands).

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Annex 1. Epidemiology data on syphilis and congenital syphilis, EU/EEA countries 2007–2017

Table A1. Distribution of confirmed cases of syphilis, EU/EEA, 2007–2017

Country	2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017	
	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate
Austria	58	-	61	-	62	-	59	-	72	-	78	-	538	-	.	.	.	.	.	.	.	.
Belgium	397	-	586	-	579	-	586	-	613	-	658	-	867	-	872	-	892	-	1531	-	1493	-
Bulgaria	440	5.8	419	5.6	420	5.6	397	5.3	314	4.3	309	4.2	354	4.9	460	6.3	465	6.5	367	5.1	516	7.3
Croatia	.	.	.	.	.	.	.	.	.	.	28	0.7	80	1.9	51	1.2	25	0.6	27	0.6	29	0.7
Cyprus	10	1.3	14	1.8	15	1.9	20	2.4	16	1.9	6	0.7	12	1.4	18	2.1	31	3.7	16	1.9	21	2.5
Czech Republic	205	2	342	3.3	697	6.7	462	4.4	372	3.5	329	3.1	402	3.8	408	3.9	554	5.3	546	5.2	560	5.3
Denmark	92	1.7	151	2.8	255	4.6	413	7.5	427	7.7	343	6.1	317	5.7	361	6.4	777	13.7	365	6.4	325	5.7
Estonia	78	5.8	71	5.3	57	4.3	69	5.2	66	5	40	3	39	3	35	2.7	25	1.9	28	2.1	34	2.6
Finland	185	3.5	211	4	194	3.6	200	3.7	173	3.2	201	3.7	153	2.8	196	3.6	243	4.4	211	3.8	175	3.2
France	597	-	570	-	541	-	657	-	784	-	865	-	1014	-	1405	-	1755	-	1863	-	1748	-
Germany	3280	4	3188	3.9	2738	3.3	3033	3.7	3702	4.6	4414	5.5	5324	6.6	5821	7.2	6705	8.3	7172	8.7	7473	9.1
Greece	197	1.8	155	1.4	259	2.3	241	2.2	272	2.4	363	3.3	300	2.7	247	2.3	320	2.9	348	3.2	-	-
Hungary	393	-	549	-	489	-	504	-	565	-	621	-	627	-	622	6.3	617	6.3	712	7.2	728	7.4
Iceland	1	0.3	2	0.6	0	0	5	1.6	2	0.6	5	1.6	3	0.9	25	7.7	23	7	30	9	52	15.4
Ireland	62	1.5	119	2.7	106	2.3	115	2.5	150	3.3	110	2.4	163	3.5	204	4.4	276	5.9	295	6.2	392	8.2
Italy	1002	1.7	927	1.6	1075	1.8	1182	2	992	1.7	1138	1.9	1170	2	1151	1.9	1060	1.7	1420	2.3	1631	2.7
Latvia	305	13.8	236	10.8	175	8.1	122	5.8	143	6.9	148	7.2	127	6.3	139	6.9	141	7.1	164	8.3	135	6.9
Lithuania	275	8.5	326	10.1	326	10.2	345	11	273	8.9	227	7.6	269	9.1	257	8.7	130	4.5	151	5.2	157	5.5
Luxembourg	14	2.9	12	2.5	13	2.6	13	2.6	28	5.5	20	3.8	27	5	27	4.9	21	3.7	27	4.7	26	4.4
Malta	11	2.7	19	4.7	16	3.9	25	6	45	10.8	35	8.4	45	10.7	49	11.4	41	9.3	40	8.9	62	13.5
Netherlands	657	-	792	-	709	-	695	-	545	-	649	-	743	-	975	-	1221	-	1515	-	1519	-
Norway	61	1.3	56	1.2	76	1.6	118	2.4	130	2.6	109	2.2	185	3.7	189	3.7	172	3.3	188	3.6	223	4.2
Poland	847	2.2	929	2.4	1255	3.3	914	2.4	941	2.5	961	2.5	1324	3.5	1147	3	1239	3.3	1291	3.4	1593	4.2
Portugal	109	1	93	0.9	145	1.4	169	1.6	144	1.4	235	2.2	155	1.5	101	1	43	0.4	73	0.7	83	0.8
Romania	4245	20.1	4006	19.4	3253	15.9	1809	8.9	2349	11.6	1717	8.5	1393	7	1267	6.4	969	4.9	947	4.8	814	4.1
Slovakia	153	2.8	228	4.2	301	5.6	328	6.1	416	7.7	412	7.6	337	6.2	369	6.8	295	5.4	373	6.9	361	6.6
Slovenia	31	1.5	63	3.1	47	2.3	40	2	79	3.9	63	3.1	35	1.7	23	1.1	43	2.1	35	1.7	48	2.3
Spain	2294	5.1	2961	6.5	2496	5.4	3187	6.9	3522	7.5	3641	7.8	3723	8	3568	7.7	3756	8.1	3356	7.2	4813	10.3
Sweden	237	2.6	165	1.8	182	2	198	2.1	206	2.2	197	2.1	275	2.9	244	2.5	326	3.3	348	3.5	384	3.8
United Kingdom	3561	5.8	3309	5.4	3185	5.1	2923	4.7	3238	5.1	3360	5.3	3665	5.7	4787	7.4	5809	9	6505	9.9	7798	11.8
Total EU/EEA	19797	4.5	20560	4.6	19666	4.4	18829	4.1	20579	4.6	21282	4.6	23666	5	25018	5.3	27974	5.9	29944	6.1	33193	7.1

** Rate: number of cases per 100 000 population*

Table A2. Confirmed cases and rates of congenital syphilis by country and year, EU/EEA, 2007–2017

Country	2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017	
	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate	Number of confirmed cases	Rate
Austria	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Belgium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bulgaria	37	49.1	23	29.6	30	37.1	34	45.0	38	53.6	29	42.0	27	40.6	24	35.5	10	15.2	13	20.0	14	21.5
Croatia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
Cyprus	-	-	-	-	0	-	0	-	0	-	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Czech Republic	3	2.6	0	0.0	0	0.0	1	0.9	0	0.0	1	0.9	1	0.9	0	0.0	4	3.6	1	0.9	1	0.9
Denmark	0	0.0	0	0.0	0	0.0	2	3.2	1	1.7	0	0.0	1	1.8	1	1.8	0	0.0	1	1.6	0	0
Estonia	1	6.3	0	0.0	0	0.0	1	6.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Finland	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
France	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Germany	3	0.4	0	0.0	3	0.5	1	0.1	2	0.3	5	0.7	3	0.4	0	0.0	3	0.4	2	0.3	3	0.4
Greece	-	-	1	0.8	0	0.0	2	1.7	3	2.8	0	0.0	1	1.1	0	0.0	2	2.2	-	-	-	-
Hungary	3	3.1	1	1.0	1	1.0	1	1.1	0	0.0	0	0.0	2	2.2	1	1.1	0	0.0	2	2.1	3	3.1
Iceland	-	-	-	-	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Ireland	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.6
Italy	8	1.4	0	0.0	12	2.1	13	2.3	7	1.3	5	0.9	7	1.4	4	0.8	5	1.0	-	-	-	-
Latvia	0	0.0	1	4.1	3	13.6	0	0.0	0	0.0	1	5.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Lithuania	1	3.3	2	6.3	4	12.4	2	6.5	0	0.0	1	3.3	2	6.7	1	3.3	3	9.5	0	0.0	1	3.3
Luxembourg	-	-	-	-	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Malta	-	-	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Netherlands	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Norway	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Poland	3	0.8	0	0.0	10	2.4	18	4.4	11	2.8	7	1.8	16	4.3	8	2.1	4	1.1	6	1.6	1	0.3
Portugal	21	20.5	14	13.4	13	13.1	11	10.9	10	10.3	6	6.7	5	6.0	7	8.5	5	5.8	2	2.3	4	4.6
Romania	26	12.1	9	4.1	7	3.1	6	2.8	10	5.1	6	3.0	3	1.6	7	3.6	5	2.5	4	2.1	6	3
Slovakia	-	-	2	3.5	4	6.5	1	1.7	1	1.6	0	0.0	0	0.0	2	3.6	0	0.0	0	0.0	0	0
Slovenia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Spain	11	2.2	10	1.9	11	2.2	5	1.0	4	0.9	1	0.2	3	0.7	6	1.4	1	0.2	4	1.0	2	0.5
Sweden	1	0.9	1	0.9	2	1.8	1	0.9	1	0.9	1	0.9	0	0.0	0	0.0	0	0.0	2	1.7	0	0
United Kingdom	4	0.5	3	0.4	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Total EU/EEA	122	3.1	67	1.6	100	2.4	100	2.4	89	2.2	63	1.6	71	1.8	61	1.5	41	1.1	37	1.1	36	1.1

** Rate: number of cases per 100 000 population*

Annex 2. Search strategy

Search of the literature review on epidemiological syphilis data

PubMed search:

Search	query	Results
#1	Search ('Syphilis'[Mesh] OR 'Syphilis, Congenital'[Mesh] OR 'Syphilis Serodiagnosis'[Mesh] OR syphili*[TW] OR Great Pox*[TW] OR 'Hutchinson's Teeth'[TW] OR Hutchinson Teeth[TW] OR 'Hutchinsons Teeth'[TW] OR lues[TW])	36757
#2	Search (case*[TI] OR cluster*[TI] OR distributed[TI] OR distribution*[TI] OR endemic*[TI] OR epidemic*[TI] OR epidemiolog*[TI] OR frequenc*[TI] OR frequent*[TI] OR inciden*[TI] OR number*[TI] OR occur*[TI] OR outbreak*[TI] OR pandemic*[TI] OR percent*[TI] OR prevalen*[TI] OR prognos*[TI] OR proportion*[TI] OR rate*[TI] OR recurren*[TI] OR reoccur*[TI] OR re-occur*[TI] OR sero epidemiolog*[TI] OR sero inciden*[TI] OR sero positiv*[TI] OR sero prevalen*[TI] OR sero survey*[TI] OR serodiagnos*[TI] OR seroepidemiolog*[TI] OR seroinciden*[TI] OR serolog*[TI] OR seropositiv*[TI] OR seroprevalen*[TI] OR serosurvey*[TI] OR spread*[TI] OR surveillance*[TI] OR time*[TI] OR trend*[TI] OR case*[OT] OR cluster*[OT] OR distributed[OT] OR distribution*[OT] OR endemic*[OT] OR epidemic*[OT] OR epidemiolog*[OT] OR frequenc*[OT] OR frequent*[OT] OR inciden*[OT] OR number*[OT] OR occur*[OT] OR outbreak*[OT] OR pandemic*[OT] OR percent*[OT] OR prevalen*[OT] OR prognos*[OT] OR proportion*[OT] OR rate*[OT] OR recurren*[OT] OR reoccur*[OT] OR re-occur*[OT] OR sero epidemiolog*[OT] OR sero inciden*[OT] OR sero positiv*[OT] OR sero prevalen*[OT] OR sero survey*[OT] OR serodiagnos*[OT] OR seroepidemiolog*[OT] OR seroinciden*[OT] OR serolog*[OT] OR seropositiv*[OT] OR seroprevalen*[OT] OR serosurvey*[OT] OR spread*[OT] OR surveillance*[OT] OR time*[OT] OR trend*[OT])	2669149
#3	Search (#1 AND #2)	9626
#4	Search (ascen*[TW] OR augmentat*[TW] OR burden[TW] OR climb[TW] OR climbed[TW] OR climbing[TW] OR detect*[TW] OR go up[TW] OR going up[TW] OR gone up[TW] OR growing[TW] OR growth[TW] OR identificat*[TW] OR increas*[TW] OR link[TW] OR linked[TW] OR mount[TW] OR mounted[TW] OR mounting[TW] OR rise[TW] OR rised[TW] OR rising[TW] OR transmi*[TW] OR upsurg*[TW] OR went up[TW])	9223806
#5	Search (case*[TW] OR cluster*[TW] OR distributed[TW] OR distribution*[TW] OR endemic*[TW] OR epidemic*[TW] OR epidemiolog*[TW] OR frequenc*[TW] OR frequent*[TW] OR inciden*[TW] OR number*[TW] OR occur*[TW] OR outbreak*[TW] OR pandemic*[TW] OR percent*[TW] OR prevalen*[TW] OR prognos*[TW] OR proportion*[TW] OR rate*[TW] OR recurren*[TW] OR reoccur*[TW] OR re-occur*[TW] OR sero epidemiolog*[TW] OR sero inciden*[TW] OR sero positiv*[TW] OR sero prevalen*[TW] OR sero survey*[TW] OR serodiagnos*[TW] OR seroepidemiolog*[TW] OR seroinciden*[TW] OR serolog*[TW] OR seropositiv*[TW] OR seroprevalen*[TW] OR serosurvey*[TW] OR spread*[TW] OR surveillance*[TW] OR time*[TW] OR trend*[TW])	14611876
#6	Search (#1 AND #4 AND #5)	9304
#7	Search ('Cluster Analysis'[Mesh] OR 'Disease Transmission, Infectious'[Mesh] OR 'Disease Outbreaks'[Mesh] OR 'Epidemics'[Mesh] OR 'Population Surveillance'[Mesh] OR 'Epidemiological Monitoring'[Mesh] OR 'Incidence'[Mesh] OR 'Prevalence'[Mesh] OR 'Morbidity'[Mesh:NoExp] OR 'Mortality'[Mesh:NoExp] OR 'Fatal Outcome'[Mesh] OR 'Mortality, Premature'[Mesh] OR 'Survival Rate'[Mesh] OR 'Global Burden of Disease'[Mesh])	953442
#8	Search ('Syphilis/epidemiology'[Mesh] OR 'Syphilis/transmission'[Mesh] OR 'Syphilis, Congenital/epidemiology'[Mesh] OR 'Syphilis, Congenital/transmission'[Mesh] OR syphili*[TI] OR Great Pox*[TI] OR (('Hutchinson's'[TI] OR Hutchinson[TI] OR Hutchinsons[TI]) AND teeth[TI]) OR lues[TI] OR syphili*[OT] OR Great Pox*[OT] OR (('Hutchinson's'[OT] OR Hutchinson[OT] OR Hutchinsons[OT]) AND teeth[OT]) OR lues[OT])	23768
#9	Search [158 AND #8]	2333
#10	Search (#3 OR #6 OR #9)	15839
#11	Search [38 AND 2007:2018[DP]]	5016

Embase.com search:

Search	query	Results
#1	syphili*:ab,ti,kw OR 'great pox*':ab,ti,kw OR lues:ab,ti,kw OR ((hutchinson* NEXT/2 teeth):ab,ti,kw)	31227
#2	case*:ti,kw OR cluster*:ti,kw OR distributed:ti,kw OR distribution*:ti,kw OR endemic*:ti,kw OR epidemic*:ti,kw OR epidemiolog*:ti,kw OR frequenc*:ti,kw OR frequent*:ti,kw OR inciden*:ti,kw OR number*:ti,kw OR occur*:ti,kw OR outbreak*:ti,kw OR pandemic*:ti,kw OR percent*:ti,kw OR prevalen*:ti,kw OR prognos*:ti,kw OR proportion*:ti,kw OR rate*:ti,kw OR recurren*:ti,kw OR	3356974

Search	query	Results
	reoccur*:ti,kw OR 're occur*':ti,kw OR serodiagnos*:ti,kw OR seroepidemiolog*:ti,kw OR seroinciden*:ti,kw OR serolog*:ti,kw OR seropositiv*:ti,kw OR seroprevalen*:ti,kw OR serosurvey*:ti,kw OR spread*:ti,kw OR surveillance*:ti,kw OR time*:ti,kw OR trend*:ti,kw OR ((sero NEXT/2 (epidemiolog* OR inciden* OR positiv* OR prevalen* OR survey*)):ti,kw)	
#3	#1 AND #2	9036
#4	'cluster analysis'/exp OR 'disease transmission'/exp OR 'epidemic'/exp OR 'outbreak'/exp OR 'surveillance'/exp OR 'disease surveillance'/exp OR 'incidence'/exp OR 'prevalence'/exp OR 'morbidity'/exp OR 'mortality rate'/exp OR 'fatality'/exp OR 'mortality'/de OR 'premature mortality'/exp OR 'survival rate'/exp OR 'burden'/exp OR 'disease burden'/exp	2333246
#5	syphili*:ti,kw OR 'great pox*':ti,kw OR lues:ti,kw OR ((hutchinson* NEXT/2 teeth):ti,kw)	20688
#6	#4 AND #5	2921
#7	((syphili* OR 'great pox*' OR 'hutchinson teeth' OR 'hutchinsons teeth' OR lues) NEAR/5 (case* OR cluster* OR distributed OR distribution* OR endemic* OR epidemic* OR epidemiolog* OR frequenc* OR frequent* OR inciden* OR number* OR occur* OR outbreak* OR pandemic* OR percent* OR prevalen* OR prognos* OR proportion* OR rate* OR recurren* OR reoccur* OR 're-occur*' OR 'sero epidemiolog*' OR 'sero inciden*' OR 'sero positiv*' OR 'sero prevalen*' OR 'sero survey*' OR serodiagnos* OR seroepidemiolog* OR seroinciden* OR serolog* OR seropositiv* OR seroprevalen* OR serosurvey* OR spread* OR surveillance* OR time* OR trend*)):ab,ti	10768
#8	#3 OR #6 OR #7	14353
#9	#8 AND [2007-2018]/py	6492

Scopus search:

Search	Query	Results
#1	TITLE-ABS((syphili* OR 'Great Pox*' OR 'Hutchinson* Teeth' OR lues) W/5 (case* OR cluster* OR distributed OR distribution* OR endemic* OR epidemic* OR epidemiolog* OR frequenc* OR frequent* OR inciden* OR number* OR occur* OR outbreak* OR pandemic* OR percent* OR prevalen* OR prognos* OR proportion* OR rate* OR recurren* OR reoccur* OR 're occur*' OR re-occur* OR 'sero epidemiolog*' OR 'sero inciden*' OR 'sero positiv*' OR 'sero prevalen*' OR 'sero survey*' OR serodiagnos* OR seroepidemiolog* OR seroinciden* OR serolog* OR seropositiv* OR seroprevalen* OR serosurvey* OR spread* OR surveillance* OR time* OR trend*)) AND PUBYEAR > 2006	3 433

Table A2.1. Number of records

-	Number of records
All	14941
After de-duplication	8299
After first geographical filter (by title)	6103
After second geographical filter (by abstract)	4690
After subject filter – by title	1361
After subject filter – by abstract	265
After full text reading filter	189

Table A2.2. De-duplication of records

De-duplicate round	Number of records
1st	12 426
2nd	11 918
3rd	11 889
4th	11 843
5th	8 904
6th	8 810
Eye-bowling	8 299

Search of the systematic review on syphilis responses

PubMed (search run on 14 December 2018)

No.	Query	Results
#1	Search ('Syphilis'[Mesh] OR 'Syphilis, Congenital'[Mesh] OR 'Syphilis Serodiagnosis'[Mesh] OR syphili*[TW] OR Great Pox*[TW] OR 'Hutchinson's Teeth'[TW] OR Hutchinson Teeth[TW] OR 'Hutchinsons Teeth'[TW] OR lues[TW])	36936
#2	Search (case*[TW] OR cluster*[TW] OR detect*[TW] OR distributed[TW] OR distribution*[TW] OR endemic*[TW] OR epidemic*[TW] OR epidemiolog*[TW] OR frequenc*[TW] OR frequent*[TW] OR inciden*[TW] OR identificat*[TW] OR number*[TW] OR occur*[TW] OR outbreak*[TW] OR pandemic*[TW] OR percent*[TW] OR prevalen*[TW] OR prognos*[TW] OR proportion*[TW] OR rate*[TW] OR recurren*[TW] OR reoccur*[TW] OR sero epidemiolog*[TW] OR sero inciden*[TW] OR sero positiv*[TW] OR sero prevalen*[TW] OR sero survey*[TW] OR serodiagnos*[TW] OR seroepidemiolog*[TW] OR seroinciden*[TW] OR serolog*[TW] OR seropositiv*[TW] OR seroprevalen*[TW] OR serosurvey*[TW] OR spread*[TW] OR surveillance*[TW] OR time*[TW] OR transmi*[TW] OR trend*[TW])	15738387
#3	Search (ascen*[TW] OR augmentat*[TW] OR burden[TW] OR climb[TW] OR climbed[TW] OR climbing[TW] OR go up[TW] OR going up[TW] OR gone up[TW] OR growing[TW] OR growth[TW] OR increas*[TW] OR link[TW] OR linked[TW] OR mount[TW] OR mounted[TW] OR mounting[TW] OR rise[TW] OR rised[TW] OR rising[TW] OR upsurg*[TW] OR went up[TW] OR emerg*[TI] OR reemerg*[TI] OR emerg*[OT] OR reemerg*[OT])	7340857
#4	Search (#1 AND #2 AND #3)	5023
#5	Search ('Cluster Analysis'[Mesh] OR 'Disease Transmission, Infectious'[Mesh] OR 'Disease Outbreaks'[Mesh] OR 'Epidemics'[Mesh] OR 'Population Surveillance'[Mesh] OR 'Epidemiological Monitoring'[Mesh] OR 'Incidence'[Mesh] OR 'Prevalence'[Mesh] OR 'Morbidity'[Mesh:NoExp] OR 'Mortality'[Mesh:NoExp] OR 'Fatal Outcome'[Mesh] OR 'Mortality, Premature'[Mesh] OR 'Survival Rate'[Mesh] OR 'Global Burden of Disease'[Mesh])	957329
#6	Search ('Syphilis/epidemiology'[Mesh] OR 'Syphilis/transmission'[Mesh] OR 'Syphilis, Congenital/epidemiology'[Mesh] OR 'Syphilis, Congenital/transmission'[Mesh] OR syphili*[TI] OR Great Pox*[TI] OR (('Hutchinson's'[TI] OR Hutchinson[TI] OR Hutchinsons[TI]) AND teeth[TI]) OR lues[TI] OR syphili*[OT] OR Great Pox*[OT] OR (('Hutchinson's'[OT] OR Hutchinson[OT] OR Hutchinsons[OT]) AND teeth[OT]) OR lues[OT])	23910
#7	Search (#3 AND #5 AND #6)	886
#8	Search (#4 OR #7)	5025
#9	Search (interven*[TW] OR respon*[TW] OR measure*[TW] OR treatment*[TW] OR control*[TW] OR prevent*[TW] OR program*[TW] OR recommend*[TW])	12761965
#10	Search (#8 AND #9)	3562
#11	Search (Guideline[PT] OR 'Health Planning Guidelines'[Mesh] OR guideline[TI] OR guidelines[TI] OR guide[TI] OR guidance[TI] OR evidence based[TI] OR best practice*[TI] OR action plan*[TW] OR response plan*[TW] OR ((systematic review[TIAB] OR meta-analy*[TIAB] OR metanaly*[TIAB] OR metaanaly*[TIAB] OR met analy*[TIAB] OR guidance[TIAB] OR guideline[TIAB] OR guidelines[TIAB] OR guide[TIAB] OR evidence based[TIAB] OR best practice*[TIAB] OR evidence synthesis[TIAB]) AND Guideline[PT]))	160845
#12	Search ('Syphilis'[Mesh] OR 'Syphilis, Congenital'[Mesh] OR 'Syphilis Serodiagnosis'[Mesh] OR syphili*[TW] OR Great Pox*[TW] OR 'Hutchinson's Teeth'[TW] OR Hutchinson Teeth[TW] OR 'Hutchinsons Teeth'[TW] OR lues[TW] OR sexual transmitted[TW] OR sexually transmitted[TW] OR std[TW] OR sti[TW])	82210
#13	Search (#11 AND #12)	888
#14	Search (#10 OR #13)	4421
#15	Search (#14 AND 2007:2018[DP])	2274

Embase.com (search run 10 December 2018)

No.	Query	Results
#1	syphili*:ab,ti,kw OR 'great pox*':ab,ti,kw OR lues:ab,ti,kw OR ((hutchinson* NEXT/2 teeth):ab,ti,kw)	31458
#2	case*:ti,kw OR cluster*:ti,kw OR detect*:ti,kw OR distributed:ti,kw OR distribution*:ti,kw OR endemic*:ti,kw OR epidemic*:ti,kw OR epidemiolog*:ti,kw OR frequenc*:ti,kw OR frequent*:ti,kw OR inciden*:ti,kw OR identificat*:ti,kw OR number*:ti,kw OR occur*:ti,kw OR outbreak*:ti,kw OR pandemic*:ti,kw OR percent*:ti,kw OR prevalen*:ti,kw OR prognos*:ti,kw OR proportion*:ti,kw OR rate*:ti,kw OR recurren*:ti,kw OR reoccur*:ti,kw OR 're occur*':ti,kw OR serodiagnos*:ti,kw OR seroepidemiolog*:ti,kw OR seroinciden*:ti,kw OR serolog*:ti,kw OR seropositiv*:ti,kw OR seroprevalen*:ti,kw OR serosurvey*:ti,kw OR spread*:ti,kw OR surveillance*:ti,kw OR time*:ti,kw OR transmi*:ti,kw OR trend*:ti,kw OR ((sero NEXT/2 (epidemiolog* OR inciden* OR positiv* OR prevalen* OR survey*)):ti,kw)	4061041
#3	ascen*:ab,ti,kw OR augmentat*:ab,ti,kw OR burden:ab,ti,kw OR climb:ab,ti,kw OR climbed:ab,ti,kw OR climbing:ab,ti,kw OR 'go up':ab,ti,kw OR 'going up':ab,ti,kw OR 'gone up':ab,ti,kw OR growing:ab,ti,kw OR growth:ab,ti,kw OR increas*:ab,ti,kw OR link:ab,ti,kw OR linked:ab,ti,kw OR mount:ab,ti,kw OR mounted:ab,ti,kw OR mounting:ab,ti,kw OR rise:ab,ti,kw OR rised:ab,ti,kw OR rising:ab,ti,kw OR upsurg*:ab,ti,kw OR 'went up':ab,ti,kw OR emerg*:ti,kw OR reemerg*:ti,kw	8728250
#4	#1 AND #2 AND #3	3177
#5	'cluster analysis'/exp OR 'disease transmission'/exp OR 'epidemic'/exp OR 'outbreak'/exp OR 'surveillance'/exp OR 'disease surveillance'/exp OR 'incidence'/exp OR 'prevalence'/exp OR 'morbidity'/exp OR 'mortality rate'/exp OR 'fatality'/exp OR 'mortality'/de OR 'premature mortality'/exp OR 'survival rate'/exp OR 'burden'/exp OR 'disease burden'/exp	2355894
#6	syphili*:ti,kw OR 'great pox*':ti,kw OR lues:ti,kw OR ((hutchinson* NEXT/2 teeth):ti,kw)	20823
#7	#3 AND #5 AND #6	1195
#8	((syphili* OR 'great pox*' OR 'hutchinson teeth' OR 'hutchinsons teeth' OR lues) NEAR/5 (case* OR cluster* OR detect* OR distributed OR distribution* OR endemic* OR epidemic* OR epidemiolog* OR frequenc* OR frequent* OR inciden* OR identificat* OR number* OR occur* OR outbreak* OR pandemic* OR percent* OR prevalen* OR prognos* OR proportion* OR rate* OR recurren* OR reoccur* OR 're occur*' OR 'sero epidemiolog*' OR 'sero inciden*' OR 'sero positiv*' OR 'sero prevalen*' OR 'sero survey*' OR serodiagnos* OR seroepidemiolog* OR seroinciden* OR serolog* OR seropositiv* OR seroprevalen* OR serosurvey* OR spread* OR surveillance* OR time* OR transmi* OR trend*) NEAR/10 (ascen* OR augmentat* OR burden OR climb OR climbed OR climbing OR 'go up' OR 'going up' OR 'gone up' OR growing OR growth OR increas* OR link OR linked OR mount OR mounted OR mounting OR rise OR rised OR rising OR upsurg* OR 'went up' OR emerg* OR reemerg*)):ab,ti	1616
#9	#4 OR #7 OR #8	4161
#10	interven*:ab,ti,kw OR respon*:ab,ti,kw OR measure*:ab,ti,kw OR treatment*:ab,ti,kw OR control*:ab,ti,kw OR prevent*:ab,ti,kw OR program*:ab,ti,kw OR recommend*:ab,ti,kw	14749981
#11	#9 AND #10	2958
#12	guideline:ti OR guidelines:ti OR guide:ti OR guidance:ti OR ((evidence NEXT/2 based):ti) OR ((best NEXT/2 practice*):ti) OR (((action* OR response*) NEXT/2 plan*):ti)	171006
#13	#1 AND #12	131
#14	((guideline OR guidelines OR guide OR guidance OR 'evidence based' OR 'best practice*' OR 'action plan*' OR 'response plan*') NEAR/5 (syphili* OR 'great pox*' OR lues OR 'hutchinson teeth' OR 'hutchinsons teeth')):ab,ti	170
#15	((((sexual OR sexually) NEXT/3 transmi*):ti) OR std:ti OR sti:ti) AND (guideline:ti OR guidelines:ti OR guide:ti OR guidance:ti OR ((evidence NEXT/2 based):ti) OR ((best NEXT/2 practice*):ti) OR (((action* OR response*) NEXT/2 plan*):ti))	265
#16	#11 OR #13 OR #14 OR #15	3378
#17	#16 AND [2007-2018]/py	2346

Scopus (search run on 10 December 2018)

No.	Query	Results
#1	TITLE-ABS-KEY (syphili* OR 'great pox*' OR lues OR 'Hutchinson Teeth' OR 'Hutchinsons Teeth')	49325
#2	TITLE (case* OR cluster* OR detect* OR distributed OR distribution* OR endemic* OR epidemic* OR epidemiolog* OR frequenc* OR frequent* OR inciden* OR identificat* OR number* OR occur* OR outbreak* OR pandemic* OR percent* OR prevalen* OR prognos* OR proportion* OR rate* OR recurren* OR reoccur* OR 're-occur*' OR 'sero-diagnos*' OR 'sero-epidemiolog*' OR 'sero-inciden*' OR 'sero-positiv*' OR 'sero-prevalen*' OR 'sero-survey*' OR serodiagnos* OR seroepidemiolog* OR seroinciden* OR serolog* OR seropositiv* OR seroprevalen* OR serosurvey* OR spread* OR surveillance* OR time* OR transmi* OR trend*)	6925730
#3	TITLE-ABS-KEY (ascen* OR augmentat* OR burden OR climb OR climbed OR climbing OR 'go up' OR 'going up' OR 'gone up' OR growing OR growth OR increas* OR link OR linked OR mount OR mounted OR mounting OR rise OR rised OR rising OR upsurg* OR 'went up') OR TITLE (emerg* OR reemerg* OR 're-emerg*')	16115375
#4	#1 AND #2 AND #3	3100
#5	TITLE-ABS (syphili* OR 'great pox*' OR 'hutchinson teeth' OR 'hutchinsons teeth' OR lues) W/5 TITLE-ABS (case* OR cluster* OR detect* OR distributed OR distribution* OR endemic* OR epidemic* OR epidemiolog* OR frequenc* OR frequent* OR inciden* OR identificat* OR number* OR occur* OR outbreak* OR pandemic* OR percent* OR prevalen* OR prognos* OR proportion* OR rate* OR recurren* OR reoccur* OR 're-occur*' OR 'sero-diagnos*' OR 'sero-epidemiolog*' OR 'sero-inciden*' OR 'sero-positiv*' OR 'sero-prevalen*' OR 'sero-survey*' OR 'sero epidemiolog*' OR 'sero inciden*' OR 'sero positiv*' OR 'sero prevalen*' OR 'sero survey*' OR serodiagnos* OR seroepidemiolog* OR seroinciden* OR serolog* OR seropositiv* OR seroprevalen* OR serosurvey* OR spread* OR surveillance* OR time* OR transmi* OR trend*) W/10 TITLE-ABS (ascen* OR augmentat* OR burden OR climb OR climbed OR climbing OR 'go up' OR 'going up' OR 'gone up' OR growing OR growth OR increas* OR link OR linked OR mount OR mounted OR mounting OR rise OR rised OR rising OR upsurg* OR 'went up' OR emerg* OR reemerg* OR 're-emerg*')	959
#6	#4 OR #5	3550
#7	TITLE-ABS-KEY (interven* OR respon* OR measure* OR treatment* OR control* OR prevent* OR program* OR recommend*)	29978605
#8	#6 AND #7	2613
#9	TITLE-ABS (guideline OR guidelines OR guide OR guidance OR 'evidence based' OR 'best practice*' OR 'action plan*' OR 'response plan*') W/5 TITLE-ABS (syphili* OR 'great pox*' OR lues OR 'hutchinson teeth' OR 'hutchinsons teeth')	133
#10	(TITLE (sexual OR sexually) next/3 TITLE (transmi*)) OR TITLE (std) OR TITLE (sti)	5682
#11	(TITLE (evidence) next/2 TITLE (based)) OR (TITLE (best) next/2 TITLE (practice*)) OR (TITLE (action* OR response*) next/2 TITLE (plan*)) OR TITLE (guideline OR guidelines OR guide OR guidance)	201,203
#12	#10 AND #11	85
#13	#8 OR #9 OR #12	2809
#14	#13 AND PUBYEAR AFT 2006	1580

Cochrane Database of Systematic Reviews (search run 14 December 2018)

Wiley platform

No.	Query	Results
#1	MeSH descriptor: [Syphilis] explode all trees	125
#2	MeSH descriptor: [Syphilis, Congenital] explode all trees	13
#3	MeSH descriptor: [Syphilis Serodiagnosis] explode all trees	23
#4	(syphili* OR 'great pox*' OR lues):ti,ab,kw (Word variations have been searched)	498
#5	(hutchinson NEAR/2 teeth):ti,ab,kw (Word variations have been searched)	0
#6	#1 OR #2 OR #3 OR #4 OR #5	499
#7	(case* OR cluster* OR detect* OR distributed OR distribution* OR endemic* OR epidemic* OR epidemiolog* OR frequenc* OR frequent* OR inciden* OR identificat* OR number* OR occur* OR outbreak* OR pandemic* OR percent* OR prevalen* OR prognos* OR proportion* OR rate* OR recurren* OR reoccur* OR 're occur*' OR serodiagnos* OR seroepidemiolog* OR seroinciden* OR serolog* OR seropositiv* OR seroprevalen* OR serosurvey* OR spread* OR surveillance* OR time* OR transmi* OR trend*):ti,ab,kw (Word variations have been searched)	803523
#8	MeSH descriptor: [Cluster Analysis] explode all trees	2192
#9	MeSH descriptor: [Disease Transmission, Infectious] explode all trees	808
#10	MeSH descriptor: [Disease Outbreaks] explode all trees	264
#11	MeSH descriptor: [Epidemics] explode all trees	70
#12	MeSH descriptor: [Population Surveillance] explode all trees	629
#13	MeSH descriptor: [Epidemiological Monitoring] explode all trees	29
#14	MeSH descriptor: [Incidence] explode all trees	9319
#15	MeSH descriptor: [Prevalence] explode all trees	4671
#16	MeSH descriptor: [Morbidity] this term only	724
#17	MeSH descriptor: [Mortality] this term only	462
#18	MeSH descriptor: [Fatal Outcome] explode all trees	12
#19	MeSH descriptor: [Mortality, Premature] explode all trees	3
#20	MeSH descriptor: [Survival Rate] explode all trees	9483
#21	MeSH descriptor: [Global Burden of Disease] explode all trees	1
#22	(sero NEXT/2 (epidemiolog* OR inciden* OR positiv* OR prevalen* OR survey*)):ti,ab,kw (Word variations have been searched)	67
#23	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	803599
#24	#6 AND #23	392
-	[Filtered by Cochrane Reviews]	[15]
-	[Filtered by Cochrane Protocols]	[2]
-	Total records exported	17 records

Google searches
allinurl: syphilis outbreak OR intervention OR response -letter -letters filetype:pdf
allinurl: sti outbreak OR intervention OR response -letter -letters filetype:pdf

Annex 3. Member State survey questionnaire

Syphilis risk assessment 2018

Dear colleagues, at the last STI coordination committee meeting in September, the increases in syphilis cases over the last few years, as well as reports of increases in congenital syphilis cases in some EU countries were highlighted. It was agreed that ECDC would develop a risk assessment which would include the latest data on syphilis and congenital syphilis cases and present evidence on effective interventions for syphilis control.

We would therefore like to ask you to complete this brief questionnaire which should take only a few minutes to complete in order to provide a better understanding of syphilis and congenital syphilis surveillance systems in the EU/EEA, the latest available syphilis data and information on any related response activities.

We would like to kindly request you to complete the questionnaire (one per country) by the 28 November 2018.

Please contact Gianfranco Spiteri (gianfranco.spiteri@ecdc.europea.eu) if you have any questions. Thank you for your collaboration.

Kind regards,
Gianfranco Spiteri
on behalf of the HIV, STI and hepatitis disease programme

Syphilis surveillance

1.1 Please choose your country:

Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lichtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom

1.2 Surveillance system data sources – syphilis

Datasources_-_syphilis.xlsx

1.3 A description of the syphilis surveillance system in your country based on data reported in TESSy is available above. Could you kindly confirm these are correct in particular with respect to the case definition in use.

Yes
No

1.4 If not, can you please provide details:

1.5 If your country has a comprehensive surveillance system for syphilis, do you consider that the surveillance system covers all diagnoses made in the country?

Yes
No
Don't know
Not applicable

1.6 If not, what is your estimate for coverage of the surveillance system?

1.7 If your country has a sentinel (or other non-comprehensive type of) surveillance system for syphilis, what proportion of syphilis diagnoses in the country do you estimate the system captures?

1.8 Have there been any changes in the syphilis surveillance system between 2010 and 2018 in your country?

Yes
No

1.9 If yes, how has the surveillance system changed?

Change in the number of reporting sites? Please describe below.
Change in reporting methodology? (e.g. case definitions; electronic reporting, etc.) – please specify
Other – please specify

1.10 Please describe any change in the number of reporting sites

1.11 Please describe any change in reporting methodology.

1.12 Please describe any other changes in the surveillance system

1.13 Do you have preliminary aggregated syphilis data from 2018?

Yes
No

1.14 Has there been an increase in reported cases in 2018 compared to 2017?

Yes
No

1.15 What are the preliminary number of cases as of 30 September 2018 (or latest available)? Please include the date and any additional relevant information.

1.16 Have you noticed a change in the epidemiology of syphilis cases in 2018 compared to previous years? (e.g. age/gender/sexual orientation/proportion of reinfections/HIV coinfection/PrEP users/chemsex, etc.)

Yes
No
Don't know

1.17 Please provide more details on changes in the epidemiology

1.18 Have you received informal reports of increases in syphilis cases in 2018?

Yes
No

1.19 Have you received reports of outbreaks of syphilis in 2018?

Yes
No

1.20 Please provide details if any increases or outbreaks have been reported

Congenital syphilis surveillance

2.1 Surveillance system data sources – congenital syphilis: datasources_-_congenital_syphilis.xlsx

2.2 A description of the congenital syphilis surveillance system in your country based on data reported in TESSy is available above. Could you kindly confirm these data are correct in particular with respect to the case definition used and applied.

Yes
No

2.3 If not, can you please provide details: . . .

2.4 If your country has a comprehensive surveillance system for congenital syphilis, do you consider that the surveillance system covers all diagnoses made in the country?

Yes
No
Don't know
Not applicable

2.5 If not, what is your estimate for coverage of the surveillance system?

2.6 If your country has a sentinel (or other non-comprehensive type of) surveillance system for syphilis, what proportion of congenital syphilis diagnoses in the country do you estimate the system captures?

2.7 Have there been any changes in the congenital syphilis surveillance system between 2010 and 2018 in your country (for example to case definitions, reporting sites, etc.)?

Yes
No

2.8 If yes, how has the surveillance system changed?

Change in the number of reporting sites? Please describe below.
Change in reporting methodology? (e.g. case definitions; electronic reporting, etc.) – please specify
Other – please specify

2.9 Please describe any change in the number of reporting sites

2.10 Please describe any change in reporting methodology.

2.11 Please describe any other changes in the surveillance system

2.12 Do you have preliminary aggregated congenital syphilis data from 2018?

Yes
No

2.13 Has there been an increase in reported cases in 2018 compared to 2017?

Yes
No

2.14 What are the preliminary number of cases as of 30 September 2018 (or latest available)? Please include the date and any additional relevant information.

2.15 Have you noticed a change in the epidemiology of congenital syphilis cases in 2018 compared to previous years?

Yes
No
Don't know

2.16 Please provide more details on changes in the epidemiology

2.17 Have you received informal reports of increases in congenital syphilis cases in 2018?

Yes
No

2.18 Please provide details if you have received informal reports of increases in congenital syphilis cases

Response

3.1 In case of increases in syphilis and/or congenital syphilis between 2010 and 2018 in your country, have there been specific response measures/activities implemented (this may include a wide range of activities, from outbreak control to strengthening public health response capacity, issuing of prevention and control strategies etc)?

Yes
No

3.2 Are the response activities described in any paper, report, published document? Could you provide a link? Otherwise please describe briefly.

3.3 Are there plans for a response that you are aware of? Please describe briefly.

Annex 4. Summary tables for literature review on the epidemiology

Table A4.1. Outbreaks/cluster of cases

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Browne, 2018 [38]	April 2016 - May 2017	USA	Outbreak	Arizona	51	American Indians	27±10.6	All (49% female)	Substance use, incarceration and being a man who had sex with men	-	early latent, primary, secondary, late latent, congenital
Tsachouridou, 2010 [56]	2010	Greece	Outbreak	Infectious Diseases Unit in AHEPA University Hospital of Thessaloniki	27	Homo- or bisexual men	41 (27–75)	-	Multiple sex partners, unprotected oral sex, and increased age among MSM	HIV+	P, S, L, NS
Goodall, 2017 [58]	2017	United Kingdom	Cluster of cases	Hampshire	55	General population	37 (16-74)	Males (100%), 75% MSM	Male, MSM, chemsex users	64% HIV -	38% were diagnosed as primary syphilis, 36% secondary syphilis and 27% early latent syphilis
Eberly, 2018 [43]	January 2017-February 2018	USA	Outbreak	Oklahoma County	239	General population	-	Females (53.6%), 18 were pregnant, and males (46.4%)	Drug use (82.0%), injection drug use (31.8%) (21.3%) traded sex for drugs or money, (60.3%) had gang affiliation	-	(102,42.7%) primary and secondary, 132 (55.2%) early latent, 5 (2.1%) late latent/unknown duration
Anderson, 2011 [35]n	2001-2010	UK	General epidemic + outbreak	City and East London	778 2001: 21 06: 115 10: 144	General population (85% MSM)	<16: 3 17–30: 27%, >40 34%	All (94% males)	-	HIV +: 32%	39% had primary syphilis, 37% secondary syphilis and 24% had early latent syphilis
Metallidis, 2011 [47]	2008-2010	Greece	Outbreak	Northern Greece	58	All, HIV+ MSM (94.82%)	-	-	Multiple sex partners, unprotected sex, HAART intake and coinfection with other STIs	HIV +	infectious syphilis
Garton, 2015 [45]	2014-2015	Australia	Outbreak	Central Australia and Katherine regions	112 cases	General population	median: 17 (15–20.5)	60 females and 52 males	-	-	Infectious syphilis
Abu-Rajab, 2011 [33]	2009	UK	Outbreak	Central Scotland	10	GU patients	17–29 (median 19.5)	All (7 females, 3 males)	-	HIV-	-
D'Angelo-Scott, 2015 [42]	Jan 2009-Jun 2010	Canada	Outbreak	Ontario	72	General population	38.8 (55)	All (94% men)	-	HIV+ 26.4%	P: 38.9%, S: 44.4%, EL 15.3%, Inf NS: 1.4%
D'Angelo-Scott, 2015 [42]	14-15	UK	Outbreak	Reading.	21	8 MSM	-	-	-	7/8MSM HIV+	P: 8, S: 10, EL: 3
Mireles, 2016 [48]	2011-2014	USA	Outbreak: Feb 2013-Dec 2013	Maricopa county	211	General population	-	-	-	-	P&S
			May – Sept 2014		96						
			March-Sept 2014	Pima county	142						

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Pearson, 2018 [51]	2016	USA	Outbreak	Florida	2011: 893 2016: 1357	-	-	Female (63%)	-	-	-
Goode, 2017 [46]	2015-2016	UK	Outbreak	Yorkshire and The Humber	15:78 16:116	General population (85% were MSM)	-	-	-	HIV+: 15:34% 16: 28%	P, S &EL
Bright, 2016 [37]	Jan 2011-Dec 2015	Australia	Outbreaks: September 2011, January 2011, July 2014, June 2014 and 31 December 2015.	Queensland, Northern Territory, Kimberley region	790	Indigenous population	↑15–19 and 20–29 years	All (45% male)	-	-	-
Frosst, 2011 [44]	2009 and 2010.	Canada	Outbreak	New Brunswick	56	General population	Highest incidence: Male 20-24 yrs	All (93% males)	-	5 cases HIV+	Infectious syphilis
CDC, 2010 [39]	January 2007-June 2009	USA	Outbreak	Arizona	106 53 (screening response) -|34 (sex partner)	American Indians	100 cases in adults and adolescents	69 females	more than one sex partner (58%) or use of alcohol (69%), cocaine (44%), or methamphetamine (9%) in the year before diagnosis	-	11 primary, 11 secondary, 39 early latent, 24 late latent, 15 of unknown duration, and six congenital
Chima-Okereke, 2014 [40]	January 2011 and December 2013.	UK	Outbreak	Rural county	50	General population, 88% MSM	-	98.0% males	-	HIV+: 18%	-
Bjekic, 2017 IN 2014 [2]	2014	Serbia	Outbreak	Belgrade	71	General population	32.4 (19–61) Highest incidence: men 30-39 and women 40-49	67 males, 85% MSM	In comparison with HIV negative, HIV positive syphilis patients were older, more frequently unemployed and MSM	HIV+: 24 (all MSM)	P:20 cases, S: 42, EL: 9
	2005-2014 (10-14)		Increasing trends		10-14: 196		-	-	-	HIV+: 42 (21.4%)	P: 33.2%, S: 46.4%, EL: 20.4%.
Spencer, 2016 [55]	2015	USA	Series of cases -Outbreak	Orange county, CA	11	5/8 MSM	24-63	males	-	5/10 HIV+	-
Moussa, 2011 [50]	Jan-Jun 2010	UK	Cluster of cases	Ipswich	5	Heterosexuals	<30yrs	3 males, 2 female	-	Negative	3 primary, 2 early latent
Bowen, 2018 [36]	February 2013–August 2015	USA	Outbreak	Alaska	134	American Indian reservation	15-60	All (57% females)	-	-	54 (40.3%) primary, 24 (17.9%) secondary, 42 (31.3%) early latent, and 14 (10.4%) late latent cases
Rea, 2017 [52]	2015-2016	Australia	Outbreak	Far North Queensland	633	Heterosexual	71% young people aged between 15-29	F=M	-	-	-
Cox, 2015 [41]	January 2011 and September 201	UK	Rural outbreak	Herefordshire	49	-	-	men (98%)	-	18% HIV+	early syphilis
Simms, 2014 [3]	Jan 2012-April 2014	UK	Outbreaks	East of England.	22	MSM	-	-	-	-	Infectious syphilis
				East of England.	19	MSM	-	-	-	-	
				Yorkshire and The Humber	15	MSM	-				

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
				Wales	47	MSM	33 (19–56)				
				Lanarkshire	21	Young heterosexuals	-				
				Tayside	-	Young heterosexuals	-				
				Welsh	17	General population	-				
Seppings, 2016 [53]	Jan 14-March 15	UK	Outbreak	Reading	26	General population (81% MSM)	-	-	-	HIV+: 7 cases	early syphilis,
Acheson, 2011 [34]	2009	UK	Outbreak	Teesside	34	-	<30y (F:83%, M:91%)	All (68% women)	-	-	P (82%)
[49]	2011	UK	Cluster of cases	South-east Hampshire	12	Young heterosexual	<25yrs	-	-	-	Early syphilis
Welfare, 2011 [57]	2008-2009	UK	Outbreak	Rochdale	12	Young heterosexuals	<20y	All (9 cases in women)	-	-	primary, secondary or early latent syphilis
van Aar, 2017 [4]	2007-2015	The Netherlands	Clusters of cases	South-eastern region	10	MSM: 9/10 Commercial SW, from eastern Europe	23 (23–25)	9/10 male	-	50.0% HIV+	-
				Amsterdam	1123	MSM	41 (33–49)	Males	-	39.6 HIV-	-
				Rotterdam, 12 municipalities in Zeeland and parts of Zuid-Holland and Noord-Braban	72	MSM	32.5 (25.5–42.5)	males	-	62.5% HIV-	-

Table A4.2. Increasing trends

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Chan, 2014 [85]	2006-2012	USA	Increasing trends	Rhode Island	320	General population	-	All	MSM	-	P&S
Brown, 2016 [136]	2012-2014	USA	Increasing trends	Florida	12,757	Non-MSM men	-	Males	-	-	P, S and latent
					-	Females	-	Females	-	-	-
Azariah, 2016 [103]	2015	New Zealand	Increasing trends	Auckland	149	All	32 (18-72)	All (92% male)	-	28% GBM HIV+	P&S (61%),
Kojima, 2018 [71]	2016	Worldwide	Increasing trends	-	-	-	-	-	-	-	-
Ngangro, 2016 [68]	2004-2015	France	Increasing trends	France	-	All	-	All (men aged 20-49, 78%)	MSM	-	P: 25%, S: 37% and EL: 38%
Bally, 2012 [65]	2012	Switzerland	Increasing trends	National	1036 (2011)	All	-	-	-	-	-
Kirby, 2017 [195]	2017	UK	-	Sexual Health Clinic at Inner city London	56	All (80% male)	42 (16- 69)	-	Chemsex, MSM	-	P (20%), S (7%)
Liu, 2017 [86]	2007-2015	USA	Increasing trends	King County	-	General population	-	-	-	-	-
Hallmark, 2016 [294]	2005-2013	USA	Increasing trends Outbreak: 2007 and 2012	Houston	-	General population	≥18 yrs	All	Black MSM, black MSW, Hispanic, MSM, anonymous sex, met partners online	-	P&S
Rietmeijer, 2013 [295]	2007-2012	USA	Increasing trends	Denver	-	MSM	-	Males	-	-	P&S
						All		All			
Psutka, 2013 [102]	2011	New Zealand	Increasing trends	NZ: Sexual health clinics	72	General population	Males: 40 (17–73) Female42 (25–57)	All (MSM: 83%)	-	18% HIV+ (all MSM)	primary, secondary, and early latent and syphilis of unknown duration with RPR≥ 1:32

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Borman, 2014 [101]	2014	New Zealand	Increasing trends	NZ: Sexual health clinics	83	General population	-	All (males: 90.1%, MSM: 86.3%)	-	HIV+: 29% of MSM	primary, secondary, and early latent and syphilis of unknown duration with RPR≥ 1:32
Orzechowska, 2018 [61]	2016	Poland	Increasing trends	Warsaw and Gdansk	570	General population	35.2 No cases 1-16	All (88.24% males.	young people, especially men, living in urban settings.	-	CS: 1.2% P: 43% L: 2.3% Asymptomatic: 53.5%
Marti-Pastor, 2015 [66]	January 2007 and December 2011	Spain	Increasing trends	Barcelona	1124	General population	MSM: 36.4 (±9.3), MSW: 37.3 (±12.3), WSM: 36.4 (±11)	All (males: 91.9, 80.7% MSM)	MSM with a university education presented the highest rates,	-	-
Ward, 2011 [100]	2005-2009	Australia	Increasing trends (in not indigenous population)	Australia	5336	Indigenous vs. not indigenous	15-40+	All	non-Indigenous population, males, ≥20 years, residents of metropolitan/ regional areas	-	-
Schillinger, 2018 [7]	2012 -2016	USA	Increasing trends	NYC	1826	NYC males	-	Males (MSM: 47%, bisexual: 44%)	black non-Hispanic and Hispanic men	HIV+: 46%	P,S &EL
Roberts, 2016 [296]	2006-2014	Worldwide	Increasing trends	-	-	HIV+ MSM	-	Males	-	-	-
Lasagabaster, 2015 [69]	2003-2013	Spain	Increasing trends	Barcelona	03:68 13:278	STI clinic patients (84% MSM)	36 year	-	-	HIV+ (03 VS. 13): 32.7 s 36.5%	P:37.5%, S:48.5% and EL:14%
Mohammed, 2016 [63]	2014	UK	Increasing trends	England	4 317	-	-	-	-	-	P, S &EL
Chow, 2017 [297]	2007-2014	Australia	Increasing trends	National: sentinel network	-	MSM	-	-	-	-	P,S & EL
Lang, 2018 [93]	2006-2016	Canada	Increasing trends	Alberta: Calgary STI Program (CSTI) and the Southern Alberta Clinic (SAC)	249	HIV-positive patients (75% MSM)	47 years (21–72)	All (94% males)	Not on HAART, HIV RNA viral loads > 1000 copies/mL, Caucasian, males and MSM	HIV+	MSM, prior alcohol abuse, prior recreational drug use and prior syphilis episode.
Sanchez, 2013 [298]	2008-2012	Spain	Increasing trends	Madrid	859	MSM	-	-	--	HIV+	-
Hiltunen-Back, 2015 [76]	2004-2014	Finland	Increasing trends	Helsinki	-	MSM	-	-	-	-	-
Van de Laar, 2012 [72]	2010	EU/EEA	Increasing trends	European	18 000	All	-	-	-	-	-
Choudhri, 2018 [87]	2010-2015	Canada	Increasing trends	National	2015: 3,321	General population	-	All: in 2015, 93.7% of males	MSM	-	-
Drummond, 2010 [73]	-	Worldwide	Increasing trends	-	-	MSM	-	Males	-	-	-
Schumacher, 2018 [89]	2009-2015	USA	Increasing trends	Baltimore City	1487	MSM	29 (15-72)	(61% MSM)	black HIV-infected MSM.	67.2% HIV+	P&S and EL
Tabidze, 2013 [90]	2006-2011	USA	Increasing trends	Chicago	-	HIV+	-	-	Black MSM ages 13–24, White MSM ages 45–54	HIV+	P, S & EL
CDC, US, 2013 [95]	2010-2011	USA	Increasing trends	Baltimore	493	MSM	30 (19-62)	Male	-	86% HIV+	P, S & EL
Gulland, 2017 [74]	2015-2016	UK	Increasing trends	UK	2015: 5281 2016: 5920	General population	-	All	-	-	-
Oliver, 2016 [178]	2014-2015	USA	Increasing trends	8 states	388	General population, 69% MSM	-	All (93% male)	-	198 cases HIV+	Ocular syphilis P (2.1%), S (26%), EL (20.4%), LL/unknown duration (49.7%), unknown (1.8%)
Su, 2011 [91]	2005-2008	USA	Increasing trends	27 states	-	MSM	Largest increase 20-29 y	-	Black and Hispanic MSM	-	P & S
Patton, 2014 [94]	2005-2012	USA	Increasing trends	USA	2005: 5.1 cases per 100,000 men, 2012:9.3	US men (MSM 77%)	men aged 25-34 had the greatest increase (17.0 to 22.2) during 2009-2012	males	-	-	P&S

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Patton, 2014 [88]	2005-2013	USA	Increasing trends	USA	2009: 11,764 9 2013*: 15,175 *Only until April 2013	General population	2009 to 2013, men aged 25–29 years (the same approximate birth cohort) had the greatest increase (48.4%, 18.2 to 27.0)	All	During 2009–2013, rates increased among Hispanic men (52.6%, from 7.6 in 2009 to 11.6 in 2013) and white men (45.9%, 3.7 to 5.4), MSM	-	**P&S**
Nicolaidou, 2013 [80]	2005-2012	Greece	Increasing trends	Athens tertiary hospital	2005:111 2012:157	General population (MSM: 45.03%)	-	All	-	-	P
Savage, 2012 [59]	2011	UK	Increasing trends	UK	2010: 2,650 2011: 2,915	General population (75% of males are MSM)	1,283 cases in MSM were in those aged 25–44 years	All	MSM	-	**P, S & EL**
Takahashi, 2018 [104]	2012-2016	Japan	Increasing trends	Japan	2012: **883** **2016:** 4564	General population	Men: 37 (28–46) Women: 26 (21–34)	All	-	-	(27.2%) were primary, 4047 (36.8%) were secondary, 3510 (31.9%) were asymptomatic, 402 (3.7%) were late (symptomatic), and 45 (0.4%) were congenital
Chen, 2014 [96]	2007-2011	USA	Increasing trends	San Francisco	-	Males	-	Males	-	HIV+	Early syphilis
Ndeikoundam Ngangro, 2018 [60]	2011-2013	France	**Increasing trends**	national health insurance system	2011: 3771 2013: 4589	General population	Highest rate of diagnosis men 40-44yr	Most were men (87% in 2011 and 89% in 2013	-	-	-
Van Aar, 2015 [299]	2007-2014	The Netherlands	Increasing trends	National STI/HIV surveillance	2011 = 426 2014 = 693	MSM	-	Male	HIV+ status	HIV+: 40%	-
Poon, 2015 [99]	2009-2011	Australia	Increasing trends	National	-	-	-	-	-	-	-
Sánchez, 2013 [77]	2008-2012	Spain	Increasing trends	Madrid	2008:65 2012: 261	HIV+ patients	40 (33–45)	Male	-	HIV+	-
Grey, 2018 [119]	2012-2016	USA	Increasing trends	USA	3,493 (2012) to 5,993 (2016)	General population	-	-	-	-	P&S
Ling, 2015 [83]	2000 to 2013.	Canada	Increasing trends	Sentinel Network	37,843	Bisexual/MSM	34 (27–43)	Male	-	-	-
Pinto-Sander, 2016 [300]	Feb 13- Jun 14	UK	Increasing trends	Brighton	207	MSM	36 years (19–60)	-	-	-	-
Jansen, 2015 [62]	2014	Germany	Increasing trends	National	5,722 cases	General population (84% MSM)	-	All (94% male)	-	-	35% were diagnosed as primary, 27% as secondary and 35% as latent syphilis,
Petrescu, 2012 [301]	2008–2009 (I) and 2010–2011	Romania	Increasing trends	Bucharest	165	General population	medium age of 31.2 years,	103 males and 62 females.	-	(28.5%) were S-HIV-coinfected	2 vs 3 cases for primary S (2 vs 3 cases), 16.2% vs 19.4% secondary S, 8.6% vs 11.1% tertiary S; for latent S 61.6% vs 56.9%; for NS 8.6% vs 11%.
Kuklova, 2011 [70]	1st January 2009 to the 31st December 2009	CZ	Increasing trends	Prague	206	Newly syphilis diagnosis in hospitalized patients. (64.7%) men having sex with men	majority of the patients were aged between 30 and 40	53 (74.3%) were men and 53 (25.7%) women	-	-	22.3% of patients with primary and 31.6% with secondary syphilis, EL: 29.1, LL: 17.0
Iacobucci, 2018 [302]	2016-2017	UK	Increasing trends	England	2016: 5955 2017: 7137	General population	-	-	-	-	-
Mayor, 2015 [303]	2013-2014	UK	Increasing trends	England	2013: 2375 2014: 3477	General population	-	-	High levels of condom-less sex, particularly between men who are HIV positive, are likely to account for most of these increases	-	-

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Vives, 2015 [75]	January 2008 and December 2013	Spain	Increasing trends	Catalonia	3286	General population	-	All (85% males)	-	HIV+: 38% of MSM	-
González-Domenech, 2015 [79]	2004-2013	Spain	Increasing trends	Malaga	196 04-08: 61 09-13: 135	HIV+	38,1 (29,7-45,4)	79.17% males (47.8% MSM)	-	HIV+	73, 9% early syphilis. P: 10.7%, S: 42.3, O:4.1%, EL: 17.3%, LL:10.2%, L: 15.3%
Fusta, 2017 [304]	2011-2015	Spain	Increasing trends	Barcelona	220	ITS clinic patients	37 ± 9,6	98% males (94% MSM).	↑ sex partners and drug use related to sex-settings	HIV+: 62% Newly HIV+ 7%	S: 45%, P: 30%, EL: 14%
Sousa-Pinto, 2016 [64]	2000-2014	Portugal	Increasing trends	Portugal mainland	1668	Hospitalized patients with syphilis as main diagnosis	-	All	-	-	(table 2)
Peterman, 2015 [97]	1963-2013	USA	Increasing trends in MSM Decreasing trends in females	National	2000: 25.1%, 2008: 78.2%, 2013: 89.7% 1995:1458 2012:1458	General population	Higher frequency in young MSM	All	-	-	**P & S**
Bremer, 2012 [67]	2010-2011	Germany	**Increasing trends**	National	2010: 3.033 2011: 3,698	General population (84% MSM, HTS 16%)	Highest incidence Men: 30-39 Women: 25-29	All (94% male)	MSM	-	-
Muldoon, 2011 [81]	2007-2009	Ireland	Increasing trends	Dublin	07: 95, 08: 136, 2009: 208	General population	35.7 (17–73) Greatest number of diagnosis: 26–35 year	93.8% male	MSM: 86.8%	HIV+ (all MSM but one)	In 2009, increases in P syphilis and S dropped
Abara, 2016 [193]	2004-2015	USA and Western Europe	Increasing trends	24 cities	-	MSM	-	male	-	-	US: racial minority MSM and MSM between 20 and 29 Years W-EU: White MSM
Stone, 2018 [92]	2010-2015	USA	Increasing trends	Central Savannah River Area (CSRA)	2010: 43 2015: 60	General population	-	↑W&M bisexual and MSM (70%)	Black men, 20-24 & 25-29	-	P&S
McNeil, 2016 [84]	1998-2015	USA	Increasing trends	North Carolina	1998~1660 2008~500 2015>1800	General population	-	-	MSM, black/African American males, <30y, HIV+	-	-
Pinto-Sander, 2015 [78]	February-2013 to June-2014	UK	Increasing trends	Brighton	207	MSM	36 years (19–60)	males	-	(46.4%) were HIV+	-
Bennett, 2018 [98]	2007-2016	USA	Increasing trends (outbreaks: 2010, 2015 & 2016)	Mississippi	5,095	General population	15–24 the highest increase	-	-	-	P,S&EL
McNeil, 2016 [84]	2014	US	Increasing trends	North Carolina	-	General population	-	-	-	-	-
Benea, 2013 [82]	2002-2011	Romania	Decreasing trends	Bucharest	2011: 2.209	General population	-	-	-	-	-

Table A4.3. Risk group: MSM and bisexual men

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Taine, 2018 [114]	2018	UK	Epidemic	-	238	MSM	-	-	-	HIV + 47.2% (2014) vs 53.2% (2017)	MSM presented with secondary syphilis in 2017
Grey, 2018 [107]	2014	USA	Epidemic	34 states	-	MSM	-	males	-	Rates HIV+ vs. HIV -/unknown 1,203 vs. 155 per 10^5	P&S
Malek, 2015 [105]	2009-2013	UK	Epidemic	England	-	MSM	15-65+	males	HIV+, 15-64y, black 'other', black Caribbean	HIV+: 09: 436 (25.5) 13: 900 (39.1)	P, S, EL

Reference	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Su, 2011 [305]	2009	USA	Epidemic	34 states and Washington, DC	6501	MSM	-	Males	-	HIV+: 51-55%	P&S
Koedijk, 2014 [110]	2006-2012	The Netherlands	Epidemic	National	2 139	MSM (±sex w/ women)	<25y vs. ≥25y	Males	young MSM (15–24): 1)from Latin America 2) commercial SW older MSM (≥25): 1) sex only w/ men 2) From Suriname/Antilles 3)	-	Infectious syphilis
Liu, 2014 [108]	-	Canada	Epidemic	Toronto	HIV+:32 HIV-: 5	MSM: HIV+ vs HIV-	HIV+: 55 (48-50) HIV-:44 (37-50)	males	HIV-: unprotected anal sex	-	Active syphilis
Grey, 2017 [111]	2014	USA	Epidemic	National	11,359	MSM	-	-	Ethnicity: black	-	P&S
de Voux, 2017 [306]	2015	USA	Epidemic	44 states	12,118	MSM	-	male	-	-	P&S
Coll, 2018 [112]	November 2009 and October 2012	Spain	Epidemic	Barcelona	21	MSM	34.2 (29.2-40.2)	Males	None	HIV -	-
Petrosky, 2016 [106]	2008-2013	USA	Increasing trends	Multnomah County, Oregon	21 cases in 2008 to 229 in 2013	MSM	08-09: 36 (30–44) 12-13: 39 (31–48)	Males	non-Hispanic whites?	HIV+: 08-09: 55.6% 12-13: 69.2%	primary, secondary, and early latent
Koedijk, 2013 [115]	2006-2011	The Netherlands	Decreasing trends	National	-	MSM	15–24y	Males	-	-	-
Thomas, 2011 [267]	2002-2009	UK	Epidemic	Wales	523	General population MSM: 62%, bisexual: 1%.	34 (14–79 yr)	All (90% males)	-	-	P: 46 %, S:29%, EL: 25%
Velicko, 2012 [116]	2007-2011	Sweden	Epidemic	National	07: 239 11:206	All (increasing % MSM in males)	-	MtoF 07:4.8, 11:5.1	-	-	-
Lefebvre, 2013 [307]	2000-2010	France	Epidemic	Nantes	36	Hospitalized syphilis cases	45 (17–75)	Male: 97% MSM:64%	-	HIV+: 11%	-
Katz, 2018 [308]	2007-2017	USA	Increasing trends	King County, WA	-	Cis-trans/MSM	>15y	-	-	-	-
Gállego-Lezáun, 2015 [109]	2005-2013	Spain	Epidemic	Palma de Mallorca	323	General population	MSM: 37.5 (20-80) HTS men: 47.3 (18-85)	All HTS:161 MSM:55	-	HIV+: 74.5% of MSM. 30.8% of HTS men	LL or L: 41.9%
Su, 2014 [113]	2014	USA	Epidemic	16 states and Washington DC	2012: MSM: 10,657 MSW: 2,174 Women: 2,098	General population	-	-	HIV+ P: 42% of MSM, 6% of MSW, and 2% of women S: 59% of MSM, 17% of MSW, and 6% of women EL: 66% of MSM, 12% of MSW, and 4% of women	-	MSM: P (15%), S (39%), EL (46%) MSW: P(22%), S (34%) EL(44%) Women: P (8%), S(32%), EL (60%)

Table A4.4. Risk group: prisoners

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Chacowry Pala, 2018 [118]	2009 and 2011	Switzerland	Epidemic	Geneva	4/270 09: 1.8% 11: 1.3%	Incarcerated people	29.8 ± 9	Males	-	-	1 case in 2011
Garriga, 2011 [117]	2011	Spain	Epidemic - Prisons	National (except Catalonia)	94	All (90.4% male)	37.8 years (SD: 10.7 years)	-	- To be a client of a sex worker (almost 40%). - Sexual relation with occasional partners	5.3% HIV-positive	(35.1% primary, 20.2% secondary and 44.7% early latent

Table A4.5. Risk group: PWID/substance use

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Grey, 2018 [119]	2012-2016	USA	Increasing trends	USA	3 493 (2012) to 5 993 (2016)	Substance use people	-	-	-	-	P&S

Table A4.6. Risk group: HIV positive

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Fuchs, 2016 [134]	September 2012 - October 2014	Germany	Epidemic	-	-	HIV+MSM	-	Male	-	HIV+	Early syphilis was detected in 4·6% and past syphilis in 44·5%
Lang, 2018 [93]	2006-2016	Canada	Increasing trends	Alberta: Calgary STI Program (CSTI) and the Southern Alberta Clinic (SAC)	249	HIV-positive patients (75% MSM)	47 years (21–72)	All (94% males)	Not on HAART, HIV RNA viral loads > 1000 copies/mL, Caucasian, males and MSM	HIV+	MSM, prior alcohol abuse, prior recreational drug use and prior syphilis episode.
Dixon, 2014 [120]	2000-2002 Vs. 2010-2012	United Kingdom	Increasing trends	-	23	Newly HIV+ MSM	00-02: 34.9 10-12: 32.6	Males	MSM, HIV+	HIV+	-
Shilaih, 2017 [121]	2004-2014	Switzerland	Increasing trends	National	226	HIV+: MSM (92%), HET (6%), IDU (2%)	MSM: 42 (37–48)	All	condomless sex with an occasional partner/stable partner*, iv drug use, smoking*	HIV+	-
Chen, 2018 [122]	2007-2014	USA	Epidemic	San Francisco	4144	HIV+ patients	-	Male, female, trans-gender	Older age at diagnosis and history of an STD, Transgender persons	HIV+	early syphilis
Costache, 2016 [127]	2015-2016	Romania	Epidemic	Bucharest	64	HIV+ patients	73% (20-39)	All	-	HIV+	-

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Pogorzelska, 2017 [128]	9/2014-12/2016	Poland	Epidemic	Northeast Poland	12	HIV+ patients	Median41.	males	-	HIV+	8 homosexual and/or bisexual. 5 sympto-matic
Lucar, 2018 [129]	2011-2015	USA	Epidemic	Columbia	123	HIV+ patients (88.6% MSM)	38.9 (31.6–47.4)	All (71% male)	younger age, Hispanic ethnicity, MSM risk, and higher nadir CD4 counts to be strongly associated with STIs (GC, S, CT)	HIV+	-
Chen, 2014 [96]	2007-2011	USA	Increasing trends	San Francisco	-	Males	-	Males	**Large burden of HIV coinfection among MSM, white, Latino, and older males with STDs.**-	HIV+	Early syphilis
Castro, 2014 [309]	2012	USA	Epidemic	Miami	86 vs 86	HIV+ vs HIV-	-	All	HIV+	-	-
Castro, 2016 [131]	March-May 2012	USA	Epidemic	Miami	26 HIV+ 24 HIV- 2	STI clinic patients. HIV+ vs. HIV-	-	-	-	+ vs -	-
Braun, 2018 [310]	2015-2017	Switzerland	Epidemic	Zurich	15	Primary HIV Infection patients	-	-	-	HIV+	40% asympto-matic and 60% sympto-matic
Farfour, 2017 [124]	2008-2015	France	Increasing trends	Île-de-France region	08-11: 108 12-15: 215	MSM, HIV+	08-11: 47 12-15: 48	-	-	HIV+	-
Lang, 2017 [123]	2006-2016	USA	Epidemic	Southern Alberta and Calgary	231 2011:12, 2014:252015:41	HIV+	42 (21-72)	males (94%)	gay male Caucasian population receiving HIV care	HIV+ 26% cases were repeated infections	-
Ganesan, 2017 [132]	2004-2015	USA	Decreasing trends	National	423	HIV+	-	-	-	-	-
Verbrugge, 2011 [133]	2008-2009	Belgium	Epidemic	-	08: 171 09: 160	HIV+ (94-95% MSM)	-	All	-	HIV+	-
Remis, 2016 [126]	2010-2012	Canada	Epidemic	Toronto	32	MSM, HIV+	49.0 (42–58)	males	-	HIV+	Active syphilis
Su, 2015 [130]	2013	USA	Epidemic	44 states and Washington, DC	651	76% MSM, 15% MSW, 9% were women	-	All	-	HIV+ (MSM: 52% MSW: 11%, women: 5%)	**P&S**
Rowley, 2015 [125]	2015	Ireland, Poland and Germany	Epidemic	Tertiary referral hospitals	175	General population (97.1% males, 86.3% MSM)	Ireland: 35 (19–77) Poland: 34 (23–68)	-	MSM, HIV+, alcohol use, illicit recreational drug use,	69.7% HIV +	Early syphilis, 42.9% secondary syph, 28.6%

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
							Germany: 35 (21–56)				primary syph,

Table A4.7. Risk group: heterosexual, older people and adolescents

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Taylor, 2016 [135]	2013-2014	USA	Epidemic	Maricopa, PH	319	Females	31 (15-85)	Females	Methamphetamine use, previous incarceration, previous STD, sex with anonymous partners	-	All
LOS Wood-Palmer, 2018 [137]	May 2017-?	USA	Cluster of cases	Los Angeles and New Orleans	-	Homeless and LGBTQ youth	15–24 years	-	Males, 20-24 yrs	NEG	-
Manteuffel, 2016 [138]	2015-2016	USA	Epidemic	Detroit	6	Young men	18-34y	Male	-	1 HIV+	-
Copeland, 2014 [139]	2009-2011	USA	Epidemic	Cook county	151	Youth	13-24	-	-	HIV+	-
Holden, 2011 [311]	2000-2009	USA	Increasing trends	Louisiana	00:21 09:119	Older adults	45 +	-	-	-	P&S
Brown, 2016 **[136]**	2012-2014	USA	Increasing trends	Florida	12,757	Non-MSM men	-	Males	-	-	P, S and latent
					-	Females	-	Females	-	-	-

Table A4.8. Risk group: migrants

Ref.	Year of event	Country of report	Type of event (outbreak, increasing trends)	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection	Comments Links
Bjekić, 2016 [140]	2016	Serbia	Epidemic	Belgrade	31 (2010) 54 (2014)	Roma population	Most frequently aged 16-19 or 40-49	Male (58.8%)	Never married, elementary school or less unemployed and HTS	--	P: 4 cases, S: 4 cases, EL: 9 cases	Prevalence: 9.6%
Soler-González, 2013 [141]	2007	Spain	Burden of disease	Lleida	87	Autochthonous vs. migrants	Migrants: 33.5 yrs Autochthonous: 49 yrs	Migrants: 57.5% males Autochthonous: 49.5% males	Migrant	-	-	-
Delcor, 2013 [142]	2009-2012	Spain	Epidemic	Barcelona	9	Immigrants	17.7 (11.0-49.3)	All (98.6% male)	-	-	-	Prevalence: 4.8%
Belhassen-Garcia, 2015 [143]	2007-2011	Spain	Epidemic	Salamanca	5	Immigrants from Sub-Saharan Africa, North Africa and Latin America	<18y	3 girls, 2 boys	All of them were African and > 14 years	-	Latent (100%)	Asymptomatic
Tafuri, 2010 [144]	May-July 2008	Italy	Epidemic	Bari	4	Refugees	7 and 52	-	African	-	-	-

Table A4.9. Risk group: pregnant women

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Burgos Anguita, 2015 [158]	2014-2015	Spain	Epidemic	Almeria	-	Pregnant women	-	Females	-	-	All
Blackman, 2018 [161]	2014-2016	USA	Epidemic	Los Angeles	265	Pregnant women	15-45 yrs	Female	History of incarceration	-	-

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Serwin, 2016 [156]	2000-2015	Poland	Epidemic	Bialystok	47	17 (36.2%) were pregnant and 30 (63.8%)	27.9±4.2	Female	-	-	In pregnant women EL: 94.1%
Zammarchi, 2012 [162]	2000-2010	Italy	Epidemic	Tuscany	185	Pregnant women	30 (17–46)	Female	-	-	LL: 140 (74.87%), EL: 4 (2.14%), P: 1 (0.53%), S: 1 (0.53%)
Aslam, 2018 [154]	2010-2014	USA	Increasing trends	National	2010Q1-2012Q4: decrease 2010q4-2014q4: increase	Women at delivery	-	Female	Black? White?	-	-
Serwin, 2013 [312]	2000-2011	Poland	Epidemic	National	637	Pregnant women	-	-	-	-	-
Burghardt, 2018 [153]	2015-2017	USA	Increasing trends	California	2015: 400, 2016: 517, 2017: 629	Pregnant women	-	Females	-	-	-
Pala, 2018 [157]	January 2011 and December 2015	Italy	Epidemic	Rome	723	General population (24% pregnant)	Men: 41.1 ± 13.6 Women: 36.3 ± 13.1	All	Chinese or Romanian	13.8% HIV+	-

Table A4.10. Risk group: others

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Clark, 2015 [166]	2010-2015	USA	Increasing trends	National	2,976	US Army	-	All (88.7% males)	Black, non-Hispanic or who were aged 20-29 years	HIV+ 24.4%	-
Stahlman, 2017 [168]	2007-2016	USA	Increasing trends	U S Army	4,742	U.S. Armed Forces	P&S syphilis: Highest rates in 20–24 and 25–29. Late: highest rates among >40	-	-	-	P&s: 40.4% L: 22.7% UNK: 22.4% LL: 14.5%
Garges, 2014 [167]	2002 to 2012	USA	Increasing trends	U.S. Army	800	US Army	-	2002 M/F ratio 0.41; 2012 M/F ratio 1.37	black-non Hispanic soldiers	-	-Primary and secondary syphilis rates have seen a slight increase in the Army in recent years

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Qyra, 2011 [165]	November 2008	Albania	Epidemic	Tirana	**6**/90	Female SW (>50%: Roma)	Median:28y	Female	-	1.08%	-
Jimenez Del Bianco, 2010 [173]	-	Spain	Epidemic	National	161	Blood donors	27 year	All (92% male)	-	higher incidence: 25-35 and over 50 years	12 primary, 40 secondary, 39 early latent, 30 late latent or tertiary and 19 unknown.
Offergeld, 2017 [313]	1999-2016	Germany	Increasing trends	German blood donor surveillance	-	General population	-	-	-	-	-
Jahn, 2013 [172]	2006-2011	Germany	Increasing trends	National	-	Blood donors	peaking at donor ages from 18-32	-	-	-	-
Politis, 2018 [170]	2010-2016	Greece	Increasing trends	National	-	Blood donors	-	-	-	-	-
Seferi, 2013 [171]	2007-2012	Albania	Increasing trends	National Blood Transfusion Centre	-	Blood donors	-	-	Higher prevalence in family replacement donors	-	-
[169]	2009-2013	Italy	Increasing trends	Liguria	2012:19 2013: 26	Blood donors	Highest incidence in 40–49 yrs	All	-	+&-	-

Table A4.11. Others

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Bhardwaj, 2016 [174]	2010-2016	Australia	Increasing trends in ocular syphilis	Tertiary hospital	7	General population	39.7±13.5	Males	Active syphilis	-	-
Cope, 2018 [179]	2014-2016	USA	Epidemic; increasing trends	North Carolina	7 123 14: 1788 15: 2659 16: 2676	HIV+ vs. HIV-	-	-	-	+ & -	All
Lobo, 2018 [180]	1 January 2010 and 31 December 2015.	USA	Epidemic	Chicago	25	Urban LGBT health clinic	-	All (12.3% MSM)	eye diagnosis, MSM, and HIV positive	HIV+: 27.8%	-
Mathew, 2014 [181]	2009-11	UK	Epidemic; ocular syphilis	Multi-city	41	General population	48.7 (20.6–75.1)	All (90.2% males)	-	HIV+: 31.7% (13) HIV-: 58.5% (24) UNK: 9.8% (4)	ES (early syphilis)
Woolston, 2015 [182]	2015	USA	Cluster of ocular syphilis cases	Seattle and San Francisco	**12**	General population	KC: 39 (29–52) SF: 52 (35–58)	Males: 11 cases MSM: 10 cases	MSM, sex worker	HIV+: 10 HIV-: 2	S: 3 LL: 2 EL: 7

Ref.	Year of event	Country of report	Type of event	Geographical level	Cases (n)	Population affected	Age (years)	Gender	Risk factors identified	HIV status	Stage of infection
Ong, 2017 [183]	January 2015 to August 2016	Australia	Increasing trends	Victoria	12	General population	35 years (30–55)	91.6% male	-	-	Ocular syphilis
Lamb, 2016 [175]	2014-2015	USA	Increasing trends Ocular syphilis	Florida	42	General population (59.5% MSM)	-	All (92% male)	-	HIV+ 45.2%	-
Dhanireddy, 2016 [176]	2014-2015	USA	Epidemic	-	200	Ocular syphilis	-	-	MSM, HIV+	-	-
Hazra, 2018 [184]	2005-2015	USA	Reinfection	Boston	05-06: 64(1.8%) 14-15: 183 (1.9%)	Natal men	-	Males	Age, HIV+	-	Reinfection increased from 0.1-0.7% (0.3 to 2% in HIV+). More likely in older men
CDC, US, 2013 [95]	2010-2011	USA	Reinfection	Baltimore	493	MSM	30 (19-62)	Male	-	86% HIV+	P, S & EL
Muldoon, 2011 [81]	2007-2009	Ireland	Reinfection	Dublin	07: 95, 08: 136, 2009: 208	General population	25–73	93.8% male	-	63% HIV+	In 2009, increases in P syphilis and S dropped
Jain, 2017 [186]	2012-2015	USA	Re infection	San Francisco	323	MSM	41.3 (10.6)	-	Greater rates among HIV+ and ketamine users	+&-	P&S
Holderman, 2016 [177]	2008-2015	USA	Increasing trends in repeated syphilis	Indianapolis MSA	1,362 in total (208 'repeated')	General population	-	-	HIV+ status	-	-
Tilchin, 2018 [189]	2009-2015	USA	Epidemic	Baltimore city	-	MSM vs nonMSM	-	males	-	MSM (↑x4.08) of HIV+	-
Tabidze, 2018 [190]	2014-2016	USA	Epidemic	Chicago	120	Individuals on PrEP	-	-	cis-males (95%), multiple sex partners (87%),	HIV-	P&S
Beymer, 2018 [187]	Oct 2014-May 2017	USA	Increasing trends (365 days before PrEP vs 365 days after PrEP)	Los Angeles	40	MSM on PrEP	All	Males	PrEP	-	-
Thibault, 2016 [188]	2014 vs. 2015	USA	Increasing trends	King County	2014: 250 2015: 397	MSM	-	Males	-	HIV+ (61%)	primary, secondary, and early latent
Tabidze, 2016 [185]	2000-2014	USA	Repeated infections	Chicago	2 111	General population	37.3 (15-70)	All	MSM (black and white), HIV+	-	P, S & EL

Table A4.12. Congenital syphilis

Ref.	Year of event	Country of report	Geographical level	Cases (n)	Mother age (years)	Gender	Risk factors identified	HIV mother status	Stage of infection
Biswas, 2018 [150]	March 13, 2012, to December 31, 2014.	USA	California (except SF)	164/2498	15–45 years	Syphilis-infected women	CS mothers: first prenatal care visit in the third trimester All: high-risk sexual behaviours, methamphetamine use, or incarceration	-	any stage
Slutsker, 2018 [148]	2010-2016	USA	NYC	68	15-44	-	20–29 years, non-Hispanic black or Hispanic, country of origin outside the United States, living in a high-morbidity or high-poverty neighbourhood	-	-
Petrescu, 2012 [301]	2008-2011	Romania	Bucharest	9	-	-	-	-	-
Currenti, 2018 [152]	2013-2017	USA	NY (except NYC)	22	-	-	Black non-Hispanic mothers (41% cases)	HIV-	64% early syphilis
Brown, 2016 [151]	2012-2014	USA	Florida	123	26.1± 5.94	-	Black mothers (64% of CS), younger	-	-
Gamell, 2011 [160]	2000-2010	Spain	Barcelona	8	-	-	-immigrant children	-	-
The Lancet, 2018 [155]	2017	USA	National	918	-	-	-	-	-
Sheffield, 2016 [314]	2012-2014	USA	USA	-	-	-	-	-	-
Lutomski, 2014 [159]	2005-2010	Ireland	Ireland	98	<24 to >30	-	Mother aged 25 and 29, a marital status classified as 'Other'	HIV-	(83.7%), the stage of syphilis was unspecified
Kamb, 2018 [147]	2012-2016	Japan	National	-	majority among 20– 29-year-olds	-	-	-	-
Cooper, 2018 [146]	2003-2016	USA	Ohio	2003:3 2016: 13	-	-	Specifically in 2010-2013, 3 major metropolitan areas	-	-
Zammarchi, 2012 [162]	2000-2010	Italy	Tuscany	8	-	-	-	HIV-	-
Peterman, 2015 [97]	1995-2012	-	-	1995: 1863, 2012:322	-	-	-	-	-
Serwin, 2013 [312]	2000-2011	Poland	-	119	-	-	-	-	-
Orzechowska, 2018 [61]	2016	Poland	Warsaw	7	-	-	-	-	-
Dhanireddy , 2016 [176]	2012 to 2014	USA	-	-	-	-	-	-	-
Sfetcu, 2013 [191]	2006-2011	Europe	16 countries	566	-	-	-	-	-
Pearson, 2018 [51]	2016	USA	Florida	2011:30 2016:60	-	-	-	-	-
Stoltey, 2016 [149]	2007-2014	USA	California	249	20-29 (n=141, 57%)	-	-	-	late syphilis (n=147, 59%)
Simms, 2017 [164]	2010-2015	UK	National	17	20 years (17–31)	12 male, 5female	-	-	P: 6, S:3, EL:1
Bowen, 2015 [145]	2012-2014	USA	National	12:334 14:458	-	-	-	-	-
Benea, 2013 [82]	2002-2011	Romania	Bucharest	01: 423 11: 10	-	-	-	-	-

Ref.	Year of event	Country of report	Geographical level	Cases (n)	Mother age (years)	Gender	Risk factors identified	HIV mother status	Stage of infection
Acheson, 2011 [34]	2006-2007	UK	Teesside	2	-	-	Linked to heterosexual outbreak	-	-
Takahashi, 2018 [104]	2012-2016	Japan	National	45	-	-	-	-	-

Annex 5. Summary tables for systematic review on response

Table A5.1. Studies reporting interventions to respond to outbreaks and or increasing trends of syphilis (other STIs) among adults

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
A. Screening								
Aim: detect syphilis (STI) infections								
Bissessor [207]	2010	Australia	Syphilis screening included in the HIV clinical monitoring (6-monthly, blood test) for MSM attending Melbourne Sexual Health Centre.	MSM HIV-positive	detect early asymptomatic syphilis infections	median number of syphilis tests/MSM increased from 1 to 2; % asymptomatic syphilis infections diagnosed increased from 21% (3/14) to 85% (41/48)	HIV care settings	PPI (pre/post-intervention comparison) **
Branger [209]	2009	Netherlands	Routine syphilis serology screening in outpatient HIV-patients	MSM HIV-positive	detect asymptomatic syphilis infections	two rounds of routine testing (4 month each) detected: 27/81 (33%) and 4/17 (24%) asymptomatic syphilis infections.	HIV care settings	observational **
Carter [206]	2016	US	Syphilis testing integrated in existing HIV POC testing program	all populations at risk of STI/HIV	detect infections	15% syphilis positivity (62/420 during six months)	community based clinics offering POCT	observational **
Cheeks [208]	2016	US	Syphilis testing every 3 to 6 months included in routine HIV laboratory monitoring in a community-based clinic	MSM HIV-positive	early detection of asymptomatic infections/re-infections	syphilis detection rate of 15.5% post-intervention vs 6.6% before.	community based clinic	PPI **
Chow [297]	2017	Australia	Frequent syphilis screening of at high risk HIV negative MSM and opt-out syphilis serology with routine HIV monitoring in HIV-positive MSM (National Syphilis Gay Action Plan introduced in 2009)	MSM HIV-positive and HIV negative	detection of early syphilis	In both HIV-negative and HIV-positive MSM testing coverage increased (48% to 91% and 42% to 77%) and mean number of tests increased (1.3 to 1.6 and 1.6 to 2.3). Decreases in secondary syphilis correlated with increasing testing coverage/frequency only in HIV-positive MSM (r = -0.87; P = .005 and r = -0.93; P = .001)	sexual health clinics	Serial cross-sectional analyses **
Cohen [254]	2016	US	Quarterly vs semi-annual or symptom-based STI/syphilis testing among MSM/transgender women using PrEP (demo project)	MSM, transgender women at high risk	early detection of syphilis/STI (CT, GC)	Without quarterly testing, 11 (20.4%) of participants with syphilis would have been missed (period of infectivity extended by up to 3 months/case).	MSM clinics	Cohort, conference abstract *
Manteuffel [138]	2016	US	POCT (in emergency department) for syphilis/HIV (rapid finger stick Syphilis Heath Check (SHC) treponemal tests) offered to men 18-34 y/o and presumptive treatment during a syphilis outbreak among HIV positive MSM	Male	Detection of new syphilis infections	6/871 (0.7%) active syphilis diagnoses among ED patients (13 months); 3/6 treated in ED with presumptive treatment	Emergency department	Observational, conference abstract *

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Stoové [214]	2012	Australia	Enhanced routine syphilis serology among MSM in clinics serving MSM in Melbourne, 2007-2010, to increase case detection and subsequently reduce the incidence.	MSM	increased detection of syphilis; reduction in syphilis incidence	Annually, among MSM: syphilis testing increased by 7% in HIV positive and by 12% in HIV negative; infectious syphilis incidence declined by 21% in HIV positive and by 29% in HIV negative (more substantial decline in 'high risk' HIV negative MSM (=10 partners in the previous 6 months; inconsistent condom use).	MSM clinics	ecologic study, conference abstract *
Aim: increase coverage/frequency of testing								
Barbee [212]	2016	US	STI self-testing of HIV positive MSM attending for HIV care (pharynx and rectum self-sampling for CT/GC and syphilis serology in the lab)	MSM HIV-positive	increase STI screening rates	increase in CT/GC testing but not for syphilis (location of serology in the lab may have acted as a barrier)	HIV care settings	PPI, conference abstract *
Brook [205]	2013	UK	SMS text reminders on re-attendance for STI testing to patients that require testing	all populations at risk of STI/HIV	increase attendance for repeat testing	41% (84/207) overall re-attendance in the text group vs 28% (47/169) in the control group (P< 0.001). No difference among patients with previous syphilis!	STI clinic	Controlled study, conference abstract *
Callander [210]	2013	Australia	Opt-out syphilis testing routinely conducted during HIV management checks among HIV-positive MSM	MSM HIV-positive	increase testing frequency	increase in the mean number of syphilis tests/man from 1.14 in 2005 to 2.32 in 2007 (P < 0.001); percentage of same-day viral load tests and syphilis test increased from 50% in 2005 to 88% in 2007 (P < 0.001)	HIV care settings	PPI **
Guy [211]	2013	Australia	Opt-out, opt-in vs risk-based strategies for same-day syphilis and HIV viral load testing of sexually active HIV-positive MSM	MSM HIV-positive	increase quarterly testing for syphilis	Syphilis testing was 5-6 times higher in clinics with opt-out and opt-in strategies compared with risk-based policies.	general practices, sexual health clinics, HIV outpatient clinics	Observational **
Ronen [218]	2018	US	Quarterly SMS testing reminders to MSM (King County, Washington)	high risk MSM	increase testing frequency	Low (13%) uptake of SMS test reminders (but other reminders in use!). Time (months) from last HIV test to asymptomatic STI diagnosis: 5.6 if no reminders, 4.8 if SMS reminder, 3.6 if non-SMS reminders.	Partner services in STI clinics	Comparative study, conference abstract *

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Stahlman [216]	2015	US	Study assessing acceptability of interventions among MSM: (1) public health testing reminder every 3 months, (2) public health visit and home testing service, (3) a Web site with information about syphilis and syphilis testing, (4) Web site automatic testing reminder every 3 months, (5) home test kit, (6) being paid to test, (7) oral prophylaxis with antibiotics	MSM with repeat syphilis infection	Assess acceptability of interventions to increase testing	Positive vs negative and/or neutral 1) 11 vs 8; 2) 7 vs 12; 3) 15vs 4; 4) 12 vs 7; 5) 14 vs 5; 6) 16 vs 2; 7) 13 vs 5. Most were open to be tested more frequently; 3), 4), 5) were regarded as most favourable. Community-based partner notification services preferred. Pre-exposure prophylaxis among the most acceptable.	public health, community services	qualitative survey *
Aim: reduce time between positive test and treatment								
Bilello [204]	2018	US	Sending STI test results by text message vs regular notification process (phone or follow-up clinic visit); 10 months, 6 counties in Florida, 2016	people tested for STI	Reduce time between positive test result and treatment	Treatment received within 4 days by 53% if notified by text message vs 42% if notified by traditional methods. Less clients that tested positives not treated or treated later than 8 days (26% vs 35%).	STI clinics	Quasi-experimental **
B. Outreach venues testing								
Aim: expand testing at high-risk venues, detect infections among persons that do not usually attend traditional testing venues								
Arumainayagam [223]	2007	UK	Outreach screening of MSM in local sauna (UK, Walsall)	MSM	detect cases that cannot be reached by traditional contact tracing	Outreach screening detected 4/51 outbreak cases. Consecutive decline in MSM cases after outreach but increases in heterosexual cases	sexual health services, sauna	observational **
Bouton [225]	2016	US	Free testing offered twice/month at commercial sex venues (CSV) (Maricopa County, Dec2013-Nov2014, period 1 and Dec2014-Nov2015, period 2) (CSV the likely places to acquire syphilis by MSM)	MSM	detect infections among MSM at CSV	Increased numbers of syphilis cases diagnosed through CSV screening (14 period 1 vs 24 period 2) but less CSV offering testing (91 period 1 vs 60 period 2). MSM less inclined to seek STD testing at CSV!	commercial sex venues, public health	comparison of two periods, conference abstract *
Haidari [222]	2014	UK, Brighton (?)	In Dec2012, MSM service modernised to target high risk cohort: a walk-in system, self-taken swabs, POCTs/HIV, dedicated clinic team for patient continuity; community informed by Terence Higgins Trust, drug and alcohol support services.	MSM at high risk	target for testing a high risk MSM cohort	2 months after vs 2 month before: increased attendance 105 (91 new) patients vs 60 (57 new patients); doubling syphilis diagnoses rate, 8% vs 4%; stable demographics (80% white UK),	MSM clinic, THT, drug and alcohol support services	PPI, conference abstract *
Jeffrey [224]	2014	UK, Newcastle	Pilot of offering STI/HIV testing and health promotion advice by sexual health staff to men attending two saunas in Newcastle (UK) 2013.	MSM	expanding testing at high risk venues (where sexual activity happens)	9 sessions, 79 men offered STI/HIV screening. 22 (28%) individuals never screened before. 3 old-treated syphilis infections.	sexual health services, MESMAC, sauna	Observational, conference abstract *

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Lampejo [226]	2018	UK, London	Outreach-based STI screening (HIV-POCT, blood testing for syphilis/HBV/HCV, self-sampling NAAT CT, GC) and sexual health advice at two large-scale adult lifestyle events (Erotica, 2013; Sexpo, 2015)	all, not specified	detect infections	>20,000 attendees to both events. 381 attendees screened (56% men); 31% never tested before for HIV; 19 (5%) diagnosed with STI, 3 (0.8%) syphilis;	sexual health services, large public events	Descriptive, *
C. Partner notification								
Aim: improve performance of partner services								
Ehlman [231]	2010	US, Washington, DC	Internet-based Partner Notification program for early syphilis infections (Washington, DC, Jan2007-Jun2008) - using internet-locating information (email, website screen names) when traditional locating data (name, phone, address) for sexual contacts were missing.	early syphilis cases and their contacts	shorten the time to notification of greater numbers of sex partners	IPN used for 43% (381/888) of sex partners of 361 early syphilis cases and led to 8% increase in number of cases with at least 1 treated sex partner, 26% more sex partners medically examined, 83% more sex partners notified of their exposure.	department of health	PPI **
Hightow-Weidman [232]	2014	US, North Carolina	Use of Internet Partner Notification ('open' and 'closed' emails) and text messaging for partner notification (txtPN) in North Carolina (2011 vs 2010).	HIV/syphilis cases and their contacts	notify partners of potential exposure to HIV/syphilis	362 in 2011 vs 133 in 2010 contacts initiated by IPN; 63.5% successfully notified using IPN; 11 new syphilis cases. txtPN used for 29 contacts that did not respond to IPN; 48% responded.	one IPN/txtPN coordinator	PPI **
Pancholy [230]	2016	US, Maricopa County	Communicable disease investigators (CDIs)placed in HIV care clinics reporting highest numbers of syphilis cases conducted partner elicitation interviews and administered bicillin (1/2 day per week, Feb2008-Dec2015)	HIV positive syphilis patients and their contacts	improve syphilis interventions indices	After CDI placement, time to treat decreased by ≈3 days; time to interview by 50%. Less partner elicitation interviews (80% vs. 41%) and less interviews yielded locatable partners (35% vs. 20%)	HIV clinics, private providers	PPI, conference abstract *
Sosa[233]	2018	US, Connecticut	An incentive program to encourage early syphilis patients to name partners during partner elicitation interviews (one gift card offered to cases that named one partner, two to those that named two...) in 2017 in Connecticut	syphilis cases and their contacts	increase number of named partners	218 cases interviewed, 86 partners named (half by 28 cases accepting incentives). Higher partner ratio for 2017 vs 2016 (0.39 vs 0.25, $p<0.05$).	partner services	PPI, conference abstract *

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Taylor [229]	2010	US, Arizona	Disease intervention specialists placed in 3 HIV clinics with high numbers of syphilis cases during 2008 -2009 to notify partners of HIV-infected persons and referring them for testing and treatment.	HIV positive syphilis patients and their contacts	improve partner services in HIV clinics	In 2009 vs 2008, more patients completed partner elicitation interviews (94% vs. 81%, P = 0.001); increases in number of locatable partners (1.1 vs. 0.6, P = 0.004), number of partners exposed/infected and brought to treatment (0.6 vs. 0.3, P = 0.02); time to interview decreased (18 days to 9 days, P = 0.02).	HIV clinics	PPI **
Washburn [234]	2014	US, NYC	Partner services restricted to syphilis cases ≤ 45 years, interviews of late latent/latent of unknown duration ceased	syphilis patients and their contacts	optimise PS, target limited resources in NYC	Number of syphilis interviews decreased (from 2041 to 1866). Partner index unchanged. P&S and EL syphilis cases more likely to be interviewed within 14 days of specimen collection (48% vs. 61%, p=<0.001 and 42% vs. 56%, p=<0.001)	partner services	PPI, conference abstract *
D. Education								
Aim: increase knowledge on and testing for syphilis (other STIs)								
Chow [237]	2016	Australia	Public health syphilis campaigns targeted to MSM (e.g. 'Drama Down Under', and 'Staying Negative') during 2007-2013	MSM	recognize symptoms, present early for treatment	Median duration of symptoms for primary syphilis (9 days), secondary syphilis (14 days) and RPR titre did not change over time (2007-2013, Melbourne sexual health centre). Public health campaigns not associated with shorter time from onset of symptoms to treatment.	public health	trend analysis of duration of symptoms in MSM with infectious syphilis exposed to public health campaigns, **
Darrow [240]	2008	US, Florida	Social marketing campaign in 2004, Florida (posters, palm cards distributed in bars, clubs, elsewhere; advertisements in local publications; billboards; syphilis alert banners on 3 Web sites; public service announcements on radio/TV)	MSM	increase knowledge, increase testing, decrease incidence of syphilis	after six months, exposure increased from 18.0% to 36.5%, but there was no impact on risky sexual practices, no increases in knowledge, clinic visits, or testing or treatment for syphilis	public health	PPI **
Endyke-Doran [236]	2007	US	Syphilis Elimination Project- a culturally appropriate health promotion with street and business outreach targeted to Hispanic community in Baltimore City (for 10 weeks, 2004). PRECEDE model used to identify and prioritise risk behaviours and gaps in services.	All (ethnic community)	increase knowledge, increase testing, decrease incidence of syphilis	Statistically significant increase in knowledge about syphilis within the Hispanic community and an increase in testing behaviours.	local business, community organisations, outreach workers	PPI **

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Gourley [241]	2014	US, Denver	'Syphilis is Up' - multi-faceted public awareness campaign targeting MSM, short term (Jan-March 2013) Denver: website, social media, mobile applications, print advertising, client outreach.	MSM	increase awareness and testing	'syphilis page' the most visited page on the Denver Public Health website; testing for syphilis in outreach increased by 22% and syphilis diagnoses by 78% during the campaign vs before.	public health, outreach	Survey, conference abstract *
Guy [238]	2009	Australia	Social marketing campaign 'Check-it-out' in 2004 in Victoria (budget $A 130230, multiple venues, targeting community attached-, non-community attached-, young- and culturally and linguistically diverse-MSM)	MSM	increase HIV/STI testing, increase regular HIV/STI testing, promote sexual health	The campaign did not significantly increase HIV/STI testing - rates were increasing since 2 years before.	public health department	PPI **
Nanin [242]	2009	US, Los Angeles	Stop the sores': social marketing campaign launched in 2002 (promotional materials in English and Spanish, advertisements in newspapers, magazines, billboards, and subway or bus placards)	MSM	increase knowledge, awareness and syphilis testing	39.1% of men exposed to the campaign reported being tested for syphilis as a result. Testing associated with HIV seropositive status, any recent unprotected anal insertive sex, recent use of methamphetamine, recent use of 'poppers,' and recent use of erectile dysfunction drugs.	public health	observational, no comparison *
Plant [243]	2014	US, Los Angeles	'Check Yourself', social marketing campaign launched in 2007, Los Angeles	MSM	increase knowledge and syphilis testing	30% (of 306) MSM in a cross-sectional survey in 2009 were both aware of the campaign and identified that the campaign was about syphilis. They were >6 times more likely to have been recently tested. Only being aware of the campaign was not associated with testing.	Public health department	cross-sectional survey, comparison **
Plant [244]	2010	US, Los Angeles	Stop the sores': social marketing campaign launched in 2002 (promotional materials in English and Spanish, advertisements in newspapers, magazines, billboards, and subway or bus placards) Los Angeles	MSM	increase knowledge, awareness and syphilis testing	MSM aware of the campaign were twice as likely to have tested for syphilis in the past 6 months vs MSM who were not aware. They all had more knowledge on syphilis.	public health	comparative study, exposed vs not exposed **
Sanchez [245]	2010	US, Bronx NY	Educational video 'Syphilis and Men', 2006 with modes of transmission, symptoms, risk-reduction strategies, treatment, and syphilis/HIV coinfection, in ED.	men at-risk	increase syphilis knowledge	Men that viewed the video (intervention group) scored higher than the control group (p<.001) in knowledge survey	clinical services (ED), community organisations	RCT ***

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Stephens [246]	2010	US, San Francisco	Dogs Are Talking -syphilis awareness social marketing campaign, 2007 San Francisco: posters, weekly advertisements in newspaper, dog-themed giveaways. Info on syphilis symptoms, risk factors and testing sites.	MSM	increase knowledge, increase testing	Among HIV-positive MSM, only, those recalling the campaign had increased syphilis testing in past 6 months (87% vs 65%, p=0.031) and more info on syphilis symptoms (p= 0.031).	public health	comparison of exposed/not exposed **
Wilkinson [239]	2016	Australia	'Drama Downunder', launched in 2008 to promote HIV/STI testing among MSM. Outdoor media, digital media, print gay media campaign material, website.	MSM	increase timely HIV/STI screening rates, community knowledge and reduce transmission	Among HIV-negative MSM: nonsignificant increases of HIV, syphilis, CT testing rates, significant for GC. Among HIV-positive MSM: no change in GC or CT testing but syphilis testing declined significantly	public health	PPI **
Aim: prevent infections, reduce incidence								
Chin [247]	2012	US	Two types of behavioural group-based interventions for adolescents: comprehensive risk reduction interventions and abstinence education interventions (vs untreated or minimally treated adolescents) on preventing pregnancy, HIV, and other STIs.	adolescents	reduce STI incidence	Group-based comprehensive risk reduction interventions were effective in reducing STIs (OR 0.65), frequency of sexual activity (OR 0.81), unprotected sexual activity (OR 0.70) and number of sex partners (OR 0.83). Results were inconclusive for the group-based abstinence education.	school and/or community settings	Review ***
Petrova [248]	2015	US	Abstinence education, comprehensive interventions (aimed at improving skills and promoting safe sex practice)	adolescents	decrease STD incidence	Abstinence interventions did not reduce STD incidence but comprehensive education programmes did reduce the risk by 4 percentage points (23% RRR).	schools, clinics	meta-analysis ***
Metsch [251]	2013	US	Brief patient-centred risk-reduction counselling with rapid HIV test (intervention) or rapid HIV test with information only (control) (2010, AWARE project). Core elements of counselling included a focus on patient's specific HIV/STI risk behaviour and negotiation of realistic and achievable risk-reduction steps. (six months)	all STI clinics patients	reduce STI incidence	There was no significant difference in 6-month composite STI incidence by study group (adjusted risk ratio, 1.12; 95% CI, 0.94-1.33). There were 250 of 2039 incident cases (12.3%) in the counselling group and 226 of 2032 (11.1%) in the information-only group.	STI clinics	RCT ***
Aim: educate healthcare workers								-
Calamai [250]	2013	Ireland	'A two-day course (BASHH) for healthcare staff in primary care, GUM/STI clinics that may encounter STI patients on regular basis (2007-2010)	HCW	build basic knowledge, skills and attitudes for effective STI patients management	12.7% increase in syphilis testing	healthcare services	PPI **

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
F. Interventions using social media								
Dowshen [257]	2015	US, Philadelphia	Social media-based (Facebook, Twitter, YouTube, Instagram) youth-driven campaign to improve knowledge and increase STI/HIV testing (Sep2012–Aug2013) www.iknowushould2.com	young adults (<25years)	improve knowledge, increase testing for STI/HIV	large increase in number of syphilis tests (1150 vs 410); increase in syphilis positive results (5 vs 3) post-campaign vs pre-campaign	healthcare services, community organisations	PPI **
Wilson [258]	2017	UK, London	e-STI testing service (self-sampling kits for CT, GC, HIV, syphilis) (intervention) or a website signposting local sexual health clinics (control)	young adults (16-30 years)	increase STI testing uptake and diagnoses	After 6 weeks, 50.0% vs. 26.6% (p<0.0001) completed an STI test, 2.8% vs 1.4% (p=0.079) diagnosed with an STI. No significant change in proportion of participants treated 1.1% vs 0.7% (p=0.231).	sexual health services (?)	RCT, conference abstract *
Bertrand [259]	2018	US, Rhode Island	STD prevention and testing campaign targeting social media platforms popular among high risk individuals (designed based on a survey of STD clinic attendees)	adolescents, young adults, MSM	improve knowledge, promote testing at STD clinic	Double number of MSM presented to STD Clinic (Nov 2017 - Jan 2018).	public health, STI services	PPI, conference abstract *
Cohen [213]	2016	US	Healthvana- online patient engagement platform and smartphone application to notify (AHF Wellness Center) clients of STI test results (2014-2015)	men	Reduce time (days) between test and notification, test and treatment	Time between STI test and notification reduced from 9 to 7 days (p < 0.001) and between STI test and treatment from 13 to 11 days (p = 0.022).	healthcare providers	PPI, conference abstract *
Coughlan [255]	2015	New Zealand, Christchurch	Facebook page was created to raise awareness of infectious syphilis, the importance of screening and where to get tested.	men, MSM	increase awareness, mobilise to testing	decrease in infectious syphilis up to no cases by end of 2012 (combined interventions)	public health, STI services	PPI **
Hunter [256]	2014	US, Milwaukee	Facebook generic message sent from a FB account created by partner services staff to identify, link, and notify individuals in a cluster of syphilis cases in young black MSM	MSM	Improve case finding, partner services	2/55 syphilis cases identified solely through FB; FB helped PS of 5 individuals	partner services	comparison of partner services during intervention against local targets **
G. Biomedical interventions								
Aim: reduce syphilis incidence								
Bolan [260]	2015	US	Prophylactic doxycycline (100 mg, daily) among high-risk HIV-positive MSM (with ≥ 2 syphilis episodes since HIV diagnosis) for 48 weeks vs contingency management (Los Angeles). STI (GC, CT, syphilis) tested at weeks 12, 24, 36, and 48.	MSM, HIV-positive, at high risk	reduce STI (CT, GC, syphilis) incidence	Reduction in STI incidence (OR = 0.27, 95% CI 0.09-0.83, p = 0.02) at week 48 for doxycycline group. Reduction in syphilis (2 vs 6 cases).	LGBT centre	RCT pilot!! **

Reference	Year of publication	Country	Intervention	Population targeted	Aim of intervention	Outcome	Services involved	Type of study Quality assessment: *** high, ** medium, * low
Molina [261]	2018	France	Post-exposure doxycycline (200 mg, single dose, oral) within 24 h after condomless sex (anal or oral), 10 months, to high risk HIV-negative MSM under PrEP.	MSM, HIV-negative, at high risk	reduce syphilis (other STI) incidence	Syphilis occurrence significantly reduced in intervention group (HR 0.27; 95% CI 0.07-0.98, p=0.047). More GI adverse events in intervention group (53% vs 41%, p=0.05).	clinics participating in ANRS IPERGAY	RCT ***
Wilson [262]	2011	Australia	Prophylactic doxycycline (100 mg, daily) with use-effectiveness of 70% among gay men	MSM	reduce syphilis incidence	Acceptability 52.7% for own benefit, 75.8% for MSM community benefit. 49% reduction in syphilis incidence in one year and 85% in 10 years (70% use-effectiveness, if taken by 50% MSM, no other interventions)	modelling	survey, modelling **

Table A5.2. Studies reporting multiple interventions for outbreak response

Reference, year of publication	Location	Time of event	No. of cases	Population affected	Reported interventions					Reported outcomes	Services involved
					Public awareness, health promotion	Healthcare provider awareness, education	Screening	Partner notification (PN)	Other		
Abu-Rajab 2011 [33]	UK, Scotland, Forth Valley National Health Service Board area	2009 (Apr-Oct)	10 (7 F, 3 M). Two cases (F) not linked to the other eight. 8/10 early latent syphilis	Heterosexuals, young population	-	-	Yes	Yes	-	Routine ANS and blood donors screening detected the first 2/7 female cases. Partner services prevented the further spread of the outbreak (all cases informed their contacts). Majority presented as early latent (only two infectious syphilis) - need for knowledge and awareness among gen pop!	ANS, blood donation services, sexual health clinics (PN)
Acheson, 2011 [34]	UK, England, north-east (Teesside area)	2009-2010 (prolonged outbreak, started in 2006)	48 (57% F in 2009, 2 CS). 82% primary syphilis	heterosexuals, young population, CS, high deprivation areas	Yes[1]	Yes	Yes	Yes[2]	-	only 50% of contacts traced (many unknown, untraceable); adverts on social networking site seen by large number of local people; NHS Teesside website impressions- 10.5 million for women, 2.74 million men	multiagency OCT; sexual health services, primary care, ANS, teenage pregnancy services
Bell, 2016 [266]	UK, Sheffield, Yorkshire (?)	Nov2015 - Jan2016	7 students: MSM (2), bisexual men (2), heterosexual men (2), F (1)	MSM, bisexual men, heterosexuals	Yes[3]	-	Yes	Yes[4]	-	28/37 (78%) of identified contacts attended; provider referral (25/29; 86%) was the most effective!	OCT, student health services
Bowen, 2018 [36]	US, American Indian reservation	2013-2015	134 (57% F, 2 CS, 2 stillbirths); 40.3% primary, 17.9% secondary, 31.3% early latent, 10.4% late latent syphilis	heterosexuals, CS;	Yes[5]	Yes[6]	Yes[7]	Yes[8]	Field treatment (for 18 persons-cases or sex partners) linked to community screening, jail, homes.	Proportion of cases identified by type of intervention (2013-2015): 3.7% routine first ANC visit; 0.7% expanded ANS (T3); 16% EMR; 3.7% community screening, 2.2% venue based screening; 40% contact tracing; 26% symptomatic testing; 8% other type screening ;	multiagency OCT, tribal health agency, local Indian health services, departments of health, CDC

Reference, year of publication	Location	Time of event	No. of cases	Population affected	Reported interventions					Reported outcomes	Services involved
					Public awareness, health promotion	Healthcare provider awareness, education	Screening	Partner notification (PN)	Other		
Coughlan, 2015 [255]	New Zealand, Christchurch	2012	26 (infectious syphilis)	MSM, bisexual men (use of social media, high risk sexual practice)	Yes[9]	Yes[10]	Yes.	Yes[11]	Enhanced surveillance in sexual health clinics - collected info to target response	Case detection by: 1) test provider: 12/26 GP, 10/26 health centre, 4/26 student health centres, family planning; 2) type of testing: 8/26 sexual contacts, 14/26 symptomatic, 3/26 asymptomatic screening, 1/26 immigrations screen.	Multidisciplinary OCT: sexual health services, public health, AIDS community-based organisation, GP.
Fernando, 2013 [264]	UK, Southend, Essex	2011-2012	42 (27 in 2011, 15 half 2012)	MSM (6/27 in 2011 HIV-positive)	Yes[12]	Yes[13]	-	-	-	Interagency, multidisciplinary working resulted in productive collaborative responses. The use of existing sexual health and MSM social/support networks enabled access to 'harder to reach' populations for STI health promotion	Multidisciplinary OCT: local health authority, public health department, HPA, GUM
Moussa, 2011 [50]	UK, English town	2010	6 (heterosexuals, 3/6 M, young) *Note: concurrent 4 MSM cases, 3/4 HIV-positive but response described for heterosexuals*	heterosexuals, young population	Yes[14]	Yes[15]	Yes[16]	Yes[17]	-	contact tracing more successful for heterosexuals vs MSM (>untraceable partners, < receptive to provider referral)	wide range of practitioners allowed a mixture of control methods to be undertaken
Morgan, 2011 [49]	UK, south-east Hampshire	2009 (Jan-Apr)	4 (heterosexual cases 2 M, 2 F)	heterosexuals, young population	Yes[18]	Yes[19]	Yes[20]	Yes[21]	-	Limited impact on young people of information campaigns. 42.5% contacts supplied with information (of those, 64.7% attended GUM). 72.5% of exposed contacts remained untested!	incident control team: GUM, primary care, public health local authorities
Thomas, 2016 [265]	UK, North Wales (rural)	Jan2013 - Jun2014	53	MSM, bisexual men, heterosexual men and women	Yes[22]	Yes[23]	Yes[24]	Yes	Enhanced surveillance, sexual network analysis, network diagram Cytoscape	POCT - 16 clients tested/no positives. 92% of 755 apps users reached by health promotion campaign. Outbreak successfully controlled but difficult to determine which interventions were most effective.	multidisciplinary OCT

EMR – electronic medical records screening prompt in healthcare facilities to remind on screening; GP – general practitioners; NCSP – National Chlamydia Screening Programme, England UK

[1]comprehensive communication plan

[2]50% contacts unknown, untraceable

[3]online health promotion via student bulletins, social media

[4]provider referral, including home visits

[5]education activities for the general public on syphilis signs, symptoms, need for testing

[6]provider education on syphilis testing and treatment, EMR

[7]symptomatic testing, community screening in high morbidity communities, outreach screening (jail), enhanced ANS (1st trim, 3rd trim, at delivery)

[8]collaborative, interagency case-interviewing and partner services

[9]a) public awareness, b) gay press, newspapers, Facebook page

[10]promote awareness, help recognise clinical features, promote testing and referral

[11]contact mapping and diagram

[12]a) general public awareness on the outbreak in local media, b) MSM sexual health and social/support networks involved, c) pharmacy awareness campaigns

[13]GPs informed on STI trends and management

[14]awareness, encouraging testing in colleges, young patient clinics, family planning clinics, NCSP

[15]GP bulletin, monthly newsletter

[16]repeat 3rd trim ANS by midwifes assessment

[17]multiple interview sessions needed

[18]a) generalised media campaign, b) youth targeted media campaign (1 000 posters, 6 000 leaflets distributed)

[19] *letters to GPs, dentists, community pharmacists, acute clinical services, GUM, sexual health clinics*
[20] *syphilis testing at NCSP sites, HIV/syphilis testing offered at contraceptive, sexual health clinics, 3rd trim ANS*
[21] *enhanced partner notification*
[22] *a) awareness raising of affected communities, b) targeted health promotion to MSM users of social networking apps*
[23] *e.g. letter to practitioners info on health board website*
[24] *syphilis POCT at local MSM sauna.*

Table A5.3: Studies reporting interventions to respond to congenital syphilis cases

Reference	Year of publication	Country	Intervention	Aim of intervention	Outcome	Type of study Quality assessment: *** high, ** medium, * low
Burghardt [153]	2018	US, California	CS prevention cascade (California) – records of pregnant women with syphilis linked with birth outcomes	identify gaps in care and opportunities for intervention	CS prevention ratio* was 72%/67%/70% in 2015/2016/2017 (varied from 39-93% by county!)	Surveillance data analysis *
Kidd [274]	2018	US (all)	CS prevention cascade (all US states) - records of pregnant women with syphilis linked with birth outcomes	identify gaps in care and opportunities for intervention	CS prevention ratio* was 75% in 2016. Off all pregnant women with syphilis: 88.0% received prenatal care, 89.4% tested, 76.9% adequately treated (at least 30 days before delivery).	Surveillance data analysis *
Johnston [277]	2016	Ireland	Evidence-based management algorithm of syphilis exposed infants	aid clinical management of syphilis exposed infants	High adherence to algorithm but 11% infants over treated - algorithm absent from infant chart and decision to treat made out-of-hours by a junior doctor	Observational, no comparison *
Matthias [276]	2018	US, Florida	System-generated weekly email notification to retrieve pregnancy status for all female syphilis field records aged 15-44 years	reduce unknown pregnancy status among women with syphilis to enable prevention of CS	The volume of flagged field records (unknown pregnancy status) had decreased by 70%.	Observational *
Matthias [272]	2017	US, Louisiana, Florida	Early prenatal syphilis screening (1st and 2nd trim) vs 3rd trim screening to prevent CS in syphilis high morbidity areas	prevent CS	Early screening averted 92% potential CS cases vs 78% screening during 3rd trim. Treatment of syphilis equally effective in preventing CS in women with early syphilis or late/unknown duration if detected during 1st and 2nd trims pregnancy	Surveillance data analysis *
Rahman [275]	2019	US, Louisiana	Congenital syphilis case review boards – reviewing the files of 79 CS cases, Jan 2016-July 2017	identify failures in practice and propose CS prevention interventions	Of 79 CS, 33% could have been prevented and 27% could have been possibly prevented. Many practitioners changed their practice following report findings.	Surveillance data analysis *
Plotzker [273]	2018	high income settings	Early prenatal syphilis screening (universal, 1st or 2nd trim)	prevent CS	Significant reduction of CS and APOs when early detection of syphilis in pregnancy was paired with BPG (cost-effective in low morbidity settings)	Review ***
			Retesting during 3rd trim and at delivery for women at high risk (definition of risk may differ by settings and local epidemiology)		Detection of 5% prenatal syphilis diagnoses in two high morbidity states in US, 2012-2014; could have prevented 5-11% of CS cases in LA, US 2015-2016.	Surveillance data analysis *

Reference	Year of publication	Country	Intervention	Aim of intervention	Outcome	Type of study Quality assessment: *** high, ** medium, * low
			Prenatal maternal treatment (benzathine penicillin G 2.4 million units i.m. single dose for primary, secondary and early latent syphilis and every week for three weeks for late latent/unknown duration syphilis) ≤30 days before delivery		CS prevention rates close to 100% if BPG given before 28 weeks of gestational age (GA), and 90-98% at any GA	Review ***
			Public health interventions - partner notification of syphilis positive pregnancies		Biological plausibility but no studies clearly demonstrated that PN reduced CS incidence.	-
		US	Public health interventions - surveillance	prevent CS	Surveillance data guide responses to syphilis outbreaks; understanding of clinical/public health gaps in CS prevention. Important to document pregnancy status of women with reactive syphilis.	
			Public health interventions - antenatal screening laws		Universal ANS associated with reduction in neonatal mortality (US).	-

** Proportion of pregnant syphilis cases who did not deliver a CS baby*

Table A5.4: Syphilis guidelines

Author/organisation and year of publication	Title	Target population	Recommendation	Strength of recommendation (if reported)	Link to document
Guidelines on screening					
ECDC and EMCDDA, 2018 [228]	Public health guidance on active case finding of communicable diseases in prison settings	people in prisons	STI testing may include risk-based, age-based and universal testing approaches.	very limited evidence of effectiveness in EU/EEA prison settings	link
US Preventive Services Task Force, 2016 [315]	Screening for syphilis infection in non-pregnant adults and adolescents	(non-pregnant) adults/adolescents at risk	Screening for infection of asymptomatic at risk populations. More frequent testing (3 months) recommended for MSM and PLWH (part of HIV care in special settings or in primary settings) *Note: at risk in US: MSM, PLWH and history of incarceration, SW, geography, race/ethnicity, being a male younger than 29 years.*	A recommendation - There is high certainty that the net benefit is substantial. The USPSTF recommends the service.	link

Author/organisation and year of publication	Title	Target population	Recommendation	Strength of recommendation (if reported)	Link to document
BASHH Clinical Effectiveness Group, 2016[221]	2016 United Kingdom national guideline on the sexual health care of men who have sex with men	MSM	All asymptomatic MSM should be tested for syphilis as part of sexual health screening (1B); annually if at low risk and 3-months if at risk. SMS text reminders should be used to increase re-attendance and STI detection rates in MSM (1C). Syphilis serology should be performed at least annually as part of routine monitoring in sexually active HIV-infected MSM (1B).	1B - Strong recommendation, moderate quality evidence 1C - Strong recommendation, low quality evidence	link
IUSTI 2014 [14]	European Guideline on the Management of Syphilis	groups at high risk	Testing for case finding of groups at high risk: patients diagnosed with STIs, HIV, HBV, HCV, persons who engage in high risk sexual behaviour: MSM, SW all at higher risk of STIs, all attendees at GUM/STI clinics	not reported	link
Guidelines on partner notification					
IUSTI 2015[235]	European guidelines for the management of partners of persons with sexually transmitted infections	all	All contacts of a syphilis case need to be informed about the possibility of infection. Look back period: 3 months for PS, 6 months for SS, 2 years for EL. Trained staff to obtain from the index patient information on: number of contacts, names of contacts, addresses, phone numbers and email addresses of contacts, insights into sexual networks, explicit details about relationship with contacts, sexual practices, use of condoms. Notifying partners by: patient referral (simple or enhanced, expedited partner therapy), contract referral or provider referral. Contact management: epidemiological treatment or testing and treatment, testing for other STIs (HIV, HCV, HBV as assessed by local epidemiology). Serological tests for syphilis should be performed at the first visit and repeated at 6 weeks and 3 months.	not reported	link

Author/organisation and year of publication	Title	Target population	Recommendation	Strength of recommendation (if reported)	Link to document
Guidelines on antenatal screening					
WHO, 2017 [316]	WHO guideline on syphilis screening and treatment for pregnant women	Pregnant women	Screening of all pregnant women for syphilis during the first antenatal care visit	Strong recommendation, moderate-quality evidence	link
BASHH, 2016 [281]	UK national guidelines on the management of syphilis 2015	Pregnant women	All pregnant women should have syphilis serology at their first antenatal clinic visit, and if risk of syphilis is recognised re-screening later in pregnancy should be offered	1A - Strong recommendation, high quality evidence	link
BASHH (amendment), 2018 [317]	Congenital syphilis in England and amendments to the BASHH guideline for management of affected infants	Pregnant women	Babies born to mothers that acquire syphilis and seroconvert late in pregnancy (prior to a mature antibody response) may have congenital infections even at a low RPR titre and with negative IgM.	not reported	link
US Preventive Services Task Force, 2018 [282]	Screening for syphilis infection in pregnant women	Pregnant women	Early universal screening for syphilis infection of all pregnant women. Women at high risk for syphilis should be rescreened early in 3rd trim (28 weeks of gestation) and again at delivery (high risk: higher prevalence settings, PLWH, history of incarceration or CSW. Repeat screening after exposure to infected partner (recommended by AAP, ACOG).	grade A	link
ECDC, 2017 [279]	Antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility in the EU/EEA – addressing the vulnerable populations	Pregnant women	Universal, voluntary, syphilis testing should take place during 1st trim of pregnancy. To be repeated during 3rd trim for pregnant women at increased risk of infection/those who refused testing. Testing at delivery if not previously tested.	Recommendation formulated based on evidence from literature, expert opinion and EU/EEA practice	link

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European Centre for Disease Prevention and Control (ECDC)

Gustav III:s Boulevard 40, 16973 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

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