La vigilancia epidemiológica desde una aproximación sindémica: la vigilancia de las infecciones de transmisión sexual y de la tuberculosis centrada en poblaciones a riesgo de infección

Alexis Sentís Fuster, 2022

Directors de tesi: Dra. Mònica Guxens, Dr. Joan A. Caylà,

i Dra. Juliana Reyes Urueña

Universitat Pompeu Fabra, Departament de Medicina i Ciències de la Vida

A la Carola, el Lucas i la Julieta i als meus pares, Mercè i Albert,

Resumen, Resum, Abstract

Resumen

La vigilancia epidemiológica desde una aproximación sindémica: la vigilancia de las infecciones de transmisión sexual y de la tuberculosis centrada en poblaciones a riesgo de infección.

El propósito principal de la tesis es contribuir en lo posible a potenciar la vigilancia de las endemias de las infecciones de transmisión sexual (ITS) y la tuberculosis (TB) en las poblaciones a riesgo de infección a través de una visión y un análisis sindémico para facilitar el diseño de intervenciones eficaces de prevención y control.

Se llevaron a cabo cinco estudios en Cataluña y Portugal incluyendo distintos diseños epidemiológicos: incidencia poblacional, cohortes retrospectivas, y series temporales, y realizándose análisis descriptivos, modelos de regresión, análisis de series temporales y de clústeres.

Los resultados mostraron como durante los últimos años, en Barcelona y Cataluña, hubo un aumento drástico de los casos notificados de ITS sobre todo en jóvenes, especialmente en mujeres jóvenes. Factores como ser hombre, el número de parejas o episodios previos de ITS o vivir en zonas urbanas se asociaron con el riesgo de presentar coinfección por el VIH. Se identificaron y caracterizaron tres clústeres diferenciados de casos de ITS en Cataluña. Un primer clúster que consistía en mujeres jóvenes que residían en zonas rurales más desfavorecidas y que presentaban más

infecciones por clamidia que los otros clústeres. Un segundo clúster mostraba predominancia de hombres que tenían sexo con hombres, residentes en zonas urbanas y menos desfavorecidas que presentaban múltiples episodios de ITS, así como unas tasas de incidencia de ITS más elevadas y una mayor coinfección por VIH que los otros dos clústeres. El tercer clúster presentaba una distribución de frecuencias de características socio epidemiológicas similar a la del global de los casos notificados. Durante la pandemia por COVID-19 hubo una reducción marcada en los casos diagnosticados y notificados de ITS, siendo esta disminución más pronunciada en mujeres y personas jóvenes.

En los estudios relacionados con la TB, los resultados muestran cómo durante los últimos años la magnitud de la tendencia descendente en el número de casos notificados en Portugal fue desigual en las distintas poblaciones analizadas (menor en personas de nacionalidad no portuguesa, niños menores de 5 años y en personas VIH negativas). La falta de adherencia al tratamiento de la infección tuberculosa latente estuvo asociada a pautas cortas del tratamiento y con determinados factores socio- epidemiológicos, clínicos y de comportamiento, que variaban en las dos áreas metropolitanas analizadas y que incluían factores como tener más de 15 años, haber nacido en el extranjero, tener una enfermedad crónica, el abuso de alcohol y el ser una persona que se inyecta drogas.

Los resultados de los estudios realizados refuerzan la consideración de que las endemias de las ITS y la TB actúan cada una de ellas como una sindemia, ya que coexisten en contextos temporales y geográficos particulares con otras infecciones o patologías (concentración de la enfermedad) e interactúan en poblaciones e

individuos con factores de riesgo particulares, los cuales aumentan la probabilidad de contraer cada una de estas infecciones (interacción de la enfermedad).

Resum

La vigilància epidemiològica des d'una aproximació sindèmica: la vigilància de les infeccions de transmissió sexual i de la tuberculosi centrada en poblacions a risc d'infecció.

El propòsit principal de la tesi és contribuir en la mesura del possible a potenciar la vigilància de les endèmies de les infeccions de transmissió sexual (ITS) i la tuberculosi (TB) en les poblacions a risc d'infecció a través d'una visió i una anàlisi sindèmica per a facilitar el disseny d'intervencions eficaces de prevenció i control.
Es van dur a terme cinc estudis a Catalunya i Portugal incloent diferents dissenys epidemiològics (incidència poblacional, cohorts retrospectives, i sèries temporals), i fent anàlisis descriptives, models de regressió, anàlisis de sèries temporals i de clústers.
Els resultats van mostrar com durant els darrers anys, a Barcelona i Catalunya, va haver-hi un augment dràstic dels casos notificats d'ITS sobretot en joves, especialment en dones joves. Factors com ara ser home, el nombre de parelles o episodis previs d'ITS, o viure en zones urbanes, es van associar amb un major risc de presentar coinfecció pel VIH. Es van identificar i caracteritzar tres clústers diferenciats de casos d'ITS a Catalunya. Un primer clúster que consistia en dones joves que residien en zones rurals més desafavorides i que presentaven més infecció per clamídia que la

resta de clústers. Un segon clúster on predominaven els homes que tenien sexe amb homes, residents a zones urbanes i menys desafavorides, que van mostrar múltiples episodis d'ITS, així com taxes d'incidència d'ITS més elevades i més coinfecció pel VIH que als altres dos clústers. El tercer clúster presentava una distribució de freqüències en les característiques socioepidemiològiques similar a les del global dels casos notificats. Durant la pandèmia de la COVID-19 va haver-hi una reducció marcada en el diagnòstic i notificació de casos d'ITS, aquesta disminució va ser més pronunciada en dones i persones joves.

En els estudis relacionats amb la TB, els resultats mostren com la magnitud de la tendència descendent en el nombre de casos notificats a Portugal els darrers anys va ser desigual en les diferents poblacions analitzades (menor en persones de nacionalitat no portuguesa, nens menors de 5 anys i en persones VIH negatives). La manca d'adherència al tractament de la infecció tuberculosa latent va estar associada amb pautes curtes del tractament i amb determinats factors socioepidemiològics, clínics i de comportament, que variaven en les dues àrees metropolitanes analitzades i que incloïen factors com ara tenir més de 15 anys, haver nascut a l'estranger, tenir una malaltia crònica, l'abús d'alcohol i ser una persona que s'injecta drogues.

Els resultats dels estudis realitzats reforcen la consideració que les endèmies de les ITS i la TB actuen cadascuna com una sindèmia, ja que coexisteixen en contextos temporals i geogràfics particulars amb altres infeccions o patologies (concentració de la malaltia) i interactuen en poblacions i individus amb factors de risc particulars, els quals augmenten la probabilitat de contraure cadascuna d'aquestes infeccions (interacció de la malaltia).

Abstract

Syndemic approach in sexually transmitted infections and tuberculosis surveillance: surveillance focused on populations at risk of infection.

The main purpose of the thesis is to contribute as much as possible to enhance the surveillance of the endemics of sexually transmitted infections (STIs) and tuberculosis (TB) in populations at risk of infection through a syndemic approach and analysis to facilitate the design of effective prevention and control interventions.

Five studies, with different epidemiological designs (population-based incidence, retrospective cohorts, and time series) were carried out in Catalonia and Portugal. Descriptive analysis, regression models, and time series and clustering analysis were performed.

The results for the STI endemic showed how in recent years, in Barcelona and Catalonia, there was a sharp increase in reported cases of STIs, especially in young people, and in particular in young women. Factors such as being male, the number of partners, the number of previous STI episodes, or living in urban areas were associated with higher risk of HIV coinfection. Three differentiated clusters of STI cases were identified and characterised in Catalonia. The first cluster consisted of young women residing in more deprived rural areas who were more affected by chlamydia than the other clusters. A second cluster consisted of predominantly men who have sex with men residing in urban and less deprived areas who showed multiple episodes of STIs, higher incidence rates of STIs and higher HIV coinfection than the two other clusters. The third cluster presented a similar frequency distribution of socio-

epidemiological characteristics to that observed in the global number of reported cases. During the COVID-19 pandemic there was a drastic reduction in diagnosed and reported cases of STIs, this decrease was more pronounced in women and young people.

In the studies related to TB, the results indicated how in recent years the magnitude of the decreasing trends in the number of cases reported in Portugal differ across different populations (lower decline in people of non-Portuguese nationality, children under 5 years of age, and in HIV-negative people). The lack of adherence to the treatment for latent TB infection was associated with short courses of treatment and with certain socio-epidemiological, clinical, and behavioural factors, such as being older than 15 years, being born abroad, having a chronic disease, alcohol abuse, and being a person who injects drugs. The main associated factors differed between the two metropolitan areas analysed.

The results from all the performed studies reinforce the consideration that both endemics, STIs and TB, behave each one as a syndemic since they coexist in particular temporal and geographic context with other infections or pathologies (concentration of the disease) and interact in populations and individuals with particular risk factors, which increase the probability of acquiring each of these infections (disease interaction).

Prefacio

Esta tesis doctoral y los artículos que la componen fueron realizados entre 2018 y 2022 dentro del programa de doctorado de biomedicina del departamento de Medicina y ciencias de la vida de la Universidad Pompeu Fabra de Barcelona. Fue supervisada por el Dr. Joan A. Caylà (Fundación fuiTB) y la Dra. Juliana Reyes (CEEISCAT) y tutorizada por la Dra. Mònica Guxens (ISGlobal, UPF). Comprende una recopilación de publicaciones científicas en coautoría que siguen los procedimientos establecidos en dicho programa de doctorado. A pesar de no haber recibido ninguna financiación específica, la labor investigadora necesaria para la realización de esta tesis ha sido apoyada y enmarcada como parte de la labor diaria realizada por el doctorando en las distintas organizaciones en las que ha desarrollo su actividad laboral durante el periodo del doctorado. Estos son la *Direção-Geral da Saúde* (DGS) en Lisboa (Portugal), el *European Centre for Disease Prevention and Control* (ECDC) en Estocolmo (Suecia), el *Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya* (CEEISCAT), y *Epiconcept* en París (Francia). Dichas organizaciones, a través de sus respectivos responsables, han facilitado todos los aspectos necesarios para que el doctorando pudiese llevar a cabo los distintos trabajos que componen las tesis.

La tesis incluye resúmenes en catalán, castellano e inglés, así como introducción, objetivos, métodos, resultados (5 artículos originales de investigación), discusión y conclusiones. La tesis aborda, desde una perspectiva sindémica, la vigilancia de las infecciones de transmisión sexual y de la tuberculosis centrada en poblaciones a

riesgo de infección. Se usan diferentes metodologías para identificar factores de riesgo o caracterizar dichas poblaciones y monitorizar o describir tendencias epidemiológicas en algunas de esas poblaciones. Los datos utilizados, siguiendo las leyes de protección de datos correspondientes, provienen de los sistemas oficiales de vigilancia epidemiológica de Cataluña y Portugal. En el primer caso el uso de los datos se inscribió dentro de la actividad laboral y de investigación aplicada que realizó el doctorando en el CEEISCAT como coordinador del equipo de vigilancia epidemiológica de los registros de VIH/ITS de Cataluña. En el segundo caso, el uso de los datos se enmarcó dentro de la labor investigadora realizada por el doctorando en la DGS durante el *European Programme for Intervention Epidemiology Training fellowship (EPIET)* entre 2017 y 2019.

Abreviaturas

VIH: virus de la inmunodeficiencia humana
ITS: infecciones de transmisión sexual
TB: tuberculosis
COVID-19: enfermedad por coronavirus de 2019
SARS-CoV-2: coronavirus de tipo 2 causante del síndrome respiratorio agudo severo
OMS: Organización Mundial de la Salud
HSH: hombres que tienen sexo con hombres
PID: persones que se inyectan drogas
EDO: enfermedades de declaración obligatoria
UE/EEE: Unión Europea/Espacio Económico Europeo
LGV: linfogranuloma venéreo
LVT: Lisboa y el Valle del Tajo
FCT: fracaso en completar el tratamiento
ITL: infección tuberculosa latente
SVIG-TB: sistema portugués de vigilancia y seguimiento de tuberculosis
REC: Repositorio Epidemiológico de Cataluña
XVEC: Red de Vigilancia Epidemiológica de Cataluña
ECDC: *European Center for Disease Prevention and Control*
SDI: sistema de notificación individualizadas
SNM: sistema de notificación microbiológica
XHUP: Red Hospitalaria de Utilización Pública de Cataluña

SGVRESP: Subdirección General de Vigilancia y Respuesta a Emergencias de Salud Pública

CDP: Centros de Diagnóstico Pulmonar

DGS: *Direção-Geral da Saúde*

DFA (*Direct Fluorescent Antibody)*: inmunofluorescencia directa

ELISA (*Enzyme-Linked ImmunoSorbent Assay*): pruebas inmunoenzimáticas

PCR (Polymerase Chain Reaction): reacción en cadena de la polimerasa

TST (*Mantoux tuberculin skin test*): prueba cutánea de la tuberculina

IGRA (*Interferon Gamma Release Assay*): ensayos de liberación de interferón gamma

OR (*Odds Ratio):* razones de probabilidad

IC: intervalo de confianza

ABS: áreas básicas de salud

ARIMA (*Autoregressive Integrated Moving Average*): modelo autorregresivo integrado de promedio móvil

EE. UU: Estados Unidos de América

PrEP: profilaxis preexposición contra el VIH

HSM: los hombres que tienen sexo con mujeres

MSH: mujeres que tiene sexo con hombres

CJAS: *centre jove d'anticoncepció i sexualitat*

ASPB: agencia de salud pública de Barcelona

TDO: tratamiento para ITL directamente observado

CDC: *Center for Disease Prevention and Control* (EE.UU)

SEE: Sociedad Española de Epidemiología

EPIET: *European Programme for Intervention Epidemiology Training*

Índice

1. Introducción

1.1. Las Sindemias. Concepto y ejemplos

El término sindemia fue acuñado por Merrill Singer a finales de los años noventa y se fue desarrollando a principios de los dos mil en el contexto de la pandemia por el virus de la inmunodeficiencia humana (VIH) intentado describir las interacciones y sinergias entre diferentes epidemias, condiciones y factores de riesgo [1]. Hace referencia a la sinergia o interacción en la coexistencia de una o más enfermedades u otros factores o condiciones, como por ejemplo sociales o de comportamiento, resultando en un exceso de carga de enfermedad en los individuos afectados [2]. Diferentes enfermedades, condiciones, o comportamientos interactúan empeorando los efectos deletéreos para la salud. Por lo tanto, el estudio de las sindemias investiga cómo interactúan ese conjunto de factores, que incluyen factores biológicos, psicológicos, sociales, económicos, políticos o ecológicos.

Muchas sindemias se han ido describiendo durante los últimos 30 años, desde las interacciones entre epidemias muy relacionadas como en el caso de VIH y las infecciones de transmisión sexual (ITS) [3], o del VIH y la tuberculosis (TB) [4], hasta sindemias que relacionan la obesidad o la diabetes con factores ambientales como el cambio climático [5] o con cambios en los sistema de alimentación debidos a factores políticos y socioeconómicos [6]. En el caso de algunas sindemias por enfermedades infecciosas hay que tener en cuenta también que unas similares sintomatologías,

procesos patológicos o factores asociados y efectos dificultan a veces una correcta caracterización y vigilancia de las distintas sindemias complicando así su prevención y control. Algunos ejemplos de ello son enfermedades como el Zika o algunas ITS, que pueden presentar similares síntomas y efectos teratogénicos [7].

Más recientemente se ha profundizado en el estudio de las sindemias en el contexto de la actual pandemia de enfermedad por coronavirus de 2019 (COVID-19) en donde la infección por el coronavirus de tipo 2 causante del síndrome respiratorio agudo severo (SARS-CoV-2), enfermedades crónicas y factores socioeconómicos interactúan [8]. Varias voces han recordado que la pandemia por el COVID-19 es en realidad una sindemia, y como tal hay que entenderla para poder proteger de la infección y de sus consecuencias a todas las personas del planeta [9].

1.2. Poblaciones a riesgo de infección

Las epidemias afectan a las personas de manera diferente según su sexo, edad, comportamientos, comorbilidades y otros factores, incluyendo el contexto social en el que viven y los sistemas que influyen las condiciones de vida, los llamados determinantes sociales de la salud [10]. Es en este contexto que diferentes conceptos relacionados se han ido desarrollando; población clave, población vulnerable o población a riesgo. En general estas definiciones hacen referencia a grupos de personas que tienen una mayor probabilidad de adquirir una infección o sufrir una enfermedad con mayor severidad.

Una vez más, fue sobre todo en el contexto de la epidemia del VIH cuando los términos de poblaciones clave y poblaciones vulnerables se acunaron y comenzaron a usarse ampliamente para referirse a las poblaciones a riesgo. En algunas guías de prevención, diagnóstico y tratamiento del VIH de la Organización Mundial de la Salud (OMS), se describe a las poblaciones clave como aquellos grupos con mayor riesgo de contraer el VIH debido a que presentan con más frecuencia conductas de riesgo, que pueden ser potenciadas por factores sociales desfavorables. Un ejemplo sería los hombres que tienen sexo con hombres (HSH), las personas en prisión o las personas que se inyectan drogas (PID) [11], [12]. La definición de población vulnerable hace referencia a grupos o poblaciones con mayor riesgo de contraer el VIH debido a la interacción con ciertas condiciones de vida o contextos socioeconómicos específicos del país o región. Un ejemplo sería la gente joven, las mujeres, los inmigrantes o, en un contexto más concreto, las mujeres adolescentes en el África subsahariana [11], [12].

Finalmente, la población a riesgo de infección se refiere a un término más genérico que hace referencia a grupos de personas en los que se observa una mayor incidencia de una infección o enfermedad. En las sindemias se pueden identificar individuos o poblaciones en los que interactúan múltiples factores de riesgo que multiplican el riesgo de contraer una infección y/o de padecer una forma más severa de una enfermedad.

1.3. La sindemia de las infecciones de transmisión sexual en Cataluña

La epidemia de las ITS sigue siendo una gran preocupación y amenaza para la salud pública mundial. Muchas de las numerosas ITS presentan una situación endémica y algunas son reemergentes y las podemos encontrar formando parte de las enfermedades de declaración obligatoria (EDO) más frecuentes en muchos países. Las ITS no diagnosticadas y no tratadas pueden dar lugar a una multitud de complicaciones, como el contraer el VIH, discapacidades a largo plazo, infertilidad, resultados adversos en el embarazo y la muerte [13], [14]. En los países de la unión Europea y del espacio económico Europeo (UE/EEE), la incidencia de las ITS ha aumentado durante las últimas décadas, entre el periodo de 2014 a 2018 los casos confirmados que se notificaron en los sistemas de vigilancia nacionales mostraron un incremento del 50% para la gonorrea, 36% para la sífilis, 68% para el linfogranuloma venéreo (LGV) y 0,6% para la clamidia [15]–[18]. Esta tendencia también se produjo en España, donde entre 2000 y 2017 se notificó un aumento del 10% en los nuevos casos de ITS, con 23975 casos de gonorrea, sífilis, clamidia y LGV reportados solo en 2017 [19], [20]. Durante 2018 y 2019, en Cataluña se registró la mayor incidencia de ITS del estado, con un aumento en el número de casos del 37%. Las tasas de incidencia fueron más elevadas en HSH, mujeres y adultos jóvenes, particularmente entre mujeres jóvenes, durante los últimos años las mujeres mostraron un aumento proporcionalmente mayor que los hombres [19], [21]. El aumento en las tasas de incidencia de las ITS puede explicarse por las

mejoras en los sistemas de vigilancia (mejor cribado, diagnóstico y notificación), la introducción de nuevos métodos de diagnóstico con mayor sensibilidad, los cambios en las actitudes y comportamientos sexuales, los cambios socioculturales y los efectos del turismo y la globalización [22].

Las ITS y la infección por el VIH son epidemias concurrentes que, además de las sinergias biológicas que presentan, ambas están influenciadas en gran medida por factores socioeconómicos y otros factores contextuales actuando por lo tanto como sindemias. Las poblaciones con las tasas de incidencia de ITS más altas tienen un mayor riesgo de contraer el VIH y las personas que viven con el VIH son más vulnerables a contraer otra ITS [23], [24].

Algunos estudios han descrito los determinantes sociales de la salud, la discriminación y las desigualdades como los principales factores asociados con la agrupación espaciotemporal de los casos de ITS [25], [26]. La identificación y caracterización de los grupos a riesgo de contraer ITS son imprescindibles para fortalecer la vigilancia integrada de las ITS y el VIH. Los datos obtenidos de tal ejercicio podrían generar información relevante para adaptar las estrategias de salud pública necesarias para abordar una endemia en constante crecimiento como lo es la endemia de las ITS.

1.4. La sindemia de tuberculosis en Portugal

A pesar de su declive en Europa y en todo el mundo, la TB y, en particular su forma resistente a los medicamentos y cuando se presenta en coinfección con el VIH, siguen siendo importantes problemas de salud pública [27], [28]. En la Región Europea de la

OMS, la disminución de la tasa de incidencia de TB entre 2014 y 2018 fue del 5,1%. En los países de la UE/EEE, en promedio, esta disminución fue del 4% y en Portugal, que tiene una de las tasas más altas de la UE/EEE, de un 1,3% (de 12,1 a 10,2/100.000 habitantes y de 21,8 a 20,8/100.000 habitantes respectivamente de 2014 a 2018) [27].

Uno de los pilares de la estrategia *End TB* de la OMS establece que para lograr en 2030 una reducción del 80% en los casos nuevos de TB y del 90% en las muertes, se necesitan actividades que tengan en cuenta la interacción TB/VIH y el manejo de las comorbilidades [28].

Como hemos comentado anteriormente, la endemia de la TB podemos definirla como sindémica, una endemia que presenta interacciones sinérgicas al combinarse frecuentemente con otras enfermedades o condiciones como el VIH, la diabetes o con algunos determinantes sociales de la salud [4], [29]. La incidencia de la TB difiere entre grupos de población y regiones. Entre otros, los grupos de población a riesgo de infección incluyen: personas con condiciones clínicas específicas (como el VIH u otra inmunosupresión), contactos estrechos de un caso de TB, migrantes de áreas con alta incidencia de TB, así como personas que viven bajo condiciones socioeconómicas desfavorables o que pertenecen a grupos ocupacionales de más riesgo [30].

Entre 2014 y 2018, tanto en la UE/EEE como en Portugal, la disminución de los nuevos caos de TB se confirmó también en algunas poblaciones a riesgo de infección, como en el de las personas infectadas por el VIH. En otras poblaciones a riesgo, como

la de los niños menores de cinco años o la de los extranjeros (nacionalidad), se observó un descenso tanto en el número de casos como en su peso relativo sobre el total de casos de TB [27]. Por otro lado, en el caso de Portugal como sucede en muchos otros países, se han descrito diferencias regionales relevantes en la incidencia de TB observándose incidencias significativamente superiores en regiones más densamente pobladas como la región de Lisboa y el Valle del Tajo (LVT) y la región Norte [31], [32]. Una descripción en detalle de la comparativa de la tendencia decreciente en el número de casos de TB en las diferentes poblaciones a riesgo de infección y en áreas con diferentes incidencias puede ayudar en el diseño de intervenciones eficaces para persistir en la disminución de nuevos casos de TB.

2. Objetivos

2.1. Propósito y objetivos generales

El propósito general de la tesis es describir las endemias de las ITS y de la TB desde una aproximación sindémica. Hemos tratado de identificar y/o describir poblaciones o grupos a riesgo de contraer dichas infecciones o de obtener peores resultados en su tratamiento. En las poblaciones a riesgo descritas, hemos examinado diferentes factores que sinérgicamente interactúan aumentando la probabilidad de contraer la infección o de presentar mayor severidad. Creemos que hay una necesidad urgente de contar con nuevos enfoques, herramientas y metodologías para mejorar la vigilancia epidemiológica y la investigación aplicada en enfermedades transmisibles que aborde la vigilancia en poblaciones a riesgo de infección desde una perspectiva sindémica. Esta aproximación y abordaje puede mejorar la prevención y el control de epidemias emergentes y reemergentes y se muestra como un factor imprescindible para acabar con algunas de las grandes epidemias de nuestro tiempo, como el VIH, la malaria, la TB, y ahora la COVID-19. Todas ellas, tienden a concentrarse en ciertas poblaciones a riesgo o vulnerables. Para lograr nuestros objetivos, hemos utilizando diferentes metodologías, algunas más comúnmente usadas en vigilancia epidemiológica como es el caso del análisis de series temporales, y otras que se han empezado a usar más recientes dentro de este campo, como las relacionadas con las técnicas de *machine learning*.

Por lo tanto, el objetivo general de esta tesis es fortalecer la vigilancia de las endemias de las ITS y la TB centrándose en los grupos poblacionales a riesgo de infección a través de una perspectiva y aproximación sindémicas.

2.2. Objetivos específicos por artículo

Estudio I

El objetivo principal de este estudio fue describir las características epidemiológicas y las tendencias en las incidencias de VIH, gonorrea, sífilis y LGV entre adolescentes y jóvenes entre 15 y 24 años en la ciudad de Barcelona entre 2007 y 2015. Además, evaluamos la asociación de potenciales factores de riesgo con la coinfección por el VIH entre los jóvenes con gonorrea, sífilis o LGV. De esta manera intentamos analizar la endemia de las ITS y su interacción con el VIH en una población a riesgo como es el caso de los adolescentes y jóvenes.

Estudio II

El objetivo principal de este estudio fue describir la epidemiología de las ITS, identificar y caracterizar clústeres socio epidemiológicos de ITS y determinar los factores asociados con la coinfección por el VIH en Cataluña durante el periodo 2017-2019. De manera similar al *estudio I*, se intentó profundizar en la sindemia de las ITS y sus interacciones con el VIH, así como en los factores de riesgo asociados a contraer una ITS, incluyendo los determinantes

socioeconómicos, y en la identificación y caracterización de clústeres de casos.

Estudio III

El objetivo de este estudio fue estimar la magnitud de la disminución, debido a la pandemia de COVID-19, en el número de casos confirmados de ITS notificados en Cataluña durante el confinamiento y la desescalada comparando los casos observados y los esperados según datos históricos. Así como, analizar la interacción de dos endemias distintas convergentes en poblaciones a riesgo de infección (o dos sindemias distintas). La distribución en el tiempo de las características epidemiológicas de los casos de ITS previos y posteriores al inicio de la pandemia por COVID-19 se compararon y se describieron los efectos de la COVID-19 en la endemia de las ITS en algunos de los grupos poblacionales a riesgo de infección por una ITS.

Estudio IV

El objetivo de este estudio fue identificar las poblaciones a riesgo de infección y regiones de Portugal que presentaron comparativamente una disminución menor en las tasas de notificación de TB entre 2010 y 2017. Por lo tanto, intentamos profundizar en la evolución de la sindemia de la TB en distintas poblaciones a riesgo y regiones en Portugal.

Estudio V

El objetivo de este estudio fue identificar los factores más relevantes asociados con el fracaso en completar el tratamiento (FCT) de la infección tuberculosa latente (ITL) en Portugal entre 2013 y 2017 y describir posibles diferencias entre las dos mayores

áreas metropolitanas, Oporto y Lisboa, en dichos factores principales involucrados. Con ello contribuir en el diseño de medidas preventivas específicas para reducir la ITL y, de esta manera, prevenir el desarrollo de TB.

Así pues, se analizó la sindemia de la TB y sus interacciones sociodemográficas, médicas y geográficas en relación a la adherencia al tratamiento de la ITL.

3. Metodología

A continuación, se expone un resumen de la metodología utilizada en cada uno de los artículos que componen la tesis, más detalles se pueden encontrar en los respectivos artículos incluidos en el apartado de resultados.

3.1. Diseño y población de los estudios

El *estudio I* es un estudio de incidencia poblacional de todos los nuevos casos confirmados de VIH, gonorrea, sífilis y LGV notificados al sistema de vigilancia epidemiológica de la ciudad de Barcelona. La población de estudio son los jóvenes de 15 a 24 años residentes en Barcelona y diagnosticados entre enero del 2007 y diciembre del 2015.

El *estudio II* es un estudio de cohortes retrospectivo de todos los casos confirmados de sífilis, gonorrea, clamidia y LGV, en Cataluña diagnosticados entre enero de 2017 y diciembre de 2019. La población de estudio es toda la población de Cataluña. Los datos se obtuvieron en este caso del Registro Catalán de VIH/ITS[33].

El *estudio III* es un estudio de series temporales interrumpidas con todos los casos de sífilis, gonorrea, clamidia y LGV, diagnosticados entre el 1 de agosto 2017 y 1 de agosto de 2020 en Cataluña también recopilados en el Registro Catalán de VIH/ITS. La población de estudio es toda la población de Cataluña.

El *estudio IV* es un estudio de series temporales de los casos de TB activa notificados al sistema portugués de vigilancia y seguimiento

de TB (SVIG-TB)[34], incluyendo los casos diagnosticados (confirmados, probables y posibles) entre 2010 y 2017. La población de estudio es toda la población de Portugal.

El *estudio V* es un estudio retrospectivo de cohortes de todos los casos de ITL diagnosticados en el SVIG-TB[34] entre 2013 y 2017. La población de estudio es toda la población de Portugal.

3.2. Sistemas de vigilancia epidemiológica

3.2.1. Vigilancia epidemiológica de las ITS y el VIH en la ciudad de Barcelona y Cataluña

Los datos recopilados por el sistema de vigilancia de las ITS y del VIH en Cataluña esta centralizado en el Registro Catalán de VIH/ITS[33], que compila a su vez información del Repositorio Epidemiológico de Cataluña (REC), una base de datos electrónica utilizada por los trabajadores de salud pública de la Red de Vigilancia Epidemiológica de Cataluña (XVEC). Las definiciones de caso utilizadas son las publicadas por el *Departament de Salut de la Generalitat de Catalunya* [35] (incluidas en la sección 3.3) las cuales se basan en las definiciones establecidas por el *European Center for Disease Prevention and Control* (ECDC) [36].

El REC recopila datos de las EDO a través de dos sistemas de información [37]:

(1) El sistema de notificación individualizada (SDI). Basado en las notificaciones de casos, incluyen información sobre las correspondientes pruebas de laboratorio según las

definiciones de caso establecidas. Según la normativa catalana de notificación obligatoria de enfermedades y brotes (Departamento de Salud de *la Generalitat de Catalunya* artículo 13 de la ley 67/2010, de 25 de mayo de 2010), la notificación nominal (o individualizada) de los casos de sífilis, gonorrea y LGV es obligatoria desde 2007 y de clamidia desde 2015; la notificación de casos de VIH fue voluntaria entre 2001 y 2010 cuando también pasó a ser obligatoria y nominal [38].

(2) El sistema de notificación microbiológica (SNM). El SNM lo integran más de 50 centros, hospitalarios y extrahospitalarios, que son mayoritariamente públicos. La cobertura del territorio se mide por el número de camas hospitalarias de agudos que componen la Red Hospitalaria de Utilización Pública de Cataluña (XHUP). Estos centros representan el 92,9% de la totalidad de camas de estos hospitales. Los microbiólogos deben declarar obligatoriamente al SNM todos los microorganismos objeto de declaración diagnosticados según criterios acordados con la Subdirección General de Vigilancia y Respuesta a Emergencias de Salud Pública (SGVRESP). También están protocolizadas y monitorizadas las resistencias antimicrobianas [39].

Ambas fuentes son complementadas por los trabajadores del XVEC con los datos compilados a través de una encuesta epidemiológica que registra datos clínicos, epidemiológicos y variables de comportamiento o preferencias sexuales. Las variables recogidas o

calculadas a partir de los datos del sistema de vigilancia de las VIH e ITS se indican en cada uno de los estudios incluidos en la tesis.

3.2.2. Vigilancia epidemiológica de la TB y la ITL en Portugal.

Los Centros de Diagnóstico Pulmonar (CDP) centralizan el diagnóstico y tratamiento de los pacientes con sospecha de TB en Portugal, así como el seguimiento del tratamiento y la articulación con las Unidades de Salud Pública. Los casos se notifican al SVIG-TB por cualquier médico que diagnostique y haga un seguimiento de pacientes con TB, en su mayoría en CDP ambulatorios de TB (integrados en atención primaria). Las definiciones de caso utilizadas son las publicadas por la *Direção-Geral da Saúde* (DGS) [40], entidad del ministerio de salud de Portugal, las cuales se basan en las definiciones establecidas por el *European Center for Disease Prevention and Control* (ECDC)[36] (incluidas en la sección 3.3).
Las notificaciones se basan en formularios en papel que posteriormente son informatizados y centralizados a nivel regional y nacional, e incluyen datos clínicos, epidemiológicos y datos de laboratorio, desde el diagnóstico hasta el alta.

3.3. Definiciones de caso

3.3.1. Definiciones de las ITS y del VIH

Definiciones de caso publicadas por el *Departament de Salut de la Generalitat de Catalunya*[35]:

a. Clamidia:

1) Criterios de laboratorio para el diagnóstico: Aislamiento de *Chlamydia trachomatis* por cultivo en una muestra del tracto genitourinario, anal o conjuntiva, o muestra clínica; o demostración de *Chlamydia trachomatis* por detección de antígenos específicos o por inmunofluorescencia directa (DFA) en una muestra clínica; o detección de fragmentos genómicos específicos de *Chlamydia trachomatis* en una muestra clínica.

2) Caso confirmado: Persona con criterios de laboratorio compatibles.

3) Caso probable: Persona con criterios clínicamente compatibles, especialmente si es relacionada epidemiológicamente.

b. Gonorrea:

1) Criterios de laboratorio para el diagnóstico: Aislamiento por cultivo de *Neisseria gonorrhoeae* en una muestra clínica; o detección de fragmentos genómicos específicos de *Neisseria gonorrhoeae* en una muestra clínica; o detección microscópica de diplococos intracelulares gramnegativos en exudados uretrales en hombres.

2) Caso confirmado: Persona con criterios de laboratorio compatibles.

3) Caso probable: Persona con criterios clínicamente compatibles, especialmente si está relacionada epidemiológicamente.

c. Sífilis infecciosa:

1) Criterios de laboratorio para el diagnóstico: Demostración de *Treponema pallidum* por microscopía de campo oscuro en las secreciones de la lesión; o demostración de *Treponema pallidum* por inmunofluorescencia directa (DFA) en las secreciones de la lesión; o detección de fragmentos genómicos específicos de *Treponema pallidum* en las secreciones de la lesión; o detección de anticuerpos frente a *Treponema pallidum* mediante pruebas específicas (TPHA, TPPA o EIA) y, además, uno de los siguientes métodos: i) FTA-ABS, EIA, inmunotransferencia; ii) prueba serológica inespecífica reactiva (VDRL, RPR); iii) o detección de anticuerpos IgM -TP.

2) Caso confirmado: Persona con criterios de laboratorio compatibles.

3) Caso probable: Persona con criterios clínicamente compatibles, especialmente si está relacionada epidemiológicamente.

d. LGV:

1) Criterios de laboratorio para el diagnóstico: Aislamiento de *Chlamydia trachomatis* por cultivo en una muestra del tracto genitourinario, anal o conjuntiva, o muestra clínica; o detección de fragmentos genómicos específicos de *Chlamydia trachomatis* en una muestra clínica, y además identificación del serovar L1, L2 o L3.

2) Caso confirmado: Persona con criterios de laboratorio compatibles.

3) Caso probable: Persona con criterios clínicamente compatibles, especialmente si está relacionada epidemiológicamente.

e. VIH:

Se considera que existe evidencia de infección por el VIH (resultado positivo de las pruebas de laboratorio) si el enfermo presenta alguno de los siguientes datos analíticos:

En adultos y niños mayores de 18 meses:

- Serologías de anticuerpos anti VIH repetidamente reactivas mediante pruebas inmunoenzimáticas (ELISA) y confirmadas por pruebas adicionales (Western Blot, inmunofluorescencia u otros)
- Resultados positivos en cultivo, reacción en cadena de la polimerasa (PCR) o detección del antígeno p24 del VIH.

En niños menores de 18 meses o bien nacidos de madres infectadas o sospechosas de estar infectadas por el VIH:

- Resultados positivos en dos determinaciones separadas (con exclusión de la sangre del cordón umbilical) de una o más de las siguientes pruebas: cultivo, PCR o detección del antígeno p24 del VIH.

3.3.2. Definiciones de la TB y la ITL

Definiciones según el *European Center for Disease Prevention and Control* (ECDC) [36], [41]:

a. ITL:

Tras la exposición a *Mycobacterium tuberculosis*, en algunas personas la respuesta inmunitaria innata es capaz de prevenir la infección. Otros desarrollan infección latente (ITL), un estado en el que el sistema inmunitario del huésped controla la replicación del bacilo hasta el punto de prevenir la progresión a TB. El diagnóstico adecuado de la ITL es un desafío debido a las limitaciones inherentes de las pruebas de diagnóstico actualmente disponibles. Tanto la prueba cutánea de la tuberculina (TST) como los ensayos de liberación de interferón gamma (IGRA) evalúan la respuesta inmunitaria adaptativa frente a *Mycobacterium tuberculosis*, pero ninguna de estas pruebas puede diferenciar entre una ITL reciente y remota (> 2-5 años), entre infección resuelta y persistente, o entre ITL y enfermedad activa.

En Portugal, a todos los pacientes diagnosticados de ITL se les ofrece tratamiento, pero el cribado de ITL es oportunista (principalmente después del contacto con un caso infeccioso de TB) y varía entre ciudades, regiones y centros de salud. Todos los pacientes que fueron diagnosticado de ITL e iniciaron tratamiento en Portugal entre los años 2013 y 2017 se incluyeron en el *estudio V*.

b. TB:

1) Criterios clínicos.

Cualquier persona que presente los siguientes criterios:

- Signos, síntomas y/o hallazgos radiológicos consistentes con TB activa en cualquier localización y

- La decisión de un médico de tratar a la persona con un ciclo completo de terapia antituberculosa

O

Un caso descubierto post mortem con hallazgos patológicos compatibles con TB activa para el cual se hubiese indicado tratamiento antibiótico antituberculoso si el paciente hubiera sido diagnosticado antes de morir

2) Criterios de laboratorio:

Criterios de laboratorio para la confirmación de casos: Al menos uno de los dos siguientes:

- Aislamiento de microorganismos del Complejo *Mycobacterium tuberculosis* (excepto *Mycobacterium bovis*-BCG) en una muestra clínica.
- Detección de ácido nucleico de microorganismos del Complejo *Mycobacterium tuberculosis* en una muestra clínica y microscopía positiva para bacilos acidorresistentes o bacilos con tinción fluorescente equivalente en microscopía óptica.

Criterios de laboratorio para un caso probable: Al menos uno de los tres siguientes:

- Microscopía para bacilos acidorresistentes o bacilos con tinción fluorescente equivalente en microscopía óptica

- Detección de ácido nucleico de microorganismos del Complejo *Mycobacterium tuberculosis* en una muestra clínica.
- Aspecto histológico de granulomas

3) Criterios epidemiológicos: No se aplica.

4) Clasificación de caso

A. Caso posible: Toda persona que cumpla los criterios clínicos.

B. Caso probable: Toda persona que cumpla los criterios clínicos y de laboratorio de caso probable.

C. Caso confirmado: Toda persona que cumpla los criterios clínicos y de laboratorio de caso confirmado.

3.4. Análisis estadísticos

Para todos los estudios se realizaron análisis descriptivos adaptados a los objetivos y datos disponibles en cada uno de ellos. En este apartado describimos análisis estadísticos específicos relativos a algunos de los trabajos (se pueden encontrar más detalles en los propios artículos adjuntos en el apartado de resultados).

3.4.1. Modelos de regresión

En el *estudio I,* examinamos los factores de riesgo asociados con la coinfección por el VIH, casos prevalentes de VIH, entre personas diagnosticadas con gonorrea, sífilis o LGV, durante el período de estudio para estimar las razones de probabilidad (OR) con sus intervalos de confianza (IC) del 95%. Entre las personas que

presentaron más de una ITS, solo se incluyó el último evento diagnosticado. Primero, ajustamos modelos de regresión logística univariada para evaluar la asociación entre el diagnóstico positivo de VIH como variable dependiente y cada uno de los posibles factores de riesgo considerados. En segundo lugar, los potenciales factores de riesgo que mostraron tener una asociación estadísticamente significativa con el diagnóstico de VIH se incluyeron en modelos de regresión logística multivariable, junto con variables de educación y país de nacimiento, factores considerados relevantes e incluidos en los modelos independientemente de si mostraron o no tener una asociación estadísticamente significativa en el análisis univariado [42].

En el *estudio II,* de manera similar al *estudio I,* evaluamos los factores de riesgo asociados con la coinfección por el VIH entre las personas diagnosticadas con ITS utilizando modelos de regresión logística multivariable para estimar las OR y los IC del 95%. Los individuos con más de un episodio de ITS fueron contados una vez (primer episodio), y los sucesivos episodios de un mismo individuo fueron agrupados en una variable que considera el número de episodios (dicha variable fue incluida en los modelos). La preferencia sexual, el país de nacimiento y el nivel educativo se excluyeron de los modelos por baja cumplimentación, inferior al 50%. Usamos la metodología *backward stepwise elimination regression* para seleccionar aquellas variables que mostraron significación estadística ($P<0.05$) en la prueba de Wald para ser incluidas en el modelo final de regresión logística multivariable.

En el *estudio V,* analizamos también las asociaciones entre variables independientes y el FCT mediante regresión logística. Todas aquellas variables que encontramos asociadas significativamente con FCT en el análisis univariable ($p < 0,05$) se incluyeron en un modelo de regresión logística para el análisis multivariable. Calculamos las OR y sus IC del 95% para FCT, ajustados por las covariables incluidas en el modelo. Repetimos el análisis restringiendo consecutivamente para cada una de las poblaciones de las áreas metropolitanas de Lisboa y Oporto. En Lisboa, el modelo de regresión que mejor se ajustaba incluía edad, país de nacimiento, presencia de enfermedad crónica y régimen de tratamiento; en Oporto, el mejor modelo de ajuste incluía la edad, el abuso de alcohol, el ser una PID y usuarios de otras drogas, estar viviendo en un centro de salud comunitario y el plan de tratamiento.

3.4.2. Análisis de clústeres mediante *K-means*

En el *estudio II*, se utilizó la metodología de *clustering k-means* para identificar clústeres sociodemográficos de ITS. Dicha metodología es un enfoque *machine learning* o de aprendizaje automático no supervisado que busca agrupar unidades heterogéneas (en nuestro caso, las áreas básicas de salud o ABS) en clústeres en función de similitudes en sus características (valores de las variables y distribución de frecuencias de las distintas categorías en las distintas ABS). El algoritmo de agrupación en distintos clústeres consiste en un procedimiento que agrupa una serie de vectores según un criterio específico, que puede ser la distancia o la

semejanza. La metodología de *clustering k-means* se basa en la distancia euclidiana para cuantificar las similitudes o diferencias entre las observaciones, la proximidad se define en términos de una función de distancia. Este método es sensible a valores atípicos y requiere procesos de validación internos y externos utilizando diferentes combinaciones de variables en los algoritmos. La validación interna de los clústeres consideró una distancia euclidiana promedio para cada clúster y similitudes entre casos según la matriz de correlación de distancias para determinar el número óptimo de clústeres para los cuales la variación intra clúster era mínima. Nuestro proceso de validación externa se basó en una descripción de las posibles variables socio epidemiológicas para determinar el algoritmo de *clustering* más apropiado para nuestro conjunto de datos. Con base en estas validaciones, los investigadores decidieron un número exacto de clústeres formados por las variables que los definían y que se incluyeron en el algoritmo. En nuestro caso, se eligieron las siguientes variables para identificar y construir los tres clústeres socio epidemiológicos finales de ITS por ABS: tasa de incidencia por cada ITS, porcentaje de mujeres, porcentaje de personas con coinfección por el VIH, mediana de edad entre todos los casos de ITS en cada ABS y el índice de privación de cada ABS.

3.4.3. Análisis de tendencia y series temporales interrumpidas

En los *estudios I, II y IV* se calcularon tasas de incidencia como se describe en cada manuscrito. En el *estudio I y II*, se analizaron las

tendencias de incidencia mediante la prueba de $\chi 2$ para tendencia lineal.

En el *estudio III*, se calculó la prevalencia de distintas variables sociodemográficas y epidemiológicas entre los casos notificados de ITS, antes del confinamiento, durante el confinamiento (del 13 de marzo al 27 de abril), en las fases de desescalada (del 28 de abril al 21 de junio) y durante la fase de nueva normalidad (desde el 22 de junio). Usamos estas fechas como puntos de cambio para un análisis de series de temporales interrumpidas de casos de ITS notificados diariamente (número total y por separado para cada una de las ITS estudiadas). Los casos notificados se modelaron con un modelo autorregresivo integrado de promedio móvil (ARIMA) para estimar el número esperado de casos de ITS notificados en cada período de estudio específico desde el confinamiento basado en los datos previos al confinamiento. Calculamos el declive total en el número de casos de ITS notificados, para estimar la magnitud de la disminución en los casos de ITS notificados en comparación con los valores esperados estimados según los datos históricos. Se incluyeron tres años de seguimiento, del 1 de agosto de 2017 al 1 de agosto de 2020, no solo para estimar los casos notificados que habríamos tenido desde el confinamiento si no hubiese habido la pandemia, del 13 de marzo al 1 de agosto de 2020, sino también para capturar posibles patrones de cambio estacional o cíclico.

En el *estudio IV,* las tasas de notificación mensual y anual de TB se calcularon como número de casos notificados por cada 100.000 habitantes. Se hizo de forma global, por sexo, por grupo de edad, por nacionalidad, por región, por status serológico para el VIH, y

para TB pulmonar vs extrapulmonar. Las disminuciones interanuales con IC del 95% para cada grupo se estimó mediante modelos de regresión de Poisson. Cuando se observaba sobre dispersión, se estimó la disminución interanual mediante regresión binomial negativa.

4. Resultados

- *Estudio I*: Sexually transmitted infections in young people and factors associated with HIV coinfection: an observational study in a large city. URL: https://bmjopen.bmj.com/content/9/5/e027245
- *Estudio II*: STI epidemic re-emergence, socio-epidemiological clusters characterisation, and HIV coinfection in Catalonia, Spain, during 2017–2019: a retrospective population-based cohort study. URL: https://bmjopen.bmj.com/content/11/12/e052817
- *Estudio III*: The impact of the COVID-19 pandemic on STI surveillance data: incidence drop or artefact? URL: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-11630-x
- *Estudio IV*: Decline of tuberculosis notification rate in different population groups and regions in Portugal, 2010-2017. URL: https://www.sciencedirect.com/science/article/pii/S2531043721001586
- *Estudio V*: Failure to complete treatment for latent tuberculosis infection in Portugal, 2013-2017: geographic, socio-demographic and medical associated factors. URL: https://link.springer.com/article/10.1007/s10096-019-03765-y

4.1. Estudio I: Sexually transmitted infections in young people and factors associated with HIV coinfection: an observational study in a large city.

Sentís A, Martin-Sanchez M, Arando M and STI-HIV group of Barcelona, et al.Sexually transmitted infections in young people and factors associated with HIV coinfection: an observational study in a large cityBMJ Open 2019;9:e027245. doi: 10.1136/bmjopen-2018-027245

URL: https://bmjopen.bmj.com/content/9/5/e027245

BMJ Open

Sexually transmitted infections in young people and factors associated with HIV coinfection: an observational study in a large city

Alexis Sentís,[1] Mario Martin-Sanchez,[1,2] Maider Arando,[3] Martí Vall,[3] María Jesus Barbera,[3] Inma Ocaña,[3] Ana González Cordón,[4] Mercè Alsina,[4] Gemma Martin-Ezquerra,[5] Hernando Knobel,[5] Mercè Gurguí,[6] Alvaro Vives,[7] Josep Coll,[8] Joan Artur Caylà,[1,9,10] Patricia Garcia de Olalla,[1,9] and STI-HIV group of Barcelona

To cite: Sentís A, Martin-Sanchez M, Arando M, *et al*. Sexually transmitted infections in young people and factors associated with HIV coinfection: an observational study in a large city. *BMJ Open* 2019;**9**:e027245. doi:10.1136/bmjopen-2018-027245

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-027245).

Received 19 October 2018
Revised 9 January 2019
Accepted 27 February 2019

For numbered affiliations see end of article.

Correspondence to
Dr Patricia Garcia de Olalla; polalla@aspb.cat

ABSTRACT

Objectives Young people are a critical target group for sexually transmitted infections (STI) surveillance due to their particular behavioural and social related vulnerability. The aim of this study was to describe the epidemiological characteristics and trends in the incidence of gonorrhoea, syphilis, HIV and venereal lymphogranuloma (LGV) among 15–24-year-olds in Barcelona, and to determine factors associated with HIV coinfection.

Design We performed a population-based incidence study covering the 2007–2015 period.

Participants All new cases of STI—HIV, gonorrhoea, infectious syphilis and LGV—notified to the epidemiological surveillance system in Barcelona between 2007 and 2015. 1218 cases were studied: 84.6% were men, 19.3% were 15–19 years old and 50.6% were born in Spain. Among men, 73.7% were men who have sex with men (MSM); among women, 85.6% were women that have sex with men.

Primary and secondary outcomes Incidence of HIV, gonorrhoea, infectious syphilis and LGV. HIV coinfection.

Results There was an increase in the incidence of gonorrhoea, from 1.9 cases per 10 000 people in 2007 to 7.6/10 000 in 2015 (p<0.01), in MSM from 27.1 to 228.8/10 000 (p<0.01). The incidence of syphilis increased from 0.4/10 000 in 2007 to 3.1/10 000 in 2015 (significant in men only, p<0.01), in MSM from 18.1 to 116.9/10 000 (p<0.01). The incidence of HIV showed a non-significant increase in men (p=0.27), and that of LGV remained stable (p=0.59). Factors associated with increased risk of HIV coinfection included being MSM (adjusted OR[ORa]=14.14, 95% CI 3.34 to 59.91) and having >10 sexual partners (ORa=4.11, 95% CI 1.53 to 11.01) or STI diagnosis during the previous 12 months (ORa=2.06; 95% CI 1.13 to 3.77).

Conclusions The incidence of gonorrhoea and syphilis among 15–24-year-olds increased, while HIV infection remained stable but with a high incidence among MSM. Being MSM, having sex with multiple partners and having a diagnosis of an STI in the previous 12 months were factors associated with HIV coinfection.

Strengths and limitations of this study

- A population-based sexually transmitted infection (STI) incidence study in young people from a large city with a robust STI surveillance system. The use of logistic regression models allowed us to disentangle factors associated with HIV coinfection.
- The inclusion of sociodemographic, clinical and behavioural variables permitted a strong description and analysis of the results.
- For some variables, the proportion of missing values was high. Nonetheless, we have included a missing category in all variables, such that all cases are considered in the models.
- The lack of data about other STI, since they were not mandatory notification diseases, may mean a loss of valuable information regarding the analysis of STI impact in a large city.

INTRODUCTION

With more than one million acquired infections per day worldwide, sexually transmitted infections (STI) remain one of the most common acute illnesses globally.[1] Although trend data can be influenced by heterogeneous reporting and differences between healthcare systems, during the last decade, there has been a clear overall increase in the incidence of *Chlamydia trachomatis*, gonorrhoea, syphilis and venereal lymphogranuloma (LGV) in Europe, including Spain.[2 3] In contrast, there has been a steady decline in HIV incidence in recent years.[4 5] A recent study based in Barcelona reported an increase in the number of STI cases, mainly in men who had sex with men (MSM) with university-level education.[6]

In 2013 in Europe, young people and MSM were the most vulnerable groups for

STI acquisition. People aged 15–24 years accounted for two-thirds of all cases of *C. trachomatis* and 39% of all cases of gonorrhoea.[2] Adolescents and young people are a critical target group for STI surveillance because they are vulnerable for various reasons, mostly related to behaviour and social factors,[7 8] and also because many young people at risk of STI are not properly screened.[9 10] Special emphasis must be placed on HIV because STI carriers have an increased risk of HIV infection[11] and adolescents infected with HIV are more likely to acquire other STI infections.[7 12]

The main aim of this study was to describe the epidemiological characteristics and trends in the incidence of HIV infection, gonorrhoea, syphilis and LGV among young people in a large city. In addition, we assessed whether HIV status was associated with prevalent risk factors among young people with gonorrhoea, syphilis or LGV.

METHODS

Study design and participants

This is a population-based incidence study of all new cases of sexually transmitted HIV, gonorrhoea, syphilis and LGV infection notified to the epidemiological surveillance system in Barcelona city using case definitions established following the European standards.[13] The target population was young people aged 15–24 years who were residents in Barcelona and diagnosed between January 2007 and December 2015 (total population of the city on 30 June 2015 was 1 604 550, of which 141.363 (8.8%) were aged 15–24 years[14]). Cases of congenital, late latent and tertiary syphilis were excluded from the study, as were cases of AIDS or cases of HIV infection in intravenous drug user or due to vertical transmission.

Variables

We analysed sociodemographic variables: sex, country of birth, educational level and age (in two categories, 15–19 and 20–24 years, in line with the most common uses by Centers for Disease Control and Prevention[15] and WHO[1]). Clinical variables: STI diagnosis in the previous 12 months and coinfection with HIV. Behavioural variables: number of sexual partners in the previous 12 months, use of condom in most recent sexual contact and sexual behaviour, categorised separately for men and women as follows. Men (three groups): MSM, including transgender women and bisexual men; men who have sex with women only (MSW); and unknown sexual behaviour. Women (three groups): women who have sex with men (WSM), including bisexual and heterosexual, women who have sex with women (WSW) and unknown sexual behaviour. In the regression models, due to the small numbers of WSW, we only used one category, 'women'.

Statistical analyses

A descriptive analysis of the epidemiological characteristics of all new cases of STI—HIV, gonorrhoea, syphilis and LGV infections—was carried out. We calculated annual incidence rates per 10 000 inhabitants, stratified by sex and sexual behaviour category. Sex-specific rates were estimated based on population data from the Barcelona municipal census for each year of study[14]; rates for the various categories of sexual behaviour were estimated based on data from the 2011 Barcelona Health Interview Survey.[16] Incidence trends were analysed using the χ^2 test for linear trend.

We examined risk factors associated with HIV coinfection, prevalent HIV cases during the study period, among persons diagnosed with gonorrhoea, syphilis or LGV. In persons with more than one STI, only the last diagnosed event was included. First, we fit bivariate logistic regression models to assess the association between positive HIV diagnosis as a dependent variable and each of the potential risk factors mentioned above. Second, potential risk factors that showed a statistically significant association with HIV diagnosis were included in multivariable logistic regression models, along with variables for education and country of birth, which are thought to be important regardless of whether or not they showed a statistically significant association in the bivariate analysis.[6]

Odds ratios (OR) and its 95% confidence intervals (CI) were estimated. All analyses were performed using STATA (V.13; Stata Corporation, College Station, Texas, USA).

Ethical considerations

In Barcelona city, surveillance of obligatory notifiable diseases is provided by the Barcelona Public Health Agency (ASPB). In compliance with article 13 of law 67/2010 (25 May 2010) of the Health Department of Generalitat de Catalunya, nominal notification of cases of gonorrhoea, syphilis and LGV has been obligatory since 2007. Notification of HIV cases was voluntary between 2001 and July 2010, and obligatory and nominal thereafter.[17]

Data confidentiality and other ethical considerations were handled according the international recommendations,[18] the Helsinki Declaration revised by the World Medical Organization in Fortaleza in 2013 and Spanish Law 15/1999 on Data Protection. Patient information was anonymised and deidentified prior to analysis and therefore no informed consent was required.

Patient and public involvement statement

Patients were not directly involved in this study; only data coming from notifiable disease surveillance systems were used.

RESULTS

Sociodemographic, clinical and behavioural characteristics of the population

This study included 1218 cases of STI, affecting 1139 persons, 187 (15.4%) of the cases were women, 235 (19.3%) were aged 15–19 years and 574 (47.1%) were born in Spain. Of the 1031 men, 62.1% were MSM and 22.2% were MSW. Of the 187 women, 160 (85.6%) were

WSM, of whom 15 were bisexual women; two of them were diagnosed with syphilis, three with gonorrhoea and ten with HIV.

The most common infection was gonorrhoea (51.9%, n=632), followed by HIV (25.4%, n=309) and syphilis (21.8%, n=266), while LGV was the least common infection with just 11 cases among MSM. Women accounted for 19.6% of cases of gonorrhoea, 11.7% of syphilis and 10.4% of HIV. The proportion of MSM among HIV cases was 84.8% (n=235), 71.5% for syphilis and 44.5% gonorrhoea (table 1).

Among cases of gonorrhoea and syphilis, men and women differed in terms of the number of sexual partners (p<0.01), with woman having significantly fewer partners than men (table 1). Also, for cases of gonorrhoea, the younger group (15–19 years) had a higher proportion of women (36.3%, vs 21.5% for men); women had lower proportion of university education and had a higher proportion of condom use (p<0.05) (table 1).

Sixty-two persons presented reinfections during the study period, resulting in 141 cases (11.6% of the total number of cases). Of those persons, 50 had two infections, eight had three, three had four and one person had five infections. The most common pattern was two consecutive gonorrhoea infections (affecting 18 persons), followed by a diagnosis of syphilis and subsequently gonorrhoea (affecting 10 persons).

Incidence and trends in incidence

The incidence of HIV decreased from 1.6/10 000 in 2007 to 0.5/10 000 in 2015. A non-significant statistical increase was observed in men (p=0.27). However, in more recent years, there has been a slightly decreasing tendency in MSM (141.5 cases per 10 000 people in 2013, and 131.5 in 2015) (figure 1).

The incidence of gonorrhoea increased from 1.9/10 000 in 2007 to 7.6/10 000 in 2015 (p<0.01). This increase was observed in both men and women (figure 2). Regarding sexual behaviour, the increase in incidence of gonorrhoea was statically significant in all three categories analysed (p<0.01), with higher incidence rates in MSM (27.1/10 000 in 2007 and 228.8/10 000 in 2015) (figure 2). The incidence of syphilis increased from 0.4/10 000 in 2007 to 3.1/10 000 in 2015, though this was only statistically significant in men (p<0.01) (figure 2). Regarding sexual behaviour, the increase of syphilis was statistically significant in MSM and MSW (p<0.01), with higher incidence for MSM (18.1/10 000 in 2007 and 116.9/10 000 in 2015) (figure 2). Finally, the incidence of LGV remained stable throughout the study period (p=0.59).

HIV COINFECTION

In the descriptive analysis of the HIV coinfection for each STI, we observed statistically significant differences between men and women. Among cases of gonorrhoea and syphilis, the proportion of HIV coinfection was 7.7% in men and 1.6% in women (p=0.01) and 16.6% of men and 0% of women, respectively. Among men, the highest rate of HIV coinfection was observed among LGV cases (63.6%).

We also observed statistically significant differences in the proportion of HIV coinfection in gonorrhoea and syphilis when stratifying by (1) sexual behaviour (75.6% and 89.7% of cases of gonorrhoea and syphilis with HIV coinfection, respectively, were MSM; p<0.01 in both cases), (2) number of sexual partners the previous 12 months (36.6% and 35.9% of cases of gonorrhoea and syphilis with HIV coinfection, respectively, had ≥10 sexual partners; p<0.01 in both cases), (3) STI diagnoses during the previous 12 months (41.5% and 28.2% of cases of gonorrhoea and syphilis, respectively, were previously diagnosed with HIV coinfection, compared with 14.04% and 12.3% with a non-HIV coinfection; p<0.01 in both cases). Among cases of gonorrhoea, but not syphilis, the proportion of HIV coinfection varied significantly between age categories (90.2% of cases of HIV coinfection were aged 20–24 years, compared with 74.6% among cases of non-HIV coinfection). Among cases of syphilis, the proportion of HIV coinfection varied significantly according to country of birth (46.1% of cases of HIV coinfection were people born in Latin America, compared with 22% of cases of non-HIV coinfection).

To identify risk factors associated with HIV coinfection, we analysed only one STI per person as it is mentioned in methods. 830 patients with gonorrhoea, syphilis or LGV were included and we found that the following variable categories were associated with increased risk of HIV coinfection: being MSM (ORa: 14.14, 95% CI 3.34 to 59.91), having ≥10 sexual partners during the previous 12 months (ORa=4.11, 95% CI 1.53 to 11.01) and having a previous diagnosis of STI during the previous 12 months (ORa=2.06; 95% CI 1.13 to 3.77) (table 2).

DISCUSSION

In this study of people aged 15–24 years residing in Barcelona city, we observed a significant increase in the incidence of gonorrhoea and syphilis in men, especially in MSM, and of gonorrhoea in women. In young people, being MSM, having 10 or more sexual partners or a previous diagnosis of STIs during the previous year showed an increased risk of HIV coinfection.

Previous studies have found that new STI diagnoses in 15–24-year-olds account for half of all new cases of STI in the USA,[7] and more than a half of those worldwide,[19] even though this age group represents only ~25% of the sexually active population.[7 15] In Europe, this group of people account for 5%, 13% and 35% of all reported cases of LGV, syphilis and gonorrhoea, respectively.[20–22] In Barcelona, this proportion was 3%, 8% and 18%, respectively.[23] Usually, higher STI rates have been described in large cities or urban areas where vulnerable populations are found more concentrated.[24 25]

Table 1 Distribution of sociodemographic, clinical and behavioural characteristics in cases of HIV, gonorrhoea, syphilis or venereal lymphogranuloma (LGV) in 15–24-year-olds in Barcelona, 2007–2015

	HIV		Gonorrhoea		Syphilis		LGV
	Men	Women	Men	Women	Men	Women	Men
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total cases	277 (100)	32 (100)	508 (100)	124 (100)	235 (100)	31 (100)	11 (100)
Age group							
15–19	36 (13.0)	7 (21.9)	109 (21.5)	45 (36.3)	31 (13.2)	6 (19.4)	1 (9.1)
20–24	241 (87.0)	25 (78.1)	399 (78.5)	79 (63.7)	204 (86.8)	25 (80.6)	10 (90.9)
Education level							
University	35 (12.6)	1 (3.1)	83 (16.3)	13 (10.5)	35 (14.9)	7 (22.6)	3 (9.1)
Secondary	118 (42.6)	11 (34.4)	131 (25.8)	44 (35.5)	63 (26.8)	10 (32.3)	7 (63.6)
Primary or less	25 (9.0)	7 (21.9)	64 (12.6)	25 (20.2)	57 (24.3)	7 (22.6)	1 (9.1)
Missing	99 (35.7)	13 (40.6)	230 (45.3)	42 (33.9)	80 (34.0)	7 (22.69	0
Country of birth							
Spain	129 (46.6)	8 (25.0)	249 (49.0)	59 (47.6)	113 (48.1)	10 (32.3)	6 (54.5)
Western countries*	15 (5.4)	0	46 (9.1)	7 (5.7)	18 (7.7)	0	1 (9.1)
Latin America	104 (37.6)	15 (46.9)	129 (25.4)	34 (27.4)	58 (24.7)	10 (32.3)	4 (36.4)
Eastern Europe	10 (3.6)	2 (6.3)	15 (2.9)	7 (5.7)	7 (3.0)	5 (16.1)	0
Other	18 (6.5)	7 (21.9)	24 (4.7)	2 (1.6)	19 (8.1)	4 (12.9)	0
Missing	1 (0.4)	0	45 (8.9)	15 (12.1)	20 (8.5)	2 (6.5)	0
Sexual behaviour							
MSW	32 (11.6)	na	160 (31.5)	na	37 (15.7)	na	0
MSM	235 (84.8)	na	226 (44.5)	na	168 (71.5)	na	11 (100)
WSM	na	32 (100)†	na	105 (84.7)‡	na	23 (74.2)§	na
Missing	10 (3.6)	0	122 (24.0)	19 (15.3)	30 (12.8)	8 (25.8)	0
STI diagnoses in the previous 12 months							
No	251 (90.6)	31 (96.9)	427 (84.0)	105 (84.7)	199 (84.7)	28 (90.3)	6 (54.5)
Yes	26 (9.4)	1 (3.1)	81 (15.9)	19 (15.3)	36 (15.3)	3 (9.7)	5 (45.5)
Number of sexual partners in the previous 12 months							
1 to 3	na	na	107 (21.1)	60 (48.4)	36 (15.3)	12 (38.7)	1 (9.1)
4 to 6	na	na	39 (7.7)	11 (8.9)	14 (6.0)	0	0
7 to 10	na	na	29 (5.7)	6 (4.8)	25 (10.6)	2 (6.5)	1 (9.1)
>10	na	na	69 (13.6)	3 (2.4)	44 (18.7)	0 (0.0)	6 (54.6)
Missing	na	na	264 (52.0)	44 (35.5)	116 (49.4)	17 (54,8)	3 (27.3)
HIV coinfection							
No	na	na	469 (92.3)	122 (98.4)	196 (83.4)	31 (100)	4 (36.4)
Yes	na	na	39 (7.7)	2 (1.6)	39 (16.6)	0	7 (63.6)
Condom use							
Yes	na	na	73 (14.4)	29 (23.4)	47 (20.0)	4 (12.9)	3 (27.3)
No	na	na	253 (49.8)	67 (54,0)	103 (43.8)	13 (41.9)	7 (63.6)
Missing	na	na	182 (35.8)	28 (22.6)	85 (36.2)	14 (45.2)	1 (9.1)

*Western countries: Western Europe, USA, Canada and Australia.
†10 women were bisexual.
‡Three women were bisexual.
§Two women were bisexual.
na, not applicable; MSM, men that have sex with men; MSW, men that have sex only with women; STI, sexually transmitted infection; WSM, women who have sex with men.

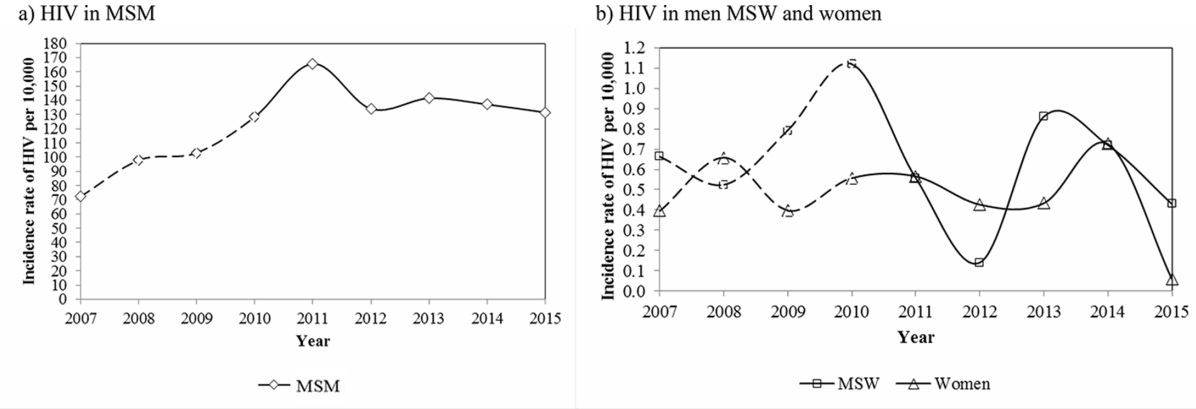

Figure 1 Incidence in people between 15 and 24 years of: HIV in MSM (men who had sex with men) (a), MSW (men who have sex with women only) (b) and in women (b) per 10 000 MSM/MSW/women. The dashed line indicates that HIV cases were subject to voluntary notification from 2007 to 2009, and obligatory and nominal notification thereafter.

To our knowledge, few studies have analysed trends in the incidence of STIs in 15–24-year-olds. For instance, in recent years, it has been observed an increase in the incidence of cases of STI among people under 20 years old in Ireland[26] and in 15–24-years old in the UK.[24 27] In this study, we observed an increase in the incidence in 15–24-year-olds in Barcelona. We want to remark that, although there was not any massive campaign or specific community project to increase STI detection or notification in Barcelona, the recent introduction of PCR for gonorrhea diagnosis may have improved the surveillance system sensitivity. Besides, STI surveillance has been a priority for ASPB even before 2007 when gonorrhoea, syphilis and LGV were declared mandatory notifiable diseases in Catalonia.[17] In spite of this, we believe that last year's observed increase specifically in Spain but also in all the European region,[2 26] mostly in large cities, is likely to be a real increase on the incidence and not only due because of an improvement on the surveillance system sensitivity or other related issues.

Moreover, the incidence of STI was higher among women,[9 28] MSM[19 29] and younger people, highlighting them as especially vulnerable populations. Our results show that MSM are a risk group for the STIs analysed, mainly for HIV, syphilis and LGV. In fact, we found that young MSM sometimes show up to 20-fold higher

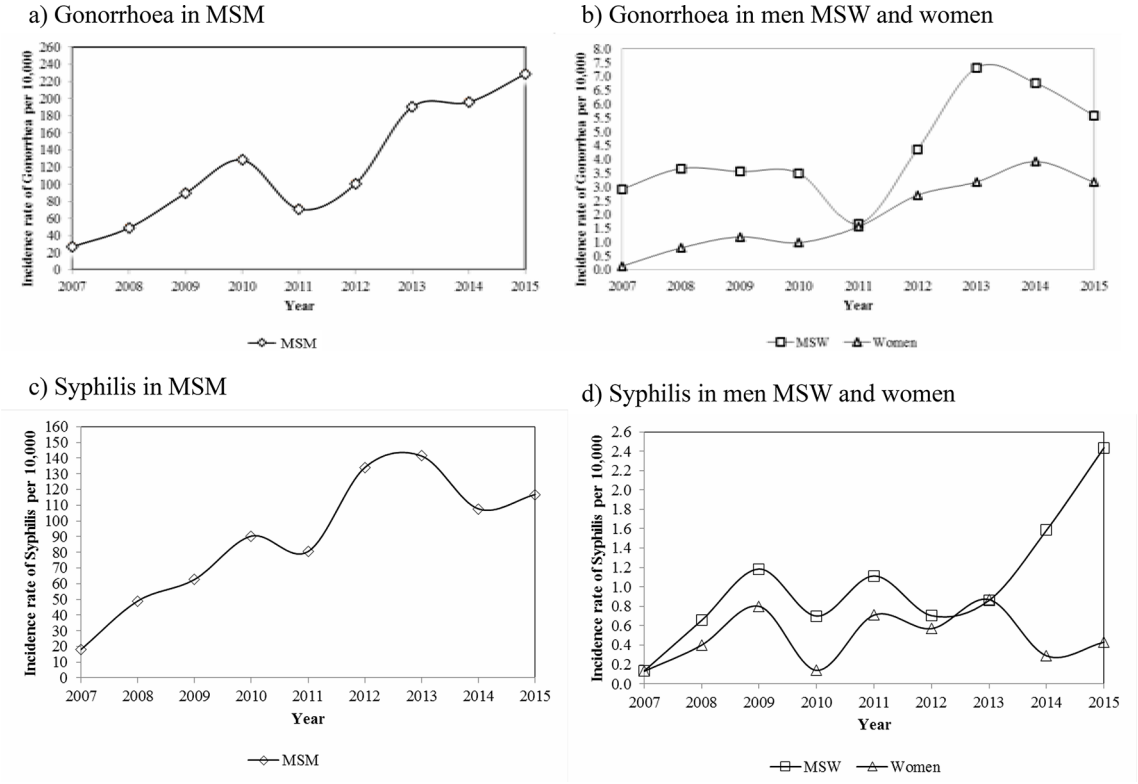

Figure 2 Incidence in people between 15 and 24 years of: gonorrhoea and syphilis in men who had sex with men (MSM) (a,c), men who have sex with women only (MSW) (b,d) and in women (b,d) per 10 000 MSM/MSW/women.

Table 2 Associated factors to HIV coinfection in 15–24-year-old patients diagnosed of gonorrhoea, syphilis or venereal lymphogranuloma in Barcelona (N=830)

Variables	ORa*	95% CI
Age		
Each more 1 year	1.13	0.96 to 1.28
Education		
Secondary or university	1.00	
Primary or less	1.03	0.47 to 2.26
Missing	0.95	0.49 to 1.84
Country of birth		
Spain	1.00	
Not Spain	1.37	0.79 to 2.38
Missing	1.01	0.35 to 2.90
Sexual behaviour		
MSW	1.00	
MSM	14.14	3.34 to 59.91
Missing (men)	4.91	0.96 to 25.13
Women	1.40	0.19 to 10.12
STI diagnoses in the previous 12 months		
No	1.00	
Yes	2.06	1.13 to 3.77
Number of sexual partners in the previous 12 months		
One to three	1.00	
Four to six	1.33	0.34 to 5.16
Seven to ten	0.89	0.21 to 3.84
>10	4.11	1.53 to 11.01
Missing	2.33	0.89 to 6.10

*This model was adjusted for all the listed variables in the table: Age, education, country of birth, sexual behaviour, previous 12 months STI diagnoses and number of sexual partners (last 12 months).
MSM, men who have sex with men; MSW, men who have sex with women only; ORa, adjusted odds ratio ; STI, sexually transmitted infection.

increase in incidence and magnitude than MSW or women. Several studies indicate a low incidence of gonorrhoea observed among women due to the difficulties to reach them.[9 28 30] Despite this, we also found that, among women diagnosed with gonorrhoea, the proportion of 15–19-year-olds was approximately 50% higher than that among men. In fact, we found that the incidence of gonorrhoea differed between men and women according to educational level, which may be due to the younger age of the female cases. These observations underline the need to put special emphasis and efforts in the youngest women. The increasing trends may also be partly due to improved coverage of epidemiological surveillance programmes, and the broader availability of more sensitive diagnostic tests.[20–22]

We stress the importance of improving programmes and interventions targeting STIs in young people. In some countries, STIs are mainly detected by general practitioners; however, specialised STI centres[31] have been shown to be more effective in diagnosing STI such as chlamydia, gonorrhoea and syphilis, especially among young men. In Barcelona in recent years, specialised STI centres have diagnosed approximately 40% of all cases of gonorrhoea (unpublished data).

Given the higher risk of HIV coinfection among young MSM also observed in the multivariate analysis and the reported increase in incidence of syphilis and gonorrhoea also in young MSM, we must remain alert to a possible increase in the incidence of HIV in this group; but as in other studies and reports,[4] our HIV results cannot corroborate this possibility at present. In fact, our results show a statistically non-significant decrease in incidence of HIV in MSM in the last few years. Moreover, HIV carriers are vulnerable to new STIs, especially MSM,[32] young people[7 12] and those who had a previous history of STI.[32] Also, the greater risk associated with a higher number of sexual partners found in the multivariate analysis is consistent with previous reports.[7 26] In light of our results, young MSM as well as young people with a high number of sexual partners or a previous diagnosis of STIs have a higher risk of acquiring HIV, which could make them potential candidates for HIV Pre-Exposure Prophylaxis (PrEP). The use of PrEP along with promotion of condom use and adherence support could be considered in young people in specific situations as some guidelines are already recommending.[33]

A limitation of our study is that, for some variables, the proportion of missing values was high. Nonetheless, we have included a *missing* category in all variables, such that all cases are considered in the models, allowing us to disentangle the direction and magnitude of association with HIV coinfection for the missing category. Also, we have to mention that we could not study chlamydial infection since, in Barcelona, this infection, probably the most frequent in young people, has been nominal notifiable since 2016.

We also stress the importance of continued efforts to develop effective interventions for STI prevention and control among young people. Screening programmes, brief behavioural counselling and partner notification often work well, depending on the setting where they are implemented, which is an important factor when designing such interventions.[34]

In conclusion, the incidence of gonorrhoea and syphilis among 15–24-year-olds has increased in Barcelona in recent years, especially in MSM, while HIV infection remains stable but with a high incidence among MSM. Factors related to specific behaviours that are more common among younger people, such as having sex with multiple partners and incorrect condom use,[7 15 19] and added to a deficient screening for some STIs[9 10] may lead eventually to an increase in HIV incidence. Our results show that previous diagnosis of a STI, sexual behaviour

and number of sexual partners are good predictors of HIV coinfection among young people diagnosed of gonorrhoea, syphilis or LGV that allow identifying them to refer for intervention. Implementing and improving STI/HIV prevention and control programmes that reduce STI in young people are needed to avert future STI and HIV acquisition, especially targeting the most vulnerable persons.

Author affiliations
[1]Epidemiology Service, Public Health Agency of Barcelona (ASPB), Barcelona, Spain
[2]Preventive Medicine and Public Health Training Unit PSMar-UPF-ASPB (Parc de Salut Mar - Pompeu Fabra University - Agència de Salut Pública de Barcelona), Barcelona, Spain
[3]Hospital de la Vall d'Hebron, Universitat Autònoma de Barcelona, Spain
[4]Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain
[5]Hospital del Mar, Universitat Autonòma de Barcelona, Barcelona, Spain
[6]Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[7]Hospital Puigvert, Universitat Autònoma de Barcelona, Spain
[8]Hospital Tries i Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain
[9]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[10]Foundation of Tuberculosis Research Unit of Barcelona, Spain

Acknowledgements We thank all the reporting physicians who have contributed to the collection and quality of the information in the surveys. The Spanish Society of Epidemiology (SEE) for rewarding with 'VII Premio Emilio Perea' the work that gave rise to this article as the second best oral senior communication in the SEE Congress held in Barcelona in September 2017.

Collaborators STI-HIV group of Barcelona: ASPB (Cristina Rius, Sonia Gil, Pilar Gorrindo, Roser Clos, Raquel Sánchez, Miriam Ros, Eva Masdeu, Pere Simon, Maria Jose Santomà), Hospital de la Vall d'Hebron (Pere Armengol, Adrià Curran, Esteve Ribera, Vicenç Falcó), Hospital de la Santa Creu i Sant Pau (Maria Gracia Mateo, M Mar Gutierrez, Pere Domingo, Joaquin López-Contreras), Hospital del Mar (Judit Villar, Ana Guelar,), Hospital Germans Tries i Pujol (Beatriz Mothe), Hospital Clínic de Barcelona (Irene Fuertes, Ana Gonzalez Cordon, José L Blanco, Felipe García, Josep Mallolas, Josep M Miró).

Contributors PGdO and JC developed the surveillance system for STI. PGdO designed the study, AS and MM carried out the bibliographic search and the statistical analysis. AS, MM, JC, PGdO, MAr, MV, MJB, IO, AG-C, MAI, GM-E, HK, MG, AV and JC interpreted the results. AS and MM prepared the manuscript. STI-HIV group of Barcelona participated in the acquisition and interpretation of the data. AS, MM, JAC, PGdO, MAr, MV, MJB, IO, AG-C, MAI, GM-E, HK, MG, AV, JC and STI-HIV group of Barcelona collaborated in the critical review and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. WHO. Sexually transmitted infections (STIs). http://www.who.int/mediacentre/factsheets/fs110/en/ (accessed 26 Feb 2018).
2. European Centre for Disease Prevention and Control. *Sexually transmitted infections in Europe 2013*. Stockholm: ECDC, 2015. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/sexual-transmitted-infections-europe-surveillance-report-2013.pdf.
3. Área de vigilancia del VIH y conductas de riesgo. *Vigilancia epidemiológica de las infecciones de transmisión sexual 1995-2015*. Madrid: Centro Nacional de Epidemiología/Subdirección General de Promoción de la Salud y Epidemiología - Plan Nacional sobre el Sida, 2017. https://www.msssi.gob.es/en/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/Vigilancia_ITS_1995_2015.pdf (accessed 8 Aug 2017).
4. Área de Vigilancia de VIH y Comportamientos de Riesgo. *Vigilancia Epidemiológica del VIH y sida en España: Sistema de Información sobre Nuevos Diagnósticos de VIH y Registro Nacional de Casos de Sida*. Madrid: S.G. de Promoción de la Salud y Epidemiología / Centro Nacional de Epidemiología - Plan Nacional sobre el Sida - ISCIII, 2016. https://www.msssi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/InformeVIH_SIDA_2016.pdf (accessed 22 May 2017).
5. European Centre for Disease Prevention and Control. *HIV and AIDS. In: ECDC. Annual epidemiological report for 2015*. Stockholm: ECDC, 2017. https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-HIV-AIDS.pdf (accessed 26 Feb 2018).
6. Martí-Pastor M, García de Olalla P, Barberá MJ, *et al*. HIV Surveillance Group. Epidemiology of infections by HIV, Syphilis, Gonorrhea and Lymphogranuloma Venereum in Barcelona City: a population-based incidence study. *BMC Public Health* 2015;15:1015.
7. Gibson EJ, Bell DL, Powerful SA. Common sexually transmitted infections in adolescents. *Prim Care* 2014;41:631–50.
8. Harden A, Brunton G, Fletcher A, *et al*. Teenage pregnancy and social disadvantage: systematic review integrating controlled trials and qualitative studies. *BMJ* 2009;339:b4254.
9. Yavorsky RL, Hollman D, Steever J, *et al*. Prevalence of sexually transmitted infections in at-risk adolescent females at a comprehensive, stand-alone adolescent health center in New York City. *Clin Pediatr* 2014;53:890–5.
10. O'Connor CA, Shubkin CD. Adolescent STIs for primary care providers. *Curr Opin Pediatr* 2012;24:647–55.
11. Newbern EC, Anschuetz GL, Eberhart MG, *et al*. Adolescent sexually transmitted infections and risk for subsequent HIV. *Am J Public Health* 2013;103:1874–81.
12. Mullins TL, Rudy BJ, Wilson CM, *et al*. Incidence of sexually transmitted infections in HIV-infected and HIV-uninfected adolescents in the USA. *Int J STD AIDS* 2013;24:123–7.
13. Generalitat de Catalunya Departament de Salut. Definició de cas de les malalties de declaració obligatòria. 2010 (Accessed 9 Aug 2017).
14. Ajuntament de Barcelona. Población de Barcelona por grandes grupos de edad. Evolución 1981-2015. http://www.bcn.cat/estadistica/castella/dades/inf/lecpadro/lec15/part1/t21.htm (Accessed 13 Oct 2016).
15. Adolescents and Young Adults | Prevention | STDs | CDC. https://www.cdc.gov/std/life-stages-populations/adolescents-youngadults.htm (Accessed 15 Sep 2017).
16. Bartoll X, Salvador M, Allué N, *et al*. *Enquesta de salut de Barcelona 2011*. Barcelona: Agència de Salut Pública de Barcelona, 2013. https://www.aspb.cat/documents/enquesta-salut-barcelona-2011-resultats-principals/.
17. Decret 67/2010, de 25 de maig, pel qual es regula el sistema de notificación de malalties de declaració obligatòria i brots epidèmics al Departament de Salut. DOGC. Diari Oficial de la Generalitat de Catalunya, 8 Juliol 2010; núm. 5666. http://cido.diba.cat/legislacio/1342856/decret-672010-de-25-de-maig-pel-qual-es-regula-el-sistema-de-notificacio-de-malalties-de-declaracio-obligatoria-i-brots-epidemics-al-departament-de-salut.
18. Rose S. International ethical guidelines for epidemiological studies: by the Council for International Organizations of Medical Sciences (CIOMS). *Am J Epidemiol* 2009;170:1451–2.
19. Dehne KL, Riedner G. Sexually transmitted infections among adolescents the need for adequate health services. http://www.who.int/child-adolescent-health (Accessed 24 Aug 2017).
20. European Centre for Disease Prevention and Control. Lymphogranuloma venereum. In: *Annual epidemiological report for 2015*. Stockholm: ECDC, 2017.
21. European Centre for Disease Prevention and Control. Syphilis. In: *Annual epidemiological report for 2015*. Stockholm: ECDC, 2017.
22. European Centre for Disease Prevention and Control. Gonorrhoea. In: *Annual epidemiological report for 2015*. Stockholm: ECDC, 2017.
23. Estadístiques de Salut. Morbiditat per malalties de declaració obligatòria a Barcelona ciutat. 2015 https://www.aspb.cat/wp-content/uploads/2017/11/Morbiditat_per_malalties_declaracio_obligatoria_Barcelona_2015.pdf (Accessed 29 Jul 2018).

24. Hughes G, Field N. The epidemiology of sexually transmitted infections in the UK: impact of behavior, services and interventions. *Future Microbiol* 2015;10:35–51.
25. Patterson-Lomba O, Goldstein E, Gómez-Liévano A, *et al*. Per capita incidence of sexually transmitted infections increases systematically with urban population size: a cross-sectional study. *Sex Transm Infect* 2015;91:610–4.
26. Davoren MP, Hayes K, Horgan M, *et al*. Sexually transmitted infection incidence among adolescents in Ireland. *J Fam Plann Reprod Health Care* 2014;40:276–82.
27. Public Health Wales. Public Health Wales HIV and STI trends in Wales HIV and STI trends in Wales. 2013 http://www.hps.scot.nhs.uk/ (Accessed 2 Jan 2019).
28. Forhan SE, Gottlieb SL, Sternberg MR, *et al*. Prevalence of sexually transmitted infections among female adolescents aged 14 to 19 in the United States. *Pediatrics* 2009;124:1505–12.
29. van der Bij AK, Stolte IG, Coutinho RA, *et al*. Increase of sexually transmitted infections, but not HIV, among young homosexual men in Amsterdam: are STIs still reliable markers for HIV transmission? *Sex Transm Infect* 2005;81:34–7.
30. Tarr ME, Gilliam ML. Sexually transmitted infections in adolescent women. *Clin Obstet Gynecol* 2008;51:306–18.
31. van den Broek IV, Verheij RA, van Dijk CE, *et al*. Trends in sexually transmitted infections in the Netherlands, combining surveillance data from general practices and sexually transmitted infection centers. *BMC Fam Pract* 2010;11:39.
32. Mulhall BP, Wright ST, De La Mata N, *et al*. Risk factors associated with incident sexually transmitted infections in HIV-positive patients in the Australian HIV Observational Database: a prospective cohort study. *HIV Med* 2016;17:623–30.
33. Recomendaciones sobre Profilaxis Pre-Exposición en adultos para la Prevención de la Infección por VIH en España. AIDS Study Group (GeSIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. http://www.cesida.org/wp-content/uploads/2013/09/gesida-guiasclinicas-2016-profilaxis_pre-exposicionVIH.pdf (Accessed 26 Dec 2018).
34. Peterman TA, Carter MW. Effective interventions to reduce sexually transmitted disease. *Sex Transm Dis* 2016;43:S1–S2.

4.2. *Estudio II*: STI epidemic re-emergence, socio-epidemiological clusters characterisation, and HIV coinfection in Catalonia, Spain, during 2017–2019: a retrospective population-based cohort study.

Sentís A, Montoro-Fernandez M, Lopez-Corbeto E The Catalan HIV and STI Surveillance Group, et al. STI epidemic re-emergence, socio-epidemiological clusters characterisation and HIV coinfection in Catalonia, Spain, during 2017–2019: a retrospective population-based cohort study

BMJ Open 2021;11:e052817. doi: 10.1136/bmjopen-2021-052817

URL: https://bmjopen.bmj.com/content/11/12/e052817

BMJ Open

STI epidemic re-emergence, socio-epidemiological clusters characterisation and HIV coinfection in Catalonia, Spain, during 2017–2019: a retrospective population-based cohort study

Alexis Sentís ,[1,2,3] Marcos Montoro-Fernandez,[1,4] Evelin Lopez-Corbeto,[1,4,5] Laia Egea-Cortés,[1,4] Daniel K Nomah,[1,6] Yesika Díaz,[1,4] Patricia Garcia de Olalla,[5,7] Lilas Mercuriali,[7] Núria Borrell,[8] Juliana Reyes-Urueña ,[1,4,5] Jordi Casabona,[1,4,5,6] The Catalan HIV and STI Surveillance Group

To cite: Sentís A, Montoro-Fernandez M, Lopez-Corbeto E, *et al*. STI epidemic re-emergence, socio-epidemiological clusters characterisation and HIV coinfection in Catalonia, Spain, during 2017–2019: a retrospective population-based cohort study. *BMJ Open* 2021;**11**:e052817. doi:10.1136/bmjopen-2021-052817

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052817).

Received 08 May 2021
Accepted 12 November 2021

For numbered affiliations see end of article.

Correspondence to
Alexis Sentís;
a.sentis@epiconcept.fr

ABSTRACT

Objectives To describe the epidemiology of sexually transmitted infections (STIs), identify and characterise socio-epidemiological clusters and determine factors associated with HIV coinfection.

Design Retrospective population-based cohort.

Setting Catalonia, Spain.

Participants 42 283 confirmed syphilis, gonorrhoea, chlamydia and lymphogranuloma venereum cases, among 34 600 individuals, reported to the Catalan HIV/STI Registry in 2017–2019.

Primary and secondary outcomes Descriptive analysis of confirmed STI cases and incidence rates. Factors associated with HIV coinfection were determined using logistic regression. We identified and characterized socio-epidemiological STI clusters by Basic Health Area (BHA) using K-means clustering.

Results The incidence rate of STIs increased by 91.3% from 128.2 to 248.9 cases per 100 000 population between 2017 and 2019 (p<0.001), primarily driven by increase among women (132%) and individuals below 30 years old (125%). During 2017–2019, 50.1% of STIs were chlamydia and 31.6% gonorrhoea. Reinfections accounted for 10.8% of all cases and 6% of cases affected HIV-positive individuals. Factors associated with the greatest likelihood of HIV coinfection were male sex (adjusted OR (aOR) 23.69; 95% CI 16.67 to 35.13), age 30–39 years (versus <20 years, aOR 18.58; 95% CI 8.56 to 52.13), having 5–7 STI episodes (vs 1 episode, aOR 5.96; 95% CI 4.26 to 8.24) and living in urban areas (aOR 1.32; 95% CI 1.04 to 1.69). Living in the most deprived BHAs (aOR 0.60; 95% CI 0.50 to 0.72) was associated with the least likelihood of HIV coinfection. K-means clustering identified three distinct clusters, showing that young women in rural and more deprived areas were more affected by chlamydia, while men who have sex with men in urban and less deprived areas showed higher rates of STI incidence, multiple STI episodes and HIV coinfection.

Conclusions We recommend socio-epidemiological identification and characterisation of STI clusters and factors associated with HIV coinfection to identify at-risk populations at a small health area level to design effective interventions.

Strengths and limitations of this study

- In this retrospective population-based cohort study, the use of data from the Catalan HIV/STI Registry allowed us to characterise the re-emergence of sexually transmitted infections (STIs), perform socio-epidemiological clustering and reveal factors associated with HIV coinfection.
- To the best of our knowledge, this is the first study to apply the k-means clustering methodology to identify and characterise distinct socio-epidemiological clusters of STI at a small health area level.
- A key limitation of this study is the high proportion of missing data around sociodemographic and lifestyle characteristics such as education level, sexual preference and country of birth. Nonetheless, our findings are consistent with previous analyses.

INTRODUCTION

The epidemic of sexually transmitted infections (STIs) continues to be a major concern and threat to global public health. Undiagnosed and untreated STIs can lead to a multitude of complications including HIV acquisition, long-term disabilities, infertility, adverse pregnancy outcomes and death.[1 2] Across Europe, incidence of STIs continue to be on the rise with confirmed cases reported in national surveillance systems increasing by 50% for gonorrhoea, 36% for syphilis, 68% for lymphogranuloma venereum (LGV) and 0.6% for chlamydia from 2014 to 2018.[3–6] This trend is reflected in Spain where new STI cases have been reported to increase 10-fold from 2000 to 2017, with 23 975 cases

of gonorrhoea, syphilis, chlamydia and LGV reported in 2017 alone.[7 8] During 2018 to 2019, the region of Catalonia in Spain recorded the highest incidence of STIs across the country, with a rise of 37% in the number of cases.[9] Incidence rates were highest among men who have sex with men (MSM), women and in young adults, particularly among young women who in recent years have shown a proportionally higher increase than men.[7 9] The surge in STI incidence rates may be explained by improvements in surveillance systems, introduction of new diagnostic methods with enhanced sensitivity, changes in sexual attitudes and behaviours, sociocultural shifts in society and the effects of tourism and globalisation.[10]

STIs and HIV infections are overlapping epidemics, which, besides from biological synergies, are largely driven by socioeconomic and other contextual factors acting as syndemics. Individuals affected by STIs are at increased risk of HIV infection and people living with HIV are more vulnerable to STIs.[11 12] Some studies have described social determinants of health, discrimination and inequalities as the main factors associated with the spatiotemporal clustering of STI cases.[13 14] While spatiotemporal clustering may be useful in grouping events or cases, other methodologies including k-means clustering allow grouping of different geographical units by common characteristics such as sociodemographic and epidemiological factors.[15] The socio-epidemiological characterisation of STIs, including association with HIV coinfection, and identification of distinct clusters are imperative to strengthen the integrated surveillance of STIs and HIV. Data from such an exercise could potentially increase the sensitivity, timeliness and representativeness of surveillance systems, and generate information to tailor public health strategies to tackle a continuously growing epidemic.

Therefore, we aimed to describe the epidemiology of STIs, identify and characterise socio-epidemiological clusters of STI and determine factors associated with HIV coinfection in Catalonia, Spain, during 2017–2019.

METHODS

Study design and data source

We conducted a retrospective population-based cohort analysis of all confirmed cases of the notifiable STIs, syphilis, gonorrhoea, chlamydia and LGV, in Catalonia between 1 January 2017 and 31 December 2019. Data were obtained from the Catalan HIV/STI Registry,[16] which uses information from the Epidemiological Repository of Catalonia (REC, in Catalan), an electronic database used by the Epidemiological Surveillance Network of Catalonia (XVEC, in Catalan). REC collects information from two sources: (1) the microbiological notification system (SNM, in Catalan) of confirmed cases from microbiological laboratories; and (2) the mandatory disease notification system (MDO, in Catalan) based on physician reporting of clinically suspected/probable and laboratory-confirmed cases as per established case definitions. Information collected through an epidemiological questionnaire that records clinical, epidemiological and behavioural variables are included along with the mandatory notification in REC (online supplemental table S1). Case definitions for surveillance reporting are standardised according to the European Union definitions established by the European Centre for Disease Prevention and Control (online supplemental table S2).[17 18]

Analysis variables

We extracted data around epidemiological, sociodemographic and clinical variables as detailed in online supplemental table S3. All individuals who had experienced at least one STI episode during the study period were linked, through the Spanish healthcare system personal identification code (CIP), to the Catalan HIV/STI Registry to identify HIV coinfections either before or after the recorded STI episode. In addition to the CIP, the Catalan HIV/STI Registry surveillance team performs checks of duplicates at least twice annually using a unique STI episode number (assigned to each notification and disease), name and date of birth. For our analysis, a deduplicated, HIV/STI-linked and anonymised version was provided.

A Basic Health Area (BHA; Àrea Bàsica de Salut (ABS), in Catalan) is a territorial unit of coverage served by a primary healthcare team. Each BHA typically serves a population of approximately 5000–25 000 people. The socioeconomic level of the BHAs was classified according to a deprivation index (calculated by the Agency of Health Quality and Assessment of Catalonia) which was attributed to each individual according to their residential address. The deprivation index is a composite measure based on indicators such as proportion of residents with low educational level, proportion of manual workers, proportion of residents with an annual income below a specified amount, and rate of premature mortality. Deprivation indices were categorised in quintiles, with the first quintile being the least deprived.[19]

Clinical variables that were extracted included reinfections, multiple STI episodes and coinfection with HIV. Reinfection was defined as an episode of the same STI detected after a defined period, which differed for each STI, following the previously recorded infection in the same individual during the study period. Multiple STI episodes were defined as total number of episodes of any STI reported for the individual during the study period (online supplemental table S3). As information regarding treatment response was not available, episodes occurring outside of the specific time frames for each STI were assumed not to be a persistent infection resulting from treatment failure.

K-means clustering of STIs

We implemented k-means to define STI clusters by sociodemographic characteristics. Specifically, the k-means clustering methodology is an unsupervised machine learning approach that seeks to group heterogeneous units (in our case BHAs) into clusters based on similarities

in characteristics (variable values and categorical distribution among the BHA).[15] A clustering algorithm is a procedure for grouping a series of vectors according to a specific criterion, which could be distance or similarity. Proximity is defined in terms of a distance function and uses a k-means clustering method based on Euclidean distance to quantify similarities or differences between observations. This method is sensitive to outliers and requires both internal and external validation processes using different combinations of variables in the algorithms. The internal clustering validation considered an average Euclidean distance for each cluster and similarities between cases according to the correlation matrix of distances to determine the optimum number of clusters for which intracluster variation is minimum. Our external validation process was based on a description of the possible socio-epidemiological variables to determine the most appropriate clustering algorithm for our data set. Based on these validations, the researchers ended up with an exact number of clusters formed by defined variables which were included in the algorithm. In our case, the following variables were chosen to identify and build the final three socio-epidemiological clusters of STI by BHA: incidence rate by each STI, percentage of women, percentage of people with HIV coinfection, median age among all STI cases in each BHA and deprivation index of each BHA.

Statistical analyses

We performed a descriptive analysis to summarise epidemiological, clinical, sociodemographic and geographical variables for the total confirmed STI cases and by STI clusters. Continuous variables were summarised as median and interquartile range (IQR), while categorical variables were reported as absolute frequencies and percentages. Annual incidence rates of STIs are described per 100 000 population for the total confirmed STI cases and by STI cluster, and calculated based on census information from the Statistical Institute of Catalonia (IDESCAT) (online supplemental table S4). Incidence trends were analysed using the χ^2 test for linear trend. For identifying and building clusters in k-means clustering, STI incidence rates were described per 1000 population due to the small population size per BHA.

We assessed risk factors associated with HIV coinfection among individuals diagnosed with STIs using multivariable logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Individuals with more than one STI episode were counted once (first episode), and successive episodes in the same individual were grouped in a variable that considers the number of episodes, and included in the models. Sexual preference, country of birth and education level were excluded from the models because more than 50% of values were missing. We used backward stepwise elimination regression to include all analysed variables that showed statistical significance (p<0.05) by the Wald test in the final multivariable logistic regression model. All analyses were performed using R Statistical Software V.3.6.1).

Ethics approval statement

Data from the Catalan HIV/STI Registry, REC and all aggregated variables used in the study were handled according to international recommendations, the Helsinki Declaration revised by the World Medical Organization in Fortaleza in 2013 and Spanish Law 3/2018 on Data protection and Public Health 33/2011. Patient information was anonymised and deidentified prior to analysis and therefore no informed consent was required.

Patient and public involvement

Patients were not directly involved in this study; only data from the nationally notifiable disease surveillance system were used.

RESULTS

STI epidemic and trends

Between 2017 and 2019, a total of 42 283 cases of STIs were reported among 34 600 individuals in Catalonia (table 1). Throughout the study period, half of all reported STIs were chlamydia (50.1%) and almost a third were gonorrhoea (31.6%). Reinfections accounted for 10.8% of all reported cases. Among the subjects affected by STIs, the events of gonorrhoea had the highest reinfection rate (15.7%), while chlamydia had the lowest occurrence of reinfection (6.7%).

The number of STI cases doubled from 9687 in 2017 to 18 872 in 2019 (table 2). The incidence rate of STIs increased by 91.3% from 128.2 cases per 100 000 population in 2017 to 248.9 cases per 100 000 population in 2019. The annual incidence rate of STIs for the period 2017–2019 was 185.5 per 100 000 population. Incidence rates increased significantly (p<0.001) from 2017 to 2019 for all STI types except for syphilis cases which remained stable over the 3 years, with the highest increase in number of cases seen in chlamydia (188.8%) followed by gonorrhoea (63.8%) and LGV (56.1%). In 2017, chlamydia and gonorrhoea represented 36.8% and 36.0% of all reported STIs, respectively, but by 2019 chlamydia accounted for 55.1% of all cases. Gonorrhoea showed the second greatest increase from 2017 to 2019, with 47.5% occurring in individuals under 30 years of age throughout the study period. This increase in the number of confirmed STI cases from 2017 to 2019 was remarkably higher in women (132% vs 75% in men) and individuals below the age of 30 years (125% vs 68% in those ≥30 years). Indeed, women under 30 years of age presented the highest decrease in both number of cases, with an increase of 155.8% versus 93.6% in men below 30 years and in incidence rates with an increase of 154.1% (from 193.6 to 491.9 per 100 000 population) versus 93.6% in men under 30 years (from 202.9 to 384.0 per 100 000 population).

The vast majority of reported cases occurred in men for all STI types except chlamydia, of which 61.9%

Table 1 Epidemiological characteristics of reported STI cases in Catalonia, Spain (2017–2019)

Characteristic	All STIs	Chlamydia	Gonorrhoea	Syphilis	LGV
Total cases, n (%)	42 283 (100)	21 202 (50.1)	13 362 (31.6)	6975 (16.5)	744 (1.8)
Sex, n (%)					
Female	16 676 (39.4)	13 125 (61.9)	2667 (20.0)	875 (12.5)	9 (1.2)
Male	25 607 (60.6)	8077 (38.1)	10 695 (80.0)	6100 (87.5)	735 (98.8)
Age, n (%)					
<20 years	4438 (10.5)	3311 (15.6)	984 (7.4)	137 (2.0)	6 (0.8)
20–29 years	17 691 (41.8)	10 707 (50.5)	5361 (40.1)	1462 (21.0)	161 (21.6)
30–39 years	11 102 (26.3)	4454 (21.0)	4116 (30.8)	2242 (32.1)	290 (39.0)
40–49 years	6092 (14.4)	2087 (9.8)	2032 (15.2)	1757 (25.2)	216 (29.0)
50–59 years	2037 (4.8)	530 (2.5)	658 (4.9)	789 (11.3)	60 (8.1)
>60 years	923 (2.2)	113 (0.5)	211 (1.6)	588 (8.4)	11 (1.5)
Sexual preference, n (%)					
MSM*	3270 (7.7)	785 (3.7)	1321 (9.9)	993 (14.2)	171 (23.0)
MSW	3149 (7.5)	1863 (8.8)	1040 (7.8)	243 (3.5)	3 (0.4)
WSW†	415 (1.0)	335 (1.6)	69 (0.5)	10 (0.1)	1 (0.1)
WSM	8189 (19.4)	7034 (33.2)	966 (7.2)	186 (2.7)	3 (0.4)
Missing (male)	19 188 (45.4)	5429 (25.6)	8334 (62.4)	4864 (69.7)	561 (75.4)
Missing (female)	8072 (19.1)	5756 (27.2)	1632 (12.2)	679 (9.7)	5 (0.7)
STI reinfection, n (%)	4558 (10.8)	1418 (6.7)	2098 (15.7)	955 (13.7)	87 (11.7)
HIV coinfection, n (%)	2443 (5.8)	467 (2.2)	897 (6.7)	893 (12.8)	186 (25.0)
Deprivation index‡					
First quintile (least deprived)	10 271 (24.3)	5185 (24.5)	3040 (22.8)	1757 (25.2)	289 (38.8)
Second quintile	7465 (17.7)	4328 (20.4)	2012 (15.1)	1037 (14.9)	88 (11.8)
Third quintile	4859 (11.5)	2763 (13.0)	1332 (10.0)	716 (10.3)	48 (6.5)
Fourth quintile	5703 (13.5)	3217 (15.2)	1578 (11.8)	827 (11.9)	81 (10.9)
Fifth quintile	7689 (18.2)	4319 (20.4)	2211 (16.6)	1079 (15.5)	80 (10.8)
Missing	6296 (14.9)	1390 (6.6)	3189 (23.9)	1559 (22.4)	158 (21.2)
Health region of residence, n (%)					
Barcelona	35 215 (83.3)	17 108 (80.7)	11 566 (86.6)	5833 (83.6)	708 (95.2)
Other regions	7068 (16.7)	4094 (19.3)	1796 (13.4)	1142 (16.4)	36 (4.8)
BHA setting					
Rural	4193 (9.9)	2614 (12.3)	1039 (7.8)	516 (7.4)	24 (3.2)
Urban	29 969 (70.9)	16 347 (77.1)	8566 (64.1)	4516 (64.8)	540 (72.6)
Missing	8121 (19.2)	2241 (10.6)	3757 (28.1)	1943 (27.9)	180 (24.2)

*Includes men who have sex with men, bisexual men and transgender men.
†Includes women who have sex with women, bisexual women and transgender women.
‡First quintile (31.52%), second quintile (40.09%), third quintile (46.27%), fourth quintile (53.98%) and fifth quintile (100%).
BHA, Basic Health Area; LGV, lymphogranuloma venereum; MSM, men who have sex with men; MSW, men who have sex with women; STI, sexually transmitted infection; WSM, women who have sex with men; WSW, women who have sex with women.

occurred in women (table 1). Among all STI cases, 78.6% were reported in individuals below 40 years of age. Chlamydia was reported most frequently among individuals below 30 years of age (66.1%), while syphilis occurred most in those above 30 years of age (77.1%). Among the 15 023 (35.5%) reported STI cases for which information regarding sexual preference was available, half (54.5%) were reported in women who have sex with men (WSM), 21.8% in MSM and 21.0% in MSW (table 1).

When examining the distribution of STI cases according to deprivation index, the highest proportion of cases was seen in less deprived areas, with 24.3% of all cases reported in the first quintile. In more deprived areas (fifth quintile), chlamydia (56%) and gonorrhoea (29%) occurred more frequently than syphilis (14%) and LGV (1%). Data around country of birth and education level were limited due to high rates of missing data (56.6% for country of birth and 76.5% for education level). Nevertheless,

Table 2 Reported STI cases and incidence rates by year in Catalonia, Spain (2017–2019)

	2017		2018		2019		
	Cases, n	Incidence rate per 100 000 population	Cases, n	Incidence rate per 100 000 population	Cases, n	Incidence rate per 100 000 population	P trend
Total							
Total	9687	128.2	13 724	180.6	18 872	245.9	<0.001
Sex							
Female[a]	3362	87.4	5503	142.2	7811	200.0	<0.001
Male[b]	6325	170.5	8221	220.4	11 061	293.4	<0.001
Age, years							
<30[c]	4607	198.4	7181	306.9	10 341	436.5	<0.001
≥30[d]	5080	97.1	6543	124.4	8531	160.8	<0.001
Sex and age							
Male <30 years[e]	2411	202.9	3347	279.5	4668	384.0	<0.001
Male ≥30 years[f]	3914	155.2	4874	192.4	6393	250.3	<0.001
Female <30 years[g]	2196	193.6	3834	335.7	5673	491.9	<0.001
Female ≥30 years[h]	1166	43.0	1669	61.2	2138	77.7	<0.001
STI type (total Catalonia[i])							
Chlamydia	3562	47.1	7240	95.3	10 400	135.5	<0.001
Gonorrhoea	3492	46.2	4088	53.8	5782	75.3	<0.001
Syphilis	2430	32.2	2175	28.6	2370	30.9	0.1572
LGV	203	2.7	221	2.9	320	4.2	<0.001
Health region of residence							
Alt pirineu i Aran[j]	10	13.9	13	18.1	33	45.7	<0.001
Barcelona[k]	8205	165.0	11 475	229.5	15 535	307.8	<0.001
Camp de Tarragona[l]	294	49.1	491	81.3	870	142.2	<0.001
Catalunya Central[m]	358	69.4	484	93.1	583	110.7	<0.001
Girona[n]	564	65.7	893	103.2	1327	151.5	<0.001
Lleida[o]	212	58.9	247	68.5	404	111.5	<0.001
Terres de l'Ebre[p]	44	24.5	121	67.7	120	67.2	<0.001
BHA setting[q]							
Rural	827	NA	1375	NA	1991	NA	NA
Urban	6475	NA	9868	NA	13 626	NA	NA
Missing	2385	NA	2481	NA	3255	NA	NA

Data source for denominators (a-q): the Statistical Institute of Catalonia (IDESCAT), online supplemental table S4.
BHA, Basic Health Area; LGV, lymphogranuloma venereum; NA, not applicable; STI, sexually transmitted infection.

we report that among cases with available information, 72.4% were observed among individuals born in Spain and 85.0% in those with secondary or higher education (online supplemental table S5).

The incidence rate of STI cases was disproportionately higher in Barcelona (83.3%) compared with the other six regions combined (table 1). Barcelona reported the highest incidence rate of STIs, while Alt Pirineu i Aran recorded the lowest consistently throughout the study period (table 2). In 2019, the incidence rate of STIs was 307.8 cases per 100 000 population in Barcelona and 45.7 cases per 100 000 population in Alt Pirineu i Aran. Nevertheless, incidence rates of STIs increased significantly from 2017 to 2019 in all regions, regardless of STI type. Similarly, the large majority of STI cases occurred in urban BHAs (70.9%) throughout the study period.

Factors associated with HIV coinfection among individuals with STIs

In total, 6% of STI episodes affected HIV-positive individuals with a higher proportion of HIV coinfection observed with cases of syphilis and LGV (13% and 25%, respectively) and the lowest with cases of chlamydia (2%) (table 1). Factors associated with HIV coinfection among individuals with STIs in the multivariable analyses are shown in table 3. The likelihood of HIV coinfection was

Table 3 Factors associated with HIV coinfection among individuals diagnosed with STIs in Catalonia, Spain (2017–2019)

Characteristic	Total, n (n=34 600)	HIV-positive, n (n=1376)	OR	95% CI	aOR	95% CI
Sex						
Female	14 938	29	1 (ref)		1 (ref)	
Male	19 662	1347	37.81	26.69 to 55.93	23.69	16.67 to 35.13
Age group, years						
<20	3696	5	1 (ref)		1 (ref)	
20–29	14 826	328	16.70	7.70 to 46.83	8.33	3.82 to 23.40
30–39	8704	595	54.17	25.05 to 151.57	18.58	8.56 to 52.13
40–49	4759	339	56.62	26.09 to 158.78	17.66	8.10 to 49.65
50–59	1748	89	39.60	17.80 to 112.58	13.06	5.84 to 37.24
>60	867	20	17.43	7.04 to 52.50	6.98	2.80 to 21.09
Deprivation index*						
First quintile (least deprived)	7679	501	1 (ref)		1 (ref)	
Second quintile	6098	210	0.51	0.43 to 0.60	0.70	0.59 to 0.83
Third quintile	4163	109	0.38	0.31 to 0.47	0.63	0.50 to 0.78
Fourth quintile	4663	186	0.60	0.50 to 0.71	0.83	0.69 to 1.00
Fifth quintile	6347	175	0.41	0.34 to 0.48	0.60	0.50 to 0.72
Missing	5650	195	0.51	0.43 to 0.60	0.51	0.39 to 0.67
STI episodes (total), n						
1	29 104	791	1 (ref)		1 (ref)	
2–4	5304	529	3.96	3.54 to 4.44	2.69	2.39 to 3.03
5–7	192	56	14.74	10.64 to 20.16	5.96	4.26 to 8.24
BHA setting						
Rural	3699	81	1 (ref)		1 (ref)	
Urban	23 812	1023	2	1.61 to 2.54	1.32	1.04 to 1.69

*First quintile (31.52%), second quintile (40.09%), third quintile (46.27%), fourth quintile (53.98%) and fifth quintile (100%).
aOR, adjusted OR; BHA, Basic Health Area; CI, Confidence Interval; OR, Odds ratio; STI, sexually transmitted infection.;

greater among males (adjusted OR (aOR) 23.69; 95% CI 16.67 to 35.13 compared with females) and in urban BHAs (aOR 1.32; 95% CI 1.04 to 1.69 compared with rural BHAs). All age groups from 20 years and above and having multiple STI episodes were also associated with greater odds of HIV coinfection. BHA deprivation indices beyond the first quintile were associated with lower likelihood of HIV coinfection among individuals with STIs.

Identification and characterisation of the socio-epidemiological clusters of STIs

Of the 373 Catalan BHAs, five (Garraf rural, Polinyà-Sentmenat, Ribes-Olivella, Roquetes-Canyelles and Viladecans 3) were excluded from the K-means clustering analysis because their delimitations and populations changed during the study period. In these five BHAs, 679 episodes were reported during the 3 years of the study period. This fact and having 5773 episodes with no information available about BHA of residence reduced the sample size for the cluster analysis from 42 283 to 35 831 STI cases. Of the 368 BHAs included in the analysis, we identified three distinct clusters (table 4). Among the included BHAs, the incidence rate of STIs in 2017–2019 was 160.6 per 100 000 population per year.

Of the three clusters, the socio-epidemiological characteristics of STI-infected individuals in cluster A most closely resembled that of the total cases reported in the Catalan surveillance system that were included in the cluster analysis. Among the 109 BHAs in cluster A, median age was 31 years compared with 29 years among all reported STI cases, median deprivation index was 31.9 versus 39.8, the proportion of men was 67.4% versus 58.1% and HIV coinfection rate was 8.8% versus 6.1% (table 4).

Cluster B consisted of the largest number of BHAs (251) and had the highest deprivation index (44.9) of all three clusters and compared with the total. The incidence rate of STIs was lower in cluster B compared with that of the total reported cases included in the cluster analysis (136.3 vs 160.6 per 100 000 population), but represented the majority of all reported STI cases (55.7%). STI-infected individuals in cluster

Table 4 Characteristics of socio-epidemiological STI clusters in Catalonia, Spain (2017–2019)

Characteristic	Cluster A	Cluster B	Cluster C	Total*
Demographics				
BHAs, n (%)	109 (29.6)	251 (68.2)	8 (2.2)	368 (100)
Median age, median years (IQR)	31 (18–60)	26 (17–58)	34 (20–58)	29 (17–59)
Median deprivation index (IQR)	31.9 (3.0–58.2)	44.9 (19.2–76.9)	25.6 (10.7–63.6)	39.8 (10.7–72.3)
Annual STI incidence rate (per 100 000 population)	162.0	136.3	721.0	160.6
Reported STI cases, n (%)				
Total	11 527 (32.2)	19 945 (55.7)	4359 (12.2)	35 831 (100)
Sex				
Female	3758 (32.6)	10 566 (53.0)	686 (15.7)	15 010 (41.9)
Male	7769 (67.4)	9379 (47.0)	3673 (84.3)	20 821 (58.1)
Country of birth				
Spain	3920 (34.0)	6910 (34.7)	1325 (30.4)	12 155 (33.9)
Outside Spain	1279 (11.1)	2819 (14.1)	435 (10.0)	4533 (12.7)
Missing	6328 (54.9)	10 216 (51.2)	2599 (59.6)	19 143 (53.4)
Sexual preference				
MSM†	1234 (10.7)	1104 (5.5)	655 (15.0)	2993 (8.4)
MSW	751 (6.5)	2164 (10.9)	64 (1.5)	2979 (8.3)
WSM‡	1440 (12.5)	6066 (30.4)	130 (3.0)	7636 (21.3)
WSW	75 (0.7)	295 (1.5)	6 (0.1)	376 (1.1)
Missing (male)	5784 (50.2)	6111 (30.6)	2954 (67.8)	14 849 (41.4)
Missing (female)	2243 (19.5)	4205 (21.1)	550 (12.6)	6998 (19.5)
STI type				
Gonorrhoea	3448 (29.9)	5240 (26.3)	1448 (33.2)	10 136 (28.3)
Chlamydia	5739 (49.8)	12 314 (61.7)	1649 (37.8)	19 702 (55.0)
Syphilis	2117 (18.4)	2263 (11.4)	1027 (23.6)	5407 (15.1)
LGV	223 (1.9)	128 (0.6)	235 (5.4)	586 (1.6)
Multiple (>1) STI episodes	1600 (13.9)	1524 (7.6)	1048 (24.0)	4172 (11.6)
HIV coinfection	1011 (8.8)	495 (2.5)	686 (15.7)	2192 (6.1)
STI incidence rate categories of BHAs				
First quintile (2.4 per 1000)	710 (6.2)	1820 (9.1)	0	2530 (7.1)
Second quintile (3.6 per 1000)	2136 (18.5)	3359 (16.8)	0	5495 (15.3)
Third quintile (5.2 per 1000)	1377 (12.0)	6588 (33.0)	0	7965 (22.2)
Fourth quintile (9.8 per 1000)	5688 (49.4)	7508 (37.6)	0	13 196 (36.8)
Fifth quintile (42.8 per 1000)	1616 (14.0)	670 (3.4)	4359 (100)	6645 (18.6)
BHA setting				
Rural	797 (6.9)	3158 (15.8)	0	3955 (11.0)
Urban	9461 (82.1)	15 787 (79.2)	4359 (100)	29 607 (82.6)
Missing	1269 (11.0)	1000 (5.0)	0	2269 (6.3)

*Of the 373 Catalan BHAs, five (Garraf rural, Polinyà-Sentmenat, Ribes-Olivella, Roquetes-Canyelles nd Viladecans 3) were excluded from the K-means clustering analysis because their delimitations and populations changed during the study period.
†Includes men who have sex with men, bisexual men and transgender men.
‡Includes women who have sex with women, bisexual women and transgender women.
BHA, Basic Health Area; IQR, Interquartile range; LGV, lymphogranuloma venereum; MSM, men who have sex with men; MSW, men who have sex with women; STI, sexually transmitted infection; WSM, women who have sex with men; WSW, women who have sex with women.

B were the youngest among all groups (26 years) and were predominantly women (53.0%), whereas men represented the majority in all other groups. Compared with the total, cluster B consisted of more rural BHAs (15.8% vs 11.0%) and had a higher proportion of heterosexual men and women (approximately 12% higher) and chlamydia cases (61.7% vs 55.0%). Rates of multiple STI episodes and HIV coinfection in cluster B were the lowest of all three clusters and compared with the total (table 4).

Cluster C consisted of only eight BHAs and had the lowest deprivation index (25.6) among all groups (table 4). The

incidence rate of STIs in cluster C was the highest among all groups (721.0 per 100 000 population), with all cases reported in urban BHAs. STI-infected individuals in cluster C were the oldest among all groups (34 years) and had the highest proportion of MSM. Similar to other clusters and the total reported cases, chlamydia remained the most common STI type; however, cluster C was characterised by higher rates of gonorrhoea (33.2%), syphilis (23.6%), LGV (5.4%), multiple STI episodes (24.0%) and HIV coinfection (15.7%).

Almost 60% of STI cases in cluster B occurred in BHAs in the three lowest quintiles of STI incidence rates, while more than 60% in cluster A occurred in areas of high STI incidence rates (fourth and fifth quintiles). All 4359 STI cases in cluster C were reported in BHAs in the highest quintile of STI incidence rate. This correlated well with the fact the number of STI cases per BHA was higher in clusters A and C (105.8 and 544.9 cases per BHA, respectively) than in the total (97.4 cases per BHA), which indicates higher proportion of high incidence rates (table 4 and figure 1).

DISCUSSION

Our findings revealed that the incidence of STIs in Catalonia almost doubled from 2017 to 2019, primarily driven

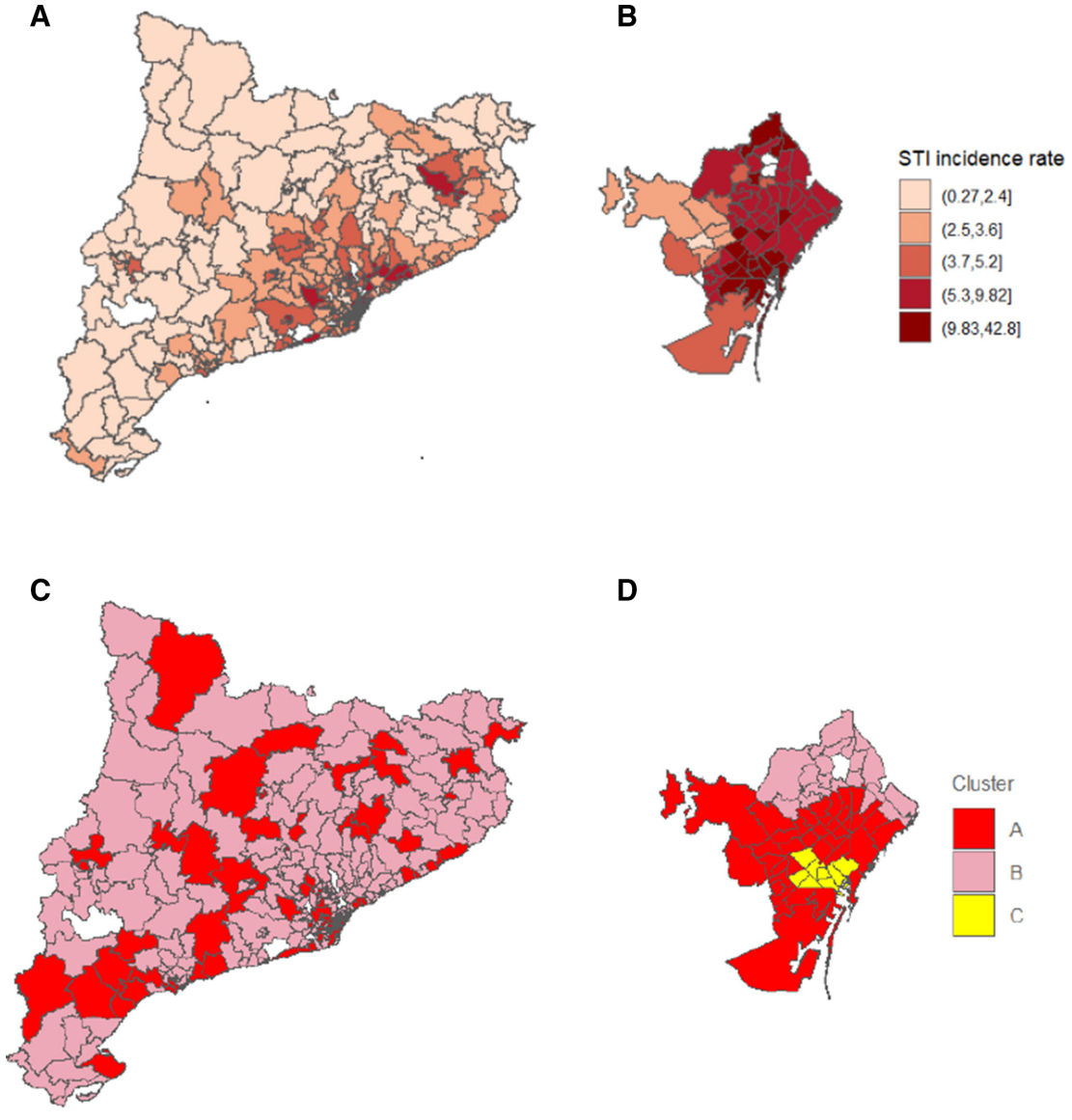

Figure 1 Incidence rates (per 1000 population) and socio-epidemiological clusters of STIs by BHA during 2017–2019. (A) STI incidence rates in Catalonia; (B) STI incidence rates in Barcelona city*; (C) STI socio-epidemiological clusters in Catalonia and (D) STI socio-epidemiological clusters in Barcelona city*. *Health Regions were used as a bigger unit of analysis than BHA. The municipality of Barcelona is shown to enhance the visualisation of cluster C. From a total of 373 Catalan BHA, five (Garraf rural, Polinyà-Sentmenat, Ribes-Olivella. Roquetes-Canyelles and Viladecans 3) were excluded from the K-means clustering analysis because their delimitations and populations changed during the study period. BHA, Basic Health Area; STIs, sexually transmitted infections.

by the increase in cases among young adults (under 30 years) and in cases of chlamydia (particularly in women) and gonorrhoea. In 2017–2019, the majority of STI cases occurred also in individuals below the age of 30 years, and those living in urban and less deprived areas, with most cases reported in Barcelona. The identification and characterisation of socio-epidemiological clusters of STI showed that young women living in rural and more deprived areas were more likely to be affected by chlamydia. Furthermore, MSM living in urban and less deprived areas showed, more frequently than other population groups, higher STI incidence rates, more multiple STI episodes and higher percentages of HIV coinfection. Similarly, the factors associated with HIV coinfection were being men, older than 20 years old, living in urban and less deprived areas and having multiple STI episodes.

After a long period of continuous reduction of STI incidence in Western countries, which coincided with the beginning and hardest times of the HIV epidemic from the 1980s to 2010s, many countries including the USA and European countries are recently reporting an ongoing re-emergence of STIs.[3–6] The rise in STI cases has been partially attributed to enhancement of surveillance systems and the introduction of improved diagnostic tools in recent years.[10] Other contributing factors, described mostly among MSM, include the use of HIV pre-exposure prophylaxis, the use of recreational drugs for sex, substance and/or alcohol abuse and widespread use of the internet and other technologies to seek sexual partners.[20–22]

Chlamydia has been reported more frequently in WSM, while syphilis, gonorrhoea and LGV were more common in MSW and MSM.[3–9] Similarly, in our study, we found different epidemiological characteristics for each STI type. Chlamydia was more common in women, mostly in WSM, with a large majority occurring in individuals below the age of 30 years. Gonorrhoea, syphilis and LGV were substantially more frequent in men, specifically among MSM, and showed higher percentages of reinfections and HIV coinfections than chlamydia. Most STI cases were observed in Spanish-born individuals and among those with secondary or higher education levels, although these findings should be interpreted with caution because of the high proportion of missing data for sexual preference and education level. Our findings are consistent with earlier studies and reports of STIs in Catalonia in 2007–2015,[12] 2012–2017[23] and 2018–2019,[9] showing a proportionally higher increase in young adults, mostly women, especially for chlamydia but also for gonorrhoea. Our findings are also consistent with that of a previous study among residents of Barcelona showing that STIs are becoming more prevalent in individuals with favourable socioeconomic status and education levels.[24]

Consistent with previous data,[12] we found that male sex, age above 20 years (particularly 30–60 years), living in urban or less deprived areas, and having multiple STI episodes were associated with an increased risk of HIV coinfection. STIs and HIV have been described as synergic infections and should be viewed as a syndemic.[25] The WHO and other public health agencies have emphasised the importance of integrating surveillance of STIs, HIV and even viral hepatitis, and strengthening understanding of determinants of these infections by linking biological and behavioural surveillance, to enhance the identification and characterisation of populations at increased risk of infection.[10 25] Sociodemographic and socioeconomic are increasingly being established as more important risk factors of STI acquisition than individual behaviours, particularly among women from disadvantaged groups.[26 27]

The k-means clustering methodology is a machine learning approach that has proven its utility and potential in classifying and grouping health-related outcomes. It has been used in the field of bipolar disorder to define cluster-based disease severity using heterogeneous variables such as sociodemographic, clinical, cognitive, vital signs and laboratory parameters.[28] More recently, its potential to monitor and group SARS-CoV-2 prevalence by magnitude and trends (higher, medium and lower) at a regional level in Italy has been described.[29] Identification of these ‘clusters of characteristics’ may be useful, in their specific context, to better detect and characterise case profiles by site or geographical area, which could ultimately lead to better-designed interventions to improve health outcomes. In a recent study of STI risk among MSMs, hierarchical cluster analysis, another machine learning methodology, identified factors other than behaviour, such as sexual networks and risk perception, that influence the vulnerability to STIs and HIV infections.[30] To the best of our knowledge, this current study is the first to apply the k-means clustering methodology to identify and characterise socio-epidemiological clusters of STI.

A key limitation of this study is the high proportion of missing data around sociodemographic and lifestyle characteristics, a common phenomenon in population-based epidemiological studies where questionnaires are used. This may have potentially introduced information bias or inaccurate representation of the true situation when describing high-risk populations. Although not formally assessed, we classify these missing data as missing completely at random due to time constraints in completion of the epidemiological questionnaires by surveillance officers and healthcare professionals who notified the diseases to the surveillance systems. Nonetheless, our findings are similar to those reported in previous analyses.[3–6 9 12 24] The age category above 60 years old may contribute to residual cofounding although the risk is minimal because it is the age group with the smallest sample size and the range is larger than for other age categories. Categorisation of the deprivation indices by quintiles could have diluted the findings if deprivation was a strong confounder or unevenly distributed, although we do not believe either event to be the case in our analysis.

A strength of our study is the inclusion of ecological variables of socioeconomic status which are highly

relevant and pertinent for describing groups at increased risk of STIs. We believe that the most valuable outcome of our study is that it shows the utility of complementing traditional epidemiological analyses with new methodologies, in this case, a machine learning approach, to combine heterogeneous data sources. This would allow identification and characterisation of target populations at increased risk of STIs to design more efficient measures to prevent and control STIs and HIV infection at a small health area level.

In conclusion, consistent with other European countries, our study found that STIs increased at an alarming rate during 2017 to 2019 in Catalonia, Spain, and continues to be a worrisome public health concern. The STI epidemic is both an issue of the health sector, and it also poses a threat to the broader global development framework and agenda. While declines in HIV infection has been observed in the last decade in Catalonia, as in many other regions in Europe, primarily due to the success of wider and earlier use of antiretroviral therapies, STI rates have been increasing dramatically, both among the MSM population, and also in heterosexual women and young adults. We found that young women living in rural and deprived areas were more likely to be affected by chlamydia, while MSM living in urban and less deprived areas had higher overall STI incidence rates, multiple STI episodes and greater likelihood of HIV coinfection. Preventative strategies must consider these populations priority targets and take into account structural social determinants identified as crucial in our analysis. Our findings suggest that monitoring the STI epidemic in accordance with determinants of health and designing intervention programmes targeted at the local context would be of paramount importance rather than using national or regional prevalence as the key monitoring variable.

Author affiliations
[1]Centre of Epidemiological Studies of Sexually Transmitted Disease and AIDS in Catalonia (CEEISCAT), Department of Health, Generalitat of Catalonia, Badalona, Spain
[2]Pompeu Fabra University (UPF), Barcelona, Spain
[3]Epidemiology Department, Epiconcept, Paris, France
[4]Fundació Institut d'Investigació Germans Trias i Pujol (IGTP), Badalona, Spain
[5]Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[6]Department of Paediatrics, Obstetrics and Gynecology and Preventive Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[7]Epidemiology Service, Public Health Agency of Barcelona, Barcelona, Spain
[8]Epidemiological Surveillance and Response to Public Health Emergencies Service in Tarragona, Agency of Public Health of Catalonia, Generalitat of Catalonia, Tarragona, Spain

Acknowledgements We thank all healthcare professionals working in STI/HIV surveillance, prevention and control in Catalonia who enable case detection, diagnosis and treatment, as well as the notification and information gathering for the epidemiological questionnaires. We thank Stefanie Chuah for her valuable support in editing the manuscript.

Collaborators The Catalan HIV and STI Surveillance Group: A Sentís, E López, V Gonzalez, R Lugo, MP Bonamusa, J Reyes, J Casabona (Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya); P Garcia de Olalla, Lilas Mercuriali, E Masdeu, M Ros, C Rius (Servei d'Epidemiologia de l'Agència de Salut Pública de Barcelona); M Company, M Danés, N Camps (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Girona); RM Vileu, G Ferrús, N Borrell, S Minguell (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Tarragona); J Ferràs (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Terres de l'Ebre); I Parrón (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública al Barcelonès Nord i Maresme); I Mòdol, A Martinez, P Godoy (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Lleida); MA Tarrès, J Pérez, M Boldú, I Barrabeig (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Barcelona Sud); E Donate, L Clotet, MR Sala (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública al Vallès Occidental i Vallès Oriental); M Carol, V Guadalupe-Fernández (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Catalunya Central) and J Mendioroz, P Ciruela, G Carmona, R Mansilla, JL Martínez, S Hernández (Subdirecció General de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública, Agència de Salut Pública de Catalunya).

Contributors AS conceptualised and designed the study. MM-F cleaned the database, MM-F, LE-C and YD performed the statistical and cluster analysis. AS, EL-C and DKN reviewed scientific literature. AS, JMR-U and JC drafted the manuscript and AS, EL-C, PGdO, LM, NB, JMR-U and JC interpreted the results. All authors critically reviewed the manuscript and approved the final version to be published. AS is the author acting as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the expression of any opinion whatsoever on the part of BMJ concerning the legal status of any country, territory, jurisdiction or area or of its authorities. Any such expression remains solely that of the relevant source and is not endorsed by BMJ. Maps are provided without any warranty of any kind, either express or implied.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Alexis Sentís http://orcid.org/0000-0002-8132-5645
Juliana Reyes-Urueña http://orcid.org/0000-0002-3122-6518

REFERENCES

1 Rowley J, Vander Hoorn S, Korenromp E, *et al*. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ* 2019;97:548–62.
2 WHO Department of Reproductive Health and Research. Report on global sexually transmitted infection surveillance, 2018. Available: https://apps.who.int/iris/bitstream/handle/10665/277258/9789241565691-eng.pdf?ua=1 [Accessed 8 Jan 2021].
3 European Centre for Disease Prevention and Control. Chlamydia infection. annual epidemiological report for 2018. Stockholm: ECDC, 2020. Available: https://www.ecdc.europa.eu/sites/default/files/documents/AER-for-2018-STI-chlamydia.pdf [Accessed 7 Aug 2021].

4 European Centre for Disease Prevention and Control. Gonorrhoea. annual epidemiological report for 2018. Stockholm: ECDC, 2020. Available: https://www.ecdc.europa.eu/sites/default/files/documents/gonorrhoea-annual-epidemiological-report-2018.pdf [Accessed 7 Aug 2021].
5 European Centre for Disease Prevention and Control. Syphilis. annual epidemiological report for 2018. Stockholm: ECDC, 2020. Available: https://www.ecdc.europa.eu/sites/default/files/documents/syphilis-aer-2018.pdf [Accessed 7 Aug 2021].
6 European Centre for Disease Prevention and Control. Lymphogranuloma venereum. annual epidemiological report for 2018. Stockholm: ECDC, 2020. Available: https://www.ecdc.europa.eu/sites/default/files/documents/lymphogranuloma-venereum-aer-2018.pdf [Accessed 7 Aug 2021].
7 Área de vigilancia del VIH y conductas de riesgo. Vigilancia epidemiológica de las infecciones de transmisión sexual, 2017. Madrid: Centro Nacional de Epidemiología, Instituto de Salud Carlos III/Plan Nacional sobre el Sida - Dirección General de Salud Pública, 2019. Available: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/Vigilancia_ITS_1995_2017_def.pdf [Accessed 27 Mar 2021].
8 Área de vigilancia del VIH y conductas de riesgo. Vigilancia epidemiológica de las infecciones de transmisión sexual, 1995-2010. Madrid: Centro Nacional de Epidemiología, Instituto de Salud Carlos III/Plan Nacional sobre el Sida - Dirección General de Salud Pública, 2012. Available: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/VigilanciaITS1995_2010.pdf [Accessed 27 Mar 2021].
9 Centre d'Estudis Epidemiològics sobres les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT). Vigilància epidemiològica de les Infeccions de Transmissió Sexual (ITS) a Catalunya. Informe anual 2019. Badalona, Spain, 2020. Available: https://canalsalut.gencat.cat/web/.content/_A-Z/S/sida/enllasos/anual_ITS.pdf [Accessed 27 Mar 2021].
10 Taylor MM, Wi TE. Transforming and integrating STI surveillance to enhance global advocacy and investment in STI control. *J Int AIDS Soc* 2019;22 Suppl 6:25361.
11 Centers for Disease Control and Prevention. HIV/AIDS & STDs. Available: https://www.cdc.gov/std/hiv/default.htm [Accessed 22 Feb 2021].
12 Sentís A, Martin-Sanchez M, Arando M, *et al*. Sexually transmitted infections in young people and factors associated with HIV coinfection: an observational study in a large City. *BMJ Open* 2019;9:e027245.
13 Le Polain De Waroux O, Harris RJ, Hughes G, *et al*. The epidemiology of gonorrhoea in London: a Bayesian spatial modelling approach. *Epidemiol Infect* 2014;142:211–20.
14 Gesink D, Wang S, Norwood T, *et al*. Spatial epidemiology of the syphilis epidemic in Toronto, Canada. *Sex Transm Dis* 2014;41:637–48.
15 Jain AK. Data clustering: 50 years beyond k-means. *Pattern Recognit Lett* 2010;31:651–66.
16 Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT). SIVES 2015 - Sistema Integrat de Vigilància Epidemiològica de la SIDA/VIH/ITS a Catalunya. Barcelona, Spain, 2015. Available: https://scientiasalut.gencat.cat/bitstream/handle/11351/3418/informe_SIVES_2015_informe_epidemiologic_CEEISCAT_2015.pdf.pdf?sequence=1&isAllowed=y [Accessed 27 Mar 2021].
17 Notifiable diseases and epidemic outbreaks. Department of health, public health agency of Catalonia, Generalitat de Catalunya, 2016. Available: https://canalsalut.gencat.cat/ca/professionals/vigilancia-epidemiologica/malalties-de-declaracio-obligatoria-i-brots-epidemics/ [Accessed 20 Jun 2021].
18 European Centre for Disease Prevention and Control. Eu case definitions, 2018. Available: https://www.ecdc.europa.eu/en/surveillance-and-disease-data/eu-case-definitions [Accessed 7 Aug 2020].
19 Agency for Health Quality and Assessment of Catalonia. Nou indicador socioeconòmic per al finançament de les ABS. Observatori del Sistema de Salut de Catalunya, 2017. Available: http://observatorisalut.gencat.cat/ca/observatori-desigualtats-salut/indicador_socioeconomic_2015/ [Accessed 6 Aug 2020].
20 Folch C, Esteve A, Zaragoza K, *et al*. Correlates of intensive alcohol and drug use in men who have sex with men in Catalonia, Spain. *Eur J Public Health* 2010;20:139–45.
21 Saberi P, Neilands TB, Lally MA, *et al*. The association between use of online social networks to find sex partners and sexually transmitted infection diagnosis among young men who have sex with men and transgender women living with HIV. *J Int Assoc Provid AIDS Care* 2019;18:232595821986732–11.
22 Jansen K, Steffen G, Potthoff A, *et al*. STI in times of PreP: high prevalence of Chlamydia, gonorrhea, and Mycoplasma at different anatomic sites in men who have sex with men in Germany. *BMC Infect Dis* 2020;20:110.
23 Vives N, Garcia de Olalla P, González V, *et al*. Recent trends in sexually transmitted infections among adolescents, Catalonia, Spain, 2012-2017. *Int J STD AIDS* 2020;31:1047–54.
24 Martí-Pastor M, García de Olalla P, Barberá M-J, *et al*. Epidemiology of infections by HIV, syphilis, gonorrhea and lymphogranuloma venereum in Barcelona City: a population-based incidence study. *BMC Public Health* 2015;15:1015.
25 Murti M, Wong J, Whelan M, *et al*. The need for integrated public health surveillance to address sexually transmitted and blood-borne syndemics. *Can Commun Dis Rep* 2019;45:63–6.
26 Hill AV, De Genna NM, Perez-Patron MJ, *et al*. Identifying Syndemics for sexually transmitted infections among young adults in the United States: a latent class analysis. *J Adolesc Health* 2019;64:319–26.
27 Jagadesh S, Combe M, Couppié P. Mapping priority neighborhoods: a novel approach to cluster identication in HIV/AIDS population. *Res Sq* 2020.
28 Fuente-Tomas Ldela, Arranz B, Safont G, *et al*. Classification of patients with bipolar disorder using k-means clustering. *PLoS One* 2019;14:e0210314.
29 Maugeri A, Barchitta M, Agodi A. A clustering approach to classify Italian regions and provinces based on prevalence and trend of sars-cov-2 cases. *Int J Environ Res Public Health* 2020;17:5286–14.
30 Blondeel K, Dias S, Furegato M, *et al*. Sexual behaviour patterns and STI risk: results of a cluster analysis among men who have sex with men in Portugal. *BMJ Open* 2021;11:33290.

4.3. Estudio III: The impact of the COVID-19 pandemic on Sexually Transmitted Infections surveillance data: incidence drop or artefact?

Sentís, A., Prats-Uribe, A., López-Corbeto, E. et al. The impact of the COVID-19 pandemic on Sexually Transmitted Infections surveillance data: incidence drop or artefact? BMC Public Health 21, 1637 (2021). https://doi.org/10.1186/s12889-021-11630-x

URL: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-11630-x

Sentís et al. BMC Public Health (2021) 21:1637
https://doi.org/10.1186/s12889-021-11630-x

BMC Public Health

RESEARCH ARTICLE Open Access

The impact of the COVID-19 pandemic on Sexually Transmitted Infections surveillance data: incidence drop or artefact?

Alexis Sentís[1,2,3,4†], Albert Prats-Uribe[5†], Evelin López-Corbeto[1,2], Marcos Montoro-Fernandez[1], Daniel Kwakye Nomah[1,6], Patrícia Garcia de Olalla[2,7], Lilas Mercuriali[7], Núria Borrell[8], Víctor Guadalupe-Fernández[9], Juliana Reyes-Urueña[1,2*], Jordi Casabona[1,2,6] and Catalan HIV and STI Surveillance Group

Abstract

Background: Before the COVID-19 pandemic, Sexually transmitted infections (STIs) were increasing in Europe, and Spain and Catalonia were not an exception. Catalonia has been one of the regions with the highest number of COVID-19 confirmed cases in Spain. The objective of this study was to estimate the magnitude of the decline, due to the COVID-19 pandemic, in the number of STI confirmed cases in Catalonia during the lockdown and de-escalation phases.

Methods: Interrupted time series analysis was performed to estimate the magnitude of decline in the number of STI reported confirmed cases - chlamydia, gonorrhoea, syphilis, and lymphogranuloma venereum- in Catalonia since lockdown with historical data, from March 13th to August 1st 2020, comparing the observed with the expected values.

Results: We found that since the start of COVID-19 pandemic the number of STI reported cases was 51% less than expected, reaching an average of 56% during lockdown (50% and 45% during de-escalation and new normality) with a maximum decrease of 72% for chlamydia and minimum of 22% for syphilis. Our results indicate that fewer STIs were reported in females, people living in more deprived areas, people with no previous STI episodes during the last three years, and in the HIV negative.

Conclusions: The STI notification sharp decline was maintained almost five months after lockdown started, well into the new normality. This fact can hardly be explained without significant underdiagnosis and underreporting. There is an urgent need to strengthen STI/HIV diagnostic programs and services, as well as surveillance, as the pandemic could be concealing the real size of the already described re-emergence of STIs in most of the European countries.

Keywords: Public health, Surveillance, communicable diseases, Sexually transmitted infections, Interrupted time series, COVID-19, Lockdown, Trends, Epidemiology

* Correspondence: jmreyes@iconcologia.net
†Alexis Sentís and Albert Prats-Uribe contributed equally to this work.
[1]Centre of epidemiological studies on sexually transmitted infections and AIDS of Catalonia (CEEISCAT). Department of Health. Generalitat de Catalonia, Badalona, Spain
[2]Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
Full list of author information is available at the end of the article

Background

Before the coronavirus disease 2019 (COVID-19) pandemic, the number of new cases of mandatory notifiable sexually transmitted infections (STIs) was increasing in many European countries. Catalonia also had a pronounced rise of chlamydia, gonorrhoea, syphilis and lymphogranuloma venereum (LGV). For the last five years, Catalonia presented the highest incidence rates of Spain in all mandatory notifiable STIs, with a 20% annual increase. The rates were highest among males who have sex with males (MSM) and young adults, mostly females aged between 20 to 24 [1]. STIs represent one of the highest burdens of disease in adolescents and young females, leading to miscarriage, pelvic inflammatory disease, and increased risk to acquire human immunodeficiency virus (HIV) [2–4]. According to data published by the Government of Catalonia, the COVID-19 pandemic hit Catalonia harshly, with 676.863 confirmed cases and 22.124 deaths by May 24th, 2021, with one of the highest number of confirmed cases in Spain [5, 6]. On March 13, the Spanish government announced a countrywide lockdown, with a mandatory stay at home ordinance, with some exceptions, such as purchasing food or medicine, going to work or attending to emergencies. Visiting intimate partners were not included in the exceptions [7]. The combined effects of the lockdown and the unprecedented pressure on health systems might have reduced the capacity to detect STIs, potentially leading to increased transmission and more severe sequelae, or a decrease in the incidence because of less exposure. The objective of this study was to estimate the magnitude of the decline, due to the COVID-19 pandemic, in the number of STI reported confirmed cases in Catalonia during the lockdown and de-escalation phases comparing the observed and expected values.

Methods

The Catalan HIV/STI surveillance systems

We used epidemiological data from all STI confirmed cases reported to the Catalan HIV/STI Registry of Catalonia [8] through the Epidemiological Repository of Catalonia (REC), an electronic database that collects data reported from health care professionals and laboratories by means of standardized notification forms and epidemiological questionnaires, both electronically or in paper. According to the mandatory notification of diseases and outbreaks Catalan regulation (Health Department of Government of Catalonia article 13 of law 67/2010, 25 May 2010), nominal notification of syphilis, gonorrhoea, and LGV cases has been mandatory since 2007 and chlamydia since 2015; the notification of HIV cases was voluntary between 2001 and 2010 when it also became mandatory and nominal. The European Centre for Disease Prevention and Control (ECDC) guidelines are used for case definition criteria and all reported cases are reviewed by epidemiologists from the Epidemiological Surveillance Network of Catalonia (XVEC) to ensure completeness and validity of the data.

Study variables

Sex, age group, and country of birth were collected from REC. Deprivation index (calculated by the Agency of Health Quality and Assessment of Catalonia) was based on the patient area of residence and categorized in quintiles, with the first quintile being the least deprived [9]. Multiple episodes by the same STI in the same individual were considered reinfections when evidence of it, proper treatment, and minimum length of time between reports existed. Time periods were defined according to specific STI treatment duration and follow up recommendations, being 364, 29, 119 and 119 days respectively for syphilis, gonorrhoea, chlamydia and LGV [10]. HIV status was confirmed checking the HIV status among individuals who had one single or more STI episodes during the study period within the Catalan HIV/STI Registry of Catalonia where previous and simultaneous HIV coinfections can be identified.

Interrupted time series and data analysis

We analysed STI reported cases between August 1st 2017 and August 1st 2020 in Catalonia. We have included three years of follow-up not only in order to estimate the reported cases we would have had from lockdown - from March 13th to August 1st, 2020- but also to capture potential seasonal or cyclic changing patterns. For each of the mentioned variables, among the STI reported confirmed cases, the total number and its distribution in the respective categories were calculated, before lockdown, during lockdown (March 13th to April 27th), on de-escalation phases (April 28th until June 21st), and during the new normality phase (since June 22nd). The main objective of the de-escalation plan was to ensure maintaining the protection of public health while gradually recovering the common daily life and economic activities after the lockdown. This transition to a “new normality” was gradual, asymmetrical, and coordinated with the autonomous communities [11]. We used these dates as change points for an interrupted time series (ITS) analysis of daily STI reported cases (overall and separately for each of them). Reported cases were modelled as autoregressive integrated moving average (ARIMA) processes to estimate expected number of STI reported cases in each specific study period since lockdown based on pre-lockdown data. We calculated the overall drop in number of STI reported cases, to estimate the magnitude of the decline in STI reported cases with historical data comparing the observed and expected values.

Results

When comparing with pre-lockdown period's data, the STI reported cases per day decreased by almost 50% in all three COVID-19 related study periods: during lockdown, de-escalation and new normality periods (from 43.8 STI reported cases/day pre-lockdown to 22.2, 23.4 and 27.9 respectively). The proportion of syphilis and LGV slightly increased (from 15% and 1.7% pre-lockdown) among the overall STI reported cases in all three COVID-19 related study periods (respectively in

Table 1 Epidemiological characteristics of the STI reported confirmed cases during the different study periods[a] in Catalonia, August 1st 2017 to August 1st 2020

	Total		Pre-lockdown		Lockdown		De-escalation Phases		New Normality	
Number of reported cases	***N* = 45,181**		***N* = 41,802**		***N* = 997**		***N* = 1266**		***N* = 1116**	
Days,n°reported cases/days	**1096**	**41.2**	**954**	**43.8**	**45**	**22.2**	**54**	**23.4**	**40**	**27.9**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
STI										
Chlamydia	23,095	51.1	21,463	51.3	472	47.3	611	48.3	549	49.1
Gonorrhoea	14,406	31.9	13,340	31.9	329	33.0	398	31.4	339	30.3
LGV[b]	815	1.8	723	1.7	28	2.8	29	2.3	35	3.1
Syphilis	6865	15.2	6276	15.0	168	16.9	228	18.0	193	17.3
Sex										
Females	17,860	39.5	16,679	39.9	340	34.1	453	35.8	388	34.7
Males	27,321	60.5	25,123	60.1	657	65.9	813	64.2	728	65.2
Age (mean, SD[c])	31.7	11.1	31.7	11.1	31.9	10.6	32.5	11.9	32.3	11.4
Age group										
< 20	5776	12.8	5384	12.9	113	11.3	154	12.2	125	11.2
20 to 29	17,334	38.4	16,052	38.4	376	37.7	477	37.7	429	38.4
30 to 39	12,076	26.7	11,180	26.7	282	28.3	321	25.4	293	26.3
40 to 49	6702	14.8	6177	14.8	155	15.5	198	15.6	172	15.4
50 to 59	2334	5.20	2124	5.1	56	5.6	83	6.6	71	6.4
≥ 60	959	2.1	885	2.1	15	1.5	33	2.6	26	2.3
Deprivation index										
First quintile	11,221	24.8	10,288	24.6	286	28.70	344	27.20	303	27.2
Second quintile	8133	18.0	7436	17.8	214	21.50	240	19.00	243	21.8
Third quintile	5329	11.8	4915	11.8	135	13.50	155	12.20	124	11.1
Fourth quintile	6150	13.6	5717	13.7	106	10.60	193	15.20	134	12.0
Fifth quintile	8246	18.3	7618	18.2	185	18.60	236	18.60	207	18.5
Missing	6102	13.5	5828	13.9	71	7.10	98	7.70	105	9.4
Country of birth										
Spain	13,861	30.7	13,316	31.9	136	13.6	207	16.4	202	18.1
Others	4913	10.9	4785	11.4	24	2.4	56	4.4	48	4.3
Missing	26,407	58.4	23,701	56.7	837	84.0	1003	79.2	866	77.6
Reinfeccion										
No	39,619	87.7	36,893	88.3	838	84.1	1019	80.5	869	77.9
Yes	5562	12.3	4909	11.7	159	15.9	247	19.5	247	22.1
HIV status										
Negative	42,809	94.8	39,628	94.8	937	94.0	1196	94.5	1048	93.9
Positive	2372	5.2	2174	5.2	60	6.0	70	5.5	68	6.1

[a]Pre-lockdown: from August 1st 2017 to March 12th 2020, lockdown: from March 13th 2020 to April 27th2020, de-escalation phases: from April 28th 2020 to June 21st 2020, new normality: from June 22nd 2020 to August 1st 2020;
[b]LGV: Lymphogranuloma venereum;
[c]SD: Standard deviation

the three study periods to 16.9%, 18%, and 17.3% for syphilis and 2.8%, 2.3% and 3.1% for LGV) meanwhile gonorrhoea and chlamydia had a small decrease (from 31.9% and 51.3% pre-lockdown to 30.3% and 49.1% in the "new normality" period for gonorrhoea and for chlamydia respectively). In addition, the proportion of STI reported cases from females was reduced when compared to males (approximately 5% between pre-lockdown and new normality periods). STI reported cases that came from areas with higher socioeconomic status increased by 5% over post-lockdown periods (see Table 1). The proportion of missing data for country of birth was high during all the different study periods and increased by 25% during lockdown (from 56.7% missing values in pre-lockdown data to 84% during lockdown). The proportion of STI reported cases in people coinfected by HIV, as well as the proportions of STI reported cases considered as reinfections, increased from pre-lockdown to new normality periods (5.2% to 6.1% and 11.7% to 22.2%, respectively). The proportion of reported cases in each age groups was similar when comparing the study periods with previous or historical data (see Table 1).

In the ITS (see Table 2, Fig. 1, and supplemental material, figure S1–S4), we observed how the number of all STI reported cases were only 49% of the expected number (decrease of – 51%, confidence interval (CI): – 59% to – 38%), based on pre-lockdown data (since August 1st 2020), with variations in the different study periods; being only 44% of the expected reported cases during lockdown (decrease of – 56%, CI: – 63% to – 46%) and slowly increasing to 55% of the expected since the new normality began on June 22nd (decrease of – 45%, CI: – 54% to – 30%). When analysing the results by type of infection we found that chlamydia's reported cases which represent more than 50% of all STI reported cases, had the highest decrease in notification over post-lockdown periods, with observed reported cases reaching only 28% of

Table 2 Comparing observed and expected number of STI reported confirmed cases during the different study periods[a] in Catalonia, August 1st 2017 to August 1st 2020

	Periods	observed	expected	upper CI[b]	lower CI[b]	difference		upper CI[b]		lower CI[b]	
All STIs	**Pre-lockdown**	41,814									
	Lockdown	997	2264	2681	1846	– 1267	–56%	– 1684	–63%	– 849	–46%
	De-escalation	1266	2546	3078	2015	– 1280	–50%	– 1812	–59%	– 749	–37%
	New Normality	1116	2026	2446	1606	– 910	–45%	– 1330	–54%	– 490	–30%
	Total	3379	6836	8205	5467	– 3457	–51%	– 4826	–59%	– 2088	–38%
Chlamydia	**Pre-lockdown**	21,463									
	Lockdown	472	1607	1731	1483	–1135	–71%	– 1259	–73%	– 1011	–68%
	De-escalation	611	2376	2535	2216	– 1765	–74%	– 1924	–76%	– 1605	–72%
	New Normality	549	1870	1997	1743	– 1321	–71%	– 1448	–73%	– 1194	–68%
	Total	1632	5853	6264	5442	– 4221	–72%	– 4632	–74%	– 3810	–70%
Gonorrhoea	**Pre-lockdown**	13,340									
	Lockdown	329	747	889	605	–418	–56%	–560	–63%	–276	–46%
	De-escalation	398	857	1037	678	– 459	–54%	– 639	–62%	–280	–41%
	New Normality	339	670	812	529	– 331	–49%	– 473	– 58%	–190	–36%
	Total	1066	2275	2738	1812	– 1209	–53%	– 1672	–61%	– 746	– 41%
Syphilis	**Pre-lockdown**	6276									
	Lockdown	168	250	337	164	–82	–33%	– 169	–50%	4	2%
	De-escalation	228	284	392	177	–56	–20%	– 164	–42%	51	29%
	New Normality	193	218	302	134	–25	–11%	–109	–36%	59	44%
	Total	589	753	1030	475	–164	–22%	– 441	–43%	114	24%
LGV[c]	**Pre-lockdown**	723									
	Lockdown	28	54	62	47	–26	–48%	–34	–55%	–19	–40%
	De-escalation	29	80	89	71	–51	–64%	–60	–67%	–42	–59%
	New Normality	35	56	63	49	–21	–38%	–28	–45%	–14	–29%
	Total	92	191	214	167	–99	–52%	– 122	–57%	–75	–45%

[a]Pre-lockdown: from August 1st 2017 to March 12th 2020, lockdown: from March 13th 2020 to April 27th2020, de-escalation phases: from April 28th 2020 to June 21st 2020, new normality: from June 22nd 2020 to August 1st 2020; bCI, confidence interval; cLGV, lymphogranuloma venereum

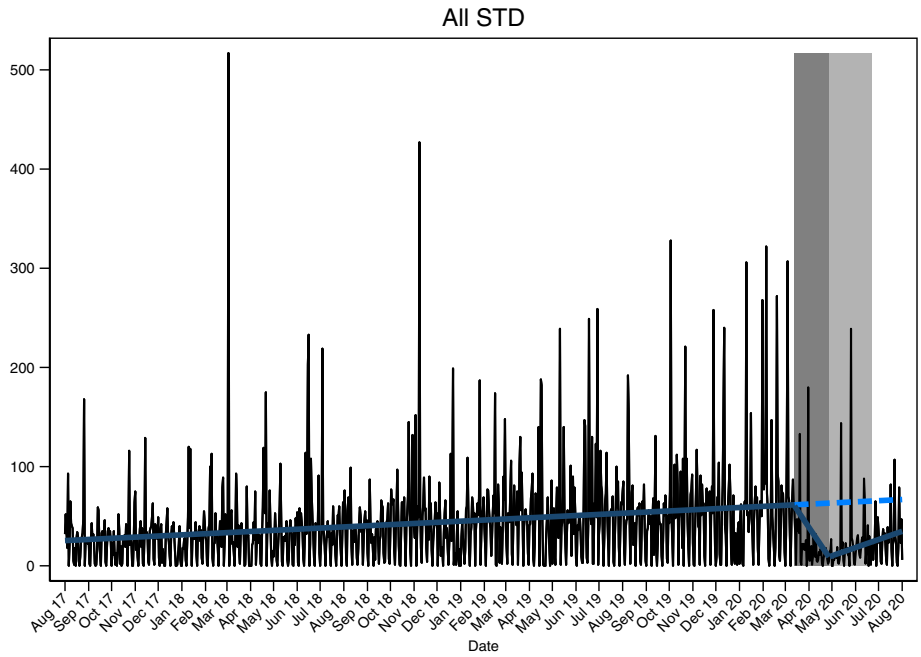

Fig. 1 Observed and expected time series trends of daily STI reported confirmed cases in Catalonia during the COVID-19 pandemic, August 1st 2017 - August 1st 2020 (dark grey: lockdown, light grey: de-escalation phases)

the expected values. Conversely, we observed that the decrease of syphilis reported cases was lower, with observed reported cases reaching 78% of those expected (see Table 2 and supplemental material, figure S1 and figure S3).

Discussion

We found that since the start of COVID-19 pandemic the number of STI reported cases was 51% less than expected, reaching an average of 56% during lockdown (50 and 45% during de-escalation and new normality) with a maximum decrease of 72% for chlamydia and minimum of 22% for syphilis. Our results indicate that STIs were less reported in females, people living in more deprived areas, people with no previous STI episodes during the last three years, and without HIV infection.

We hypothesize that the decline in the number of STI reported cases was higher in females based on the annual STI notification rates in the region where chlamydia has been usually higher among females and syphilis among males [1]. STIs, including chlamydia infection are predominantly asymptomatic in females, and are detected primarily through screening. During lockdown, mobility restrictions may have decreased healthcare seeking behaviour in asymptomatic individuals with high-risk exposures. This decrease could be even greater for people living in more deprived areas. Additionally, people who already visited sexual health care for previous STI episodes in the last three years, or HIV positive are more likely to seek health care.

To the best of our knowledge, few analysis have described the estimated magnitude and impact of the COVID-19 pandemic on the expected number of STIs compared to the most recent historical data. Although few articles have analysed STI incidences during lockdown, some authors argue that the plausible decrease of sexually relations during the COVID-19 pandemic may partially explain the apparent drop in the number of STI incidence [12–14]. In spite of these, different stakeholders have started raising awareness about disruptions in sexual health services including STI and HIV testing and detection [15, 16]. Moreover, it has been estimated that in the Atlanta (State of Georgia, United States), if sexual behaviour rebounds while service interruption persists, cases will increase in hundreds for HIV and in thousands for STIs for the next five years [17]. Berzkalns et al. performed a study in King County (State of Washington, United States) where the number of sexual health clinic visits decreased 55% during lockdown. Although after lockdown numbers returned to pre-lockdown values, around lockdown, from January–July 2020, the number of STIs diagnosed declined differently depending on the STI, from 9% for gonorrhoea to 22% for early latent syphilis [18]. They suggested that a real decline may have happened, but the larger decline in asymptomatic STIs probably indicates decreased

screening. Similarly, Chow et al. described that, although a relevant decrease in the total number of consultations occurred in the Melbourne Sexual Health Centre during the lockdown, for more severe conditions such as pelvic inflammatory disease or infectious syphilis, a similar number of consultations to the pre-lockdown period was observed [19]. Recently, an article from the EuroTEST COVID-19 impact assessment consortium described that, among 34 countries in the World Health Organization (WHO) European Region and in different testing settings, 95% of them declared to have tested less than half the expected number of people between March and May 2020, a decline that continued at lesser degrees until August 2020 [20]. Then, this decline probably is due to the effect of a combination of factors; changes in the people's behaviour, sexual relationships or fear of visiting a health care setting [21], less available resources to diagnose and notify STIs (including human resources), and surveillance systems which were not able to integrate the immediate reaction to a pandemic, while coping with their regular surveillance activities.

Conclusions

Our results showed that the STI notification sharp decline was maintained almost five months since lockdown, well into the new normality. This can hardly be explained without significant underdiagnoses and underreporting. The gradual increase in the number of STI reported cases that we observed after lockdown may be pointing out the possibility that lockdowns did not completely disrupt STI transmission. As discussed in the present article, with the available current scientific evidence, it seems that the observed decrease in the number of STI reported cases during the current COVID-19 pandemic is probably due to a combination of factors. More research is needed in order to disentangle the specific role and relevance that has had underdiagnosis, underreporting, and the decrease in sexual risk activities and other potential factors in this decline. Finally, we truly believe that there is an urgent need to strengthen STI/HIV diagnostic programs and services, as well as surveillance, as the pandemic could be concealing the real size of the already described re-emergence of STIs [22].

Abbreviations

COVID-19: The coronavirus disease 2019; STI: Sexually transmitted infections; LGV: Lymphogranuloma venereum; MSM: Males who have sex with males; HIV: Human immunodeficiency virus; REC: Epidemiological repository of Catalonia; XVEC: The Epidemiological Surveillance Network of Catalonia; ECDC: European Centre for Disease Prevention and Control; ITS: Interrupted time series; ARIMA: Autoregressive integrated moving average; CI: Confidence interval; WHO: World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-021-11630-x.

Additional file 1: Fig. S1. Expected and observed time series trends of daily Chlamydia reported confirmed cases in Catalonia, August 1st 2017 - August 1st 2020 (dark grey: lockdown, light grey: de-escalation phases). **Fig. S2**. Expected and observed time series trends of daily Gonorrhoea reported confirmed cases in Catalonia, August 1st 2017 - August 1st 2020 (dark grey: lockdown, light grey: de-escalation phases). **Fig. S3**. Expected and observed time series trends of daily Syphilis reported confirmed cases in Catalonia, August 1st 2017 - August 1st 2020 (dark grey: lockdown, light grey: de-escalation phases). **Fig. S4**. Expected and observed time series trends of daily lymphogranuloma venerum (LGV) reported cases in Catalonia, August 1st 2017 - August 1st 2020 (dark grey: lockdown, light grey: de-escalation phases).

Acknowledgements

We thank all the reporting physicians and people working in HIV/STI surveillance in Catalonia who have contributed in the collection and quality of the information in the surveys including the Catalan HIV and STI Surveillance Group, which is composed by the following members: A Sentís, E López, V Gonzalez, R Lugo, MP Bonamusa, J Reyes, J Casabona (Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya); P Garcia de Olalla, Lilas Mercuriali, R Clos, R Rodriguez, M Masdeu, M Ros, P Simon, I Avellaneda, A Artigas,C Rius (Servei d'Epidemiologia de l'Agència de Salut Pública de Barcelona); M Company, M Danés, N Camps (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Girona); RM Vileu, G Ferrús, N Borrell, S Minguell (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Tarragona); J Ferràs (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Terres de l'Ebre); I Parrón (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública al Barcelonès Nord i Maresme); I Mòdol, A Martinez, P Godoy (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Lleida); MA Tarrès, J Pérez, M Boldú, I Barrabeig (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Barcelona Sud); E Donate, L Clotet, MR Sala (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública al Vallès Occidental i Vallès Oriental); M Carol, V Guadalupe-Fernández (Servei de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública a Catalunya Central) and J Mendioroz, P Ciruela, G Carmona, R Mansilla, JL Martínez, S Hernández (Subdirecció General de Vigilància Epidemiològica i Resposta a Emergències de Salut Pública, Agència de Salut Pública de Catalunya).

Authors' contributions

AS and JC conceptualized the paper. AS and APU designed the study. MMF cleaned the database. AS and APU reviewed scientific literature, performed the statistical analysis, and drafted the manuscript. AS, APU, JC, JRU, ELC, DN, PG, LM, NB, VGF, and Catalan HIV and STI Surveillance Group interpreted the results and contributed to improving the content in the sections of their expertise. The Catalan HIV and STI Surveillance Group managed and verified all the reported cases. All the authors collaborated in the critical review and approved the final manuscript.

Funding

AP-U is supported by Fundacion Alfonso Martin Escudero and the Medical Research Council (grant numbers MR/K501256/1, MR/N013468/1).

Availability of data and materials

Public access to the database(s) is close. Data sharing is not possible because patients' individual privacy could be compromised. Although data was de-identified to be handled, some aggregated results could be sensitive when communicated at a population level. For this reason, the analysis and dissemination of this data is handled by public health authorities with surveillance responsibilities and avoiding disaggregation by small geographical areas.

Declarations

Ethics approval and consent to participate

Ethics approval by an ethics committee was not necessary according to national regulations; Data from mandatory notifiable disease in REC application were handled according to Spanish Organic Law 3/2018 on Data protection and guarantee of Digital Rights, and Law 33/2011 on General Public Health. Patient information was anonymized and deidentified before handed over for analysis and therefore no informed consent was required. Patients were not directly involved in this study; only data coming from notifiable disease surveillance systems were used which did not imply any additional approval requirements. Data was handled anonymously by researchers from the Centre of epidemiological studies on sexually transmitted infections and AIDS of Catalonia (CEEISCAT) (Department of Health, Generalitat of Catalonia, Spain), which has the mandate of collect, analyse and disseminate STI/HIV surveillance data in Catalonia, as part of their routine functions.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Centre of epidemiological studies on sexually transmitted infections and AIDS of Catalonia (CEEISCAT). Department of Health. Generalitat of Catalonia, Badalona, Spain. [2]Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain. [3]Pompeu Fabra University (UPF), Barcelona, Spain. [4]Epiconcept, Epidemiology Department, Paris, France. [5]Centre for Statistics in Medicine, Botnar Research Centre, NDORMS, University of Oxford, Oxford, UK. [6]Department of Paediatrics, Obstetrics and Gynecology and Preventive Medicine, Universitat Autónoma de Barcelona, Badalona, Spain. [7]Epidemiological Service of Public Health Agency of Barcelona, Barcelona, Spain. [8]Epidemiological Surveillance and Response to Public Health Emergencies Service in Tarragona Camp, Agency of Public Health of Catalonia, Generalitat of Catalonia, Tarragona, Spain. [9]Epidemiological Surveillance and Response to Public Health Emergencies Service in Central Catalonia, Agency of Public Health of Catalonia, Generalitat of Catalonia, Manresa, Spain.

Received: 17 October 2020 Accepted: 13 August 2021
Published online: 07 September 2021

References

1. Centre of epidemiological studies on sexually transmitted infections and AIDS of Catalonia (CEEISCAT). Vigilància epidemiològica de les infeccions de transmissió sexual a Catalunya. 2019. www.ceeiscat.cat. Accessed 7 Aug 2020.
2. STD Facts - STDs & Pregnancy Detailed Fact Sheet. https://www.cdc.gov/std/pregnancy/stdfact-pregnancy-detailed.htm. Accessed 24 May 2021.
3. WHO. Sexually transmitted infections (STIs). https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis). Accessed 7 Aug 2020.
4. HIV/AIDS & STDs. https://www.cdc.gov/std/hiv/default.htm. Accessed 22 Feb 2021.
5. Situación de COVID-19 en España a 19 de mayo de 2021. Equipo COVID-19. RENAVE. CNE. CNM (ISCIII). Informe n° 79. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Informes COVID-19/INFORMES COVID-19 2021/Informe n° 79. Situación de COVID-19 en España a 19 de mayo de 2021.pdf. Accessed 24 May 2021.
6. Generalitat de Catalunya, Departament de Salut. Dades COVID https://dadescovid.cat/. Accessed 24 May 2021.
7. Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por el COVID-19. Boletin oficial del estado. Sec. I. Pág. 25390. https://www.boe.es. Accessed 24 May 2021.
8. SIVES 2015 - Sistema Integrat de Vigilància Epidemiològica de la SIDA/VIH/ITS a Catalunya. 2015. https://scientiasalut.gencat.cat/bitstream/handle/11351/3418/informe_SIVES_2015_informe_epidemiologic_CEEISCAT_2015.pdf.pdf?sequence=1&isAllowed=y. Accessed 27 Mar 2021.
9. Agency for Health Quality and Assessment of Catalonia. Nou indicador socioeconòmic per al finançament de les ABS. Observatori del Sistema de Salut de Catalunya. 2017. http://observatorisalut.gencat.cat/ca/observatori-desigualtats-salut/indicador_socioeconomic_2015/. Accessed 6 Aug 2020.
10. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR Recomm Rep 2015; 64 (No. RR-3): 33, 37, 57, 64.https://www.cdc.gov/std/tg2015/toc.htm. Accessed 2 Sep 2020.
11. Plan para la transición hacia una nueva normalidad. 28 de abril 2020. Gobierno de España. Ministerio de Sanidad. https://www.lamoncloa.gob.es/consejodeministros/resumenes/Documents/2020/PlanTransicionNuevaNormalidad.pdf. Accessed 25 May 2021.
12. Mohamed A, Hammoud LM, et al. Physical distancing due to COVID-19 disrupts sexual behaviours among gay and bisexual men in Australia. JAIDS J Acquir Immune Defic Syndr. https://pubmed.ncbi.nlm.nih.gov/32740374/.
13. Alpalhão M, Filipe P. The impacts of isolation measures against SARS-CoV-2 infection on sexual health. AIDS Behav. 2020;1(8):1–2259. https://doi.org/10.1007/s10461-020-02853-x.
14. Balestri R, Magnano M, Rizzoli L, Infusino SD, Urbani F, Rech G. STIs and the COVID-19 pandemic: the lockdown does not stop sexual infections. J Eur Acad Dermatol Venereol. 2020:jdv.16808. https://doi.org/10.1111/jdv.16808.
15. Tang K, Gaoshan J, Ahonsi B. Sexual and reproductive health (SRH): a key issue in the emergency response to the coronavirus disease (COVID-19) outbreak. Reprod Health. 2020;17(1):59. https://doi.org/10.1186/s12978-020-0900-9.
16. Sanchez TH, Zlotorzynska M, Rai M, Baral SD. Characterizing the impact of COVID-19 on men who have sex with men across the United States in April, 2020. AIDS Behav. 2020;24(7):2024–32. https://doi.org/10.1007/s10461-020-02894-2.
17. Jenness SM, Le Guillou A, Chandra C, Mann LM, Sanchez T, Westreich D, et al. Projected HIV and bacterial STI incidence following COVID-related sexual distancing and clinical service interruption. medRxiv. 2020. https://doi.org/10.1101/2020.09.30.20204529.
18. Berzkalns A, Thibault CS, Barbee LA, Golden MR, Khosropour C, Kerani RP. Decreases in reported sexually transmitted infections during the time of COVID-19 in King County, WA: decreased transmission or screening? Sex Transm Dis. 2021;48(8S):S44–9. https://doi.org/10.1097/OLQ.0000000000001463.
19. Chow EPF, Hocking JS, Ong JJ, Phillips TR, Fairley CK. Sexually transmitted infection diagnoses and access to a sexual health service before and after the National Lockdown for COVID-19 in Melbourne, Australia. Open Forum Infect Dis. 2021;8(1). https://doi.org/10.1093/ofid/ofaa536.
20. Simões D, Stengaard AR, Combs L, Raben D. Impact of the COVID-19 pandemic on testing services for HIV, viral hepatitis and sexually transmitted infections in the WHO european region, march to august 2020. Eurosurveillance. 2020;25(47):2001943. https://doi.org/10.2807/1560-7917.ES.2020.25.47.2001943.
21. Alessandra L, Francesca M, Maria Gabriella D, Massimo G, Antonio C, Mauro Z. Is COVID-19 affecting the epidemiology of STIs? The experience of syphilis in Rome. Sex Transm Infect. 2020; sextrans-2020-054543. https://doi.org/10.1136/sextrans-2020-054543.
22. Williamson DA, Chen MY. Emerging and reemerging sexually transmitted infections. N Engl J Med. 2020;382(21):2023–32. https://doi.org/10.1056/NEJMra1907194.

Publisher's Note

4.4. Estudio IV: Decline of tuberculosis notification rate in different population groups and regions in Portugal, 2010-2017.

A. Sentís, A. Prats-Uribe, V.R. Peixoto, J.A. Caylà, M.D. Gomes, S. Sousa, R. Duarte, I. Carvalho, C. Carvalho, Decline of tuberculosis notification rate in different populations and regions in Portugal, 2010–2017, Pulmonology, 2021,
ISSN 2531-0437,
https://doi.org/10.1016/j.pulmoe.2021.08.002.

URL:
https://www.sciencedirect.com/science/article/pii/S2531043721001586

Pulmonology 000 (xxxx) 1–8

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Decline of tuberculosis notification rate in different populations and regions in Portugal, 2010–2017

A. Sentís[a,b], A. Prats-Uribe[c], V.R. Peixoto[d,e], J.A. Caylà[f], M.D. Gomes[g,h], S. Sousa[h,i], R. Duarte[g,j,k], I. Carvalho[h,l], C. Carvalho[i,*]

[a] *Epiconcept, Epidemiology Department, Paris, France*
[b] *Pompeu Fabra University (UPF), Barcelona, Spain*
[c] *Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, United Kingdom*
[d] *NOVA National School of Public Health, Public Health Research Centre, Universidade Nova de Lisboa, Lisbon, Portugal*
[e] *Comprehensive Health Research Centre, Universidade Nova de Lisboa, Lisbon, Portugal*
[f] *Foundation of Tuberculosis Research Unit of Barcelona, Spain*
[g] *EPIUnit, Institute of Public Health, University of Porto, Porto, Portugal*
[h] *National Tuberculosis Programme, Directorate-General of Health, Lisbon, Portugal*
[i] *Multidisciplinary Unit for Biomedical Research (UMIB), Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal*
[j] *Public Health Science and Medical Education Department, Faculty of Medicine, University of Porto, Porto, Portugal*
[k] *Pulmonology Department, Hospital Centre of Vila Nova de Gaia/Espinho EPE, Vila Nova de Gaia, Portugal*
[l] *Pediatric Department, Hospital Centre of Vila Nova de Gaia/Espinho EPE, Vila Nova de Gaia, Portugal*

Received 14 June 2021; accepted 12 August 2021
Available online xxx

KEYWORDS
Tuberculosis;
Portugal;
Notification rate;
Time trend analysis

Abstract
Background: Tuberculosis (TB) incidence declined in Portugal in recent decades, but trends differ between regions and population subgroups. We investigated these differences to inform prevention and control programmes.
Methods: We extracted TB notifications from the Portuguese National TB Surveillance System (SVIG-TB) in 2010–2017, disaggregated by region, age group, nationality and HIV status. We calculated notification rates using denominators from the Portuguese National Institute of Statistics and the Joint United Nations Programme on HIV/AIDS and performed stratified time series analysis. We estimated interannual decline percentages and 95% confidence intervals (CI) using Poisson and binomial negative regression models.
Results: The overall TB notification rate decreased from 25.7 to 17.5/100,000 population from 2010 to 2017 (5.2%/year) in Portugal. Interannual decline did not differ significantly between regions, but it was smaller amongst non-Portuguese nationals (-1.57% [CI: -4.79%, 1.75%] vs -5.85% [CI: -6.98%, -4.70%] in Portuguese nationals); children under five years of age (+1.77% [CI:

* Corresponding author.
E-mail address: cfcarvalho@icbas.up.pt (C. Carvalho).

https://doi.org/10.1016/j.pulmoe.2021.08.002

Please cite this article in press as: A. Sentís, A. Prats-Uribe, V.R. Peixoto et al., Decline of tuberculosis notification rate in different populations and regions in Portugal, 2010–2017, Pulmonology (2021), https://doi.org/10.1016/j.pulmoe.2021.08.002

-4.61%, 8.58%] vs -5.38% [CI: -6.33%, -4.42%] in other age groups); and HIV-negative people (-6.47% [CI: -9.10%, -3.77%] vs -11.29% [CI; -17.51%, -4.60%] in HIV-positive).
Conclusions: The decline in TB notification rates in Portugal during the study period has been steady. However, the decline amongst non-Portuguese nationals, children under five years of age and non-infected-HIV patients was lower. No significant differences were observed between regions. Changes in TB epidemiology in specific risk groups and geographical areas should be closely monitored to achieve the objectives of the End TB Strategy. We recommend intensifying screening of TB in the subpopulations identified.

Introduction

Tuberculosis (TB) incidence is steadily declining in Europe, although it remains high worldwide and in some European countries. TB is still as a major public health problem, also due to drug-resistant forms and with HIV-coinfection.[1,2] In the World Health Organization (WHO) European Region and in the European Union/European Economic Area (EU/EEA) the average annual decline of the TB incidence rate was 5.1% between 2015 and 2019 (11.9 to 9.6/100,000 inhabitants from 2015 to 2019 in EU/EEA).[1] In Portugal, which has one of the highest notification rates in the EU/EEA, the average annual decline was 5.0% (from 21.2 to 17.2/100,000).[1] Out of all cases notified in 2019 in the EU/EEA, 76.9% were new cases and 9.7% had been previously treated for TB (13.4% with unknown previous history of TB).[1]

The WHO End TB strategy states that to achieve a reduction of 80% in new TB cases and 90% in deaths by 2030, collaborative TB/HIV activities, and management of comorbidities are needed.[2]

As for other infectious diseases, we can describe TB as syndemic: it is an old endemic disease, presenting a synergic interaction with and worsening the independent damages of other diseases or conditions such as HIV, diabetes, or many social determinants of health (deprivation and inequities of health amongst others).[3,4] TB affects differently specific population groups and geographical areas. amongst others, risk groups include specific clinical conditions (such as HIV or other immunosuppression), close contact with a TB case or migration from an area with a high incidence of TB, as well as unfavoured socioeconomic and occupational groups.[5] In some risk groups, like HIV-infected, a decline in TB incidence rates was observed in the EU/EEA and in Portugal between 2015 and 2019. The relative weight of other groups, such as children under five years of age and immigrants, increased despite the overall decline in incidence.[1] In Portugal regional differences in risk of TB have been reported, with more densely populated regions such as Lisbon and Tagus Valley (LTV) and North regions being more affected.[6-8]

To analyse the differences in magnitude of decline and to better understand risk from surveillance data, further analysis of the available data is needed. We aimed at identifying population groups and geographical areas in Portugal with smaller decline in TB notification rates, to inform targeted prevention and control interventions.

Methods

Study design and participants

Time trend analysis study. We performed a time series analysis of active TB cases notified to the Portuguese TB clinical notification and follow-up surveillance system (SVIG-TB), including cases diagnosed between 2010 and 2017.

Case definition and TB surveillance system (SVIG-TB)

All confirmed, probable, and possible cases of TB diagnosed in 2010—2017 were retrieved from SVIG-TB. The case definition used is in line with EU case definitions.[9] Cases are notified to SVIG-TB by any physician diagnosing and following-up TB patients, mostly at TB outpatient centres (part of public primary care). The notifications are based on paper forms that are subsequently computerised and centralised at the regional and national levels, and include clinical, epidemiological and laboratory data, from diagnosis to discharge.[10]

Definition of variables and potentially associated factors

Sociodemographic and medical characteristics of TB patients were collected from SVIG-TB. We analysed the variables Sex (Female, Male), Age (<5 and 5 or more), Nationality (Portuguese, non-nationals), Site of infection (Extrapulmonary, Pulmonary), HIV status (Positive, Negative), and region of residence (North, Centre, Lisbon and Tagus Valley [LTV], Alentejo, Algarve, Azores, Madeira).

Denominators

We obtained denominators for each analysed year by Region, Age, Sex and Nationality from the Portuguese National Institute for Statistics[11] and estimates of people living with HIV in Portugal from Joint United Nations Programme on HIV/AIDS (UNAIDS) data 2019 report.[12]

Statistical analyses

Patients were described using counts and proportions for each of the categorical independent variables included. Age was described as Median (IQR) and proportion of <5 years old. Monthly and yearly notification rates of TB were calculated as number of cases notified per 100,000 inhabitants.

This was done overall and stratified by sex, age group, nationality, and region of residence. Further indicators of yearly notification rates of HIV+ and HIV- TB, Pulmonary and Extrapulmonary TB were computed overall. Interannual declines with 95% confidence intervals (CI) for each group were estimated using Poisson regression models. If overdispersion was observed the interannual decline was estimated using negative binomial regression. Analyses were performed using STATA (version 14; Stata Corporation, College Station, TX, USA).

Ethical approval

In this study, patients were not directly involved; anonymized data were extracted from the national TB clinical notification and follow-up surveillance system (SVIG-TB) and analysed by authors at Directorate-General of Health, as part of their routine functions of surveillance and control of communicable diseases. The study was performed following the indications of the Helsinki Declaration (reviewed in Tokyo, October 2004).

Informed consent

Patients' data were anonymized prior to analysis and, for that reason, informed consent was not required.

Results

From 2010 to 2017, the yearly notifications of TB in Portugal decreased from 2715 to 1800, corresponding to 25.7 and 17.5 notifications per 100,000 population, respectively (global decrease of 33.7% and a yearly decrease of 5.2%). The regions with greatest reduction in incidence were Madeira (56.0%), Algarve (39.7%) and Alentejo (35.3%) (Fig. 1, Supplementary Table S1). Madeira had the greatest yearly decrease in incidence, followed by Algarve (5.4%), North (5.4%) and Lisbon and Tagus Valley (LTV) (5.2%) (Table 1).

Amongst the 18,550 TB cases included in the analysis, 12,504 were confirmed (67.4%), 3122 probable (16.8%) and 2924 possible (15.8%). Three out of the seven Portuguese regions represented 91.6% of all the notifications (LTV 41.6%, North 36.4%, and Centre 13.6%). Proportion of male cases was 65.6% overall (highest in Algarve, 68.4%, and lowest in LTV, 63.0%). The median age was 47 years old (lowest in LTV, 44, highest in Centre region, 49); patients under 5 years of age represented 1% of all cases (highest proportions in Madeira and North region – 1.3% and 1.2%, respectively – and lowest in Centre region, 0.6%). The proportion of Portugal-born cases was 85.8% (lowest LTV, 73.3%, and highest North region and Madeira – 96.5% and 95.6%, respectively).

Regarding clinical characteristics, 10.7% of all notified cases were HIV-infected patients. HIV coinfection prevalence was highest in LTV and Algarve (16.2% and 11.8%, respectively) and lowest in Azores and Madeira (1.6% and 3.8%, respectively). Extrapulmonary TB accounted for 27.9% of all cases (proportion ranging from 9% in Azores to 30.7% in LTV) (Table 2).

The interannual decline in notification rate was significantly smaller in non-Portuguese nationals (−1.57%, CI: −4.79%, 1.75%) than in Portuguese-born individuals (−5.85%, CI: −6.98%, −4.70%); in children under five years (+1.77%, CI: −4.61%, 8.58%) than in other ages (−5.38%, CI: −6.33%, −4.42%); and in HIV-negative people (−6.47%, CI: −9.10%, −3.77%) than in HIV-positive (−11.29%, CI; −17.51%, −4.60%) (Table 3).

Discussion

Despite the overall decreasing trend in TB notification rate in Portugal from 2010 to 2017, we found that decline in TB notification rates was smaller in non-Portuguese nationals,

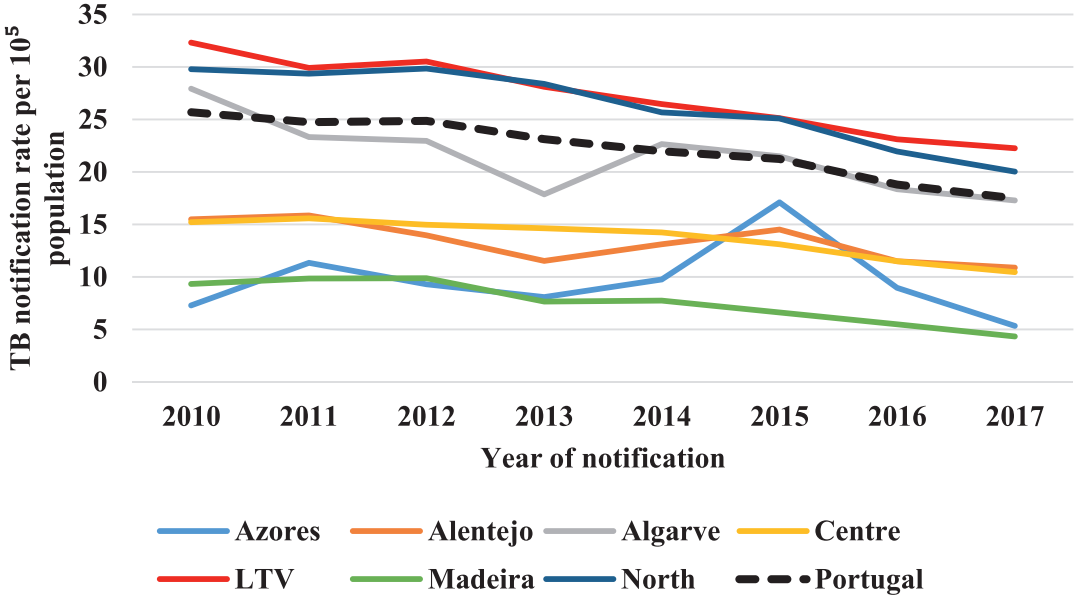

Figure 1 Tuberculosis notification rate in Portugal by region, 2010–17.
*LTV: Lisbon and Tagus Valley

Table 1 Tuberculosis notification rate decline (interannual change) per 100,000 population and comparative average difference rate by region in Portugal, 2010–17.

Region	Notification rate 2010 (per 100,000 population)	Notification rate 2017 (per 100,000 population)	Interannual change
Portugal	25.7	17.5	−5.3% (−6.2, −4.4)
Centre	15.2	10.5	−5.0% (−6.6, −3.4)
Lisbon and Tagus Valley	32.3	22.3	−5.2% (−6.1, −4.3)
North	29.8	20.0	−5.4% (−6.4, −4.4)
Alentejo	15.5	10.9	−4.4% (−8.2, −0.5)
Algarve	27.9	17.3	−5.4% (−8.3, −2.4)
Azores	7.3	5.3	−0.03% (−6.1, 6.4)
Madeira	9.3	4.3	−9.9% (−16.0, −3.5)

HIV-negative individuals and children under five years of age (although numbers were very small for children). Most cases were notified in the three most populated Portuguese regions (Lisbon and Tagus Valley, North and Centre) but no significant differences were observed in the regional interannual declines.

Lisbon and Tagus Valley (LTV) had higher proportions of female and younger cases, non-Portuguese nationals, HIV-coinfected and extrapulmonary TB than the other six regions. These regional differences correlate well with previous evidence that had described that the most frequent risk factors for TB, and for failure to complete latent TB (LTBI) treatment, are different in LTV (cases are more frequently migrant or living with HIV) and North region (where alcohol abuse and injecting drugs seem to be more frequently associated).[6-8]

In Portugal, from 2015 to 2019, the TB notification rate decreased by 18.9% (from 21.2 to 17.2 cases per 100,000 population) which is close to the 20% reduction set as interim milestone at the WHO End TB Strategy for 2015–2020.[2] According to this document, the reduction was expected to be of 50% for 2020–2025, 80% for 2025–2030 and 90% for 2030–2035. Sub-notification of TB, as it has been described in many countries,[13,14] could play a role in the observed reduction in notification rates in Portugal – although this reduction was similar to the 19% described for the WHO European region from 2015 to 2019.[15] In U.S, a country with a very low incidence of TB (under 5/100,000 population)[16] there was an average decrease of only 2.1% per year in 2012–2019.

When comparing the regional declines in TB notification rates, we did not observe significant differences in Portugal. However, our results showed how those regions with higher notifications rates, mostly North and LTV, were also those with highest interannual declines. Similarly, regions with lower notifications rates (mostly Azores and Alentejo) were also the ones with lowest interannual declines.

Interannual declines in TB notification rates allow a better understanding of the evolving situation than the overall decrease in the number of cases, as the latter indicator does not consider rate increases in intermediate years within the study period. This is illustrated by the regions of Madeira, Algarve, Alentejo, Azores and LTV (Fig. 1). We believe that the interannual changes are more robust when drawing conclusions because are less affected by sporadic annual changes that can be due by a vast range of causes (including outbreaks or under-diagnosis/under-notification because of any external causes, such as the current COVID-19 pandemic).

Finally, the fact that some regions with lower incidence rates of TB at the start of the study period showed a smaller decline in notification rates could be partially explained by a smaller likelihood of receiving targeted interventions.

The results of this study showed that the declines in TB notification rates were smaller in children under five year's old and non-Portuguese nationals, although numbers were very small for children. Factors such as improved reporting and better diagnosing tools and guidelines, might have played a role. Although with some degree of uncertainty due to the small number of cases, incidence of TB in HIV-positive patients seemed to have a greater decline than in HIV-negative, which may be due to more intensive latent TB screening and preventive treatment, and to an increased antiretroviral coverage amongst HIV positive in the latest years. These results seem to be confirmed by the latest surveillance reports.

Despite the overall decline during the last years in the number of TB notifications, an increase of the total number or the relative weight of some specific groups has been described.[1] Number of cases in children under 15 in Portugal and EU/EEA changed from 43 (2.0%) and 2262 (3.7%) in 2015 to 63 (3.6%) and 1995 (3.9%) in 2019, respectively. In immigrants, the number of reported cases in Portugal and EU/EEA changed from 367 to 18,543 in 2015 (16.7% and 28.2% of all TB cases reported in that year, respectively) to 419 and 17,181 (23.7% and 34.5%) in 2018, respectively. In some other risk groups, such as HIV-coinfected, the number of cases in Portugal and EU/EEA declined from 232 (11.7%) and 1248 (4.6%) in 2015 to 133 (11.0%) and 502 (3.1%) in 2019, respectively. Regarding 2019 data of extrapulmonary TB, Portugal had higher proportions than the average in the EU/EEA (26.0% vs 22.5%).[1]

In our study we found steeper declines in notification rates in men than in women, although differences were not significant. Men are more frequently affected by TB, which has been attributed to the fact that they present other social, behavioural and occupational risk factors for TB more frequently than women.[17,18] However, recent evidence described a steeper decline in TB incidence rates in men and at older ages in the U.S., China and India.[19]

Table 2 Sociodemographic and medical characteristics of tuberculosis patients notified by region in Portugal, 2010–2017 ($N = 18,550$).

	Portugal		Region											
			Centre		LTV*		North		Alentejo		Algarve		Azores		Madeira	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	18,550		2525	13.6	7,7	41.6	6745	36.4	452	2.4	763	4.1	190	1.0	159	0.9
Sex																
Female	6380	34.4	822	32.6	2857	37	2222	32.9	128	28.3	241	31.6	56	29.5	54	34
Male	12,170	65.6	1703	67.4	4859	63	4523	67.1	324	71.7	522	68.4	134	70.5	105	66
Age																
Median (IQR)	47 (34, 61)		49 (36, 65)		44 (33, 59)		48 (36, 62)		53 (39, 71)		47 (35, 64)		46.5 (34, 56)		46 (36, 55)	
Under 5	174	1.0	15	0.6	67	0.8	81	1.2	4	0.9	5	0.7	0	0	2	1.3
>5 years	18,350	98.9	2510	99.4	7629	98.9	6664	98.8	448	99.1	758	99.3	184	96.8	157	98.7
Missing	26	0.1	0	0	20	0.3	0	0	0	0	0	0	6	3.2	0	0
Nationality																
Portuguese	15,909	85.8	2405	95.3	5654	73.3	6513	96.5	420	93.0	612	80.2	153	80.5	152	95.6
Non-nationals	2421	13.1	117	4.6	1887	24.4	229	3.4	30	6.6	151	19.8	0	0	7	4.4
Missing	220	1.1	3	0.1	175	2.3	3	0.1	2	0.4	0	0	37	19.5	0	0
HIV status																
Positive	1980	10.7	151	6.0	1248	16.2	460	6.8	22	4.9	90	11.8	3	1.6	6	3.8
Negative	13,801	74.4	2040	80.8	5209	67.5	5353	79.4	373	82.5	635	83.2	69	36.3	122	76.7
Missing	2769	14.9	334	13.2	1259	16.3	932	13.8	57	12.6	38	5.0	118	62.1	31	19.5
Site of infection																
Extrapulmonary	5186	27.9	668	26.5	2371	30.7	1796	26.6	101	22.3	185	24.2	17	9.0	48	30.2
Pulmonary	13,261	71.5	1833	72.6	5275	68.4	4944	73.3	351	77.7	575	75.4	172	90.5	111	69.8
Missing	103	0.6	24	0.9	70	0.9	5	0.1	0	0	3	0.4	1	0.5	0	0

* Lisbon and Tagus Valley.

Table 3 Tuberculosis notification rate decline (interannual change) per 100,000 inhabitants by population group in Portugal, 2010–17.

Variable	Notification rate (2010/17)	Interannual Change	95% Confidence Interval	
			Lower	Upper
Sex				
Female	16.3/11.8	−4.63%	−6.20%	−3.03%
Male	36.0/23.8	−5,44%	−6.18%	−4.70%
Age				
Under 5	3.6/5.9	+1.77%	−4.61%	8.58%
>5 years	26.7/18.0	−5,38%	−6.33%	−4,42%
Nationality				
Portuguese	23.2/15.1	−5,85%	−6,98%	−4,70%
Non-nationals	81.7/74.4	−1,57%	−4,79%	1,75%
HIV status				
Positive	837.5/329.3	−11.29%	−17.51%	−4.6%
Negative	19.1/10.2	−6.47%	−9.10%	−3.77%
Site of infection				
Extrapulmonary	7.1/4.9	−4,80%	−5,97%	−3,62%
Pulmonar	18.4/12.5	−5,52%	−6,32%	−4,71%

The main strength of this study is that it included high-quality data at national level for some of the most important risk groups for TB. The main limitation is the lack of information about other specific risk factors such as drug-using, homelessness, or incarceration. There is a need to collect information about these conditions, amongst other determinants of health.[20,21] Active case finding in at-risk subgroups has been described as an effective way to strengthen TB prevention and control.[22] CDC and ECDC have started analysing changes and trends in different risk groups and regions.[1,16] but we still need to better monitor transmission and overlaps in these groups and obtain more precise data on the risk factors for TB as time changes.[5]

Other limitations include missing data, especially for HIV status (approximately 15% missing), which could have had biased our results. Our analysis includes only data until 2017, although at the time of submission more up-to-date data was available. In the context of the current COVID-19 pandemic, it has been described that most severe COVID-19 cases also have an increased prevalence of latent tuberculosis infection (LTBI).[23] More research is needed to disentangle if COVID-19 could favour progression to TB or worsen outcomes and to learn more about the direct and indirect effects of the COVID-19 pandemic in TB prevention and control, including those related to social determinants of health.[24,25] TB and COVID-19 have been associated with health inequities, disadvantaged socio-economic status, and poverty.[26] A recent study showed lower mortality rates in immigrants diagnosed with COVID-19 and TB, although differences were attributed to the fact that migrants tend to be younger and with fewer comorbidities.[27] Although it might be too soon to assess the impact that the COVID-19 pandemic may have had on the TB incidence, data from 33 centres in 18 countries have already showed a worldwide disruption of the TB services during the first four months of the pandemic.[28] In Barcelona, the socioeconomic and health consequences of the COVID-19 pandemic probably had a relevant impact on TB surveillance and control in the city, where a decline of almost 20% on the number of notifications and new diagnostics was observed.[29]

A recent modelling study predicted long-lasting TB incidence increases in three countries with a high TB burden due to lockdown-related disruptions.[14] Either way, all resources used to screen, diagnose, and treat TB or COVID-19 must be synergic in order to tackle both conditions and optimize resources.[30] As it has been mentioned, the apparent success in Portugal achieving the WHO End TB Strategy milestone reduction from 2015 to 2020,[2] has to be monitored to end TB by 2035. Above all, the possible under-notification due to the COVID-19 pandemic in 2020 and the likely scenario of TB incidence increase "pos-COVID-19" must be considered.[14]

We recommend systematic screening of TB in migrants originating from high incidence countries, as well as raising awareness of local clinicians for the most affected population groups to consider the diagnosis of TB and ensuring that new-borns with specific risk factors are timely offered BCG vaccination. We also recommend strengthening contact tracing above all in immigrants and in settings where children are more frequently involved. Community health workers should be more frequently integrated in the response to TB, both at operational and strategical levels, to facilitate and enhance contact tracing and LTBI-TB treatment in special circumstances where idiomatic or cultural barriers exist.[31]

We recommend further regional-local analysis to tailor more specific interventions. We hope that the present study may also contribute to improve epidemiological surveillance, focusing on monitoring changes in risk groups and in specific geographical areas to plan prevention and control interventions more effectively, supporting the National TB Programme objective of further reducing incidence of tuberculosis in Portugal.[32]

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2021.08.002.

References

1. European Centre for Disease Prevention and Control (ECDC)/ World Health Organization Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2021 –2019 data. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2021-2019-data. Accessed August 7, 2021.
2. World Health Organization (WHO). The End TB Strategy. Geneva: WHO; 2015. Available at: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy. Accessed August 7, 2021.
3. Kwan C, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011;24(2):351–76. https://doi.org/10.1128/cmr.00042-10.
4. Littleton J, Park J. Tuberculosis and syndemics: implications for pacific health in New Zealand. Soc Sci Med. 2009;69 (11):1674–80. https://doi.org/10.1016/j.socscimed.2009.08.042.
5. European Centre for Disease Prevention and Control (ECDC). Review of reviews and guidelines on target groups, diagnosis, treatment and programmatic issues for implementation of latent tuberculosis management. Stockholm: ECDC; 2018. Available at: https://www.ecdc.europa.eu/en/publications-data/review-reviews-and-guidelines-target-groups-diagnosis-treatment-and-programmatic. Accessed August 7, 2021.
6. Franco I, Sousa P, Gomes M, Oliveira A, Gaio AR, Duarte R. Social profile of the highest tuberculosis incidence areas in Portugal. Rev Port Pneumol. 2016;22(1):50–2. https://doi.org/10.1016/j.rppnen.2015.08.006.
7. Felgueiras M, Cerqueira S, Gaio R, Felgueiras Ó, Duarte R. Comparative study between tuberculosis incidence rates in the two largest metropolitan areas of Portugal. Arch Bronconeumol. 2018;54(11):595–6. https://doi.org/10.1016/j.arbres.2018.05.003.
8. Direção-Geral da Saúde (DGS) – Programa Nacional para a Infeção VIH/SIDA. Infeção VIH, SIDA e Tuberculose em números –2014. Lisbon: DGS; 2014. Available at: https://www.dgs.pt/estatisticas-de-saude/estatisticas-de-saude/publicacoes/portugal-infecao-vih-sida-e-tuberculose-em-numeros-2014-pdf.aspx Accessed 10 Jan 2019.
9. European Commission (EC). Commission Implementing Decision (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitions. Brussels: EC; 2018. Available at: http://data.europa.eu/eli/dec_impl/2018/945/oj.
10. Direção-Geral da Saúde (DGS). Tuberculose – Sistema SVIG-TB Webpage: https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/tuberculose1/sistema-svig-tb.aspx. Accessed 23 Jan 2021.
11. Statistics Portugal. Webpage: https://www.ine.pt/xportal/xmain?xpgid=ine_main&xpid=INE&xlang=en. Accessed 23 Jan 2021.
12. United Nations Joint Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2019. Geneva: UNAIDS; 2019. Available at: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data. Accessed May 30, 2021.
13. Kwak N, Hwang SS, Yima AJ. Effect of COVID-19 on tuberculosis notification, South Korea. Emerg Infect Dis. 2020;26 (10):2506–8. https://doi.org/10.3201/eid2610.202782.
14. Cilloni L, Fu H, Vesga JF, Dowdy D, Pretorius C, Ahmedov S, et al. The potential impact of the COVID-19 pandemic on the tuberculosis epidemic a modelling analysis. EClinicalMedicine. 2020;28. https://doi.org/10.1016/j.eclinm.2020.100603. Article 100603.
15. World Health Organization (WHO). Global tuberculosis report 2020. Geneva: WHO; 2020. Available at: https://www.who.int/publications/i/item/9789240013131. Accessed August 7, 2021.
16. Schwartz NG, Price SF, Pratt RH, Langer AJ. Tuberculosis - United States, 2019. MMWR Morb Mortal Wkly Rep. 2020;69 (11):286–9. https://doi.org/10.15585/mmwr.mm6911a3.
17. Marçôa R, Ribeiro AI, Zão I, Duarte R. Tuberculosis and gender – factors influencing the risk of tuberculosis among men and women by age group. Pulmonology. 2018;24(3):199–202. https://doi.org/10.1016/j.pulmoe.2018.03.004.
18. Kyu HH, Maddison ER, Henry NJ, Mumford JE, Barber R, Shields C, et al. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2018;18(3):261–84. https://doi.org/10.1016/s1473-3099(17)30703-x.
19. Cui Y, Shen H, Wang F, Wen H, Zeng Z, Wang Y, et al. A long-term trend study of tuberculosis incidence in china, india and united states 1992–2017: a joinpoint and age–period–cohort analysis. Int J Environ Res Public Health. 2020;17(9):3334. https://doi.org/10.3390/ijerph17093334.
20. European Centre for Disease Prevention and Control (ECDC). Social determinants and risk factors in tuberculosis surveillance in the EU/EEA. Stockholm: ECDC; 2018. Available at: https://www.ecdc.europa.eu/en/publications-data/social-determinants-and-risk-factors-tuberculosis-surveillance-eueea. Accessed August 7, 2021.
21. de Colombani P, Hovhannesyan A. Wolfheze Working Group on Social Determinants of TB and Drug Resistant TB. Social determinants and risk factors for tuberculosis in national surveillance systems in Europe. Public Health Action. 2015;5(3):194–201. https://doi.org/10.5588/pha.15.0026.
22. Zenner D, Southern J, Van Hest R, DeVries G, Stagg HR, Antoine D, et al. Active case finding for tuberculosis among high-risk groups in low-incidence countries. Int J Tuberc Lung Dis. 2013;17(5):573–82. https://doi.org/10.5588/ijtld.12.0920.
23. Ong C, Migliori GB, Raviglione M, MacGregor-Skinner G, Sotgiu G, Alffenaar J, et al. Epidemic and pandemic viral infections: impact on tuberculosis and the lung. Eur Respirat J. 2020;56 (4):2001727. https://doi.org/10.1183/13993003.01727-2020.
24. Visca D, Ong CWM, Tiberi S, Centis R, D'Ambrosio L, Chen B, et al. Tuberculosis and COVID-19 interaction: a review of biological, clinical and public health effects. Pulmonology. 2021;27 (2):151–65. https://doi.org/10.1016/j.pulmoe.2020.12.012.
25. Migliori GB, Tiberi S, García-Basteiro AL, Duarte R. Tuberculosis and its future in the COVID-19 era: the Pulmonology series 2021. Pulmonology. 2021;27(2):94–6. https://doi.org/10.1016/j.pulmoe.2020.10.005.
26. Duarte R, Aguiar A, Pinto M, Furtado I, Tiberi S, Lönnroth K, et al. Different disease, same challenges: social determinants of tuberculosis and COVID-19. Pulmonology. 2021;27 (4):338–44. https://doi.org/10.1016/j.pulmoe.2021.02.002.
27. Motta I, Centis R, D'Ambrosio L, García-García JM, Goletti D, Gualano G, et al. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. Pulmonology. 2020;26(4):233–40. https://doi.org/10.1016/j.pulmoe.2020.05.002.
28. Migliori G, Thong P, Akkerman O, Alffenaar J, Álvarez-Navascués F, Assao-Neino M, et al. Worldwide effects of coronavirus disease pandemic on tuberculosis services, January-April 2020.

Emerg Infect Dis. 2020;26(11):2709–12. https://doi.org/10.3201/eid2611.203163.
29. Millet J, Orcau A. COVID y TB en Barcelona. Enf Emerg. 2021;20(1):27–45. Available at: http://enfermedadesemergentes.com/articulos/a772/Jornada_TBC_2021_MESA2.pdf. Accessed August 7, 2021.
30. Comella-del-Barrio P, De Souza-Galvão ML, Prat-Aymerich C, Domínguez J. Impact of COVID-19 on tuberculosis control. Arch. Bronconeumol. 2021;57(S2):5–6. https://doi.org/10.1016/j.arbres.2020.11.016.
31. Ospina JE, Orcau À, Millet J-P, Sánchez F, Casals M, Caylà JA. Community health workers improve contact tracing among immigrants with tuberculosis in Barcelona. BMC Public Health. 2012;12:158. https://doi.org/10.1186/1471-2458-12-158.
32. Direção-Geral da Saúde (DGS). Tuberculose em Portugal: Desafios e Estratégias 2018. Lisbon: DGS; 2018. Available at: https://www.dgs.pt/documentos-e-publicacoes/tuberculose-em-portugal-desafios-e-estrategias-2018-.aspx. Accessed August 7, 2021.

4.5. Estudio V: Failure to complete treatment for latent tuberculosis infection in Portugal, 2013-2017: geographic, socio-demographic and medical associated factors.

Sentís, A., Vasconcelos, P., Machado, R.S. et al. Failure to complete treatment for latent tuberculosis infection in Portugal, 2013–2017: geographic-, sociodemographic-, and medical-associated factors. Eur J Clin Microbiol Infect Dis 39, 647–656 (2020). https://doi.org/10.1007/s10096-019-03765-y

URL: https://link.springer.com/article/10.1007/s10096-019-03765-y

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-019-03765-y

ORIGINAL ARTICLE

Failure to complete treatment for latent tuberculosis infection in Portugal, 2013–2017: geographic-, sociodemographic-, and medical-associated factors

Alexis Sentís[1,2,3,4,5] · Paula Vasconcelos[1,2] · Rita Sá Machado[1,2] · Joan A. Caylà[6] · Mònica Guxens[3,4,5,7] · Vasco Peixoto[1,2] · Raquel Duarte[1,8,9,10] · Isabel Carvalho[1] · Carlos Carvalho[1,11,12]

Received: 11 September 2019 / Accepted: 7 November 2019

Abstract

There is conflicting evidence about factors associated with failure to complete treatment (FCT) for latent tuberculosis infection (LTBI). We aim to identify the geographic, sociodemographic, and medical factors associated with FCT in Portugal, highlighting the two main metropolitan areas of Porto and Lisbon. We performed a retrospective cohort study including LTBI patients that started treatment in Portugal between 2013 and 2017. We calculated adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) using multivariable logistic regression to identify geographic, sociodemographic, and medical factors associated with FCT. Data on completion of treatment were available for 15,478 of 17,144 patients (90.3%). Of those, 2132 (13.8%) failed to complete treatment. Factors associated with FCT were being older than 15 years (aOR, 1.65 (95% CI = 1.34–2.05) for those aged 16 to 29), being born abroad (aOR, 2.04 (95% CI = 1.19–3.50) for Asia; aOR, 1.57 (95% CI = 1.24–1.98) for Africa), having a chronic disease (aOR, 1.29 (95% CI = 1.04–1.60)), alcohol abuse (aOR, 2.24 (95% CI = 1.73–2.90)), and being intravenous drug user (aOR, 1.68 (95% CI = 1.05–2.68)). Three-month course treatment with isoniazid plus rifampicin was associated with decreased FCT when compared with 6- or 9-month courses of isoniazid-only (aOR, 0.59 (95% CI = 0.45–0.77)). In Lisbon metropolitan area, being born in Africa, and in Porto metropolitan area, alcohol abusing and being intravenous drug user were distinctive factors associated with FCT. Sociodemographic and medical factors associated with FCT may vary by geographical area and should be taken into account when planning interventions to improve LTBI treatment outcomes. This study reinforces that shorter course treatment for LTBI might reduce FCT.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-019-03765-y) contains supplementary material, which is available to authorized users.

✉ Carlos Carvalho
ccarvalho@arsnorte.min-saude.pt

[1] Directorate-General of Health, Lisbon, Portugal

[2] European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, (ECDC), Stockholm, Sweden

[3] ISGlobal, Barcelona, Spain

[4] Pompeu Fabra University (UPF), Barcelona, Spain

[5] Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain

[6] Foundation of Tuberculosis Research Unit of Barcelona, Barcelona, Spain

[7] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre–Sophia Children's Hospital, Rotterdam, The Netherlands

[8] Public Health Science and Medical Education Department, Faculty of Medicine, University of Porto, Porto, Portugal

[9] EPIUnit, Institute of Public Health, University of Porto, Porto, Portugal

[10] Pulmonology Department, Hospital Centre of Vila Nova de Gaia/Espinho EPE, Vila Nova de Gaia, Portugal

[11] Department of Public Health, Northern Regional Health Administration, Porto, Portugal

[12] Multidisciplinary Unit for Biomedical Research (UMIB), Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

Published online: 03 December 2019

Keywords Latent tuberculosis infection · Treatment · Adherence · Risk factors · Associated factors · Non-completion

Introduction

Approximately one-fourth of the worldwide population is affected by latent tuberculosis infection (LTBI), 5–10% of whom will develop active tuberculosis (TB) during their lifetime mainly in the first 2 years after infection [1, 2]. LTBI cases are asymptomatic and potential future new cases of TB; therefore, if they are not diagnosed and treated, TB elimination will be not attained [1, 3]. In addition to being a close contact of individuals with active TB, those living in communities with high TB incidence rates and in poorly ventilated and crowded environments have an increased risk of acquiring LTBI [1, 4].

Portugal has one of the highest TB notification rates in the European Union (EU) (17.8 TB cases/100,000 inhabitants in 2016, vs. an average of 11.4 in the EU) [5]. From 2012 to 2016, TB cases have decreased an average of 20% in EU countries and 30% in Portugal [5]. All cases of LTBI that started treatment should be notified to the Portuguese TB surveillance system, but those who did not start treatment will not be reported. The number of LTBI cases reported increased from 600 in 2000 to 3246 in 2013 [6], reflecting national efforts to better screen, notify, and treat LTBI [7].

It has been estimated that the treatment of LTBI could avoid approximately 90% of the cases that would result from progression to active TB [8]. In the EU, in spite of the high treatment initiation rates, the proportion of individuals failing to complete (FCT) LTBI treatment broadly differs within all the risk groups to develop TB [9]. Although with conflicting results, different factors such as age, gender, country of birth, substance abuse, HIV coinfection, treatment regimen, treatment adverse effects, missing early clinical visits during treatment, and receiving information about disease and treatment have been associated with FCT [10–14]. Geographical differences in the TB risk factors have also been described, between regions, metropolitan areas, rural and urban spaces, or even in smaller geographic areas [15, 16]. In Portugal, the metropolitan areas of the two main cities (Lisbon and Porto, which are respectively part of the Lisbon and Tagus Valley (LTV) and Northern Health Regions) present the highest TB notification rates in the country [17, 18], but risk factors for TB seem to be different [6, 17].

In this study, we aim to identify the most relevant factors associated with FCT in Portugal between 2013 and 2017, and to identify possible differences between the two main metropolitan areas, Porto and Lisbon, in order to inform specific preventive measures to reduce LTBI and, in this way, prevent the TB development.

Methods

Study design and participants

We performed a retrospective cohort study using nationwide anonymized data from the national TB clinical notification and follow-up surveillance system (SVIG-TB), between the years 2013 and 2017. These data are routinely collected from paper notification forms, used mainly in TB outpatient centres, where all patients are followed up until the end of treatment. The Lisbon metropolitan area includes 18 municipalities and had 2,833,679 inhabitants in 2017. The Porto metropolitan area includes 17 municipalities and had 1,719,702 inhabitants.

LTBI can be defined as an asymptomatic infection characterized by an immune response to *Mycobacterium tuberculosis* antigens [19]. In Portugal, all patients diagnosed LTBI are offered treatment, but the screening of LTBI is opportunistic (mainly after contact with an infectious case of TB) and might vary between cities, regions, and healthcare centres. All the patients that were diagnosed with LTBI and started treatment in Portugal between the years 2013 and 2017 were included in the study. Treatment outcome was dichotomized as follows: (i) success to complete treatment (SCT): LTBI patients that started and finished the treatment during the study period, and (ii) failure to complete treatment (FCT): LTBI patients that started but did not complete the treatment, with a recorded treatment outcome of "therapeutic failure" or "interruption or withdrawal". LTBI patients that started treatment and did not have a treatment outcome recorded were classified as "unknown treatment outcome" and excluded from the analysis, including 51 patients with unknown status that died after the treatment started (cause of death not known). All LTBI records in the database had at least one confirmatory test with a positive result, an IGRA or TST. Treatment regimen was categorized as isoniazid-only (6-month course if duration of treatment was more than 4 months and less than 8 months, 9-month course if treatment was longer than 8 months, other courses if treatment was shorter than 4 months), rifampicin-only (4-month course), and combination of isoniazid and rifampicin (3-month course).

Variable definition and potentially associated factors

Sociodemographic potentially associated factors included sex, age, continent/region/country of birth, incarceration at start of

treatment, and living in a community health centre. Medical factors included LTBI treatment regimen, previous treatment for TB or LTBI, and previous chronic disease or other factors potentially associated with treatment, such as chronic liver disease (LCD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), alcohol abuse, intravenous or other drugs used (IDU), and directly observed treatment (DOT). We computed the variables "region" and "metropolitan areas" of Lisbon and Porto (according to the European Nomenclature of Territorial Units for Statistics—NUTS 2 and NUTS 3, respectively) from the variable "municipality of residence". The variable "region" was used in the descriptive analysis in order to obtain a regional picture and "metropolitan area" to highlight the main metropolitan areas (Porto and Lisbon), where different risk factors for TB have been described [6, 17], and performed separated models. Failure to complete treatment (FCT) was defined as having a treatment outcome of "therapeutic failure" (if the patient developed active TB during LTBI treatment) or "interruption or withdrawal" (when for adverse effects or patient personal reasons the treatment was stopped) recorded.

Statistical analyses

We described the LTBI patients in terms of geographic, sociodemographic, and medical factors using proportions and measures of central tendency. We characterized the cases with unknown treatment outcome (missing information) in order to identify possible biases. We tested associations between independent variables and FCT using logistic regression. All those variables that we found to be significantly associated with FCT at the univariable analysis ($p < 0.05$) were included in a logistic regression model for the multivariable analysis. We calculated odds ratios and their 95% confidence intervals for FCT, adjusted for the co-variables included in the model. We repeated the analysis restricting the population from Lisbon and Porto metropolitan areas. In Lisbon, the best fitting regression model included age, country of birth, having a chronic disease, and treatment regimen; in Porto, the model included age, alcohol abuse, IDU, and users of other drugs, living in a community health centre and treatment regimen. Analyses were performed using STATA (version 14; Stata Corporation, College Station, TX, USA).

Results

Descriptive analysis

From 2013 to 2017, overall 17,144 LTBI cases were recorded in the national TB clinical notification and follow-up surveillance system (SVIG-TB), from whom 15,478 had available data on treatment outcome (90.3%). From those, 13,346 (86.2%) succeeded to complete treatment (SCT) and 2132 (13.8%) failed to complete treatment (FCT).

Women and men were similarly represented. 79.8% of the LTBI cases were between 30 and 69 years old. The Northern and LTV regions were the most represented, with 9003 (52.5%) and 4265 (24.9%) of the recorded LTBI cases and 20.8% and 25.3% of cases failing to complete treatment, respectively. The country of birth was Portugal approximately in 90% of the individuals in all groups. Within those people not born in Portugal, the highest percentages were people born in Africa and in Asia. Among patients that completed treatment, the most common LTBI treatment regimen was isoniazid-only for 6 or 9 months (54.9 and 32.2%, respectively), followed by the combination of isoniazid and rifampicin for 3 months (7.3%), rifampicin-only for 4 months (2.6%), and finally isoniazid-only courses for 4 months or less (2.0%). The proportion of LTBI patients treated under DOT was 8.1% (Table 1). Characteristics of cases with known treatment outcome are compared in Table 1 and those of cases with unknown treatment outcome in Supplementary Table S1.

The proportion of those treated with both isoniazid and rifampicin simultaneously was higher in SCT, 7.3% than in FCT, 3.8%. For those that finished the treatment (SCT), the shorter treatment regimen was isoniazid and rifampicin simultaneously with 92 days as median (Md) (interquartile range (IQR), 91–101) followed by treatment only with rifampicin (Md, 123 days (IQR, 121–133)) and treatment only with isoniazid (Md, 191 days (IQR, 183–273)). The DOT showed higher percentage for the SCT than in the FCT, 8.38% vs. 6.43%. Cases with unknown treatment outcomes showed values between those observed in STC and FCT (Supplementary Tables S1).

Multivariable analysis

Table 2 shows the analysis of the association between FCT and the studied geographic, socioeconomic, and clinical factors. After adjusting for the remaining covariables included in the regression models, we found the following characteristics to be independently associated with FCT: (i) being more than 15 years old when compared with those under 15 years old, mostly when they were between 16 and 29 years or ≥ 70 years old (adjusted odds ratio (aOR), 1.65 (95% CI, 1.34–2.04)) and 1.55 (95% CI, 1.19–2.03), respectively); (ii) living in Northern, LTV, and Algarve regions when compared with living in the Central region (aOR, 1.17 (95% CI, 0.97–1.41), 1.24 (95% CI, 1.01–1.53), and 1.63 (95% CI, 1.23–2.17), respectively); (iii) being born in Africa or Asia when compared with being born in Portugal (aOR, 1.57 (95% CI, 1.24–1.98) and 2.04 (95% CI, 1.19–3.50), respectively). Chronic disease, alcohol abuse, and injectable drug use were also significantly associated with FCT (aOR, 1.29 (95% CI, 1.04–1.60), 2.24 (95% CI, 1.73–2.90), and 1.68 (95% CI,

Table 1 Geographic, sociodemographic, and medical characteristics of patients initiating treatment for latent tuberculosis infection in Portugal between 2013 and 2017, according to treatment outcome ($N = 15,478$)

Geographic and sociodemographic characteristics			Medical characteristics		
	SCT[a], *N* (%)[b]	FCT[c], *N* (%)[b]		SCT[a], *N* (%)[b]	FCT[c], *N* (%)[b]
	13,346	2132		13,346	2132
Sex			Chronic liver disease		
Women	6921 (51.9)	1069 (50.1)	No	13,188 (98.8)	2090 (98.0)
Men	6425 (48.1)	1063 (49.9)	Yes	158 (1.2)	42 (2.0)
Age, median (IQR[d])	43 (30–55)	44 (30–55)	Chronic kidney disease		
Missing	9 (0.1)	3 (0.1)	No	13,314 (99.8)	2115 (99.2)
Age, categorized			Yes	32 (0.2)	17 (0.8)
0–15 years	1366 (10.2)	158 (7.4)	COPD[e]		
16–29 years	1908 (14.3)	358 (16.8)	No	13,225 (99.1)	2101 (98.5)
30–49 years	5166 (38.7)	820 (38.5)	Yes	121 (0.9)	31 (1.5)
50–69 years	4184 (31.4)	658 (30.9)	Diabetes mellitus		
≥ 70 years	713 (5.3)	135 (6.3)	No	13,009 (97.5)	2070 (97.1)
Missing	9 (0.1)	3 (0.1)	Yes	337 (2.5)	62 (2.9)
Region of residence			Alcohol abuse		
North	7134 (53.5)	1151 (54.0)	No	12,561 (94.1)	1932 (90.6)
Lisbon and Tagus valley (LTV)	3184 (23.9)	569 (26.7)	Yes	302 (2.3)	111 (5.2)
Central	1684 (12.6)	185 (8.7)	Missing	483 (3.6)	89 (4.2)
Algarve	722 (5.4)	143 (6.7)	Intravenous drug users		
Alentejo	345 (2.6)	52 (2.4)	No	12,857 (96.3)	2004 (94.0)
Açores	190 (1.4)	15 (0.7)	Yes	121 (0.9)	46 (2.2)
Madeira	87 (0.6)	17 (0.8)	Missing	368 (2.8)	82 (3.8)
Metropolitan area			Users of other drugs		
Lisbon	2628 (19.7)	498 (23.3)	No	12,623 (94.6)	1965 (92.2)
Porto	3290 (24.6)	590 (27.7)	Yes	367 (2.7)	87 (4.1)
Rest of the country	7428 (55.7)	1044 (48.0)	Missing	356 (2.7)	80 (3.7)
Continent/region/country of birth			DOT[f]		
Portugal	12,491 (93. 6)	1940 (91.0)	No	11,226 (84.1)	1850 (86.8)
Africa	473 (3.5)	118 (5.5)	Yes	1119 (8.4)	137 (6.4)
Eastern Europe	101 (0.8)	22 (1.0)	Missing	1001 (7.5)	145 (6.8)
South and central America	102 (0.8)	14 (0.7)	Treatment regimen		
Asia	70 (0.5)	22 (1.0)	Only isoniazid (H)	11,893 (89.1)	1988 (93.3)
Western/central Europe, USA	84 (0.6)	13 (0.6)	≤ 4 months	263 (2.0)	NA
Missing	25 (0.2)	3 (0.2)	~ 6 months	7332 (54.9)	NA
Incarceration			~ 9 months	4298 (32.2)	NA
No	12,960 (97.1)	2087 (97.9)	Only rifampicin (R)	338 (2.6)	45 (2.1)
Yes	181 (1.4)	12 (0.6)	R and H	978 (7.3)	81 (3.8)
Missing	205 (1.5)	33 (1.5)	Missing	137 (1.0)	18 (0.8)
Living in a community health center			Previously treated (PT)		
Yes	425 (3.2)	61 (2.9)	No	13,218 (99.0)	2105 (98.7)
Missing	228 (1.7)	33 (1.5)	Yes	128 (1.0)	27 (1.3)
			Compliance in PT		
			No	46 (35.9)	15 (55.6)
			Yes	52 (40.6)	9 (33.3)
			Missing	30 (23.5)	3 (11.1)

Those variables with no missing category = no missing values were found

NA, not available (no date of treatment completion)

[a] *SCT*, success to complete treatment
[b] *N* (%), total number (percentage)
[c] *FCT*, failure to complete treatment
[d] *IQR*, interquartile range
[e] *COPD*, chronic obstructive pulmonary disease
[f] *DOT*, directly observed therapy

1.05–2.68), respectively). Incarceration and completing treatment under direct observation by a healthcare worker were significantly associated with a lower risk of FCT (aOR, 0.37 (95% CI, 0.17–0.82)). Finally, LTBI cases treated with a 3-month course of isoniazid plus rifampicin seemed to be less likely to fail to complete treatment than those receiving a 6- or 9-month course of isoniazid (aOR, 0.59 (95% CI, 0.45–0.77)) (Table 2).

In the metropolitan areas, the factors associated with FCT were (i) in Lisbon, being born in Africa when compared with being born in Portugal (aOR, 1.41 (95% CI, 1.07–1.84)), and being treated with a 3-month course of rifampicin when compared with being treated with a 6- or 9-month course of isoniazid (aOR, 1.91 (95% CI, 1.11–3.28)), aOR and (ii) in Porto, being more than 15 years old, alcohol abuser (aOR, 2.64 (95% CI, 1.67–4.16)) and IDU user (aOR, 2.52 (95% CI, 1.10–5.79)) (Tables 3 and 4). Cases not living in Lisbon or Porto metropolitan areas had characteristics similar to those shown in Table 2 (Supplementary Table S2).

Discussion

We found that the FCT was associated with increasing age, region of notification (higher estimates in LTV, Northern, and Algarve regions), and the country of birth (higher for those born in Asia or Africa). Having a chronic disease, alcohol abusing, and being an IDU also were associated with higher risk of FCT. Being incarcerated and receiving LTBI treatment under direct observation by a healthcare worker were associated with lower risk of FCT. Treatment with the shorter 3-month course of isoniazid plus rifampicin was associated with a lower risk of FCT than the standard 6- or 9-month course of isoniazid-only. In the metropolitan areas of Lisbon and Porto, the factors independently associated with a higher risk of FCT were (i) in Lisbon, being born in Africa and treated with a 3-month course of rifampicin-only and (ii) in Porto, being older than 15 years old, alcohol abusing, and injecting/using other drugs.

Many studies have been published analysing factors associated with failure to complete treatment in TB but not so many regarding failure to complete treatment in LTBI. Our study is focused on failure to complete LTBI treatment, which is a crucial activity as is indicated in WHO End TB strategy [20]. This study showed a lower FCT rate (14%) than what was previously reported in other countries (varying from 20 to 60%) [12, 21]. We attribute this low FCT rate to the efforts performed by the different actors in Portugal in their aim to increase the number of LTBI cases diagnosed and treated as well as the treatment completion and success. Since the creation of the current National TB Programme (NTP) in 1995, LTBI screening and effective follow-up of patients in specialized TB services in primary care (TB outpatient centres) have been implemented and a robust surveillance system that included notification of not only TB but also LTBI cases was put in place. NTP current strategies and main actions to be developed can be found in the report "challenges and strategies in Tuberculosis in Portugal" [7]. On the other hand, as we only included patients that started treatment for LTBI in this study (and not all the patients that had LTBI diagnosed), it might be argued that FCT is being underestimated. Similarly, the cut-off of 4 months of treatment that we accepted to correspond to a complete 6-month course of isoniazid-only could be also underestimating FCT (although 75% of those patients received a 183-day or longer course of isoniazid-only). Uncontrolled characteristics in the 9% of patients that had unknown treatment outcome did not seem to bias our findings, as their characteristics are similar to those patients included in the analysis and had known outcome.

Lower FCT in children and teenagers is probably due to a closer follow-up by their families (frequently, other relatives are simultaneously being treated for TB or LTBI) and healthcare services increased concern when younger age groups are diagnosed LTBI. Incarcerated patients also seem to be less prone to FCT, which could be explained by the fact that these patients are daily treated for LTBI under direct observation by a healthcare worker (more than two-thirds of the incarcerated patients were doing DOT). DOT in Portugal is recommended only to TB patients but not to LTBI patients, which could explain why other patients that usually have higher FCT rates (such is the case of IDU) showed lower FCT rates in our study (as IDU cases in methadone programs will often receive simultaneously LTBI treatment under observation).

The studies that aim to disentangle the factors associated to FCT in LTBI had shown conflicting results. Priest et al. have been describing that females had increased risk of FCT [22] but Lobue et al. found the opposite [23]. In both cases, they described higher risk of FCT at older ages and in those non-national individuals that more recently arrived to the host

Table 2 Adjusted associations between geographic, socioeconomic, and medical factors and failure to complete treatment (FCT) for latent tuberculosis infection (n = 15,478)

	FCT			
	N	%	aOR[a]	95% CI[b]
Age, categorized				
0–15 years	158	9.47	Ref.	
16–29 years	358	14.48	1.65	1.34–2.04
30–49 years	820	12.36	1.32	1.09–1.60
50–69 years	658	12.26	1.27	1.04–1.54
≥ 70 years	135	13.62	1.55	1.19–2.03
Region of residence				
Central	185	8.49	Ref.	
North	1151	12.78	1.17	0.97–1.41
Lisbon and Tagus Valley (LTV)	569	13.34	1.24	1.01–1.53
Algarve	143	15.54	1.63	1.23–2.17
Alentejo	52	11.50	1.04	0.71–1.53
Açores	15	6.88	0.77	0.42–1.42
Madeira	17	16.04	1.43	0.80–2.55
Continent/region/country of birth				
Portugal	1940	12.15	Ref.	
Africa	118	17.61	1.57	1.24–1.98
Eastern Europe	22	16.79	1.52	0.92–2.51
South and central America	14	10.69	0.87	0.42–1.70
Asia	22	21.15	2.04	1.19–3.50
Western and central Europe	13	12.26	0.84	0.44–1.59
Incarceration				
No	2087	12.55	Ref.	
Yes	12	5.58	0.37	0.17–0.82
Chronic disease				
No	1994	12.22	Ref	
Yes	138	16.61	1.29	1.04–1.60
Alcohol abuse				
No	1932	12.05	Ref.	
Yes	111	24.94	2.24	1.73–2.90
Intravenous drug users				
No	2004	12.20	Ref.	
Yes	46	23.59	1.68	1.05–2.68
Users of other drugs				
No	1965	12.17	Ref.	
Yes	87	17.90	1.27	0.93–1.73
Directly observed therapy				
No	1850	12.75	Ref.	
Yes	137	10.25	0.79	0.64–0.96
Treatment regimen				
Isoniazid-only (~ 6- or ~ 9-month course)	1988	12.91	Ref.	
Isoniazid + rifampicin (~ 3 months)	81	7.03	0.59	0.45–0.77
Rifampicin-only (~ 4 months)	45	10.95	0.75	0.52–1.07

Logistic regressions model adjusted for all the listed variables

[a] *aOR*, adjusted odds ratio

[b] *CI*, confidence interval

Table 3 Adjusted association between potential factors and failure to complete treatment (FCT) for latent tuberculosis infection in Lisbon metropolitan area ($n = 3545$)

	FCT		aOR[a]	95% CI[b]
	N	%		
Age, categorized				
0–15 years	72	14.72	Ref.	
16–29 years	117	19.50	1.25	0.89–1.74
30–49 years	147	11.93	0.76	0.56–1.04
50–69 years	137	13.06	0.84	0.61–1.15
≥ 70 years	24	13.87	0.93	0.56–1.56
Continent/region/country of birth				
Portugal	393	13.43	Ref.	
Africa	82	1 8.14	1.41	1.07–1.84
Eastern Europe	6	13.33	1.00	0.41–2.41
South and central America	4	8.51	0.59	0.21–1.67
Asia	6	19.35	2.10	0.81–5.42
Western and central Europe	5	15.15	1.15	0.44–3.03
Treatment regimen				
Isoniazid-only (~ 6- or 9-month course)	464	13.97	Ref.	
Isoniazid + rifampicin (~ 3 months)	12	9.84	0.58	0.31–1.06
Rifampicin-only (~ 4 months)	19	27.14	1.91	1.11–3.28

Logistic regression model adjusted for all the listed variables

[a] *aOR*, adjusted odds ratio

[b] *CI*, confidence interval

community or those individuals being born abroad [22, 23]. Fiske et al. found that the FCT was not associated with race, sex, age, and place of birth but with other risk factors such as treatment with isoniazid or interview at start of treatment outside of a healthcare setting (both of these having higher FCT) [13]. In our study, we did not find an association between FCT and sex but we found it with age (higher risk for older than 15 years old) and place of birth (higher risk for those individuals born in Africa or Asia).

Ambrona de Marcos et al. suggested that patients understanding about LTBI and its treatment improved treatment completion [12], and, in another study, Hirsch-Moverman et al. found that circumstances related to social determinants of health such as alcohol or other drug addiction, homelessness, or not being married were associated with increased FCT in LTBI treatment [24]. Actually, in a systematic review performed by Stuurman et al., it was found that shorter treatment regimens, having less adverse effects during course of treatment, not abusing alcohol, not being part of vulnerable groups, and DOT had higher completion rates [25]. However, only shorter treatment regimens and social interventions were associated with higher completion rates, whereas DOT or incentive interventions showed contradictory results [25]. In a clinical trial, Belknap et al. found similar results in treatment completion when comparing DOT vs. weekly self-administered isoniazid and rifapentine [26]. Recently, it has been described that, in both children and adults, the 4-month regimen of rifampicin is similar in terms of efficacy to 9 months of isoniazid, and the treatment adherence is superior [10, 11]. In spite that approximately 90% of our patients were being treated only with isoniazid (54.9% following the 6-month course), our results suggest the same than most of the previous studies: shorter course treatments and DOT can reduce FCT.

The facts of being dependent on alcohol or drug user showed an increased risk of FCT. Regarding place of residence, we only analysed by region/metropolitan area and not smaller geographical areas (where probably we could better analyse socioeconomic status–related variables) and we only can see how the more populated regions (LTV and Northern regions) had more LTBI patients starting treatment. These regions and Algarve showed higher FCT rates than the central region. Taking into account the number of cases of active TB reported in Portugal, similar number of LTBI patients would be expected in LTV and Northern regions. However, this study showed that in Northern region, the number of LTBI treatments per TB patient was twice the number found in LTV region—possibly reflecting regional policy differences that have to be addressed. The FCT is slightly higher in LTV than in the Northern region, despite the fact that the proportions of IDU and alcohol-abusing patients (factors shown to be associated with FTC) are higher in the Northern region. This could be explained by the even higher FCT in those being born abroad, a subgroup of the population that tends to be more

Table 4 Adjusted association between potential factors and failure to complete treatment (FCT) for latent tuberculosis infection in Porto metropolitan area ($n = 4167$)

	FCT		aOR[a]	95% CI[b]
	N	%		
Age, categorized				
0–15 years	38	9.45	Ref.	
16–29 years	82	15.21	1.60	1.06–2.43
30–49 years	248	14.98	1.48	1.03–2.14
50–69 years	185	13.43	1.36	0.94–1.98
≥ 70 years	37	19.17	2.06	1.24–3.44
Living in a community health center				
No	572	14.03	Ref.	
Yes	9	26.47	1.84	0.66–5.11
Chronic disease				
No	553	13.90	Ref.	
Yes	37	19.47	1.40	0.94–2.10
Alcohol abuse				
No	536	13.51	Ref.	
Yes	32	29.36	2.64	1.67–4.16
Intravenous drug users				
No	558	13.82	Ref.	
Yes	14	33.33	2.52	1.10–5.79
Users of other drugs				
No	551	13.80	Ref.	
Yes	22	24.44	1.17	0.63–2.19
Treatment regimen				
Isoniazid-only (~ 6 or 9-month course)	578	14.43	Ref.	
Isoniazid + rifampicin (~ 3 months)	3	6.12	0.37	0.11–1.25
Rifampicin-only (~ 4 months)	9	8.33	0.48	0.23–1.01

Logistic regressions model adjusted for all the listed variables

[a] *aOR*, adjusted odds ratio

[b] *CI*, confidence interval

concentrated in Lisbon metropolitan area. Although not much scientific evidence is available yet, there have been studies describing the probable association between some chronic conditions or risk factors such as CKD [27, 28], DM [29], lung cancer [30], COPD, or smoking [31] and an increased vulnerability to infection and an increased likelihood of progression from LTBI to active TB [32]. However, having a chronic disease seems to be also associated with a higher FCT rate, probably due to increased toxicity, described as one of the main causes of FCT [33]. In our study, we found that having a chronic disease seems to be associated with FCT in LTBI.

In Portugal, in 2014, the most prevalent identified risk factor for TB differed in the two biggest urban areas: in Lisbon was being migrant or living with HIV and in Porto was alcohol abuse and being IDU [6]. Our results are consistent with these data, as we found that the main determinants of FCT were in Lisbon, being born in Africa, and in Porto, alcohol abusing and intravenous drug using. These differences may help in future opportunistic LTBI screenings identifying vulnerable populations in both metropolitan areas. Therefore, we believe that there are important geographical differences that should be taken into account when planning specific measures to fight TB. In our study, we did not have access to HIV status. If available, these data could bring valuable additional information to our analysis as the longer 9-month isoniazid-only treatment course is recommended for these patients.

To our knowledge, few studies have analysed FCT and associated factors using all available national data in a country. The main strength of this study is the sample size, as all LTBI cases starting treatment in Portugal from 2013 to 2017 were included. The main limitation is the lack of information regarding later development of TB. This would allow us to make further analysis to try to assess the role of FCT and associated factors in later development of TB. Further studies are needed to address this question. Factors like effectiveness of LTBI treatment (i.e. not developing active TB after completion of LTBI treatment) and drug-related adverse effects were not addressed in this study and so we cannot recommend shorter treatment regimens based solely on the decreased probability of FCT. Another limitation is that patients that are diagnosed LTBI but do not start treatment are not reported to the National Tuberculosis Program. This fact could bring a selection bias, as these patients could have different characteristics than those who effectively start treatment for LTBI.

In conclusion, we believe that our study brings new insights on failure to complete LTBI treatment, showing the relevance of some possible determinants, such as age, chronic disease, alcohol abuse, drug use, and geographical factors such are country of birth, region, or metropolitan area of residence. Our study reinforces the evidence that shorter course treatments for LTBI are more likely to be completed, particularly in individuals at an increased risk of FCT. WHO End TB strategy states that the LTBI treatment should be a priority for TB programs—our study shows some aspects that must be taken into consideration in order to plan effective public health interventions in this area.

Acknowledgements The authors would like to thank all the healthcare workers that contribute to screening, treatment, and notification of TB and LTBI cases in Portugal. In addition, many thanks are given to Daniel Thomas and Graça Lima, for all their support and supervision to Alexis Sentís during his European Programme for Intervention Epidemiology Training (EPIET) fellowship.

Authors' contributions AS and CC designed the study. AS cleaned the database, reviewed scientific literature, performed the statistical analysis, and drafted the manuscript. AS and CC interpreted the results. All the authors collaborated in the critical review and approved the final manuscript.

Funding information Mònica Guxens is funded by a Miguel Servet II fellowship (CPII18/00018) awarded by the Spanish Institute of Health Carlos III. The rest of the authors have declared no funding.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval In this study, patients were not directly involved; anonymized data were extracted from the national TB clinical notification and follow-up surveillance system (SVIG-TB) and analysed by authors at Directorate-General of Health, as part of their routine functions of surveillance and control of communicable diseases. The study was performed following the indications of the Helsinki Declaration (reviewed in Tokio, October 2004).

Informed consent Patient's data were anonymized prior to analysis and, for that reason, informed consent was not required.

References

1. European Centre for Disease Prevention and Control. Review of reviews and guidelines on target groups, diagnosis, treatment and programmatic issues for implementation of latent tuberculosis management. Stockholm: ECDC; 2018. [cited 2019 10]. www.ecdc.europa.eu https://doi.org/10.2900/318458
2. Comstock GW, Livesay VT WS. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974 [cited 2019 23];99:131–8. http://www.ncbi.nlm.nih.gov/pubmed/4810628: https://doi.org/10.1093/oxfordjournals.aje.a121593
3. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J 2015 [cited 2019 23];45:928–52. http://www.ncbi.nlm.nih.gov/pubmed/25792630 https://doi.org/10.1183/09031936.00214014
4. Rosales-Klintz S, Bruchfeld J, Haas W, Heldal E, Houben RMGJ, van Kessel F, et al Guidance for programmatic management of latent tuberculosis infection in the European Union/European Economic Area. Eur Respir J 2019 17 [cited 2019 23];53:1802077. http://www.ncbi.nlm.nih.gov/pubmed/30655449 https://doi.org/10.1183/13993003.02077-2018
5. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2018–2016 data. Stockholm: European Centre for Disease Prevention and Control, 2018. 2018 [cited 2019 7]. www.ecdc.europa.eu/en/ https://doi.org/10.2900/1940
6. Programa Nacional para a Infeção VIH/SIDA. Direção-Geral da Saúde. Infeção VIH, SIDA e Tuberculose em números – 2014. [cited 2019 10]. https://www.dgs.pt/estatisticas-de-saude/estatisticas-de-saude/publicacoes/portugal-infecao-vih-sida-e-tuberculose-em-numeros-2014-pdf.aspx
7. DGS. Tuberculose em Portugal Desafios e Estratégias. 2018 [cited 2019 7]. https://www.dgs.pt/documentos-e-publicacoes/tuberculose-em-portugal-desafiose-estrategias-2018-.aspx
8. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. Int J Infect Dis 2017 1 [cited 2019 23];56:68–76. https://www.ijidonline.com/article/S1201-9712(16)31223-1/fulltext https://doi.org/10.1016/J.IJID.2016.11.006
9. Sandgren A, Vonk Noordegraaf-Schouten M, van Kessel F, Stuurman A, Oordt-Speets A, van der Werf MJ. Initiation and completion rates for latent tuberculosis infection treatment: a systematic review. BMC Infect Dis 2016 17 [cited 2019 10];16:204. http://www.ncbi.nlm.nih.gov/pubmed/27184748 https://doi.org/10.1186/s12879-016-1550-y
10. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med 2018 2 [cited 2019 10];379:440–53. http://www.nejm.org/doi/10.1056/NEJMoa1714283 https://doi.org/10.1056/NEJMoa1714283
11. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah J, et al Safety and side effects of rifampin versus isoniazid in children. N Engl J Med 2018 2 [cited 2019 10];379:454–63. http://www.nejm.org/doi/10.1056/NEJMoa1714284 https://doi.org/10.1056/NEJMoa1714284
12. Ambrona de Marcos V, Bach Foradada P, Alsedà Graells M, Duque Jiménez T, Delgado Roche E, Aguilar Ariza R, et al [Compliance of latent tuberculosis infection treatment in a cohort of TB contacts]. Rev. Esp. Salud Publica 2018 [cited 2018 19];92. http://www.ncbi.nlm.nih.gov/pubmed/30131485
13. Fiske CT, Yan F-X, Hirsch-Moverman Y, Sterling TR, Reichler MR, Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team. Risk factors for treatment default in close contacts with latent tuberculous infection. Int J Tuberc Lung Dis 2014 1 [cited 2018 19];18:421–7. http://www.ncbi.nlm.nih.gov/pubmed/24670696 https://doi.org/10.5588/ijtld.13.0688
14. Moro RN, Borisov AS, Saukkonen J, Khan A, Sterling TR, Villarino ME, et al Factors associated with noncompletion of latent tuberculosis infection treatment: experience from the PREVENT TB Trial in the United States and Canada. Clin Infect Dis 2016 1;62:1390–400. https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw126 https://doi.org/10.1093/cid/ciw126
15. Goswami ND, Hecker EJ, Vickery C, Ahearn MA, Cox GM, Holland DP, et al Geographic information system-based screening for TB, HIV, and Syphilis (GIS-THIS): a cross-sectional study. PLoS One 2012 2 [cited 2019 14];7:e46029. https://dx.plos.org/10.1371/journal.pone.0046029 https://doi.org/10.1371/journal.pone.0046029
16. Sun W, Gong J, Zhou J, Zhao Y, Tan J, Ibrahim A, et al A spatial, social and environmental study of tuberculosis in China using statistical and GIS technology. Int. J. Environ. Res. Public Health 2015 27 [cited 2019 14];12:1425–48. http://www.ncbi.nlm.nih.gov/pubmed/25633032 https://doi.org/10.3390/ijerph120201425
17. Franco I, Sousa P, Gomes M, Oliveira A, Gaio AR, Duarte R Social profile of the highest tuberculosis incidence areas in Portugal. Rev Port Pneumol (English Ed) 2016 1 [cited 2019 28];22:50–2. https://www.sciencedirect.com/science/article/pii/S2173511515001621 https://doi.org/10.1016/j.rppnen.2015.08.006
18. Felgueiras M, Cerqueira S, Gaio R, Felgueiras Ó, Duarte R Comparative study between tuberculosis incidence rates in the two largest metropolitan areas of Portugal. Arch Bronconeumol 2018 [cited 2019 8];54:595–6. http://www.ncbi.nlm.nih.gov/pubmed/29884424 https://doi.org/10.1016/j.arbres.2018.05.003
19. WHO | Latent tuberculosis infection (LTBI) - FAQs. WHO 2017 [cited 2019 10]; https://www.who.int/tb/areas-of-work/preventive-care/ltbi/faqs/en/
20. World Health Organization. Latent tuberculosis infection Updated and consolidated guidelines for programmatic management. [cited 2019 10]. http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf
21. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. Int J Tuberc Lung Dis 2008 [cited 2019 21];12:1235–54. http://www.ncbi.nlm.nih.gov/pubmed/18926033
22. Priest DH, Vossel LF, Sherfy EA, Hoy DP, Haley CA. Use of intermittent rifampin and pyrazinamide therapy for latent tuberculosis infection in a targeted tuberculin testing program. Clin Infect Dis 2004 15 [cited 2019 17];39:1764–71. http://www.ncbi.nlm.nih.gov/pubmed/15578397 https://doi.org/10.1086/425610

23. LoBue PA, Moser KS Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med 2003 15 [cited 2019 17];168:443–7. http://www.ncbi.nlm.nih.gov/pubmed/12746255 https://doi.org/10.1164/rccm.200303-390OC
24. Hirsch-Moverman Y, Bethel J, Colson PW, Franks J, El-Sadr W Predictors of latent tuberculosis infection treatment completion in the United States: an inner city experience. Int J Tuberc Lung Dis 2010 [cited 2019 21];14:1104–11. http://www.ncbi.nlm.nih.gov/pubmed/20819254
25. Stuurman AL, Vonk Noordegraaf-Schouten M, van Kessel F, Oordt-Speets AM, Sandgren A, van der Werf MJ Interventions for improving adherence to treatment for latent tuberculosis infection: a systematic review. BMC Infect Dis 2016 8 [cited 2019 21];16:257. http://www.ncbi.nlm.nih.gov/pubmed/27268103 https://doi.org/10.1186/s12879-016-1549-4
26. Belknap R, Holland D, Feng P-J, Millet J-P, Caylà JA, Martinson NA, et al Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection. Ann Intern Med 2017 21 [cited 2019 21];167:689. http://www.ncbi.nlm.nih.gov/pubmed/29114781 https://doi.org/10.7326/M17-1150
27. Shu C-C, Wu V-C, Yang F-J, Pan S-C, Lai T-S, Wang J-Y, et al Predictors and prevalence of latent tuberculosis infection in patients receiving long-term hemodialysis and peritoneal dialysis. PLoS One 2012 [cited 2019 23];7:e42592. http://www.ncbi.nlm.nih.gov/pubmed/22916137 https://doi.org/10.1371/journal.pone.0042592
28. Shu C-C, Hsu C-L, Lee C-Y, Wang J-Y, Wu V-C, Yang F-J, et al Comparison of the prevalence of latent tuberculosis infection among non-dialysis patients with severe chronic kidney disease, patients receiving dialysis, and the dialysis-unit staff: a cross-sectional study. PLoS One 2015 [cited 2019 23];10:e0124104. http://www.ncbi.nlm.nih.gov/pubmed/25919813 https://doi.org/10.1371/journal.pone.0124104
29. Lee M-R, Huang Y-P, Kuo Y-T, Luo C-H, Shih Y-J, Shu C-C, et al Diabetes mellitus and latent tuberculosis infection: a systemic review and meta-analysis. Clin Infect Dis 2016 16 [cited 2019 23];64:ciw836. http://www.ncbi.nlm.nih.gov/pubmed/27986673 https://doi.org/10.1093/cid/ciw836
30. Fan W-C, Ting W-Y, Lee M-C, Huang S-F, Chiu C-H, Lai S-L, et al Latent TB infection in newly diagnosed lung cancer patients-a multicenter prospective observational study. Lung Cancer 2014 1 [cited 2019 23];85:472–8. http://www.ncbi.nlm.nih.gov/pubmed/25063540 https://doi.org/10.1016/j.lungcan.2014.07.001
31. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J 2010 [cited 2019 23];35:27–33. http://www.ncbi.nlm.nih.gov/pubmed/20044459 https://doi.org/10.1183/09031936.00072909
32. ECDC. Programmatic management of latent tuberculosis infection in the European Union. 2018 [cited 2019 27]. https://ecdc.europa.eu/en/publications-data/programmatic-management-latent-tuberculosis-infection-european-union
33. Hirsch-Moverman Y, Shrestha-Kuwahara R, Bethel J, Blumberg HM, Venkatappa TK, Horsburgh CR, et al Latent tuberculous infection in the United States and Canada: who completes treatment and why? Int J Tuberc Lung Dis 2015 1 [cited 2019 21];19:31–8. http://www.ncbi.nlm.nih.gov/pubmed/25519787 https://doi.org/10.5588/ijtld.14.0373

5. Discusión, conclusiones y recomendaciones

5.1. Discusión, conclusiones y recomendaciones para los estudios relacionados con la sindemia de las infecciones de transmisión sexual (estudios I, II, y III)

5.1.1. Discusión

Después de un largo período de disminución continua de la incidencia de las ITS en los países occidentales, que coincidió con el comienzo y los momentos más difíciles de la epidemia del VIH desde la década de 1980 hasta la de 2010, muchos países, incluidos los Estados Unidos de América (EEUU) y muchos países europeos, informaron un resurgimiento continuo de las ITS [15]–[18]. El aumento de los casos de ITS se ha atribuido en parte a la mejora de los sistemas de vigilancia y a la introducción de mejores herramientas de diagnóstico en los últimos años [22],[42]. Otros factores contribuyentes, descritos principalmente en HSH, incluyen el uso de profilaxis preexposición contra el VIH (PrEP), el uso de drogas recreativas para el sexo, abuso de sustancias y/o alcohol y el uso generalizado de Internet y otras tecnologías para buscar parejas sexuales [44]–[46].

En el *estudio I*, se observó entre 2007 y 2015 un aumento significativo de la incidencia de ITS en jóvenes de 15 a 24 años en la ciudad de Barcelona; de gonorrea y sífilis en hombres, especialmente en HSH, y de gonorrea en mujeres. En global, el

número de casos fue tres veces superior para gonorrea y seis veces superior para sífilis durante dicho periodo. Estudios anteriores describen que los nuevos diagnósticos de ITS en personas de 15 a 24 años representan la mitad de todos los casos nuevos de ITS en los EE. UU. [47] y más de la mitad de los casos en todo el mundo [48], a pesar de que este grupo de edad solo representa aproximadamente el 25% de la población sexualmente activa [47], [49]. En Europa, en 2015, los jóvenes entre 15 y 24 años representaban el 5%, el 13% y el 35% de todos los casos notificados de LGV, sífilis y gonorrea, respectivamente [50]–[52]. En Barcelona, también en 2015, esta proporción fue del 3%, 8% y 18%, respectivamente [53]. Pocos estudios han analizado las tendencias en la incidencia de ITS en personas de 15 a 24 años como nosotros hemos hecho en el *estudio I y II*. En los últimos años se ha descrito un aumento de la incidencia de casos de ITS entre menores de 20 años en Irlanda [54] y de gonorrea entre 13 y 15 años en Cataluña [55]. Los adolescentes y los jóvenes son un grupo de riesgo crítico en la vigilancia de las ITS por varias razones, en su mayoría relacionadas con comportamientos o conductas de riesgo y factores sociales [47]–[49], pero también porque muchos jóvenes en riesgo de contraer una ITS no son cribados adecuadamente [56], [57]. Además hay que tener en cuenta que factores relacionados con comportamientos específicos que son más comunes entre los jóvenes, como tener relaciones sexuales con múltiples parejas y el uso incorrecto del preservativo [47]–[49], pueden sumarse a una detección deficiente de algunas ITS [56], [57] y así conducir eventualmente a un aumento en la incidencia del VIH. Por lo tanto,

se debe hacer especial hincapié en las interacciones sidémicas de las ITS con el VIH en los adolescentes y jóvenes ya que cuando se ven afectados por una ITS tienen un mayor riesgo de coinfección por el VIH [58] de la misma manera que aquellos infectados por el VIH tienen mayor probabilidad de adquirir otras ITS [47], [59].

Nuestros resultados muestran que, entre los jóvenes afectados por alguna de las ITS incluidas en el estudio, aquellos grupos entre los analizados con mayor riesgo de presentar coinfección por el VIH son ser HSH, declarar tener 10 o más parejas sexuales o haber presentado un diagnóstico previo de ITS durante el año anterior. Además, los HSH jóvenes es un grupo de riesgo de contraer cualquier de las ITS analizadas, principalmente VIH, sífilis o LGV. Se puede observar cómo los HSH, muestran un aumento de incidencia de hasta 20 veces superior que los hombres que tienen sexo con mujeres (HSM) o las mujeres. Por otro lado, varios estudios indican que la baja incidencia de gonorrea entre las mujeres es debido, en gran parte, a las dificultades para que lleguen a la consulta, poder testearlas y diagnosticarlas [56], [60]–[62]. Nuestros resultados en el *estudio I* mostraron como la proporción de personas más jóvenes (entre 15 a 19 años) entre el total (de 15 a 24 años) de las que contrajeron una ITS fue aproximadamente un 50% superior para las mujeres que para los hombres. También, observamos que la incidencia de gonorrea difería entre hombres y mujeres según el nivel educativo, lo que creemos pudo deberse, por lo menos en parte, a la menor edad de los casos notificados en las mujeres. Estas observaciones subrayan la necesidad de poner especial énfasis y esfuerzo en la vigilancia de las ITS en los jóvenes

en general, y específicamente en los HSH y en las mujeres más jóvenes.

De manera similar al *estudio I*, en el *estudio II*, entre 2017 y 2019, se observó como el número de ITS se duplicó en Cataluña principalmente por el aumento de clamidia y gonorrea en mujeres y menores de 30 años. Se describió una mayor proporción de diagnósticos de ITS en personas que vivían en áreas urbanas y menos desfavorecidas. Del total de casos de ITS, el 7% fueron reinfecciones por la misma ITS en el *estudio I*, el 6% fueron reinfecciones por cualquiera de las ITS analizadas en el *estudio II* y el 12% y 11% fueron coinfectados por el VIH (*estudio I y II* respectivamente). A diferencia del *estudio I,* en el *estudio II* la clamidia también pudo ser analizada, y se observó cómo esta fue más común en mujeres, principalmente en mujeres que tiene sexo con hombres (MSH), presentándose la gran mayoría de los casos en personas menores de 30 años. La gonorrea, la sífilis y el LGV fueron sustancialmente más frecuentes en hombres, sobre todo en HSH, y las personas infectadas por estas ITS mostraron porcentajes más altos que las infectadas por clamidia en coinfecciones por VIH y en reinfecciones por la misma u otra ITS. La mayoría de los casos de ITS se observaron en individuos nacidos en España y entre aquellos con niveles de educación secundaria o superior, aunque estos hallazgos deben interpretarse con cautela debido a la baja cumplimentación para las variables de preferencia sexual y nivel educativo. Nuestros hallazgos son consistentes con estudios e informes anteriores de ITS en Cataluña en 2012-2017[63] y 2018-2019 [21], que muestran un aumento proporcionalmente mayor en

adultos jóvenes, en su mayoría mujeres, especialmente para clamidia pero también para gonorrea. En el *estudio II*, encontramos que el sexo masculino, la edad superior a 20 años (particularmente entre 30-60 años), vivir en áreas urbanas o menos desfavorecidas y tener múltiples episodios de ITS se asociaron con un mayor riesgo de coinfección por el VIH.

La OMS y otras agencias de salud pública han enfatizado la importancia de integrar la vigilancia de las ITS, el VIH e incluso las hepatitis virales, así como incluir la vigilancia conductual y de comportamientos de riesgo, para mejorar la identificación y caracterización de las poblaciones a riesgo de infección [22], [64]. También se ha descrito cómo los factores sociodemográficos y socioeconómicos podrían estar incluso más asociados a contraer una ITS que los comportamientos individuales, particularmente entre mujeres de grupos económicamente más desfavorecidos [65], [66]. En el *estudio II*, la identificación y caracterización de clústeres socio epidemiológicos de ITS mostró que las mujeres jóvenes que vivían en zonas rurales más desfavorecidas presentaban más frecuentemente infección por clamidia. Los HSH que vivían en áreas urbanas y menos deprimidas mostraron, con mayor frecuencia que los otros clústeres identificados, tasas de incidencia de ITS más elevadas, más episodios múltiples por ITS y porcentajes superiores de coinfección por el VIH.

De cualquier manera, creemos que el resultado más valioso del *estudio II* es que muestra la utilidad de complementar los análisis epidemiológicos tradicionales con nuevas metodologías o técnicas de análisis de datos, como es el caso del *machine learning*, para

combinar fuentes de datos heterogéneas. Esta metodología nos posibilita la identificación y caracterización de las poblaciones a riesgo de contraer una ITS. En definitiva, proporciona información de gran utilidad para el diseño y la planificación de intervenciones eficientes para prevenir y controlar las ITS y la infección o coinfección por el VIH a nivel de área de salud pequeña como lo son, en nuestro caso en Cataluña, las áreas básicas de salud (ABS).

En el *estudio III*, pudimos observar el impacto de la sindemia por la COVID-19 en la notificación de las ITS en el sistema de vigilancia de ITS/VIH en Cataluña con una reducción promedio para todas las ITS durante los primeros 5 meses de la pandemia del 51%. Nuestros resultados muestran una reducción proporcionalmente mayor en las ITS reportadas en mujeres, personas que viven en áreas más económicamente desfavorecidas, personas sin episodios previos de ITS durante los últimos tres años y sin coinfección por VIH. Entre las ITS analizadas, con una reducción del 72% en el número de notificaciones, la infección por clamidia fue la que presentó un mayor descenso, la sífilis con una reducción de las notificaciones del 22% fue la que presentó el menor descenso. En los últimos informes de vigilancia de las ITS en Cataluña se puede observar como la clamidia representa la mayor parte de todas las ITS reportadas y afecta mayoritariamente a mujeres jóvenes, la sífilis afecta más a hombres de mediana edad. En el año 2021, el 54% de los casos de clamidia se dieron en mujeres y la edad media de todos los casos fue de 28 años, datos que contrastan con el 89% de los casos de sífilis en hombres con una media de edad para todos los casos de 39 años [67]. Por lo tanto, esa reducción superior de los

casos notificados de clamidia en relación a los esperados en comparación con otras ITS durante la pandemia por el COVID-19, visualiza una vez más a la mujer, y en especial a la mujer joven, no solo como un grupo de especial vulnerabilidad por el riesgo de contraer la infección, sino que también por la menor detección de la infección sobre todo en situaciones adversas.

Durante el confinamiento y la pandemia, además de una disrupción en los servicios de atención sexual, incluidos el testeo y detección de ITS y del VIH [68], [69], las restricciones de movilidad podrían haber disminuido la búsqueda de atención médica en personas asintomáticas con exposiciones de alto riesgo. Hay que tener en cuenta que las ITS, incluida la infección por clamidia, son predominantemente asintomáticas en las mujeres y se detectan principalmente a través de pruebas de detección y cribados que deberían realizarse a las poblaciones y contactos de riesgo [70].

En el *estudio III*, la disminución de las notificaciones de ITS durante el COVID-19 también parece haber resultado mayor para las personas que viven en áreas más desfavorecidas, y seguramente con un menor o peor acceso a los servicios de salud. Por otro lado, es probable que las personas VIH positivas o las que ya habían buscado atención médica por episodios previos de ITS, presentasen más probabilidades de buscar atención médica en caso de contraer una ITS durante la pandemia por el COVID-19. Todo ello ayudaría a explicar nuestros resultados. La disminución en las notificaciones de ITS y las diferencias de esta disminución entre las distintas poblaciones es probablemente de origen multifactorial y se deba al efecto de una combinación de factores; cambios en el

comportamiento de las personas y en las relaciones sexuales, miedo a acudir a un centro de salud [71], menor disponibilidad de recursos para diagnosticar y notificar las ITS (incluidos recursos humanos), y unos sistemas de vigilancia que no lograron dar toda la respuesta necesaria, no solo ante la pandemia de COVID-19, sino también en relación a las actividades regulares de vigilancia epidemiológica para otras infecciones.

5.1.2. Fortalezas y Limitaciones

Las principales limitaciones de los *estudios I, II, y III* son:

i) Para algunas variables, la proporción de *missings* fue alta. No obstante, cuando fue posible, los incluimos en forma de categoría para ser considerados en los modelos, lo que nos permitió desentrañar la dirección y la magnitud de la asociación a estudio para esa categoría "*missing"*. A pesar de la baja cumplimentación de variables relacionadas con características sociodemográficas y de estilo de vida, como el nivel educativo, la preferencia sexual y el país de nacimiento, los valores obtenidos sin tener en cuenta los "*missings"* son similares y consistentes con otros estudios y análisis previos.

ii) La falta de datos sobre otras ITS, puede suponer una pérdida de información valiosa para un análisis más global.

iii) El no disponer de índices de privación a nivel individual y la falta de información sobre algunas variables socioeconómicas o de comportamientos de riesgo, como el uso de drogas o del preservativo, impiden una

caracterización más en detalle de las poblaciones a riesgo de infección.

Las principales fortalezas de los *estudios I, II, y III* son:

- Los datos provienen de sistemas de vigilancia implementados y robustos en cuanto a la calidad de los datos.
- La inclusión de variables sociodemográficas, clínicas y de comportamiento o preferencia sexual permitió una descripción y caracterización de las poblaciones a riesgo de infección en profundidad.
- Se utilizaron métodos novedosos o poco habituales en estudios similares que permitieron responder a nuestras preguntas de investigación:
    i) En el *estudio II*, el método de *machine learining k-means* nos permitió identificar y caracterizar distintos clústeres socio epidemiológicos de ITS a nivel de un área de salud pequeña (ABS).
    ii) En el *estudio III*, se utilizaron series temporales interrumpidas para evaluar el impacto de la pandemia de COVID-19 en la sindemia de las ITS y cuantificar la magnitud estimada en el descenso de las notificaciones de ITS según los datos esperados basados en los datos históricos.

5.1.3. Conclusiones

En el *estudio I* se observó un aumento alarmante de la incidencia de gonorrea y sífilis entre los jóvenes de 15 a 24 años en la ciudad de

Barcelona entre los años 2007 y 2015, especialmente en los HSH, mientras que la infección por VIH se mantuvo estable, pero con una alta incidencia entre los HSH. También en el *estudio II,* esta vez con resultados para toda Cataluña, y de manera similar a como se observaba en otros países europeos, se describe como durante el período 2017-2019 las ITS prácticamente se doblaron en número de casos. Todo ello confirma la sindemia de las ITS como un problema de salud pública de primer orden. El aumento fue mayor en mujeres y en menores de 30 años. En los dos estudios la proporción de reinfecciones fue de un 11-12% y de coinfección por el VIH de un 6-7%. La clamidia solo se pudo analizar en el *estudio* II, pero junto con la gonorrea parecen representar la gran mayoría de las ITS notificadas. Si bien en Cataluña, como en muchas otras regiones de Europa, en la última década se ha observado una disminución en los nuevos casos de infección por el VIH principalmente debido al éxito del uso más amplio y temprano de terapias antirretrovirales, las tasas de ITS han aumentado dramáticamente, sobre todo entre la población HSH, las mujeres heterosexuales y los adultos jóvenes (sobre todo mujeres jóvenes).

En el *estudio II*, identificamos clústeres socio epidemiológicos de ITS a nivel de área pequeña, un primer clúster en donde predominaban las mujeres jóvenes que vivían en áreas rurales y desfavorecidas que se mostraron más afectadas por la clamidia, y un segundo clúster en el cual predominaban los HSH que vivían en áreas urbanas y menos desfavorecidas que presentaban tasas de incidencia de ITS más elevadas, múltiples episodios de ITS y una mayor proporción de coinfección por el VIH.

En el *estudio I*, entre los jóvenes con ITS, ser HSH, tener relaciones sexuales con múltiples parejas o un diagnóstico previo de ITS en los últimos 12 meses fueron factores asociados a la coinfección por el VIH. En el *estudio II*, lo fueron ser de sexo masculino, tener entre 30-39 años (vs. <20 años), tener múltiples episodios de ITS y vivir en zona urbana. Vivir en los ABS más desfavorecidos se asoció con menor probabilidad de coinfección por el VIH.

En el *estudio III*, nuestros resultados mostraron que la marcada disminución en las notificaciones de ITS se mantuvo casi cinco meses desde el inicio del confinamiento por la pandemia de COVID-19. Esto difícilmente puede explicarse sin un infra diagnóstico y una infra notificación significativos. Durante la pandemia se reportaron proporcionalmente menos ITS de lo esperado en mujeres, en personas VIH negativas, que vivían en áreas más desfavorecidas, y sin episodios previos de ITS durante los últimos tres años. Por lo tanto, la disminución de las notificaciones afectó proporcionalmente más algunos grupos de personas que a otros.

5.1.4. Recomendaciones

Es necesario implementar y/o mejorar los programas de prevención y control de ITS/VIH para evitar y reducir las infecciones por ITS y VIH, especialmente en grupos poblacionales a riesgo de infección.

Destacamos la importancia de mejorar los programas e intervenciones dirigidos a las mujeres y a los más jóvenes. En algunos países, las ITS son detectadas principalmente por médicos

de familia o generalistas; sin embargo, los centros especializados en ITS [72] han demostrado ser más efectivos en el diagnóstico de algunas ITS como la clamidia, gonorrea y sífilis, especialmente entre los jóvenes. Además, se deberían fortalecer o incluso ampliar algunos dispositivos asistenciales específicos como lo son en la ciudad de Barcelona *el centre jove d'anticoncepció i sexualitat* (CJAS) o la Unidad de enfermedades de transmisión sexual de Drassanes. Finalmente, también creemos que sería relevante intensificar el contacto directo con jóvenes dentro de las actividades desarrolladas en los servicios de salud pública o vigilancia epidemiológica fortaleciendo y ampliando la vigilancia activa, los estudios de contactos y la promoción de la salud en menores de 18 años. En este sentido, como ejemplo pueden servir algunos programas o intervenciones específicas dirigidas a las jóvenes llevadas a cabo por la agencia de salud pública de Barcelona (ASPB) como "*Salut sexual i reproductiva en dones immigrades i autòctones* (SIRIAN)" o "*parlem-ne no et tallis*".

En el *estudio I y II*, de entre el total de personas con una ITS (jóvenes de entre 15 a 24 años en el *estudio I*), se determinaron los factores asociados con la coinfección por el VIH. En el *estudio II*, además se identificaron tres distintos clústeres socio epidemiológicos de ITS a nivel de área pequeña de salud (ABS). Para cada uno de los clústeres se describió la incidencia de cada una de las ITS, así como la distribución de frecuencias de las características de los individuos dentro de cada clúster incluyendo información sobre el sexo, edad, preferencias sexuales y factores socioeconómicos. Nuestros hallazgos sugieren que incluir los

determinantes sociales de la salud en la monitorización de la endemia de ITS puede ser de gran ayuda en el diseño de intervenciones efectivas. Las poblaciones a riesgo de contraer ITS o/y VIH deben ser consideradas como objetivos prioritarios para la vigilancia y se debe profundizar en la identificación y caracterización de clústeres de características y factores de riesgo permitiendo así el diseño e implementación de intervenciones preventivas, de detección precoz o control en individuos o grupos de individuos según sus características.

En el *estudio III*, además de describir el impacto de la COVID-19 en la sindemia de las ITS, se describe como ese impacto es diferente en las diferentes poblaciones a riesgo de infección. Creemos firmemente que existe una necesidad urgente de fortalecer los programas y servicios de diagnóstico de ITS/VIH, así como la vigilancia, ya que la pandemia por COVD-19 podría estar todavía ocultando el tamaño real de la reemergencia de las ITS en muchas regiones del mundo.

5.2. Discusión, conclusiones y recomendaciones para los estudios relacionados con la sindemia de la tuberculosis (estudio IV y V)

5.2.1. Discusión

En Portugal, de 2015 a 2019, la tasa de notificación de TB disminuyó un 18,9% (de 21,2 a 17,2 casos por 100.000 habitantes), cifra que se acerca a la reducción del 20% fijada como hito

intermedio en la Estrategia *End TB* de la OMS para 2015-2020 [28]. Según este documento, la reducción que se espera es de un 50%, 80% y 90% para los periodos 2020-2025, 2025-2030 y 2030-2035 respectivamente. Aunque la reducción en Portugal durante el periodo 2015-2019 fue similar a la del 19% descrito para toda la región europea de la OMS, la infra notificación de TB podría haber jugado un papel en la disminución de casos como ya ha sido descrito en algunos países [73], [74].

En el *estudio IV*, los resultados muestran como a pesar de la tendencia decreciente en la tasa de notificación de TB en Portugal de 2010 a 2017 (5,2%/año), la disminución fue menor en los ciudadanos no portugueses, personas VIH negativas y niños menores de cinco años. La mayoría de los casos fueron notificados en las tres regiones portuguesas más pobladas (LVT, Norte y Centro) pero no se observaron diferencias significativas en el declive promedio interanual regional. Nuestros resultados mostraron cómo aquellas regiones con mayores tasas de notificación, sobre todo las regiones Norte y LVT, también fueron las que presentaron descensos interanuales ligeramente mayores, aunque sin ser diferencias estadísticamente significativas. Del mismo modo, las regiones con las tasas de notificación más bajas (principalmente Azores y Alentejo) fueron las que presentaron menores descensos interanuales. El hecho de que algunas regiones con menores tasas de incidencia de TB al comienzo del período de estudio mostraran una menor disminución de las tasas de notificación podría explicarse en parte por una menor probabilidad

de recibir intervenciones específicas precisamente por presentar bajas tasas de incidencia.

Los resultados de este estudio indicaron una disminución en las tasas de notificación de TB inferior en niños menores de cinco años (aunque el tamaño muestral fue muy pequeño para este grupo) y en ciudadanos de nacionalidad no portuguesa. Aunque también con cierto grado de incertidumbre debido a la pequeña cantidad de casos, la incidencia de TB en personas VIH-positivas parecía presentar una mayor disminución que en las VIH-negativas, lo que podría deberse a un cribado de ITL y un tratamiento preventivo más intensivos, así como a un aumento de la cobertura antirretroviral, entre los seropositivos en los últimos años.

En este estudio encontramos también descensos más pronunciados en las tasas de notificación en hombres que en mujeres, aunque no fueron diferencias significativas. De confirmarse este menor descenso podría deberse a los mismos factores que hacen que los hombres estén más afectados por la TB y que incluyen factores de riesgo sociales, conductuales y ocupacionales [75], [76]. Sin embargo, en contra de esta hipótesis, ha sido descrita recientemente una disminución más pronunciada en hombres en las tasas de incidencia de TB en EE. UU., China e India [77].

En el contexto actual, el ejemplo de la interacción COVID-19 y TB, es muy ilustrativo del tipo de interacciones que se pueden generan entre sindemias y sus efectos. Es necesario analizar si el COVID-19 favorece la progresión a TB o empeora el pronóstico de la misma y así aprender más sobre los efectos directos e indirectos de la pandemia por el COVID-19 en la prevención y el control de la TB,

incluidos los efectos producidos a través de los determinantes sociales de la salud [78], [79]. TB y COVID-19 se han asociado con mayores desigualdades en salud, así como con situaciones socioeconómicas desfavorables y pobreza [80]. Aunque un estudio reciente mostró tasas de mortalidad inferiores en inmigrantes diagnosticados de COVID-19 y TB, dichas diferencias se atribuyeron al hecho de que los inmigrantes tienden a ser más jóvenes y con menos comorbilidades [81]. Es posible que sea demasiado pronto para evaluar el impacto de la pandemia por COVID-19 en la incidencia de TB, pero un estudio reciente describe como en 33 centros de 18 países diferentes se han producido interrupciones de sus servicios en TB durante los primeros cuatro meses de la pandemia [82]. Según se informa en el *Global TB Report 2022* de la OMS, tras un descenso en el 2020 a nivel mundial de los principales indicadores para TB con el inicio de la pandemia por el COVID-19, los nuevos datos indican un aumento paulatino de los nuevos casos, muertes y casos resistentes a medicamentos de TB [83]. Como pasó en muchos lugares del mundo, el contexto socioeconómico y sanitario debido a la pandemia tuvieron un impacto significativo en la vigilancia y control de la TB en Barcelona donde se describió una disminución superior al 10% en el número de notificaciones y nuevos diagnósticos de TB [84]. Relacionado con esta disminución en la detección de casos y su notificación, podemos leer un estudio reciente que estima que la incidencia de TB aumentará a medio-largo plazo en tres países con alta carga de TB (India, Kenia y Ucrania) debido a las interrupciones relacionadas con el

confinamiento [85]. De cualquier manera, todos los recursos utilizados para diagnosticar y tratar la TB o el COVID-19 deben ser optimizados para hacer frente a ambas condiciones a la vez de la manera más eficaz posible [86].

Por otro lado, ha sido estimado que el tratamiento de la infección ITL podría evitar aproximadamente el 90% de los casos de progresión a TB activa [87]. Hay que tener en cuenta que la estrategia *End* TB de la OMS establece que el tratamiento de la ITL debe ser una prioridad para todos los programas de lucha contra la TB. Nuestro *estudio V* mostró tasas de FCT para ITL en Portugal durante el periodo 2013-2017 más bajas (14%) que las reportadas previamente en otros estudios (que varían del 20 al 60%) [88], [89]. Atribuimos esta baja tasa de FCT a los esfuerzos realizados por los diferentes actores en Portugal en su objetivo de aumentar el número de casos de ITL diagnosticados y tratados, así como de la consecución de la finalización y el éxito del tratamiento. Desde la creación del actual Programa Nacional de TB en 1995 en Portugal, se ha implementado el cribaje de ITL y el seguimiento efectivo de pacientes en servicios especializados de TB en atención primaria (centros ambulatorios de TB) así como un sólido sistema de vigilancia que incluye la notificación no solo de los casos de TB sino también los de ITL [90].

Aunque con resultados contradictorios entre estudios, diferentes factores como la edad, el sexo, el país de nacimiento, el abuso de sustancias, la coinfección por el VIH, el régimen de tratamiento, los efectos adversos del tratamiento, y la falta de visitas clínicas iniciales durante el tratamiento y de provisión de información sobre

la enfermedad de una manera oportuna y temprana se han asociado con el FCT [89], [91]–[94]. Por otro lado, en este caso en TB activa, se han descrito diferencias geográficas en cuanto a los principales factores de riesgo (entre regiones, áreas metropolitanas, áreas rurales/urbanas, o incluso en áreas más pequeñas) [95], [96]. En Portugal, las áreas metropolitanas de las dos ciudades principales (Lisboa y Oporto) presentan las tasas de notificación de TB más elevadas del país [31], [32] pero los principales factores de riesgo de la TB en cada una de ellas parecen ser diferentes, según un estudio realizado el 2014; en Lisboa los factores más relevantes eran ser migrante o vivir con VIH y en Oporto el abuso de alcohol y ser una PID [31], [97].

En el *estudio V* el FCT en ITL se asoció con un aumento de la edad del paciente, la región de notificación del caso (mayor FCT en las regiones de LTV, Norte y Algarve) y el país de nacimiento (mayor FCT para los nacidos en Asia o África). Tener una enfermedad crónica, el abuso del alcohol y ser una PID también se asociaron con un mayor riesgo de FCT. Estar encarcelado y recibir tratamiento para ITL directamente observado (TDO) de un trabajador de salud se asoció con un menor riesgo de FCT. Los tratamientos de 3 meses de isoniazida más rifampicina se asociaron con un menor riesgo de FCT comparado con el estándar de 6 o 9 meses de isoniazida sola. En las áreas metropolitanas de Lisboa y Oporto, los factores asociados con un mayor riesgo de FCT fueron: i) en Lisboa, haber nacido en África y recibir un tratamiento de 3 meses con rifampicina sola, y ii) en Oporto, ser mayor de 15 años, abuso de alcohol y ser una PID. Hay que tener en cuenta que según

el número de casos de TB activa informados en Portugal, se esperaría un número similar de pacientes con ITL en las regiones LTV y Norte. Sin embargo, en la región norte la razón de número de tratamientos de ITL por casos de TB activa fue el doble que en la región LTV, lo que posiblemente refleja diferencias en las políticas regionales de prevención y control de la TB.

El FCT fue menor en niños y adolescentes probablemente debido a un seguimiento más cercano por parte tanto de los servicios de salud como de sus familias (es frecuente que otros familiares estén siendo tratados simultáneamente por TB o ITL). A pesar de que aproximadamente el 90 % de los pacientes estaban siendo tratados solo con isoniazida (54,9% con el ciclo de 6 meses), nuestros resultados sugieren lo mismo que la mayoría de los estudios previos, tratamientos de ciclo más cortos y TDO pueden reducir el FCT en ITL.

5.2.2. Fortalezas y Limitaciones

Las principales limitaciones del *estudio IV* son:

- La cumplimentación baja especialmente para el VIH (variable no cumplimentada en un 15% de los casos). Este hecho podría haber sesgado nuestros resultados, y que, en realidad, no hubiese una mayor disminución en el número de casos de TB en las personas VIH positivas.
- La falta de datos estratificados para todos los potenciales subgrupos poblacionales que se pueden obtener al combinar las variables disponibles en el estudio (por ejemplo, tasas de

TB en personas VIH positivas por regiones o por sexo). Disponer de estos datos nos hubiese permitido hacer análisis estratificados y/o multivariados y así poder estimar la disminución en el número de casos de TB en subgrupos pertenecientes a varias poblaciones a riesgo de manera simultánea.

Las principales fortalezas del *estudio IV* son:

- Se incluyen datos de calidad a nivel nacional para algunos de los grupos más relevantes a riesgo de infección para la TB.
- Se aporta un análisis de las disminuciones promedio interanuales en las tasas de notificación de TB durante el periodo de estudio. En algunas ocasiones, este indicador puede ser más útil que el análisis de tendencias de los números absolutos de casos de TB ya que las variaciones promedio interanuales se ven menos afectadas por cambios de tendencias esporádicos/anuales.

Las principales limitaciones del *estudio V* son:

- La falta de información para cada individuo sobre el desarrollo posterior de ITL a TB. Tener esta información nos permitiría evaluar el papel del FCT en la ITL y sus factores relacionados en el posterior desarrollo hacía TB.
- Factores como la efectividad del tratamiento para la ITL (es decir, no desarrollar TB activa después de completar el tratamiento de ITL) y los efectos adversos relacionados con los medicamentos no se abordaron en este estudio, por lo

que no podemos recomendar regímenes de tratamiento más cortos basados únicamente en la menor probabilidad de FCT.

- La falta de información sobre otros potenciales factores de riesgo de FCT como el consumo de drogas, la falta de vivienda o encarcelamiento. Debido a las múltiples interacciones entre la TB y diferentes factores sociales, en futuros estudios sería relevante incluir información sobre estas condiciones además de otros determinantes sociales de la salud.
- Los pacientes diagnosticados de ITL que finalmente no inician tratamiento no son reportados. Este hecho podría inducir un sesgo de selección, ya que estos pacientes podrían tener características diferentes a los que efectivamente inician tratamiento para la ITL. Así pues, los pacientes que inician tratamiento y que, por lo tanto, son incluidos en el estudio, podrían presentar un nivel socioeconómico más favorable de lo que en realidad sería el nivel del conjunto de los pacientes con ITL.
- Hubo un nueve por ciento de los pacientes que tenían un resultado de tratamiento desconocido. A pesar de ello la distribución de las frecuencias de las distintas características en este grupo fueron similares a las de los pacientes que tenían un resultado conocido y que fueron incluidos en los análisis.
- No tuvimos acceso a los datos relacionados con la infección por el VIH. Estos datos podrían aportar una valiosa

información adicional, ya que se recomiendan ciclos de tratamiento más largos en pacientes VIH positivos.

- El corte de inicio que aceptamos para la categoría "curso completo de 6 meses con isoniazida sola" se estableció en los 4 meses. Este hecho también podría estar infra estimando el FCT (aunque el 75% de los pacientes en esa categoría recibieron 183 días o más de tratamiento único con isoniazida).

Las principales fortalezas del *estudio V* son:

- La principal fortaleza de este estudio es el tamaño de la muestra, ya que se incluyeron todos los casos de ITL que iniciaron tratamiento en Portugal entre 2013 y 2017, pocos estudios han analizado el FCT y los factores asociados utilizando todos los datos nacionales disponibles.
- Se incluyen variables geográficas, socioeconómicas y clínicas lo que permite un análisis en profundidad del FCT en la ITL.
- Se han publicado muchos estudios que analizan los factores asociados a el FCT en la TB, pero solo unos pocos sobre el FCT en la ITL.

5.2.3. Conclusiones

El *estudio IV*, muestra como a pesar de la disminución de la incidencia de TB en Portugal entre 2010 y 2017, hay ciertas poblaciones que presentan menor declive durante el periodo de estudio. La disminución fue menor entre ciudadanos no

portugueses, niños menores de 5 años y pacientes no infectados por el VIH. Como se ha comentado en la discusión, este hecho seguramente se puede explicar por distintas interacciones sindémicas que hacen que ciertos factores de riesgo de infección o asociados con la detección de la TB afecten más a unas poblaciones que a otras. Por otro lado, a pesar de que aquellas regiones con mayores tasas de notificación presentaban un ligero mayor descenso y las de menores tasas un ligero menor descenso, no se observaron diferencias significativas en la disminución promedio interanual entre regiones.

La búsqueda activa de casos en poblaciones a riesgo se ha descrito como una forma eficaz de fortalecer la prevención y el control de la TB [98]. Tanto el CDC como el ECDC ya monitorizan cambios de tendencias en los nuevos casos de TB en diferentes grupos de riesgo y regiones [27], [99]. A pesar de ello, aún se necesita disponer de una monitorización de la transmisión de la TB para los distintos grupos a riesgo de infección así como identificar y controlar las interacciones o asociaciones entre dichos grupos para obtener información detallada y precisa sobre las poblaciones a riesgo de infección por TB y sus factores relacionados [30]. En algunas ocasiones en las que se requiere una evaluación de la tendencia a medio-largo termino (a partir de 5-7 años), el análisis de las variaciones promedio interanuales puede ser más útil que el análisis de tendencia de números absolutos a la hora de sacar conclusiones robustas para el diseño de intervenciones, ya que las variaciones promedio interanuales se ven menos afectadas por cambios de tendencia esporádicos/anuales que podrían deberse a una amplia

gama de causas (incluidas brotes o infra diagnóstico/infra notificación debido a cualquier causa externa, como por ejemplo la pandemia de COVID-19). En definitiva, la monitorización de la variación promedio interanual de las poblaciones a riesgo de infección puede ser un indicador de utilidad para poder estimar las tendencias o cambios en la incidencia de TB en diferentes periodos de estudio y así monitorizar la consecución de los objetivos de la Estrategia *End TB*. El éxito aparente de Portugal al lograr la reducción de la tasa de incidencia de TB en un 20% como marca la propia estrategia *End TB* para el periodo 2015-2020, debe ser monitorizada para asegurar en lo posible poder acabar con la TB para el año 2035. Además, la posible infra notificación debido a la pandemia de COVID-19 en 2020, así como un posible escenario de aumento de la incidencia de TB "pos-COVID-19", deben ser considerados al planificar las medidas y recursos de prevención y control necesarios.

Finalmente, en el *estudio V,* se estima el impacto negativo de diferentes factores sociodemográficos, clínicos y de comportamiento en los resultados del FCT para la ITL. Los resultados muestran como diferentes factores dentro de la sindemia de la TB pueden contribuir no solo a incrementar el riesgo de infección, sino que también pueden producir peores resultados en el tratamiento o en la adherencia al mismo. El *estudio V* aporta nuevos conocimientos sobre la relevancia de algunos factores que pueden aumentar el riesgo de FCT en la ITL, como tener más edad, la nacionalidad (como *proxy* de país de nacimiento y de factores relacionados con los determinantes sociales de la salud), la

presencia de enfermedades crónicas, el abuso del alcohol y el ser PID. El análisis diferenciado según región o área metropolitana de residencia mostró diferencias en cuanto a los factores de riesgo más relevantes de FCT. Por otro lado, el estudio refuerza la evidencia de que en la ITL es más probable que se complete un tratamiento de ciclo más corto, particularmente en individuos con un mayor riesgo de FCT.

En conclusión, optimizar la detección de TB y ITL en las poblaciones a riesgo de infección, como por ejemplo las descritas en el *estudio IV,* y el asegurar una buena adherencia al tratamiento en la ITL en grupos a más riesgo de FCT, como los identificados en el *estudio V,* se encuentran entre las actividades que se requieren para el fortalecimiento de la vigilancia epidemiológica, así como la prevención y el control en la sindemia de la TB.

5.2.4. Recomendaciones

Teniendo en cuenta nuestros resultados estas serían nuestras recomendaciones específicas:

- Intensificar la detección oportunista de TB en al menos las tres poblaciones identificadas en el *estudio IV* como aquellas que presentaron una menor disminución de la tasa de incidencia; ciudadanos de nacionalidad extranjera, niños menores de 5 años y pacientes no infectados por el VIH.
- Intentar aumentar la sensibilización de los médicos para que consideren y tengan presente el diagnóstico de TB en aquellas

poblaciones para las cuales se observan peores resultados en la detección y descenso de las tasas de TB.

- Un cribado sistemático de TB en inmigrantes originarios de países de alta incidencia.
- Asegurar que a los recién nacidos con factores de riesgo específicos se les ofrezca de manera oportuna la vacuna de la BCG.
- Fortalecer el estudio de contactos, sobre todo en inmigrantes y en entornos donde hay niños con más frecuencia.
- Tener en cuenta diferentes factores que puedan influenciar el FCT en ITL (como los descritos en el *estudio V*) y de esta manera resolver la ITL antes de que esta pueda evolucionar a TB activa.

Además consideramos que los trabajadores comunitarios de salud deberían integrarse con más frecuencia en los equipos de respuesta a la TB, tanto a nivel operativo como estratégico, para facilitar y mejorar el estudio de contactos y el tratamiento de la ITL y de la TB, sobre todo cuando existen barreras idiomáticas o culturales [100]. La vigilancia epidemiológica de la TB debería seguir fortaleciéndose para poder identificar mejor las poblaciones a riesgo de infección en cada área geográfica de intervención y monitorizar las tendencias temporales, cambios de incidencia o los resultados terapéuticos en cada una de esas poblaciones. Se requiere de un análisis en profundidad a nivel regional-local para adaptar las intervenciones de la mejor manera posible a cada área específica. De esta manera creemos se puede mejorar en la planificación de actividades e intervenciones de prevención y control a nivel local,

regional o nacional para seguir trabajando para seguir reduciendo la incidencia de TB.

5.3. Conclusiones y recomendaciones globales

Los manuscritos presentados muestran como las ITS y la TB actúan como sindemias y describen algunas de las múltiples interacciones que ambas presentan con otras epidemias o factores, presentándose con más frecuencia en determinadas poblaciones a riesgo, y que pueden aumentar las probabilidades de infección y/o gravedad de la enfermedad, así como pueden hacer disminuir el éxito del tratamiento o la adherencia al mismo. Consideramos que una vigilancia epidemiológica realizada desde una aproximación sindémica, como la que hemos llevado a cabo en los estudios que componen la tesis, puede proporcionar una descripción detallada de ambas endemias (la de las ITS y la de la TB), permitiendo la identificación y caracterización de las distintas poblaciones a riesgo de infección. La monitorización de las incidencias y de sus factores asociados en dichas poblaciones puede ser de gran ayuda en el diseño, rediseño o evaluación de intervenciones. También en la evaluación del impacto que pueden representar eventos relevantes, como en el *estudio III,* donde evaluamos el impacto del COVID-19 en los casos de ITS reportados al sistema de vigilancia. Todo ello, creemos puede contribuir a fortalecer la vigilancia epidemiológica, y por consiguiente mejorar la prevención y el control de las sindemias de las ITS y la TB.

La implementación de una vigilancia epidemiológica desarrollando esta perspectiva sindémica centrada en grupos a riesgo supone un desafío por diversos motivos. Primero, por la falta de datos y/o la baja cumplimentación en algunas variables de las encuestas epidemiológicas, lo que dificulta poder capturar información de factores claves como los relacionados con comportamientos de riesgo, conductas sexuales o datos demográficos y socioeconómicos. La buena cumplimentación de estos datos permitiría una descripción y caracterización más holística y en detalle de las personas o poblaciones más afectadas y sus factores de riesgo. Segundo, la falta de variables de enlace estables, o variables identificadoras de los individuos que sean las mismas en las diferentes bases de datos, dificulta el enlace entre bases de datos y, por lo tanto, la obtención de algunas variables de interés para la vigilancia. Un ejemplo sería la falta de enlace en muchas ocasiones entre las bases de vigilancia epidemiológica, datos laboratoriales, datos administrativos y sociodemográficos, o historia clínica. Consideramos que de esta manera se pierde una gran oportunidad de recoger información, ya sea de manera individualizada o en forma de datos agregados, de múltiples variables o factores que interaccionan y/o caracterizan cada una de las sindemias.

Otro de los principales desafíos, quizá de más fácil solución que los dos primeros, es el promover, como paradigma, una vigilancia epidemiológica en donde el concepto de sindemia tenga un papel central, y que esta perspectiva se enseñe en las distintas etapas formativas, no solo a los profesionales de la salud pública, sino también a todos los profesionales de la salud en general. Un

enfoque sidémico en la formación contribuiría a una respuesta, tratamiento o investigación de la infecciones más completa y optimizada.

A pesar de que desde los años 90 se ha ido desarrollando el concepto de sindemia para algunas enfermedades transmisibles, parece que no ha sido hasta el contexto actual con el COVID-19 que se ha hecho más hincapié en las interacciones que hacen que el SARS-CoV-2 no afecte a todos por igual, ya sea en el riesgo de infectarse, de enfermar o en la severidad. También la pandemia por el COVID-19 ha puesto en relieve los ejes de desigualdad que no facilitan que los recursos empleados en los cuidados de los enfermos de COVID-19 sean distribuidos de manera equilibrada y equitativa (tanto en prevención, diagnóstico, o tratamiento). Finalmente, se ha podido visibilizar el estrés y el desafío que supone una pandemia para el control no solo de la misma, sino también para el control de otras infecciones o endemias como las ITS y la TB. Esto es debido sobre todo al desvío de recursos humanos, económicos y materiales hacía la nueva situación pandémica. Este impacto negativo puede ser compensado o revertido de alguna manera si estos recursos dedicados para luchar contra el COVID-19, sobre todo los humanos, pueden ser transferidos o compartidos, y no desmantelados en los momentos pandémicos de desescalada, para la vigilancia epidemiológica, prevención y control de otras epidemias.

En el anexo 1, incluimos un protocolo de monitorización de la seroprevalencia de SARS-CoV-2 en una red centinela de pacientes de atención primaria en el área metropolitana de Barcelona que

hemos publicado recientemente. En este protocolo combinamos las metodologías y los diseños de estudios epidemiológicos utilizados en los diferentes estudios que componen la tesis con el objetivo precisamente de implementar una vigilancia epidemiológica desde una aproximación sindémica. Esto incluye, por ejemplo, del uso de técnicas de *machine learning* para la identificación de clústeres o el uso de análisis de series temporales interrumpidas para la evaluación de intervenciones o eventos de manera similar a como hemos empleado ambas en los *estudios III y IV* respectivamente.

Por lo tanto, recomendamos en la medida de lo posible adoptar este nuevo paradigma de sindemia en las diferentes actividades desarrolladas dentro de la vigilancia epidemiológica, tanto al diseñar o rediseñar los sistemas de vigilancia, como en la recogida, análisis o interpretación de datos, así como en el diseño de intervenciones de prevención y control. Debemos asegurarnos que el esfuerzo realizado y los avances acontecidos durante la pandemia de COVID-19 en la integración de datos de múltiples fuentes así como en el uso de nuevas metodologías y herramientas, beneficie y proporcione también los datos y herramientas necesarias para poder describir y caracterizar otras sindemias no tan solo teniendo en cuenta las variables o factores más frecuentemente monitorizados como la edad o la comorbilidad, sino otros que la mayoría de las veces son olvidados como el género, los determinantes sociales de la salud, o los relacionados con determinadas conductas o comportamientos de riesgo.

Todo ello creemos fortalecería y aumentaría la efectividad de los sistemas de vigilancia epidemiológica haciéndolos más útiles en la

preparación y respuesta a epidemias, así como en su integración con los otros sistemas dentro de los servicios de la salud como son la atención primaria y la hospitalaria.

6. Bibliografia

[1] M. Singer, *Introduction to Syndemics: A Critical Systems Approach to Public and Community Health*. Wiley, 2009.

[2] M. Singer and S. Clair, "Syndemics and Public Health: Reconceptualizing Disease in Bio-Social Context," *Med. Anthropol. Q.*, vol. 17, no. 4, pp. 423–441, Dec. 2003, doi: 10.1525/MAQ.2003.17.4.423.

[3] H. J. de V. Guest Editor: Kenneth H Mayer, "Understanding and addressing the HIV and STI syndemics.," *J. Int. AIDS Soc.*, vol. 22, supple, [Online]. Available: https://onlinelibrary.wiley.com/toc/17582652/2019/22/S6

[4] C. Kwan and J. D. Ernst, "HIV and tuberculosis: a deadly human syndemic," *Clin. Microbiol. Rev.*, vol. 24, no. 2, pp. 351–376, Apr. 2011, doi: 10.1128/CMR.00042-10.

[5] B. A. Swinburn *et al.*, "The Global Syndemic of Obesity, Undernutrition, and Climate Change: The Lancet Commission report," *Lancet*, vol. 393, no. 10173, pp. 791–846, Feb. 2019, doi: 10.1016/S0140-6736(18)32822-8.

[6] M. Everett and J. N. Wieland, "Diabetes among oaxaca's transnational population: an emerging syndemic" *Ann. Anthropol. Pract.*, vol. 36, no. 2, pp. 295–311, Nov. 2012, doi: 10.1111/NAPA.12005.

[7] C. J. Carlson and E. Mendenhall, "Preparing for emerging infections means expecting new syndemics," *Lancet*, vol. 394, no. 10195, p. 297, Jul. 2019, doi: 10.1016/S0140-6736(19)31237-1.

[8] E. Courtin and P. Vineis, "COVID-19 as a Syndemic," *Front. Public Heal.*, vol. 9, p. 1401, Sep. 2021, doi: 10.3389/FPUBH.2021.763830/BIBTEX.

[9] R. Horton, "Offline: COVID-19 is not a pandemic," *Lancet*, vol. 396, no. 10255, p. 874, Sep. 2020, doi: 10.1016/S0140-6736(20)32000-6.

[10] "Determinantes sociales de la salud - OPS/OMS | Organización Panamericana de la Salud." https://www.paho.org/es/temas/determinantes-sociales-salud (accessed Mar. 24, 2022).

[11] "WHO EMRO | Vulnerable groups and key populations at

increased risk of HIV | Health topics | AIDS and sexually transmitted diseases." http://www.emro.who.int/asd/health-topics/vulnerable-groups-and-key-populations-at-increased-risk-of-hiv.html (accessed Mar. 24, 2022).
[12] "WHO | Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations – 2016 Update" https://www.ncbi.nlm.nih.gov/books/NBK379697/ (accessed Feb. 24, 2022).
[13] J. Rowley *et al.*, "Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016," *Bull. World Health Organ.*, vol. 97, no. 8, pp. 548-562P, Aug. 2019, doi: 10.2471/BLT.18.228486.
[14] WHO Department of Reproductive Health and Research, "Report on global sexually transmitted infection surveillance," 2018. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/277258/9789241565691-eng.pdf?ua=1
[15] "European Centre for Disease Prevention and Control. Chlamydia infection. Annual epidemiological report for 2018. Stockholm: ECDC; 2020.".
[16] "European Centre for Disease Prevention and Control. Gonorrhoea. Annual epidemiological report for 2018. Stockholm: ECDC; 2020."
[17] "European Centre for Disease Prevention and Control. Syphilis. Annual epidemiological report for 2018. Stockholm: ECDC; 2020."
[18] "European Centre for Disease Prevention and Control. Lymphogranuloma venereum. Annual epidemiological report for 2018. Stockholm: ECDC; 2020."
[19] "Área de vigilancia del VIH y conductas de riesgo. Vigilancia epidemiológica de las infecciones de transmisión sexual, 1995-2010. Madrid: Centro Nacional de Epidemiología, Instituto de Salud Carlos III/Plan Nacional sobre el Sida - Dirección General de Salud Pública, 2012", [Online]. Available: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/VigilanciaITS1995_2010.pdf
[20] "Área de vigilancia del VIH y conductas de riesgo. Vigilancia epidemiológica de las infecciones de transmisión sexual, 2017. Madrid: Centro Nacional de Epidemiología, Instituto de Salud Carlos III/Plan Nacional sobre el Sida -

Dirección General de Salud Pública, 2019", [Online]. Available: https://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/sida/vigilancia/Vigilancia_ITS_1995_2017_def.pdf
[21] Centre d'Estudis Epidemiològics sobres les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), "Vigilància epidemiològica de les Infeccions de Transmissió Sexual (ITS) a Catalunya, Informe anual 2019," Badalona, Spain, 2020. [Online]. Available: https://canalsalut.gencat.cat/web/.content/_A-Z/S/sida/enllasos/anual_ITS.pdf
[22] M. M. Taylor and T. E. C. Wi, "Transforming and integrating STI surveillance to enhance global advocacy and investment in STI control," *J. Int. AIDS Soc.*, vol. 22, no. S6, p. 25361, 2019, doi: 10.1002/jia2.25361.
[23] "CDC | HIV/AIDS & STDs." https://www.cdc.gov/std/hiv/default.htm (accessed Feb. 22, 2021).
[24] A. Sentís *et al.*, "Sexually transmitted infections in young people and factors associated with HIV coinfection: An observational study in a large city," *BMJ Open*, vol. 9, no. 5, p. e027245, May 2019, doi: 10.1136/bmjopen-2018-027245.
[25] O. Le Polain De Waroux, R. J. Harris, G. Hughes, and P. D. Crook, "The epidemiology of gonorrhoea in London: A Bayesian spatial modelling approach," *Epidemiol. Infect.*, vol. 142, no. 1, pp. 211–220, Jan. 2014, doi: 10.1017/S0950268813000745.
[26] D. Gesink, S. Wang, T. Norwood, A. Sullivan, D. Al-Bargash, and R. Shahin, "Spatial epidemiology of the syphilis epidemic in Toronto, Canada," *Sex. Transm. Dis.*, vol. 41, no. 11, pp. 637–648, Nov. 2014, doi: 10.1097/OLQ.0000000000000196.
[27] "European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2020 – 2018 data. Stockholm: ECDC; 2020", doi: 10.2900/0737073.
[28] "WHO | The End TB Strategy," *WHO*, 2020, Accessed: Jan. 20, 2021. [Online]. Available: http://www.who.int/tb/strategy/en/
[29] J. Littleton and J. Park, "Tuberculosis and syndemics: Implications for Pacific health in New Zealand," *Soc. Sci.*

Med., vol. 69, no. 11, pp. 1674–1680, Dec. 2009, doi: 10.1016/j.socscimed.2009.08.042.
[30] European Centre for Disease Prevention and Control., "Review of reviews and guidelines on target groups, diagnosis, treatment and programmatic issues for implementation of latent tuberculosis management. Stockholm: ECDC; 2018." doi: 10.2900/318458.
[31] I. Franco, P. Sousa, M. Gomes, A. Oliveira, A. R. Gaio, and R. Duarte, "Social profile of the highest tuberculosis incidence areas in Portugal," *Rev. Port. Pneumol. (English Ed.*, vol. 22, no. 1, pp. 50–52, Jan. 2016, doi: 10.1016/J.RPPNEN.2015.08.006.
[32] M. Felgueiras, S. Cerqueira, R. Gaio, Ó. Felgueiras, and R. Duarte, "Comparative Study Between Tuberculosis Incidence Rates in the Two Largest Metropolitan Areas of Portugal," *Arch. Bronconeumol.*, vol. 54, no. 11, pp. 595–596, Nov. 2018, doi: 10.1016/j.arbres.2018.05.003.
[33] Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT). "SIVES 2015 - Sistema Integrat de Vigilància Epidemiològica de la SIDA/VIH/ITS a Catalunya," 2015. Accessed: Mar. 27, 2021. [Online]. Available: https://scientiasalut.gencat.cat/bitstream/handle/11351/3418/informe_SIVES_2015_informe_epidemiologic_CEEISCAT_2015.pdf.pdf?sequence=1&isAllowed=y
[34] Direção-Geral da Saúde, "Sistema de Vigilância de Tuberculose (SVIG TB)." https://www.dgs.pt/prevencao-e-controlo-da-doenca/doencas-transmissiveis/areas-de-intervencao/tuberculose/sistema-de-vigilancia-de-tuberculose.aspx (accessed May 23, 2019).
[35] Departament de salut, Generalitat de Catalunya, "Definició de cas de les malalties de declaració obligatòria," 11a. edició: Barcelona, 2010. Accessed: Aug. 09, 2017. [Online]. Available: file:///C:/Users/Alexis/Desktop/spdefimdo.pdf
[36] "European Centre for Disease Prevention and Control. EU case definitions, 2018." https://www.ecdc.europa.eu/en/surveillance-and-disease-data/eu-case-definitions (accessed Aug. 07, 2020).
[37] "Departament de salut.Agència de Salut Pública de Catalunya (ASPCAT), Generalitat de Catalunya. Declaració epidemiològica."

https://salutpublica.gencat.cat/ca/ambits/vigilancia_salut_publica/sistemes-de-declaracio-epidemiologica/ (accessed Aug. 05, 2022).
[38] "Decret 67/2010, de 25 de maig, pel qual es regula el sistema de notificación de malalties de declaració obligatòria i brots epidèmics al Departament de Salut. DOGC. Diari Oficial de la Generalitat de Catalunya, 8 Juliol 2010; núm. 5666." [Online]. Available: http://cido.diba.cat/legislacio/1342856/decret-672010-de-25-de-maig-pel-qual-es-regula-el-sistema-de-notificacio-de-malalties-de-declaracio-obligatoria-i-brots-epidemics-al-departament-de-salut.
[39] "Malalties de declaració obligatòria i brots epidèmics. Departament de Salut, Agència de Salut Pública de Catalunya, Generalitat de Catalunya, 2016" https://canalsalut.gencat.cat/ca/professionals/vigilancia-epidemiologica/malalties-de-declaracio-obligatoria-i-brots-epidemics/ (accessed Jun. 20, 2021).
[40] "Direção-Geral da Saúde. Despacho n.º 15385-A/2016 de 21 de dezembro 2016." https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/sinave/legislacao.aspx (accessed Aug. 02, 2022).
[41] European Centre for Disease Prevention and Control., "Programmatic management of latent tuberculosis infection in the European Union," 2018. Accessed: May 27, 2019. [Online]. Available: https://ecdc.europa.eu/en/publications-data/programmatic-management-latent-tuberculosis-infection-european-union
[42] M. Martí-Pastor *et al.*, "Epidemiology of infections by HIV, Syphilis, Gonorrhea and Lymphogranuloma Venereum in Barcelona City: a population-based incidence study.," *BMC Public Health*, vol. 15, p. 1015, 2015, doi: 10.1186/s12889-015-2344-7.
[43] S. Mills, T. Saidel, R. Magnani, and T. Brown, "Surveillance and modelling of HIV, STI, and risk behaviours in concentrated HIV epidemics," in *Sexually Transmitted Infections*, Dec. 2004, vol. 80, no. SUPPL. 2, pp. ii57–ii62. doi: 10.1136/sti.2004.011916.
[44] C. Folch, A. Esteve, K. Zaragoza, R. Munoz, and J. Casabona, "Correlates of intensive alcohol and drug use in men who have sex with men in Catalonia, Spain.," *Eur. J.*

Public Health, vol. 20, no. 2, pp. 139–145, Apr. 2010, doi: 10.1093/eurpub/ckp091.

[45] P. Saberi, T. B. Neilands, M. A. Lally, S. G. Hosek, and L. Hightow-weidman, "The Association between Use of Online Social Networks to Find Sex Partners and Sexually Transmitted Infection Diagnosis among Young Men Who Have Sex with Men and Transgender Women Living with HIV," vol. 18, pp. 1–11, 2019, doi: 10.1177/2325958219867324.

[46] K. Jansen *et al.*, "STI in times of PrEP: High prevalence of chlamydia, gonorrhea, and mycoplasma at different anatomic sites in men who have sex with men in Germany," *BMC Infect. Dis.*, vol. 20, no. 1, Feb. 2020, doi: 10.1186/s12879-020-4831-4.

[47] E. J. Gibson, D. L. Bell, and S. A. Powerful, "Common Sexually Transmitted Infections in Adolescents," *Prim. Care Clin. Off. Pract.*, vol. 41, no. 3, pp. 631–650, 2014, doi: 10.1016/j.pop.2014.05.011.

[48] K. L. Dehne and G. Riedner, "Sexually transmitted infections among adolescents the need for adequate health services." Accessed: Aug. 24, 2017. [Online]. Available: http://www.who.int/child-adolescent-health

[49] "CDC | Adolescents and Young Adults | Prevention | STDs." https://www.cdc.gov/std/life-stages-populations/adolescents-youngadults.htm (accessed Sep. 15, 2017).

[50] "European Centre for Disease Prevention and Control. Lymphogranuloma venereum. Annual epidemiological report for 2015. Stockholm: ECDC; 2017." Accessed: Feb. 25, 2018. [Online]. Available: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-Lymphogranuloma-venereum.pdf

[51] "European Centre for Disease Prevention and Control. Syphilis. Annual epidemiological report for 2015. Stockholm: ECDC; 2017." Accessed: Feb. 25, 2018. [Online]. Available: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-syphilis.pdf

[52] "European Centre for Disease Prevention and Control. Gonorrhoea. Annual epidemiological report for 2015. Stockholm: ECDC; 2017." Accessed: Feb. 25, 2018. [Online]. Available: https://ecdc.europa.eu/en/publications-

data/gonorrhoea-annual-epidemiological-report-2015
[53] "Agencia de salut pública de Barcelona. Morbiditat per malalties de declaració obligatòria a Barcelona ciutat 2015 Estadístiques de Salut. Barcelona 2017" Accessed: Jul. 29, 2018. [Online]. Available: https://www.aspb.cat/wp-content/uploads/2017/11/Morbiditat_per_malalties_declaracio_obligatoria_Barcelona_2015.pdf
[54] M. P. Davoren, K. Hayes, M. Horgan, and F. Shiely, "Sexually transmitted infection incidence among adolescents in Ireland.," *J. Fam. Plann. Reprod. Health Care*, vol. 40, no. 4, pp. 276–82, Oct. 2014, doi: 10.1136/jfprhc-2013-100596.
[55] N. Vives *et al.*, "Increase in gonorrhoea among very young adolescents, Catalonia, Spain, January 2012 to June 2013.," *Euro Surveill.*, vol. 18, no. 33, p. 20560, Aug. 2013, Accessed: Feb. 25, 2018. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/23968876
[56] R. L. Yavorsky *et al.*, "Prevalence of sexually transmitted infections in at-risk adolescent females at a comprehensive, stand-alone adolescent health center in New York City.," *Clin. Pediatr. (Phila).*, vol. 53, no. 9, pp. 890–5, Aug. 2014, doi: 10.1177/0009922814533816.
[57] C. A. O'Connor and C. D. Shubkin, "Adolescent STIs for primary care providers.," *Curr. Opin. Pediatr.*, vol. 24, no. 5, pp. 647–55, Oct. 2012, doi: 10.1097/MOP.0b013e328357bf86.
[58] E. C. Newbern *et al.*, "Adolescent sexually transmitted infections and risk for subsequent HIV.," *Am. J. Public Health*, vol. 103, no. 10, pp. 1874–81, Oct. 2013, doi: 10.2105/AJPH.2013.301463.
[59] T. L. K. Mullins, B. J. Rudy, C. M. Wilson, H. Sucharew, and J. A. Kahn, "Incidence of sexually transmitted infections in HIV-infected and HIV-uninfected adolescents in the USA," *Int. J. STD AIDS*, vol. 24, no. 2, pp. 123–127, Feb. 2013, doi: 10.1177/0956462412472425.
[60] S. E. Forhan *et al.*, "Prevalence of Sexually Transmitted Infections Among Female Adolescents Aged 14 to 19 in the United States," *Pediatrics*, vol. 124, no. 6, pp. 1505–1512, Dec. 2009, doi: 10.1542/peds.2009-0674.
[61] M. E. Tarr and M. L. Gilliam, "Sexually transmitted infections in adolescent women.," *Clin. Obstet. Gynecol.*, vol. 51, no. 2, pp. 306–18, Jun. 2008, doi:

10.1097/GRF.0b013e31816d7386.
[62] D. Lepusić and S. Radović-Radovcić, “Risk factors for sexually transmitted infections among young adolescents.,” *Coll. Antropol.*, vol. 37, no. 2, pp. 455–8, Jun. 2013, Accessed: Aug. 01, 2016. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/23940989
[63] N. Vives *et al.*, “Recent trends in sexually transmitted infections among adolescents, Catalonia, Spain, 2012–2017:,” *https://doi.org/10.1177/0956462420940911*, Aug. 2020, doi: 10.1177/0956462420940911.
[64] M. Murti *et al.*, “The need for integrated public health surveillance to address sexually transmitted and blood-borne syndemics,” *Canada Commun. Dis. Rep.*, vol. 45, no. 2/3, pp. 63–66, Feb. 2019, doi: 10.14745/ccdr.v45i23a03.
[65] A. V. Hill, N. M. De Genna, M. J. Perez-Patron, T. D. Gilreath, C. Tekwe, and B. D. P. Taylor, “Identifying Syndemics for Sexually Transmitted Infections Among Young Adults in the United States: A Latent Class Analysis,” *J. Adolesc. Heal.*, vol. 64, no. 3, pp. 319–326, Mar. 2019, doi: 10.1016/j.jadohealth.2018.09.006.
[66] Jagadesh S, Combe M, Couppié P, et al “Mapping priority neighborhoods: A novel approach to cluster identication in HIV/AIDS population,” *Res. Sq.*, 2020, doi: 10.21203/rs.3.rs-17843/v1.
[67] Centre d’Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), “Vigilància epidemiològica de les infeccions de transmissió sexual a Catalunya. Informe anual 2021” Badalona, Spain, 2022. Accessed: Dec. 01, 2022. [Online]. Available: www.ceeiscat.cat
[68] K. Tang, J. Gaoshan, and B. Ahonsi, “Sexual and reproductive health (SRH): A key issue in the emergency response to the coronavirus disease (COVID-19) outbreak,” *Reprod. Health*, vol. 17, no. 1, p. 59, Apr. 2020, doi: 10.1186/s12978-020-0900-9.
[69] T. H. Sanchez, M. Zlotorzynska, M. Rai, and S. D. Baral, “Characterizing the Impact of COVID-19 on Men Who Have Sex with Men Across the United States in April, 2020,” *AIDS Behav.*, vol. 24, no. 7, pp. 2024–2032, Jul. 2020, doi: 10.1007/s10461-020-02894-2.
[70] “European Centre for Disease Prevention and Control | Facts

about chlamydia." https://www.ecdc.europa.eu/en/chlamydia/facts (accessed Jul. 24, 2022).

[71] L. Alessandra, M. Francesca, D. Maria Gabriella, G. Massimo, C. Antonio, and Z. Mauro, "Is COVID-19 affecting the epidemiology of STIs? The experience of syphilis in Rome," *Sex. Transm. Infect.*, p. sextrans-2020-054543, 2020, doi: 10.1136/sextrans-2020-054543.

[72] I. V. F. van den Broek, R. A. Verheij, C. E. van Dijk, F. D. H. Koedijk, M. A. B. van der Sande, and J. E. A. M. van Bergen, "Trends in sexually transmitted infections in the Netherlands, combining surveillance data from general practices and sexually transmitted infection centers.," *BMC Fam. Pract.*, vol. 11, p. 39, 2010, doi: 10.1186/1471-2296-11-39.

[73] N. Kwak, S. S. Hwang, and A. J. Yima, "Effect of COVID-19 on Tuberculosis Notification, South Korea," *Emerg. Infect. Dis.*, vol. 26, no. 10, Oct. 2020, doi: 10.3201/EID2610.202782.

[74] L. Cilloni *et al.*, "The potential impact of the COVID-19 pandemic on the tuberculosis epidemic a modelling analysis," *EClinicalMedicine*, vol. 28, Nov. 2020, doi: 10.1016/j.eclinm.2020.100603.

[75] R. Marçôa, "Tuberculosis and gender – Factors influencing the risk of tuberculosis among men and women by age group," *Pulmonology*, vol. 24, no. 3. Elsevier Espana S.L.U, pp. 199–202, May 01, 2018. doi: 10.1016/j.pulmoe.2018.03.004.

[76] H. H. Kyu *et al.*, "The global burden of tuberculosis: results from the Global Burden of Disease Study 2015," *Lancet Infect. Dis.*, vol. 18, no. 3, pp. 261–284, Mar. 2018, doi: 10.1016/S1473-3099(17)30703-X.

[77] Y. Cui *et al.*, "A long-term trend study of tuberculosis incidence in china, india and united states 1992–2017: A joinpoint and age–period–cohort analysis," *Int. J. Environ. Res. Public Health*, vol. 17, no. 9, May 2020, doi: 10.3390/ijerph17093334.

[78] D. Visca *et al.*, "Tuberculosis and COVID-19 interaction: A review of biological, clinical and public health effects," *Pulmonology*, vol. 27, no. 2, pp. 151–165, Mar. 2021, doi: 10.1016/J.PULMOE.2020.12.012.

[79] G. B. Migliori, S. Tiberi, A. L. García-Basteiro, and R. Duarte, “Tuberculosis and its future in the COVID-19 era: The Pulmonology series 2021,” *Pulmonology*, vol. 27, no. 2, pp. 94–96, Mar. 2021, doi: 10.1016/J.PULMOE.2020.10.005.

[80] R. Duarte *et al.*, “Different disease, same challenges: Social determinants of tuberculosis and COVID-19,” *Pulmonology*, vol. 27, no. 4, pp. 338–344, Jul. 2021, doi: 10.1016/J.PULMOE.2021.02.002.

[81] I. Motta *et al.*, “Tuberculosis, COVID-19 and migrants: Preliminary analysis of deaths occurring in 69 patients from two cohorts,” *Pulmonology*, vol. 26, no. 4, pp. 233–240, Jul. 2020, doi: 10.1016/J.PULMOE.2020.05.002.

[82] G. B. Migliori *et al.*, “Worldwide Effects of Coronavirus Disease Pandemic on Tuberculosis Services, January-April 2020,” *Emerg. Infect. Dis.*, vol. 26, no. 11, pp. 2709–2712, Nov. 2020, doi: 10.3201/EID2611.203163.

[83] “ WHO | Global Tuberculosis Report 2022,” 2022. Accessed: Dec. 01, 2022. [Online]. Available: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022

[84] “Millet J, Orcau A. COVID y TB en Barcelona. Enf Emerg. 2021;20 (1):27-45.”.

[85] L. Cilloni *et al.*, “The potential impact of the COVID-19 pandemic on the tuberculosis epidemic a modelling analysis,” *EClinicalMedicine*, vol. 28, Nov. 2020, doi: 10.1016/J.ECLINM.2020.100603.

[86] P. Comella-del-Barrio, M. L. De Souza-Galvão, C. Prat-Aymerich, and J. Domínguez, “Impact of COVID-19 on Tuberculosis Control,” *Arch. Bronconeumol.*, vol. 57, pp. 5–6, Apr. 2021, doi: 10.1016/J.ARBRES.2020.11.016.

[87] G. J. Fox, C. C. Dobler, B. J. Marais, and J. T. Denholm, “Preventive therapy for latent tuberculosis infection—the promise and the challenges,” *Int. J. Infect. Dis.*, vol. 56, pp. 68–76, Mar. 2017, doi: 10.1016/J.IJID.2016.11.006.

[88] Y. Hirsch-Moverman, A. Daftary, J. Franks, and P. W. Colson, “Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada.,” *Int. J. Tuberc. Lung Dis.*, vol. 12, no. 11, pp. 1235–54, Nov. 2008, Accessed: Jan. 21, 2019. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/18926033

[89] V. Ambrona de Marcos *et al.*, "[Compliance of latent tuberculosis infection treatment in a cohort of TB contacts].," *Rev. Esp. Salud Publica*, vol. 92, 2018, Accessed: Dec. 19, 2018. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/30131485

[90] Direção-Geral da Saúde,, "Tuberculose em Portugal Desafios e Estratégias," 2018. Accessed: Feb. 07, 2019. [Online]. Available: file:///C:/Users/Alexis/Desktop/Rastreios TBC/01. Bibliografia/PNTB.pdf

[91] D. Menzies *et al.*, "Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults," *N. Engl. J. Med.*, vol. 379, no. 5, pp. 440–453, Aug. 2018, doi: 10.1056/NEJMoa1714283.

[92] T. Diallo *et al.*, "Safety and Side Effects of Rifampin versus Isoniazid in Children," *N. Engl. J. Med.*, vol. 379, no. 5, pp. 454–463, Aug. 2018, doi: 10.1056/NEJMoa1714284.

[93] C. T. Fiske, F.-X. Yan, Y. Hirsch-Moverman, T. R. Sterling, M. R. Reichler, and Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team, "Risk factors for treatment default in close contacts with latent tuberculous infection," *Int. J. Tuberc. Lung Dis.*, vol. 18, no. 4, pp. 421–427, Apr. 2014, doi: 10.5588/ijtld.13.0688.

[94] R. N. Moro *et al.*, "Factors Associated With Noncompletion of Latent Tuberculosis Infection Treatment: Experience From the PREVENT TB Trial in the United States and Canada," *Clin. Infect. Dis.*, vol. 62, no. 11, pp. 1390–1400, Jun. 2016, doi: 10.1093/cid/ciw126.

[95] N. D. Goswami *et al.*, "Geographic Information System-based Screening for TB, HIV, and Syphilis (GIS-THIS): A Cross-Sectional Study," *PLoS One*, vol. 7, no. 10, p. e46029, Oct. 2012, doi: 10.1371/journal.pone.0046029.

[96] W. Sun *et al.*, "A Spatial, Social and Environmental Study of Tuberculosis in China Using Statistical and GIS Technology," *Int. J. Environ. Res. Public Health*, vol. 12, no. 2, pp. 1425–1448, Jan. 2015, doi: 10.3390/ijerph120201425.

[97] Direção-Geral da Saúde, Programa Nacional para a Infeção VIH/SIDA. "Infeção VIH, SIDA e Tuberculose em números – 2014." Accessed: Jan. 10, 2019. [Online]. Available: file:///C:/Users/Alexis/Desktop/Rastreios TBC/01. Bibliografia/RELATORIO.pdf

[98] D. Zenner *et al.*, "Active case finding for tuberculosis among

high-risk groups in low-incidence countries [State of the art series. Case finding/screening. Number 3 in the series],” *Int. J. Tuberc. Lung Dis.*, vol. 17, no. 5, pp. 573–582, May 2013, doi: 10.5588/ijtld.12.0920.

[99] N. G. Schwartz, S. F. Price, R. H. Pratt, and A. J. Langer, “Tuberculosis — United States, 2019,” *MMWR. Morb. Mortal. Wkly. Rep.*, vol. 69, no. 11, pp. 286–289, Mar. 2020, doi: 10.15585/MMWR.MM6911A3.

[100] J. E. Ospina, À. Orcau, J.-P. Millet, F. Sánchez, M. Casals, and J. A. Caylà, “Community health workers improve contact tracing among immigrants with tuberculosis in Barcelona,” *BMC Public Health*, vol. 12, no. 1, Dec. 2012, doi: 10.1186/1471-2458-12-158.

7. Anexo

7.1. Anexo 1. Monitoring of SARS-CoV-2 seroprevalence among primary healthcare patients in the Barcelona Metropolitan Area: the SeroCAP sentinel network protocol.

Sentís A, Torán P, Esperalba J, *et al*. Monitoring of SARS-CoV-2 seroprevalence among primary healthcare patients in the Barcelona Metropolitan Area: the SeroCAP sentinel network protocol. *BMJ Open* 2022;12:e053237. doi: 10.1136/bmjopen-2021-053237

UCL: https://bmjopen.bmj.com/content/12/2/e053237

BMJ Open

Monitoring of SARS-CoV-2 seroprevalence among primary healthcare patients in the Barcelona Metropolitan Area: the SeroCAP sentinel network protocol

Alexis Sentís,[1,2] Pere Torán,[3,4] Juliana Esperalba,[5] Cristina Agustí ,[1,2] Miguel Ángel,[6,7] Munoz Gema Fernández,[8] Eva Dopico,[9] Betlem Salvador-González,[10] Maria Victoria González,[1,2] Anna Bordas ,[1] Andrés Antón,[11] Concepció Violan,[12] Marcos Montoro-Fernández,[1] Jordi Aceiton,[1] Laia Egea-Cortés,[1] Lucía Alonso,[1] Rosalia Dacosta-Aguayo,[12] Laura Calatayud,[13] Yolanda Lejardi,[14] Jacobo Mendioroz,[15] Josep Basora,[16] Juliana Reyes-Urueña ,[1,2] Jordi Casabona[1,2]

To cite: Sentís A, Torán P, Esperalba J, *et al*. Monitoring of SARS-CoV-2 seroprevalence among primary healthcare patients in the Barcelona Metropolitan Area: the SeroCAP sentinel network protocol. *BMJ Open* 2022;**12**:e053237. doi:10.1136/bmjopen-2021-053237

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-053237).

Received 14 May 2021
Accepted 14 January 2022

For numbered affiliations see end of article.

Correspondence to
Dr Cristina Agustí;
cagusti@iconcologia.net

ABSTRACT

Introduction SARS-CoV-2 seroprevalence studies are currently being recommended and implemented in many countries. Forming part of the COVID-19 monitoring and evaluation plan of the Catalan Government Health Department, our network aims to initiate a primary healthcare sentinel monitoring system as a surrogate of SARS-CoV-2 exposure in the Barcelona Metropolitan Area.

Methods and analysis The seroCAP is a serial cross-sectional study, which will be performed in the Barcelona Metropolitan Area to estimate antibodies against SARS-CoV-2. From February 2021 to March 2022, the detection of serum IgG antibodies against SARS-CoV-2 trimeric spike protein will be performed on a monthly basis in blood samples collected for diverse clinical purposes in three reference hospitals from the three Barcelona healthcare areas (BCN areas). The samples (n=2588/month) will be from patients attended by 30 primary healthcare teams at 30 basic healthcare areas (BHA). A lab software algorithm will systematically select the samples by age and sex. Seroprevalence will be estimated and monitored by age, sex, BCN area and BHA. Descriptive and cluster analysis of the characteristics and distribution of SARS-CoV-2 infections will be performed. Sociodemographic, socioeconomic and morbidity-associated factors will be determined using logistic regression. We will explore the association between seroprevalence, SARS-CoV-2 confirmed cases and the implemented measures using interrupted time series analysis.

Ethics and dissemination Ethical approval was obtained from the University Institute Foundation for Primary Health Care Research Jordi Gol i Gurina ethics committee. An informed consent is not required regarding the approval of the secondary use of biological samples within the framework of the COVID-19 pandemic. A report will be generated quarterly. The final analysis, conclusions and recommendations will be shared with the stakeholders and communicated to the general public. Manuscripts resulting from the network will be submitted for publication in peer-reviewed journals.

Strengths and limitations of this study

- The seroCAP network will provide data to estimate seroprevalence by sex, age range (>24 years) and geographical healthcare area unit with a precision of ±1.6% every 3 months.
- The planned monitoring strategy could be a useful seroprevalence measure to monitor the roll-out of a SARS-CoV-2 vaccination strategy.
- The strategy will allow the measurement of the association of socioeconomic deprivation with SARS-CoV-2 infection and vaccination.
- Seroprevalence results will be compared with population data of SARS-CoV-2 confirmed cases to perform time series and cluster analysis in order to monitor the epidemic, and evaluate public health interventions including vaccination campaigns.
- The seroCAP sentinel surveillance network will interfere very little in the routine activities of the participating centres and. It may help to monitor and evaluate COVID-19 or other communicable diseases in the future.

INTRODUCTION

Background

In November 2019, the first outbreak of COVID-19 was reported in China (Wuhan Province). Subsequentially, WHO declared a SARS-CoV-2 pandemic and 191 countries confirmed new cases. A state of alarm was proclaimed in Spain on 13 March 2020, and lockdown commenced. By 27 April

2020, Spain globally ranked ninth with the quantity of confirmed cases (n=3 488 469) and had recorded 77 799 deaths since the pandemic had been announced.[1] On 5 April 2020, Spain registered the highest percentage of COVID-19 excess mortality in Europe (156%).[2]

With respect to Catalonia, the second Spanish autonomous community with the highest number of confirmed cases,[3] when the first COVID-19 wave peaked on 26 March 2020, there were 2336 confirmed cases (3667 suspected cases). At the time of the second wave peak on 21 October 2020, there were 6143 confirmed cases (28 697 suspected ones).

Since the end of 2020, the healthcare systems of many countries including Spain have once again been under extreme pressure due to the new rise in incidence rates. Such a situation has led to the adoption of new measures to control the spread of the virus until vaccination campaigns have become universal. Most countries have population-based data regarding SARS-CoV-2 infections by means of serological and molecular markers integrated into their COVID-19 surveillance systems. Although, from an epidemiological perspective, interpretation of SARS-CoV-2 seroprevalence data is hindered by the unknown duration of both natural and vaccine protection, seroprevalence studies, as part of COVID-19 surveillance strategies, are recommended.[1] Currently, many countries are trying to ascertain the number of individuals exposed/infected, the way the disease is spread, and how to identify SARS-CoV-2 infection changes over time.[2] A systematic review and meta-analysis performed by Rostami *et al*[3] analysed 47 studies involving 399 265 individuals from 23 countries. The SARS-CoV-2 seroprevalence in the general population varied from 0.37% to 22.1%. Few representative population-based prospective studies at a national or regional level have been published so far. In Switzerland, Stringhini *et al*, between 6 April 2020 and 9 May 2020, observed an increasing seroprevalence from 4.8% to 10.8% in 2766 participants from 1339 households,.[4] A retrospective, repeated cross-sectional analysis of anti-SARS-CoV-2 spike antibodies in weekly intervals from the beginning of February to July 2020 in New York city showed a stabilised seroprevalence at the 20% level in the routine care group by the end of the study.[5] Similarly, blood donors and pregnant women showed a seroprevalence of 19% by the end of February 2021 in Sweeden,[6] In the Spanish study of SARS-CoV-2 seroprevalence (EN-COVID), the results published on 15 December 2020 showed an 11.6% seroprevalence in Catalunya (95% CI 9.9 to 13.7) from 6490 sampled individuals. Relevant differences were found between the four Catalan provinces; highest values in Barcelona with 12.4% (95% CI 10.2% to 15.0%) and lowest in Tarragona with 5.6% (95% CI 3.6% to 8.795% CI).[7] In a seroprevalence study performed during the first epidemic wave (end of April–beginning of May 2020) in two basic healthcare areas (BHA) in Barcelona, a 5.5% seroprevalence (defined as being positive for IgM and/or IgG SARS-CoV-2 in rapid serological tests) was observed among asymptomatic individuals, and 40% of those with compatible COVID-19 syndrome.[8]

The propagation pattern of SARS-CoV-2 infection is made up of many biological, behavioural and structural factors, including vaccine coverage. Nevertheless, social inequalities have a profound impact on COVID-19 morbidity and mortality. Indeed, social determinants, such as poverty, physical environment and race/ethnicity, can considerably affect COVID-19 outcomes.[9] The mechanisms are totally different, yet, in a similar manner to the HIV epidemic in the 1980s when transmission shifted from specific core groups to marginalised, discriminated individuals with overlapping vulnerabilities,[10] such subgroups are currently very sensitive to SARS-CoV-2.

A number of institutions, including public health agencies, have highlighted the necessity to analyse and address health inequalities in the COVID-19 pandemic. In the UK, the risk of dying has been reported to be higher among older adults, ethnic minorities and those living in areas with worse socioeconomic deprivation indices.[11] In Catalunya, higher mortality rates occurred in individuals aged 80 or older, and were greater in men than in women at all socioeconomic levels. Nevertheless, the lower the socioeconomic level the greater the mortality for both sexes.[12] In Barcelona, the elderly and those living in areas with higher deprivation indices presented higher incidence and mortality rates for COVID-19.[13] In Japan, research on the characteristics and distribution of cases has permitted the design of more effective strategies to specifically target high-risk population groups for the prevention and control of SARS-CoV-2 infection.[13] Thus, as the number of cases decreases, the monitoring of population subgroups at higher risks becomes crucial in controlling the spread of COVID-19.[12]

Aim

Our aim is to establish a network of primary healthcare teams in the Barcelona Metropolitan Area to systematically monitor SARS-CoV-2 seroprevalence over time. The information obtained will be linked to sociodemographical, epidemiological and clinical variables to identify potential individual and associated factors, and thus better design and implement preventive and control measures. This initial pilot network will be later expanded with systematised methodology to other Catalan health regions and institutions.

Objectives

Main objectives

1. To describe SARS-CoV-2 seroprevalence over time by age group, sex and geographical area among primary healthcare attendees in the Barcelona Metropolitan Area, from February 2021 to March 2022.
2. To identify multilevel associated factors with SARS-CoV-2 seroprevalence among primary healthcare attendees in the Barcelona Metropolitan Area.
3. To differentiate between previously infected participants and those that have received the SARS-CoV-2 vaccine with individuals who presented a positive result for SARS-CoV-2 IgG antibodies in our study.

4. To correlate SARS-CoV-2 seroprevalence over time with population-based preventive and control interventions, including lockdowns, mobility restrictions and vaccine coverage.
5. To identify and characterise clusters of SARS-CoV-2 infection using both seroprevalence and epidemiological surveillance from the Barcelona Metropolitan Area.

METHODS AND ANALYSIS

Setting

In 2019, the Barcelona Metropolitan Area had a population of 5 047 597 and was composed of three healthcare areas (BCN areas): Barcelona city, North Metropolitan Area and South Metropolitan Area.[14] Each of the BCN areas has a different number of BHAs. The BHAs are located in specified geographical areas where a PCT is in charge of attending the population. The BHA is the smallest administrative territorial health unit in Catalunya, and covers territories with a population of between 5000 and 25 000 individuals. For the purpose of this study, the BHA was used as the minimum geographical study unit.

Study design

A serial monthly cross-sectional study to detect IgG antibodies to SARS-CoV-2 in biological samples from primary healthcare attendees in the Barcelona Metropolitan Area between February 2021 and March 2022.

Sample size calculation

As there are no SARS-CoV-2 seroprevalence estimations available for each area of the Barcelona Metropolitan Area, we used those seroprevalences reported for the different Catalan provinces by the Spanish Ministry of Health in December 2020.[7] Taking into account population and estimated seroprevalence, we have calculated the necessary sample size for each BCN area with a 95% confidence and an accuracy of±1.27%. This represents 2588 blood samples/month per BCN area (7764 in total) (online supplemental table 1).

The sample size was distributed by age group (25–49, 50–64, 65–79, ≥80) and sex, in order to achieve a quarterly precision of±2.07% (monthly precision of±3.59%) for each stratum of sex/age in each BCN area (online supplemental table 2).

Study population and participants

The total sample size calculated for each BCN area was distributed among nine specific BHAs in the North and South Metropolitan area and 12 in BCN city (30 PCTs located in 30 different BHAs in total) (online supplemental table 3). The BHAs were previously chosen taking into account tertiles of BHA socioeconomic deprivation index[15] and tertiles of SARS-CoV-2 incidence[16] (ensuring at least nine BHAs for each BCN area, the result of combining both tertile variables in a cross-table). Such a strategy permits a heterogeneous population, in terms of both variables, in the different BCN areas in all the sampling campaigns. Online supplemental table 3 depicts the chosen BHA in each BCN area.

According to each of the BCN areas, the biological samples are processed at the respective reference laboratory hospital: Vall d'Hebron University Hospital for Barcelona city, Germans Trias i Pujol University Hospital for North Barcelona, and Bellvitge University Hospital for South Barcelona.

All patients with a blood extraction performed for any health reason in the participant BHA could potentially be chosen to be included in the analysis. Through the design and implementation of an automatic algorithm, the information technology (IT) department of each hospital will systematically select a specific number of samples distributed among the different BCN areas and BHA as mentioned above. Starting day 1 of each month (when each sampling campaign will begin) and until the sample size has been reached in each BCN area for each sex-age-BHA stratum, all potential eligible blood samples will be selected and tested.

Patient and public involvement

No patient involved

Circuits of samples and results

The main output from the network will be the serology results for IgG against SARS-CoV-2. They will be added to the original blood test request indicating that the test is serology monitoring and the research project number. No additional samples need to be taken. In this way, the laboratory personnel can identify the samples when the test needs to be performed. The results are uploaded as usual to the hospital and primary care patient's electronic health record by the IT teams. This procedure avoids the study interfering with the usual daily laboratory routine.

All individuals who have had blood samples extracted for any clinical purpose, and who are potentially eligible to participate in the study, will be informed about the possibility of inclusion. In each BHA, a healthcare professional has been chosen as a reference and contact person for the research team members in charge of controlling data collection and management.

The study's purpose and objectives will be communicated to the patients at the BHA by: (1) general information displayed in posters and screens located at the BHA waiting rooms and (2) through the BHA professionals. In this way, we can ensure that patients are informed and may decline to participate at any time. General practitioners, nurses and other staff will inform individuals about the study when the blood test is ordered, scheduled and at sample extraction. In the case that patients express to any BHA professional their refusal to participate, this person, via the BHA contact, will inform the research team. The BHA contact will note in the patients' electronic health record their refusal to participate. Phone calls and emails will be done on a daily basis to the research team (including the contact individual in the laboratory corresponding to its BCN area) with the list of patients

declining to participate. The research team will inform the IT software managers to not admit these patients in the selection algorithm. Patients whose algorithm has been selected will be told by the PCT that their SARS-CoV-2 serological results (IgG) can be consulted in the online health patient portal (La Meva Salut app). Those patients with a positive result will be informed through the online health patient portal and by a phone call of their general practitioner (GP) or nurse, that a positive result indicates natural exposure to the SARS-CoV-2 virus or as a result of the vaccine, not active infection. They should contact their GP only if they have recently been in close contact with a confirmed case and have not have already been studied or vaccinated or if they currently have COVID-19 compatible symptoms such as cough, shortness of breath or fever. They are reminded that protective measures must be continued.

Data collection and study variables

Individual data

Sociodemographic data (sex, date of birth and BHA where the sample was taken), IgG results (qualitatively as positive/negative) and date of sample extraction will be collected by the microbiology research team at the reference hospitals, and provided anonymously to the network data managers. The IT teams of each hospital will create a unique, anonymous hospital identifier. The laboratory team in each hospital will provide the BHA where the samples are taken every week, a list of the analysed samples' serological results, including the newly created identifiers and the variables specified above.

As participants could be identified in the laboratory databases (only by the microbiology research team at the reference hospitals), we will perform a data linkage with the Data Analytics Programme for Health Research and Innovation (PADRIS), explained in detail elsewhere.[17] We will thus obtain information related to SARS-CoV-2 vaccination (manufacturer, number of doses, date of doses, refusal to vaccination (date and reason)), SARS-CoV-2 diagnosis made by a clinician, and/or SARS-CoV-2 positive result by a nucleic acid amplification test from respiratory samples, and/or antigen or antibodies detection according to the Spanish Ministry of Health guidelines,[18] 1 year after project commencement.

Aggregated data

These data, collected and provided by the Primary Care Services Information System,[19] will include information from different sources in order to obtain the following information:

1. COVID-19 surveillance system data: (1) Number of new COVID-19 cases confirmed or tested positive for SARS-CoV-2/total residents (BHA—BCN area—health region); (2) Median age (and IQR) and sex of the COVID-19 cases confirmed or tested positive for SARS-CoV-2/total residents (BHA—BCN area—health region); (3) Number of new COVID-19 cases confirmed or tested positive for SARS-CoV-2/total people tested (BHA—BCN area—health region); (4) Number of new COVID-19 cases confirmed or tested positive for SARS-CoV-2/Number of suspected cases (BHA—health region); (5) Number of patients hospitalised for COVID-19/total residents (BHA—BCN area—health region) and (6) Number of deaths by COVID-19 as a main cause of death/total residents (BHA—BCN area—health region).
2. Sociodemographic, socioeconomic and comorbidity variables by BHA: (1) Median age, nationality and sex; (2) Deprivation index, values from 0 to 100 (calculated by the Agency for Health Quality and Assessment of Catalunya)[15]; (3) urbanicity, rural or urban (from MEDEA index)[20] and (4) Comorbidities: Charlson Index,[21] and adjusted Morbidity Groups (GMA) classification (number of comorbidities, five severity levels and seven different categories).[22 23]

No missing data are expected.

Microbiological analysis

Determination of IgG serum antibodies against SARS-CoV-2 trimeric Spike protein

Serum samples were centrifuged 10 min at 3000 rpm and stored at 4°C until processing.

Screening will be performed by a new generation of chemiluminescence immunoassay (CLIA) intended for detection of IgG antibodies to SARS-CoV-2 trimeric S in human serum with 99.4% sensitivity and 99.8% specificity,[24] and 93.6% sensitivity and 100% specificity according an independent evaluator.[25]

Serum testing will be conducted in the microbiology laboratories of each BCN area using the LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin, Vercelli, Italy) on the LIAISON XL platform. This test discriminates between negative (<13 binding antibody units (BAU/mL) and positive (≥13 BAU/mL) samples. If the test is positive, the subject is considered seropositive. The LIAISON SARS-CoV-2 TrimericS IgG Assay is an indirect CLIA for the detection of IgG antibodies against SARS-CoV-2 in human serum or plasma samples. The main components of the test are magnetic particles (solid phase) coated with recombinant trimeric spicular protein of SARS-CoV-2 and a reagent conjugated with mouse monoclonal antibodies against human IgG, linked to an isoluminol derivative. Antibody concentrations are expressed as BAU/mL are referenced in relation to the First International Standard of the WHO for immunoglobulin against SARS-CoV-2 (20/136).[26] A positive result indicates the patient has been infected by SARS-CoV-2 in the past and/or he or she has received at least one dose of a COVID-19 vaccine.

Analysis plan and statistical analysis

Estimation of SARS-CoV-2 seroprevalence, description of the sociodemographic characteristics of seroprevalent cases and factors associated with seroprevalence

To answer objectives 1–3, we will calculate seroprevalence and its 95% CI by age, sex, BCN area and BHA of residence.

In addition to the crude seroprevalence of SARS-CoV-2 in the primary care attendees, prevalence will be adjusted

for 99.4% test sensitivity % and 99.8% specificity by LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin, Vercelli, Italy).[24] The 95% CI will be set for the crude and adjusted estimates.

Every 3 months, and at the end of the study, we will compare the seroprevalence results in the different subgroups (by age and sex) and areas (BCN areas and BHA) using the χ^2 test for qualitative variables and one-way analysis of variance test for quantitative ones. Moreover, for the same groups, subgroups and areas we will perform a descriptive analysis of the characteristics and distribution of SARS-CoV-2 seroprevalence. Finally, we will analyse the associated factors with SARS-Cov-2 seroprevalence. First, we will fit a selection method based on logistic regression to assess the association between SARS-CoV-2 seroprevalence as a dependent variable and each of the factors mentioned above. Second, multivariable logistic regression models will be performed.

We will describe the proportion of seroprevalent cases for SARS-CoV-2 individuals who have received the SARS-CoV-2 vaccine, and the proportion of participants with a previous SARS-CoV-2 diagnosis and/or a SARS-CoV-2 positive result.

Time series analysis to explore associations between SARS-CoV-2 seroprevalence and SARS-CoV-2 confirmed infected cases.

To answer objective 4, we will perform a time series analysis of SARS-CoV-2 confirmed infected cases and SARS-CoV-2 seroprevalence. We will explore the association between the time series of the incidence rate of SARS-CoV-2 infection confirmed by laboratory (PCR) and rapid antigen test (assumed as confirmed cases), both extracted from the PADRIS database; and the seroprevalence repeated measurements resulting from our study (for the Barcelona health region and for all three BCN areas). We will perform the analysis using lag times of 2 and 3 weeks between both time series, the incidence rate of SARS-CoV-2 infection confirmed cases and seroprevalence, according to the time average for developing antibodies against SARS-CoV-2 after being exposed to the virus.[27] Analysis of interrupted time series of SARS-CoV-2 seroprevalence and SARS-CoV-2 confirmed infected cases will be carried out to assess the public health implemented measures including vaccination programmes. The confirmed cases will be modelled as Autoregressive Integrated Moving Average (ARIMA) processes to estimate the expected numbers to be compared with those observed, and assess the impact of the different analysed measures. To do so, absolute and relative changes between expected-observed confirmed cases at each time point of the implemented measures will be calculated.

K-means and spatial-temporal cluster analysis

In order to address objective 5, we will perform a cluster analysis using two different approaches: K-means and spatial-temporal cluster analysis. By employing both we can better identify and describe clusters of SARS-CoV-2 incidence and SARS-CoV-2 seroprevalence by BHA.

K-means methodology is a machine-learning technique that identifies and groups analysis units (in our case BHA) based on their similarities of characteristics.[28] K-means methodology will be used to identify clusters of SARS-CoV-2 incidence by BHA, taking into account the rest of the variables described above. In addition, we will identify the spatial-temporal cluster of SARS-CoV-2 infection incidence and seroprevalence by BHA using *SaTScan*.[29 30] Finally, in order to characterise the identified BHA clusters, we will perform a descriptive analysis using the variables by BHA: individual variables, related to the samples used to calculate seroprevalence, and aggregated ones, related to the population's characteristics.

Study limitations

This network will provide neither a population-representative sample nor a population seroprevalence estimate. Its objective is to establish a sentinel SARS-CoV-2 infection surveillance of individuals attending primary care in the Barcelona health region. Nevertheless, a high percentage of the population at some point request a blood test, thus the seroCAP network will provide relevant information about seroprevalence by age group and sex in the targeted population. The relative lack of representativeness will be counterbalanced by combining the seroprevalence results with population data from SARS-CoV-2 infection confirmed cases. With these findings, time series and cluster analyses will be carried out to monitor the epidemic, and evaluate interventions such as vaccination campaigns. The current campaigns, and the as yet unknown duration of antibodies after infection or vaccination, may also alter our seroprevalence results. Nevertheless, the joint analysis of seroprevalence with these and other factors will provide a useful picture for the monitoring and evaluation of the pandemic. An issue that may have an impact on our results is the differences in the patients' characteristics between those who take part and those who decline, which could lead to a selection bias. However, as participation does not require any additional procedure, it is expected that most patients will take part. While we will not monitor samples from children and adolescents, SARS-CoV-2 seroprevalence data will be available from ongoing projects focusing on paediatric populations promoted by the Catalan Department of Health.

We will not have information for each individual regarding comorbidities and socioeconomic status. Nevertheless, aggregated information from the BHA will allow us to characterise SARS-CoV-2 infections by health area. A dynamic picture of the BHA heterogeneous sample, with different sociodemographic, socioeconomic and medical characteristics, will provide vital knowledge to prevent and control COVID-19. A strength of our study is using the BHA—the smallest administrative territorial health unit in Catalunya—as a geographical study unit. This approach could potentially facilitate future management of the COVID-19 epidemic.

ETHICS AND DISSEMINATION

Data confidentiality and other ethical considerations will be managed under the recommendations of Law 14/2007 on Biomedical Research, and the Royal Decree (RD) 1716/2011. These stipulate the basic requirements for the authorisation and operation of biobanks for biomedical research purposes and the treatment of human biological samples. Our project complies with Article 58 of Law 14/2007 and article 24 of RD 1716/2011 which deal with the exceptional treatment of human biological samples for biomedical research in the absence of consent from the source subject, as it is of general interest within the framework of the COVID-19 pandemic.[31 32] The Health Department of the Catalan Generalitat data protection office is preparing an agreement to be signed by all the research team organisations to align with the ethical considerations mentioned above, and recommended by the same office. We strongly believe that the project's data and results will be valuable within the current context of the international public health emergency as declared by the WHO for the COVID-19 pandemic. In addition to taking into account the urgent need for information coming from seroprevalence studies. Our approach is, moreover, reinforced by Spanish Bioethics Committee recommendations issued in a resolution concerning the secondary use of health data and biological samples without informed consent within the framework of the COVID-19 pandemic of 28 April 2020.[33] For all the reasons mentioned above, the Ethics Committee consider informed consent will not be required. However, all potential participants will be informed about the study and refusal to take part is considered.

As previously mentioned, the IT hospital teams will create unique, anonymous patient and hospital identifiers that will allow unlinked anonymous testing in the sentinel population. The laboratory data (serology results and the other individual variables) will be sent every month to the research team of the Catalan Centre of Epidemiological Studies on Sexually Transmitted Infections and AIDS (CEEISCAT) using these anonymous identifiers. The study data will be kept on the Microsoft SQL Server database server of CEEISCAT. Patients' reidentification will not be possible by the members of CEEISCAT, as only the microbiologist investigators have the link between the anonymous identifiers and the personal identifier. Data will be stored until the project is finished. This includes all postdata analysis and the development of reports, presentations at conferences or scientific articles. The microbiologist investigators and the research team of IDIAP Jordi Gol will send the weekly serology results to the referent individual at the respective BHA. This individual will inform the general practitioners of those patients with positive results, they will then decide how to proceed according to each BHA clinical protocols. The results will also be available for the participating patients in their electronic medical registers. We believe that such procedures, with prior ethical committee evaluation, will permit further studies employing individual identification to gather more information. The Health Department of the Catalan Government and the Ministry of Health of Spain will be duly informed about the preliminary and final results of the study. The study could be easily replicated and promoted to the whole territory of Catalonia and other autonomous regions of Spain, for the latter it would be necessary to have access to the vaccination data as we have in Catalonia.

Study registration

Ethical approval was obtained from the University Institute Foundation for Primary Health Care Research Jordi Gol I Gurina (IDIAPJGol) ethics committee with code 20/167-PCV on 22 October 2020.

Publication plan

This network will provide information on how the virus is spreading, help to characterise the exposed population, and identify possible clusters of transmission. All of which is crucial information to better design effective strategies for the prevention and control of the COVID-19 epidemic in Catalunya.

CEEISCAT will quarterly generate a report with preliminary results to give feedback to the stakeholders. The final analysis, conclusions and recommendations will be shared with all the stakeholders and communicated to the general public. Any manuscript that arises from the network will be submitted for publication in peer-reviewed journals.

Author affiliations
[1]Centre of epidemiological studies on sexually transmitted infections and AIDS of Catalunya (CEEISCAT). Department of Health, Generalitat of Catalunya, Badalona, Spain
[2]Instituto de Salud Carlos III, Madrid, Spain
[3]Unitat de Suport a la Recerca Metropolitana Nord, IDIAP Jordi Gol, Barcelona, Spain
[4]Departament de Medicina, Universitat de Girona, Girona, Spain
[5]Department of Microbiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[6]Gerència Territorial de Barcelona, Institut Català de la Salut, Barcelona, Spain
[7]IDIAP Jordi Gol, Barcelona, Spain
[8]Microbiology Department, Laboratori Clínic Metropolitana Nord, Hospital Germans Trias i Pujol, Badalona, Spain
[9]Microbiology Department, Laboratori Clínic Territorial Metropolitana Sud, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain
[10]Unitat de Suport a la Recerca Costa de Ponent, Direcció Atenció Primària Costa de Ponent, Gerència Territorial Metropolitana Sud, Institut Català de la Salut, Barcelona, Spain
[11]Microbiology Department, Hospital Vall d'Hebron, Barcelona, Spain
[12]Unitat de Suport a la Recerca Metropolitana Nord, IDIAP Jordi Gol, Mataró, Spain
[13]Microbiology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain
[14]Direcció Assistencial Atenció Primària, Institut Catala De La Salut, Barcelona, Spain
[15]Subdirecció general de Vigilància i Resposta a Emergències. Agència de Salut Pública de Catalunya, Departament de Salut, Barcelona, Spain
[16]Direction, IDIAP Jordi Gol, Barcelona, Spain

Twitter Cristina Agustí @ixmucane77 and Concepció Violan @concepcioviolan

Acknowledgements The authors thank the Heath Department of the Catalan Government (Spain), especially Robert Fabregat, all the healthcare professionals acting as a COVID-19 pandemic health taskforce in Catalonia, microbiologist professionals, primary healthcare and public health workers that made possible this network.

Contributors JC conceptualised and AS, JC and JMR-U designed the study. AS, CA, PT, JE, MAM, GF, ED, BS-G, MVG, AA and JMR-U agreed and planned all the operational procedures. AS, JMR-U, CA, MM-F, JA, LA and LE-C developed the data analysis plan. AS and CA reviewed scientific literature and drafted the final version of the protocol. AB, AA, CV, RD-A, LC, YL, JM and JB contributed to improving the content in the sections of their expertise. All authors made a critical review and approved the final manuscript.

Funding This work will be supported by the Health Department of the Government of Catalunya (No grant number).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Cristina Agustí http://orcid.org/0000-0002-5259-2242
Anna Bordas http://orcid.org/0000-0001-5640-8433
Juliana Reyes-Urueña http://orcid.org/0000-0002-3122-6518

REFERENCES

1 European Centre for Disease Prevention and Control (ECDC). Strategies for the surveillance of Covid-19. Stockholm, 2020. Available: https://www.ecdc.europa.eu/en/publications-data/strategies-surveillance-covid-19
2 CDC. COVID-19 serology surveillance strategy. Available: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/serology-surveillance/index.html [Accessed 22 Feb 2021].
3 Rostami A, Sepidarkish M, Leeflang MMG, *et al*. SARS-CoV-2 seroprevalence worldwide: a systematic review and meta-analysis. *Clin Microbiol Infect* 2021;27:331–40.
4 Stringhini S, Wisniak A, Piumatti G, *et al*. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet* 2020;396:313–9.
5 Stadlbauer D, Tan J, Jiang K, *et al*. Repeated cross-sectional sero-monitoring of SARS-CoV-2 in New York City. *Nature* 2021;590:146-150.
6 Castro Dopico X, Muschiol S, Christian M, *et al*. Seropositivity in blood donors and pregnant women during the first year of SARS-CoV-2 transmission in Stockholm, Sweden. *J Intern Med* 2021;290:666–76.
7 Ministerio de Ciencia en Innovación, Miniterio de Sanidad, Consejo Interterritorial Sistema Nacional de Salud I de SCI. *Estudio Ene-covid: cuarta ronda Estudio nacional de sero-epidemiologia de la infeccion por SARS-COV-2 en Espana*. Madrid, 2020.
8 Carlos B, Jordi S, Diana F. Seroprevalence against COVID-19 and follow-up of suspected cases in primary health care in Spain. *medRxiv* 2020.
9 Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. *Lancet Respir Med* 2020;8:659–61.
10 Hargreaves J, Davey C, Auerbach J, Group for lessons from pandemic HIV prevention for the COVID-19 response. Three lessons for the COVID-19 response from pandemic HIV. *Lancet HIV* 2020;7:e309–11.
11 Public Health England. Disparities in the risk and outcomes of COVID-19. London, 2020. Available: www.facebook.com/PublicHealthEngland [Accessed 22 Jan 2021].
12 Agència de Qualitat i Avaluació Sanit ries de Catalunya (AQuAS). Desigualtats socioeconòmiques en El Nombre de casos I La mortalitat per COVID-19 a Catalunya. Barcelona, 2020. Available: http://aquas.gencat.cat [Accessed 23 Feb 2021].
13 Normile D. Japan ends its COVID-19 state of emergency. *Science* 2020.
14 Idescat. Padró municipal d'habitants. Població. Per sexe, edat quinquennal i regions sanit ries. Catalunya. Available: https://www.idescat.cat/pub/?id=pmh&n=13312 [Accessed 22 Jan 2021].
15 Colls C, Mias M, García-Altés A. [A deprivation index to reform the financing model of primary care in Catalonia (Spain)]. *Gac Sanit* 2020;34:44-50.
16 Dades COVID INICI. Available: https://dadescovid.cat/ [Accessed 22 Jan 2021].
17 Agència de Qualitat i Avaluació Sanit ries de Catalunya, Departament de Salut. Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya -PADRIS-. Barcelona, 2017. Available: http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2017/Programa_analitica_dades_PADRIS_aquas2017.pdf
18 Contenido. *Estrategia de Deteccion precoz, vigilancia Y control de COVID-19 Actualizado a 26 de febrero de 2021 Este documento HA sido aprobado POR La Ponencia de Alertas Y planes de Preparación Y Respuesta Y POR La Comisión de Salud Pública del Consejo Interterritorial Y presentado al Consejo Interterritorial del Sistema Nacional de Salud*, 2021.
19 Coma E, Méndez L. Experiencias para compartir SISAP : 4 años buceando en mares de datos. *AMF Actual en Med Fam* 2010;6:473–6 http://amf-semfyc.com/web/article_ver.php?id=132
20 Felícitas Domínguez-Berjón M, Borrell C, Cano-Serral G, *et al*. Construcción de un índice de privación a partir de datos censales en grandes ciudades españolas (Proyecto Medea). *Gac Sanit* 2008;22:179–87.
21 Brusselaers N, Lagergren J. The Charlson comorbidity index in registry-based research: which version to use? *Methods Inf Med* 2017;56:401–6.
22 Clèries M, Monterde D, Vela E, *et al*. [Clinical validation of 2 morbidity groups in the primary care setting]. *Aten Primaria* 2020;52:96–103.
23 Hughes JS, Averill RF, Eisenhandler J, *et al*. Clinical risk groups (CRGs): a classification system for risk-adjusted capitation-based payment and health care management. *Med Care* 2004;42:81–90.
24 Bonelli F, Blocki FA, Bunnell T, *et al*. Evaluation of the automated LIAISON® SARS-CoV-2 TrimericS IgG assay for the detection of circulating antibodies. *Clin Chem Lab Med* 2021;59:1463–7.
25 Jung K, Shin S, Nam M, *et al*. Performance evaluation of three automated quantitative immunoassays and their correlation with a surrogate virus neutralization test in coronavirus disease 19 patients and pre-pandemic controls. *J Clin Lab Anal* 2021;35:1–9.
26 National Institute for Biological Standards and Control. WHO international standard first who international standard for anti-SARS-CoV-2 immunoglobulin (human) NIBSC code: 20/136 Instructions for use (version 2.0), 2020. Available: http://www.nibsc.org/standardisation/international_standards.aspx
27 Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing | CDC. Available: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html [Accessed 23 Feb 2021].
28 Demidenko E. The next-generation k-means algorithm. *Stat Anal Data Min* 2018;11:153–66.
29 Desjardins MR, Hohl A, Delmelle EM. Rapid surveillance of COVID-19 in the United States using a prospective space-time scan statistic: detecting and evaluating emerging clusters. *Appl Geogr* 2020;118:102202.
30 Hohl A, Delmelle E, Desjardins M. Rapid detection of COVID-19 clusters in the United States using a prospective space-time scan statistic: an update. Available: https://github.com/CSSEGISandData/COVID-19 [Accessed 24 Feb 2021].
31 Agencia Estatal Boletín Oficial del Estado. BOE.es - Documento BOE-A-2007-12945. Available: https://www.boe.es/buscar/doc.php?id=BOE-A-2007-12945 [Accessed 24 Feb 2021].
32 Agencia Estatal Boletín Oficial del Estado. Disposición 18919 del BOE núm. 290 de 2011 2011.
33 Comité de Bioética de España. Documentación Y publicaciones del Comité de Bioética de España. Available: http://www.comitedebioetica.es/documentacion/index.php [Accessed 22 Jan 2021].

8. PhD portafolio

❖ **Congresos - Presentaciones Orales**

- *The impact of the COVID-19 pandemic on Sexually Transmitted Infections surveillance data: incidence drop or artefact?* ESCAIDE. Noviembre 2021 (on-line)
- *STI epidemic re-emergence, socioepidemiological clustering, and factors associated with HIV coinfection in Catalonia, Spain, 2017-2019.* Reunión anual de la SEE. Septiembre 2020 (on-line).
- Infecciones de transmisión sexual en jóvenes entre 15 y 24 años. Barcelona, 2007-2015. Reunión anual de la SEE. Septiembre 2017. Barcelona, España.

❖ **Congresos – Presentaciones de poster**

- *STI epidemic re-emergence, socioepidemiological clustering, and factors associated with HIV coinfection in Catalonia, Spain, 2017-2019.* ESCAIDE. Noviembre 2021 (on-line)
- *Failure to complete treatment for latent tuberculosis infection in Portugal, 2013-2017: geographic, sociodemographic and medical associated factors.* ECCMID 2020 (cancelada pero publicado en el *abstract book*).
- *Decline of tuberculosis notification rate in different population groups in Portugal, 2010-2017.* ESCAIDE, Noviembre 2019, Estocolmo, Suecia.

❖ **Cursos:**

- EPIET Introductory Course, Spetses, Grecia, del 25 de septiembre al 13 de octubre del 2017.
- EPIET Outbreak Investigation module, Berlin, Alemania, del 4 al 8 de diciembre del 2017.
- EPIET Multivariable Analyses module, Nicosia, Chipre, del 16 al 20 de abril del 2018.
- EPIET Rapid Assessment module, Atenas, Grecia, del 14 al 19 de mayo del 2018.
- EPIET Project Review module, Lisboa, Portugal, del 27 al 31 de agosto del 2018.
- EPIET Time Series Analyses module, Bruselas, Bélgica, del 5 al 9 de noviembre del 2018.
- EPIET Vaccinology module, Roma, Italia, del 24 al 28 de junio del 2019.
- EPIET Project Review Module, Praga, República Checa, del 26 al 29 de agosto del 2019.

❖ **Otros:**

- Premio a la mejor comunicación oral en la Reunión anual de la SEE: "VII PREMIO "EMILIO PEREA" A LAS MEJORES COMUNICACIONES SENIORS". Septiembre 2017. Barcelona, España.
- *European Programme for Intervention Epidemiology Training* (EPIET). Cohorte 2017. *European Centre for*

Disease Prevention and Control (ECDC). Abril 2017. Estocolmo, Suecia.

9. Agraïments

Vull agrair tot el suport de la directora i supervisors de tesi, no només en l'àmbit professional, sinó sobretot en l'àmbit personal. A la Mònica Guxens per haver-me donat l'oportunitat d'iniciar el doctorat amb ella i el seu equip, per les lliçons inicials tan importants sobre com fer bona recerca en epidemiologia i salut pública. Al Joan Caylà per introduir-me en el món de l'epidemiologia de les malalties infeccioses i saber transmetrem la seva integritat i compromís. A la Juliana Reyes per la seva companyonia, per compartir llargues jornades de treball conjunt durant la pandèmia així com reptes i visions professionals. A tots ells per saber transmetrem la seva gran curiositat, dedicació i motivació i per continuar donant-me sempre suport malgrat el llarg camí, interrupcions i els canvis en la línia de recerca. També vull agrair a l'Albert Prats i en Carlos Carvalho per les seves col·laboracions, ha estat tot un plaer el treball en equip i aprendre de vosaltres.

A la meva família, Carola, Lucas i Julieta, i als meus pares, Mercè i Albert, per facilitar i fer sempre possible tot allò que ens proposem, per la seva alegria, saber viure i suport incondicional.

A totes i tots aquells, família, companyes i companys de l'ISGlobal, del servei d'epidemiologia de l'ASPB, Hospital del Mar, CEEISCAT, EPIET, EpiConcept i DGS, que han fet possible l'aprenentatge professional i personal i gaudir del camí durant aquests anys.

10. Sobre l'autor

És metge especialista en nefrologia i salut pública amb formació en epidemiologia de camp (EPIET *fellowship,* ECDC). Ha treballat com a metge en diferents entorns, inclosa la pràctica clínica en hospitals, investigació, salut pública i epidemiologia. Els darrers anys, ha treballat en el camp la vigilància epidemiològica, control de brots i investigació aplicada en epidemiologia de les malalties transmissibles en l'àmbit local/regional, nacional i internacional. Entre el 2019 i 2021 va treballar com a coordinador de l'equip de vigilància del registre català de VIH/ITS i membre de l'equip de monitoratge de la COVID-19 com a part dels sistemes de vigilància sentinella de la COVID-19 del CEEISCAT. Des de l'inici del 2021 treballa a Epiconcept, on actualment és coordinador del *work package* de vigilància al projecte H2020 - PANDEM2 (*preparedness and response*), co-coordinador científic a l'estudi de l'ECDC "efectivitat vacunal (EV) i impacte de les vacunes contra la COVID-19 a través de dades d'exposició i *outcomes* recopilats de forma rutinària mitjançant registres de salut" (VEBIS, lot 4), i donant suport en altres projectes de vigilància epidemiològica, EV i activitats formatives per a agències de salut pública nacionals i internacionals.