DOCTORADO EN SALUD Y DESARROLLO EN LOS TRÓPICOS, ESCUELA DE DOCTORADO "STUDII SALAMANTINI"

Utilidad del Conjunto Mínimo Básico de Datos como herramienta de estudio de la fiebre de duración intermedia en el Sistema Sanitario Español

Línea de investigación: Impacto epidemiológico de los principales agentes causantes de fiebre de duración intermedia en España (1997-2015)

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PROGRAMA DE DOCTORADO EN **SALUD Y DESARROLLO EN LOS TRÓPICOS**, ESCUELA DE DOCTORADO "STUDII SALAMANTINI, UNIVERSIDAD DE SALAMANCA

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CERTIFICAN QUE

Dña. **BEATRIZ RODRÍGUEZ ALONSO**, Licenciada en Medicina y Cirugía, médico especialista en Medicina Interna, ha llevado a cabo en el Departamento de Medicina, bajo nuestra tutela, la Tesis Doctoral titulada **"Utilidad del Conjunto Mínimo Básico de Datos como herramienta de estudio de la fiebre de duración intermedia en el sistema sanitario español".**

A nuestro parecer, el presente trabajo aúna los criterios de innovación, singularidad y significación, evidencia médica y relevancia científica, méritos académicos, forma y fondos requeridos para postularse como **Tesis por compendio de publicaciones** ante el Tribunal correspondiente para la obtención del **GRADO DE DOCTORA** por la **UNIVERSIDAD DE SALAMANCA**.

Y para que conste, firman el presente certificado en Salamanca, a 04 de junio de 2021.

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PROGRAMA DE DOCTORADO EN **SALUD Y DESARROLLO EN LOS TRÓPICOS**, ESCUELA DE DOCTORADO "STUDII SALAMANTINI, UNIVERSIDAD DE SALAMANCA

Se presenta este documento de Tesis Doctoral en la modalidad de Tesis por compendio de artículos para optar al Título de "Doctora en Medicina" por la Universidad de Salamanca. Se aportan tres artículos publicados y uno en proceso de publicación en revistas científicas del ámbito contextual desarrollado en la Tesis e indexadas en el *Science Citation Reports*. A nuestro parecer, los cuatro trabajos realizados por la doctoranda como primera autora, aportan gran relevancia, originalidad y su ejecución es excelente.

ARTÍCULO PRIMERO:

Título: Epidemiological Scenario of Q fever hospitalized patients in the Spanish Health System: What's new.

Revista: International Journal of Infectious Diseases

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ARTÍCULO SEGUNDO

Título: Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997–2015).

Revista: International Journal of Infectious Diseases

Autores:

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ARTÍCULO TERCERO:

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ARTÍCULO CUARTO:

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me enseñaste más que las dos juntas.

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Hasta siempre equipo.

Abreviaturas

- CAUSA: Complejo Asistencial Universitario de Salamanca.
- CIE- CM: Clasificación Internacional de Enfermedades, modificación clínica.
- CIE-9-CM: "*International Classification of Diseases, Ninth revision, Clinical Modification*"
- CIE-10-ES: "*International Classification of Diseases, 10th Revision, Clinical Modification*"
- CMBD: Conjunto Mínimo Básico de Datos.
- CMV: citomegalovirus.
- EDO: enfermedad de declaración obligatoria.
- FDI: fiebre de duración intermedia.
- FOD: fiebre de origen desconocido.
- FSF: fiebre sin foco.
- GRD: Grupos Relacionados por el Diagnóstico.
- TNF: factor de necrosis tumoral.
- OMS: Organización Mundial de la Salud.
- PMC: categorías de gestión de pacientes (*Patient Management Categories).*
- POA (marcador): presente en la admisión (*Present on Admisson)*
- SNS: Sistema Nacional de Salud
- VEB: virus de Epstein-Barr

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Introducción

DEFINICIÓN DE FIEBRE

Fiebre

La fiebre se define como la elevación de la temperatura corporal central por encima del rango diario de un individuo. Puede estar provocada por enfermedades infecciosas, pero también, autoinflamatorias, autoinmunes y neoplásicas.

La temperatura corporal normal se mantiene bastante estable, si bien sufre variaciones a lo largo del día, controlada por el centro termorregulador situado en el hipotálamo anterior. Éste centro equilibra el exceso de producción de calor, derivado de la actividad metabólica exotérmica generada fundamentalmente en el músculo y el hígado, con la disipación de calor a través de la piel y la respiración (1). La elevación de los niveles de prostaglandina E2 es el desencadenante del reajuste del centro termorregulador. Esto provoca la activación de las neuronas del centro vasomotor, que median un proceso vasoconstrictor, y también la activación de las neuronas sensibles al calor que aumentan la producción de calor en la periferia. Al mismo tiempo, la termogénesis en el tejido adiposo y el hígado, contribuye a aumentar la temperatura central. Por tanto, la fiebre también se regula a nivel de dicho centro termorregulador hipotalámico.

La temperatura media del ser humano se establece en 36.8 ± 0.4ºC (2,3), con una variación media de 0.5ºC a lo largo del día, siendo mínima a las 06:00 y máxima a las 16:00. La fiebre se define como una temperatura matutina > 37.2ºC o vespertina > 37.7ºC (3).

Si bien los métodos periféricos (membrana timpánica, axilar y oral) no son tan precisos como los centrales (catéter de arteria pulmonar, vejiga urinaria, termometría esofágica y rectal) para la determinación de la temperatura corporal, sí son los más prácticos, lo que los convierte en los más utilizados (4).

El lugar de toma de temperatura en el que se obtiene una cifra más próxima a la temperatura central real es el recto y, en segundo lugar, la membrana timpánica. Debido al papel que juega la boca en la respiración, la toma de la temperatura oral suele ser 0.6ºC inferior a la rectal.

CLASIFICACIÓN DEL SÍNDROME FEBRIL

El síndrome febril suele coexistir con una clínica que orienta sobre su origen. Habitualmente, los niños y jóvenes suelen ser los más afectados por procesos víricos y parasitarios y, a medida que avanza la edad, las infecciones bacterianas van adquiriendo más entidad (5).

Clásicamente, los síndromes febriles en Medicina Interna se clasificaban en fiebre aguda o de corta duración y fiebre de origen desconocido (6,7). Sin embargo, no es infrecuente la presencia de fiebre como único signo persistente en el tiempo. Este proceso, caracterizado por la presencia de fiebre y la ausencia de signos clínicos o síntomas orientativos, de denomina fiebre sin foco aparente (FSF) (8).

FIEBRE DE DURACIÓN INTERMEDIA

Este término fue acuñado por primera vez por Gutiérrez-Ravé *et al.* en 1986 (9). Posteriormente, Espinosa *et al.* clasificarían la fiebre sin foco en tres entidades en base a su cronología facilitando de este modo su manejo clínico (10).

i) La **fiebre de corta duración** es aquella fiebre aguda de duración menor a siete días y cuya causa más frecuente la constituyen las infecciones virales.

ii) La **fiebre de origen desconocido (FOD)** se define como un síndrome febril de más de tres semanas de duración, con temperatura objetivada > 38.3ºC y cuyo origen continúa siendo incierto tras una semana de pruebas complementarias hospitalarias. Sus agentes causales, proceso diagnóstico y enfoque terapéutico, varían en función de diferentes aspectos que no entraremos a considerar.

iii) La **fiebre de duración intermedia (FDI)** se define como el síndrome febril (≥ 38ºC) adquirido en la comunidad, de más de siete y menos de veintiocho días de evolución, sin clínica orientativa, y que, tras una evaluación inicial que incluya historia clínica completa, exploración física, sistemáticos de sangre y orina y radiografía de tórax en dos proyecciones, permanece sin diagnóstico (5,8). Esta entidad ha adquirido una categoría individual de forma muy reciente existiendo actualmente una estrategia diagnóstica y terapéutica bien definida (10).

Las causas de la FDI son poco conocidas como también son escasos los estudios que las analizan (10–12). En nuestro ámbito geográfico, el 70% de los casos está provocado por enfermedades infecciosas diseminadas (rickettsiosis, brucelosis, síndrome mononucleósico), seguidas de infecciones localizadas (7,7%), constituyendo las vasculitis y neoplasias menos del 2% (10).

Sin embargo, en los últimos años, se han producido cambios tanto en la incidencia como en la etiología de las infecciones responsables de fiebre de duración intermedia en España. Esto es debido no solo a las alteraciones de infecciones ya conocidas o los cambios en las condiciones socio-económicas y sanitarias, sino también a la presencia de patógenos emergentes que han logrado adaptar sus ciclos vitales al organismo humano. Además, el cambio climático ha propiciado la llegada de nuevas especies parasitarias a zonas geográficas cuyas condiciones meteorológicas previas, hacían imposible su supervivencia, se han introducido nuevas vacunas en los calendarios vacunales, etc. (5,13–16).

El primer estudio que encontramos sobre la etiología e incidencia de la FDI en nuestro país, fue llevado a cabo por Espinosa *et al*. en la década de los 80 en Sevilla, donde casi el 70% de 505 casos de FDI registrados fueron provocados por enfermedades infecciosas sistémicas, siendo la fiebre Q (21%), la brucelosis (19%), el tifus murino (8,5%) y el síndrome mononucleósico (9%) los agentes etiológicos más frecuentemente observados. Otras causas de FDI menos habituales fueron las infecciones localizadas (7,7%), representando los abscesos intraabdominales el 2,2%; y las vasculitis y neoplasias que no alcanzaron el 2% (17–19). Cabe señalar que casi en el 19% de las FDI, el agente causal se mantiene desconocido y el proceso se autolimita (17). Concluye señalando a la fiebre Q y al tifus murino como principales agentes etiológicos de la FDI (10); proponiendo un protocolo de actuación que culmina con la recomendación de uso de doxiciclina empíricamente (20).

En un estudio posterior, el mismo grupo de trabajo (Espinosa *et al.)* recogió 179 pacientes, reafirmándose la fiebre Q como la principal causa bacteriana de la FDI y objetivándose un descenso llamativo de los casos de brucelosis, del 19.2% en los años 80 al 3.3% en 2004-2005, igualándose al tifus murino, en el período evaluado (10).

Finalmente, la misma autora, llevaría a cabo su tesis doctoral sobre la FDI, recogiendo 333 nuevos pacientes más que corroborarían los datos obtenidos en estudios previos y confirmarían el descenso de la brucelosis a un discreto 2.4% entre 2006 y 2009 (21).

Actualmente, tanto por el desarrollo exponencial de nuevos métodos diagnósticos como por las causas citadas previamente, han entrado en escena otras entidades causales de síndromes febriles como los virus*:* principalmente el parvovirus B-19 y los virus del grupo herpes. Además, se ha producido también un incremento de la incidencia de fiebres secundarias a procesos neoformativos o conectivopatías, principalmente (5). Constituye un factor determinante por su potencial papel como factor de confusión, la aplicación, en muchos casos empírica de la doxiciclina y también la instauración de medidas de intervención a nivel tanto sanitario como veterinario que han relegado entidades como la brucelosis a un descenso paulatino del número de casos en los últimos años.

En la **tabla 1** se identifican los principales estudios sobre series de fiebre de duración intermedia en España.

Actualmente en nuestro país el conjunto principal de agentes causales de FDI está constituido por i) *Coxiella burnetii* causante de la **fiebre Q**, principal causa de FDI en España,

ii) bacterias de la familia *brucellaceae,* causantes de la **brucelosis**, iii) especies del género *Rickettsia* enfermedades causantes del **tifus murino** y iv) *Bartonella henselae* causante de la **enfermedad por arañazo de gato**.

Por tanto, la recomendación de Espinosa *et. al* con respecto a la utilización de doxiciclina empíricamente (10) en los casos de FDI en España es válida y se mantiene vigente, ya que resulta apropiada para tratar el espectro bacteriano que constituye el grupo causal más frecuente.

La fiebre Q es una zoonosis, considerada un problema de salud pública a nivel mundial en la actualidad. Puede presentarse como casos esporádicos o en forma de brotes y existen colectivos de riesgo como profesionales expuestos (veterinarios, ganaderos), embarazadas y personas sitas en zonas endémicas ya sea por viajes o por residencia habitual (22). Se distribuye mundialmente con una incidencia variable en función de latitudes. En Europa, la horquilla de incidencia descrita se sitúa entre los 0,09 casos/100.000 habitantes/año del Reino Unido (23) y los 2,5-4 casos/100.000 habitantes/año descritos en Francia (22). En la literatura disponible no se ha logrado identificar una cifra unificada de incidencia en España dada la vasta variabilidad entre comunidades autónomas (24). Andalucía y el País Vasco concentran el mayor número de pacientes (25), que se agrupan principalmente en las zonas rurales (26). Se considera una enfermedad benigna, ya que únicamente entre el 2-5% de los pacientes diagnosticados de fiebre Q precisan ingreso hospitalario (25,27,28) y la mortalidad no alcanza el 3% (26,29,30).

La brucelosis, aún lidera la lista de principales zoonosis a nivel mundial (31). La incidencia real es desconocida, dado el infradiagnóstico existente (32). Se estima una media de 500.000 casos al año en todo el mundo y una incidencia muy oscilante entre 0,02 y 268,81/100.000 habitantes/año. Tan amplia variabilidad viene determinada por la localización geográfica y la estación del año, sin olvidar la situación veterinaria y las condiciones higiénicas (33–36). En zonas endémicas la brucelosis humana puede alcanzar cifras incluso del 7,7%. Sin embargo, con las medidas de intervención llevadas a cabo para su control, la incidencia se ha ido reduciendo en los últimos años (37,38). En Europa, los casos se acumulan principalmente en la cuenca mediterránea, entre Grecia, Italia y España (33–36). Con un tratamiento adecuado y precoz la mortalidad se reduce hasta prácticamente el 0% (39), alcanzando cifras de entre el 2 y el 5% en las formas complicadas (31).

El tifus murino o endémico es una zoonosis de distribución universal. Aunque se han descrito casos en viajeros (40,41), se considera una enfermedad autóctona de zonas endémicas como el Sudeste asiático, Norte-américa, Sudáfrica, Australia y algunos países europeos principalmente Grecia (11,42–48). A pesar de que se trataba de una enfermedad con un control epidemiológico favorable, la adaptación a nuevos reservorios (gato, perro, zarigüeya) y nuevos vectores (principalmente la pulga del gato, *Ctenocephalides felis)*, así como la identificación de una nueva especie de *Rickettsia (R.felis)* que provoca un cuadro clínico similar al producido por *R. typhi,* han propiciado la reaparición de casos de tifus murino en países desarrollados (49–51). Sin embargo, su trascendencia a nivel global continúa siendo una incógnita. La seroprevalencia del tifus endémico varía entre el 1-20% (52,53), lo que implica un porcentaje de infección no desdeñable. Sin embargo, las series de pacientes son escasas (54). La epidemiología en España es desconocida, probablemente debido a que, a pesar del repunte que ya se está produciendo en los países desarrollados, no es una enfermedad de declaración obligatoria en nuestro país.

La enfermedad por arañazo de gato es una zoonosis responsable de importantes problemas de salud en todo el mundo. Según los datos disponibles en la literatura, la prevalencia de infección es mucho más alta de lo que se detecta clínicamente. Su incidencia global es difícil de estimar dada la variabilidad de las cifras que oscilan entre el 0,7 y el 57% dependiendo del país en que se analice y del nivel prefijado para considerar un resultado positivo (55–61). Esta labor resulta aún más complicada teniendo en cuenta que no se trata de una enfermedad de declaración obligatoria en muchos países. La mayoría de los datos disponibles, provienen de Estados Unidos, que aporta una incidencia de 9,3/100.000 habitantes/año en pacientes ambulatorios y de 0,8/100.000 habitantes/año en pacientes hospitalizados (62). En la literatura, se han encontrado algunos estudios sobre las características de los pacientes hospitalizados por enfermedad por arañazo de gato (63–66).

Tabla 1. Series de fiebre de duración intermedia en España, principales agentes causales.

Estudio	Autor	Fecha	Lugar	Nº casos	Diagnóstico final	Principales agentes causales
Tesis doctoral: Cambios en el espectro etiológico de la fiebre de duración intermedia en el sur de Europa (2015) (21)	Nuria Isabel Espinosa Aguilera	01/11/2006-01/11/2009	Andalucía (Sevilla, Málaga, Almería, Jaén, Córdoba, Granada, Huelva)	333	64.2%	31.8% Infección vírica 14.4% Fiebre Q 2.4% Tifus murino 2.4% Brucelosis
The changing etiology of fever of intermediate duration (10)	Nuria Espinosa, Elías Cañas, Máximo Bernabeu-Wittel, Amalia Martín, Pompeyo Viciana y Jerónimo Pachón	1983-1989	Hospital Virgen del Rocío (Sevilla)	505	81.1%	21.4% Fiebre Q 19.2% Brucelosis 18.5% Rickettsiosis 7.3% Tifus murino
The changing etiology of fever of intermediate duration (10)	Nuria Espinosa, Elías Cañas, Máximo Bernabeu-Wittel, Amalia Martín, Pompeyo Viciana y Jerónimo Pachón	2004-2005	Hospital Virgen del Rocío (Sevilla)	179	60.9%	11.7% Fiebre Q 6% Rickettsiosis 3.3% Brucelosis 3.3% Tifus murino
Fiebre de duración intermedia en un área urbana de Madrid: espectro etiológico y estrategia diagnóstica (2013) (67)	F. Montoya, R. Mayayo, V. Hontañón, M. Lizarriturry, F. Arnalich, J.M. Peña	abril 2012-junio 2013	Hospital Universitario de La Paz (Madrid)	98	51%	28% etiología vírica 12% Fiebre Q 12% Chlamydia
Clinical spectrum of fever of intermediate duration in the south of Spain (2018) (12)	Parra Ruiz J, Pena Monje A, Tomás Jiménez C, Parejo Sánchez MI, Vinuesa García D, Muñoz Medina L, et al.	2000-2005	Hospital Clínico San Cecilio, Granada	233	34%	13.6% Fiebre Q 6.8% CMV 4.7% Rickettsiosis 2.5% VEB 2.1% Brucelosis
Fiebre de duración intermedia. Análisis de 2054 casos de un único centro (2015) (68)	Pérez Arellano JL et al	1998-2015	Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria	2054	43%	14.5% Fiebre Q 10.1% Rickettsiosis 4.1% VEB 3.7% CMV

CONJUNTO MÍNIMO BÁSICO DE DATOS (CMBD)

Dentro de cualquier sistema sanitario la información constituye el recurso más valioso y disponible, puesto que interconecta a todos los demás y determina tanto la planificación como la gestión de los mismos.

El objetivo principal de un sistema de información hospitalario consiste en optimizar la gestión de los recursos y la atención al paciente, facilitando la toma de decisiones.

Desde la década de los noventa, la informatización de los hospitales españoles ha experimentado un desarrollo exponencial, más marcadamente desde la creación del Conjunto Mínimo Básico de Datos (CMBD) en 1992. Sin embargo, resulta difícil comprender lo básico de los sistemas de información sanitaria de los que disponemos actualmente con respecto a otros sectores. La justificación para este decalaje podría radicar en la gran variedad, complejidad y dinamismo inherentes a la actividad hospitalaria.

El primer paso para la gestión de una cantidad ingente de información se basa en su clasificación. Así, en un hospital encontramos tres tipos de datos: administrativos, médico-administrativos y clínicos. Los primeros son los más fáciles tanto de obtener como de estandarizar y, dado que repercuten directamente a nivel económico, los sistemas informáticos para su gestión han sido los más potenciados. Sin embargo, respeto a los dos tipos restantes, se han desarrollado múltiples sistemas sin resultado del todo satisfactorio.

HISTORIA DE LOS SISTEMAS DE INFORMACIÓN HOSPITALARIOS

Es en la década de los 50 cuando se comienza a intuir la necesidad de creación de sistemas de información sanitaria que faciliten la clasificación, almacenamiento y accesibilidad de la misma. A pesar de esta idea supuso el germen de los sistemas de información sanitaria tal y como los conocemos, el enfoque fue erróneo desde el principio. Se diseñaron estos proyectos como meros caudales de contabilidad que requerían costosos sistemas informáticos, imposibles de asumir por muchos hospitales.

Ya en los 70, se rectificó la perspectiva, pero el objetivo se mantuvo equivocado: se comprendió la necesidad de inclusión de la información clínica en estos sistemas, pero con la finalidad de minimizar los costes, manteniendo en un segundo plano las necesidades del personal implicado en la atención al paciente.

Finalmente, en los años 80, se produjo el cambio necesario que encaminaría a estos sistemas de gestión hasta nuestros días. Se introdujeron conceptos como la estancia media hospitalaria y los grupos relacionados por el diagnóstico, cuya definición ya reflejaba lo

imprescindible de los datos clínicos para la consecución de los fines económicos pretendidos. Esto desembocó, en la década de los 90, en los tan anhelados sistemas dinámicos de información clínico-administrativa que permitían el flujo continuo de datos de ambas modalidades y, finalmente, la gestión y planificación de los recursos en función de estos datos, su utilización para la investigación y, cerrando el círculo, la evaluación de la calidad de la asistencia proporcionada.

SISTEMAS SANITARIOS EN USO EN LA ACTUALIDAD

Actualmente existen tres sistemas básicos de información sanitaria con características bien diferenciadas: los registros, las encuestas y los sistemas de notificación.

i) Las **encuestas** son sistemas de recogida de datos, no obligatorios, que se llevan a cabo de forma transversal cada 3 meses mediante la cumplimentación de formularios denominados encuestas de morbilidad hospitalaria y sobre una muestra representativa de la población.

ii) Los **sistemas de notificación** son sistemas de registro de aquellas enfermedades que se recogen en la lista de Enfermedades de declaración obligatoria (EDO). En teoría deberían recogerse todos los casos de estas enfermedades, pero existe un importante sesgo de subnotificación. Debe llevarse a cabo por los profesionales de la salud mediante la cumplimentación de una serie de formularios estandarizados.

iii) Los **registros** son sistemas de recogida de datos, obligatorios, que se realizan de forma continuada y engloban a la totalidad de la población. En España los datos se envían inicialmente a cada autonomía para su gestión y se remiten posteriormente al Ministerio de Sanidad de forma periódica. Dentro de estos últimos se encuentra el Conjunto Mínimo Básico de Datos (CMBD).

EL CONJUNTO MÍNIMO BÁSICO DE DATOS (CMBD)

En 1969, en Ginebra, el Grupo de Estudio de la OMS emitió la recomendación de instaurar un conjunto básico de datos a partir de cada historia del paciente hospitalizado. En 1974 fue establecido en Estados Unidos el *Uniform Hospital Discharge Data Set* compuesto por 14

ítems. En 1981 sería aceptado en Europa y 3 años después, el Ministerio de Sanidad y Consumo instauraría la obligatoriedad de recogida de estos datos en todo informe de alta emitido para cada paciente en España. Hasta 1992 se ensayarían diferentes prototipos con diversos resultados hasta que, en ese mismo año, la Secretaría General del Sistema Nacional de Salud del Ministerio de Sanidad y Consumo establecería el CMBD al Alta Hospitalaria como el sistema seleccionado, con un plazo máximo de 11 meses para su implementación en todos los centros hospitalarios administrados por el INSALUD-GD.

El CMBD incluía un conjunto de datos administrativos y clínicos (14 ítems) de manera estandarizada por cada contacto asistencial con el objetivo de constituir una base de datos normalizada, válida, fiable y comparable de todos los hospitales del Sistema Nacional de Salud (SNS). Los objetivos específicos eran:

1. La existencia de una única historia clínica por paciente y hospital, fácilmente accesible.
2. La disponibilidad de los recursos informáticos necesarios que garantizaran la adecuada codificación de los datos.
3. La posibilidad de analizar esta información con fines clínicos y/o epidemiológicos.

Esta información debía enviarse de forma trimestral al Sistema Nacional de Salud.

Dado su bajo coste y elevada disponibilidad, el CMBD se ha convertido en una de las principales herramientas de cuantificación de la efectividad, eficiencia y calidad de la asistencia sanitaria.

PRINCIPALES UTILIDADES DEL CONJUNTO MÍNIMO BÁSICO DE DATOS (CMBD)

La codificación de los diagnósticos y las intervenciones quirúrgicas realizadas se llevó a cabo hasta 2015 mediante la Clasificación Internacional de Enfermedades (CIE-9-MC) y posteriormente mediante el CIE-10-ES.

Actualmente el CMBD se compone de una serie de ítems:

i) Administrativos: i) código de identificación personal, ii) número de historia clínica; iii) fecha de nacimiento; iv) sexo; v) país de nacimiento; vi) código postal del domicilio habitual; vii) municipio de domicilio habitual; viii) régimen de financiación; ix) fecha y hora de inicio de la atención sanitaria; x) fecha y hora de la orden de ingreso; xi) tipo de contacto; xii) tipo de visita; xiii) procedencia (atención primaria, urgencias, etc);

xiv) circunstancias de la atención; xv) servicio responsable de la atención; xvi) fecha y hora de fin de la atención; xvii) tipo de alta.

ii) Clínicos: i) diagnóstico principal; ii) diagnósticos secundarios; iii) marcador POA (*present on admision);* iv) procedimientos; v) procedimientos externos; vi) códigos morfológicos de neoplasia.

Con la combinación y análisis de estos ítems, es posible la aplicación de sistemas de clasificación de pacientes como los GRD (Grupos Relacionados por el Diagnóstico) o PMC (*Patient Management Categories*). En función de las características del paciente y los diagnósticos al ingreso, se aplican una serie de algoritmos que permiten la clasificación de cada paciente en un GRD de severidad y un GRD de riesgo de mortalidad.

Por tanto, la implantación del CMBD en los hospitales del Sistema Sanitario Español permite: i) la evaluación de la actividad asistencial y los resultados obtenidos; ii) la planificación, gestión y optimización de los recursos, asegurando así que cada paciente reciba la mejor calidad asistencial disponible y facilitando la toma de decisiones a los profesionales sanitarios; iii) la comparación entre diferentes servicios y/o hospitales; iv) la actualización de la pirámide poblacional con los datos de sexo y edad; v) conocer los datos de mortalidad.

Objetivos

OBJETIVO PRINCIPAL

Análisis del CMBD como herramienta para la valoración clínico-epidemiológico de cuatro enfermedades infecciosas causantes de fiebre de duración intermedia.

OBJETIVOS ESPECÍFICOS

1. Análisis clínico y epidemiológico mediante el CMBD de los pacientes ingresados en hospitales de la red del Sistema Nacional de Salud español diagnosticados de infección por *Coxiella burnetii* entre los años 1997 y 2015.

2. Valoración clínica y epidemiológica mediante el CMBD de los pacientes hospitalizados en hospitales de la red del Sistema Nacional de Salud diagnosticados de infección por *Rickettsia spp.* durante el periodo 1997-2015.

3. Estudio clínico y epidemiológico mediante el CMBD de los pacientes hospitalizados en Hospitales de la red del Sistema Nacional de Salud con enfermedad por arañazo de gato entre los años 1997-2015.

4. Evaluación clínica y epidemiológica mediante a partir del CMBD de los pacientes ingresados en Hospitales de la red del Sistema Nacional de Salud con infección por *Brucella spp.* entre 1997-2015.

Material y métodos

Los datos a analizar se han extraído del Conjunto Mínimo Básico de Datos (CMBD), que incluye un conjunto de datos estandarizado y preestablecido de carácter clínico y administrativo por cada contacto asistencial de cada paciente. El CMBD nos permite conocer la demanda asistencial y la morbilidad atendida en los dispositivos de atención especializada, y hace posible la comparación entre diferentes servicios de salud (nacionales, autonómicos e interhospitalarios) así como el desarrollo de estudios de investigación clínica y epidemiológica. Los diagnósticos y los procedimientos llevados a cabo se codificaban de acuerdo con la "*International Classification of Diseases, Ninth revision, Clinical Modification*" (CIE-9-CM) hasta 2015 y posteriormente mediante la "*International Classification of Diseases, 10th Revision, Clinical Modification"* (CIE-10-ES).

Para la obtención de esta información se cumplimentó la solicitud correspondiente (**https://www.mscbs.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/SolicitudCMBD.htm**), debidamente justificada y se envió al Ministerio de Sanidad que nos remitió los datos. Dicha información está disponible para cualquier investigador que la solicite, si bien es necesaria la aceptación de una cláusula de confidencialidad por la cual, únicamente la persona solicitante de dichos datos y su equipo, pueden hacer uso de los mismos. Todos los datos proporcionados se encuentran anonimizados previamente a su cesión al equipo investigador.

Se solicitó la aprobación del Comité Ético para la Investigación Clínica del Complejo Asistencial Universitario de Salamanca (CAUSA).

Posteriormente se procedió a la descodificación de las variables y a la selección de aquellas susceptibles de análisis estadístico en nuestro estudio.

El diagnóstico principal se definió como aquel que motivó el ingreso hospitalario, mientras que los diagnósticos secundarios se interpretaron como aquellos que ya estaban descritos en el paciente en el momento de ingreso o que se establecieron durante el mismo.

Se llevó a cabo un estudio descriptivo longitudinal retrospectivo de aquellos pacientes ingresados los hospitales del Sistema Nacional de Salud Español entre el 1 de enero de 1997 y el 31 de diciembre de 2015, diagnosticados de infección por cada uno de los microorganismos analizados en nuestro estudio. Se procedió también a la elaboración de tablas y figuras con el objetivo de facilitar la compresión y hacer los resultados más visuales.

Por último, se realizó una búsqueda bibliográfica sistemática para conocer la situación epidemiológica de cada microorganismo y poder establecer un estudio comparativo con los resultados obtenidos en nuestros análisis. La metodología pormenorizada de cada uno de ellos, se encuentra detallada en el apartado "material y métodos" de cada uno de los artículos.

Resultados

Los resultados de este trabajo doctoral vienen estructurados como artículos originales, que dan respuesta a cada uno de los diferentes objetivos previamente referidos. Así, se exponen los artículos de los que consta esta tesis doctoral.

Artículo Primero

Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: What´s new.

Objetivo: Llevar a cabo el análisis clínico, epidemiológico y económico de los pacientes infectados por *Coxiella burnetti* que requirieron hospitalización entre 1997 y 2015.

Principales resultados: Se identificaron 4.214 pacientes diagnosticados de fiebre Q en el intervalo de tiempo analizado. Dos tercios fueron varones con una edad media de 50 años. La mayoría de los casos se produjeron entre marzo y agosto. La estancia media hospitalaria fue de 13.8 días, viéndose incrementada en los pacientes de mayor edad. Económicamente, el gasto sanitario ascendió a más de 154 millones de euros.

Conclusiones: La fiebre Q continúa siendo una importante zoonosis en España con una incidencia estable pero un elevado número de casos. La sospecha clínica puede mejorar el pronóstico y reducir la estancia hospitalaria y la mortalidad. El Conjunto Mínimo Básico de Datos (CMBD) se postula como una herramienta estadística excepcional para esta finalidad.

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Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: What's new

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ABSTRACT

Objectives: The objective of this study was to assess the epidemiology and burden of Q fever (QF) in Spain.
Methods: We designed a retrospective descriptive study using the minimum basic data set in patients admitted to hospitals of the National Health System between 1998 and 2015 with a diagnosis of Q fever (ICD-9: 083.0.).
Results: We found 4214 hospitalized patients with a mean age (±SD) of 50.9 ± 19.3 years. The male/female ratio was 3:1. The incidence rate was between 0.41 and 0.65 cases per 100,000 person-years over the 18-year period. The highest incidence of cases was from March to August ($p = 0.024$). 21.1% patients had pneumonia, 17.5% had liver disease, and only 3.2% had endocarditis. The average hospital stay was 13.8 days (±12.8). A total of 117 (2.8%) patients died. The total mean cost of QF is approximately €154,232,779 (€36,600 ± 139,422 per patient).
Conclusions: QF is an important zoonosis in Spain with a stable incidence rate and high cost for hospitalization. Older patients have a more severe clinical picture and higher mortality, which can be decreased with early clinical suspicion.

Introduction

Q fever (QF), whose causative agent is *Coxiella burnetii*, is a zoonosis and is a significant public health problem. QF has three types of reservoirs: i) domestic or peridomestic animals, mainly goats, sheep and cattle and to a lesser extent cats and dogs. ii) "wild" animals, mainly rodents and small mammals, and occasionally birds, reptiles, amphibians and fish; and iii) ticks (Pérez-Arellano et al., 2018; Musso and Raoult, 1995). QF can present as sporadic cases or through outbreaks in a specific region. Risk groups include exposed professionals, and pregnant women, immunocompromised patients, and patients with valvular disease at risk for chronic Q fever after acute infection (Million et al., 2013). Currently, the greatest risk factor is living in or traveling to an endemic area (Hartzell et al., 2008; Hackert et al., 2012; Stern et al., 2018; Handy Marshall et al., 2018).

QF is considered a benign disease (Damasceno and Guerra, 2018; Greiner et al., 2018), since only 2–5% of the patients diagnosed with QF require hospitalization (Greiner et al., 2018;

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Fraile Fariñas and Muñoz Collado, 2010). Infection in humans occurs mainly by inhaling pseudospores, although other avenues of minor importance include transfusions, interhuman transmission and tick bites (Damasceno and Guerra, 2018; Honarmand, 2012; Milazzo et al., 2002; Kruszewska et al., 1996).

QF has a wide spectrum of disease manifestations, with two main clinical presentations: i) *acute Q fever* can present with intermediate duration fever associated with respiratory manifestations and/or liver disorders, and ii) *persistent localized infections* can be developed after an acute infection (symptomatic or not) with vascular (endocarditis, aneurysms or vascular grafts) or osteoarticular involvement Fournier et al., 1998. Both forms can present with nonspecific symptoms (Million et al., 2013; Stern et al., 2018; Dahlgren et al., 2015a; National Notifiable Diseases Surveillance System (NNDSS), 2009; Anderson et al., 2013; Kampschreur et al., 2015; Delsing et al., 2010), and these forms of presentation can vary widely according to the geographical location. Historically, it is more frequent as pneumonia in the north (Cilla et al., 2008) and as acute hepatitis in the central and southern regions (Fraile Fariñas and Muñoz Collado, 2010).

With respect to epidemiology, QF is distributed worldwide (Damasceno and Guerra, 2018), with a variable global incidence rate (Eldin et al., 2017). In Europe, the incidence rate varies widely between countries: 0.09 cases/100,000 in the United Kingdom (Halsby et al., 2017) to 2.5–4 cases/100,000 in France (Pérez-Arellano et al., 2018; Hackert et al., 2012). In Spain, it is an endemic and a notifiable disease (Ministerio de Sanidad Servicios Sociales e Igualdad, 2015). Since 2013, the number of human cases reported by Spain has continuously increased, which is mostly explained by the reporting system changing from voluntary to compulsory (Centre for Disease Prevention and Control E, 2019). We do not know the Spanish incidence rate, and it varies widely depending on the region of focus (Alende-Castro et al., 2018). The largest number of case notifications occurs in Pais Vasco (Fraile Fariñas and Muñoz Collado, 2010; Cilla et al., 2008) and Andalucia (Fraile Fariñas and Muñoz Collado, 2010), and there are still more cases in rural areas (Eldin et al., 2017).

The mortality rate of QF is less than 3% (Anderson et al., 2013; Eldin et al., 2017; Woldehiwet, 2004), though a recent study in California described a lethality rate of 10% (Akamine et al., 2019). We have not found studies about the economic impact of QF in Spain.

The aim of our study was to evaluate the epidemiological and economic impact of in-patients diagnosed with QF in Spain between 1998 and 2015.

Methods

This is a retrospective longitudinal descriptive study of hospitalized patients diagnosed with *Coxiella burnetii*, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), 083.0, in Spanish public hospitals between January 1, 1998 and December 31, 2015, an 18-year study period.

This study analyzes the data provided by hospital discharge records (HDR). HDR meets all hospital discharges produced in the network of general hospitals in the NHS (National Health System). The data contained in this record are those established in the hospitalization minimum data set (CMBD in Spanish) provided by the Health Information Institute of the Ministry of Health and Equality. CMBD provides the usual demographic data (age, sex, and place of residence), clinical variables (diagnoses and procedures) and variables related to the episode of hospitalization as a circumstance of admission (urgent or programmed), patient discharge (discharge to address, transfer to another hospital or death), average stay and cost estimates. Diagnoses and procedures collected were coded using the ICD-9-CM. **Primary diagnosis** is the pathological process that is considered the main cause or reason for the patient's admission to the hospital, according to optional criteria. **Secondary diagnoses** coexist with it at the time of admission or develop throughout the hospital stay and influence the duration of treatment or treatment. Patients with missing data were excluded from the study.

Statistical analysis

The incidence rates were calculated by dividing the number of new cases of disease *(numerator)* per year/period by the population at risk *(denominator)* in a period of time (person-years) ($\times$100,000) and expressed as *"cases per 100,000 person-years"*. As it is not possible to accurately measure disease-free periods, the total number of person-time at risk can be estimated approximately and satisfactorily when the size of the population is stable, multiplying the average population size studied by the duration of the observation period. Thus, the population at risk was obtained from annual data published by the National Institute of Statistics (INE, http://www.ine.es/). Incidence rates were computed by autonomous community and year to assess temporal and geographical patterns. Results in terms of mean rates by autonomous community were plotted in maps for the whole study period.

The lethality rate was calculated by dividing the number of deaths (numerator) by the number of patients with a specific disease (denominator) ($\times$ 100).

The cost estimate was the weighted average of the average costs of the GRD of all cases of a given unit, group or process. It was calculated by multiplying the number of cases of each GRD and Level of Severity by their average cost and dividing by the total number of cases of said unit. These data were calculated for each case/patient by the CMBD. We estimated the average cost ($\pm$ SD, Standard deviation) for the total of cases/patient cohort.

The results were expressed as absolute value (n) and percentage (%) for categorical variables and as the mean, standard deviation (SD), median, and range (minimum value, maximum value) for continuous variables. The chi-square test was used to compare the association between categorical variables, such as clinical and demographic variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for OR. Continuous variables were compared using Student's t-test or the Mann–Whitney test for two groups, depending on their normal or non-normal distribution. ANOVA allowed us to analyze the influence of independent nominal variables on a continuous dependent variable. A p-value <0.05 was considered statistically significant Data analysis was performed using SPSS 23 (*Statistical Package for the Social Sciences*).

Ethics statement

This study obtained data from CMBD provided by the Ministry of Social Services of Health and Equality (Ministerio de Servicios Sociales, Sanidad e Igualdad, MSSSI). Researchers working can request databases by completing a questionnaire available on the MSSSI website, where a signed confidentiality commitment is required. All patient data are anonymized and identified by the MSSSI before they are provided to the applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers; they must request the data directly from the MSSSI. The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because it is an epidemiological study, written consent was not obtained. All data analyzed were anonymized.

Results

Incidence rates

Between January 1998 and December 2015 (18-year study period), a total of 4214 cases with ICD-9-CM: 083.0 (QF) were registered with HDR in Spain. Chronologically, we observed an irregular distribution of cases throughout the study period, a minimum value of 183 cases (4.3%) in 2001, and a maximum value of 304 cases (7.2%) in 2013. The period incidence rate was 0.53 cases per 100,000 person-years. The annual incidence rates ranged between a minimum and maximum value of 0.41–0.65 cases per 100,000 person-years in 2009 and 2013, respectively, as shown in Figure 1. Attending to primary diagnosis, we found an incidence rate of 0.38 cases per 100,000 person-years.

Geographic and temporal distribution

When analyzing incidence rates in Spain, we observed differences between Spanish autonomous communities. Islas Canarias and Islas Baleares had the highest incidence rates (1.48 and 1.43 cases per 100,000 person-years, respectively) (Figure 2). In total, 25% of patients come from municipalities of less than 5000 inhabitants, and 75% (3/4) of patients come from municipalities greater than 5000 inhabitants.

Figure 3 shows the distribution of QF cases according to the month in which it was diagnosed. Months with the highest incidence of cases were from March to August ($p = 0.024$).

Clinical features of QF-related hospitalizations

The main clinical and epidemiological data of the patient cohort are shown in Table 1. Most cases were men (3147, 74.7%). Thus, the male/female ratio was 3:1. The mean (±SD) age was 50.9 (±19.3) years. Only 1.9% (78) of cases occurred in the pediatric population. A total of 589 patients (13.98%) were between 0 and 29 years old. Most patients (2189, 51.95%) were between 30–59 years old. A total of 1385 of the patients (32.87%) were between 60 and 89 years old. Only 51 patients were ≥ 90 years old in our cohort. Three out of four cases (3071, 72.9%) were main diagnosis, and the mean hospital stay was 13.8 (±12.8) days. Table 2 shows that the variables obtained statistically significant results when comparing patients with primary diagnosis *vs.* secondary diagnosis ($p < 0.05$). The mean age was lower among patients with primary diagnosis, 49.2 ± 18.5 *vs.* 55.4 ± 20.4, and the mean hospital stays increased by 5 days among patients with secondary diagnostics, 17.5 ± 16.1 *vs.* 12.4 ± 10.9.

The most frequent comorbidities in these patients were respiratory diseases, digestive diseases, circulatory diseases, other infectious and parasitic diseases, and neoplasms, in order of frequency. A total of 891 (21.1%) patients were diagnosed with pneumonia, 736 patients had liver disease (17.5%), and 136 (3.2%) had endocarditis. Others were 59 pericarditis, 10 meningitis, 14 encephalitis/myelitis. Attending to the main diagnosis, the highest pneumonia incidence rate was in Aragon and Islas Baleares (IR: 0.08, both of them), and the highest hepatitis incidence rate was in Islas Baleares, Islas Canarias and Castilla y León (IR: 0.02) (Figures 3 and 4).

There were no significant differences between age (<50 years *vs.* ≥50 years) and the primary diagnosis of hepatitis (45.3% *vs.* 54.7%, $p = 0.550$). However, we found significant differences when the primary diagnosis was pneumonia (40% *vs.* 60%, $p = 0.025$). The diagnosis of pneumonia was more frequent in > 50 years.

Mortality and economic analysis

A total of 117 (2.8%) patients died. Of these, 46 deaths were patients with the primary diagnosis code (43/3071, 1.5%). Table 3 shows the clinical and epidemiological characteristics of the patients who died.

The lethality rate was 1.50 per 100 (range, minimum value 0 per 100 in 2005 and maximum value 3.37 per 100 in 2013). Figure 1 shows the number of deaths (QF primary diagnosis) each year and annual lethality rates per 100. When analyzing lethality rates in Spain, we observed differences between Spanish autonomous communities. Asturias had the highest lethality rate (7.69 per 100), followed by Cantabria (5.71 per 100), both in Northern Spain (Figure 2). When we focused on the primary diagnosis, we observed the highest lethality rate in Cantabria (5.88) and the second highest rate in Aragón (3.09). Deaths due to pneumonia predominated in Asturias (50%) and Galicia (20%), while hepatitis

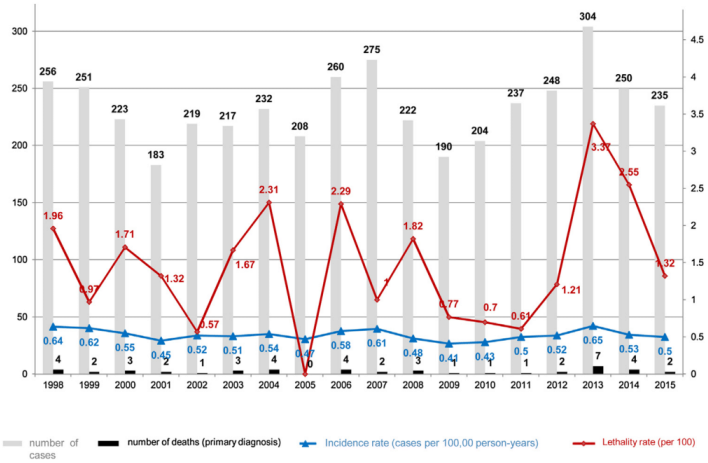

Figure 1. Temporal distribution of number of cases, number of deaths, incidence rate, and lethality rate.

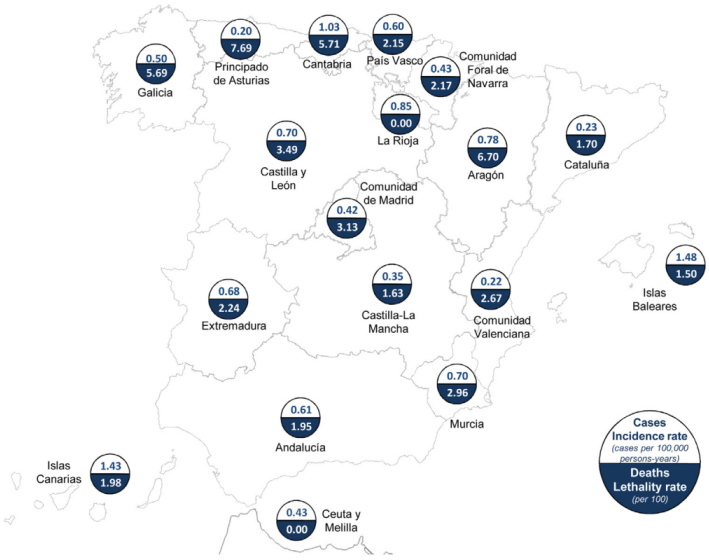

Figure 2. QF incidence and lethality rates by region, Spain (1997–2015).

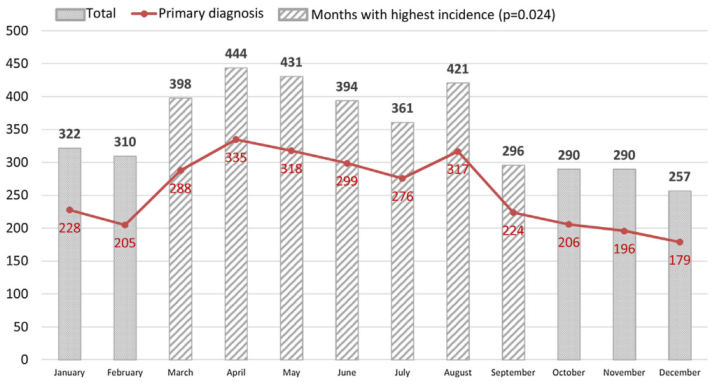

Figure 3. Distribution of cases of QF in-patients during the months of the year, total cases and primary diagnosis.

was the main cause of mortality in Murcia (66.67%) and Comunidad Valenciana (25%).

Finally, we estimated the global cost of this cohort of patients, and the main data are shown in Table 4. Hospital admitted patients with a diagnosis of QF in Spain (from 1998 to 2015) had a total cost of approximately €154,232,779. Mean (±SD) cost per patient, €36,600 ± 139,422.

Discussion

Incidence rates

A total of 4214 cases of QF (codes ICD-9-CM: 083.0) were registered with HDR in Spain between January 1998 and December 2015. The period incidence rate for our cohort of patients was 0.53 cases per 100,000 person-years, and it remained stable (or even slightly decreased between 1998 and 2015).

Our data provide a higher incidence rate in Spain compared to rates described in other European countries, such as the British Isles, with a stable incidence of approximately 0.15 to 0.35 cases per 100,000 inhabitants (Wallensten et al., 2010; Wilson et al., 2010; Hussain-Yusuf et al., 2012), while in France, the annual incidence of acute QF is 2.5/100,000 persons (Frankel et al., 2011). It is remarkable that the incidence in Spain remains stable compared to another French study where the incidence shows a continuous increase (Frankel et al., 2011). This phenomenon might have several explanations: i) use of new techniques that increase the diagnostic possibilities (Bolaños-Rivero et al., 2017a), ii) a better knowledge of the disease and, therefore, of its suspicion, iii) a

Table 1
Main epidemiological and clinical data of patients.

Variable	N = 4214 cases (100%) n (%)
Age	
Mean ± SD, years	50.9 ± 19.3
Gender	
Male	3147 (74.7)
Diagnosis causing the hospitalization	
Primary diagnosis	3071 (72.9)
Secondary diagnosis	1143 (27.1)
Pneumonia	891 (21.1)
Primary diagnosis	142/891 (15.9)
Secondary diagnosis	749/891 (84.1)
Liver disease	736 (17.5)
Primary diagnosis	53/736 (7.2)
Secondary diagnosis	683/736 (92.8)
Acute and sub-acute endocarditis	136 (3.2)
Primary diagnosis	21/136 (15.4)
Secondary diagnosis	115/136 (84.6)
Hospital readmission	
Hospital readmission[a]	3784 (89.8)
New episode	430 (10.2)
Overall mortality	117/4214 (2.8)
Q-fever (primary diagnosis) mortality	46/3071 (1.5)
Pneumonia (primary diagnosis) mortality	7/142 (4.9)
Liver disease (primary diagnosis) mortality	5/53 (9.4)
Hospital stay	
Mean ± SD, days	13.8 ± 12.8

[a] Hospital readmission: for the same year and center within 30 days after a previous discharge.

more adequate record of the number of cases, iv) different patterns of disease transmission (Bolaños-Rivero et al., 2017b), and v) the presence of outbreaks that increase the incidence of the disease. This French study shows a maximum incidence between March and August, which is identical to our data (Frankel et al., 2011). Although the real impact of QF in Spain may be greater, we only see the tip of the iceberg.

Geographic and temporal distribution

Although classic Q fever has been considered a predominantly rural disease (due to contact with animals, mainly cattle and goats), only 25% of our cases are of rural origin (<5,000 inhabitants) (Pérez-Arellano et al., 2018) and there are a significant number of cases (75%) from urban areas, which do not have contact with animals. Classically, Andalucía and Pais Vasco are the communities with the highest incidence rate described (Fraile Fariñas and Muñoz Collado, 2010; Cilla et al., 2008). Therefore, in our study, we obtained the highest incidence rates in Islas Canarias and Baleares with no clear explanation.

Clinical features of QF-related hospitalizations

In general, although cases in children and the elderly are described, QF is a disease that predominantly affects adults in middle age and with a male predominance (Pérez-Arellano et al., 2018). Therefore, most patients diagnosed with QF in Europe are in the age range of 15–45 years according to the literature (Eldin et al., 2017). Our cohort has a significantly higher mean age (50.9 ± 19.3 years) as expected, and our cases in elderly and pediatric ages are very few in possible relation to the mechanisms of acquisition of this pathology.

In our study, the male/female ratio was 3:1, and in previous studies, we found a similar ratio of 2.5:1 (Pérez-Arellano et al., 2018; Parker et al., 2006). Among the factors involved, hormonal modifications (protective role of 17-ß-estradiol) that take place after puberty have been described in addition to the risk and environmental exposure (Emmanouil and Raoult, 2012; Leone et al., 2004; Raoult et al., 2005). In our work, 15.9% patients had pneumonia, 7.2% had liver disease and 3.2% patients had endocarditis. It is difficult to compare these results with those provided in the literature for several reasons: i) In our work, exclusively admitted patients are evaluated, so the less severe forms are underrepresented. ii) The definitions of "pneumonia" and "hepatitis" are not unequivocal. For example, "hepatitis" could mean a hepatitis A-like syndrome, or a two-fold increase in serum liver enzymes (Bolaños-Rivero et al., 2017a). iii) As it happens when different countries are compared, there is also a different distribution of clinical forms within Spain: pulmonary in the north and "hepatic" in the south and in the Canary Islands (Bolaños et al., 2003; Jado et al., 2012). In addition to the different bacterial load, there are data to suggest that strain differences are important in

Table 2
Primary diagnosis *vs* secondary diagnosis of QF.

	Primary diagnosis N_1 = 3071, n (%)	Secondary diagnosis N_2 = 1143, n (%)	p-Value OR (95%CI)[a]
Age			
Mean ± SD, years	49.2 ± 18.5	55.4 ± 20.4	<0.001
≥50	1431 (46.6)	703 (61.5)	1.8 (1.5–2.1)
<50	1640 (53.4)	440 (38.5)	
Gender			
Male	2333 (76.0)	814 (71.2)	0.002
Female	738 (24.0)	329 (28.8)	1.3 (1.1–1.5)
Type of hospital admission			
Urgent	2758 (89.8)	982 (85.9)	<0.001
Programmed	300 (9.8)	160 (14.0)	1.5 (1.2–1.8)
Others/unknown	13 (0.4)	1 (0.1)	
Hospital readmission			
Hospital readmission	2819 (91.8)	965 (84.4)	<0.001
New episode	252 (8.2)	178 (15.6)	2.1 (1.6–2.5)
Type of discharge			
Home	2976 (96.9)	1029 (90.0)	<0.001
Transfer to another hospital	21 (0.7)	28 (2.4)	
Voluntary discharge	9 (0.3)	6 (0.5)	
Transfer to social-health center	7 (0.2)	5 (0.4)	
Others/unknown	12 (0.4)	4 (0.3)	
Hospital stay			
Mean ± SD, days	12.4 ± 10.9	17.5 ± 16.1	<0.001
Exitus letalis	46 (1.5)	71 (6.2)	>0.001, 4.3 (2.9–6.3)

[a] Only when it is a significant p-value.

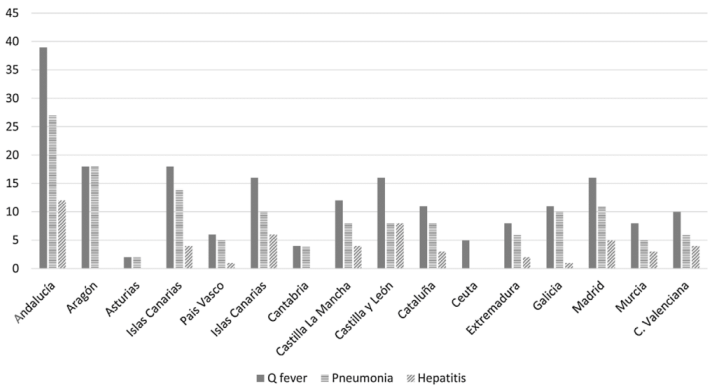

Figure 4. Number of cases of QF of in-patients in Spain during 1997–2015 (primary diagnosis).

Table 3
Main variables association with mortality of QF in-patients.

	$N_0 = 117$ *Exitus letalis* n (%)	p-Value, OR (95%CI)[a]
Age		
Mean ± SD, years	69.9 ± 15.4	<0.001
≥50 years	106 (90.6)	9.8 (5.2–18.3)
<50 years	11 (9.4)	
Gender		
Male	82 (70.1)	0.246
Female	35 (29.9)	
Diagnosis causing the hospitalization		
Secondary diagnosis	71 (60.7)	<0.001
Primary diagnosis	46 (39.3)	4.3 (2.9–6.3)
Type of hospital admission		
Urgent	110 (94.0)	0.177
Programmed	7 (6.0)	
Hospital readmission		
New episode	26 (22.2)	<0.001
Hospital readmission	91 (77.8)	2.6 (1.6–4.1)
Hospital stay		
Mean ± SD, days	22.8 ± 21.4	<0.001

[a] Only when it is a significant p-value.

their association with clinical manifestations (Jado et al., 2012). These data suggest the need to include QF in our differential diagnosis when an in-patient has pneumonia, hepatitis or endocarditis (Leone et al., 2004). In addition, some studies describe a significantly lower average age in patients with hepatitis and greater age in patients with pulmonary involvement, and the results of our work corroborate lung involvement.

Mortality analysis

Our lethality rate was 2.8%, which is similar to the rate described in the USA from 2000 to 2012 (2%) (Dahlgren et al., 2015b). Nevertheless, a recent study in California described a lethality rate of 10% (Akamine et al., 2019), and the death attributed to QF was associated with an average diagnostic delay of 65.5 days (Akamine et al., 2019). Our data show that older patients have a more severe clinical picture and higher mortality. These findings seem to tip the balance towards the first hypothesis: the scarce clinical suspicion has delayed the diagnosis. Therefore, efforts to carry out a timely diagnosis and an earlier initiation of treatment are essential to improve the prognosis (Raoult and Marrie, 1995) and may result in fewer hospitalizations and fewer severe complications. This result is supported by our work, where the lethality rate is higher in Asturias and Cantabria (7.69 and 5.71, respectively), although the highest incidence rate is not in these communities. In addition, regions with higher incidences have lower mortality. An explanation would be a greater clinical suspicion, which would condition a diagnosis and earlier treatment, thus reducing the mortality rate. A very slight decrease in the mortality rate was observed during the period of our study (1.96 in 1998 and 1.32 in 2015). Although we cannot extrapolate our results to the general population (since we only include hospitalized patients), it is possible to appreciate that they are in the same line as available literature (Akamine et al., 2019).

It is remarkable that in our study, the small reduction in the incidence rate was greater than that in the mortality rate. We think that there could be two possible causes for this: i) the scarce clinical suspicion that we have about the presence of this pathology or ii) the lower tendency to hospitalize these patients for trivializing the clinical symptoms.

Economic analysis

The mean hospital stay for our cohort of patients was 13.8 ± 12.8 ($p < 0.001$), but it increased noticeably when we focused on the patients who died (22.8 ± 121.4). We have not found data on hospital stay in the available literature.

We also calculated the approximate cost of in-patients with a diagnosis of QF in Spain (from 1998 to 2015): €154,232,778.60. The mean (±SD) cost per patient was €36,600.09 (±139,421.85). Note that the highest mean (±SD) cost occurs in patients who died €51,814.29 (±215,505.52) ($p < 0.001$). We were also not able to find data about the economic cost of QF anywhere.

It should be noted that the difference in costs according to involvement is higher in patients with hepatitis. We must not forget that we have only taken into account the costs in terms of hospitalization, but according to the literature, up to 20% of these patients suffer a chronic fatigue syndrome (Hickie et al., 2006; Reukers et al., 2019) after the referral of the QF, which incurs additional costs due to sick leave and medical consultations. The cluster of cases collected from patients diagnosed with this syndrome is in Europe and Australia (Hickie et al., 2006).

Table 4
Main burden data of QF in-patients.

	N	Descriptive statistics Mean ± SD	p-Value
Cost by diagnosis			
Q-Fever primary diagnosis	3071	38,706.82 ± 136,553.41	0.108
Q-Fever secondary diagnosis	1143	30,939.75 ± 146,763.57	
Cots by type (primary diagnosis)			
Pneumonia	142	23,123.73 ± 88,066.07	0.001
Hepatitis	53	52,566.41 ± 176,565.36	
Cost by type of hospital admission			
Urgent	3740	33,351.86 ± 126,270.37	0.008
Programmed	460	51,259.83 ± 207,084.28	
Cost by type of hospital readmission			
Hospital readmission	3071	37,201.61 ± 141,040.00	0.406
New episode	430	31,306.68 ± 124,300.10	
Cost in mortality			
Overall mortality	117	51,814.29 ± 215,505.52	<0.001
Primary diagnosis mortality	46	70,396.45 ± 196,525.91	
Global cost			
Total, €	4214	154,232,778.60	
Mean ± SD, €	4214	36,600.09 ± 139,421.85	

Limitations and conclusions

Even if the CMBD provides information from a network of hospitals that covers more than 99% of the population living in Spain (http://www.msssi.gob.es/), this study provides fairly accurate estimates of the incidence. The main limitations of this study are determined by several factors: i) the use of sources such as the CMBD for purposes other than research and clinical care; ii) the use of the ICD-9 code, which has certain classification limitations with respect to the ICD-10, which is more modern and has fewer qualifying errors; iii) encoding error may exist and cannot be amended as the data included in the CMBD are irreversible; iv) not being able to access the medical history prevented us from confirming the diagnosis and identifying the possible associated factors involved, such as work activity and the difficulty of assessing the origin of patients (rural vs. urban), and does not provide information about tests used for QF diagnosis, which impairs the quality of the data; v) in considering only patients in public hospitals and not including nonhospital cases or private centers, for example, those who are ill who are not admitted or who did not receive medical care, in addition to those treated in private hospitals, would be excluded, thus, hospital records underestimate the real burden of QF in Spain. This study only reflects the patients who died while hospitalized, which could underestimate the mortality; and finally, vi) the estimated cost is approximate and less than the real cost, since in this work, only hospital costs have been included. In any case, our findings reported here have potential implications for public policy.

We aimed to relieve the lack of official epidemiological data, but we also contributed to generating hypotheses that will be worthy of exploration in further investigations.

We have demonstrated that QF is an important zoonosis in Spain with a period incidence rate that remained stable. The overall mortality rate is approximately 3%, and older patients have a more severe clinical picture and higher mortality. Additionally, having an early clinical suspicion can influence a decrease in mortality. Additionally, this study shows a high cost for hospitalization due to QF. Finally, there is a need for a common national strategy on data collection, monitoring, and reporting, which would facilitate a more accurate picture and strategic control measures design. Improving human and animal QF surveillance will be useful, both in gaining extended disease knowledge and reducing morbidity and related costs. Furthermore, industrial and regulatory measures need to be implemented in parallel, as an integrated and multisectoral approach is the only way to successfully prevent and control QF. The CMBD could be a good complementary epidemiological analysis system for the study of hospital management of QF.

Conflict of interest statement and funding source

All authors declare no potential conflicts of interest and no sources of support.

Ethical approval

The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because it is an epidemiological study, written consent was not obtained. All data analyzed were anonymized.

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Artículo Segundo

Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997-2015)

Objetivos: Analizar el impacto epidemiológico de los pacientes hospitalizados por tifus murino en el intervalo analizado (1997-2015) a partir del CMBD.

Principales resultados: Entre el 1 de enero de 1997 y el 31 de diciembre de 2017, se registraron 99 casos de tifus murino ingresados en los hospitales del Sistema Sanitario español, con una incidencia media de 0.12 casos/100.000habitantes/año, si bien se objetivó un acúmulo de casos entre 2013 y 2015. Geográficamente, las Islas Canarias y Andalucía, registraron el mayor número de casos y estacionalmente, el grueso de los casos se agrupó entre agosto y octubre. El 72.7% de los casos se diagnosticó en un entorno urbano. El 63.6% de los pacientes fueron hombres con una media de edad de 46.4 años. El tifus murino fue el diagnóstico principal en el 86.9% de los casos, lo que tuvo gran influencia en la estancia media hospitalaria, que se incrementó en 7.8 días de media en aquellos pacientes con diagnóstico secundario. El 1% de los pacientes falleció.

Conclusiones: A pesar de que la infección por tifus murino se considera poco frecuente en nuestro país, sigue un patrón lentamente ascendente. Teniendo en cuenta que solo el 22% de los pacientes con tifus precisan ingreso hospitalario, la incidencia reflejada en este trabajo podría ser incluso cinco veces mayor. El grueso de casos se sitúa en las Islas Canarias y Andalucía a finales del verano y principios del otoño. La población más comúnmente afectada son los varones de mediana edad. El CMBD ha demostrado ser un excelente recurso para el análisis epidemiológico de esta infección.

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Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997–2015)

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ABSTRACT

Objective: The aim of this study was to analyze the epidemiological impact of murine typhus in patients who required hospitalization in the National Health System (SNS) in Spain between 1997 and 2015.
Background: Murine typhus (MT) is a zoonosis caused by *Rickettsia typhi*. MT is transmitted from rats, cats, dogs, and opossums to humans by their fleas. The clinical picture is characterized by headache, fever, rash, and liver function alteration. The prevalence of MT is considered underestimated since most cases are mild and self-limited. However, up to 10% of patients develop serious complications such as pneumonia or acute kidney injury and may even need admission to intensive care units.
Methods: This was a retrospective longitudinal descriptive study of inpatients diagnosed with *Rickettsia typhi* infection (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], 081.0) in Spanish public hospitals between January 1, 1997, and December 31, 2015. Data were obtained from the Minimum Basic Data Set (MBDS, CMBD in Spanish), which includes information about inpatients admitted to the National Health System (NHS) hospitals provided by the Health Information Institute of the Ministry of Health and Equality.
Results: Ninety-nine inpatients were included. The incidence rate of MT was 0.12 (95% CI, 0.09-0.14) cases per one million person-years. Cases were irregularly distributed throughout the period of study, with a slight upward trend between 2013 and 2015. The Canary Islands had the highest incidence rate: 2.17 (95% CI, 1.69–2.64) cases per one million person-years (80 cases). Most patients were men (63.6%). The mean age (±SD) was 46.4 years (±19). Five patients were under 15 years old. Approximately 85.9% of cases required urgent hospital admissions. The average hospital stay was 11 days (±9.9). Only 1 patient died.
Conclusions: Although considered uncommon, the incidence of MT seems to be increasing slowly. Most cases occurred in middle-aged men between late summer and early autumn in Spain. The Canary Islands and Andalusia registered the highest number of cases. The MBDS is an appropriate approach to study MT hospital management.

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Introduction

Endemic (murine) typhus is a febrile syndrome caused by different species of the genus *Rickettsia*. Although *Rickettsia typhi* is considered the primary causative agent of endemic typhus, this syndrome can be caused by other flea-borne *Rickettsia* species, such as *Rickettsia felis,* and the recently identified *R. felis*-like organisms *Rickettsia asembonensis* and *Candidatus Rickettsia senegalensis* (Civen and Ngo, 2008; Azad and Beard, 1998; Bernabeu-Wittel and Segura-Porta, 2005; Howard and Fergie, 2018; Bolaños et al., 2004; Robaina -Bordón et al., 2020). The classic *Rickettsia typhi* life cycle involves commensal rats of the subgenus *Rattus* (such as *R. rattus* and *R. norvegicus*) and their fleas (especially *Xenopsylla cheopis*). Adaptation to new reservoirs (cats, dogs, opossums) and vectors, in particular the cat flea (*Ctenocephalides felis*), has led to the reappearance of cases of infection caused by *Rickettsia typhi* in developed countries.

In most cases, the clinical picture is mild and self-limited, characterized by a fever of intermediate duration, headache, arthromyalgia, and rash (Robaina -Bordón et al., 2020; Taylor et al., 1986; Dumler et al., 1991; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). The most frequent laboratory test abnormalities are thrombocytopenia, hyponatremia, hypertransaminasemia, dissociated cholestasis, and haematuria (Robaina -Bordón et al., 2020; Taylor et al., 1986; Dumler et al., 1991; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). The diagnostic suspicion of MT is based on clinical manifestations and epidemiological data, while diagnostic confirmation is usually made by serology (Robaina -Bordón et al., 2020; Taylor et al., 1986; Dumler et al., 1991; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). Molecular diagnosis can be useful in the first two weeks of the disease (Bolaños-Rivero et al., 2017). *R. typhi* infection is a zoonosis of universal distribution. Although MT has occasionally been described in travelers (Angel-Moreno et al., 2006; Delord et al., 2014), it is usually an autochthonous disease found in Southeast Asia, North America, South Africa, Australia, and some European countries (mainly Greece) (Dumler et al., 1991; Taylor et al., 1986; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). However, the overall importance of this infection is not well known.

The seroprevalence of endemic typhus ranges from 1 to 20% according to several studies (Bolaños-Rivero et al., 2011; Niang et al., 1998), which implies a high frequency of infection, at least in some areas. On the other hand, a clinical series of MT cases are scarce, with the maximum number of patients being 250 in unicentric series (Robaina -Bordón et al., 2020), which suggests that the usual form of MT is mild and/or that there is little diagnostic suspicion of this disease. However, several series of severe complications of MT have been reported, with the main ones described being renal (Hernández-Cabrera et al., 2004), pulmonary (van der Vaart et al., 2014), hepatic (Silpapojakul et al., 1996), neurological (Stephens et al., 2018), and multi-systemic complications (Bernabeu-Wittel et al., 1998). Elevated age, associated comorbidities, late onset of treatment, and antimicrobial coverage with trimethoprim-sulfamethoxazole are considered the main risk factors for complications. The overall epidemiology in Spain is unknown, probably because it is not a notifiable disease. The objective of this study is to evaluate the impact of murine typhus in the Spanish National Health System during the period from 1997-2015.

Material and methods

This was a retrospective longitudinal descriptive study of inpatients diagnosed with *Rickettsia typhi* infection (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], 081.0) in Spanish public hospitals between January 1, 1997, and December 31, 2015. Data were obtained from the Minimum Basic Data Set (MBDS, CMBD in Spanish), which includes information about inpatients admitted to the National Health System (NHS) hospitals provided by the Health Information Institute of the Ministry of Health and Equality.

This study analysed data provided by Hospital Discharge Records (HDRs). HDRs bring together all data on hospital discharges produced in the network of general hospitals of the NHS. The data contained in these records are those established in the MBDS, which is the primary information source about morbidity and healthcare processes of inpatients. HDRs provide primary demographic (age, sex, and place of residence) and clinical (diagnoses and procedures) data as well as variables related to the hospitalization process itself, such as the type of admission (urgent or programmed), destination of the patient (home medical discharge, transfer to another hospital or death), and average hospital stay. Diagnoses and procedures collected were coded according to the International Classification of Diseases, Clinical Modification (ICD-9-CM). *Principal diagnosis* was defined as the condition that caused hospital admission. *Secondary diagnoses* (up to 13) are "other diagnoses" or conditions that coexist at the time of admission or develop subsequently that affect patient care during hospitalization.

Diagnostic criteria for murine typhus were a patient with a compatible clinical picture (undifferentiated febrile illness, a rash, thrombocytopenia, or mildly elevated liver function tests) and confirmed serological test. Patients with missing data were excluded from the study.

Statistical analysis

The incidence rates were calculated by dividing the number of new cases of murine typhus (numerator) by the population at risk in a period of time (denominator) multiplied by 1,000,000. It was expressed as "cases per one million person-years." As it is not possible to accurately measure disease-free periods, person-time at risk was estimated by multiplying the average population size by the duration of the period of observation. Information on the population at risk was obtained from annual data published by the National Institute of Statistics (INE in Spanish). The 95% confidence interval (95% CI) for incidence rates were calculated. Incidence rates were calculated for each autonomous region and year to assess temporal and geographical patterns. The results in terms of mean rates by autonomous regions were plotted in maps for the whole study period. The results were expressed as absolute values and percentages for categorical data and as the mean ± the standard deviation (SD) or median followed by its interquartile range (IQR[Q3-Q1]) or simple range (minimum value, maximum value) for continuous variables. The chi-squared test was used to compare the association between categorical variables in different patient groups. Measured outcomes were expressed as the odds ratio (OR) followed by its 95% CI. Continuous variables were compared with Student's t-test if data followed a normal distribution or the Mann-Whitney test if not. An ANOVA was used to analyze continuous variables among three or more groups.

Additionally, the corresponding regression models were applied for multivariate analysis. A p-value of less than 0.05 was considered to indicate statistical significance. Data analysis was performed using IBM SPSS Statistics version 23.0 (Statistical Package for the Social Sciences, Inc. Chicago, IL, USA).

Ethics statement

This study is based on the medical data of patients collected in the MBDS. These data are the responsibility of the Ministry of Social Services of Health and Equality (MSSHE) that retains and organizes them. All patient data furnished by the MBDS are anonymized and identified by the MSSHE before being given to applicants. According to this confidentiality commitment signed with the MSSHE, researchers cannot provide these data to other researchers. The protocol and ethics statement of this study were approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Since the data were collected from an epidemiological database, written consent was not obtained.

Results

Incidence

There were 99 registered cases of murine typhus infection in Spain between January 1997 and December 2015. The incidence rate was 0.12 (95% CI, 0.09-0.14) cases per one million person-years. The incidence rate in men was double that of women, 0.15 (95% CI, 0.11-0.19) *vs.* 0.08 (95% CI, 0.05-0.11) cases per one million person-years. Cases were irregularly distributed throughout the period of study, with a slight upward trend between 2013 and 2015. The minimum annual incidence rate was 0.05 (95% CI, 0.02-0.12) cases per one million person-years (two cases) in 1997 and 2000. The maximum yearly incidence rate was 0.25 (95% CI, 0.10-0.39) cases per one million person-years (11 cases) in 2006 (Figure 1).

Geographic distribution and seasonality

The Canary Islands had the highest incidence rate: 2.17 (95% CI, 1.69-2.64) cases per one million person-years (80 cases). No cases were registered in some autonomous regions (Figure 2).

The temporal distribution of MT cases is shown in Figure 3, being more frequent between August and October.

Clinical data

Most of the patients (63,6%) were men. The mean age (±SD) was 46.4 years (±19). Five patients were under 15 years old. The clinical and epidemiological characteristics of the participants are shown in Table 1. Eighty-five (85.9%) cases involved urgent hospital admissions. Most patients (96, 97%) returned home after hospital discharge. Murine typhus was recorded as the principal diagnosis in 86 (86.9%) cases. Differences between patients with a principal diagnosis of murine typhus and patients in whom their secondary diagnosis included murine typhus are listed in Table 2. It should be noted that the average hospital stay increased by eight days among patients with a secondary diagnosis of MT, 17.8 ± 18.3 *vs.* 10.0 ± 7.5 ($p = 0.004$). Seventy-two (72.7%) patients were residents in urban areas, and 22.2% came from rural areas (urban/rural ratio, 3:1; $p < 0.001$). The characteristics of rural and urban cases are described in Table 3.

Figure 4 shows the main clinical manifestations associated with this infection. Thirty-three (33.3%) patients were cared for by the Internal Medicine Service, and 15 (15.2%) were treated at the Infectious Diseases Service. In one-third of the cases, it was impossible to know which hospital service treated the patients. We have no data about patients who required admission in an intensive care unit. Only one (1%) patient (an 85-year-old female living in Andalusia) died.

Discussion

Between January 1997 and December 2015, a total of 99 cases with murine typhus had registered HDRs in Spain, with an incidence rate of 0.12 cases per million person-years. This incidence is lower than that reported in other countries, such as Korea (0.8 cases per million person-years) (Chang et al., 2018) or Croatia (5.7 cases per million person-years) (Punda-Polić et al., 2008). Although several factors can explain these differences (i.e., economic level or particular characteristics of the biological cycle), an essential feature is that our study probably underestimates the real impact of MT in the general population since only hospitalized patients have been included. In fact, taking into account that the estimated percentage of patients with *Rickettsia typhi* infection requiring hospital admission is approximately 22% (Robaina -Bordón et al., 2020), the incidence of MT could be five times higher than that calculated between 1997 and 2015. With these data in mind, we suggest that MT ought to be a notifiable disease in Spain. Despite the significant variations during the studied period, endemic typhus should be considered a re-emerging disease since its incidence seems to be increasing slowly in recent years (Raoult and Roux, 1997).

In Spain, most MT cases of inpatients were reported in the Canary Islands and Andalusia, which is consistent with the global series communicated by other authors (Bernabeu-Wittel and Segura-Porta, 2005; Robaina -Bordón et al., 2020; Miguélez et al.,

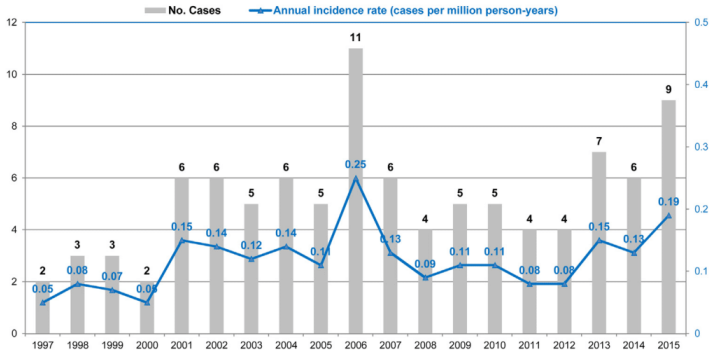

Figure 1. Temporal distribution of cohort (1997-2015) total population of Spain: cases and annual incidence rate *(cases per million person-years)*.

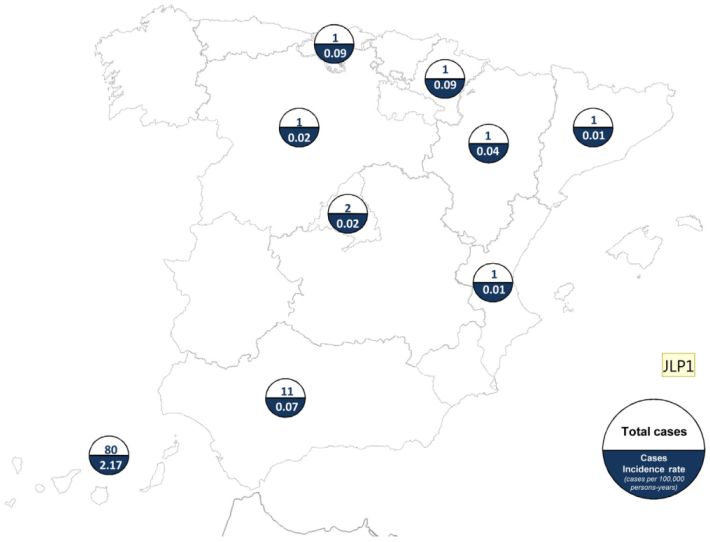

Figure 2. Distribution of the cases and incidence rates (cases per million persons-years) according to the Autonomous Community to which the hospital belongs.

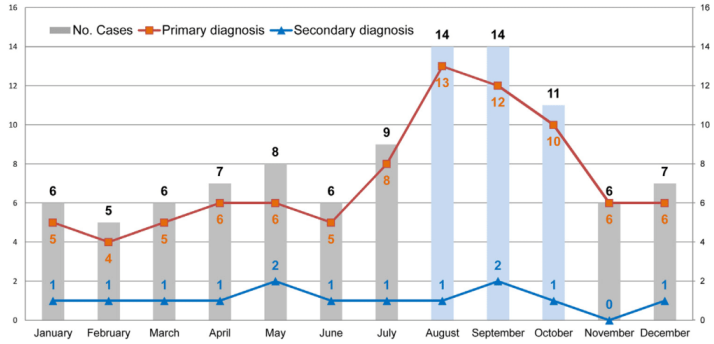

Figure 3. Temporary distribution (months of the year) of cases of murine typhus.

2003). Differences in incidence between autonomous regions could be explained by the existence of different forms of biological cycles. Additionally, it should be noted that these communities maintained a high risk of poverty during the period studied, which may increase the possibility of exposure to the "classic cycle" (Instituto Nacional de Estadística, 2015). In any event, we endorse Didier Raoult's phrase about Q fever, in this case, applied to murine typhus: "differences in prevalence are mainly related to differences in interest" (Raoult, 1994). Regarding the origin areas, 72.7% of patients were residents in urban areas, and 22.2% came from rural areas. The data associated with the place of residence reported in other publications vary considerably. In some series, patients are mostly concentrated in rural areas (Miguélez et al., 2003; Psaroulaki et al., 2012; Chaliotis et al., 2012; Tsioutis et al., 2014), while in others, they mainly live in cities, especially those with major international seaports (Bernabeu-Wittel and Segura-Porta, 2005; Howard and Fergie, 2018; Adjemian et al., 2010; Kuo et al., 2017). This discrepancy may reflect the existence of different forms of the biological cycle, which confirms that the ecology of endemic typhus is complex. The seasonal prevalence of murine typhus during late summer and autumn observed in our series has been described previously (Tsioutis et al., 2017). This temporal pattern seems to be related to the increased propagation activity of the vector linked to higher temperatures; however, it should be noted that the same seasonal predominance does not occur in certain areas, suggesting different transmission profiles (Civen and Ngo, 2008; Murray et al., 2017).

Endemic typhus is diagnosed predominantly in middle-aged men in Spain, with a similar male-to-female ratio (2:1) to other clinical series (Miguélez et al., 2003) but higher than that in others

Table 1
Main data of patients included in the study.

Variable	N = 99 cases (100%) n (%)
Age (years)	
Mean ± SD	46.4 ± 19.0
Median (IQR)	44 (63–33)
0-14 years	5 (5.1)
15-44 years	45 (45.5)
45-74 years	41 (41.4)
≥75 years	8 (8.1)
Gender	
Male	63 (63.6)
Female	36 (36.4)
Diagnosis causing the hospitalization (ICD-9-CM: 083.0)	
Principal/main diagnosis	86 (86.9)
Second diagnosis	13 (13.1)
Rural vs. urban cases	
Rural	22 (22.2%)
Urban	72 (72.2%)
Unknown	5 (5.1%)
Comorbidity	
Kidney involvement	6 (6.1)
Lung involvement	9 (9.1)
Neurological involvement	13 (13.1)
Mental and behavioral disorders	32 (32.3)
Cardiovascular involvement	43 (43.4)
Type of hospital admission	
Urgent	85 (85.9)
Programmed	14 (14.1)
Hospital readmission	
Hospital readmission (30 days after a previous discharge)	95 (96.0)
New episode	4 (4.0)
Type of discharge	
Home	96 (97.0)
Transfer to another Hospital	1 (1.0)
Transfer to social-health center	1 (1.0)
Exitus letalis	1 (1.0)
Hospital stay (days)	
Mean ± SD	11.0 ± 9.9
Median (IQR)	8 (13–5)
Range (Minimum value, Maximum value)	(2, 70)

Table 3
Rural *vs.* urban cases in study.

Variable	Rural	Urban	Unknown	Total
Age (years)				**p = 0.566**
< 45	9 (40.9)	38 (50.2)	3 (60.0)	50 (50.5)
≥ 45	13 (59.1)	34 (47.2)	2 (40.0)	49 (49.5)
Gender				**p = 0.615**
Men	15 (68.2)	44 (61.1)	4 (80.0)	63 (63.6)
Women	7 (31.8)	28 (38.9)	1 (20.0)	36 (36.4)
Total	**22 (100)**	**72 (100)**	**5 (100)**	**99 (100)**

(Chang et al., 2018). However, when the incidence of clinical cases (Robaina -Bordón et al., 2020) is compared with the infection rate in the same geographical region (Bolaños-Rivero et al., 2011), the latter indicates a similar distribution, which suggests that the clinical manifestation of the disease varies according to sex. The mean age of our patients is similar to that reported by other authors in the MT global series, although in our study, admitted patients presented a more serious clinical picture. These data disagree with the description of a more serious clinical picture of this disease in people over 65 years of age (Tsioutis et al., 2014).

Most, 86.9%, of the cases of MT were registered as a principal diagnosis; only 13.1% of the cases were registered as a secondary diagnosis. The visceral manifestations of MT are quite variable depending on the published series. In this series, cardiovascular events predominate, although the study design cannot exclude that they correspond to pre-existing diseases. However, in other studies, pulmonary (Tsioutis et al., 2017) or renal (Hernández-Cabrera et al., 2004) manifestations predominate. The explanation of these differences may be due to any of three different factors: *i)* the methodology of the study, *ii)* the complementary examinations performed in each patient (i.e., performing lumbar puncture increases the number of patients diagnosed with meningitis) (Hernández-Cabrera et al., 2004) and *iii)* the potential existence of *R. typhi* strains with different tissue tropisms. The average hospital stay is ten days in cases with a primary diagnosis, although it is

Table 2
Main diagnosis *vs* secondary diagnosis.

Variables	Main diagnosis N_1 = 86 n (%)	Second diagnosis N_2 = 13 n (%)	p-value*
Age (years)			
Mean ± SD	45.8 ± 18.9	50.0 ± 19.7	0.351
<45 years	45 (52.3)	5 (38.5)	
≥45 years	41 (47.7)	8 (61.5)	
Gender			
Male	52 (60.5)	11 (84.6)	0.092
Female	34 (39.5)	2 (15.4)	
Rural vs. urban cases total			0.757
Rural	20 (90.9)	2 (9.1)	
Urban	62 (86.1)	10 (13.9)	
Unknown	4 (80.0)	1 (20.0)	
Clinical/Comorbidity			
Acute renal failure, unspecified	4 (4.7)	2 (15.4)	0.131
Type of hospital admission			
Urgent	73 (84.9)	12 (92.3)	0.474
Programmed	13 (15.1)	1 (7.7)	
Hospital readmission			
Hospital readmission	84 (97.7)	11 (84.6)	0.126
New episode	2 (2.3)	2 (15.4)	
Type of discharge			
Home	84 (97.7)	12 (92.3)	0.073
Transfer to another Hospital	0	1 (7.7)	
Transfer to social-health center	1 (1.2)	0	
Exitus letalis	1 (1.2)	0	0.696
Hospital stay (days)			
Mean ± SD	10.0 ± 7.5	17.8 ± 18.3	0.007*

* Statistical significance level of 5% ($p < 0.05$).

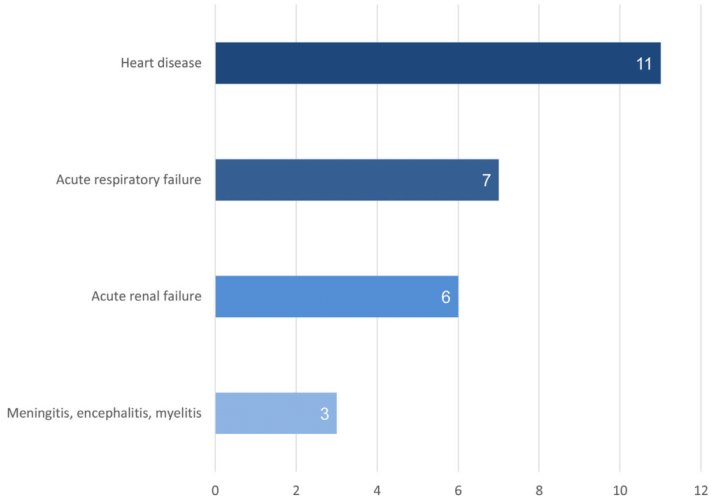

Figure 4. Clinical manifestations associated with murine typhus.

significantly longer in cases with a secondary diagnosis. We have not found a series of patients admitted with MT similar to that provided in this study, with which to make a comparison. The mortality of MT in this series is low (1%), which is consistent with the available data (Robaina -Bordón et al., 2020). However, this study may also underestimate mortality since it includes only patients who died while hospitalized. Additionally, having an early clinical suspicion and treatment can influence a decrease in mortality.

The MBDS provides data from public hospitals in Spain that cover more than 99% of the population; thus, this study provides relatively accurate estimates of the incidence of MT. The main *limitations* of this study are due to several factors:

[1] The use of sources such as the MBDS for purposes other than health care and research,
[2] The use of the ICD-9 for codification, which has some limitations in comparison with the ICD-10 in that ICD-10 is more recent and has fewer qualifying errors,
[3] The potential existence of encoding errors,
[4] The impossibility of accessing patient data to verify data, and
[5] The MBDS includes only public hospital inpatients, not patients in ambulatory hospitals or those with private health insurance.

Therefore, as discussed above, these data underestimate the real incidence of MT in Spain during the period of this study.

In summary, our data suggest that MT is a re-emerging zoonosis in Spain. Most cases occurred in middle-aged men between late summer and early autumn in Spain. The Canary Islands and Andalusia registered the highest number of cases. Also, MT is not as mild as traditionally believed. Finally, we insist on the need for a common national strategy for data collection to monitor and report new cases, aiming to facilitate a more accurate picture of TM infection and to make strategic control measures. The MBDS could be an excellent approach to study MT hospital management.

Conflict of interest statement and funding source

All authors declare no potential conflicts of interest and no sources of support.

Ethical approval

The procedures described here were carried out following the ethical standards outlined in the 2013 revised version of the Declaration of Helsinki. Additionally, this study was approved by the Bioethics Committee of CAUSA. At all times, we maintained the confidentiality of the patients' personal data.

Informed consent

Not applicable.

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Artículo Tercero

Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997-2015)

Objetivo: Analizar la trascendencia epidemiológica de la enfermedad por arañazo de gato en España entre 1997 y 2015, en aquellos pacientes que requirieron ingreso hospitalario.

Principales resultados: Se registraron 781 pacientes diagnosticados de enfermedad por arañazo de gato en los hospitales españoles en el período de tiempo analizado. El grupo de mayor riesgo estaba conformado por pacientes en torno a los 30 años con una tendencia no muy marcada hacia el género masculino. El radio de incidencia fue de 0.93 casos /100.000 habitantes/ año. La mayor parte de los casos se agrupó entre septiembre y enero. Las comunidades autónomas más afectadas fueron Asturias y Cantabria. La estancia media hospitalaria ± SD fue de 8.4 días (± 8.9). La tasa de mortalidad fue del 1.3%.

Conclusiones: La enfermedad por arañazo de gato es una zoonosis que causa un número de casos no despreciable en nuestro país, manteniéndose estable a lo largo de los años. Su incidencia real probablemente esté infraestimada. Impera la necesidad de una estrategia nacional de control de esta zoonosis para establecer unas medidas dirigidas, si no a su erradicación, a una reducción importante de la incidencia. El CMBD constituye un sistema de información sanitaria realmente útil para el estudio epidemiológico de esta enfermedad.

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ORIGINAL ARTICLE

Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997–2015)

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Abstract
Cat scratch disease, whose causative agent is *Bartonella henselae*, is an anthropozoonosis with a worldwide distribution that causes significant public health problems. Although it is an endemic disease in Spain, the available data are very limited. The aim of our study was to describe cat scratch disease inpatients in the National Health System (NHS) of Spain. This was a retrospective descriptive study using the minimum basic data set (CMBD in Spanish) in patients admitted to hospitals of the NHS between 1997 and 2015 with a diagnosis of cat scratch disease (ICD-9: 078.3). We found 781 hospitalized patients diagnosed with cat scratch disease. The mean age (± SD) was 30.7 ± 25.3 years old. The male/female ratio was 1.1:1. The incidence rate over the study period was 0.93 (95% CI, 0.86–0.99) cases per million person-years. The incidence rate in men was 0.98 cases per million person-years and that in women was 0.88 cases per million person-years. The cases were more frequent from September to January. A total of 652 (83.5%) cases were urgent hospital admissions. The average hospital stay was 8.4 ± 8.9 days. The overall lethality rate of the cohort was 1.3%. We have demonstrated that CSD causes a substantial burden of disease in Spain, affecting both adult and pediatric patients with a stable incidence rate. Our data suggest that CSD is benign and self-limited, with low mortality, and its incidence is possibly underestimated. Finally, there is a need for a common national strategy for data collection, monitoring, and reporting, which would facilitate a more accurate picture and the design of more strategic control measures. Hospital discharge records (HDRs) could be a good database for the epidemiological analysis of the hospital management of CSD.

Keywords Cat scratch disease · *Bartonella henselae* · Spain · Burden · Epidemiology

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Introduction

Cat scratch disease (CSD) is caused by aerobic, intracellular gram-negative bacilli; these infectious agents have relatively fastidious growth characteristics and are in the genus *Bartonella* [1–3]. The main species responsible for CSD is *Bartonella henselae*, although some cases produced by *B. clarridgeiae* have also been described [4].

Cats, especially younger and stray cats, constitute the fundamental reservoir of both *Bartonella* species [5]. *Ctenocephalides felis* is the arthropod vector responsible for the horizontal transmission of *B. henselae* between cats [1, 2, 4, 5]. Transmission to humans occurs primarily through inoculation (perhaps from infected flea feces) of a cat scratch or bite wound and less commonly through contact with mucosa (e.g., conjunctiva). In a study conducted in Korea, cat ownership was significantly associated with *B. henselae* seropositivity. A total of 9.8% of individuals who had cats showed seropositivity, compared with 2.0% of those without contact with cats [6]. In a Spanish study [7], 31.6% of healthy seropositive individuals reported exposure to cats.

B. henselae has a special tropism for endothelial cells as well as for CD-34 hematopoietic precursors [1–3, 5]. The host response to *B. henselae* infection differs depending on the immune state [3]. In immunocompetent individuals, a granulomatous and suppurative response develops, whereas in immune-compromised individuals, a vascular proliferation response is elicited [1–3].

B. henselae infection and CSD occur worldwide. Considering the data provided in the literature, the prevalence of infection, verified through serological studies, indicates the prevalence of infection is much higher than clinically detected. It seems to be that serology is influenced by seasonality [8]. Thus, seroprevalence studies demonstrate the presence of *B. henselae* infection in many countries in Europe [7, 9–17] (including Spain [7, 14–17]), Asia [18, 19], and America [20, 21]. The seroprevalence rate is highly variable, ranging from 0.7 to 57.0% depending on the country [7, 9–21], study group (general population, veterinarians [17], or forest workers [13]), subjects (healthy [7, 9–12, 14, 15, 20, 21], HIV-infected individuals [14, 16], and febrile patients [18]), and, above all, the serologic titer cut-off point used to define positive cases (1:64 [7, 11, 14, 16, 17],, 1:128 [15, 21], or 1:256 [9, 10, 12, 19, 20], respectively). The true incidence of CSD is difficult to determine, since it is not a reportable disease in many countries. Most of the data on the incidence of CSD come from the USA, with the annual incidence estimated at 9.3/100,000 inhabitants for outpatients and at 0.8/100,000 persons for inpatients [22]. In addition, differences between geographical areas [22, 23] and even within the same state [24] have been verified.

Most patients with CSD present a benign, self-limiting clinical picture characterized by isolated lymphadenopathy with fever and no other signs or symptoms [3]. However, between 4.0 and 9.6% of patients present more serious manifestations that require hospital admission [25–28], and several factors of the host (i.e., age, sex, immune status) and the causative agent (inoculum size, strain specificity, and source of infection) have been related to this clinical variability [28]. Atypical manifestations of CSD like retinitis/neuroretinitis, conjunctivitis, neuritis, encephalitis, hepatosplenic disease, osteomyelitis, erythema nodosum, and endocarditis range between 1.5 and 20% [29]. In the literature, there are few studies about the characteristics of inpatients with CSD [25–27, 30]. Therefore, the aim of this study was to evaluate the clinical and epidemiological impact of CSD in inpatients in Spain.

Materials and methods

We conducted a retrospective descriptive analysis of hospitalized patients with cat scratch disease, ICD-9-CM diagnosis code 078.3, from January 1, 1997, to December 31, 2015, in Spanish public hospitals. This study analyzes the data provided by hospital discharge records (HDRs). HDRs catalog all hospital discharges produced in the network of general hospitals in the National Health System (NHS). The data contained in HDRs are those established in the hospitalization minimum data set (CMBD in Spanish). CMBD is the main database for the associated morbidity and the care process of patients treated in hospitals. It provides usual demographic data (age, sex, and place of residence; *urban areas*: agglomerations with more than 5000 inhabitants; *rural areas*: agglomerations with less than 5000 inhabitants), clinical variables (diagnoses and procedures), and variables related to the episode of hospitalization, such as circumstance of admission (urgent: an urgent admission is one that does not meet the requirements of the programmed admission and has been regularly attended in the emergency area; or programmed: an admission is programmed when it has been concerted with a previous date, independently of the patient comes from a waiting list or not), patient discharge (discharge to their home, transfer to another hospital, or death), and average length of stay. Diagnoses and procedures collected were coded using the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM). The primary diagnosis is defined as the condition, after study, which occasioned the admission to the hospital, according to the ICD-9-CM code refers to the condition that, at the end of the hospitalization process, is considered the cause of the patient's admission to the hospital for the patient's admission to the hospital. Secondary diagnosis codes (up to 13) are diagnoses that coexist with the primary diagnosis at the time of admission or develop during admission.

A case was defined as any patient with the ICD-9-CM code for cat scratch disease (078.3) listed as either a primary or

secondary diagnosis in their HDR. Patient records with missing data were excluded from this study.

Statistical analysis

The incidence rates were calculated by dividing the number of new cases of cat scratch disease (numerator) per year by the population at risk (denominator) in a period of time (person-years) multiplied by 1,000,000 and expressed as "cases per million person-years." As it is not possible to accurately measure disease-free periods, the total person-time at risk can be estimated satisfactorily when the size of the population is stable by multiplying the average population size studied by the duration of the observation period. Thus, the population at risk was obtained from annual data published by the National Institute of Statistics (INE, http://www.ine.es/). The 95% confidence interval (95% CI) for the incidence rate was calculated for a better clinical application of the results. Incidence rates were computed by age, sex, autonomous community, and year to assess temporal and geographical patterns. Mean rates by autonomous community for the whole study period were plotted on maps. The lethality rate was calculated by dividing the number of primary diagnosis deaths (numerator) by the number of individuals with a primary diagnosis of a specific disease (denominator) (× 100). The results were expressed as absolute value (n), proportion (n/N), and percentage (%) for categorical variables and as the mean, standard deviation (SD), median, interquartile range (IQR) (Q1–Q3), and range (minimum value, maximum value) for continuous variables. A χ^2 test was used to compare the association between categorical variables, such as clinical and demographic variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for the OR. Continuous variables were compared with Student's t test or the Mann-Whitney test for two groups, depending on whether the data had a normal or non-normal distribution. The ANOVA allowed us to analyze the influence of independent nominal variables on a continuous dependent variable. Additionally, we applied the corresponding regression models for multivariate analysis. We considered a statistically significant difference from chance at a p value < 0.05. Data analysis was performed using SPSS 25 (Statistical Package for the Social Sciences).

Ethics statement

This study is based on medical data of patients collected in the CMBD. These data are the responsibility of the Ministry of Social Services of Health and Equality (Ministerio de Servicios Sociales, Sanidad e Igualdad, MSSSI) that compiles and organizes them. All patient data provided by the CMBD are anonymized and deidentified by the MSSSI before they are provided to the applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers, so other researchers must request the data directly from the MSSSI. The protocol and ethics statement of this study were approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because the data were obtained from an epidemiological database, written consent was not obtained. All data analyzed were anonymized.

Results

Incidence and geographic distribution

A total of 781 cases with the ICD-9-CM code for cat scratch disease were registered in Spain during the 19-year study period. The incidence rate over the study period was 0.93 (95% CI, 0.86–0.99) cases per million person-years. The incidence rate in men was 0.98 (95% CI, 0.89–1.08) cases per million person-years, and in women, it was 0.88 (95% CI, 0.79–0.97) cases per million person-years. Chronologically, we observed an irregular distribution of cases during the study period. The annual incidence rate was highest in 1997, 1.25 (95% CI, 0.90–1.60) cases per million person-years (49 cases). Annual incidence rates were lowest in 2006 and 2011, both 0.74 (95% CI, 0.50–0.99) cases per million person-years (33 and 35 cases, respectively). In the last 2 years of the period, annual incidence rates increased, 1.18 (95% CI, 0.87–1.49) cases per million person-years (55 cases) in 2014 and 1.20 (95% CI, 0.89–1.51) cases per million person-years (56 cases) in 2015 (Fig. 1).

The distribution of CSD cases by month of diagnosis in which it was diagnosed is shown in Fig. 2. The cases were more frequent from September to January (autumn and winter seasons).

We analyzed the incidence rates in different regions of Spain (see map, Fig. 3). Incidence was highest in the north—Asturias had 3.28 (95% CI, 2.49–4.06) cases per million person-years and Cantabria had 2.99 (95% CI, 1.95–4.02) cases per million person-years—and lowest in the central region; Madrid autonomous community 0.24 (95% CI, 0.15–0.33) had cases per million person-years. A total of 551 (70.6%) cases originated from urban environments, 188 (24.1%) cases originated from rural environments, and the origins of 42 (5.4%) cases were unknown. No statistically significant differences related to the urban vs. rural origin of the cases were observed ($p > 0.05$).

Distribution by age and sex

Table 1 shows the main epidemiological and clinical data of the patients studied. The proportions of men (51.9%) and

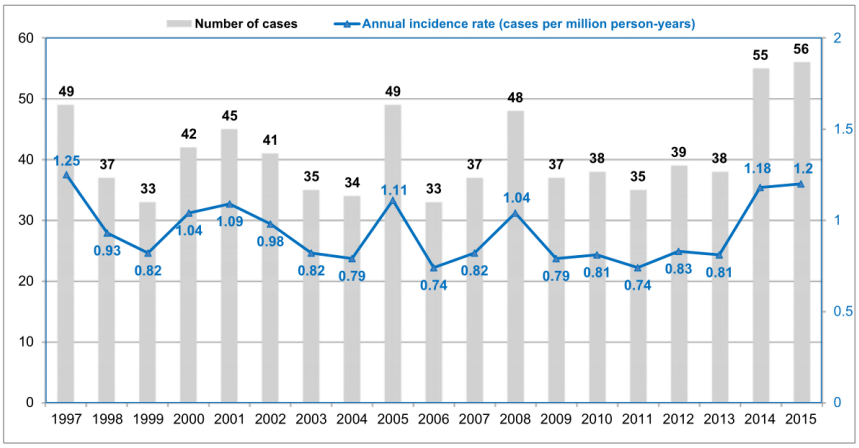

Fig. 1 Temporal distribution of cat scratch disease inpatients in Spain, 1997–2015: cases and annual incidence rate (*cases per* million *person-years*)

women (48.1%) were similar. The mean (SD) age was 30.7 years (25.3), 333 cases (42.6%) were in children (0–14 years), 338 (43.3%) in adults (> 14–64 years), and 110 (14.1%) in elderly patients.

Figure 4 shows the distribution age (5-year groups) of CSD (number of cases and incidence rates). The highest overall average incidence rates by 5-year age groups were among children 0–14 years of age (ages 0–4, 2.16 cases per million person-years; ages 5–9, 3.00 cases per million person-years; and ages 10–14, 2.97 cases per million person-years). As of 15 years of age, overall average incidence rates by 5-year age groups were less than 1 case per million person-years. In boys, the highest average incidence rate was for 10–14 years of age (3.54 cases per million person-years), and in girls, the highest average incidence rate was for 5–9 years of age (2.65 cases per million person-years).

There were significant differences between the seasonal distribution of cases and the demographic variables. The number of cases was higher in women in spring (50.4%) and summer (57.1%), while the number of cases was higher in men in autumn (51.9%) and winter (55.5%) (p = 0.046). Half of the cases (50.9%) that occurred in the autumn season

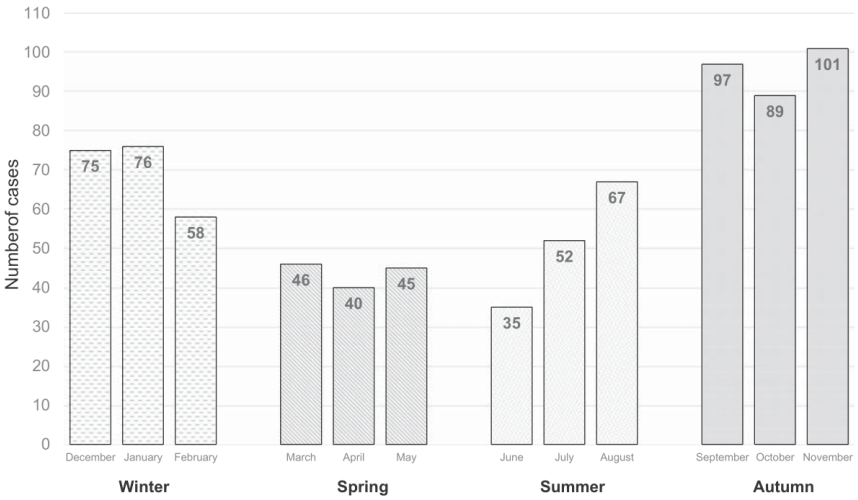

Fig. 2 Distribution of cat scratch disease cases in the months of the year ($p < 0.001$)

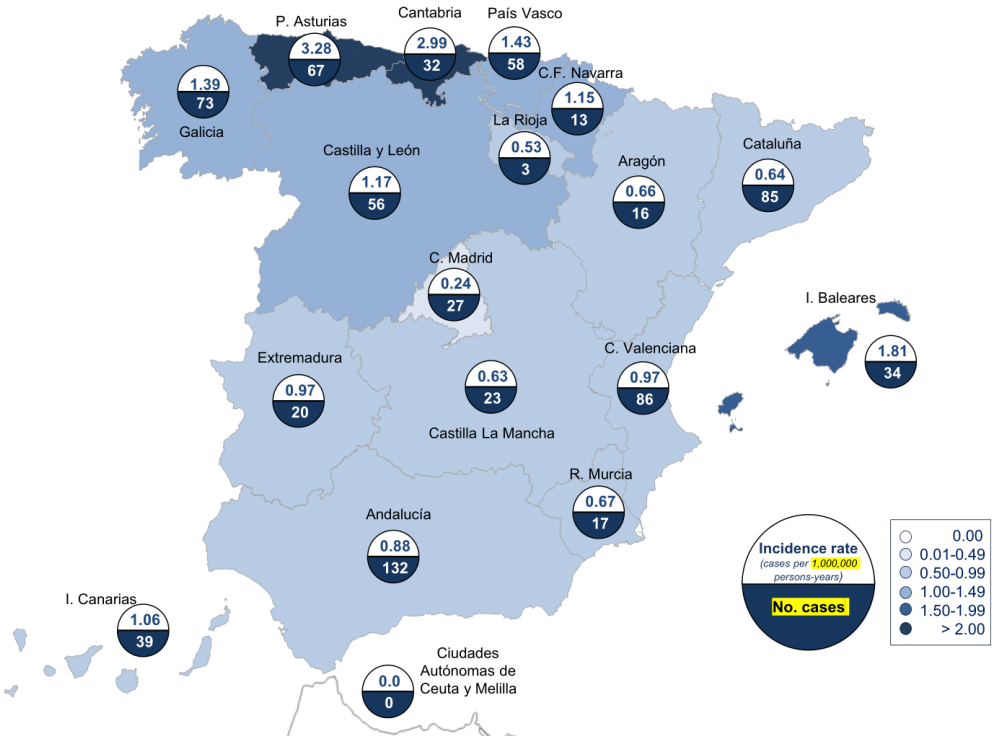

Fig. 3 Cat scratch disease incidence by region, Spain (1997–2015)

were in the pediatric population (0–14 years old). In the summer months, the percentage of cases increased significantly, up to 24%, in the population over 65 ($p < 0.001$).

Clinical features

A total of 652 (83.5%) cases were urgent hospital admissions. Most patients (758, 97.1%) were sent home after hospital discharge. The average (SD) hospital stay was 8.4 days (± 8.9) (median (IQR), 6 (3–10)) (see Table 1). Hospitalizations with cat scratch disease as the primary diagnosis were 568 (72.7%), with 213 (27.3%) cases as the secondary diagnosis. In Table 2, epidemiological, clinical, and mortality differences between patients with primary and secondary diagnosis codes were compared. Forty (5.1%) patients had neoplasms: eight digestive cancer, six hematological neoplasm, four lung neoplasm, three breast cancer, two leiomyoma sarcoma, and others. Only two had HIV. The mean age of patients with a primary diagnosis code was lower than those with a secondary diagnosis code (mean ± SD, 28.6 ± 24.1 *vs.* 36.3 ± 27.7, $p < 0.001$). Additionally, average hospital stays increased by 3 days among patients with secondary diagnosis codes (mean ± SD, 7.8 ± 6.4 vs. 10.1 ± 13.3, $p = 0.001$). In relation to the service responsible for patient hospital care, 1 out of 5 cases (228, 28.2%) was referred and treated in the Internal Medicine Service and 164 (21.0) cases in the Pediatric Service.

Cohort mortality

The overall lethality rate of the cohort was 1.3% (10 deaths), 6 women and 4 men. The lethality rate of a primary diagnosis of cat scratch disease was 0.53 per 100 (3 primary diagnosis deaths/568 primary diagnoses); 2 deaths were in 1997 (lethality rate, 4.76 per 100) and 1 death was in 2012 (lethality rate, 3.13 per 100). Mortality among people > 65 years was 3.6% (4/110), and among the population aged 15–64, it was 1.8% (6/338), that is, 3.6% vs. 1.8% (OR = 2.08 95% CI (1.1–7.5)). The mortality distribution was 3 in Cantabria autonomous community, 2 in Andalusia, and 1 in Aragon, Castile and Leon, Castile La Mancha, Madrid, and Catalonia, with no significant differences ($p = 0.125$). All deaths with a primary

Table 1 Main data patients included in the study

Variables	*N* = 781 cases *n* (%)
Gender	
Male	405 (51.9)
Female	376 (48.1)
Age (years)	
Mean ± SD	30.7 ± 25.3
Range (minimum value, maximum value)	(0, 91)
Age 0–14 years	333 (42.6)
Age 15–64 years	338 (43.3)
Age ≥ 65 years	110 (14.1)
Type of diagnosis (ICD-9-CM code 078.3)	
Primary diagnosis	568 (72.7)
Secondary diagnosis	213 (27.3)
Comorbidity	
Neoplasms	40 (5.1)
Enlarged lymph nodes	140 (17.9)
HIV	2 (0.3)
Type of hospital admission	
Urgent	652 (83.5)
Programmed	129 (16.5)
Type of discharge	
Home	758 (97.1)
Transfer to another hospital	4 (0.5)
Transfer to social-health center	2 (0.3)
Voluntary discharge	5 (0.6)
Others/unknown	2 (0.3)
Overall mortality	10/781 (1.3)
Cat scratch disease primary diagnosis mortality	3/568 (0.53)
Secondary diagnosis mortality	7/213 (3.28)
Hospital stay (days)	
Mean ± SD	8.4 ± 8.9
Median (IQR)	6 (3–10)
Range (minimum value, maximum value)	(0, 91)

diagnosis of CSD (3 patients) were in the Cantabria autonomous community (lethality rate, 12.50 per 100).

Discussion

A total of 781 hospitalized patients with cat scratch disease were registered with HDR in Spain between January 1997 and December 2015. The incidence rate for our cohort of patients during the study period was 0.93 cases per million person-years, and it remained stable with a small increase in the last two years of the study. Our cohort showed a similar incidence rate with respect to that of Nelson et al. [27] and presented a higher number of cases in autumn, unlike other studies [27], which showed an increase in cases in January. One of the most interesting points of our series is that all patients who were hospitalized had symptomatic disease since most epidemiological studies in Europe and Spain are based on screening studies of different asymptomatic groups [7, 9–12, 14, 15, 20, 21]. This makes it difficult to compare our study with others, except for the work of Nelson et al. [27] carried out in inpatients. Our figures were much higher than those of the latter study. This report also analyzed possible risk factors associated with *Bartonella* infection.

Previously published studies indicate that *B. henselae* infections are more common in children than in adults [31]. Nevertheless, other works do not show this tendency to pediatric involvement [12]. Indeed, one of the highlights of our study is that approximately 60% of patients are adults, perhaps because we only analyzed inpatients. However, the impact of disease on the pediatric group is definite, as we show in Fig. 4. Our data differ from those of other authors on the way it does not show significant differences with respect to sex, as observed in the study of Pons et al. in Spain and Aydin et al. in Turkey [7, 32]. Some studies show that the *B. henselae* seroprevalence was 8.3% in urban areas, 11.9% in semi-rural areas, and 0% in rural areas [7]. However, our analysis shows no differences regarding the origin of disease for rural vs. urban patients. We hypothesize that these seroprevalence studies are not comparable with our work due to methodological design.

Given the methodological limitations of this study, we would like to highlight the difficulty of considering cases such as those with a secondary diagnosis.

CSD is the main and most frequent clinical presentation of *B. henselae* infection and typically presents as subacute regional lymphadenopathy after a scratch or bite from a cat [33]. Although the literature describes that in immunocompetent patients, CSD occurs mostly in children and adolescents and rarely in older persons [34], in our study, most of the patients were adults without immunosuppression. However, *B. henselae* infection can be particularly severe for immunocompromised patients, such as those with AIDS, in whom vascular proliferative lesions (bacillary angiomatosis and bacillary peliosis) may develop [35]. When assessing risk factors, in our data, it should be noted the low incidence of HIV with CSD symptoms; there were only two HIV cases and 40 cases of patients with tumors identified in contrast to the available literature [14, 16].

The prognosis for complete recovery in immunocompetent patients with CSD is excellent. Significant morbidity occurs in 5–10% of cases, usually due to central or peripheral nervous system involvement or to multisystemic disseminated disease. One episode of cat scratch disease confers lifelong immunity to all patients [36].

Very few studies analyze the overall mortality attributed to CSD, which is generally considered a benign disease. The fatal cases were patients with endocarditis and cerebral

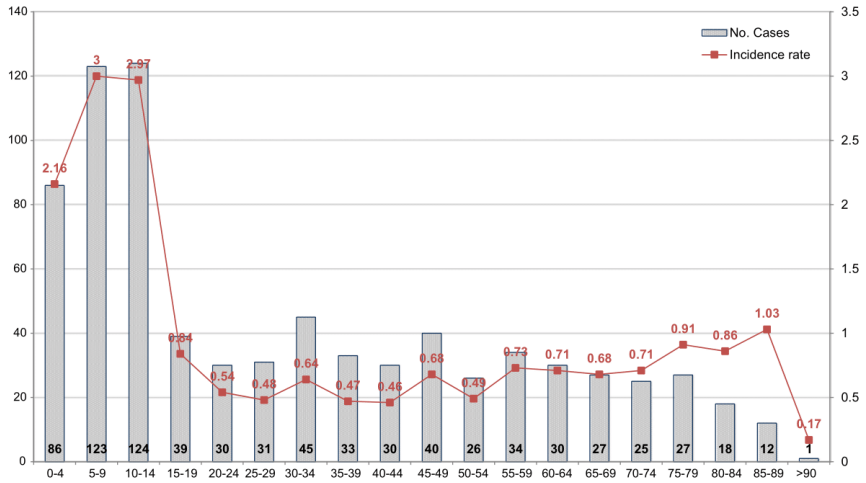

Fig. 4 Distribution age (5-year groups) of cat scratch disease (No. of cases and incidence rates—*cases per* million *person-years*), Spain, 1997–2015

involvement, usually with delays in diagnosis [27, 28]. The lethality rate in our study was approximately 1.3%. Our data show that older patients have a higher mortality. The delay in diagnoses in this group could be one of the essential factors for a worse prognosis. Therefore, carrying out a timely diagnosis and an early start of treatment are essential to improve the prognosis and may result in fewer hospitalizations and serious complications.

Because the CMBD provides information from a network of hospitals that covers more than 99% of the population living in Spain (http://www.msssi.gob.es/), this study provides fairly accurate estimates. However, there were several factors that were limitations in our study: (*i*) the use of sources such as the CMBD for purposes other than research and clinical care; (*ii*) the use of the ICD-9, which has certain classification limitations with respect to the ICD-10, which is more modern and has fewer qualifying errors; (*iii*) encoding error may exist and cannot be amended as the data included in the CMBD are irreversible; (*iv*) not being able to access the medical history did not allow us to confirm the diagnosis, identify the possible associated factors involved, and find information about the tests used for CSD diagnosis (which

Table 2 Primary diagnosis vs. secondary diagnosis

Variables	Primary diagnosis, $N_1 = 568$ *n* (%)	Secondary diagnosis, $N_2 = 213$ *n* (%)	*p* value*
Age (years), mean ± SD; n (%)	28.6 ± 24.1	36.3 ± 27.7	< 0.001*
Age 0–14 years	254 (44.7)	79 (37.1)	0.004*
Age 15–64 years	248 (43.7)	90 (42.3)	
Age ≥ 65 years	66 (11.6)	44 (20.7)	
Gender, *n* (%)			
Male	306 (53.9)	99 (46.5)	0.065
Female	262 (46.1)	114 (53.5)	
Type of hospital admission, *n* (%)			
Urgent	477 (84.0)	175 (82.2)	0.542
Programmed	91 (16.0)	38 (17.8)	
Type of discharge, *n* (%)			
Home	558 (98.8)	200 (97.1)	0.110
Others	7 (1.2)	6 (2.9)	
Mortality, *n* (%)	3 (0.5)	7 (3.3)	0.002*
Hospital stay (days); mean ± SD	7.8 ± 6.4	10.1 ± 13.3	0.001*

*Statistical significance level of 5% ($p < 0.05$)

lowers the quality of the data in this matter), the diagnostic techniques used in our patients and the clinic where they received care. For example, the 078.3 code could have been inappropriately used for care of a cat scratch wound but not actual CSD. Additionally, in some cases, the 078.3 code may have been recorded as a rule-out diagnosis when CSD was not actually confirmed. To our knowledge, there are no data on the sensitivity and specificity of the 078.3 code for CSD. (*vi*) In considering only patients in public hospitals and not including nonhospital cases or private centers, for example, those who are ill who are not admitted or who did not receive medical care, in addition to those treated in private hospitals, would be excluded; thus, hospital records underestimate the real burden of CSD in Spain. This study only reflects the patients who died while hospitalized, which could underestimate the mortality; and finally, (*vii*) the estimated cost is not evaluated in this study. In any case, our findings reported here have potential implications for public policy. We not only aimed to relieve the lack of official epidemiological data but we also expect to have contributed to generating hypotheses that will be worthy of further investigation. Our data showed that the systematic search of HDR may be an adequate method for studying those diseases with scarce epidemiological data.

We have demonstrated that CSD causes a substantial burden of disease in Spain, affecting both adult and pediatric patients with a stable incidence rate. Our data suggest that CSD is benign and self-limited, with low mortality, and that its incidence may be underestimated. Finally, there is a need for a common national strategy for data collection, monitoring, and reporting, which would facilitate a more accurate picture and the design of more strategic control measures. HDRs could be a good epidemiological database for the study of hospital management of CSD.

Author Contributions Study design: MBG, BRA, and JLPA
Data collection: VVT, MAS, ALB, and ARA
Data analysis: MAS and HMRA
Writing: MBG, JLPA, JPLL, and BRA

Compliance with ethical standards

This study is based on medical data of patients collected in the CMBD. These data are the responsibility of the Ministry of Social Services of Health and Equality (Ministerio de Servicios Sociales, Sanidad e Igualdad, MSSSI) that compiles and organizes them. All patient data provided by the CMBD are anonymized and deidentified by the MSSSI before they are provided to the applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers, so other researchers must request the data directly from the MSSSI.

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

Ethical approval The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because it is an epidemiological study, written consent was not obtained. All data analyzed were anonymized.

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Terms and Conditions

Artículo Cuatro

Epidemiological Assessment of 5,598 Brucellosis Inpatients in Spain (1997-2015)

Objetivos: Llevar a cabo un análisis epidemiológico de los pacientes ingresados por brucelosis en España entre 1997 y 2015. Establecer una comparación entre los datos obtenidos a partir del CMBD y los registrados en el sistema de enfermedades de declaración obligatoria (EDO).

Principales resultados: Entre 1997 y 2015, 5.598 pacientes diagnosticados de brucelosis precisaron ingreso hospitalario, alcanzando dicha zoonosis una incidencia de 0.67 casos /100.000habitantes/año. El grupo en el que se identificó mayor riesgo de infección fue de hombres en torno a la quinta década de la vida. El 56.9% de los casos fueron de procedencia urbana. La estancia media hospitalaria fue de 12.6 días (± 13.1). La tasa de mortalidad fue del 1.5%

Conclusiones: Durante el período analizado, se observa una reducción exponencial y progresiva del número de casos de brucelosis que precisaron ingreso hospitalario. El grupo de pacientes de mayor riesgo lo componen hombres en torno a los 45 años de procedencia urbana. La tasa de mortalidad en los pacientes ingresados es muy baja (1.5%), por lo que en pacientes que no precisaron ingreso se presupone aún menor. El CMBD se posiciona como una herramienta superior al sistema EDO para el análisis epidemiológico de esta enfermedad.

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Epidemiological Assessment of 5,598 Brucellosis Inpatients in Spain (1997-2015)

Short title

Brucellosis in Spain, 1997-2015.

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ABSTRACT

Brucellosis remains one of the main zoonoses worldwide. Epidemiological data on human brucellosis in Spain are scarce. The objective of this study was to assess the epidemiological characteristics of inpatient brucellosis in Spain between 1997 and 2015. A retrospective longitudinal descriptive study was performed. Data were requested from the Health Information Institute of the Ministry of Health and Equality, which provided us with the Minimum Basic Data Set of patients admitted to the National Health System. We also obtained data published in the System of Obligatory Notifiable Diseases. A total of 5,598 cases were registered. The period incidence rate was 0.67 (95% CI, 0.65-0.68) cases per 100,000 person-years. We observed a progressive decrease in the number of cases and annual incidence rates. A total of 3,187 cases (56.9%) came from urban areas. The group most at risk comprised men around the fifth decade of life. The average (±SD) hospital stay was 12.6 days (± 13.1). The overall lethality rate of the cohort was 1.5%. The number of inpatients diagnosed with brucellosis decreased exponentially. The group of patients with the highest risk of brucellosis in our study was males under 45 years of age and of urban origin. The lethality rate has reduced to minimum values. It is probable that hospital discharge records could be a good database for the epidemiological analysis of the hospital management of brucellosis and offer a better information collection system than the notifiable diseases system (EDO in Spanish).

Keywords

Brucella spp.; Brucellosis; Malt fever; Mediterranean fever; Epidemiology; Fever of intermediate duration; Spain.

INTRODUCTION

Brucellosis is an infectious disease caused by several species of facultative intracellular and slow-growing gram-negative coccobacilli of the genus Brucella(1–3). It is the main bacterial zoonosis in the world(1), and the main species responsible for human disease are *B. melitensis*, *B. abortus*, *B. suis* and *B. canis*(3). *B. melitensis* is the most virulent species and the main causal agent of human brucellosis(3). Three main biotypes of *B. melitensis* with different geographic distributions have been described(2). The main forms of transmission of brucellosis to humans are the consumption of unpasteurized milk or derivatives (i.e., raw milk, soft cheese, butter and ice cream) from infected animals and contact with mucous membranes or inhalation of aerosols derived from infected animals(2). Other less frequent forms of infection are those acquired in clinical laboratories as well as vertical and horizontal human-to-human transmission(3).

Human brucellosis is usually an acute systemic disease with an incubation period of 2 to 24 weeks(3). Some patients may present relapses even after receiving treatment or develop chronic osteoarticular (peripheral arthritis, sacroiliitis, and spondylitis), genitourinary (epididymo-orchitis), neurological (meningoencephalitis, meningovascular disease, brain abscesses, and demyelinating syndromes), or endocarditis presentations(1–5). A delay in diagnosis of more than 14 days significantly increases the rate of complications, estimated between 4-25%(1,6). As the clinical manifestations of brucellosis are not pathognomonic, the diagnosis is based on the use of direct microbiological studies (cultures or nucleic acid amplification tests) or indirect tests (serology)(7). The treatment of brucellosis is based on the use of antimicrobials, usually in combination and prolonged(8,9). Mortality in adequately treated patients is minimal, although in complicated forms (i.e., endocarditis or meningoencephalitis), it can reach 2% to 5%.

The actual incidence of human brucellosis is unknown, averaging 500,000 cases worldwide each year, although this figure is probably underestimated(6). The incidence of human brucellosis is highly variable (0.02-268.81 per 100,000 person-years) depending on the country, being higher in the Middle East, central Asia, and African Mediterranean rim and lower in central and southern Latin America, Western Europe (Greece, Italy and Spain) and North America(10–13). Furthermore, the data are not uniform within each country and vary depending on the time period(11–13). Epidemiological data on human brucellosis in Spain are scarce(14), so the objective of this study was to assess the epidemiological characteristics of inpatient brucellosis in Spain between 1997 and 2015.

PATIENTS AND METHODS

This is a retrospective longitudinal descriptive study of hospitalized patients diagnosed with brucellosis in Spanish public hospitals between January 1, 1997, and December 31, 2015. This study analyses the data provided by hospital discharge records (HDRs). HDRs include all hospital discharges produced in the network of general hospitals in the National Health System (NHS). The data contained in this record are those established in the Hospitalization Minimum Data Set (CMBD in Spanish). The CMBD is the main clinical-administrative database for knowledge of morbidity and the care process of patients treated in all public and private hospitals in Spain. It provides usual demographic data (age, gender, and place of residence), identifies the care provider (centre, unit), the patient (medical record number, health card number), clinical variables (diagnoses and procedures) and variables related to the episode of

hospitalization, as a circumstance of admission (urgent or scheduled), patient discharge (discharge to your address, transfer to another hospital or death), and average stay. Diagnoses and procedures collected are coded using the International Classification of Diseases, Clinical Modification (ICD-9-CM). *Principal diagnosis* was defined as the condition after study, which occasioned admission to the hospital, according to the ICD-9-CM Official Guidelines for Coding and Reporting. *Secondary diagnoses* (up to 13) are *"other diagnoses"* or conditions that coexist at the time of admission or develop subsequently and that affect patient care during the current episode.

Our data were obtained from the Minimum Basic Data Set (CMBD in Spanish) of patients admitted to the NHS (National Health System) with ICD-9-CM diagnosis code 023-Brucellosis, provided by the Health Information Institute of the Ministry of Health and Equality. Patients with missing data were excluded from the study.

We also obtained data published in the System of Obligatory Notifiable Diseases (in Spanish, EDO, www.mscbs.gob.es), one of the information systems that integrates the National Network of Epidemiological Surveillance of Spain (in Spanish, RENAVE), which establishes the list of obligatory notifiable diseases, their notification modalities and the periodic diffusion of information in the Weekly Epidemiological Bulletin.

Statistical analysis

Data analysis was performed using SPSS 26 (Statistical Package for the Social Sciences). Descriptive statistics were used to analyse the data initially. Categorical variables were summarized as frequencies (n) and percentages (%) and continuous variables as the mean, standard deviation (SD), median, interquartile range (IQR) (Q_3-Q_1), and range (minimum value, maximum value). For categorical variables, the odds ratio (OR) was used as a measure of association, and the 95% confidence interval (CI) of the OR was utilized to assess the precision of this estimate. Chi-square (χ^2) test was used to assess the difference in proportions amongst subgroups and Student's t-test, the Mann-Whitney test and ANOVA test were applied to obtain the level of significance in continuous variables. Logistic regression model was applied to get the predicted category that had the maximum estimated probability and constructed cross tables to evaluate the accuracy of prediction classification (B coefficient is an odds ratio [OR=Exp(B)] and Wald chi-square test). The level of significance was expressed as p-values. A p-value <0.05 was considered statistically significant.

Incidence rates were computed by autonomous community and year to assess temporal and geographical patterns. The results in terms of mean rates by autonomous community were plotted on maps for the whole study period. The *incidence rate* was calculated by dividing the number of new cases of brucellosis (numerator) per

year/period by the population at risk (denominator) in a period of time (person-years) multiplied by 100,000 and expressed as “cases per 100,000 person-years”. As it is not possible to accurately measure disease-free periods, the total person-time at risk can be estimated approximately and satisfactorily when the size of the population is stable, multiplying the average population size studied by the duration of the observation period. Thus, the population at risk was obtained from annual data published by the National Institute of Statistics (INE, http://www.ine.es/). The 95% confidence interval (95% CI) for the incidence rate was calculated for a better clinical application of the results. The *lethality rate* was calculated by dividing the number of deaths caused by a disease in a period and area (numerator) by the number of cases diagnosed for the same disease in the same period and area (denominator) (x100). It is the proportion of cases in a designated population of a particular disease, which die in a specified period of time. It is also known as *Case fatality rate*. Lethality is a better measure of clinical significance of the disease than mortality.

RESULTS

Temporal and geographical distribution

A total of 5,598 cases with ICD-9-CM Diagnosis code 023 were registered in Spain during the 19-year study period, 1997-2015. The period incidence rate was 0.67 (95% CI, 0.65-0.68) cases per 100,000 person-years. We observed a progressive decrease in the number of cases and annual incidence rates (**Figure 1**), with the highest in 1997, 2.23 (95% CI, 2.37-2.08) cases per 100,000 person-years (876 cases), and the lowest in 2015, 0.16 (95% CI, 0.12-0.19) cases per 100,000 person-years (74 cases). When we compared the data recorded in the CMBD with the data reported in the EDO system, there were significant differences between the two health information systems (**Table 1**). At the beginning of the study period, more cases were recorded in the EDO system (2140 *vs.* 876), with a higher rate (5.45 *vs.* 2.23 cases per 100,000), while at the end of the study period, more cases were recorded in the CMBD (74 *vs.* 50), with a higher rate (0.16 *vs.* 0.11 cases per 100,000).

The disease has a seasonal component, with a higher number of cases in the spring and summer months (from March to August), although there are cases throughout the year. The distribution of brucellosis cases in Spain during the months of the year is shown in **Figure 2**.

The geographical distribution of cases is shown in **Figure 3**. The highest incidence rates correspond to the central regions of the Iberian Peninsula: Extremadura, 2.31 (95% CI, 2.10-2.52) cases per 100,000 person-years, and Castilla-La Mancha, 1.60 (95% CI, 1.47-1.73) cases per 100,000 person-years. In contrast, Islas Canarias and

Baleares, Cantabria and the Mediterranean coastal areas had the lowest incidence rates.

More than half of the cases (56.9%; 3187) came from urban areas (population with more than 5,000 inhabitants), compared to 29.2% (1637) from rural areas (population with less than 5,000 inhabitants) (see **Table 2).** In some regions of Spain, cases of rural origin were more frequent than those of urban origin (p<0.001): Cantabria (63.8% *vs.* 36.2%), Castilla y León (63% *vs.* 37%), Navarra (61.2% *vs.* 38.8%), and Extremadura (60.2% *vs.* 39.8%). On the other hand, other autonomous communities had a higher number of patients of urban origin: Andalucía (72.2% *vs.* 27.8%), Galicia (79.5% *vs.* 20.5%), Cataluña (83.7% *vs.* 16.3%), C. Valenciana (87.3% *vs.* 16.3%), País Vasco (96.6% *vs.* 3.4%), Murcia (97.4% *vs.* 2.6%), and Madrid (98% *vs.* 2%). No significant differences were observed associating rural/urban origin with seasonality (p=0.884).

Annual evolution of brucellosis cases in each region (Autonomous Community) of Spain is analysed in **Figure 4**. There are significant differences (p <0.001) in the percentage distribution of the cases annually. The global profile of Spain varied throughout the entire period, being most striking in the Islas Canarias, Cantabria, La Rioja and Melilla.

Distribution by gender and age

The number of cases in men (73.8%) was three times higher than that in women (26.2%), with a male/female ratio of 3:1 (4131/1465): incidence rate in men, 1.00 (95% CI, 1.03-0.97) cases per 100,000 person-years *vs.* In women, 0.34 (95% CI, 0.32-0.36) cases per 100,000 person-years. The mean (±SD) age was 45.8 years (± 21.1) [median (IQR), 46.4 (63-15)], range (0, 101). A total of 8.5% (476 cases) of the sample corresponded to the paediatric population (0-14 years), with 338 (43.3%) adults (15-64 years) and 110 (14.1%) elderly patients (**Table 2**).

There were statistically significant differences between men and women in the percentage distribution of cases by decades of age, as shown in **Table 3** (p<0.001). Thus, the highest percentages in men were in those from 30 to 59 years old, while in women, they were in those 60 to 79 years old. In addition, the percentage of men of rural origin was slightly higher than that of urban origin, 78.9% *vs.* 71.3% (p=0.015); the percentage of patients over 45 years of age of rural origin was slightly higher than that of urban origin, 55.7% *vs.* 52.8% (p=0.058). There were no significant differences in seasonality among the age groups (p = 0.547).

Clinical data

Hospitalizations with ICD-9-CM Diagnosis code 023 as the principal diagnosis code represented 3767 (67.3%), with 1831 (32.7%) cases as secondary diagnosis code.

Most cases (4991, 89.2%) were coded as *unspecified brucellosis:* ICD-9-CM Diagnosis code 023.9, as shown in **Table 2**.

Table 4 compares patients with principal diagnosis *vs.* secondary diagnosis. The mean age of patients with a principal diagnosis code was lower than that of those with a secondary diagnosis code [mean ± SD, 41.5 ± 20.2 *vs.* 54.7 ± 20.1, p<0.001]. Additionally, average hospital stays increased by 3 days among patients with a secondary diagnosis code [mean ± SD, 11.6 ± 10.5 *vs*. 14.8 ± 17.1, p<0.001].

Categorical variables were analysed using a logistic regression model. All independent variables included in the multivariate model were significantly associated (p<0.05) with the dependent variable: principal diagnosis *vs.* secondary diagnoses, except for the rural or urban origin of the patients. The coefficients were positive (risk factor) and significant for the variables age, gender, type of hospital admission and type of discharge. Therefore, a logistic regression model allowed us to predict that a principal diagnosis is associated with a higher probability of a male patient, under 45 years of age, with urgent admission and home discharge but a lower probability of death/failure. In relation to the type of hospital admission, 4624 (82.6%) cases were urgent. Most cases (5,337, 95.3%) were sent home after hospital discharge. The average (±SD) hospital stay was 12.6 days (± 13.1) [median (IQR), 9 (15-5)] (see **Table 2**).

We do not know the service responsible for the patient's discharge in three quarters of the sample. Of the remaining 25% in which the responsible service was known, half of them (718, 12.8%) were treated in the Internal Medicine Service, followed by the Paediatric Service (62, 1.1%).

Cohort lethality

The overall lethality rate of the cohort was 1.50 per 100 (84 deaths/5,598 total). The principal diagnosis lethality rate for brucellosis was 0.32 per 100 (12 deaths/3,755 total principal diagnoses). The highest annual brucellosis principal diagnosis lethality rate was 3.17% in 2008, decreasing to 0% since then. The lethality rate in males was 1.43 per 100 (59 deaths/4,131 total males) and 1.71 per 100 females (25 deaths/1465 total females). Lethality rates varied according to age: 0-14 years (0 deaths/476); 15-44 years, 0.32 per 100 (7 deaths/2,183 cases); 45-64 years, 1.15 per 100 (19 deaths/1,657 cases); and >65 years, 4.52 per 100 (58 deaths/1,282 cases). The lethality rate was 1.22 per 100 (20 deaths/1,637 cases) in rural environments and was 1.88 per 100 (60 deaths/3,187 cases) in urban patients.

DISCUSSION

During the study period, 5,598 hospital admissions for brucellosis were registered, which represents an incidence rate of 0.67 cases per 100,000 inhabitants per year.

Taking into account that the worldwide incidence ranges between 0.02-268.81 per 100,000 person-years in endemic areas(11–13), Spain is at the lower limit. However, Spain has a clearly higher rate than other endemic areas, such as Australia and China(6,15), but a lower rate than other European countries, such as Greece and Italy(11). However, the data obtained in hospitalized patients do not include asymptomatic infections(16), so in some countries, the incidence of brucellosis may be underestimated by 12–18 times(17).

The evolution of human brucellosis incidence rates in Spain from 1997 until 2015 has decreased progressively, and there are indirect data on the progressive decline since then. There are several non-exclusive explanations for these data: *i)* the source of information (CMBD *vs.* EDO). This decrease is more significant in the EDO notification system (5.45 cases to 0.11 cases per 100,000). These data are justified by the methodological differences in data collection; thus, while the CMBD is a mandatory record for hospitals in our National Health System, the EDO system is a reporting system based on the ethical responsibility of health professionals. For this reason, it is likely that the CMBD is a more reliable information collection system than the EDO system for inpatients. *ii)* The establishment of control programmes(18). *iii)* The better knowledge of the disease that implies an earlier diagnosis and a more effective treatment. The results between the different registry systems suggest the need for unique quality registries.

The incidence of brucellosis varies widely not only among countries but also among different regions of the same country. In Spain, the highest incidence is observed in interior regions (Extremadura and Castilla la Mancha), similarly to the situation in other countries (i.e., China)(15) but different from that in others (i.e., Australia)(6). However, it is extremely low in some regions (i.e., Canary Islands), which suggests an imported origin of the infection in these areas(19). These differences suggest that demographic, occupational, and socioeconomic factors may play a role. In Spain, slightly more than half of the cases come from urban areas, although the limit used in the definition of rural or urban areas is somewhat arbitrary, which may explain the similarity with some series(20) and the differences with others(6). In general, the most affected areas are those least economically developed and/or with the highest livestock density (sheep and goats)(10).

In this study, the number of cases in men was three times higher than that in women. This finding is similar to the results obtained in agricultural areas and different from those described in livestock areas(20). The average age was 45.8 years, similar to that reported in other studies(20). When the incidence relationship with both magnitudes

was evaluated, it was observed that it was higher in younger men (30-59 years) and older women (60-79 years), an aspect not described, to our knowledge, in other series. In our study, the annual period with the highest number of cases covers from March to July, which is similar to other series(20).

The fact that brucellosis has been identified as the primary diagnosis in more than 67% of cases indicates a much higher diagnostic suspicion than in other infections that cause fever of intermediate duration(21,22). The mean stay of individuals with a secondary diagnosis is significantly longer than that in the primary forms. This result seems quite logical, since there is a longer delay in time to diagnosis and, predictably, a greater number of complications that prolong the stay; predictably, a greater number of complications prolong the stay.

One of the main limitations of this study is that we do not know the diagnostic method applied individually. Thus, secondary diagnoses could be due to a positive serological test, and be both an acute infection and a "serological sequel" of an old infection.

In this series, the mortality of brucellosis cases is clearly lower than that in the literature, being zero since 2008, although it increases with age ($p < 0.001$). This could be due to being an endemic area where the diagnostic suspicion is greater than that in other areas. In our series, we found a higher lethality rate in women than in men, and these data are probably biased because the cohort of women is older than the cohort of men. We also detected that in urban cases, the lethality rate is higher than in rural cases.

The CMBD is a standardized registry of patients that is carried out in most of the hospitals in our country and is therefore not exposed to the biases that limit other types of registries that involve voluntary declaration. This aspect gives it two fundamental advantages: the first is that the number of individuals who make up the sample is very large, and the second is that such a large sample n makes it very representative of the population. However, the design of the CMBD has limitations, such as the absence in the registry of patient comorbidities, clinical manifestations, the results of complementary tests and the therapeutic measures used.

In summary, inpatient diagnosis for brucellosis decreased exponentially in the study period in Spain, probably due to success of veterinary control programmes and/or an earlier diagnosis and treatment. The highest incidence rates corresponded to the central and interior regions of Spain, and the group of patients with the highest risk of suffering from brucellosis in our study by logistic regression was males under 45 years of age and of urban origin. The lethality rate has also been reduced to minimum values. It is probable that hospital discharge records (HDRs) could be a good database for the

epidemiological analysis of the hospital management of brucellosis and offer a better information collection system than the EDO system.

Ethical approval

This study is based on medical data of patients collected in the CMBD. These data are the responsibility of the Ministry of Social Services of Health and Equality (*Ministerio de Servicios Sociales, Sanidad e Igualdad*, MSSSI) that collects and organizes them. All patient data provided by the CMBD are anonymized and deidentified by the MSSSI before they are provided to applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers, so other researchers must request the data directly from the MSSSI. The protocol and ethics statement of this study were approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA-Salamanca, Spain CEIMc) with the assigned Code PI 2021 03 708. Because the data were obtained from an epidemiological database, written consent was not obtained. All data analysed were anonymized.

Consent to participate

Because the data were obtained from an epidemiological database, written consent was not obtained. All data analysed were anonymized.

Consent to publish

All authors consent to publish.

Authors contributions

Study design: MBG, BRA, and JLPA
Data collection: VVT, MAS, ALB, and ARA
Data analysis: MAS, HA, MBG
Writing: MBG, JLPA, JPLL, and BRA

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Competing interests

The authors declare that they have no conflicts of interest.

Availability of data and materials

Available in public deposits in www.mscbs.gob.es.

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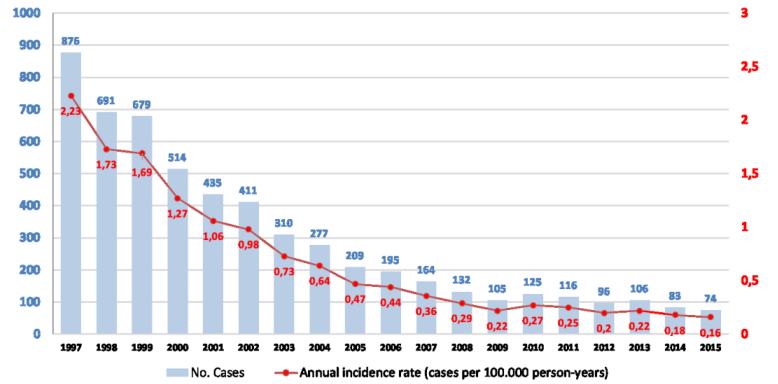

Figure 1. Temporal distribution of human brucellosis in Spain, 1997-2015: cases and annual incidence rate (cases per 100.000 person-years)

Figure 1

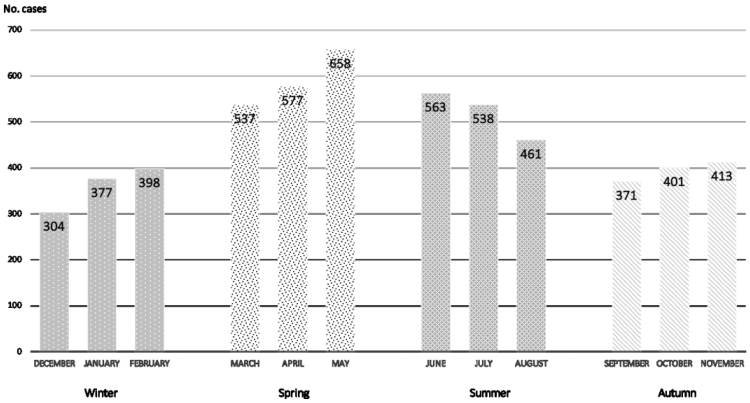

Figure 2. Distribution of brucellosis cases in Spain in the months of the year, 1997-2015

Figure 2

Figure 3. Number of cases and incidence rates (cases per 100,000 person-years) by regions, Spain, 1997-2015

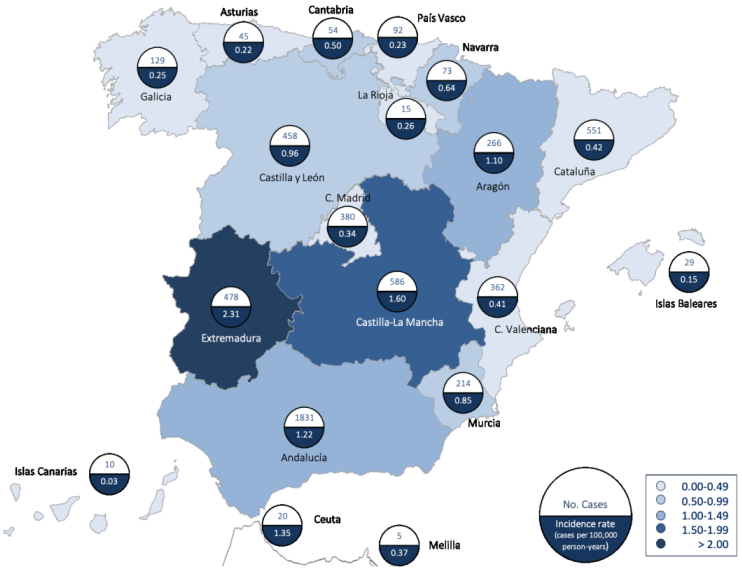

Figure 3

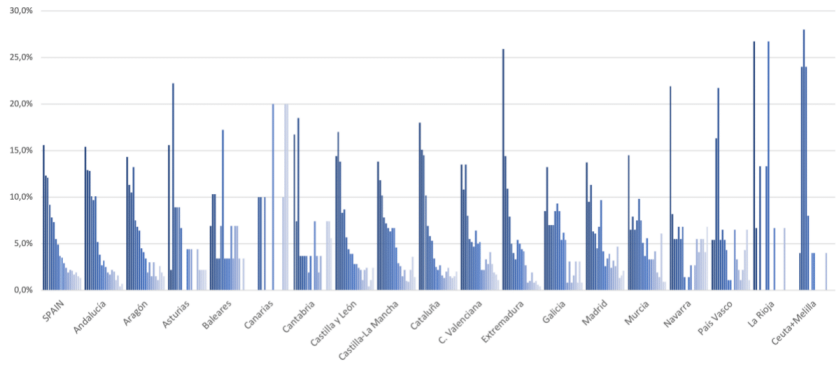

Figure 4. Annual percentage distribution of brucellosis cases by autonomous communities of Spain in the study period, 1997-2015

Figure 4

Table 1. Human Brucellosis in Spain, 1997-2015: Minimum Basic Data Set (CMBD in Spanish) *vs.* System of Obligatory Notifiable Diseases (EDO in Spanish)

Year	CMBD			EDO	
	No. Cases	Cases per million	Cases per 100.000	No. Cases	Cases per 100.000
1997	876	22.28	2.23	2140	5.45
1998	691	17.34	1.73	ND	ND
1999	679	16.89	1.69	ND	ND
2000	514	12.69	1.27	ND	ND
2001	435	10.58	1.06	ND	ND
2002	411	9.82	0.98	ND	ND
2003	310	7.26	0.73	ND	ND
2004	277	6.41	0.64	ND	ND
2005	209	4.74	0.47	ND	ND
2006	195	4.36	0.44	ND	ND
2007	164	3.63	0.36	ND	ND
2008	132	2.86	0.29	ND	ND
2009	105	2.25	0.22	ND	ND
2010	125	2.66	0.27	ND	ND
2011	116	2.46	0.25	104	0.22
2012	96	2.03	0.20	88	0.19
2013	106	2.25	0.22	104	0.22
2014	83	1.77	0.18	83	0.18
2015	74	1.59	0.16	50	0.11
TOTAL	5598	6.68	0.67	-	-

*ND: No data.

Table 2. Main demographic and clinical data of Brucellosis inpatients in Spain from 1997 to 2015

Variables	N=5598 cases (100%) n (%)
Age (years)	
Mean ± SD	45.8 ± 21.1
Range (Minimum value, Maximum value)	(0, 101)
Age 0-14 years	476 (8.5)
Age 15-44 years	2183 (39.0)
Age 45-64 years	1657 (29.6)
Age ≥65 years	1282 (22.9)
Gender	
Male	4131 (73.8)
Female	1465 (26.2)
Undetermined	2 (0.0)
Rural vs. Urban environment	
Rural (population with more than 5,000 inhabitants)	1637 (29.2)
Urban (population with less than 5,000 inhabitants)	3187 (56.9)
Foreigners	17 (0.3)
Unknown	757 (13.5)
ICD-9-CM: 023 code	5598 (100.0)
Brucella melitensis (023.0)	365 (6.5)
Brucella abortus (023.1)	24 (0.4)
Brucella suis (023.2)	5 (0.1)
Brucella canis (023.3)	2 (0.0)
Other (023.8)	211 (3.8)
Unspecifed (023.9)	4991 (89.2)
Diagnosis causing the hospitalization	
Principal diagnosis	3767 (67.3)
Secondary diagnosis	1831 (32.7)
Type of hospital admission	
Urgent	4624 (82.6)
Programmed	965 (17.2)
Others/unknown	9 (0.2)
Type of discharge	
Home	5337 (95.3)
Transfer to another Hospital	118 (2.1)
Transfer to Social-Health Center	4 (0.1)
Voluntary discharge	25 (0.4)
Others/unknown	30 (0.5)
Overall lethality	84/5598 (1.50)
Brucellosis principal diagnosis lethality	12/3755 (0.32)
Hospital stay (days)	
Mean ± SD	12.6 ± 13.1
Range (Minimum value, Maximum value)	(0, 194)

Table 3. Patient cohort description according to age groups and gender

Age groups, years	Total, N=5596 n (%)	Male, N_1=4131 n (%)	Female, N_2=1465 n (%)	p-value
0-9	243 (4.3)	146 (3.5)	97 (6.6)	p < 0.001
10-19	460 (8.2)	331 (8.0)	128 (8.7)	
20-29	715 (12.8)	540 (13.1)	174 (11.9)	
30-39	831 (14.8)	648 (15.7)	183 (12.5)	
40-49	808 (14.4)	656 (15.9)	152 (10.4)	
50-59	829 (14.8)	635 (15.4)	194 (13.2)	
60-69	863 (15.4)	626 (15.2)	237 (16.2)	
70-79	613 (11.0)	407 (9.9)	206 (14.1)	
80-89	212 (3.8)	128 (3.1)	84 (5.7)	
>90	24 (0.4)	14 (0.3)	10 (0.7)	

Table 4. Principal diagnoses code *vs.* Secondary diagnoses code : (a) Bivariate analysis, (b) Multivariate analysis

	Principal diagnosis N_1=3767	Secondary diagnosis N_2=1831	(a) Bivariate analysis	
Variables	n (%)	n (%)	p-value	OR (95% CI for OR)
Age (years), mean± SD	41.5 ± 20.2	54.7 ± 20.1	<0.001	
Age 0-14 years	420 (11.1)	56 (3.1)	<0.001	
Age 15-44 years	1682 (44.7)	501 (27.4)		
Age 45-64 years	1064 (28.2)	593 (32.4)		
Age ≥65 years	601 (16.0)	681 (37.2)		
<45 years	2102 (55.8)	557 (30.4)	<0.001	2.9 (2.5-3.2)
≥45 years	1665 (44.5)	1274 (69.6)		
Gender				
Male	2831 (75.2)	1300 (71.0)	0.001	1.2 (1.1-1.4)
Female	934 (24.8)	531 (29.0)		
Origin of the cases				
Rural	1057 (33.4)	580 (35.0)	0.239	0.9 (0.8-1.1)
Urban	2112 (66.6)	1075 (65.0)		
Type of hospital admission				
Urgent	3264 (86.6)	1360 (74.3)	<0.001	2.2 (1.9-2.5)
Programmed	498 (13.2)	467 (25.5)		
Type of discharge				
Home	3668 (97.4)	1669 (91.2)	<0.001	3.6 (2.8-4.6)
Others	99 (2.6)	162 (8.8)		
Exitus letalis	12 (0.3)	72 (3.9)	<0.001	0.08 (0.04-0.14)
Hospital stay (days), mean±SD	11.6 ± 10.5	14.8 ± 17.1	<0.001	

(b) Multivariate analysis: Binary logistic regression model (Dependent variable: principal diagnosis *vs* secondary diagnosis)							
Independent	B	Standard	Wald	gl	Sig.	Exp(B)	95% CI for

variables		error					Exp(B)	
							lower	upper
Age	0.938	0.062	227.903	1	0.000	2.554	2.261	2.885
Gender	0.186	0.067	7.603	1	0.006	1.205	1.055	1.375
Type of hospital admission	0.690	0.075	84.009	1	0.000	1.994	1.720	2.311
Hospital readmission	0.872	0.105	69.057	1	0.000	2.392	1.948	2.939
Type of discharge	0.742	0.160	21.459	1	0.000	2.101	1.535	2.876
Exitus letalis	-1.510	0.355	18.075	1	0.000	0.221	0.110	0.443
Constant	-1.855	0.198	87.415	1	0.000	0.156		

Tabla 2. Tabla resumen de los resultados obtenidos en nuestro proyecto de investigación

	Nº pacientes y tasa de incidencia	Tendencia	Edad media	Género H:M	Rural/ Urbano	CCAA de mayor IR	Época del año	Estancia hospitalaria Media		Tasa de mortalidad	
								Diagnóstico primario	Diagnóstico secundario	Diagnóstico primario	Diagnóstico secundario
Fiebre Q	4.214 pac IR: 0.53	Estable	50.9 ± 19.3	3:1	Urbano	Canarias y Baleares	Marzo-agosto	13.8 ± 12.8		2.8%	
								12.4 ± 10.9	17.5 ± 16.1	1.5%	6.2%
Tifus murino	99 pac IR: 0.012	Ascendente	46.4 ± 19	2:1	Urbano	Canarias y Andalucía	Agosto-octubre	11.0 ±9.9		1%	
								10.0 ± 7.5	17.8 ± 18.3	1%	-
Enf. arañazo de gato	781 pac IR: 0.093	Estable	30.7 ±25.3	1.1:1	Urbano	Asturias y Cantabria	Septiembre-enero	8.4 ± 8.9		1.3%	
								7.8 ± 6.4	10.1 ± 13.3	0.5%	3.3%
Brucelosis	5.598 pac IR: 0.67	Descendente	45.8 ± 21.1	3:1	Urbano	Extremadura y Castilla la mancha	Marzo-agosto	12.6 ± 13.1		1.5%	
								11.6 ± 10.5	14.8 ± 17.1	0.3%	3.9%

Discusión general y sintetizada de los principales hallazgos de la tesis

En este trabajo se ha llevado a cabo un análisis clínico-epidemiológico de cuatro de los principales agentes causantes de fiebre de duración intermedia en España utilizando para ello el Conjunto Mínimo Básico de Datos de los pacientes hospitalizados durante el período comprendido entre los años 1997 y 2015 en el SNS.

Hemos recogido en total 4.214 casos de fiebre Q, 99 de tifus murino, 781 de bartonelosis y 5.598 de brucelosis.

Coxiella burnetti, Rickettsia spp., Bartonella henselae y Brucella spp. son zoonosis conocidas desde hace décadas, ampliamente descritas y fácilmente tratables. Sin embargo, la mayor parte de ellas, como se refleja en este trabajo doctoral, mantienen una incidencia estable a lo largo del periodo de estudio y solamente la brucelosis presenta un claro descenso. Esto podría ser debido a que se trata de la única de las cuatro zoonosis que se halla en el listado de enfermedades de declaración obligatoria (EDO) en nuestro país.

La incidencia de fiebre Q y de enfermedad por arañazo de gato se mantiene estable a lo largo de los años. Sin embargo, el tifus murino muestra una clara tendencia ascendente presentándose como una enfermedad re-emergente en nuestro país. Esto probablemente se deba a la aparición de mecanismos de transmisión alternativos (inhalación de heces desecadas de pulgas), de nuevos vectores (otros tipos de pulgas, *ctenocephalides felis*) y desde otros reservorios (perros, gatos, zarigüeyas) así como a la identificación de *R.felis*, que origina un cuadro clínico similar al del tifus murino. Si bien es cierto que su incidencia se mantiene aún en cifras bajas, muy inferior a la de cualquiera de las otras tres zoonosis analizadas, en los años 2000 y 2012 se registraron incidencias del 0.05 y 0.08/millón de habitantes/ año, mientras en 2015 estos valores ascendieron a 0.19/millón de habitantes/año. Resulta llamativo que no se haya declarado ninguna alerta sanitaria ante esta duplicación de la tasa de incidencia.

En las cuatro zoonosis, podemos objetivar que, en las comunidades autónomas con mayores tasas de incidencia, la tasa de mortalidad es más baja. Esto muy probablemente sea debido a

que la existencia de una mayor sospecha clínica, implica un diagnóstico más precoz y un tratamiento más inmediato con un mejor pronóstico.

Sin discrepancias destacables con la literatura, hemos observado que los casos de fiebre Q y brucelosis se concentran entre los meses de marzo y agosto, los de tifus murino entre agosto y octubre y los de enfermedad por arañazo de gato entre septiembre y enero.

A pesar de que tienden a considerarse enfermedades del ámbito rural, nuestro estudio muestra un claro predominio en zonas urbanas. Esto podría deberse a la translocación de las explotaciones ganaderas clásicamente rurales hacia zonas urbanas junto con un posible cambio en el perfil de pacientes.

Respecto a la clínica de presentación de las cuatro enfermedades que nos ocupan, son cuadros clínicos clásicos en la literatura, sin variaciones a lo largo de los años. La fiebre Q puede presentarse como neumonía (21,1%); afectación hepática (17,5%) o endocarditis (3,2%). El tifus murino puede debutar con afectación cardíaca (11,1%); fracaso respiratorio (7,07%); fallo renal agudo (6,06%) o afectación del sistema nervioso central: meningitis, encefalitis o mielitis (3,03%).

Al comparar los porcentajes de diagnósticos primario y secundario en cada enfermedad, podemos observar mayor frecuencia de diagnósticos secundarios. Por tanto, es posible que la sospecha clínica ante estas zoonosis sea escasa. También se objetiva cómo, cuándo el diagnóstico es primario, la estancia media hospitalaria y la tasa de mortalidad se reducen considerablemente.

Quizá tendamos a pensar que, al tratarse de enfermedades con una baja incidencia y una baja tasa de mortalidad, su impacto a nivel epidemiológico y sanitario es escaso. Sin embargo, las cifras nos demuestran lo contrario. Solo se ha podido llevar a cabo una estimativa de costes de la fiebre Q puesto que son los únicos datos económicos que se nos han proporcionado. Los pacientes ingresados por fiebre Q entre 1997 y 2015 han supuesto un gasto estimado al Sistema Sanitario español de 154.232.779€, una media de 36.600 ± 139.442€ por paciente. Estas cifras no incluyen los costes de aquellos pacientes que no fueron hospitalizados. Por tanto, a los motivos epidemiológicos y sanitarios, podemos añadir también el factor económico para hacer patente la necesidad del control de estas zoonosis.

La única de estas cuatro enfermedades que se incluye dentro del sistema EDO en España es la brucelosis, siendo también la única que presenta un claro descenso de la incidencia a lo

largo de los años. Por tanto, a pesar de la subnotificación que ha demostrado nuestro estudio al comparar los casos notificados mediante el sistema EDO respecto a los registrados en el CMBD, el sistema de notificación parece efectivo. Esto probablemente sea debido a que se haya propiciado una estrategia sanitaria más agresiva o simplemente a la existencia de alguna, a diferencia de las otras tres enfermedades cuyos casos no se notifican.

Sin embargo, la brucelosis no es la que presenta una mayor tasa de mortalidad, si no que se posiciona en segundo lugar seguida muy de cerca por la bartonelosis. Nos gustaría sugerir que quizás todas estas zoonosis deberían someterse a un control más estricto, empezando por la fiebre Q que presenta una tasa de mortalidad que prácticamente duplica a la de la brucelosis.

En nuestro estudio se identifican una serie de limitaciones que se enumeran a continuación: i) a pesar de que el CMBD recoge información hospitalaria que cubre más del 99% de la población española, existe un pequeño porcentaje que se escapa a su escrutinio (http://www.msssi.gob.es/) por lo que nuestro estudio solo nos proporciona una estimación de las tasas de incidencia; ii) la clasificación CIE-9, utilizada hasta 2015, recoge menos variables que las registradas en la clasificación CIE-10, instaurada posteriormente y que proporciona más información; iii) a pesar de que la posibilidad de sesgos en la recogida de los datos es mínima respecto a otros sistemas de información sanitaria, la información incluida en el CMBD no es modificable por lo que pueden existir errores de codificación irreversibles; iv) la inclusión únicamente de los pacientes registrados en los hospitales públicos, excluye a aquellos que no solicitaron atención sanitaria o lo hicieron en hospitales privados, por lo que nuestra estimativa probablemente infravalore las cifras reales.

Por todos los hallazgos descritos en este trabajo doctoral creemos necesario el desarrollo de sistemas de información más efectivos y estudios reglados para establecer el impacto real de estas zoonosis en nuestro sistema sanitario, que posibiliten la implantación de estrategias sanitarias, veterinarias y ambientales conjuntas más efectivas para el control de las mismas.

Conclusiones

a. La fiebre Q es una zoonosis importante en España con una tasa de incidencia de 0,53/100.000 habitantes/año durante el periodo de estudio el número de casos se han mantenido estables. Las islas Canarias y Baleares ostentan las mayores tasas de incidencia de todo el territorio. Los pacientes de edad avanzada presentan un cuadro clínico más grave y mortal. La tasa de mortalidad global es aproximadamente del 3%.

b. El tifus murino presenta una tasa de incidencia en torno a 0,012/100.000 habitantes/año, con un lento incremento durante los años de estudio. La mayoría de los casos se describen en las Islas Canarias y Andalucía en hombres de mediana edad, entre finales de verano y principios de otoño. La tasa de mortalidad ronda el 1%.

c. La enfermedad por arañazo de gato presenta una tasa de incidencia de 0,093/ 100.000habitantes/año y se mantiene estable durante el periodo de estudio. Afecta tanto a la edad pediátrica como a los adultos. En general es una patología benigna y autolimitada. El mayor número de casos se registraron entre septiembre y enero. La mortalidad se sitúa en torno al 1%.

d. La brucelosis presenta una tasa de incidencia de 0,67/100.000habitantes/año con una marcada disminución del número de casos durante el periodo de estudio. El grupo de pacientes con mayor riesgo fue el de los varones menores en torno a los 45 años y de origen urbano. Las regiones del centro y el interior de España son las que presentan mayor número de casos. La mortalidad se ha reducido a valores mínimos con unas cifras de mortalidad que rondan el 1,5%.

e. Es probable que el Conjunto Mínimo Básico de Datos sea una buena herramienta para el análisis clínico-epidemiológico de las cuatro zoonosis estudiadas y puede postularse como un sistema de información sanitaria superior al sistema EDO.

f. Es necesario el establecimiento de sistemas de información más efectivos para valorar el impacto real de estas infecciones en nuestro Sistema Nacional de Salud y que faciliten a su vez la implantación de medidas y estrategias sanitarias, veterinarias y ambientales conjuntas más eficientes para el control de las mismas.

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Anexos

INDICE DE ANEXOS

ANEXO 1 - Informe de la Comisión académica del programa de doctorado.

ANEXO 2: Informe favorable del Comité ético del CAUSA

COMPLEJO ASISTENCIAL UNIVERSITARIO D SALAMANCA
Paseo de San Vicente, 58-182
37007 Salamanca
Comité Ético de Investigación con Medicamentos
Teléfono: 923 29 11 00 – Ext. 55 515

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E-mail: comite.etico.husa@saludcastillayleon.es

DICTAMEN DEL COMITE DE ETICA DE LA INVESTIGACION CON MEDICAMENTOS DEL AREA DE SALUD DE SALAMANCA

Dña. Mª Belén Vidriales Vicente, Secretaria Ténica del Comité de Ética de la Investigación con medicamentos del Área de Salud de Salamanca,

C E R T I F I C A

Que este Comité, en su reunión del 22/03/2021 (Acta 2021/03), ha evaluado el Proyecto de Investigación titulado

"Impacto epidemiológico de los principales agentes causantes de fiebre de duración intermedia en España (1997-2015)

Código CEIm: PI **2021 03 708**

del que es Investigador Principal Don Moncef Belhassen Garcia

del Servicio de Medicina Interna

y valorado de acuerdo con la Ley 14/2007 de Investigación Biomédica, Principios éticos de la Declaración de Helsinki de la Asociación Médica Mundial sobre principios éticos para investigaciones médicas con seres humanos, así como el resto de principios éticos y normativa legal aplicable en función de las características del estudio

Considera que dicho estudio cumple los requisitos necesarios y es viable para su realización en este centro, por lo que **INFORMA FAVORABLEMENTE** para la realización de dicho estudio

Y para que conste, lo firma en Salamanca con fecha 31 de marzo de 2021

MARIA BELEN VIDRIALES VICENTE - DNI 07851455Z
Firmado digitalmente por MARIA BELEN VIDRIALES VICENTE - DNI 07851455Z
Fecha: 2021.03.31 15:39:10 +02'00'

LA SECRETARIA

Fdo.: Dra.. Dña. Mª Belén Vidriales Vicente

Composición del CEIm del Área de Salud de Salamanca
Presidente: D. Luis Muñoz Bellvís (Jefe de Servicio de Cirugía General y Aparato Digestivo)
Vicepresidente: D. Enrique Nieto Manibardo (Delegado de protección de datos del CAUSA)
Secretaria: Dña. María Belén Vidriales Vicente (Jefe de Sección de Hematología. Representante de la Comisión de Investigación IBSAL). Vocales: D. Ricardo Tostado Menéndez (Farmacólogo Clínico); Dña. Silvia Jiménez Cabrera (Farmacia Hospitalaria); Dña. Ascensión Hernández Encinas (Profesora Titular Matemática aplicada, Universidad de Salamanca. Presidenta ASCOL, representante de los pacientes); Dña. Mª Teresa Arias Martín (Enfermera de Salud Mental. Miembro del Comité de Bioética Asistencial); Dña. Mª del Carmen Arias de la Fuente (Técnico Gestor de Ensayos Clínicos); Dña. Berta Bote Bonaechea (Especialista en Psiquiatría); Dña. Ángela Rodríguez Rodríguez (Responsable Unidad de Enfermera. S. de Hematología); Dña. Cristina Hidalgo Calleja (Especialista de Reumatología); D. Guzmán Franch Arcas (Especialista en Cirugía General y Aparato Digestivo); D. Antonio Márquez Vera (Fisioterapeuta); Dña. Ana Martín García (Especialista en Cardiología); Dña. Teresa Martín Gómez (Especialista en Oncología); D. Andrés Miguel Plata Alonso (Farmacéutico de Atención Primaria); Dña. Carmen Velayos Castelo (Profesora Titular Ética y Filosofía Política, Universidad de Salamanca); D. Manuel Angel Gómez Marcos (Médico de Atención Primaria. Responsable de la Unidad de Investigación de Atención Primaria de Salamanca)

ANEXO 3: Índices de calidad de las publicaciones

ARTÍCULO 1	Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: What´s new.
REVISTA	International Journal of Infectious Diseases
IMPACT FACTOR	3.202
QUARTILE	Q1
ISSN	1201-9712
IDIOMA	Inglés

ARTÍCULO 2	Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997-2015)
REVISTA	International Journal of Infectious Diseases
IMPACT FACTOR	3.202
QUARTILE	Q1
ISSN	1201-9712
IDIOMA	Inglés

ARTÍCULO 3	Epidemiological of cat scratch disease among inpatients in the Spanish Health System (1997-2015)
REVISTA	European Journal of Clinical Microbiology & Infectious Diseases
IMPACT FACTOR	2.837
QUARTILE	Q1
ISSN	09349723, 14354373
IDIOMA	Inglés

ARTÍCULO 4	Epidemiological Assessment of 5,598 Brucellosis Inpatients in Spain (1997-2015)
REVISTA	Epidemiology and Infection
IMPACT FACTOR	2.152
QUARTILE	Q2
ISSN	0950-2688 (print) 1469-4409 (web)
IDIOMA	Inglés

ANEXO 4: Aceptación co-autoría

VNiVERSiDAD D SALAMANCA
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IMPRIMIR RESTABLECER

D. /Dª. MONTSERRAT ALONSO SARDÓN

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997-2015).
Rodríguez Alonso B, Alonso-Sardón M, Rodrigues Almeida HM, Romero-Alegria Á, Pardo-Lledias J, Velasco-Tirado V, López-Bernus A, Pérez Arellano JL, Belhassen-García M.
Eur J Clin Microbiol Infect Dis. 2021 Apr;40(4):849-857. doi: 10.1007/s10096-020-04087-0. Epub 2020 Oct 29. PMID: 33118059

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Int J Infect Dis. 2020 Jan;90:226-233. doi: 10.1016/j.ijid.2019.10.043. Epub 2019 Nov 4. PMID: 3169813

Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997-2015).
Rodríguez-Alonso B, Almeida H, Alonso-Sardón M, Velasco-Tirado V, Robaina Bordón JM, Carranza Rodríguez C, Pérez Arellano JL, Belhassen-García M.
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Epidemiol Infect. 2021 May 14:1-18. doi: 10.1017/S0950268821001151. Epub ahead of print. PMID: 33985607.

Y MANIFIESTO QUE:

☑ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando BEATRIZ RODRÍGUEZ ALONSO expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando BEATRIZ RODRÍGUEZ ALONSO acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 9 de mayo de 2021

Fdo: ALONSO SARDON MONTSERRAT - 10196322P

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IMPRIMIR RESTABLECER

D. /Dª. Cristina Carranza Rodríguez

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

1. Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: What's new. Int J Infect Dis 2020; 90:226-233

2. Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997–2015). Int J Infect Dis. 2020; 96: 165-171

Y MANIFIESTO QUE:

☐ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando _____ expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando Beatriz Rodríguez Alonso acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 10 de mayo de 2021

Fdo: Cristina Carranza Rodríguez

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IMPRIMIR RESTABLECER

D. /Dª. Jose Luis Pérez Arellano

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

Rodríguez Alonso B, Alonso-Sardón M, Rodrigues Almeida HM, Romero-Alegria Á, Pardo-Lledias J, Velasco-Tirado V, López-Bernus A, Pérez Arellano JL, Belhassen-García M. Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997-2015). Eur J Clin Microbiol Infect Dis. 2021 Apr;40(4):849-857.

Rodríguez-Alonso B, Almeida H, Alonso-Sardón M, Velasco-Tirado V, Robaina Bordón JM, Carranza Rodríguez C, Pérez Arellano JL, Belhassen-García M. Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997-2015). Int J Infect Dis. 2020 Jul;96:165-171.

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Y MANIFIESTO QUE:

☑ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando Beatriz Rodriguez Alonso expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando Beatriz Rodriguez Alonso acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 9 de mayo de 2021

PEREZ ARELLANO JOSE LUIS - 15845426J
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Fdo: _____

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IMPRIMIR RESTABLECER

D. /Dª. HUGO MIGUEL RODRIGUES ALMEIDA

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997-2015).
Rodríguez Alonso B, Alonso-Sardón M, Rodrigues Almeida HM, Romero-Alegria Á, Pardo-Lledias J, Velasco-Tirado V, López-Bernus A, Pérez Arellano JL, Belhassen-García M.
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Y MANIFIESTO QUE:

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☑ Como COAUTOR/A del trabajo del doctorando BEATRIZ RODRÍGUEZ ALONSO acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 20 de mayo de 2021

HUGO MIGUEL
Fdo: RODRIGUES ALMEIDA

Firmado digitalmente por HUGO MIGUEL RODRIGUES ALMEIDA
Nombre de reconocimiento (DN): c=PT, o=Cartão de Cidadão, ou=Assinatura Qualificada do Cidadão, ou=Cidadão Português, sn=RODRIGUES ALMEIDA, givenName=HUGO MIGUEL, serialNumber=BI13596735, cn=HUGO MIGUEL RODRIGUES ALMEIDA
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IMPRIMIR RESTABLECER

D. /Dª. José María Robaina Bordón

HAGO CONSTAR:

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Salamanca a 20 de mayo de 2021

Fdo: José María Robaina Bordón

COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO

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IMPRIMIR RESTABLECER

D. /Dª. Moncef Belhassen-García

HAGO CONSTAR:

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☐ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando _____ expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando Beatriz Rodríguez Alonso acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 26 de mayo de 2021

Fdo: BELHASSEN GARCIA MONCEF - 70864634R

Firmado digitalmente por BELHASSEN GARCIA MONCEF - 70864634R
Fecha: 2021.05.25 20:47:18 +02'00'

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IMPRIMIR RESTABLECER

D. /Dª. Virgina Velasco Tirado

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997-2015).
Rodríguez Alonso B, Alonso-Sardón M, Rodrigues Almeida HM, Romero-Alegria Á, Pardo-Lledias J, Velasco-Tirado V, López-Bernus A, Pérez Arellano JL, Belhassen-García M.
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Y MANIFIESTO QUE:

☐ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando _____ expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando Beatriz Rodríguez Alonso acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a de mayo de 2021

Fdo: VELASCO TIRADO VIRGINIA - 53108621B

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IMPRIMIR RESTABLECER

D. /Dª. Amparo López Bernús

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997-2015).
Rodríguez Alonso B, Alonso-Sardón M, Rodrigues Almeida HM, Romero-Alegria Á, Pardo-Lledias J, Velasco-Tirado V, López-Bernus A, Pérez Arellano JL, Belhassen-García M.
Eur J Clin Microbiol Infect Dis. 2021 Apr;40(4):849-857. doi: 10.1007/s10096-020-04087-0. Epub 2020 Oct 29. PMID: 33118059

Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: What's new.
Rodríguez-Alonso B, Almeida H, Alonso-Sardón M, López-Bernus A, Pardo-Lledias J, Velasco-Tirado V, Carranza-Rodríguez C, Pérez-Arellano JL, Belhassen-García M.
Int J Infect Dis. 2020 Jan;90:226-233. doi: 10.1016/j.ijid.2019.10.043. Epub 2019 Nov 4. PMID: 3169813

Epidemiological Assessment of 5,598 Brucellosis Inpatients in Spain (1997-2015).
Rodríguez-Alonso B, Almeida H, Alonso-Sardón M, Velasco-Tirado V, Romero-Alegria Á, Pardo-Lledias J, López-Bernus A, Pérez Arellano JL, Belhassen-García M.
Epidemiol Infect. 2021 May 14:1-18. doi: 10.1017/S0950268821001151. Epub ahead of print. PMID: 33985607.

Y MANIFIESTO QUE:

☑ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando Beatriz Rodríguez Alonso expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando Beatriz Rodríguez Alonso acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 28 de mayo de 2021

Firmado por LOPEZ BERNUS AMPARO - 07986495K el día 28/05/2021 con un certificado emitido

Fdo: AMPARO LOPEZ BERNUS

COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO

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D. /Dª. JAVIER PARDO LLEDIAS

HAGO CONSTAR:

Que soy COAUTOR/A de los siguientes trabajos:

1. Rodriguez Alonso B, Alonso-Sardón M, Rodrigues Almeida H, Romero-Alegria A, Pardo-Lledias J, Velasco-Tirado V, López-Bernús A, Perez Arellano JL, Belhassen-García M. Epidemiological scenario of cat scratch disease among inpatients in the Spanish health system (1997-2015). European Journal of Clinical Microbiology and Infectious Diseases. Aceptado como publicación octubre 2020.
2. B Rodríguez-Alonso, Almeida H, c, Velasco-Tirado V, Alonso Sardon M, Romero-Alegria A, Pardo-Lledias J, López-Bernus A, Pérez Arellano JL, Belhassen Garcia M. Epidemiological Assessment of 5,598 Brucellosis Inpatients in Spain (1997-2015). Epidemiology & Infection. DOI: 10.1017/S0950268821001151

Y MANIFIESTO QUE:

☐ Como COAUTOR/A NO DOCTOR/A del trabajo del doctorando _____ expreso mi RENUNCIA a presentar el artículo como parte de otra Tesis Doctoral.

☑ Como COAUTOR/A del trabajo del doctorando BEATRIZ RODRIGUEZ ALONSO acepto que dicho trabajo sea presentado como parte de su Tesis Doctoral y declaro que el doctorando es el autor principal de la investigación recogida en estos trabajos.

Salamanca a 1 de junio de 2021

Fdo: Javier Pardo Lledias

COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO