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Impact of pneumocystosis on the Spanish health care system, 1997–2020: Profile of HIV and non-HIV immunocompromised patients

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ABSTRACT

Background: *Pneumocystis jirovecii* is an opportunistic fungus recognized for causing *P. jirovecii* pneumonia. The global prevalence is thought to be higher than 400,000 annual cases, although detailed information about epidemiological patterns is scarce.
Methodology: A retrospective longitudinal descriptive study was performed among patients with diagnosis of pneumocystosis according to Classification of Diseases 9th edition, Clinical Modification (code 136.3 for the cases from 1997 to 2015; and 10th edition code B59.0 for cases from 2016 to 2020 in Spanish public hospitals from 1 January 1997–31 December 2020.
Results: A total of 25289 cases were diagnosed. The period incidence rate was 2.36 (95 % CI, 2.33–2.39) cases per 100,000 person-years. Infection was more frequent among men (72.2 %) than among women (27.8 %). Comorbidity was the main characteristic of this cohort. Up to 72.3 % of pneumocystis-infected patients (18293) had HIV coinfection. During the study period, there was a progressive decrease in the number of HIV coinfected cases as the group of patients without HIV infection increased, with the largest group in 2017. The lethality rate in the cohort was 16.7 %. The global cost was €229,234,805 and the average (± SD) cost per patient was €9065 (± 9315).
Conclusions: The epidemiology of pneumocystosis in Spain has changed in the last two decades. We noted in our study the possibility of a reemergence among non-HIV immunocompromised patients as patients with hematological and nonhematological neoplasia and other risk groups. The lethality of pneumocystosis continues to be high, and the underlying diseases are the main variable associated with lethality.

Introduction

Pneumocystis jirovecii (formerly known as *Pneumocystis carinii f. sp. hominis*) [1] is a ubiquitous ascomycetous fungus and opportunistic pathogen that can cause severe pneumonia (PCP) in immunocompromised humans [2]. Profound immunosuppression, especially T-cell depletion and dysfunction, is the primary risk factor for PCP. Therefore, risk factors for PCP include human

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immunodeficiency virus (HIV) and a low CD4 count, transplant recipients, hematopoietic cell patients, cancer (particularly hematologic malignancies), certain inflammatory or rheumatologic conditions, and patients with corticosteroid and immunomodulating agents (chemotherapeutic agents and other immunosuppressive medications). Among children, malnourished children and those with inherited immunodeficiency syndromes and cancer are particularly susceptible [3].

The primary mode of transmission of *Pneumocystis jirovecii* is *via* the airborne route. Serologic studies show that primary infection occurs early in life, with 75 % of humans infected by the age of four years [4].

Traditionally, patients with PCP typically present with respiratory failure associated with fever, rapidly progressive dyspnea and dry cough [2], although it should be noted that clinical signs of PCP are nonspecific, and definitive diagnosis requires direct detection of the organism in lower respiratory secretions or tissue. Non-HIV patients with PCP have more symptoms and signs, worse radiology and higher mortality with treatment [5,6].

Trimethoprim sulfamethoxazole (TMP-SMX) remains the first-line prophylaxis and treatment, although intolerance or allergy, and rarely treatment failure, may necessitate alternate therapeutics, such as dapsone, pentamidine, atovaquone, clindamycin, primaquine and, most recently, echinocandins as adjunctive therapy. However, when diagnosed rapidly and treated, survival rates are high. In patients infected by HIV, adjunctive corticosteroid use in treatment has shown a mortality benefit [7].

The incidence increased dramatically with the emergence of the HIV epidemic in the 1980 s, and PCP continues to be the main AIDS-defining diagnosis in Spain, with 27 % of newly diagnosed patients (https://www.sanidad.gob.es). Moreover, the numbers of other individuals with cellular immunodeficiency, such as cancer patients receiving chemotherapy, bone marrow and solid organ transplant recipients, and patients treated with steroids or other immunosuppressive medications [8], continue to grow [9], and this could be the cause of the reemergence of this fungal infection[10]. Thus, the global incidence estimated is thought to be higher than 400,000 annual cases worldwide [11].

According to these facts, the clinical and epidemiological characteristics of PCP may have changed. Thus, the aim of this study was to evaluate the epidemiological status of pneumocystis among patients in Spain from 1997 to 2020.

Materials and methods

Study design and population

We performed a *retrospective longitudinal descriptive study* of hospitalized patients diagnosed with PCP in public hospitals of the Spanish National Health System (NHS) during a 24-year study period from January 1, 1997, to December 31, 2020. **Inclusion criteria:** Patients with a principal and/or secondary diagnosis of PCP according to the *International Classification of Disease* diagnosis codes: *code 136.3*, 9th edition (ICD-9-CM), reported cases from 1997 to 2015; and *code B59.0*, 10th edition (ICD-10), reported cases from 2016 to 2020. **Exclusion criteria:** Patients with missing data were excluded from the study.

Data collection

This study analyzes the data provided by Hospital Discharge Records (HDRs). HDRs include all hospital discharges produced in the network of general hospitals in the NHS. Data were obtained from the Minimum Basic Data Set (CMBD in Spanish). CMBD is the main database for knowledge of morbidity attended and the care process of patients treated in hospitals. It provides usual demographic data (age, sex, and place of residence), clinical variables (diagnoses and procedures) and variables related to the episode of hospitalization, such as a circumstance of admission (urgent or programmed), patient discharge (discharge to your address, transfer to another hospital or death), and average stay. Diagnoses and procedures collected are coded using the ICD-9-CM and ICD-10. *Principal diagnosis* was defined as the condition after study that occasioned admission to the hospital, according to the ICD-9-CM or ICD-10 Official Guidelines for Coding and Reporting. *Secondary diagnoses* are *"other diagnoses"* or conditions that coexist at the time of admission or develop subsequently and that affect patient care during the current episode. These diagnoses allowed us to classify and perform a statistical analysis of the comorbidities associated with PCP in homogeneous groups.

Data analysis

The incidence rate was calculated by dividing the number of new cases of PCP (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 figure 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/). [Average estimated population of Spain, 1997–2020: 44,666,698 inhabitants; 21,966,759 men and 22,699,938 women]. 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 autonomous community and year to assess temporal and geographical patterns. The 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 sick patients with a specific disease (denominator) (x100).

Categorical variables were expressed as absolute values (n) and percentages (%), and continuous variables were analyzed with the mean and standard deviation (SD) if normally distributed and with the median and interquartile range (IQR) (Q_3-Q_1) if nonnormally distributed. A chi-square (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 OR. Continuous variables were compared with Student's t test or the Mann–Whitney test for two groups, depending on their normal or nonnormal distribution. ANOVA allowed us to analyze the influence of independent nominal variables on a continuous dependent variable. Additionally, we applied the corresponding logistic regression model for multivariate analysis of categorical variables. A *p value* of < 0.05 was considered significant. Analysis was conducted in SPSS 26 (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, https://www.sanidad.gob.es) that custody 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 was

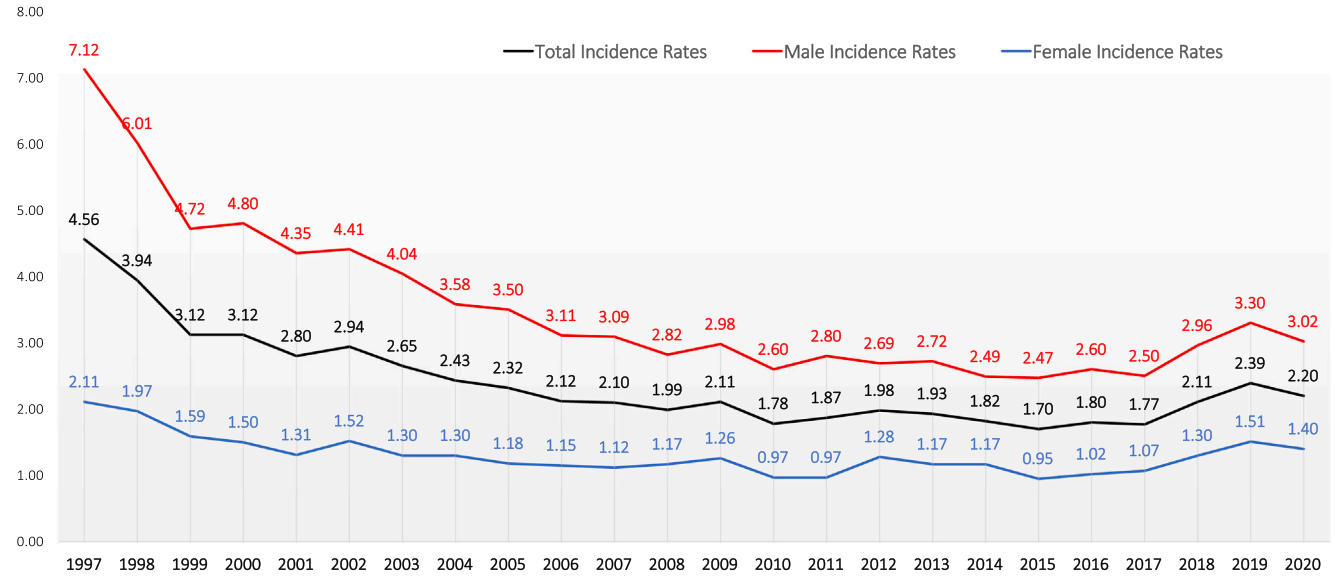

Fig. 1. Temporal evolution of annual incidence rates (IR) for Pneumocystosis in Spain, 1997–2020 *(cases per 100,000 person-years)*: male *versus* female.

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

From 1997–2020, a total of 25289 patients were admitted in Spain with infection by *Pneumocystis jirovecii*. The period incidence rate was 2.36 (95 % CI, 2.33–2.39) cases per 100,000 person-years. A progressive decrease in the incidence rate was observed throughout the study period, from 1997 (IR, 4.56) to 2015 (IR, 1.70). In 2019 (IR, 2.39) and 2020 (IR, 2.20), incidence rates increased again (see Fig. 1).

The highest incidence rates corresponded to the northern regions of the Iberian Peninsula: País Vasco, 2.91 (95 % CI, 2.76–3.06) cases per 100,000 person-years and Principado de Asturias, 2.89 (95 % CI, 2.68–3.10) cases per 100,000 person-years. On the other hand, the lowest incidence rate was in the central region, Castilla-La Mancha, 1.06 (95 % CI, 0.97–1.16) (Fig. 2).

Table 1 summarizes the main clinical features of the PCP cases throughout the study period. Infection was more frequent among men (72.2 %) than among women (27.8 %). The mean (± SD) age was 45 years (± 17.1). The average hospital stay was 22 days (± 21.5). Only 41 (0.2 %) patients had a single diagnosis of PCP infection; thus, multiple comorbidities (88.6 % were diagnosed with 3 or more comorbidities) were the main characteristic of this cohort analyzed. Table 2 includes a list of the most frequent diseases associated with PCP: 18293 pneumocystis-infected patients (72.3 %) had HIV coinfection. Other associated immunosuppressive diseases or diagnoses, such as nonlymphoid and hematopoietic neoplasms (2433 cases; 9.6 %), lymphoid and hematopoietic malignant neoplasms (2330 cases; 9.2 %) and transplanted organ and tissue (618 cases; 2.4 %), were highlighted.

Table 3 is a synopsis of the statistical analysis we conducted according to the main groups of disorders associated with PCP, stratified into HIV- and non-HIV-infected patients. Among the PCP cases with HIV coinfection (18293), a total of 1187 cases (6.5 %) were also diagnosed with malignant neoplasms, 938 (5.1 %) nonlymphoid and hematopoietic neoplasms *versus* 249 (1.4 %) lymphoid and hematopoietic malignant neoplasms, *i.e.*, The occurrence of nonlymphoid and hematopoietic neoplasms was five times greater (OR=5.2; 95 % CI, 4.5–6.1, $p < 0.001$). In contrast, the occurrence of lymphoid and hematopoietic malignant neoplasms is higher among patients without HIV coinfection (29.7 % *versus* 21.4 %). A total of 618 patients received an organ and tissue transplant, most of whom (606 subjects included in Table 3) did not have HIV coinfection, and only 12 patients were diagnosed with HIV coinfection. The category "autoimmune disorders" includes rheumatoid arthritis, polyarteritis nodosa and other necrotizing vasculopathies, systemic lupus erythematosus, sarcoidosis, systemic sclerosis (scleroderma), pulmonary fibrosis and interstitial pulmonary diseases, Crohn's disease and ulcerative colitis, autoimmune hemolytic anemia and multiple sclerosis; in total, 1336 patients, 294 with HIV coinfection and 1042 without HIV coinfection. Statistically significant differences were observed between groups for all variables included in the analysis ($p < 0.001$), except for seasonal presentation of cases ($p > 0.05$).

We found differences in the incidence of new cases of pneumocystis during the period of study, according to their predisposing diseases. Thus, whereas the incidence of PCP in HIV patients decreased throughout the study period (1793 cases/year in 1997 to nadir 374 cases/year in 2020), in the rest of the risk groups, cases increased discretely throughout the study period, except for malignant neoplasms among patients without HIV coinfection, which increased exponentially (Fig. 3). The longest average hospital stay was obtained in the lymphoid and hematopoietic malignant neoplasms and autoimmune disorders and HIV coinfection groups (29 and 27 days, respectively), and consequently, the average cost per patient was €11,345 and €12,092, respectively. Table 3 shows statistically significant differences between the mean cost and comorbidity diagnostic groups. The global cost of this cohort of hospital-admitted patients with a diagnosis of PCP in Spain (from 1997 to 2020) was €229,234,807; the average (± SD) cost per patient was €9065 (± 9315) (Table 1). The average cost per year increased progressively from 1997 (4634 €) until 2013 (12,800 €), when the highest average cost per year was recorded. Between 2013 and 2020 (12,252 €), the average cost has fluctuated slightly up-down annually. Fig. 4 shows the increase in spending in addition to the difference in cost between the HIV positive and HIV negative groups.

The overall inpatient lethality rate of the cohort was 16.7 % (4226 deaths/25289 total PCP). Therefore, we did not detect differences between males and females (16.6 % among men *versus* 16.9 % among women; $p = 0.546$). Survival was higher in younger patients than in older patients (89.2 %, 15–44; 84 %, 0–14; 80.2 %, 45–65; and 64.5

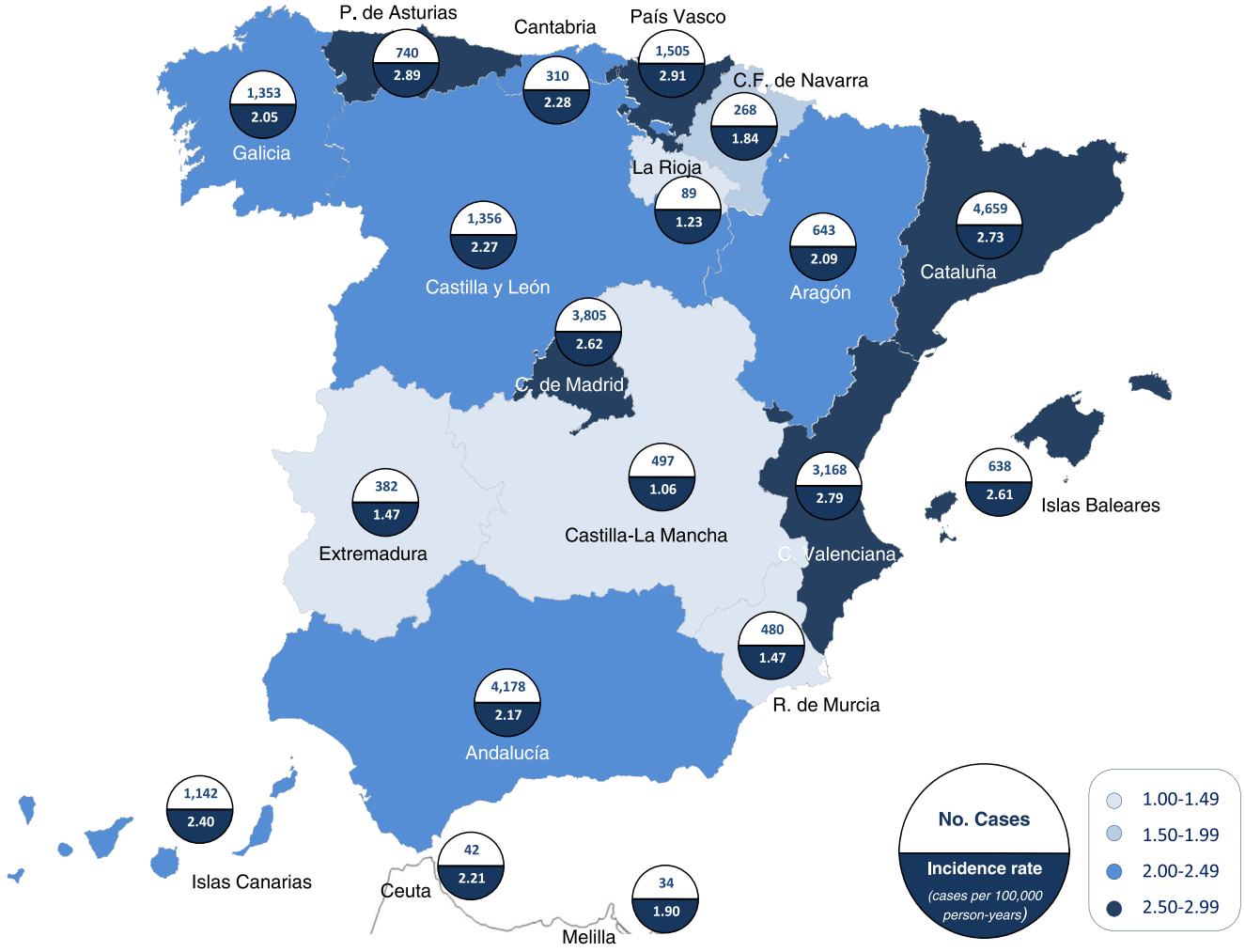

Fig. 2. Number of cases and of Incidence rates of Pneumocystosis by regions, Spain (1997–2020).

%, > 65; p < 0.001). The age Group 15–44 years had the lowest case fatality rate (10.8 %); 45–64 years, 19.8 %; and those over 65 years had the highest case fatality rate, 35.5 %. The case fatality rate in the pediatric population was 16 % (p < 0.001). Fig. 5 illustrates the annual case fatality rates. A gradual increase in the mortality of the cohort was observed throughout the study period (from 12.3 % in 1997 to 21.9 % in 2020). We also found significant differences in mortality according to the type and number of comorbidities associated with PCP. Overall, the case fatality rate was higher in non-HIV patients than in HIV patients (26.1 % *versus* 13.1 %); if patients had other comorbidities, the case fatality rate increased; thus, the highest case fatality rate among patients with HIV coinfection was in the lymphoid and hematopoietic malignant neoplasm group (31.7 %), while in the non-HIV coinfection group, the highest case fatality rate was in patients with nonlymphoid and hematopoietic neoplasms (33.3 %) and autoimmune diseases (31.2 %), as shown in Table 3. Case fatality rates were estimated for other associated underlying disorders, such as essential hypertension (25.8 %), diabetes mellitus (24.4 %), chronic obstructive pulmonary disease, emphysema and unspecified chronic bronchitis (18.5 %), and tuberculosis (18.9 %). The logistic regression model predicts the probability of *exitus letalis* with age and presence of comorbidities; thus, the probability of death increases in patients over 65 years of age who present HIV plus hematologic (50 %, mainly due to non-Hodgkin's disease, myeloid leukemia and multiple myeloma) or nonhematologic (58 %, in particular by malignant neoplasm of lung and prostate) neoplasms associated with PCP [Exp(B)= 2.18; 95 % CI, 1.63–2.91; p < 0.001].

Discussion

In this paper, we retrospectively studied the epidemiology of infection by *Pneumocystis jirovecii* (PJ) in Spain from 1997 to 2020 using data from inpatients recorded by the national public health system. This method has been previously used by our group to assess changes in the epidemiology of other fungal diseases in Spain [12].

Thus, we found a mean incidence rate during the study period of 2,36 cases/100,000 person-years, below the counts previously referred by Calderon JE et al., who using similar epidemiological methods found during the period 1998–2004 an annual average of 3,4 cases/100,000 person [13]. These data are in the low range of the figures shown by Bongomin et al., who used different epidemiological methods to estimate a global incidence of approximately 5.79 (± SD 10.96) cases per 100,000 [14], reporting the highest and lowest incidence in Nigeria (48.3) and Bangladesh (0.04 cases per 100,000), respectively. Seventy-seven percent of the cases were reported in Africa, followed by America (10 %), Europe (7 %) and Asia (6 %) [14]. Differences in the estimations across countries can be associated with differences in the HIV prevalence in the different countries and the accessibility to highly active antiretroviral therapy (HAART), with rates ranging from 2 % to 60 % in AIDS populations [14].

Table 1
Overall data of Pneumocystis cases in Spain during 1997–2020.

Qualitative/Categorical variables	N = 25289 cases (100 %) n (%)
Gender	
Male	18249 (72.2)
Female	7036 (27.8)
Other	4 (0.0)
Age ranges (years)	
0–14 years	343 (1.4)
15–44 years	14355 (56.8)
45–64 years	7213 (28.5)
≥65 years	3378 (13.4)
Diagnosis causing hospitalization (ICD-9: 136.3; ICD-10: B59)	
Principal diagnosis	6024 (23.8)
Secondary diagnosis	19265 (76.2)
No. of associated comorbidities or diagnoses	
Pneumocystosis single diagnosis	41 (0.2)
1 associated comorbidity/diagnosis	893 (3.5)
2 associated comorbidities or diagnoses	1946 (7.7)
3 or more associated comorbidities or diagnoses	22409 (88.6)
Type of hospital admission	
Urgent/Unscheduled	22245 (88.0)
Programmed	2953 (11.7)
Unknown	91 (0.3)
Circumstance to hospital discharge	
Home	19372 (76.6)
Transferred to another hospital	663 (2.6)
Transferred to social-health center	180 (0.7)
Voluntary discharge	580 (2.3)
Others/unknown	268 (1.1)
Lethality	4226 (16.7)

Quantitative variables	**Mean (±SD)**	**Median (IQR)**	**Range**
Age (years)	45 (±15.2)	42 (53–35)	(0, 103)
Hospital stays (days)	22 (±21.5)	17 (27–10)	(0, 861)
Cost (€)	9064.60 (±9315.50)	6572.05 (9426.87–4663.55)	(0.00, 127571.17)

We showed in our paper a progressive decrease in the incidence rate throughout the study from 1997 to 2017. During this period, we found that the progressive decrease in PCP was only attributable to the drop in the number of patients coinfected with HIV. This decrease in PCP in HIV has been pointed out by other authors. In a study performed in the HAART era [15], a drop in the incidence rate of PCP between patients with HIV infection was found, from 13,3 cases per 1000 HIV negative infected patients to 3,3 per 1000 in 2015 [15]. After 1996, with the addition of protease inhibitors and non-nucleoside inhibitors of transcriptase inverse to regimens with inhibitors of transcriptase inverse analogs of nucleotide, HAART radically changed the natural history of infection caused by HIV with a suppression of viral load and improved immunosuppression, especially in developing countries. Moreover, the addition of primary and secondary prophylaxis for PCP to HAART therapy contributed to an effective decrease in this infection. Other current global strategies for the control of HIV infection, such as 95–95–95 UNAIDS targets (95 % of people with HIV diagnosed, 95 % on antiretroviral treatment, 95 % with viral load suppression) and pre-exposure prophylaxis for HIV (PrEP), could contribute to the control of HIV infection and consequently to the decrease in PCP in this population in Spain and worldwide [16].

However, as we found in our work, coinfection by HIV continues to be the most frequent disease involved in PCP in Spain. This fact supports that we still need extra efforts to improve the percentage of early diagnoses of HIV before immunosuppression develops (https://www.ecdc.europa.eu/en/news-events/ecdc-and-who-call-improved-hiv-testing-europe).

On the other hand, from 2018 onward, we detected a possible reemergence of cases of PCP associated with patients without HIV infection. As we presented in our work, from 2018, the numbers of PCP cases associated with other diseases or immunosuppression factors were higher than those associated with HIV. These data have been noted by other authors [17].

The increase in the incidence of PCP in recent years could be attributed to the introduction in assistance microbiology laboratories of more sensitive diagnostic methods as polymerase chain reaction or detection (1,3)-B-D-Glucan, which improve diagnostic yield in different samples [18]. However, considering that there are important differences in the increase of incidence between the different groups of patients, we think that the improvement of diagnosis methods can´t be the main raison of this reemergence.

Among patients without HIV infection, there are several disorders associated with PCP [19], although lymphoid and other hematological neoplasms and nonhematologic neoplasms are the most frequently found. Thus, the cases of PCP in this group of patients tripled in the period of study. Leukemia lymphoblastic and other lymphoproliferative diseases are frequently complicated with PJ infection, reaching up to 16 % of patients with this disease without prophylaxis [20]. This fact could be due to the immunological dysfunction of lymphocytes by their own disease or by the use of depleting drugs. The guideline recommends chemoprophylaxis of PCP mainly in leukemia lymphoblastic acute, from induction to end of maintenance, and in patients with other hematologic neoplasia mainly, whereas they have treatment with drugs such as steroids, fludarabine, cyclophosphamide and rituximab, although prophylaxis is optional in other hematological neoplasms [21].

Other interesting data in our work were the high number of PCP cases associated with neoplastic solid organs, with figures higher than those found in hematological neoplasia in recent years. A consensus document noted that the main groups at risk for PCP were patients treated with steroids and brain tumors treated with temozolomide and radiotherapy [22].

Although the overall incidence rate of neoplasia has decreased in the last two decades in Spain, the increase in survival (SEOM, https://www.seom.org) and population aging could contribute to this increase in PCP. Moreover, the addition of immunotherapy drugs, such as small molecule kinase inhibitors[23] and others, to

Table 2
Underlying diseases associated to pneumocystis cases in Spain during 1997–2020.

Immunosuppressive conditions	N = 25289 (100 %) n (%)
HIV-infection	**18293 (72.3)**
Lymphoid and haematopoietic malignant neoplasms	**2330 (9.2)**
Hodgkin's disease	220 (0.9)
Non-Hodgkin's disease	839 (3.3)
Multiple myeloma	279 (1.1)
Lymphoid leukemia	509 (2.0)
Myeloid leukemia	303 (1.2)
Monocytic leukemia	20 (0.1)
Other leukemias	23 (0.1)
Non-lymphoid and haematopoietic neoplasms	**2433 (9.6)**
Malignant neoplasm of bronchus and lung	484 (1.9)
Malignant neoplasm of breast/Carcinoma *in situ* of breast	167 (0.7)
Gliomas and other malignant neoplasm of brain	123 (0.5)
Malignant neoplasm of prostate	81 (0.3)
Transplanted organ and tissue	**618 (2.4)**
Kidney transplant	226 (0.9)
Bone marrow transplant	59 (0.2)
Lung transplant	13 (0.1)
Systemic autoimmune and inflammatory diseases	151 (0.6)
Rheumatoid arthritis	141 (0.6)
Polyarteritis nodosa and other necrotizing vasculopathies	95 (0.4)
Systemic lupus erythematosus	44 (0.2)
Sarcoidosis	24 (0.1)
Systemic sclerosis (scleroderma)	
Other immunomediated diseases	712 (2.8)
Pulmonary fibrosis & other Interstitial pulmonary diseases	161 (0.6)
Crohn's disease & ulcerative colitis	95 (0.4)
Autoimmune hemolytic anemia	9 (0.0)
Multiple sclerosis	
Other associated underlying disorders	1939 (7.7)
Essential hypertension	1339 (5.3)
Diabetes mellitus type 1 or 2	2193 (8.7)
Chronic obstructive pulmonary disease, emphysema & unspecified chronic bronchitis	1238 (4.9)
Tuberculosis	

classical chemotherapy regimens could be involved in the rise in PCP cases after 2017.

During the study period, the figures of PCP among patients with transplant organs and tissues also tripled. These data are not surprising because the number of transplant organ and tissue procedures in Spain in these last three decades has also tripled, and Spain is the country with the highest number of these procedures, reaching 115 per million inhabitants in 2019. Moreover, the mean age and survival have continued to increase in the transplant population (ONT, https://www.ont.es). We think that good adherence to prophylaxis guidelines has been very important for the control of this severe infection in our country.

We also studied PCP in other groups of immunosuppressed patients, such as patients with immunological diseases. In a cohort of PCP patients in Norway, 15 % had an immunomediated disorder [17]. Recently, Ghembanza et al., in a nonsystematic review, established that the overall incidence of PCP among patients with autoimmune and inflammatory disease is usually low. However, there are factors involved in the higher risk for PCP in this population, such as a higher dose of corticoids, the association of cyclophosphamide or the underlying disease, such as granulomatosis with polyangiitis and polyarteritis nodosa [24]. In our work, we found that patients had rheumatoid arthritis, polyarteritis nodosa and other necrotizing vasculopathies. Other groups of immune diseases, such as interstitial lung disease, inflammatory bowel disease (Crohn's disease and ulcerative colitis), autoimmune hemolytic anemia and multiple sclerosis, were represented.

Another objective of our study was to assess whether the rate of PCP was related to different climatic areas or seasons. In our study, we did not observe variations in the incidence of cases in relation to them. These results contrast with previous studies performed on *Pneumocystis jirovecii* [25], in which they found an association between low temperatures and season with fungal incidence rate.

We also evaluated the burden in Spain. The burden of PCP has been evaluated in the LIFE programme [14]. The highest burdens have been estimated in Africa (Nigeria, Kenya and Tanzania). On the other hand, the lowest PCP burdens have been reported in Denmark, Hungary, Qatar and Israel [14]. In Spain, PCP is very high and steadily increasing over time. In this manner, the global cost of this cohort of hospital-admitted patients with a diagnosis of PCP was €229,234,807 and the average (± SD) cost per patient was €9065 (± 9315). Other infectious conditions requiring hospitalization in Spain include Q fever, with a total cost of €154,232,779 (€36,600 mean cost per patient)[26] and strongyloidiasis with a total cost of €8681,062 and mean cost per patient of €17,122 [27,28]; the mean hospital admission cost was €5676, €104.2 million annually for all patients attended for a pneumococcal disease in Spanish hospitals [28].

Finally, the overall lethality rate of the cohort was above 16 %; no differences between males and females were observed. This lethality rate is similar to that described in the literature (10–30 %) and can be even higher if the diagnosis is delayed [29]. Mortality is variable depending on the underlying disease, being in HIV patients a third part of found it in the group with lymphoid and hematopoietic malignant neoplasms. The lower lethality of HIV patients with PCP compared with non-HIV patients with PCP may be explained, at least partially, by one or both of the following factors: i) patients with HIV infected with PCP tend to be younger and have a lower rate of comorbid conditions; ii) there is increased awareness of PCP and its presentation in patients with HIV, which may lead to earlier diagnosis and treatment initiation [30]. In a recent meta-analysis, risk factors for mortality from non-HIV-related PCP were age, concomitant with other pulmonary diseases at diagnosis of PCP, solid tumors, CMV coinfection, LDH, lymphocyte count, invasive ventilation during hospitalization, and pneumothorax [31]. In our work, we also found that underlying disease could be involved in fatal outcomes. We aimed to relieve the lack of official epidemiological data, but we also hope to contribute to the development of hypotheses that will be worthy of exploration in further investigations.

Limitations

The CMBD provides hospital data for more than 99 % of the Spanish population. It is the most extensive clinical-administrative database available in our National Health System. Its sample size is enormous, and we can affirm that its analysis would fall within BIG-DATA research. Selection errors do not represent a significant proportion. Classification errors do occur more frequently, but they do not affect the overall morbidity recorded or its measurement. Therefore, the CMBD provides valid information for epidemiological studies, although the data are limited exclusively to the set of hospitalized patients. In this regard, we are aware that there is always a small percentage of lost information, so our data should be considered a very rough approximation of the epidemiological impact of PCP in Spain. The main limitations of our study are as follows. i) The possibility of bias in the collection of CMBD data is minimal compared to other health information systems, but the information included is not modifiable so any coding error is irreversible; ii) the ICD-9 classification, used until 2015, includes fewer variables than those registered in the ICD-10 classification, established later and which provides more information; iii) the inclusion of only patients hospitalized in public hospitals implies the loss of information of those who suffered the disease on an outpatient basis or requested medical assistance in primary care or in private hospitals, thus, hospital records underestimate the real burden of PCP in Spain; iv)

Table 3
Association analysis of the main pathological comorbidity groups associated with Pneumocystosis in Spain during 1997–2020: HIV *versus* non-HIV coinfected[a].

VARIABLES	**HIV coinfected Only HIV** **N_1= 717 (3.9 %) n (%)**	**L&H malignant neoplasms N_2= 249 (1.4 %) n (%)**	**Non-L&H neoplasms N_3= 938 (5.1 %) n (%)**	**Autoimmune disorders N_4= 294 (1.6 %) n (%)**	**p-value**	**Non-HIV coinfected Transplanted organ & tissue N_5= 606 (8.7 %) n (%)**	**L&H malignant neoplasms N_6= 2081 (29.7 %) n (%)**	**Non-L&H neoplasms N_7= 1495 (21.4 %) n (%)**	**Autoimmune disorders N_8= 1042 (14.9 %) n (%)**	**p-value**
Gender										
Male	541 (75.5)	213 (85.5)	776 (82.7)	224 (76.2)	< 0.001 * *	405 (66.8)	1309 (62.9)	940 (62.9)	552 (53.0)	< 0.001 * *
Female	176 (24.5)	36 (14.5)	162 (17.3)	70 (23.8)		201 (33.2)	779 (37.1)	555 (37.1)	490 (47.0)	
Age ranges (years)										
0–14 years	4 (0.6)	-	-	-	< 0.001 * *	32 (5.3)	116 (5.6)	33 (2.2)	14 (1.3)	< 0.001 * *
15–44 years	591 (82.4)	156 (62.7)	568 (60.6)	164 (55.8)		138 (22.8)	380 (18.3)	140 (9.4)	142 (13.6)	
45–64 years	114 (15.9)	85 (34.1)	339 (36.1)	124 (42.2)		271 (44.7)	676 (32.5)	649 (43.4)	313 (30.0)	
≥ 65 years	8 (1.1)	8 (3.2)	31 (3.3)	6 (2.0)		165 (27.2)	909 (43.7)	673 (45.0)	573 (55.1)	
Mean (± SD)	37 (± 8.9)	43 (± 9.7)	42 (± 10.5)	44 (± 10.7)	< 0.001 * *	52 (± 18.1)	56 (± 20.0)	61 (± 15.1)	62 (± 17.2)	< 0.001 * *[a]
Pneumocystosis codes (ICD-9: 136.3; ICD-10: B59)										
Principal diagnosis	176 (24.5)	25 (10.0)	100 (10.7)	23 (7.8)	< 0.001 * *	384 (63.4)	984 (47.3)	704 (47.1)	497 (47.7)	< 0.001 * *
Secondary diagnosis	541 (75.5)	224 (90.0)	838 (89.3)	271 (92.2)		222 (36.6)	1097 (52.7)	791 (52.9)	545 (52.3)	
Type of hospital admission										
Urgent/Unscheduled	620 (86.5)	212 (85.1)	802 (85.5)	261 (88.8)	< 0.001 * *	457 (75.4)	1607 (77.2)	1306 (87.4)	884 (84.8)	< 0.001 * *
Programmed	95 (13.2)	36 (14.5)	129 (13.8)	32 (10.9)		148 (24.4)	470 (22.6)	1862 (12.4)	155 (14.9)	
Unknown	2 (0.3)	1 (0.4)	7 (0.7)	1 (0.3)		1 (0.2)	4 (0.2)	3 (0.2)	3 (0.3)	
Circumstance to hospital discharge										
Home	642(89.5)	155 (62.2)	686 (73.1)	201 (68.4)	< 0.001 * *	448 (73.9)	1477 (71.0)	890 (59.5)	652 (62.6)	< 0.001 * *
Transferred to another hospital	9 (1.3)	6 (2.4)	28 (3.0)	13 (4.4)		17 (2.8)	56 (2.7)	44 (2.9)	36 (3.5)	
Transferred to social-health center	-	-	9 (1.0)	1 (0.3)		2 (0.3)	20 (1.0)	32 (2.1)	15 (1.4)	
Voluntary discharge	26 (3.6)	5 (2.0)	14 (1.5)	6 (2.0)		4 (0.7)	4 (0.2)	3 (0.2)	4 (0.4)	
Others/unknown	7 (1.0)	4 (1.6)	5 (0.5)	-		7 (1.2)	23 (1.1)	28 (1.9)	10 (1.0)	
Seasons										
Spring	199 (27.8)	56 (22.5)	244 (26.0)	90 (30.6)	> 0.050 * *	131 (21.6)	501 (24.1)	408 (27.3)	262 (25.1)	> 0.050 * *
Summer	169 (23.6)	58 (23.3)	247 (26.3)	67 (22.8)		174 (28.7)	500 (24.0)	381 (25.5)	260 (25.0)	
Autumn	155 (21.6)	69 (27.7)	215 (22.9)	65 (22.1)		138 (22.8)	510 (24.5)	354 (23.7)	254 (24.4)	
Winter	194 (27.1)	66 (26.5)	232 (24.7)	72 (24.5)		163 (26.9)	570 (27.4)	352 (23.5)	266 (25.5)	
Hospital stays (days), mean (± SD)	13 (± 8.3)	29 (± 23.8)	25 (± 21.5)	27 (± 54.2)	< 0.001 * *	25 (± 19.0)	26 (± 22.7)	21 (± 17.6)	26 (± 29.3)	< 0.001 * *[a]
Cost (€), mean (± SD)	4694.54 (± 2711.50)	11,345.35 (± 10,430.37)	10,518.19 (± 9406.70)	12,091.58 (± 10,639.93)	< 0.001 * *	10,218.00 (± 11,998.38)	12,015.83 (± 13,004.70)	7807.19 (± 8830.05)	10,471.99 (± 13,961.09)	< 0.001 * *[a]
Lethality rate	33 (4.6)	79 (31.7)	196 (20.9)	73 (24.8)	< 0.001 * *	128 (21.1)	501 (24.1)	498 (33.3)	325 (31.2)	< 0.001 * *

[a] Table does not include the total number of cases, it only displays the results obtained in the most relevant homogeneous comorbidity groups. **Chi-square (χ^2) test. ***ANOVA.

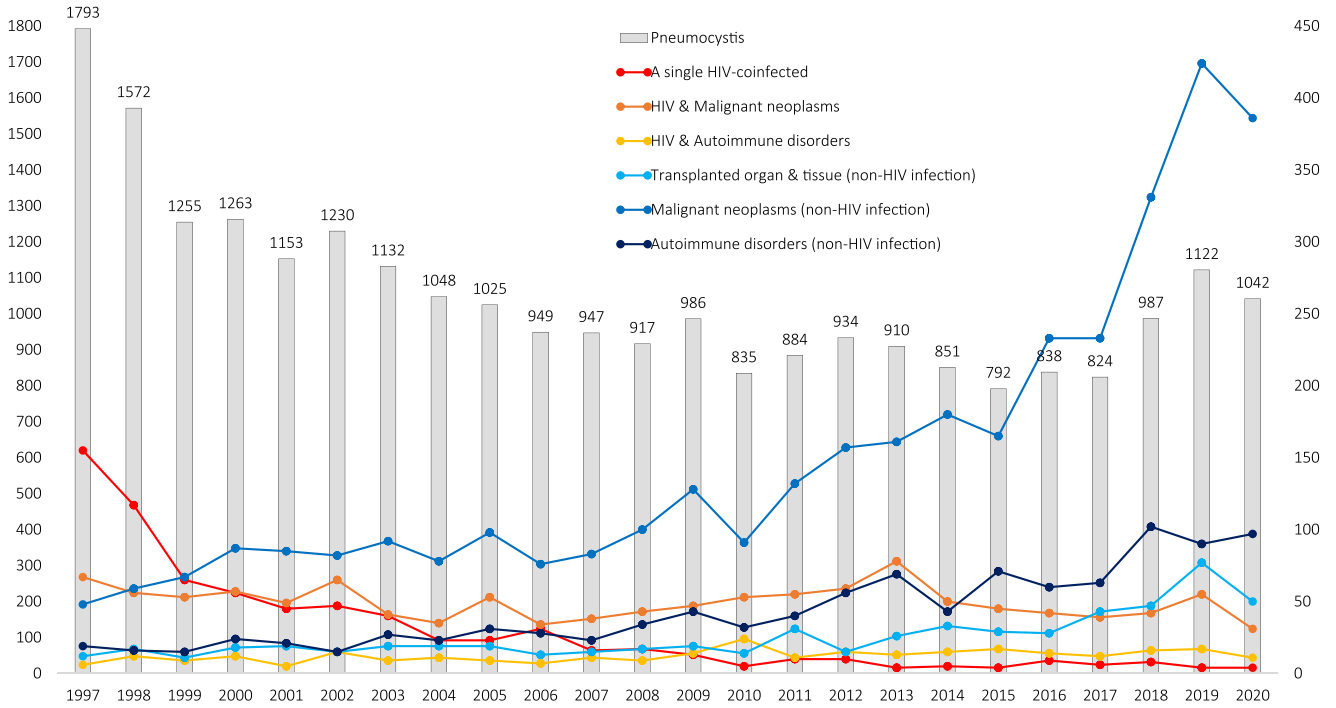

Fig. 3. Temporal distribution of comorbidity associated with Pneumocystosis in Spain, 1997–2020.

due the clinic of PCP is nonspecific and that the definitive diagnosis requires the direct detection of the organism in the secretions of the lower respiratory tract, in some cases it makes the correct diagnosis difficult; v) not being able to access the medical history prevented us from confirming the diagnosis and identifying the possible associated factors involved, which impairs the quality of the data; vi) given that only hospitalization costs have been included in the economic estimate, it is likely an underestimation since costs derived, for example, from sick leave have not been taken into account. In any case, our findings reported here have potential implications for public policy. Therefore, as discussed above, these data underestimate the real incidence and the actual costs of PCP in Spain during the period of this study.

In conclusion, the epidemiology of PCP in Spain has changed in the last two decades. A decrease in the number of PCP cases is only attributable to the drop in cases of patients coinfected with HIV, although currently HIV continues to be the main cause of this infection. We noted in our study the possibility of a reemergence among non-HIV immunocompromised patients as patients with hematological and nonhematological neoplasia and other risk

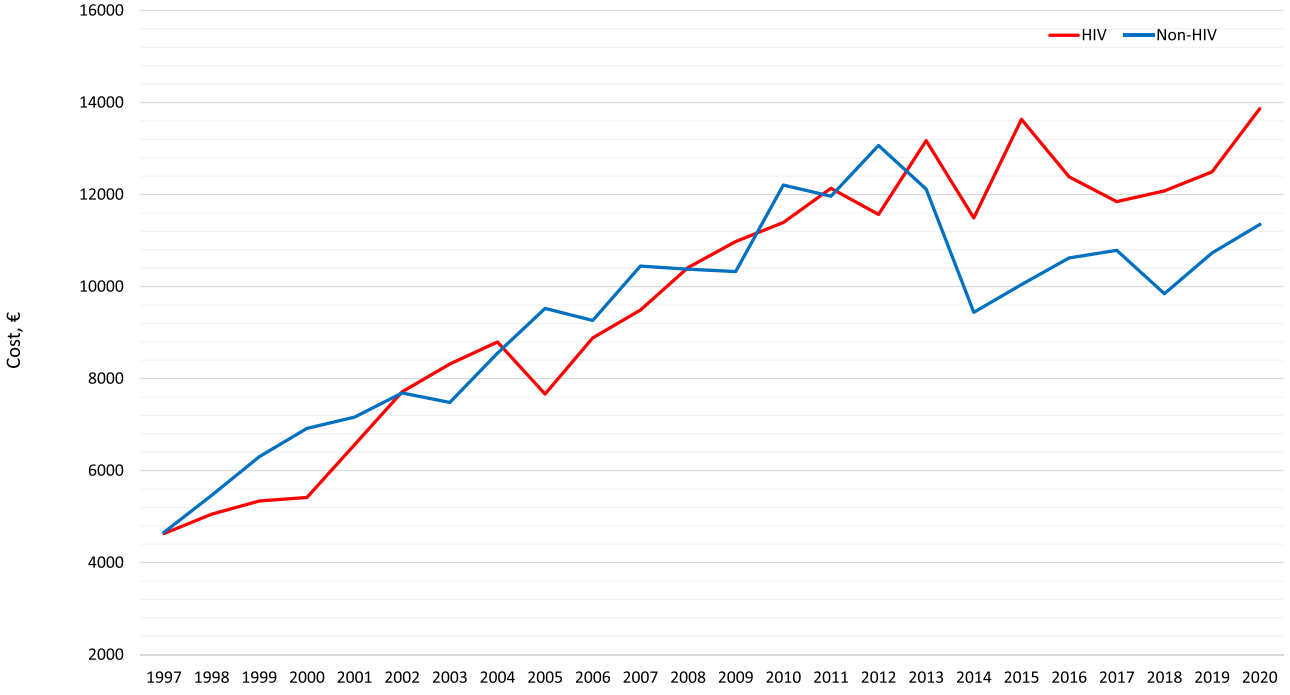

Fig. 4. Pneumocystosis in Spain: Mean cost per year of discharge in HIV *versus* non-HIV patients.

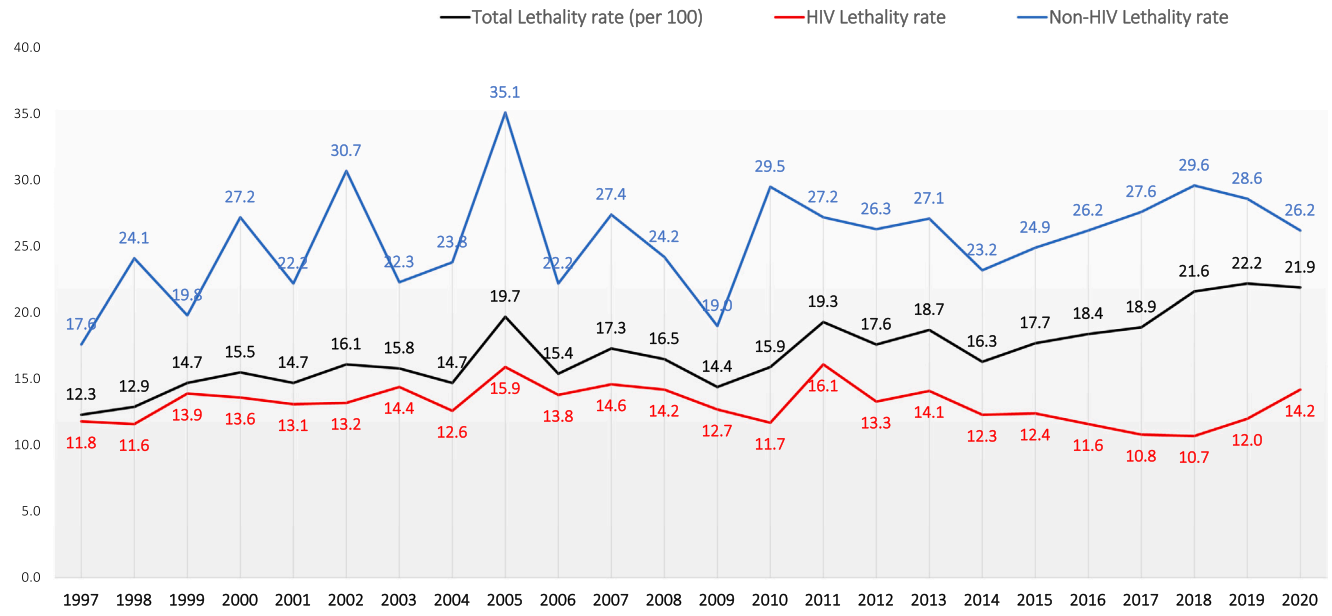

Fig. 5. Temporal evolution of annual lethality rates (LR) for Pneumocystosis in Spain, 1997–2020 *(per 100)*: HIV *versus* non-HIV.

groups. The lethality of PCP continues to be high, and the underlying diseases are the main variable associated with lethality. These data make it necessary to point out the importance of raising awareness about PCP as a possible cause of respiratory infection in this population and necessitate clear guidelines for the management and prevention of this serious infection.

Ethical approval

The procedures carried out in this study are consistent with the principles set forth in the Declaration of Helsinki revised in 2013. This study was also approved by the Bioethics Committee of CAUSA (Complejo Asistencial Universitario de Salamanca). Data obtained from CMBD are confidential even to the researchers who developed this study. Since this was an epidemiological study, informed consent was not obtained.

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None declared.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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