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Global burden of chronic pulmonary aspergillosis complicating sarcoidosis

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ABSTRACT: Chronic pulmonary aspergillosis (CPA) may complicate pulmonary sarcoidosis. We re-estimated the global burden of sarcoidosis and the burden of CPA complicating sarcoidosis.

We searched the literature and reference lists of retrieved papers to identify all published sarcoidosis incidence and prevalence data. We estimated the frequency of CPA from 11 papers relating to >3,000 patients with sarcoidosis to derive CPA patient numbers. We applied an annual attrition rate of 15% (range 10–25%) to estimate the global burden of CPA.

We estimate that the annual incidence of sarcoidosis is 344,000 patients worldwide and the prevalence is ~1,238,000 cases, distributed as follows: 165,979 in Europe, 224,000 in the Americas, 492,892 in Africa, 80,023 in the Eastern Mediterranean, 41,660 in the West Pacific and 234,010 in Southeast Asia. CPA complicates sarcoidosis in 3–12% of cases. Using a 6% frequency, we estimate a global burden of 71,907 (range 35,954–143,815 (3–12%)) CPA cases complicating sarcoidosis, with 24% and 37% of cases estimated to be present in the Americas and Africa, because of the higher incidence of sarcoidosis in black people.

As CPA responds to long-term antifungal therapy, which may prevent life-threatening haemoptysis, screening periodically for CPA in those with pulmonary sarcoidosis may be important, especially in patients requiring corticosteroid therapy.

KEYWORDS: Aspergilloma, *Aspergillus* fungal ball, burden of disease, cavitation, fibrosis, lobectomy, precipitins

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Chronic pulmonary aspergillosis (CPA) complicates fibrocystic sarcoidosis with one or more aspergillomas in a pre-existing cavity [1, 2]. Invasive aspergillosis may supervene if high-dose corticosteroids are used. Many other conditions can be complicated by CPA, although data from the National Aspergillosis Centre, Manchester, UK, implicates sarcoidosis in 7.1% of our patients [3]. Other conditions include prior pulmonary tuberculosis, allergic bronchopulmonary aspergillosis (ABPA), pneumothorax, bullous lung disease, nontuberculous mycobacterial pulmonary infection and chronic obstructive pulmonary disease (COPD) [1, 3].

The morbidity of CPA includes marked systemic and pulmonary symptoms, such as weight loss, fatigue, breathlessness and haemoptysis [4, 5], some of which may be masked by long term corticosteroids. Antifungal therapy is effective in ameliorating symptoms and reducing recurrence of haemoptysis in >60% of patients [4–10], and may reduce progressive lung fibrosis. Overall, treated CPA has a 20–33% short-term mortality and a 50% mortality over 5 yrs [6, 11], but one small cohort showed that almost all patients with sarcoidosis and CPA had died within 2 yrs [12].

In this study, we aimed to use published clinical and population data as inputs to model estimates of the likely global burden of sarcoidosis, and then estimate the burden of CPA related to sarcoidosis worldwide. As numerous population estimates for sarcoidosis are not available, and there are few high-quality prospective cohort studies of CPA in the context of pulmonary sarcoidosis, our approach has been to use literature values where they exist and extrapolate from these globally. By necessity, our estimates are crude, perhaps appropriately referred to as ''Fermi calculations'', after the Nobel-prize winning physicist Enrico Fermi. Nonetheless, order of magnitude estimates are still useful and can provide a basis for future more precise studies.

METHODS

We estimated adult sarcoidosis and CPA burden by World Health Organization (WHO) region and for the largest countries as shown in figure 1.

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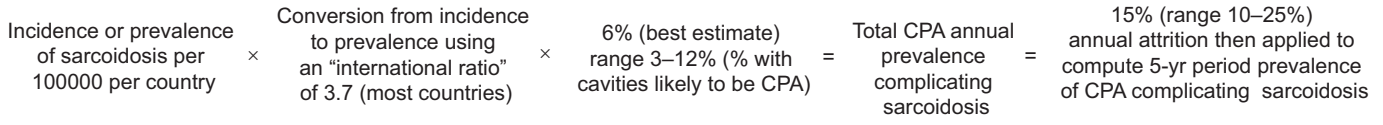

FIGURE 1. Factors used in estimation of chronic pulmonary aspergillosis (CPA) complicating sarcoidosis.

We searched the literature extensively, including book chapters, for population-based estimates of sarcoidosis, and then separately for aspergillosis complicating sarcoidosis. Search terms included ''sarcoidosis'' with ''epidemiology'', ''frequency'', ''rate'', ''incidence'' and ''prevalence''. References of retrieved papers were also examined.

Sarcoidosis burden

For sarcoidosis, we had a combination of incidence and prevalence studies, also with wide variation in estimates both in existing reviews (table S1) and primary studies (table S2).

We chose an overall US incidence of 13.8 out of 100,000, a weighted average of the highest among female African–Americans (39.1 out of 100,000) and the lowest among male Caucasian Americans (9.6 out of 100,000) [13]. Country-specific data for Portugal, Sweden, Denmark, Belgium and Korea were quoted from THOMEER *et al.* [14], and older data for Germany, the Netherlands, Italy, Norway, Czechoslovakia, Hungary, Poland, Yugoslavia, Canada, Argentina, Brazil, Australia and New Zealand are summarised by LEITCH [15].

Prevalence studies demonstrate similar variation by region and ethnicity, being more common in northern Europeans and black people living in the USA. Proportions per 100,000 population ranged from 0.1 to 64 [14–16]. Available individual country prevalences were used for the UK [17], Israel [18], Iceland [19], Spain (pulmonary sarcoidosis only) [20], Greece [21], Switzerland [22], Japan [23] and the USA [24]. Extrapolations were made as follows: China and Vietnam were assumed to be similar to Singapore Chinese [25]; India, Pakistan and Bangladesh, to Singapore Indians [25]; Philippines, Thailand and Indonesia, to Singapore Malaysians [25]; Congo, Nigeria and Ethiopia, to UK black people [26]; Egypt and Iran, to Turkey [27]; and Russia, to Finland [23].

To move to a common metric, we decided to convert annual incidence to prevalence for a 5-yr period. Published prevalence/incidence ratios vary from 2.5 in Finland [23], through 3.7 based on Japanese and Greek data [21, 23], to 6.7 currently active/incident cases in Switzerland [22] and 7.8 in Belgium [15], so we settled on a conservative estimate of 3.7. We started with countries with populations exceeding 50 million and extended to each WHO region by assuming similar values for countries with populations <50 million as for those with >50 million.

CPA in sarcoidosis

We next estimated the frequency of CPA in sarcoidosis using a ''scoping review'' methodology [28]. The relative proportion of patients with sarcoidosis who have parenchymal pulmonary disease varies from 66% to 90% (tables S1 and S2) [15, 29], but most do not have cavitation (table 1). We searched the literature extensively for series of sarcoidosis cases containing details of the rate of cavitation, aspergilloma and/or *Aspergillus* serology. Search terms included ''sarcoidosis'' with ''aspergilloma'', ''aspergillosis'', ''case series'', ''cohort'', ''longitudinal, ''follow up'', ''outcome'' or ''mortality'', as well as the reference lists of the articles obtained. Grey literature, such as conference abstracts and doctoral theses, were not searched. Our files of pre-1990 aspergillosis papers were also searched by hand. Every paper retrieved with cohort information on sarcoidosis was read, and accepted if a denominator provided rates of cavitation and information on aspergillomas visible radiologically and/or *Aspergillus* immunoglobulin (Ig)G (precipitins) serology (table 1).

Handling attrition among CPA cases

The time-frames of observation of sarcoidosis varied substantially, and one small study from the USA indicated that most patients with pulmonary sarcoidosis complicated by CPA had died after 2 yrs [12]. However, this is not our experience and most of our patients with CPA complicating sarcoidosis are alive and stable ⩾5 yrs after diagnosis. Given the lack of periodic screening for CPA, it is likely that most cases of CPA are identified in existing cohorts over many years. Hence, these cohorts essentially provide a period prevalence of variable duration. For consistency, we applied an annual 15% attrition (mostly death and occasionally transplantation) rate to our prevalence estimates to establish disease burden for a 5-yr period.

RESULTS

Sarcoidosis

We estimated that the annual incidence of sarcoidosis is 344,000 patients worldwide and therefore the prevalence is ~1,238,000 cases, distributed as follows: 165,979 in Europe, 224,000 in the Americas, 492,892 in Africa, 80,023 in the East Mediterranean, 41,660 in the West Pacific and 234,010 in Southeast Asia. The annual incident cases and prevalence for the countries with populations >50 million are shown in table 2 and prevalence for all countries that have estimated it in figure 2. The remarkably low burden of sarcoidosis in some countries, such as Brazil and Mexico, is a function of a low annual incidence of <0.3 out of 100,000 (351 cases in Mexico), which contrasts with the high annual incidence in the USA of 13.8 out of 100,000 (41,734 cases). Cleary, some countries' burden is an estimate based on figures from other countries, notably Nigeria, Ethiopia and the Democratic Republic of Congo, because of some ethnicity similarities but with no environmental commonality (which may or may not be important).

CPA complicating sarcoidosis

There was much variation in the frequency of cavitation and fungal ball observation in sarcoidosis (table 1). In US studies up to 1984, cavitation rates varied from 2% to 12.5% and aspergilloma rates from 1% to 11% [29–36]. In later studies from Israel, Turkey and France, aspergilloma rates varied from 0% to 2.1% [1, 37, 38]. In particular, in France, HOURS *et al.* [1] found 41 (3.9%) out of 1,060 patients with pulmonary cavitation in those

TABLE 1 Sources providing data on the frequency of chronic pulmonary aspergillosis in patients with sarcoidosis

Year	Country	Sampling method	Imaging	Denominator n	Pulmonary cavitation	Aspergilloma	Aspergillus precipitins	[Ref.]
1963	USA	Long/retro	CXR	133	2 (2)	1 (1)	ND	[30]
1970	USA	Long/retro	CXR	300	25 (12.5)	10 (4)	ND	[31]
1973	USA	Long/retro	CXR	150	42 (28)#	1 (0.8)	ND	[32]
1976	USA	Long/retro	CXR	68	NS	3 (4.4)	ND	[33]
1979	USA	Long/retro	CXR	>600	ND	12 (2)	ND	[34]
1983	USA	Long	CXR	103	NS	11 (11)	ND	[35]
1984	USA	Cross-sect	CT	100	NS	10 (10)	12 (12)	[29]
1985	Israel	Long/retro	CXR	197	50 (25)#	0	ND	[36]
2002	Turkey	Cross-sect	CT	70	2 (2.9)	NS	ND	[37]
2008	France	Long/retro	CT	1060	41 (3.9)	21 (2.1)	ND	[1]
2011	USA	Long/retro	CT	427	NS	10 (2.3)	NS	[38]

Data are presented as n (%), unless otherwise stated. Long: longitudinal; retro: retrospective; Cross-sect: cross-sectional; CXR: chest radiograph only; CT: chest radiograph and computed tomography of the thorax; NS: not stated; ND: not determined. #: incidence of fibrosis, not cavitation, which was not stated.

with pulmonary sarcoidosis. In 18 patients, an aspergilloma was present on initial computed tomography scan and, in three more, one developed during follow-up, a 51% rate in those with cavitation and a 2% rate overall. In the USA, PENA *et al.* [36] found 10 patients with an aspergilloma among 427 (2.3%) patients with pulmonary sarcoidosis. Neither study utilised

TABLE 2 Estimated incidence and prevalence of sarcoidosis and chronic pulmonary aspergillosis (CPA) complicating sarcoidosis in countries with populations exceeding 50 million

Country	Population in 2005 [39]	Sarcoidosis				CPA 6% (range 3–12%)	
		Incidence per 100000 per year	Incidence cases	Prevalence per 100000	Prevalence cases	Annual incident cases	5-yr period prevalence cases (less attrition)
China	1312253000	0.56#	7349	2.1	27190	441 (220 – 882)	1387 (693–2773)
India	1130618000	4.57¶	51669	16.9	191176	3100 (1550–6200)	9750 (4875–19500)
USA	302741000	13.8	41734	51	154415	2504 (1252–5008)	7875 (3938–15750)
Indonesia	219210000	1.30¶	2850	4.8	10544	171 (85–42)	538 (269–1075)
Brazil	186075000	0.1	101	0.2	372	6 (3–12)	19 (9–38)
Pakistan	165816000	4.57¶	7578	16.9	28038	455 (227–909)	1430 (715–2860)
Bangladesh	153122000	4.57¶	6998	16.9	25891	420 (210–840)	1320 (660–2641)
Russia	143470000	11+	16356	28	40459	1674 (837–3347)	2063 (1032–4127)
Nigeria	140879000	19.8§	27894	73.3	103208	981 (491–1963)	5264 (2632–10527)
Japan	127449000	1.3	1657	4.7	5990	99 (50–199)	305 (153–611)
Mexico	105330000	0.3	351	1.2	1299	21 (11–42)	66 (33–133)
Philippines	85496000	1.3¶	1111	4.8	4112	67 (33–133)	210 (105–419)
Vietnam	84074000	0.56#	471	2.1	1742	28 (14–56)	89 (44–178)
Germany	82409000	4	3118	14	11537	187 (94–374)	588 (294–1177)
Egypt	77154000	4f	3086	14.8	11419	185 (93–370)	582 (291–1165)
Ethiopia	74661000	19.8§	14783	73.3	54697	887 (443–1774)	2790 (1395–5579)
Turkey	71169000	4	2847	14.8	10533	171 (85–342)	537 (269–1074)
Iran	70765000	4f	2831	14.8	10473	170 (85–340)	534 (267–1068)
Thailand	65946000	1.3¶	857	4.8	3172	51 (26–103)	162 (81–324)
France	61013000	3	1649	10	6101	99 (49–198)	311 (156–622)
UK	60261000	5	4000	27	16270	240 (120–480)	830 (415–1660)
(DR) Congo	59077000	19.8§	11697	73.3	43280	702 (351–1404)	2207 (1104–4415)
Italy	58645000	2	1427	9	5278	86 (43–171)	269 (135–538)

DR: Democratic Republic. #: assumed to be similar to Singaporean Chinese; ¶: assumed to be similar to Singaporean Malaysian; +: assumed to be similar to Finland; §: assumed to be similar to UK black people; f: assumed to be similar to Turkey.

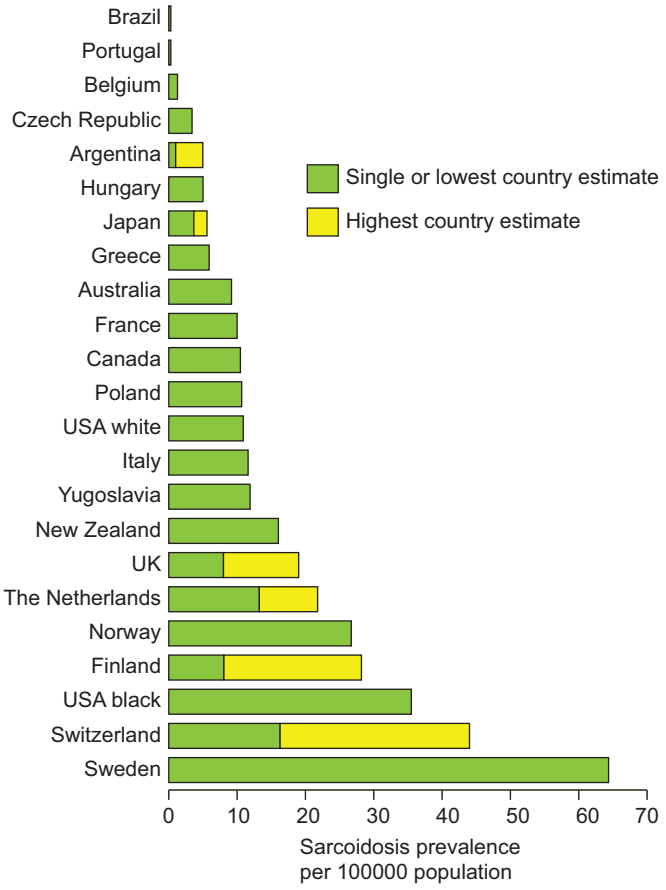

FIGURE 2. Variable published prevalence per 100,000 population of pulmonary sarcoidosis in different countries, and in the USA between black and white people. If more than one estimate is available, then both are presented. Rates vary from 0.2 out of 100,000 in Brazil to 64.4 out of 100,000 in Sweden. Data from supplementary tables S1 and S2.

Aspergillus serology, unlike WOLLSCHLAGER and KHAN [29] in 1984. Synthesising this literature, we used a best estimate of 6% prevalence of CPA in patients with sarcoidosis for all countries, with deterministic sensitivity analyses using a range from a low of 3% to a high of 12%, recognising the somewhat arbitrary selection of these values.

The annual incidence of CPA complicating sarcoidosis is estimated to be 20,640 patients using the 6% proportion. The 5-yr period prevalence after attrition is estimated to be 71,907 (range 35,954–143,815; 3–12%) patients worldwide. Table 1 shows the estimated CPA burden in the countries with a population >50 million, and includes lower and higher estimates of 3% and 12% alongside the best estimate of 6%. Overall, 24% and 37% of cases are thought to be present in the Americas and Africa, respectively, because of the higher incidence of sarcoidosis in black people. In countries with a population of >50 million, the burden is estimated to be 39,127 patients, to which India 9,750 (range 4,875–19,500) and the USA 7,875 (range 3,938–15,750) contribute nearly 45% of the cases.

DISCUSSION

Sarcoidosis represents 7–17% of CPA cases in our and other series [3]. There are substantial datasets describing the incidence and prevalence of sarcoidosis from some countries, but unfortunately not from many of the large Asian or South American countries. The marked ethnic differences illustrated by the Singaporean and London data are remarkable. The Chinese, Malay and Indian incidence rates in Singapore were 0.56, 1.3 and 4.57 per 100,000 [25] and, in London, the rates of Caucasians, Indians and black people were 1.5, 16.8 and 19.8 per 100,000 [26]. In the USA, the male Caucasian rate was 9.6, whereas it was 29.8 in black people [24]. NUNES *et al.* [40] proposed a global annual incidence of sarcoidosis of 17.8 per 100,000. If applied to the global population aged >25 yrs in 2005 [39], 620,152 new cases would be expected annually. This figure appears higher than our figure of 370,912, but given that "the Fermi method" provides approximate estimates with a precision of about one log, then they are of the same magnitude. There is substantial uncertainty in annual incidence rates in very large populations, notably China, Indonesia, Africa and Brazil. Locally ascertained data would be most helpful in improving the accuracy of our estimates.

The primary means we have used to estimate CPA burden is radiographic. However, our own data suggest that only ~25% of patients with CPA have an aspergilloma [7], the remainder having one or more cavities. This may be problematic in some patient groups who develop CPA, notably those with sarcoidosis in whom pulmonary cavities pre-date the development of CPA. In addition to the radiographic image of an aspergilloma in sarcoidosis, the diagnosis of CPA usually relies on positive *Aspergillus* IgG serology. ~90% of cases of CPA have detectable *Aspergillus fumigatus* precipitins or other IgG antibodies, with some variation between assays [41, 42]. In other patients, the diagnosis relies on biopsy and/or culture. While almost all cases of CPA are caused by *A. fumigatus*, rare patients are described with *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus nidulans* infection [5, 43–45], with the implication that IgG antibody to *A. fumigatus* may not be present if infection is due to these species. So CPA case ascertainment is likely to be incomplete in sarcoidosis. Other diagnostic tests, such as histological demonstration of hyphae in biopsied cavities, cultures of *Aspergillus* spp. and/or PCR *Aspergillus* assays [46] may assist in diagnosis.

As patients with fibrocystic pulmonary sarcoidosis have pulmonary cavities, the criteria for diagnosis of CPA are either the presence of a fungal ball and/or serum *Aspergillus* IgG antibodies. These were prospectively assessed in only one study [29], and this study found the highest rate of CPA complicating sarcoidosis. This suggests that, in the absence of active testing for CPA, underdiagnosis plagues adequate detection of CPA among this clinical population with chronic respiratory disease. There may be ethnic differences in the rate of CPA, or in its progression or other manifestations, but data are currently lacking. One surprise is the lack of reports of CPA or aspergilloma from Scandinavia, given the high prevalence of sarcoidosis there.

A few CPA cases (1–17%) undergo curative surgery, usually within the first year of CPA diagnosis [47], but sometimes the outcome from this is death. In addition, CPA itself is a progressive disease with an annual mortality varying from ~10% [11] to ~30% after referral to hospital [6]. We have directly accounted for this in our 5-yr period prevalence

estimates of CPA by introducing an annual attrition rate of 15% (range 10–25%). However, a mortality rate of nearly 100% over 2 yrs was seen in a small US series from the 1980s [12], and it is possible that we have significantly underestimated attrition. In our experience, the severity of the combination of the underlying pulmonary disease, combined with the extent of lung destruction caused by CPA, is the major determinant of survival. No study has provided information on the relationship between lung function and outcome, in the context of CPA, to allow this to be modelled.

CPA complicates several different pulmonary diseases other than sarcoidosis, notably those with classical pulmonary tuberculosis, nontuberculous mycobacterial infection, ABPA and COPD [3]. We have estimated the frequency of CPA as a sequel to tuberculosis and estimate the annual global incident cases to be 372,000 and the 5-yr period prevalence 1.17 million, also assuming a 15% attrition [48]. We have also estimated the global 5-yr period prevalence of CPA complicating ABPA at 345,000 persons, using a 15% attrition rate DENNING *et al*. [49]. Therefore, our estimates rank sarcoidosis as a relatively uncommon cause of CPA, especially considering that COPD, which we have not estimated, is the most common underlying diagnosis in our experience [7].

While some genetic risk factors for CPA are probably important in the development of CPA, such as a Toll-like receptor 4 polymorphism or cytokine aberrations [50, 51], the use of corticosteroids could be either helpful or a hindrance. Corticosteroid suppression of the aberrant inflammatory response in sarcoidosis may prevent ongoing lung fibrosis and cavity formation. However, such suppression also leaves the patient open to progression of chronic to invasive aspergillosis, which may be fatal [52–54]. Possibly, the use of oral antifungal agents to prevent progression of aspergillosis, in the face of corticosteroid use, would be helpful, but such management has never been formally studied. In any case, intravenous and long-term oral antifungal therapy reduces morbidity and mortality in these patients [4–10]. Indeed, there are even emerging data suggesting that antifungal therapy may be helpful in sarcoidosis directly, through an uncertain mechanism of action [55]. Screening with *Aspergillus* IgG antibody testing may be a cost-effective means of identifying patients with CPA early in fibrocystic sarcoidosis, permitting explicit decisions around both corticosteroid and antifungal medical management.

STATEMENT OF INTEREST

Statements of interest for all authors can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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