Global burden of chronic pulmonary aspergillosis complicating sarcoidosis

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Running title: Global burden of CPA in sarcoidosis
ABSTRACT

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

**Methods** 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 10 papers relating to >2700 patients with sarcoidosis to derive CPA patient numbers. We applied an annual attrition rate of 15% (range 10-25%) to estimate global burden of CPA.

**Findings** We estimate that the annual incidence of sarcoidosis is 344,000 patients worldwide and the prevalence is approximately 1,238,000 cases, distributed in: 165,979 (Europe), 224,000 (Americas), 492,892 (Africa), 80,023 (E. Mediterranean), 41,660 (W. Pacific) and 234,010 (SE Asia). CPA complicates sarcoidosis in 3-12% of cases. Using a 6% frequency, we estimate a global burden of 71,907 (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.

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

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INTRODUCTION
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 implicates sarcoidosis in 7.1% of our patients \(^3\). Other conditions include prior pulmonary tuberculosis, allergic bronchopulmonary aspergillosis (ABPA), pneumothorax, bullous lung disease, non-tuberculous mycobacterial pulmonary infection and COPD \(^1,3\).

The morbidity of CPA includes marked systemic and pulmonary symptoms such as weight loss, fatigue, breathlessness, and hemoptysis \(^4,5\), some of which may be masked by long term corticosteroids. Antifungal therapy is effective in ameliorating symptoms and reducing recurrence of hemoptysis in over 60% of patients \(^4,5,6,7,8,9,10\), and may reduce progressive lung fibrosis. Treated CPA overall has a 20-33% short term mortality and a 50% mortality over 5 years \(^6,11\), but one small cohort showed that almost all patients with sarcoidosis and CPA had died within 2 years \(^12\).

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. Necessarily 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 WHO region and for the largest countries as shown in Figure 1. 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 (Supplementary Table S1a. and primary studies (supplemental table S2)

[Supplementary Tables S1 & S2 here]

We chose an overall US incidence of 13.8/100,000, a weighted average of the highest among female African Americans (39.1/100,000) and the lowest among male Caucasian Americans (9.6/100,000) 13 Country specific data for Portugal, Sweden, Denmark, Belgium, Korea are quoted by Thomeer et al (2005) 14 and older data for Germany, Netherlands, Italy, Norway, Czechoslovakia, Hungary, Poland, Yugoslavia, Canada, Argentina, Brazil, Australia and New Zealand are summarized by Leitch (2000) 15.

Prevalence studies demonstrate similar variation by region and ethnicity, being more common in northern Europeans and Blacks living in the USA. Proportions per 100,000 population ranged from 0.1 to 64 14-16 ; Available individual country prevalence 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 assumed to be similar to Singapore /Chinese 25; India, Pakistan and Bangladesh, to Singapore Indians 25; Philippines, Thailand and Indonesia, to Singapore Malays 26; Congo, Nigeria and Ethiopia, to UK blacks 26; Egypt and Iran, to Turkey 27; and Russia, to Finland 23.

[Figure 1 about here]

To move to a common metric, we decided to convert annual incidence to prevalence for a five year 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 50M and extended to each WHO region, by assuming similar values for countries with populations <50M as those with >50M.
CPA in Sarcoidosis

We next estimated the frequency of CPA in sarcoidosis using a ‘scoping review’ methodology. The relative proportion of patients with sarcoidosis who have parenchymal pulmonary disease varies from 66 to 90% (Table S1 & S2) but most do not have cavitation (see 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 IgG (precipitins) serology (Table 1).

[Table 1 about here]

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 years. However this is not our experience and most of our patients with CPA complicating sarcoidosis are alive and stable at least 5 years 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, occasional transplantation) rate to our prevalence estimates to establish disease burden for a five year period.

RESULTS

Sarcoidosis

We estimated that the annual incidence of sarcoidosis is 344,000 patients worldwide and therefore the prevalence is approximately 1,238,000 cases, distributed as follows: 165,979 (Europe), 224,000 (Americas), 492,892 (Africa), 80,023 (E. Mediterranean),
41,660 (W. Pacific) and 234,010 (SE Asia). The annual incident cases and prevalence for the countries with populations over 50M is shown in Table 2 (columns 3-6) 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 <0.3/100,000 (351 cases in Mexico) which contrasts with the high annual incidence in the USA of 13.8/100,000 (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% \(^{29-35,38}\). In later studies from Israel, Turkey and France, aspergilloma rates varied from 0% to 2.1% \(^{1,36,37}\). In particular, Hours (2008) in France found 41 of 1060 (3.9%) patients with pulmonary cavitation in those with pulmonary sarcoidosis \(^1\). In 18 patients an aspergilloma was present on initial CT and in 3 more one developed during follow up, a 51% rate in those with cavitation, and a 2% rate overall. In the USA, Pena found 10 patients with an aspergilloma among 427 (2.3%) patients with pulmonary sarcoidosis \(^38\). Neither study utilized Aspergillus serology, unlike Wollschlager and Khan in 1984 \(^29\). Synthesizing 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 high of 12%, recognizing 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 five year period prevalence after attrition is estimated to be 71,907 (range 35,954 – 143,815; 3-12% proportion) patients worldwide. Table 1 (columns 7 & 8) shows the estimated CPA burden in the countries with >50M
population, 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 Blacks. In countries with a population of >50M, the burden is estimated to be 39,127 patients of which India 9,750 (4,875 – 19,500) and the USA 7,875 (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. So 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 Caucasian, Indian and Black rates were 1.5, 16.8 and 19.8 per 100,000 \(^{26}\). In the US, the male Caucasian rate was 9.6, whereas it was 29.8 in Blacks \(^{24}\). Nunes proposed a global annual incidence of sarcoidosis of 17.8 per 100,000 \(^{39}\). If applied to the global population over 25 years of age in 2005 \(^{40}\), 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 suggests that only about 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 predate 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. About ~90% of cases of CPA have detectable *A. 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 *A. niger*, *A. flavus* and *A. nidulans* infection \(^5\).
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 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. In only one study were these prospectively assessed 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 few currently. 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, but sometimes the outcome from this is death. In addition CPA itself is a progressive disease with an annual mortality varying from ~10% to around 30% after referral to hospital. We have directly accounted for this in our five year 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 years was seen in a small US series from the 1980’s, 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 modeled.

CPA complicates several different pulmonary diseases other than sarcoidosis, notably those with classical pulmonary tuberculosis, non-tuberculous mycobacterial infection, ABPA and COPD. 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-yaer period prevalence 1.17 million, also assuming a 15% attrition. We have also estimated the global 5-yaer period prevalence of CPA complicating ABPA at 345,000 persons,
using a 15% attrition rate (Denning et al, submitted) \(^{49}\). 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 probably are 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 IV 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.
Role of authors
DWD conceived the project, collected and interpreted the clinical and epidemiological literature and wrote the primary draft. AP sourced WHO and population data, undertook the modeling and contributed to writing. DCC read the relevant clinical and epidemiological literature and challenged the assumptions made in early models and drafts, revised the paper’s structure and contributed to writing. All authors were involved in multiple on-line and telephone conversations, discussed the work at a British Thoracic Society meeting and approved the final draft of the manuscript. David Denning acts as the guarantor of the work.

Acknowledgements
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Conflicts of interest
Dr Denning holds founder shares in F2G Ltd a University of Manchester spin-out company and has received grant support from F2G as well as the Fungal Research Trust, the Wellcome Trust, the Moulton Trust, The Medical Research Council, The Chronic Granulomatous Disease Research Trust, the National Institute of Allergy and Infectious Diseases, National Institute of Health Research and the European Union, AstraZeneca and Basilea. He currently or previously acted as an advisor/consultant to F2G, Basilea, Vicuron (now Pfizer), Pfizer, Schering Plough (now Merck), Nektar, Daichi, Astellas, Gilead, York Pharma and Lab21. He has been paid for talks on behalf of Merck, Astellas, Novartis, Merck, Dainippon and Pfizer. Alex Pleuvry is a Director and shareholder in Oncalex, an independent consultancy, with no specific financial interest in respiratory or fungal disorders. Dr Cole is a tenured professor, with consultancies on environmental health to public health units but none on respiratory or fungal disorders or their treatment.
REFERENCES


Figure 1. Factors used in estimation of CPA complicating sarcoidosis

- Incidence or prevalence of sarcoidosis per 100,000 per country
- Conversion from incidence to prevalence using an “International ratio” of 3.7 (most countries)
- 6% (best estimate) range 3-12% (% with cavities likely to be CPA)

= Total CPA annual prevalence complicating sarcoidosis

= 15% (range 10-25%) annual attrition then applied to compute 5 year period prevalence of CPA complicating sarcoidosis
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 (solid/green = lower estimate; lighter/yellow, upper estimate). Rates vary from 0.2/100,000 in Brazil to 64.4/100,000 in Sweden. Taken from supplementary Tables 1 and 2.
**Table 1. Sources providing data on the frequency of chronic pulmonary aspergillosis in patients with sarcoidosis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Sampling method</th>
<th>Imaging</th>
<th>Denominator</th>
<th>Pulmonary cavitation N (%)</th>
<th>Aspergilloma N (%)</th>
<th>Aspergillus Precipitins N (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963</td>
<td>US</td>
<td>Long / retro</td>
<td>CXR</td>
<td>133</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>ND</td>
<td>30</td>
</tr>
<tr>
<td>1970</td>
<td>US</td>
<td>Long / retro</td>
<td>CXR</td>
<td>300</td>
<td>25 (12.5)</td>
<td>10 (4)</td>
<td>ND</td>
<td>31</td>
</tr>
<tr>
<td>1973</td>
<td>US</td>
<td>Long / retro</td>
<td>CXR</td>
<td>150</td>
<td>42 (28)(^a)</td>
<td>1 (0.8)</td>
<td>ND</td>
<td>32</td>
</tr>
<tr>
<td>1976</td>
<td>US</td>
<td>Long / retro</td>
<td>CXR</td>
<td>68</td>
<td>NS</td>
<td>3 (4.4)</td>
<td>ND</td>
<td>33</td>
</tr>
<tr>
<td>1979</td>
<td>US</td>
<td>Long / retro</td>
<td>CXR</td>
<td>&gt;600</td>
<td>ND</td>
<td>12 (2)</td>
<td>ND</td>
<td>34</td>
</tr>
<tr>
<td>1984</td>
<td>US</td>
<td>Cross sect</td>
<td>CT</td>
<td>100</td>
<td>NS</td>
<td>10 (10)</td>
<td>12 (12)</td>
<td>29</td>
</tr>
<tr>
<td>1985</td>
<td>Israel</td>
<td>Long / retro</td>
<td>CXR</td>
<td>197</td>
<td>50 (25)(^a)</td>
<td>0</td>
<td>ND</td>
<td>36</td>
</tr>
<tr>
<td>2002</td>
<td>Turkey</td>
<td>Cross sect</td>
<td>CT</td>
<td>70</td>
<td>2 (2.9)</td>
<td>NS</td>
<td>ND</td>
<td>37</td>
</tr>
<tr>
<td>2008</td>
<td>France</td>
<td>Long / retro</td>
<td>CT</td>
<td>1060</td>
<td>41 (3.9)</td>
<td>21 (2.1)</td>
<td>ND</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>US</td>
<td>Long/retro</td>
<td>CT</td>
<td>427</td>
<td>NS</td>
<td>10 (2.3)</td>
<td>NS</td>
<td>38</td>
</tr>
</tbody>
</table>

Long = longitudinal; retro = retrospective; Cross sect = cross sectional; CXR = chest radiograph only; CT = chest radiograph and computed tomography of the thorax

\(^a\) Incidence of fibrosis, not cavitation, which was not stated

NS = not stated; ND = not done.
Table 2 Estimated Incidence and prevalence of sarcoidosis and chronic pulmonary aspergillosis complicating sarcoidosis in countries with populations exceeding 50M

<table>
<thead>
<tr>
<th>Country</th>
<th>Population* (2005)</th>
<th>Sarcoidosis</th>
<th>CPA 6% (range 3-12%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Incidence / 100,000/year</td>
<td>Incidence (cases)</td>
</tr>
<tr>
<td>China</td>
<td>1,312,253,000</td>
<td>0.56</td>
<td>7,349</td>
</tr>
<tr>
<td>India</td>
<td>1,130,618,000</td>
<td>4.57b</td>
<td>51,669</td>
</tr>
<tr>
<td>United States</td>
<td>302,741,000</td>
<td>13.8</td>
<td>41,734</td>
</tr>
<tr>
<td>Indonesia</td>
<td>219,210,000</td>
<td>1.30</td>
<td>2,850</td>
</tr>
<tr>
<td>Brazil</td>
<td>186,075,000</td>
<td>0.1</td>
<td>101</td>
</tr>
<tr>
<td>Pakistan</td>
<td>165,816,000</td>
<td>4.57b</td>
<td>7,578</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>153,122,000</td>
<td>4.57b</td>
<td>6,998</td>
</tr>
<tr>
<td>Russia</td>
<td>143,470,000</td>
<td>11.4</td>
<td>16,356</td>
</tr>
<tr>
<td>Nigeria</td>
<td>140,879,000</td>
<td>19.8</td>
<td>27,894</td>
</tr>
<tr>
<td>Japan</td>
<td>127,449,000</td>
<td>1.3</td>
<td>1,657</td>
</tr>
<tr>
<td>Mexico</td>
<td>105,330,000</td>
<td>0.3</td>
<td>351</td>
</tr>
<tr>
<td>Philippines</td>
<td>85,496,000</td>
<td>1.3</td>
<td>1,111</td>
</tr>
<tr>
<td>Vietnam</td>
<td>84,074,000</td>
<td>0.56</td>
<td>471</td>
</tr>
<tr>
<td>Germany</td>
<td>82,409,000</td>
<td>4</td>
<td>3,118</td>
</tr>
<tr>
<td>Egypt</td>
<td>77,154,000</td>
<td>4</td>
<td>3,086</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>74,661,000</td>
<td>19.8</td>
<td>14,783</td>
</tr>
<tr>
<td>Turkey</td>
<td>71,169,000</td>
<td>4</td>
<td>2,847</td>
</tr>
<tr>
<td>Iran</td>
<td>70,765,000</td>
<td>4</td>
<td>2,831</td>
</tr>
<tr>
<td>Thailand</td>
<td>65,946,000</td>
<td>1.3</td>
<td>857</td>
</tr>
<tr>
<td>France</td>
<td>61,013,000</td>
<td>3</td>
<td>1,649</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>60,261,000</td>
<td>5</td>
<td>4,000</td>
</tr>
<tr>
<td>Congo (DR)</td>
<td>59,077,000</td>
<td>19.8</td>
<td>11,697</td>
</tr>
<tr>
<td>Italy</td>
<td>58,645,000</td>
<td>2</td>
<td>1,427</td>
</tr>
</tbody>
</table>


DR – Democratic Republic

* assumed to be similar to Singaporean Chinese, b assumed to be similar to Singaporean Malays, c assumed to be similar to Singaporean Malays, d assumed to be similar to Finland, e assumed to be similar to UK Blacks, f assumed to be similar to Turkey.
Supplementary table 1 and 2. Published papers, reviews and book chapters describing the incidence or prevalence of sarcoidosis in various populations.

[Additional file, with references]