Eur Respir J 2001; 18: Suppl. 32, 2s–16s
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European Respiratory Journal
ISSN 0904-1850
ISBN 1-904097-01-4

REPORT OF WORKING GROUP 1

Interstitial lung diseases: an epidemiological overview

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Interstitial lung diseases: an epidemiological overview. M. Demedts, A.U. Wells, J.M. Antó, U. Costabel, R. Hubbard, P. Cullinan, H. Slabbynck, G. Rizzato, V. Poletti, E.K. Verbeken, M.J. Thomeer, J. Kokkarinen, J.C. Dalphin, A. Newman Taylor. ©ERS Journals Ltd 2001.

ABSTRACT: Epidemiological studies on interstitial lung diseases (ILDs) may be schematically subdivided into the following major types: 1) quantifications of disease, broken down into incidence, prevalence and mortality data; 2) identification of aetiological factors; and 3) clinical epidemiological studies. Epidemiological data may be obtained from different sources or population groups, using different study designs such as systematic national statistics, population-based data and registries, and large case series of specific diseases.

Differences in results between epidemiological studies may be due to real differences in incidence, but may also be due to changes in disease definitions and classifications, differences in the epidemiological design of the studies, or even registration bias.

Comparative epidemiological data of different ILDs are almost limited to the general population study in Bernalillo County and to national mortality statistics, which should be interpreted with great caution. Also, some, mostly national registries of the different ILDs have been carried out by specific medical profession groups (especially pulmonologists), which clearly underestimate the real incidence of ILDs, but in which the comparison of the relative frequencies is probably accurate. Based on all these comparative studies, sarcoidosis and idiopathic pulmonary fibrosis appear to be the most frequent ILDs, followed by hypersensitivity pneumonitis and ILD in collagen vascular disease, when classical pneumoconioses are not included. There is also a relatively large group of nonspecific fibrosis.

Much more data have been published on the epidemiology of specific forms of interstitial lung disease. Most information is available on the epidemiology of sarcoidosis, and those data are probably the most accurate. Data on idiopathic pulmonary fibrosis have the disadvantage of the recent changes in definition and classification of this disease. Hypersensitivity pneumonitis has been studied epidemiologically, especially in some exposure groups such as farmers and pigeon breeders, and in some regions in North America, UK, France and Scandinavia. Estimates of frequencies of interstitial lung disease in collagen vascular disease or of drug-induced interstitial lung disease are less accurate and more variable, depending on diagnostic criteria. Notwithstanding the aforementioned problems, this report tries to provide a balanced overview of the epidemiology of different interstitial lung diseases.

Eur Respir J 2001; 18: Suppl. 32, 2s–16s.

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Keywords: Classification
death certificates
epidemiology
incidence
prevalence
registration

General epidemiological aspects

Introductory remarks on epidemiological studies

Diffuse interstitial (or parenchymal) lung diseases (ILDs) represent a very large group of more than 200 different entities, many of which are rare or "orphan" diseases. Much remains unknown or debatable for many of these ILDs, notably issues of prevalence, incidence and mortality rates.

Epidemiology can be defined as the study of the distribution of disease and of the factors that determine this distribution (see article by ANTÓ and CULLINAN [1] in this Supplement). This apparently simple definition includes a wide number of applications. The most important are; the measurement of the magnitude of health problems (including prevalence, incidence and associated burdens); the identification of geographical and temporal distributions (including the relevant patterns of clustering); the investigation of outbreaks and clusters; the study of natural history and aetiology (including both environmental and genetic determinants); the assessment of validity and reproducibility of diagnostic tests that define disease; and the identification and assessment of preventive and therapeutic measures.

The successful application of epidemiology to the previous topics is based on the appropriate use of a

large array of concepts and methods, many of which have evolved over previous decades and are still evolving [2]. There is now growing evidence that inconsistency of results between different studies is, in part, due to the presence of different types of bias ranging from selection to information bias or insufficient adjustment of confounding factors [3]. Recently, the introduction of evidence-based approaches has resulted in a number of guidelines that are helpful for a critical appraisal of epidemiological investigations [4].

In ILD, the major types of epidemiological studies can be subdivided into the following categories.

The quantification of disease. This is subdivided into incidence (number of new cases per year), prevalence (number of cases at a single point of time) and mortality. The study population is preferentially unselected (*i.e.* mass population screening), but the study may also be directed to selected populations, *e.g.* specific age groups or professions. In acute or recurring subacute ILD, such as hypersensitivity pneumonitis, incidence rates may be the best way to quantify the disease, whereas in chronic forms, prevalence rates may be more appropriate. Mortality data may provide variable quantification for several reasons (see later).

The identification of aetiological factors. This is performed by surveying outbreaks of disease and identifying environmental and genetic associations, thereby allowing the formulation of pathogenic hypotheses. Different study designs are possible, *e.g.* a cohort study or a case-control study.

Clinical epidemiological studies. This is the characterization of disease behaviour, including patterns of clinical presentation, natural history, treated course, responsiveness to therapy and the definition of prognosis.

Classification and definition of interstitial lung disease

Internationally accepted disease definitions and classifications are a prerequisite without which, useful comparisons cannot be made between population studies (see article by ANTÓ and CULLINAN [1] in this Supplement). Recently, a number of important consensus statements have been published [5–7], and it now appears likely that, for the first time, worldwide agreement will be reached on the classification of the idiopathic interstitial pneumonias (IIPs) (see Review by DU BOIS and WELLS [8] in this Supplement).

In the whole group of ILDs, several types of classification have been applied, such as systematic classifications based on aetiology or on specific disease entities [9, 10], or alternative classifications based on clinical, histological, or radiological patterns [5, 11]. Systematic classifications, *e.g.* the one by CRYSTAL *et al.* [9] or the International Classification of Diseases (ICD)-9 [10], in which each individual ILD is mentioned only once, are appropriate for epidemiological studies. The classification by CRYSTAL *et al.* [9] in ILD of known and unknown aetiology (table 1), is useful in this regard and easy to apply. It is possible to refine this classification by subdividing ILD of unknown aetiology (65% of all ILD) into diseases confined to the lung (most frequently idiopathic pulmonary fibrosis (IPF)) and lung diseases associated with systemic diseases (such as sarcoidosis and connective tissue diseases). Alternative approaches include histological classifications, such as that proposed by SCHWARZ [11], based upon responsiveness to treatment, and classifications based upon clinical plus aetiological features at first presentation, of the sort recently proposed by the British Thoracic Society (BTS) [5]. However, these two latter classifications [5, 11], in which individual ILD may be classifiable into more than one subgroup, cannot be adapted easily to epidemiological studies. For example, pulmonary sarcoidosis is most often associated with a good response to treatment. However, a smaller subgroup with end-stage fibrotic disease would be grouped separately in the histological classification of SCHWARZ [11], which is based upon the reversibility of disease. Similarly, in the BTS classification [5], which is based on clinical features at first presentation, hypersensitivity pneumonitis may be classified in the subgroup of "episodic ILD" as well as in that of "chronic ILD".

In order to be able to compare the data from different epidemiological studies it is mandatory that the same definitions for the disease entities are applied. Some of these entities have highly specific histological features on the basis of which the diseases

Table 1. – Classification of interstitial lung diseases (ILDs) according to aetiology

ILD of known aetiology
Inhaled agents
Inorganic dust, gases or fumes
Organic material *e.g.* hypersensitivity pneumonitis
Drugs *e.g.* antimicrobial, chemotherapeutic agents
Infections: bacterial, fungal, viral, protozoal
Radiation
Neoplasia *e.g.* lymphangitis carcinomatosis
Systemic toxic agents *e.g.* paraquat
Transplantation rejection
Other organ disorders
Hepatitis, cirrhosis
Left heart failure
Chronic uraemia
Inflammatory bowel disease
ILD of unknown aetiology
IIP: IPF, NSIP, DIP/RBILD, COP, AIP
Sarcoidosis
ILD due to collagen vascular disease
Angiitis and granulomatosis
Eosinophilic pneumonias
Histiocytosis X (Langerhans′ cell granulomatosis)
Hereditary and familial disorders *e.g.* tuberous sclerosis
Storage disorders *e.g.* amyloidosis, alveolar proteinosis

AIP: acute interstitial pneumonia; COP: cryptogenic organising pneumonia; DIP: desquamative interstitial pneumonia; IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; NSIP: non-specific interstitial pneumonia; RBILD: respiratory bronchiolitis interstitial lung disease. Adapted from [9].

may be defined. Other entities, however, are morphologically nonspecific and the diagnosis has to rely on the combination of clinical (including radiological) and pathological presentation. One striking example of a group of diseases, in which a change in classification has had major consequences, is that of the IIP (see Review by DU BOIS and WELLS [8] in this Supplement). Until some years ago, large registries of patients with ILD [12–14] and epidemiological studies on IPF [15, 16] were based upon the pathological classification of LIEBOW [17] from ~30 years ago. However, it is now apparent that recent modifications made by KATZENSTEIN and MYERS [18] have increased the clinical relevance of disease classification. This evolution is not surprising since both classifications are separated by 3 decades of research into both aetiopathogenic mechanisms and histological specificity, and also to structure-function correlations and clinicopathological specificity. As a result, for some of the ILDs originally considered idiopathic, aetiology has been elucidated and other entities are now more accurately described in terms of spatial and temporal distribution in the lung parenchyma, which has led to new terminologies (see article by VERBEKEN [19] in this Supplement). In the recent International Consensus Statement on Nomenclature [6] a clear distinction has been made between IPF, histologically defined as usual interstitial pneumonia (UIP), and the other forms of IIP, especially the recently defined entity of nonspecific interstitial pneumonia (NSIP) (table 2). Historically, the 5-yr survival of patients with IPF was ~50% [20, 21]. However, it is now known that the subgroup with UIP has a 5-yr survival of only 20% [22], whereas well over half of the cases with desquamative interstitial pneumonia (DIP) or NSIP have a better outcome [22–24]. By contrast, acute interstitial pneumonia (AIP), first described by HAMMAN and RICH [25, 26] and subsequently characterized as a separate entity by KATZENSTEIN *et al.* [27], has an appallingly bad prognosis. The grouping together of UIP, NSIP, DIP and AIP in large epidemiological series was unavoidable. However, the distinct natural histories and treated courses of these entities demand that further epidemiological studies be performed. Before this work can be undertaken, a final consensus must be reached on disease classification by the American Thoracic (ATS) and European Respiratory Society (ERS), which will hopefully be published this year.

Table 2. – Classifications of idiopathic interstitial pneumonias (IIP)

Pathologic		Clinical-pathologic
LIEBOW [17]	KATZENSTEIN and MYERS [18]	ICS [6]
Chronic	Chronic	IPF always has
UIP	UIP	UIP pathology
DIP	DIP/RBILD	Other entities
BIP	NSIP	AIP
GIP	Acute	DIP
LIP	AIP	RBILD
		NSIP
		LIP
		COP

AIP: acute interstitial pneumonia; BIP: bronchiolitis interstitial pneumonia; COP: cryptogenic organizing pneumonia; DIP: desquamative interstitial pneumonia; GIP: giant cell interstitial pneumonia; ICS: International consensus statement; IPF: idiopathic pulmonary fibrosis; LIP: lymphocytic interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; RBILD: respiratory bronchiolitis interstitial lung disease; UIP: usual interstitial pneumonia.

Furthermore, it may be difficult to differentiate between IIP and other ILD of unknown or even known (but not recognized) aetiology, and thus, misclassifications are inevitable even in published data. AIP may be confused with other clinical entities characterized by rapidly progressive interstitial pneumonia [28]. Furthermore, the ILD patterns associated with inflammatory bowel disease (IBD) (*e.g.* NSIP, DIP, and granulomatous or eosinophilic lung disease) may escape detection or be wrongly considered as unrelated to the IBD [29].

In addition, radiological or histological organizing pneumonia (OP) patterns associated with a variety of exogenous causes, may be wrongly considered as cryptogenic organizing pneumonia (COP; otherwise known as idiopathic bronchiolitis obliterans organizing pneumonia (BOOP)) [30, 31]. Finally, chronic fibrotic ILD with honeycombing due to an exogenous cause that is no longer identifiable, can wrongly be classified as IPF because of its UIP pathological pattern.

Diagnostic criteria and techniques

Epidemiological studies require standardized and detailed diagnostic criteria. More recent technical diagnostic tools are more sensitive (*e.g.* bronchoalveolar lavage (BAL), high-resolution computed tomography (HRCT)), and some ILDs may now be easier to detect and diagnose. For instance, it has been suggested that the increase in mortality rates due to IPF reported by JOHNSTON *et al.* [32], in several countries between 1979 and 1992, could, at least in part, be due to more accurate diagnosis.

Usually, a stepwise approach is taken in the diagnosis of ILD, starting with a noninvasive evaluation (detailed history, physical findings, blood tests, imaging techniques, lung function tests), followed by semi-invasive procedures (fibreoptic bronchoscopy with BAL and transbronchioloalveolar biopsies (TBB)) and then by more invasive, mostly surgical biopsy techniques, *e.g.* open lung biopsy or video-assisted thoracic surgery (VATS). Historically, the histopathological assessment of a surgical biopsy specimen has been viewed as the "gold standard" among the diagnostic tests in ILD, especially in IPF, but it is clear that only small, possibly nonrepresentative, samples can be obtained. Furthermore, high proportions of patients with IPF are too compromised (due to severe respiratory disease or associated cardiac disease) to undergo a surgical procedure. In a further large subgroup, either the patient declines the

procedure or the physician does not believe that practical management would be influenced by findings at biopsy. As a result, few patients with IPF undergo surgical biopsy evaluation. For example, in two UK surveys of patients with IPF, only 7.5% [33] and 12% [34], respectively, had an open lung biopsy. It must also be emphasized that for large-scale epidemiological (especially multicentre) studies, detailed information on the reliability of the histopathological classification of ILD should be available. To date, no systematic studies on intra- and interobserver pathological variability have been performed. For these reasons, surgical biopsy evaluation has never been a satisfactory diagnostic "gold standard" for epidemiological studies.

Thus, it is clear that other diagnostic strategies must be developed for epidemiological studies, especially in IPF. Fortunately, it is now increasingly accepted that in IPF (and in most other ILDs), a secure diagnosis can often be made by HRCT, now considered an alternative means of evaluating morphological appearances. In some patients, a specific diagnosis can be obtained from the CT appearances alone; a correct first choice diagnosis is made by computed tomography (CT) in 75–90% of patients with various major ILDs, including sarcoidosis, silicosis, IPF, lymphangitis carcinomatosis, and Langerhans′ cell histiocytosis [35–37] (table 3). However, CT findings must be integrated with the clinical evaluation and other investigations in order to reach a specific diagnosis. In this regard, BAL continues to play a crucial diagnostic role. The BAL pattern may be lymphocytic in sarcoidosis (with an increase in the CD4/CD8 ratio in most patients) and extrinsic allergic alveolitis (with a normal or decreased CD4/CD8 ratio), neutrophilic and possibly eosinophilic in IPF, or mainly eosinophilic in a variety of disorders (table 4). Surgical biopsy procedures are increasingly reserved for patients in whom the CT appearances are indeterminate, and those in whom CT findings and other clinical and investigative features are at odds. Thus, histological evaluation is a crucial, final diagnostic arbiter in difficult cases, but can no longer be used to select representative patient groups for epidemiological studies. A new "gold standard" definition has long been needed.

Table 3. – High-resolution computed tomography pattern of major interstitial lung diseases

Linear and reticular pattern
Idiopathic pulmonary fibrosis
Collagen/vascular disease
Asbestosis
Nodular or reticulonodular pattern
Sarcoidosis
Silicosis
Lymphangitis carcinomatosis
Parenchymal opacification (consolidation/ground glass)
Organizing pneumonia
Hypersensitivity pneumonitis
Chronic eosinophilic pneumonia
Haemorrhage
Cystic abnormalities
Langerhans′ cell histiocytosis
Lymphangioleiomyomatosis

Table 4. – Bronchoalveolar lavage pattern of major interstitial lung disease

Neutrophilic
IPF
Collagen/vascular disease
Asbestosis
AIP
Lymphocytic
Sarcoidosis
Hypersensitivity pneumonitis
Silicosis
Eosinophilic
(Chronic) eosinophilic pneumonia
Churg Strauss syndrome
Hypereosinophilic syndrome
Mixed cellularity
BOOP/OP
Collagen/vascular disease
DIP
Abnormal macrophage morphology
Hypersensitivity pneumonitis
Alveolar proteinosis
RBILD
Alveolar haemorrhage

AIP: acute interstitial pneumonia; BOOP: (bronchiolitis obliterans) organizing pneumonia; DIP: desquamative interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; RBILD: respiratory bronchiolitis interstitial lung disease; OP: organizing pneumonia.

The ATS/ERS core committee has redefined diagnostic criteria for IPF [6]. According to the new definition, IPF is now recognized as a distinct and specific form of chronic fibrosing interstitial pneumonia, limited to the lung and associated with UIP on surgical biopsy. In the absence of a surgical lung biopsy, the presence of all of the major, and three of the four minor diagnostic criteria listed in table 2 of the Review by DU BOIS and WELLS [8] in this Supplement, increases the likelihood of a correct clinical diagnosis of IPF. Notably, the new techniques, HRCT and BAL, are included among the four major criteria [6]. In IPF, the HRCT shows patchy, predominantly subpleural, bilateral reticular abnormalities, often with associated traction bronchiectasis and bronchiolectasis and/or subpleural honeycombing. Ground-glass opacities may be present but should be limited in extent. The accuracy of a confident diagnosis of IPF made on HRCT by a trained observer appears to be ~90% [32–34] and ~70% in patients with histological UIP [38]. Today, a surgical lung biopsy in suspected IPF can be limited to those patients who show an atypical pattern on HRCT or in BAL (*e.g.* a predominant lymphocytosis) or an atypical clinical presentation (*e.g.* young age or short duration of illness).

The diagnosis of sarcoidosis needs a compatible clinical picture of a systemic disease, histological demonstration of noncaseating granulomas and exclusion of other diseases capable of producing a similar histological or clinical picture [7]. TBB is the recommended diagnostic procedure in most cases. In some cases of sarcoidosis, biopsy proof is not needed. Clinical and/

or radiological features alone may be diagnostic for patients with stage I (reliability of 98%) or stage II (89%) disease [39]. Furthermore, patients with the classic Löfgren's syndrome, patients with a BAL lymphocytosis and an increased CD4/CD8 ratio, or those with the appearance of a panda and lambda pattern on a total body gallium scan, may prevent the need for invasive diagnostic procedure (see Review by COSTABEL [40] in this Supplement). HRCT is not routinely indicated in patients with sarcoidosis, except for detection of complications if chest radiographic findings are atypical, or in those patients with a normal chest radiograph but a high clinical suspicion of the disease [7].

In extrinsic allergic alveolitis (hypersensitivity pneumonitis), biopsy is rarely required (see Review by BOURKE *et al.* [41] in this Supplement). The diagnosis is usually based on: 1) systemic symptoms and signs (fever and weight loss together with dyspnoea, cough and crackles in acute cases associated with an appropriate exposure); 2) evidence of ILD (either by imaging studies or pulmonary function tests); and 3) evidence of exposure (demonstration of antigen in the environment, improvement of symptoms after withdrawal from antigen, or detection of antibody to a specific triggering agent in patients' serum and/or BAL).

In doubtful cases, supportive criteria are: 1) BAL with >40% lymphocytes; 2) HRCT pattern with widespread ground-glass attenuation mixed with areas of "mosaic perfusion", variably associated with poorly defined centrilobular micronodules in a nonsmoker; 3) a positive inhalation challenge; and 4) compatible histological changes on open lung biopsy specimen. It is notable that in this ILD, the new techniques, HRCT and BAL, have also been included in the set of diagnostic criteria [42].

Also, for other entities of ILD (table 1), diagnostic criteria have been redefined in recent decades. It is not possible to enumerate all of these in the present report. It must be emphasized that for all these diseases the most precise current definitions and criteria should be used in all epidemiological studies.

Sources/population groups for epidemiological studies

Epidemiological data may be obtained from different sources or population groups, using different study designs.

Routine national statistics. National mortality statistics. A major disadvantage of these is that the language used for codes may differ from that used in clinical practice. Coding practices may vary from country to country, not all ILDs result in death and the validity of the recorded diagnoses is rarely known (see later).

Hospital patient episode data. No detailed, validated data are available on this. It has been estimated that every year in the USA, 15% of respiratory physician outpatient visits and 100,000 hospital admissions are for ILD [43]. In the pulmonary division of the University Hospital Gasthuisberg of the Katholieke Universiteit Leuven, ~10% of the outpatient visits and ~5% of the hospital admissions are for ILD (including occupational ILD). However, not all centres will collect detailed patient episode data, and when comparing statistics from different centres, there will probably be variation in coding practices.

Population-based data. Systematic population-based studies. Examples include screening of schoolchildren or army recruits (which has been helpful in estimating the prevalence of sarcoidosis [7, 44, 45]) and screening of "at risk" professions for occupational lung diseases [46, 47]. No such data are available on other ILDs.

Primary care data. In countries with a prominent primary healthcare system, it may be possible to derive population-based data directly from computerized primary care records [48]. The validity of these data needs to be carefully established.

Registries and large case series of specific diseases. A number of registries of ILD have been established in different areas, including New Mexico [12], Belgium [13, 49], Germany [14] and Italy [50] (see article by THOMEER *et al.* [51] in this Supplement). These registries are based mostly on physicians' referrals and are undoubtedly subject to selection bias, *e.g.* pulmonologist notification compared with internists' or general practitioners'. More disease-specific registries are also available for IPF [52, 53], Farmer's lung [54, 55] and other types of hypersensitivity pneumonitis [56]. For rare ILD, generating large case series is difficult and often requires national or international collaboration. Using the BTS organization, efforts have been made to identify all cases of lymphangioleiomyomatosis [57] and familial IPF in the UK [58]. In France there is a nationwide registry of orphan lung diseases (GERM"O"P; Groupe D'études et de recherche sur les maladies "orphelines" pulmonaires) that is coordinated in Lyon.

Differences in results between different registry programmes may be due, in part, to real differences in incidence between countries or regions of countries. ILD due to exposure to the organic dust of *Saccharopolyspora rectivirgula* (previously known as *Micropolyspora faeni*), for instance, appears to be exceptionally high in some countries [56, 59]. In addition, new exposure risks to various harmful agents are being increasingly recognized. Notwithstanding the resulting diagnostic and classification problems, these new exposure risks may also help to unravel pathogenetic mechanisms. As an illustration, the description of a giant cell interstitial pneumonia (GIP) with cannibalistic multinucleated giant cells in diamond polishers in Flanders using a new type of cobalt disk [60], documented the occurrence of so-called hard metal lung due to exposure to cobalt, not sintered to tungsten carbide, as well as the link between cobalt exposure and GIP.

Differences in data sets in different registry programmes may also be due to differences in the design of

the study or even to a registration bias, although epidemiological studies should always conform to the general standard requirements of completeness in registering incidence and prevalence, and to requirements of accurate detection methods and control groups. Despite this, some biases may be unavoidable, especially if mortality data are studied (see later).

Comparative epidemiological data for different interstitial lung diseases

Population data

Few data are available on the epidemiology of ILD in the general population as few systematic large-scale registration programmes on ILD have been published. In a population-based study in Bernalillo County, New Mexico, COULTAS *et al.* [12] found a prevalence of ILD of 81 per 10^5 in males and 67 per 10^5 in females, and an incidence of 32 per 10^5 per yr in males and of 26 per 10^5 per yr in females. They also calculated the prevalence and incidence of several subgroups of ILD (table 5). A potential limitation of this study is the fact that in only ~7% of the ILD patients, the diagnosis was confirmed by open lung biopsy. Despite this concern, this study shows that the incidence/prevalence of several ILDs, especially IPF, are much higher than previously published figures.

If the frequency data for ILD in the study of COULTAS *et al.* [12] are compared with the registries by pneumologists in Flanders [13, 49], Germany [14] and Italy [50], the distributions show some remarkable similarities but also differences (see table 1 in article by THOMEER *et al.* [51] in this Supplement). In the New Mexico registry, prevalences of sarcoidosis (12%) and especially hypersensitivity pneumonitis (0%) were lower, and prevalences of nonspecific fibrosis (32%), pneumoconiosis (14%) and ILD due to connective tissue disease (13%) were higher than in the European registries. Drug-induced ILDs are very low in all registries (1.9–3.3%) and are undoubtedly underestimated (see Review by CAMUS *et al.* [61] in this Supplement). A major problem of most registries, such as the aforementioned European ones [13, 14, 49, 50], is that they are often incomplete and underestimate the true incidence of drug-induced ILDs.

Mortality data

Official mortality data may be more systematic than other registries, but have several disadvantages. These include the possibility that classification may be incorrect due to the peculiarities of ICD codes, that mortality rates differ significantly for the different ILD (*e.g.* very low in sarcoidosis) and the fact that for some categories of systemic diseases, such as sarcoidosis or collagen vascular diseases, it is not mentioned whether the lung was involved and/or was the cause of death. Therefore, the type of data from these national mortality registries is quite different from that obtained from incidence or prevalence registries.

COULTAS and HUGHES [62] examined death certificates and state mortality data in patients in New Mexico with a clinical diagnosis of ILD before death, and concluded that an ILD was listed somewhere on the death certificate in <50% of the patients, and as an immediate cause of death for only 15%.

A critical analysis of mortality data is, therefore, not inappropriate. Most countries routinely code cause of death using death certificates and these provide a potential source of data on disease incidence for ILD. These data will obviously be most appropriate for diseases that usually lead to death, such as IPF, and are of little use for diseases with a good prognosis, such as sarcoidosis. Nevertheless, in 1980 TURNER-WARWICK *et al.* [20] found that in patients known to have cryptogenic fibrosing alveolitis (CFA, which is synonymous to IPF) in their lifetime, the cause of death was directly attributed to CFA in only 55%. In the ICD-9 [10], a specific disease code for CFA/IPF was introduced for the first time (516.3). Studies by JOHNSTON and coworkers on the use of this new code for death certificates [32] and hospital admission data [15] in the UK, suggest that most patients who are coded as having CFA do have this disease, but that about half of the people known to have CFA are not coded correctly and many receive the less precise code of "postinflammatory fibrosis" (515) [32]. In the USA, an underreporting of IPF/CFA is also likely due to use of the less precise ICD code 515 instead of 516.3. Despite the limitations of using these data, there does appear to be an increase in the annual number of deaths from CFA in the UK and a number of other industrialized countries [32, 63].

Table 5. – Prevalence and incidence of interstitial lung diseases (ILDs) and of several subgroups of ILD in males and females in the Bernalillo County, New Mexico from October 1988 until September 1990

	Prevalence per 10^5		Incidence per 10^5 per yr	
	Male	Female	Male	Female
Total interstitial lung disease	80.9	67.2	31.5	26.1
Idiopathic pulmonary fibrosis (516.3)	20.2	13.2	10.7	7.4
Postinflammatory pulmonary fibrosis (515)	10.1	14.3	3.9	4.1
Sarcoidosis (135/517.8)	8.3	8.8	0.9	3.6
Connective tissue disease (517.0/517.2–8/710/710.1–4/710.9/714.81)	7.1	11.6	2.1	3.0
Drugs and radiation (508.1)	1.2	2.2	1.8	1.1
Occupational/environmental (495.0–9/500–505)	20.8	0.6	6.2	0.8

Between brackets the numbers of the "International Classification of Diseases 1975, 9th revision" (ICD-9) of the World Health Organization [10] are given. Adapted from [12].

Strikingly, to the best of the authors' knowledge, large-scale mortality data comparing state mortality data and registries by pulmonologists for different ILDs have not been published. In the framework of a pilot study, the mortality data from the registry of the University Hospital Gasthuisberg of Leuven [64], have been compared with the data of the National Institute of Statistics of Belgium [65] (table 6). In the University Hospital Gasthuisberg, the percentage of 5-yr mortality was highest in IPF (44%, all groups together *i.e.* UIP, DIP, *etc.*) and lowest in sarcoidosis (2%); 8.4% of all registered ILD patients had died within 5 yrs due to IPF and only 0.62% due to sarcoidosis. Conversely, the national mortality statistics showed overall mortality rates for IPF (0.05 per 10^5) that were similar to those for hypersensitivity pneumonitis (0.06 per 10^5), but were much lower than those for sarcoidosis (0.15 per 10^5) and connective tissue disease (0.39 per 10^5); however, the percentage of mortalities that were due to failure of the lungs in these latter two diseases are not known.

Interstitial lung disease in children

The spectrum of paediatric ILD includes a large, heterogeneous group of rare disorders that differ from the adult forms of ILD [66]. Because ILDs in children are rare, there are no epidemiological prevalence or incidence data, and most studies in the literature present only small numbers relative to those reported for ILD in adults. It is estimated that 20% of cases of ILD in children are caused by an infectious agent, a percentage much higher than that shown in adult ILD populations. Infectious aetiologies of ILD include adenovirus bronchiolitis/pneumonia leading to bronchiolitis obliterans, and chronic lung disease from influenza, Mycoplasma and Chlamydia infections. Recurrent aspiration secondary to gastroesophageal reflux is another known cause of ILD [67]. The "classic" forms of idiopathic ILD (UIP, DIP, lymphoid interstitial pneumonia (LIP) and BOOP/OP) rarely occur in childhood [66], and often have a significant morbidity and a poor prognosis [68]. The most frequent forms are LIP or follicular bronchiolitis and NSIP; the latters response to corticosteroids in childhood disease is similar to that in adult disease [69]. Open lung biopsy appears to make a substantial contribution to the management of ILD in children, since it resulted in a change of management in 56% of cases in one study [69]. Paediatric ILD should be considered as quite distinct from adult ILD in most cases and especially in IIPs.

Familial interstitial lung disease

The occurrence of familial forms of ILD suggests the potential importance of genetic influences such as major histocompatibility complex (MHC) alleles and fibrogenic gene polymorphisms in the aetiology (see Report of Working Group 2 by VERLEDEN *et al.* [70] in this Supplement). Few epidemiological data are available on the frequency of familial ILD [71]. In sarcoidosis, familial forms have been described in 1–8% of cases [45, 72], particularly mother/child, monozygote twins and same-sex pair associations. These studies of family relationships have not found a clear Mendelian pattern to the inheritance of sarcoidosis, but rather an inherited predisposition for the disease, which is probably polygenic.

Cases of familial IPF/CFA are rare and account for <1% of all cases in the UK. In most cases, the inheritance appears to be autosomal dominant, with variable penetrance, and one study has demonstrated evidence of subclinical alveolitis in asymptomatic first-degree relatives [73]. Clinically, the familial disease appears to be indistinguishable from the idiopathic condition, but may present at a younger age, although this may be the result of active screening. Other inherited forms of ILD, such as tuberous sclerosis complex and the metabolic storage diseases, are more clearly familial [74, 75].

Epidemiology of specific forms of interstitial lung disease

Except for sarcoidosis, there are few large-scale, epidemiological data available for any specific ILD *e.g.* based on systematic chest radiograph examinations in large populations. Yet even in sarcoidosis, some of the data are subject to inclusion bias because several series are derived from subspeciality clinics,

Table 6. – Mortality data of some major groups of interstitial lung diseases (ILDs) from the University Hospital Gasthuisberg (Leuven) and from the National Institute of Statistics (NIS) of Belgium

Disease	UZ Gasthuisberg registry 5-yr mortality			Yearly mortality by NIS (1986–1992)
	n of that diagnosis	% of that diagnosis	% of all registered ILDs	n per 10^5 population
Sarcoidosis	5	2	0.62	0.15 (135)
Hypersensitivity pneumonitis	38	12	1.56	0.06 (495)
Connective tissue disease	45	33	2.31	0.39 (517/710)
Idiopathic pulmonary fibrosis	62	44	12.4	0.05 (16.3)
Total of ILDs	220		22.0	0.65

Between brackets the codes of the "International Classification of Diseases 1975, 9th revision" (ICD-9) of the World Health Organization [10] are given. Adapted from [64, 65].

such as chest or ophthalmology units. Some data are available for other relatively frequently observed ILDs (table 7) [84, 85].

Sarcoidosis

From radiographic population screening programmes (especially for detection of tuberculosis), a global prevalence of 10–40 per 10^5 and an incidence of 10 per 10^5 has been estimated [44, 45]. The incidence appears to be higher in some countries (Scandinavia), some population groups (*e.g.* 40 per 10^5 in African Americans) and in some families [86–92]. International pulmonary registries have illustrated differences in the presentation of sarcoidosis in different countries [86]; in Asia the majority of cases presented with a radiological stage I (mediastinal and hilar lymphadenopathies), and a positive tuberculin skin test was found more frequently than in other countries. However, erythema nodosum has not been reported in the Japanese [93, 94], is rare in African Americans, is the presenting symptom in 18% of cases in Finland [94] and occurs in about 30% of British sarcoidosis patients [95]. In the USA, a higher percentage of patients <40-yrs-old was found (68% of the patients in USA) than in other countries, as well as a higher percentage of patients of African background (58% of all sarcoidosis patients in the USA).

Sarcoidosis is rarely reported in Portugal, India, Saudi Arabia or South America, partly because of the absence of mass screening programmes, and probably also because of the presence of other, more commonly recognized granulomatous diseases (tuberculosis, leprosy, fungal infection). Further, in Catalonia (Spain), an incidence of only 1.2 per 10^5 inhabitants has been reported [96].

Few mortality data on sarcoidosis are available. A 5-yr mortality rate of 2% has been reported by a referral university hospital [64] (table 6). A review of autopsy records of Japanese nationwide data and of two American institutions (Mayo Clinic, Rochester and University of Southern California, Los Angeles) showed that in Japan, heart involvement was the most common cause of death, and in Western countries, lung involvement was most common, with a mortality of about 5% [96]. FLEMING [97] reported much higher mortality rates among patients with cardiac sarcoidosis in 1988.

Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis

For IPF, changes in definitions from the old histological classification by LIEBOW [17] to the recent adaptation by KATZENSTEIN and MYERS [18] and the ATS/ERS Consensus [6] have to be taken into account. In addition, the histological pattern of UIP may be found in conditions other than IPF, *e.g.* drug-induced or collagen vascular ILD, asbestosis, *etc.* (see the Review by DU BOIS and WELLS [8] in this Supplement).

The exact incidence, prevalence and mortality of IPF are not known [98]. SCOTT *et al.* [76] estimated a prevalence for IPF of 3–6 cases per 10^5 in the general population. More recently, COULTAS *et al.* [12] found a prevalence of IPF of 20 per 10^5 in males and 13 per 10^5 in females. They found an incidence of 11 per 10^5 per yr in males and of 7 per 10^5 per yr in females (table 7), but the criteria that provided the basis for these data are not precisely defined. About 80% of the IPF patients are $\geqslant$65-yrs-old.

Among seven countries, HUBBARD *et al.* [16] found a large variation in mortality data of IPF/CFA (ICD 516.3) from 0.03–1.3 per 10^5 and of postinflammatory fibrosis (ICD 515) from 0.6–1.7 per 10^5 (table 8), which they attributed, at least to some extent, to differences in classification. Indeed, the countries with higher frequencies for postinflammatory fibrosis tended to have lower frequencies for IPF and *vice versa*. In England, the mortality rate of IPF in 1979 was estimated at ~1.5 per 10^5 population in males (standardized for age) and 1 per 10^5 in females [32]. In Japan, the mortality rate for IPF was estimated to be 3.0 per 10^5 [99]. In the USA, MANNINO *et al.* [100] found higher age-adjusted mortality rates in Whites than in African-Americans, but this finding has been attributed to incomplete reporting [6].

Death certificates of IPF may contain errors due to several causes: cases of IPF (ICD 516.3) may be coded as having died from other causes (*e.g.* infection, heart failure), and may be coded as postinflammatory

Table 7. – Summary of estimates of incidences and prevalences of some more frequent interstitial lung diseases

	Incidence	Prevalence	References
Sarcoidosis	$10/10^5$	$10–40/10^5$ population	[44, 45]
Idiopathic pulmonary fibrosis		$3–6/10^5$ population	[76]
	$7–11/10^5$	$13–20/10^5$ population	[12]
Farmer's lung		$10–200/10^5$ population	[54, 55]
		$4–170/10^3$ farmers	[59, 77]
Pigeon breeder's lung		$1–100/10^3$ breeders*	[78]
Budgerigar fancier's lung		$5–75/10^3$ fanciers	[79]
Systemic lupus erythematous		10% of $40/10^5$ population	[80, 81]
Systemic sclerosis		20–65% of $10/10^5$ population	[82, 81]
Rheumatoid arthritis		20% of $2/10^2$ population	[83]

*: prevalence in Budgerigar fanciers was 3.4% (0.5–7.5%) [79].

Table 8. – Crude mortality rates for idiopathic pulmonary fibrosis (ICD 516.3) and postinflammatory fibrosis (ICD 515) in 1987 in seven countries [16]

Country	Idiopathic pulmonary fibrosis per 10^5	Postinflammatory fibrosis per 10^5
England, Wales	1.3	1.1
Scotland	1.1	1.0
New Zealand	0.6	0.6
Australia	0.5	1.0
Canada	0.3	1.4
USA	0.1	1.7
Germany	0.03	0.6

ICD: International Classification of Diseases 1975, 9th revision [10].

pulmonary fibrosis (ICD 515). PANOS *et al.* [101] found that of their IPF patients who died, respiratory failure was the cause in 39%, cardiovascular disease in 27%, lung cancer in 10% and other causes in 18%. For all these reasons, statistics by death certification generally underreport the diagnosis [15, 20, 32, 62, 76]. JOHNSTON *et al.* [32] and HUBBARD *et al.* [16] found that mortality rates increased in most countries in the years after 1979, which in part may be due to improved diagnostic skills (see earlier).

In a cohort study in England, HUBBARD *et al.* [102] found that in newly diagnosed cases of CFA/IPF (*i.e.* incident cases) median survival was only 2.9 yrs and that the expected life span in these cases was reduced to ~7 yrs. Median survival for prevalent cases was 9 yrs compared to an expected 13 yrs. They concluded that the estimate of a median survival for CFA/IPF of ~5 yrs in previous clinical case series [20, 21, 99], in which prevalent cases were also included, may thus have been influenced by this inclusion bias.

Hypersensitivity pneumonitis/extrinsic allergic alveolitis

The list of different aetiological agents and sources of antigens capable of inducing hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis (EAA) is already enormously long and continues to grow. However, as SELMAN [56] states, "the literature is replete with a number of HP-like disorders". Indeed, some factors may cause HP and other forms of inhalation pathology, such as organic dust toxic syndrome (ODTS), chemical pneumonitis and inhalation fever. ODTS is much more frequent than hypersensitivity pneumonitis: it is at least 20–50 times more common than farmer's lung in Sweden [103]. In many publications reporting high incidences of HP (*e.g.* farmer's lung), cases of ODTS may also have been included. However, the mechanism, evolution and prognosis of ODTS is quite different from that of HP.

The two most extensively studied forms of HP are farmer's lung and pigeon breeder's lung (table 7). The prevalence of farmer's lung has been estimated to range from 10–200 per 10^5 inhabitants in different zones of England [54] and in Finland [55], and 4–170 per 1,000 farmers in France [59] and the USA [77] (see Review by BOURKE *et al.* [41] in this Supplement).

Prevalence of clinical disease in pigeon breeders has in the past, been estimated at ~1 per 1,000 [78], but more recently, prevalences of >10% and sensitization rates of 32% have been reported in those with regular high exposure [104].

The prevalence of HP varies markedly between countries, due to the local climate, season, geographical conditions, local customs, smoking history and presence of industrial manufacturing plants. As many as 50% of individuals exposed to environmental antigens that can cause hypersensitivity pneumonitis develop a lymphocytic alveolitis but remain asymptomatic [105], whereas only a few develop clinical symptoms of the disease. Cigarette smokers have a very low incidence of HP compared with nonsmokers [104, 106], which has been attributed to the low level of expression of costimulatory molecules (*e.g.* B7) on alveolar macrophages from smokers, and to their resistance to further upregulation [107]. Furthermore, some cofactors might enhance the risk of developing the disease, such as endotoxin exposure or viral infection, as has been shown in a mouse model of HP where Senda virus infection increases susceptibility for up to 6 months [108]. A highly significant increase in prevalence of farmer's lung in dairy farmers in the French Doubs province has been found with increasing altitude [109]. A genetic predisposition, *e.g.* a particular HLA specificity [110, 111], may also enhance the risk of developing HP (see also Report of Working Group 3 by NEMERY *et al.* [112] in this Supplement).

Interstitial lung disease in connective tissue disease

Lung involvement is now considered a major source of morbidity in connective tissue disorders (CTD). In systemic sclerosis (SSc) and polymyositis/dermatomyositis (PM/DM), pulmonary disease (including ILD, aspiration pneumonitis and pulmonary vascular disease) is now the most common cause of death. In rheumatoid arthritis (RA), up to 20% of fatalities are due to bronchopneumonia [113, 114]. Therefore, it is surprising that estimates of the prevalence of pulmonary involvement vary widely in CTD. The major difficulty, which also applies to ILD in general, is that the frequency of diagnosing ILD is critically dependent upon the methods used to detect lung abnormalities (see Review by LAMBLIN *et al.* [115] in this Supplement).

Symptoms are unreliable in defining lung involvement in CTD. Exertional dyspnoea is common, especially in SSc (occurring in at least half of the patients) [116]. However, dyspnoea cannot be used as a marker of ILD, as it often occurs when the work of locomotion is increased (in arthritis or myositis) without lung involvement. Furthermore, the opposite is sometimes true: the presence of severe systemic disease may prevent patients exercising sufficiently to experience dyspnoea, despite severe impairment in lung function tests. Thus, objective methods must be employed, but estimates of prevalence of ILD remain

highly variable. In general, ILD is most commonly identified in histological or autopsy studies and in lung function surveys. CT often demonstrates abnormalities not seen on plain chest radiography. A highly variable proportion of patients have evidence of alveolitis on BAL (although it is not yet clear whether subclinical alveolitis is synonymous with early ILD in CTD).

The difficulty in defining prevalence is well-illustrated in individual CTD. In SSc, pulmonary fibrosis is one of the American Rheumatism Association's (ARA) diagnostic criteria for the disease [117]; pulmonary fibrosis is found at autopsy in >75% of patients [118, 119] and lung function abnormalities are found in 90%. ILD is seen on chest radiography in 25–65% [82], with the highest prevalence amongst CTD; on CT, limited fibrosis is identified in a further subgroup with normal chest radiograph appearances [120]. Thus, even in a disease in which ILD is present in the majority of patients, in most studies the prevalence may be variably estimated as lying between 25% and 90%.

In diseases in which clinically overt ILD is less common, such as RA, the data on prevalence are even more conflicting. In an open lung biopsy study of volunteers with RA (most without clinical evidence of lung involvement), histological abnormalities compatible with ILD were identified in 60% [121]. This finding is consistent with the observations that gas transfer is reduced in 40% of unselected RA patients [122] and that lung disease is evident on CT in up to 50% [123, 124]. However, in striking contrast, there is evidence of pulmonary fibrosis on chest radiography in only 1–20% (in three very large chest radiographic series of unselected patients with RA [83, 125, 126]). Thus, it can be argued that clinically significant ILD is difficult to predict.

These findings are mirrored in ankylosing spondylitis (AS), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). In general, plain chest radiographic series show a prevalence of pulmonary fibrosis of <10% [80, 127, 128]; however, on CT, ILD is present in $\geq$30% of patients [129–131], and subclinical alveolitis on BAL is common [132, 133]. The definition of the prevalence of pulmonary fibrosis in SS has been particularly hampered by failure to discriminate between primary and secondary SS in early series (lung disease in secondary SS being ascribable to the primary CTD), and variations in diagnostic criteria for SS [134]. PM/DM is less well studied; ILD is clinically overt in up to 30% of patients [135], but no single definitive evaluation of large numbers of patients has been performed.

It may be concluded that through the use of sensitive diagnostic methods such as CT and BAL, evidence of ILD can be identified in a majority, or large minority of patients with CTD. However, with the use of chest radiography and traditional clinical evaluation only, ILD is identified in <10%, except in SSc and PM/DM. The dilemma in epidemiological studies is whether to view subclinical ILD, detectable only on CT or at BAL, as part of a continuum with clinically overt ILD. Present data do not justify this assumption: it is not clear whether subtle interstitial abnormalities identified using highly sensitive tests necessarily evolve into important fibrotic lung disease. However, appropriate longitudinal studies should be designed to address this issue.

It, therefore, appears to be difficult to provide meaningful data on prevalence of ILD in CTD. The prevalence of RA is estimated at 2% and evidence of ILD on chest radiography and routine lung function may be present in up to 20% of these patients [83] (table 7). The prevalence of SLE is 40 per 10^5 population [81] with an estimated clinically relevant ILD of 10% [80] and the prevalence of SSc is 10 per 10^5 population [81] with ILD in 20–65% of these [82].

Drug-induced interstitial lung disease

Drug-induced lung diseases often have no pathognomonic signs or symptoms [136] and are underdiagnosed (see Review by Camus *et al.* [61] in this Supplement). Indeed, they account only for 2.5–3% of all ILD in several registries [12–14, 49, 50]. In fact, some cases of presumed IIP may be due to unrecognized drug-induced ILD.

Several groups of drugs are especially prone to induce ILD; some examples are listed below.

Antitumour drugs. Cytotoxic antibiotics. Bleomycin lung is the most studied example, with a reported incidence which varies from 2–40% [137], although in the larger studies rates of 8–10% have been observed [138]. At a cumulative dose >500 $mg \cdot m^{-2}$, toxicity occurs in 17% [138]. Mitomycin has been reported to induce pulmonary fibrosis in 2–12% of patients [139].

Alkylating drugs. Cyclophosphamide causes early-onset ILD with a low incidence, estimated at <1% [136]. Busulphan may cause ILD 12–24 months after initiation of treatment in ~4% of cases [136].

Antimetabolites. Carmustine used in high doses induces early-onset pulmonary fibrosis in 10–30% of patients, and late-onset fibrosis (after a latency period of 8–17 yrs) in 35% of the surviving patients.

Miscellaneous. Interleukin-2, according to early reports, causes radiographic infiltrates in 70–80%, but with more recent treatment approaches, the rate of severe pulmonary toxicity has been reduced to 5%, and in most cases the abnormalities resolve within 3–5 days after cessation of therapy [140].

Antiarrhythmic agents. Amiodarone. Pulmonary toxicity has an incidence of ~5% and among these cases fatality rates range from 10–20% [141].

Procainamide. Between 50–90% of patients taking procainamide for longer than 2 months develop serum antinuclear antibodies (ANA); 10–20% of these ANA-positive patients develop symptomatic drug-induced SLE; 40–80% of these have pulmonary

manifestations, which, in up to 40%, are accompanied by bibasilar pulmonary infiltrates [140].

Antibiotics. In particular, beta-lactams, sulphonamides, antimalaria drugs, tetracyclines, erythromycin and some tuberculosis medications may induce idiosyncratic pulmonary infiltrates with eosinophilia (PIE-syndrome). The precise incidence is not known. Nitrofurantoin may cause severe acute toxicity in ~1 out of 5,000 new administrations [142]; mixed interstitial and alveolar infiltrates on chest radiograph are seen in ~16% of these patients and are associated with a mortality of 0.5% [143]. Chronic pulmonary toxicity occurs in 1 of 750 patients on long-term therapy for asymptomatic bacteriuria; >70% fail to improve or show significant residual pulmonary abnormalities, and mortality has been reported at 8–10% [140].

Anticonvulsants. Diphenylhydantoin may cause several forms of pulmonary toxicity and carbamazepine also causes an acute hypersensitivity syndrome, but the incidences of these are not well known.

Anti-inflammatory agents. Aspirin at severe overdoses is complicated in 10–15% of cases by pulmonary oedema, which leads to mortality in 1–2% of young and otherwise healthy patients with prompt recognition of the overdose, but in up to 25% of older patients with multiple medical problems [144]. Nonsteroidal anti-inflammatory drugs may cause acute pulmonary hypersensitivity reactions, with bilateral interstitial infiltrates occurring in some cases after <1 week, and in others up to 3 yrs after the first exposure to the drug [145]. Methotrexate pulmonary toxicity occurs in 1–5% of patients with rheumatoid arthritis and in as many as 10–14% of patients treated for primary biliary cirrhosis [146, 147]. Gold may cause interstitial pneumonitis in <1% of patients. Gold toxicity occurs, on average, after 3 months of therapy and at a cumulative dose of ~700 mg [136]. Penicillamine use in patients with RA is associated with chronic alveolitis/fibrosis, hypersensitivity pneumonitis, alveolar haemorrhage and bronchiolitis obliterans [140]. There is still some debate concerning the relative contribution that penicillamine and the underlying RA make to the genesis of the pulmonary abnormalities. Azathioprine is rarely associated with the development of chronic pneumonitis and fibrosis.

Conclusions and outlook

The working group conclude that there is little good epidemiological data on interstitial lung disease, that many questions remain unanswered, and that there is a great need for future studies. Amongst these questions and needs, the following represent a nonexhaustive list of what is required: the frequency of interstitial lung disease with reliable estimates of incidence and prevalence; the validity of registries including both passive and active methods of data collection; the mortality due to interstitial lung disease, as well as the validity of current vital statistics; the occurrence of interstitial lung disease in children including incidence, prevalence and mortality; further studies of the role of exogenous factors such as occupation in interstitial lung disease of unknown aetiology; further studies of the role of genetic factors in interstitial lung disease of exogenous origin; uniform and adequate definitions and classifications of interstitial lung disease in prevalence, incidence and mortality studies on interstitial lung disease; and operative criteria for case-definition in epidemiological studies.

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