INT J TUBERC LUNG DIS 11(2):122–133

STATE OF THE ART SERIES
Occupational lung disease in high- and low-income countries,
Edited by M. Chan-Yeung
NUMBER 1 IN THE SERIES

Occupational asthma in the developing and industrialised world: a review

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SUMMARY

Occupational asthma is the most common occupational lung disease in industrialised countries, and the second most common occupational lung disease reported after pneumoconioses in developing countries. The median proportion of adult cases of asthma attributable to occupational exposure is between 10% and 15%. The population attributable fraction appears to be similar in industrialised and developing countries characterised by rapid industrialisation (13–15%), but lower in less industrialised developing countries (6%). The high-risk occupations and industries associated with the development of occupational asthma vary depending on the dominant industrial sectors in a particular country. High-risk exposure to cleaning agents and pesticide exposure in developing countries appear to be as important as exposure to isocyanates, cereal flour/grain dust, welding fumes, wood dust and, more recently, hairdressing chemicals, commonly reported in industrialised countries. The reported mean annual incidence of occupational asthma in developing countries is less than 2 per 100 000 population, compared to very high rates of up to 18/100 000 in Scandinavian countries. While occupational asthma remains under-recognised, especially in developing countries, it remains poorly diagnosed and managed and inadequately compensated worldwide. Primary and secondary preventive strategies should be directed at controlling workplace exposures, accompanied by intense educational and managerial improvements. Appropriate treatment remains early removal from exposure to ensure that the worker has no further exposure to the causal agent, with preservation of income. However, up to one third of workers with occupational asthma continue to remain exposed to the causative agent or suffer prolonged work disruption, discrimination and risk of unemployment.

KEY WORDS: occupational asthma; developing countries; industrialised countries

RECENT STUDIES of the global burden of disease over the last two decades indicate that occupational lung diseases such as chronic obstructive pulmonary disease (COPD), asthma and pneumoconioses caused by exposure to airborne particulates are a major contributor to mortality and disability, particularly in developing countries. These chronic respiratory diseases comprise close to 10% of all occupational diseases reported in industrialised countries such as the United Kingdom, and appear to be much higher in rapidly industrialising developing countries such as Nigeria.[1,2] While occupational asthma (OA) is the most common of the occupational lung diseases in most industrialised countries, OA is the second most common occupational lung disease reported after pneumoconioses in developing countries such as South Africa.[3]

International reviews suggest that the median proportion of adult cases of asthma attributable to occupational exposure is between 10% and 15%.[4] The population attributable fraction appears to be similar in industrialised and rapidly industrialising developing countries such as China (15%) and South Africa (13%),[5,6] but lower in less industrialised developing countries such as Zambia (6%).[7] However, studies in both industrialised and developing countries suggest that, depending on the industry, work-related factors can be responsible for up to one third of all adult asthma cases.[8,9]

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Article submitted 11 May 2006. Final version accepted 9 June 2006.

DEFINITIONS

Work-related factors operating through a number of different pathophysiological mechanisms are responsible for various manifestations of asthma.[10] Work-related asthma can be broadly defined as 1) OA or asthma caused by specific agents in the workplace, and 2) work-aggravated asthma or pre-existing asthma worsened by workplace exposures.[11] There are two major forms of occupational asthma: 1) allergic (immunological) asthma, characterised by a latency period required for developing allergic sensitisation prior to the development of symptoms, and 2) irritant-induced (non-immunological) asthma characterised by rapid onset of asthma following single or multiple exposures to high concentrations of irritant compounds. There is, however, no globally accepted definition of OA, as this would vary depending on the purpose for which it is used. These may include epidemiological studies, voluntary surveillance schemes, workplace-based medical surveillance programmes, clinical diagnosis and medico-legal evaluations for the purposes of obtaining worker compensation. Due to these differences and the lack of access to reliable and well-validated diagnostic tools, OA remains under-recognised, poorly managed and inadequately compensated, especially in developing countries.[12,13] Recent initiatives in South Africa have attempted to address these issues, such that the Workers Compensation dispensation covers all types of work-related asthma: occupational asthma (immunological), occupational asthma (irritant-induced), work-aggravated asthma and the variant syndromes (e.g., asthma-like disorders) (Table 1). All three entities now require compulsory notification according to the legislative imperatives of the country's Workers Compensation and Health and Safety laws. These definitions draw to a large extent on definitions derived through consensus statements of professionals in industrialised countries.[11]

EPIDEMIOLOGY

Incidence

In the absence of complete registries for OA worldwide, the true frequency of the disease remains unknown.[14] International comparisons on the incidence of OA, however, suggest a wide variation between industrialised and developing countries, with a rising incidence in industrialised countries. Very high incidence rates are reported by Scandinavian countries (7–18/100 000), with Finland reporting the highest incidence, Western Europe and the USA having intermediate rates (2.4–4.3/100 000), while developing countries such as South Africa and Brazil (Sao Paulo) report a much lower incidence of 1.8/100 000 and 1.7/100 000, respectively (Figure).[3,9,15,16] Despite this relatively low incidence in South Africa, regional differences exist, with a much higher incidence reported in the Western Cape province, which is highly urbanised (2.5/100 000). The gender distribution of OA appears to be inconsistent, with some countries reporting a slightly higher incidence in men (Sweden, UK, France, Brazil), while others report higher rates for women

Table 1 Diagnostic criteria for defining various entities of work-related asthma under the Workers Compensation System in South Africa

Occupational asthma (immunological) as per circular instruction 176*	Occupational asthma (irritant-induced) as per circular instruction 177*	Work-aggravated asthma as per circular instruction 184*
Requires all 4 criteria (A–D)	Requires all 5 criteria	Requires all 5 criteria
A A medical practitioner's diagnosis of asthma and physiological evidence of reversible airways obstruction or airways hyper-responsiveness.	1 Medical history indicating the absence of pre-existing asthma-like complaints.	1 Medical history indicating pre-existing asthma or history of asthma symptoms, prior to the start of employment or exposure to the known aggravating agent.
B An occupational exposure preceding the onset of asthma symptoms.	2 Onset of symptoms after a single or multiple exposure(s), incident(s) or accident(s).	2 Presence of work-related exposures preceding and/or associated with the onset of an asthma attack or the worsening of symptoms.
C An association between symptoms of asthma and work exposure.	3 Occupational exposure to a gas, smoke, fume, vapour or dust with irritant properties.	3 Presence of work-related factors known to aggravate asthma symptoms (e.g., cold air, dusty work, chemical or biological irritants, indoor air pollutants, physically strenuous work, second-hand smoke)
D An exposure and/or physiological evidence of the relationship between asthma and the workplace environment (requires D1and preferably one or more of D2–D5)	4 Onset of symptoms within 24 hours of exposure with persistence of symptoms for at least 3 months. (An association between symptoms of asthma and exposure.)	4 Increase in symptoms or medication requirements, or documentation of work-related changes in PEFR or FEV_1 after start of employment or occupational exposure.
1 Workplace exposure to agent reported to give rise to occupational asthma.	5 Presence of airflow obstruction on pulmonary function tests and/or presence of NSBH on tests done at least 3 months after exposure.	5 Presence of reversible airflow obstruction and/or NSBH on pulmonary function testing.
2 Work-related changes in FEV_1 or PEFR.		
3 Work-related changes in serial testing of NSBH (e.g., methacholine challenge test).		
4 Positive specific bronchial challenge test.		
5 Positive skin prick test or raised specific IgE antibody level to the suspected agent.		

* As published in the Government Gazette, Pretoria. Republic of South Africa. http://www.labour.gov.za/programmes/
FEV_1 = forced expiratory volume in one second; PEFR = peak expiratory flow rate; NSBH = non-specific bronchial hyper-responsiveness.

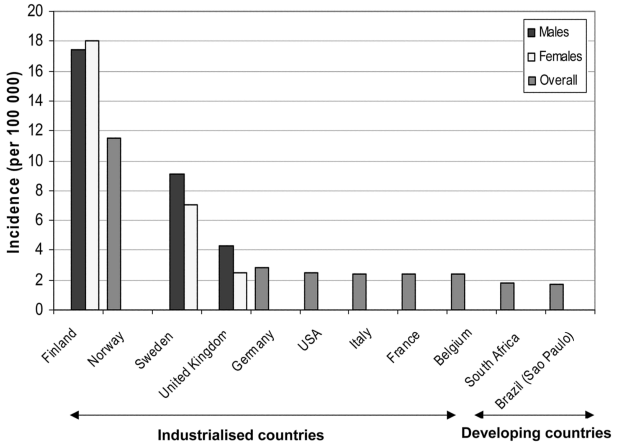

Figure Mean annual incidence rate of occupational asthma in industrialised and developing countries (adapted from [3,9,15,16]).

(Finland, USA, Europe).[3,9,17] The differences observed appear to reflect the preponderance of men or women in particular industrial sectors of the economy in these countries. Published data on OA incidence rates according to age are limited and demonstrate inconsistent trends, either increasing with age (UK) or with much higher rates in the 15–29 year age group (France).[17,18] There appears to be much more consistent evidence, however, in the patterns of the two major manifestations of OA reported in industrialised and developing countries, with most studies demonstrating much higher proportions (70–90%) of allergic compared to irritant-induced OA.[9,16,17]

High-risk industries and occupations

Some common industries and occupations appear to be consistently associated with a higher incidence of OA.[14] These include bakers and pastry makers (most European and Scandinavian countries, New Zealand), spray painters, especially in the car manufacturing industry (Norway, France, UK, Spain, New Zealand), and health care workers (France, Italy, Belgium) (Table 2).[9,16,17] These patterns are also observed in developing countries such as South Africa.[3] In certain countries, such as Norway, Germany and France, hairdressers appear to be at high risk.[9,17] Interestingly, unlike other industrialised countries, in Finland the agricultural sector (farming, animal husbandry) has the second highest incidence rates among women workers.[9] This pattern is very similar to developing countries such as Zambia.[7] Countries such as New Zealand and South Africa have smelting aluminium and refining platinum operations that also report a high incidence of OA.[3,9] Cleaners and janitors are commonly reported high-risk occupations in both industrialised (USA) and developing countries (Brazil, South Africa).[3,9,15] Lumber and wood product workers in Africa (Zambia) are other high-risk occupations.[7]

Causative agents

In most industrialised countries, the main causes of asthma, ranked according to the proportion of total reported cases per country, include isocyanates, cereal flour/grain dust, welding fumes and wood dust (Table 3).[9,16,18] Exposure to animal epithelia, hair and secretions is commonly reported in Finland among laboratory animal workers and agricultural workers.[9] Latex allergy-related asthma appears to be less common in industrialised countries due to the introduction of latex-free gloves in most health care settings, as demonstrated in Canada.[19] However, the introduction of new agents containing persulfates in the hairdressing industry (hair dyes, hair fixing, hair waving solutions) are emergent causes in France and Germany.[9,17] In developing countries, the spectrum of OA-causing agents is more diverse and less consistent, due to uneven industrial development and the relatively under-developed or non-existent surveillance systems in most countries,

Table 2 Common industries and/or jobs associated with occupational asthma in industrialised and developing countries (adapted from [3,8,9,15,16])

Industrialised countries (Finland, Sweden, Norway, Italy, France, Spain, Germany, United Kingdom, USA, Canada, New Zealand)	Developing countries (South Africa, China, Brazil, Zambia)
• Manufacturing: bakers and pastry makers, car/coach spray painters, motor vehicle manufacturing, machine and metal product assemblers, painters and lacquerers, chemical/petroleum workers, cooks/ butchers, welders, furnacemen, plastic product workers, floor layers, leather and shoe workers, seafood processors	• Manufacturing: car/coach spray painters, bakers and pastry makers, grain milling, chemical/foam/ plastic product workers, metal/electric/electronic workers, lumber/wood product workers, rubber product workers, pharmaceutical workers
• Health care and social work: health service workers, veterinary surgeons, laboratory technologists	• Health care and social work: health service workers
• Agriculture, forestry and fishing: farmers, stock breeders of poultry/dairy	• Agriculture, forestry and fishing: farmers
• Service work: hairdressers, janitors/cleaners	• Service work: janitors/cleaners/ housekeepers
• Commercial work: wholesalers and retailers, clerks	• Mining: platinum refinery workers
• Mining: aluminium smelter workers	

Table 3 Common causes of occupational asthma in industrialised and developing countries (adapted from [3,8,9,15,16])

Industrialised countries (Finland, Sweden, Norway, Italy, France, Germany, UK, USA, Canada, New Zealand, Singapore)	Developing countries (South Africa, China, Brazil, Zambia)
• Isocyanates	• Cleaning agents
• Cereal flours/grain dust	• Thermal degradation products (plastics, rubber)
• Welding fumes	• Latex proteins
• Wood dust	• Isocyanates
• Animal epithelia, hairs, secretions	• Cereal flours/grain dust
• Aldehydes	• Agricultural products
• Latex proteins	• Metallic products (e.g., platinum)
• Persulfate salts	• Solvent petroleum derivatives
• Solder flux	• Wood dust
• Seafood	

resulting in a large proportion of cases going unreported.[7] Between 1997 and 1999, the surveillance programme in South Africa (SORDSA), reported isocyanates (a component of automotive spray paints and polyurethane foam products), latex proteins, flour and grain and platinum salts as the most common agents.[3] In a study of patients presenting with acute asthma in emergency casualty units at two large public hospitals, the most commonly cited exposures were cleaning agents, dyes and paints.[8] This pattern has some similarities with data from Brazil (Sao Paulo) demonstrating cleaning agents and isocyanates to be the common putative agents in addition to other chemicals (thermal degradation products of plastics/rubber and solvent petroleum derivatives).[15] Chemicals, petrochemicals, pesticides and other agricultural products such as organic dusts are also major agents identified among Zambian and Chinese workers with work-related respiratory symptoms and asthma.[5,7,20,21] When comparing data between industrialised and developing countries, it must be borne in mind that putative agents identified among patients with OA in developing countries have to a large extent been based on clinical impression supported by simple diagnostic tools rather than more objective tests such as specific bronchial challenge tests.

Epidemiological studies in selected developing countries

Although a number of epidemiological studies in high-risk workplaces have been conducted in many industrialised countries, studies in developing countries are few. One of the difficulties with comparing prevalence of OA is not only the definition, but also the diagnostic methods used. For example, the prevalence of OA when specific inhalation challenge tests are used is much lower than symptom-based surveys using questionnaires only. In the final analysis, however, the prevalence or incidence is primarily dependent on the agent concerned as well as on the degree of exposure. South Africa appears to be one of the few developing countries where the epidemiology of occupational allergic asthma has been better characterised. The patterns of work-related asthma are quite diverse, demonstrating an array of economic activities associated with the disease (Table 4).[22–37] A large proportion of these studies have been conducted in food processing workplaces, where a much higher prevalence of work-related allergic asthma is reported in grain (wheat) milling plants (17%) and bakeries (11%) than in animal processing plants (fish, 3%). A high prevalence of work-related asthma (15–30%) has also been reported among workers handling isocyanates in automotive repair shops and in chemical processing activities. Chemical processing plants such as platinum refineries appear to cause a much higher disease burden than vanadium plants. The prevalence of work-related asthma in wood working operations, such as sawmills and furniture plants, appears to be lower (3–7%). Notably absent are epidemiological studies on irritant-induced asthma, despite the presence of large industries where high-risk exposures may be more prevalent.

Epidemiological studies in other countries in Africa are limited. Studies among traditional grain market workers (n = 277) in Morocco have observed a significantly higher prevalence of respiratory symptoms (64%), lung function abnormalities (37%) and skin reactivity to potential occupational allergens (30%) compared to a non-exposed group.[38] Similar findings were observed among flour mill workers (n = 373) for respiratory symptoms (64%) and lung function abnormalities (small airway obstruction) (32%), but a much higher prevalence of skin reactivity was observed to flour dust allergens (42%).[39] These studies among grain mill workers demonstrate a higher prevalence of asthma symptoms than similar studies in South Africa (25%) (Table 4).[22–24] Studies in Ethiopia among workers in cement (32%, n = 53) and cigarette (15%, n = 67) factories demonstrated a much higher prevalence of asthma symptoms than in unexposed subjects.[40] These cement (packing, rotary kiln) and tobacco (blending, packing and making) workers also had significantly greater and consistent impairment of small airway function. Studies among small-scale wood industries in Tanzania (n = 546) involved in manual planing, sawing, carving and drilling various, mainly indigenous, species of hardwood (teak, mahogany, bloodwood, camphor, cedar, blackwood) and softwood (podo, cyprus, pine) demonstrated a slightly higher prevalence of work-related asthma symptoms (5–7%) than sawmillers in Nigeria (4%).[41,42] The mean peak expiratory flow rate (PEFR) in the latter group of workers was significantly lower than in the control subjects. The findings of these studies among wood workers are very similar to the studies performed in South Africa (3–7%) (Table 4).[36,37]

Table 4 Occurrence of occupational respiratory allergy and asthma in selected workforces in South Africa

Type of workforce, author, year published	*n*	Outcome measure	Agent/s implicated	Prevalence/ incidence
Grain mill Jeebhay 2000, 2005[22]	111	Work-related grain dust allergic asthma*	Wheat, storage pests (mealworm, cockroach, storage mites)	17%
Yach 1985[23]	582	Asthma symptoms		23–25%
Grain mill Bartie 2004[24]	84	Work-related asthma symptoms	Maize, storage pests (weevils)	7%
Soybean processing Mansoor 2004[25]	115	Work-related soybean allergic asthma*	Soybean	IR: 2/1000 person months
Supermarket bakeries Jeebhay 2005[26]	517	Occupational asthma	Cereal flour (wheat, rye) and fungal alpha-amylase	11%
Poultry processing Rees 1998[27]	134	Asthma symptoms	Feed, poultry matter (feathers, droppings, serum)	12%
Seafood processing Jeebhay 2003[28]	594	Occupational asthma	Fish products, fish parasite (*Anisakis*)	3%
Vineyards Jeebhay 2002[29]	207	Work-related spider mite allergic asthma*	Spider mite	7%
Hospitals (high-risk group) Potter 2001[30]	717	Work-related latex allergic asthma*	Natural rubber latex protein	9%
Experimental laboratory Lopata 2004[31]	10	Work-related locust allergic asthma*	Locust matter (wings, faeces, body)	30%
Chemical processing/packaging Soderlund 1993[32]	20	Work-related asthma	Toluene di-isocynate	30%
Automotive spraypainting Randolph 1997[33]	40	Asthma symptoms	Hexamethylene di-isocyanate	10–15%
Platinum refinery Calverley 1995[34]	78	Platinum salt sensitivity	Platinum salts	24-month CI: 41%
Vanadium plant Irsigler 1999[35]	1440	Asthma symptoms	Vanadium pentoxide	24-month CI: 11%
Furniture plant Pitt 1985[36]	27	Work-related asthma symptoms	Wood dust (yellow wood, stinkwood, blackwood, imbuia)	7%
Sawmill plant Fox 2004[37]	392	Asthma	Wood dust (pine wood)	3%

* Work-related asthma symptoms + allergic sensitisation with or without spirometry changes.
IR = incidence rate; CI = cumulative incidence.

Very few isolated epidemiological studies have been reported in other parts of the developing world beyond Africa. A study of two silk filatures (processing natural silk) in India reported a 17% prevalence of OA due to silkworm allergens.[43] Workers in a cement factory in the United Arab Emirates had a two-fold higher prevalence of asthma compared to an unexposed group (6% vs. 3%).[44] The causative agents or work processes were, however, not identified. Women performing indoor jobs in Iran had an 11% prevalence of asthma ($n = 561$), which was more prevalent among those involved with bread baking, carpet weaving and poultry feeding activities.[45] A study of Malaysian rice millers ($n = 122$) reported an increased propensity for allergic symptoms, including asthma related to rice husk dust.[46] Epidemiological studies on latex allergy and asthma have mainly been reported from developing countries in South-East Asia. In a study of 314 workers exposed to latex during tapping and glove manufacture activities in Thailand, 20% reported work-related asthma symptoms, but the prevalence of latex sensitisation on skin prick test was <2%, despite high concentrations of airborne exposure.[47] Similarly, the prevalence of latex allergic asthma symptoms among hospital staff in Hong Kong was also low (3%).[48] These findings are in contrast to epidemiological studies in South Africa, where a much higher prevalence of sensitisation and work-related asthma (9%) has been reported.[30] Few small-scale studies among Chinese workers have reported a high prevalence (27%) of work-related wheeze and lung function impairment among painters exposed to toluene di-isocyanate during the process of handling polyurethane varnish in a furniture manufacturing factory.[49] These figures are very similar to studies among South African workers (10–30%).[32,33] Unlike the South African studies in the food harvesting and processing industry, a low prevalence (<2%) of buckwheat allergy and doctor-diagnosed asthma have been reported among Chinese workers producing buckwheat noodles ($n = 25$) and agricultural researchers ($n = 16$).[26,29,50] However, spider mite-related allergy and asthma among Korean workers on fruit (apple, pear, citrus) farms are reported to be much higher (12%) than among table grape farm workers (7%) in South Africa, with both studies reporting high pesticide use on these farms.[29,51]

DIAGNOSIS

Approaches to the diagnosis of OA vary between countries in the industrialised world and between developing and industrialised countries. In most countries, a stepwise approach is often used, with the extent of the investigation being largely dependent on the definition subscribed to in the particular country, the purpose of the investigation and the level of diagnostic capabilities available (Table 1).[52] This is evident in the reports of various surveillance programmes for occupational lung diseases in these countries (Table 5).[3,15,16,53–56] While clinicians in most countries, and especially in developing countries, rely on clinical and occupational histories, their use of other diagnostic modalities varies. Despite the great reliance on questionnaires for identifying workers with occupational asthma, due to their high sensitivity, their specificity is quite low.[14] Although there is no fully validated questionnaire for diagnosing OA, recent studies suggest that the use of more standardised questionnaire items can improve the specificity of the instrument.[57,58] For high molecular weight (HMW) agents (protein agents >5–10 kDa), the data suggest that improvement in symptoms at weekends and on vacations is quite sensitive in the diagnosis of occupational asthma, the presence of wheezing at work as well as ocular-nasal symptoms (itching) at work is more specific.

Serial PEFR measurements are more commonly used by South African and UK physicians (51–56%), and less so by their Belgian and French (25–38%) counterparts (Table 5). Their use was much higher for workers currently exposed to low molecular weight (LMW) agents (chemical agents <5 kDa) in the South African group, as immunological tests for a number of these agents are not available. The Brazilian group relied more on pulmonary function tests as opposed to serial PEFR measurements in their clinical assessments, as a considerable proportion (~40%) of workers were still at work at the time of the first consultation, although PEFR meters are probably the most accessible tool in developing countries.[58] Some studies suggest that combining serial PEFR measurements with the forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio obtained from spirometry optimises the sensitivity and specificity in detecting non-specific bronchial hyper-responsiveness (NSBH) and may in fact be the simplest first-level investigation for OA among symptomatic workers.[14,53] When both of these tests are available for use by clinicians, serial PEFR data demonstrating work-related decline and subsequent improvements on leave, together with NSBH while at work, support the diagnosis of OA.[52] In the UK, serial monitoring of PEFR is more frequently used by specialist units than general chest physicians and compensation boards. However, considerable variations can exist in the interpretation of these serial PEFR tests by expert clinicians, which may lead to inconsistencies in the diagnosis of asthma. This highlights the need for objective criteria to ensure greater consistency in the interpretation of serial PEFR records.[52] Furthermore, the lack of appropriate country-specific reference values for a number of developing regions of the world poses further impediments when using pulmonary function tests to evaluate very early lung function impairment.[58]

Immunological tests (specific IgE [69%] more than skin prick tests [56%]) are more commonly used by South African physicians to investigate workers with asthma exposed to HMW agents and some LMW agents (e.g., platinum salts) (Table 5). However, the lack of commercially available standardised allergen extracts for skin prick tests or specific IgE determination, especially in most developing countries, poses further constraints in utilising this diagnostic modality to differentiate between the irritative and allergic basis of symptoms experienced by workers exposed to these agents.[52,58]

Although specific bronchial challenge tests represent the gold standard in the diagnosis of OA, reliance on these tests overall is generally lower (1–7%) in developing countries than industrialised countries (6–90%) due to technological, time and economic considerations (Table 5). Studies in the USA and Canada suggest that only 12% of institutions perform the test, due either to the absence of specialised facilities

Table 5 Diagnostic methods used for the evaluation of occupational asthma cases in selected industrialised and developing countries (adapted from [3,15,16,53–56])

Method (% usage)	South Africa (SORDSA) HMW	South Africa (SORDSA) LMW	Brazil (Sao Paulo Municipality)	UK (SWORD)	France	Belgium	Canada (Quebec)
Clinical and occupational history	—	—	100	96	92	80	—
Pulmonary function tests	—	—	92	62	24	13	—
Serial PEFR measurements	24	51	38	56	33	25	—
Specific IgE tests	69	14	—	18	48	59*	—
Skin prick tests (specific allergens)	56	17	—	—	—	59*	—
Non-specific bronchial challenge	4	17	—	—	53	93	—
Specific bronchial challenge	1	7	—	6	11	40	90

* Combined figure.
SORDSA = Surveillance of Work-Related and Occupational Respiratory Diseases in South Africa; SWORD = Surveillance of Work-related and Occupational Respiratory Disease; HMW = high molecular weight; LMW = low molecular weight; PEFR = peak expiratory flow rate.

or to the lack of available diagnostic agents to conduct the test.[54] Compensation boards in Canada (Quebec) use a constellation of tests, but rely to a large extent (90%) on the results of specific bronchial challenge tests (as opposed to other Canadian provinces, where they are used much less or not at all), as do Italian centres, to confirm the diagnosis of OA. Most experts agree, however, that improving the exposure methodology, in the laboratory or in workplace settings, aimed at LMW agents and ensuring that the lowest possible concentrations are used will contribute to more extensive use of the test.

Recent studies in industrialised countries suggest that markers of inflammation using non-invasive methods, such as exhaled nitric oxide and induced sputum to assess inflammatory cells and soluble markers of cell activation, can be used as an adjunct to making the diagnosis of OA. The available data suggest that the latter test may be able to differentiate between asthma due to HMW and LMW compounds, although more validation studies are required.[52]

NATURAL HISTORY AND DETERMINANTS

OA is probably the result of an interaction between multiple genetic, environmental and behavioural influences. A general framework for the natural history of immunological OA encompasses several stages, including onset of exposure, development of sensitisation, inception of OA, removal from exposure and remission or persistence of the disease. The latency period between the onset of exposure and the onset of asthma symptoms is highly variable. The majority of patients, however, develop asthma within the first 1–2 years of exposure.[59] Sensitisation to LMW agents requires a shorter interval than sensitisation to HMW compounds,[59] and the latency period seems to be shorter for laboratory animal allergens than for cereal flour,[60] indicating that the natural history for onset of OA differs depending on the sensitising agent. Rhinoconjunctivitis often precedes the onset of IgE-mediated OA and should be considered an important risk factor of OA.[61] Although many factors influence the host response after exposure to workplace agents, four determinants have received particular attention.

Exposure/response relationships

Several cohort studies found that the risk of developing OA is determined less by individual susceptibility (e.g., atopy, tobacco smoking, human leukocyte antigen [HLA] phenotype) and more by the level of exposure to specific agents in the workplace.[62] In general, the higher the exposure the greater the risk, and by implication, lowering the level of exposure reduces the incidence of disease. The intensity of exposure necessary for initial sensitisation is probably higher than that required to elicit symptoms in the sensitised subject. A relationship between indices of exposure to a sensitising agent and work-related respiratory symptoms or bronchial hyperresponsiveness (BHR) has been found.[63]

Atopy

Atopy, defined as a history of allergic disorders, or more commonly a positive skin prick test to common environmental allergens, is considered a risk factor for IgE-mediated sensitisation to HMW occupational agents. Atopic individuals are thus at increased risk of asthma due to HMW occupational agents, but atopy itself is a weak predictor of sensitisation and development of OA. On the other hand, atopic individuals are not at increased risk of developing OA due to LMW compounds that do not induce an IgE-response, such as isocyanates and plicatic acid.[64]

Atopy and pre-exposure respiratory symptoms during the pollen season were found to affect the incidence of specific sensitisation in a cohort of apprentices in the fields of animal health technology, pastry making, and dental-hygiene technology.[60]

Cigarette smoking

Smoking has been shown to be a risk factor for the development of specific IgE antibodies against occupational agents, although not necessarily for asthma. In the occupational setting, current smokers are at a higher risk of developing sensitisation to HMW agents and to some LMW agents that cause asthma through an IgE-mediated mechanism, such as platinum salts and acid anhydrides.[65] On the other hand, cigarette smoking does not increase the risk of asthma caused by LMW agents for which an IgE-mediated mechanism is not important, such as di-isocyanates and red cedar. Nielsen et al. provide a comprehensive review on the adjuvant effects of smoking on sensitisation to several HMW and LMW occupational agents.[66] They found that adjuvant effects of smoking depends on the type of allergen, and not on whether or not sensitisation was promoted by atopy.

Genetic predisposition

Several genetic factors are probably responsible for allergen sensitisation, which is determined and restricted by HLA genotype, including sensitisation to occupational agents.[65] HLA class II molecules are important factors for the specificity of the response to occupational agents such as acid anhydrides,[67] di-isocyanates,[68] Western red cedar,[69] complex platinum salts,[70] natural rubber latex[71] and laboratory animal proteins.[72] However, evidence of HLA association in di-isocyanate-induced asthma has not been confirmed by other investigators.[73] HLA associations are not strong enough to be used for prevention.[65] Other groups of genes that could be involved in OA due to di-isocyanates are the superfamily of glutathione S-transferase (GST) enzyme,[74] which serves as an important protector of cells from oxidative stress products, and N-acetyltransferase enzymes, the slow acetylator genotypes showing the high-

est risk.[75] These results, however, need to be replicated in different populations to estimate population-wide effects of genetic risk factors for OA.

MANAGEMENT AND FOLLOW-UP

Evidence-based guidelines for the management of OA clearly state that the likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent, in workers who have relatively normal lung function at the time of diagnosis, and in workers who have shorter duration of symptoms prior to diagnosis or prior to avoidance of exposure.[14] Early diagnosis and early avoidance of further exposure are thus the cornerstones of patient management for patients with immunological OA. Whenever feasible, the patient should be relocated to a job category without exposure. The use of respirators is usually ineffective.[14] Redeployment to a low exposure area may lead to improvement or prevent deterioration in some workers, but its effectiveness is largely unknown. For patients with irritant-induced asthma, however, they may usually keep working in the same position, provided that measures are taken to prevent further exposures to high concentrations of irritant agents.[76]

Pharmacological treatment of OA does not differ from that of other types of asthma, and should comply with published asthma guidelines. Efforts should be made to increase the use of inhaled corticosteroids, which are usually underutilised, particularly in developing countries.[77] General measures such as cessation of smoking and avoidance of exposure to common aeroallergens to which the patients may also be sensitised, or to environmental irritants, should always be recommended.

Impairment and disability evaluation should be carried out as soon as the asthma is stabilised (temporary) and 2 years later (permanent), and patients should be counselled about compensation.[78] Nevertheless, responsiveness to methacholine continues to improve 2 or more years after cessation of exposure to agents causing OA.[79]

At adequate doses, subcutaneous immunotherapy with natural rubber latex extract in health care workers seems to be a useful treatment in reducing cutaneous and respiratory symptoms, but it should be considered high-risk treatment due to the appearance of systemic reactions. There are anecdotal reports of not very well controlled studies using immunotherapy with wheat flour, African maple wood, sea squirt and rat epithelium extracts.[80] Table 6 outlines the main steps in the management of OA as proposed by Canadian guidelines.[76]

A significant proportion of patients with OA continue to experience asthma symptoms and NSBH after removal from occupational exposure. Symptoms and NSBH persist in about 70% of affected workers.[65]

Table 6 Management of occupational asthma (adapted from [76])

1 Asthma treatment according to published asthma guidelines
   - Assessment and control of non-occupational sensitisers and other asthma triggers
   - Pharmacotherapeutic interventions
   - Patient education
2 Work exposure
   - For immunological occupational asthma, avoid any further exposure to causative agents. If this is not possible, then reduce exposure as much as possible
   - For irritant-induced occupational asthma, avoid further high-level exposure
3 Assist patient with relevant compensation claim and rehabilitation
4 Consider other co-workers affected and notify public health and company

Two years or more after removal from exposure to the offending agent, about 60% of subjects show a decrease but a persistence of specific BHR to HMW and LMW agents.[81] The persistence of asthma after cessation of exposure is associated with the presence of airway inflammation.[82]

Malo et al. reported that inhaled corticosteroids induce a small but significant overall improvement in the asthmatic condition in subjects with OA caused by HMW and LMW agents after withdrawal from exposure.[83] The beneficial effect is, however, more pronounced if inhaled steroids are given soon after diagnosis.

PREVENTION

Most regulatory bodies and all legislatures consider occupational asthma to be more important in terms of prevention and compensation.

Primary prevention

Complete elimination of the sensitising agent is a secure way of preventing exposure, but this is difficult to achieve. A more practical approach may be reduction in exposure and implementation of measures to limit the number of subjects exposed. However, there is as yet no evidence that reliably allows the setting of clear-cut no-effect threshold levels. Control of other known determinants should also be considered, such as atopy and smoking. Education, labelling and warning systems, environmental monitoring and management programmes are important determinants indirectly related to primary prevention, as they are a prerequisite to implementation of the above controls.

As no single marker of predisposition is sufficiently discriminatory to be useful for pre-employment selection, screening out of potential new employees is highly inefficient and hampered by legal and ethical issues.[84] The positive predictive values of screening criteria are too poorly discriminating for screening out potentially susceptible individuals, particularly in the case of atopy where the trait is highly prevalent.[14]

About 30–40% of young adults in industrialised countries are atopic, and their general exclusion would dramatically reduce the numbers of potential new employees. However, it may be important to identify those individuals with previous sensitisation or clinical symptoms caused by the agent to which they will be exposed in a particular occupation. Persons with established occupational IgE-mediated allergy (rhinitis or asthma) from a particular agent ought not to be employed in a new position where there is further exposure to the same or similar (or cross-reacting) agent.

Controlling exposure in the workplace

Enforcing suitable exposure levels to occupational sensitisers is difficult, as there are very few health-based legal standards. Occupational asthma and allergy to enzymes used in the detergent industry[85] and to platinum salts used in the refining industry[86] have been successfully controlled via the use of preclinical, clinical and industrial hygiene safety programmes designed to minimise sensitisation and the development of disease. Laboratory animal allergy can also be effectively prevented by a targeted programme, including education and training, modification of work practices, engineering controls, the use of personal protective equipment and a standardised system of surveillance.[87] Available data indicate that preventive measures to avoid occupational latex allergy, mainly the complete replacement of powdered latex gloves with low-protein, powder-free gloves and the use of latex-free materials by sensitised individuals, have led to a decrease in the incidence of latex allergy among health care workers.[19,88] A multicomponent, simple control measures surveillance programme for isocyanates in an automotive coatings business has been successfully implemented in parts of North America, Europe and Latin America.[89]

Secondary prevention

Secondary prevention is practised through regular medical surveillance of employees, and is aimed at the early detection of sensitisation and occupational rhinitis/asthma. Respiratory questionnaires are generally used in surveillance programmes, although these are neither standardised nor validated. Sensitisation can be detected by means of skin prick tests or testing for serum-specific IgE antibody. It should be borne in mind that asymptomatic skin sensitisation commonly occurs, as do work-related symptoms due to other allergens or workplace irritants.

Tertiary prevention and compensation

This form of prevention aims to minimise the consequences for a worker who has already developed OA. The key to tertiary prevention is thus offering medical care to affected workers as well as assisting patients with relevant compensation claims and rehabilitation. OA results in serious socio-economic consequences:[90] about one third of workers with OA are unemployed up to 6 years after diagnosis, and they suffer financially.[14] Medico-legal compensation systems should be implemented (if not already available) in every country for workers with OA, and they need to offer adequate financial coverage. It should be noted, however, that many workers in industrialised countries refrain from even making claims because they know this will result in discrimination and lower incomes.[90] Physicians should support affected workers in the pursuit of appropriate compensation, and should report occupational disease to the corresponding worker's compensation system and occupational health agency. Although most compensation systems are administered by national agencies, there is considerable heterogeneity between countries. In the USA, disputes are usually settled through litigation in adversarial settings. Elsewhere, employers are usually responsible for compensating the affected workers through a general system. In some countries, workplace aggravated asthma may also be eligible for compensation. Systems that incorporate retraining, such as the Quebec system in Canada, may be more effective than those that do not.

Reliance upon schedules or lists of the diseases covered distinguishes workers' compensation systems in the USA, UK, France and South Africa from those in some industrialised countries in Europe and parts of Canada, where compensation is allowed for all occupational-related diseases. When restrictive lists of covered exposures are used, it is essential that these lists be upgraded frequently.[56]

In conclusion, OA remains under-recognised, poorly managed and inadequately compensated, especially in developing countries. There is a need for more widespread surveillance systems, using internationally accepted definitions, to identify trends in the incidence of OA across various industries, including the informal sector. Further studies need to focus on characterising the risk associated with exposures to cleaning agents, pesticides and hairdressing chemicals in both developing and industrialised countries. Epidemiological studies focusing on chronic low level chemical exposures and the development of irritant-induced asthma in various workplace settings may contribute towards a better understanding of this entity and lead to better control. The need for validated instruments (questionnaires, immunological tests, serial PEFR) that are easily accessible, administered and interpreted using uniformly accepted protocols will enhance the recognition of the disease, especially in developing countries. There is a need for more studies evaluating interventions among workers exposed to common sensitisers such as isocyanates and cereal flours so as to develop intervention packages for widespread use in resource-poor settings and in small- and medium-scale industries in both industrialised and developing countries, where OA due to these agents is still widespread.

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RÉSUMÉ

L'asthme professionnel est la maladie pulmonaire professionnelle la plus courante dans les pays industrialisés et dans les pays en développement et la deuxième maladie pulmonaire professionnelle la plus courante après la pneumoconiose. La proportion médiane des cas d'asthme attribuables à une exposition professionnelle se situe entre 10% et 15%. La fraction attribuable dans la population semble similaire dans les pays industrialisés et en développement, atteignant des taux de 13% à 15% dans les pays en industrialisation rapide et de 6% dans les pays dont l'industrie est moins développée. Les professions et industries à haut risque en rapport avec l'apparition d'un asthme professionnel varient en fonction des secteurs industriels dominants dans un pays déterminé. Les expositions à haut risque à des agents de nettoyage et les expositions aux pesticides dans les pays en développement semblent être des expositions aussi importantes que celles habituellement signalées dans les pays développés (isocyanates, poussière de farine ou de grains, céréales, fumées de soudure, poussière de bois et, plus récemment, produits chimiques pour la coiffure). L'incidence annuelle moyenne signalée pour l'asthme professionnel dans les pays en développement est inférieure à 2 pour 100 000 par comparaison avec des taux très élevés atteignant 18/100 000 en Scandinavie. Alors que l'asthme professionnel, particulièrement dans les pays en développement, n'est pas suffisamment reconnu, il reste médiocrement diagnostiqué et pris en charge et indemnisé de façon inadéquate dans le monde entier. Des stratégies de prévention primaires et secondaires devraient être orientées vers le contrôle des expositions sur le lieu de travail, en association avec des améliorations importantes dans l'éducation et la prise en charge. Le traitement approprié reste un écartement précoce de l'exposition afin de s'assurer que le travailleur ne sera plus exposé à l'avenir à l'agent causal tout en préservant ses revenus. Toutefois, jusqu'à un tiers des travailleurs atteints d'asthme professionnel reste exposé à l'agent causal et souffre de façon prolongée d'interruptions de travail et de discrimination et risque de chômage.

RESUMEN

El asma ocupacional es la enfermedad pulmonar laboral más frecuente en los países desarrollados y la segunda más común, tras las neumoconiosis, en los países en vías de desarrollo. La proporción media de casos de asma en adultos atribuible a la exposición laboral es del 10–15%. La fracción de población afectada es similar en los países desarrollados y en los países en desarrollo caracterizados por una rápida industrialización (13–15%), pero es menor en los países menos industrializados (6%). Las profesiones y tipos de industria que se asocian con un mayor riesgo de asma ocupacional varían en función de los sectores industriales predominantes en cada país. La exposición a productos de limpieza y a pesticidas en los países en desarrollo parece ser tan importante como la exposición a isocianatos, harina o polvo de cereales, humos de soldadura, serrín de madera, y más recientemente a productos químicos de peluquería, que habitualmente se describen en los países desarrollados. La incidencia media anual de asma ocupacional reportada en los países en vías de desarrollo es menor de 2 por 100 000, comparado con las tasas mucho más altas de hasta 18/100 000 en los países escandinavos. Mientras que el asma ocupacional es una enfermedad escasamente reconocida, especialmente en los países en desarrollo, continúa estando infradiagnosticada y tratada, así como inadecuadamente compensada, en todo el mundo. Las estrategias de prevención primaria y secundaria deberían encaminarse al control de la exposición laboral, acompañado de programas educativos intensivos y mejoras en su manejo. El tratamiento adecuado consiste en el cese completo de la exposición, para asegurar que el trabajador no sufrirá una exposición continua al agente causal, tratando de preservar los ingresos. Sin embargo, hasta una tercera parte de los trabajadores con asma ocupacional continúan expuestos al agente causal o sufren bajas laborales, discriminación profesional y desempleo.