

## Respiratory Diseases of Adults



Frank E. Speizer, Susan Horton, Jane Batt, and Arthur S. Slutsky

Adult respiratory diseases in the developing world are a major burden in terms of morbidity and mortality and, particularly as related to chronic respiratory disease, are of increasing concern (Murray and Lopez 1996). For many years, the leading cause of adult respiratory disease mortality has been tuberculosis, which still kills far more people than it should, given the increased efficacy of treatment and preventive regimens (see chapter 16). However, the burden of other acute and chronic adult respiratory diseases, which is the focus of this chapter, has been rising throughout the world. These diseases fall into four categories: acute diseases, such as pneumonia and influenza; chronic diseases, such as chronic obstructive pulmonary disease (COPD) and asthma; occupational lung diseases, such as byssinosis, asbestosis, and coal worker's pneumoconiosis; and other parenchymal lung diseases, such as immune-related lung diseases. Lung cancer, tuberculosis, and AIDS-related lung diseases are dealt with in chapters 29, 16, and 18, respectively.

### ACUTE DISEASES: PNEUMONIA AND INFLUENZA

Obtaining figures on the incidence and burden of pneumonia and influenza in adults throughout the developing world has been surprisingly difficult. Much of the research and surveillance has been directed toward the pediatric age group (see chapter 25). In 2000, fatal lower respiratory infections, as a class that represents serious pneumonia and influenza, were reported as the cause of 120 deaths per million men and 76 deaths per million women worldwide for the 15 to 59 age group (WHO 2000). For both sexes in this age group, this statistic represents approximately one-third of the deaths caused by tuberculosis. However, for the age groups over 60, rates of death from lower respiratory disease more than double

for each decade of life, whereas rates of death from tuberculosis remain relatively constant. Notably, acute respiratory diseases—in addition to tuberculosis—remain major concerns among adults with AIDS.

The diagnosis of pneumonia varies according to the patient's access to medical care. Often the diagnosis is made simply on the basis of cough and fever. For patients with access to a hospital, the likelihood of obtaining a chest x-ray increases; generally the infection is bacteriologically confirmed only in the most sophisticated medical centers. The natural history of pneumonia without antibiotic treatment varies with the etiologic agent and the patient's underlying comorbid conditions and age. Mortality resulting from these lower respiratory diseases is approximately 10-fold higher in people age 60 to 69 than in people age 15 to 59 (WHO 2000). Comorbid conditions, malnutrition, low socioeconomic status, and cigarette smoking each play a role in increasing the incidence of disease and worsening the prognosis, both with and without treatment.

From studies conducted in the developed world, it would be reasonable to conclude that common antibiotics for pneumonias that occur outside a hospital setting would effectively reduce days lost from work and, in the absence of other morbid conditions, mortality. The few studies in which sputum specimens have been cultured suggest that *Streptococcus pneumoniae* is found in between 40 and 50 percent of the cases. Gram-negative organisms or mixed infections are often isolated, and thus, the use of broad-spectrum antibiotics is warranted (Hooi, Looi, and Ng 2001; Hui and others 1993; Lieberman and others 1996). As would be expected, increased use of antibiotics has resulted in increased resistance to common antibiotics. In addition, 10 to 15 percent of these cases may be tuberculosis (Dolin, Raviglione, and Kochi 1994).

Scott and others (2000) suggested that, despite the similarity of the mortality rates for hospital-treated pneumonia in developing and developed countries, there are important differences in the age distributions. The median age at death among Kenyan adults was 33 years, in contrast to more than 65 years in more developed countries. Many patients in developing countries present late in the course of the disease. Often they die before an appropriate diagnostic workup can be completed, thus leading to an underestimate of case-fatality rates.

Signs and symptoms of influenza can vary from trivial to explosive. Although the disease is usually self-limiting, it can result in both severe incapacity and, when not properly treated, potentially fatal secondary pneumonia. Clearly, patients with comorbid conditions, the very young, pregnant women, and

the elderly are at greater risk of suffering from complications from influenza. Those criteria, along with the adequacy of supply, form the basis for choosing who should be considered for vaccination each year. Because the symptoms of influenza can be quite similar to those of bacterial pneumonia, influenza may often be misdiagnosed as pneumonia. Generally, influenza is more self-limiting than pneumonia, although the infectivity and transmission of influenza from person to person can be substantial. The current threat of H5N1 influenza has resulted in increased human and avian surveillance and preparations for a possible pandemic (box 35.1).

The recent 2003 outbreak of severe acute respiratory syndrome (SARS; see chapter 53) emphasizes the importance of accurate and open surveillance and a coordinated response in

### Box 35.1

#### H5N1 Influenza

Clearly, of even greater concern is the potential for a new influenza A pandemic, as occurred in 1918 and more recently in 1958 and 1968, from a newly altered strain of avian influenza. With each additional bird-to-human case, modest genetic mutation or re-assortment increases the chance for the avian virus to be altered to become established and virulent in mammalian species. This may result in the establishment of sustained transmission among humans. While the pandemics of 1958 and 1968 were together responsible for approximately 3 million deaths, mostly in the very young, the elderly, and in those with comorbid conditions, the 1918 episode is believed to have caused over 40 million deaths, mostly in the age group 15 to 35 years. This potential for greatly increased mortality among such a robust population has fueled recent concern (WHO 2005a).

This concern has become more immediate with the identification of a sub-strain of influenza A, H5N1, first identified in 1997 in Hong Kong when it jumped from poultry to humans and killed six of 18 infected people. Virtually all of the original cases were believed to have been bird-to-human transmission. Since that time there have been a few hundred serologically confirmed cases in Cambodia, Indonesia, Thailand, and Vietnam, with high case fatality but no sustained evidence of ongoing human-to-human transmission (WHO 2005b).

The H5N1 strain is highly pathogenic among poultry. During 2003–2004 it resulted in outbreaks in 8 countries in Asia, with over 100 million birds dying from disease or being culled. More recently, though an additional 150 million birds have been culled, because much of the developing world's poultry economy depends on rural backyard

sources, it is not clear how effective these control measures have been. Although these efforts were thought to help control the spread of the virus, permanent ecological reservoirs appear to have become established in wild fowl and domestic chickens over a relatively broad region of Southeast Asia. WHO authorities have expressed concern about the finding that migratory birds that are infected with H5N1 but are relatively asymptomatic have spread viable viruses over large regions with subsequent infection in domestic poultry. Furthermore, more recently there has been evidence of disease in wild and zoo mammals as well as isolated cases of infection in domestic cats. Recent reports from Vietnam include two cases in humans infected through the consumption of uncooked duck blood. Further investigation of possible person-to-person transmission is underway. Recently, WHO (2005b) stated, “The possible spread of H5N1 avian influenza to poultry in additional countries cannot be ruled out. WHO recommends heightened surveillance for outbreaks in poultry and die-offs in migratory birds, and rapid introduction of *containment measures*, as recommended by FAO and OIE. Heightened vigilance for cases of respiratory disease in persons with a history of exposure to infected poultry is also recommended in countries with known poultry outbreaks. The provision of clinical specimens and viruses, from humans and animals, to WHO and OIE/FAO reference laboratories allows studies that contribute to the assessment of pandemic risk and helps ensure that work towards vaccine development stays on course.”

Humans have little natural immunity to the H5N1 viruses. Thus, in contrast to the usual influenza epidemics, which affect the very young, elderly, and those with

comorbid conditions, virtually the entire population in an exposed community is at risk. In human cases of avian influenza, following the initial respiratory infection, mortality results from two distinct processes. One process begins with relatively rapid onset of respiratory distress from hypoxia associated with ARDS.<sup>a</sup> The alternative process results from secondary bacterial infection with a variety of organisms. In the documented H5N1 influenza infections in humans, respiratory symptoms are most prominent. However, in one case of encephalitis in a child from Vietnam, H5N1 influenza virus was identified in cerebrospinal fluid and fecal matter, and in throat and serum samples. Isolates from several cases were resistant to two commonly used antiviral medications (amantadine and rimantadine), while two other antiviral medications (oseltamivir and zanamivir) still appear to be effective.

There is no way to predict the outcome of these ongoing events. What seems evident is that if human-to-human transmission becomes established, a pandemic will follow.

Source: Authors.

a. ARDS is defined as Acute Respiratory Distress Syndrome resulting from multiple causes, the most likely in this situation being an immunological reaction to the virus.

Given the lack of natural immunity, there is considerable concern that even if adequate vaccines were available, distribution on a worldwide basis would be limited by economic considerations as well as distribution problems in the developing world. Efforts are underway to identify the genetic make-up of the strains of H5N1 that will yield the most effective vaccines and to produce such vaccines in a cost-effective manner. Testing H5N1 vaccines based on recently identified viruses in normal healthy volunteers suggests the immunologic response may be adequate, but several months of production would be necessary to produce adequate supplies for one region, let alone for worldwide distribution. Stockpiles of effective antiviral medications are being generated in some countries. In the interim, WHO has encouraged the rapid reporting of cases and the establishment of procedures for better public health intervention strategies before and during a pandemic (WHO 2005c). Many countries have developed pandemic influenza preparedness plans in anticipation of such an event.

**Table 35.1** Public Health Measures in the SARS Episode, 2003

Procedure	Comment
1. Isolation of patients	Isolate rapidly after onset of symptoms.
2. Quarantine of contacts	Usually at home, but separate from patients. When in contact with unexposed subjects, wear masks and avoid public transportation and visits to crowded places.
3. Education	Reduce delay between onset of symptoms and isolation. In endemic areas, get subject to monitor temperature daily. Use fever hotlines, fever evaluation clinics.
4. Thermal screening	Monitor temperature of travelers from endemic areas (not proven effective).
5. Increased social distance	Cancel mass gatherings. Close schools, theaters, public facilities. Require use of masks in public settings.
6. Disinfection	Practice frequent hand washing. Use aerosol disinfectant agents.
7. Travel advisories	Postpone unessential travel. Screen travelers at entry and exit (not proven effective). Distribute health notices to travelers.

Source: Data compiled and summarized from Bell 2004.

controlling the spread of newly active influenza strains. The potential for global spread and the occurrence of worldwide epidemics of influenza (presumed to be transmitted to humans from domesticated or wild animals and then through close proximity to humans with symptomatic disease—generally to caregivers) points out the importance of continued surveillance for such episodes (Low and McGeer 2004). The lessons learned from the SARS epidemic reinforce the importance of proven traditional public health measures, such as finding and isolating cases, quarantining close contacts, and improving infection control practices (Bell 2004). Those methods, along with several other, less traditional efforts, were presumed to be

part of the reason the epidemic was contained as promptly as it was (see table 35.1). However, because of the high case-fatality rate, the disease caused significant disruption throughout the world.

### **Economic Impact of Influenza and Cost-Effectiveness of Interventions in the Developed World**

Influenza is common in developed countries. Annually, it affects 10 to 20 percent of the U.S. population (Lee and others 2002); those affected experience on average a loss of 2.8 workdays per episode. Those over 65 years of age are more

susceptible to complications, increased costs of hospitalization, and even death. The cost of outbreaks can be large. The costs of the 1996–97 epidemic in Germany were estimated at US\$1,045 million, and the annual costs of outbreaks at US\$11 million to US\$18 million (WHO 2002a).

For those over age 65, many countries encourage preventive vaccinations annually, on the basis of studies suggesting that vaccination (either opportunistic or in a campaign) is cost-effective in elderly populations (for example, see the model of Scuffham and West 2002). Given a good antigenic match, inactivated influenza vaccines prevent laboratory-confirmed illness in 70 to 90 percent of healthy adult vaccine recipients (WHO 2002a). Vaccination is less costly than chemoprophylaxis (with ion-channel inhibitors such as amantadine and rimantadine, or with neuraminidase inhibitors such as zanamivir and oseltamivir) or early treatment with the same drugs. In both the institutionalized and the healthy elderly, vaccination substantially reduces overall mortality from influenza (by 40 to 68 percent).

The cost-effectiveness of vaccination for healthy working-age adults, taking into account workdays lost, is a matter of debate. Demicheli and others (2000) concluded that the most cost-effective option for healthy adults age 14 to 60 was to take no action. However, these authors include only medical costs in their calculations. Postma and others (2002) reviewed 11 studies. Only one shows cost savings on the basis of medical costs alone, but nine of them implied cost savings from vaccination if the value of lost work is included. Because of differences in costs and health care usage patterns, data on cost savings in developed countries cannot be helpfully extrapolated to developing countries.

### **Economic Impact of Influenza in the Developing World**

In Hong Kong, China (where there is a milder year-round pattern of infection, little influenza-related mortality, and low reported work losses), a model suggested that vaccination was not cost saving, even if targeted to the elderly (Fitzner and others 2001). The only case for vaccination was if it controlled the emergence of highly virulent strains and prevented transmission to the rest of the world. According to the World Health Organization (WHO), much less is known about the impact of influenza in the developing world. However, in the tropics, where viral transmission normally continues year-round, influenza outbreaks tend to have high attack and case-fatality rates. For example, during an influenza outbreak in Madagascar in 2002, more than 27,000 cases were reported within three months and 800 deaths occurred despite rapid intervention. An investigation of this outbreak, coordinated by WHO, found that health consequences were severe in poorly nourished populations with limited access to adequate health care (WHO 2002b). It is not possible to extrapolate the exact

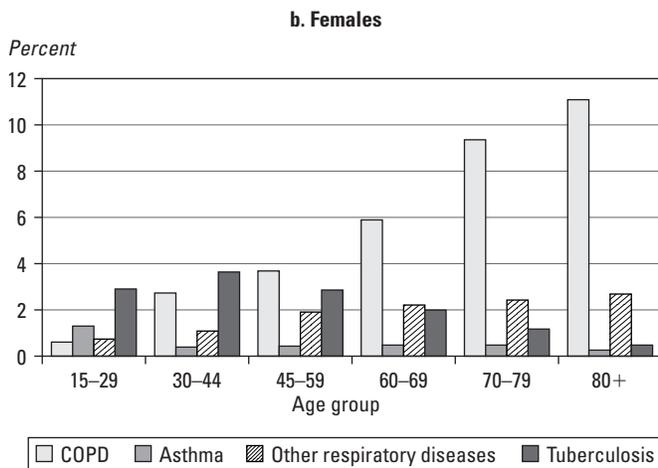
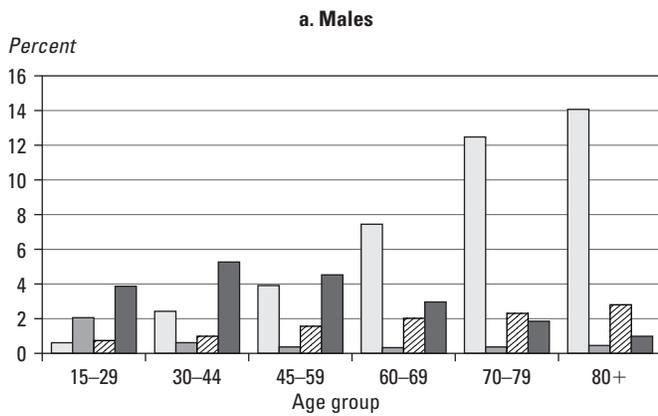
annual burden of influenza in the tropics from data on such occasional and severe outbreaks. Because many areas (for example, Sub-Saharan Africa) do not have surveillance centers, not enough is known at this point to make policy recommendations. There are also no readily available estimates of the cost-effectiveness of influenza vaccination in those environments. (For further discussion of the role of vaccination, see chapter 20.)

## **CHRONIC RESPIRATORY DISEASES: NATURE, CAUSES, AND BURDEN**

COPD and asthma have very different diagnoses and causes; hence, they are discussed in separate sections. However, the treatments for these different chronic respiratory diseases share similarities, and that discussion is therefore combined. One of the difficulties in defining COPD on a worldwide basis is that three distinct levels are used, depending on the sophistication of the health care system in the country where the patient is being evaluated:

- *Chronic bronchitis* with and without obstruction, which may be part of the COPD diagnosis, is defined by the presence of chronic cough and phlegm for three months per year for two or more years and is generally assessed by standardized questionnaires.
- *Obstructive airways disease* is often assessed by reduced pulmonary function as measured by simple spirometry and the presence of a reduced ratio of the forced expiratory volume in one second ( $FEV_1$ ) divided by the vital capacity (VC).
- For *emphysema*, which is also part of the syndrome of COPD, pulmonary function (changes in lung volume and reduced diffusion capacity), x-ray evidence of bullae formation, hyperinflation of the chest, and (with the use of high-resolution CT scanning) the presence of characteristic changes in lung architecture all may contribute to the diagnosis.

What is apparent is that not all these diagnostic procedures are applied equally, particularly in the developing world; thus, COPD may be seriously underreported. The 1998 Workshop Report by the WHO and the National Institutes of Health (NIH) on “Global Strategy for the Diagnosis, Management, and Prevention of COPD,” developed as part of the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2001), uses an international standard for defining the level of obstruction from COPD. This strategy should improve worldwide estimates. This standard definition will still require the use of equipment that measures pulmonary function (Buist 2002). Over the next several years, as the price and distribution of this equipment becomes more favorable and as more groups



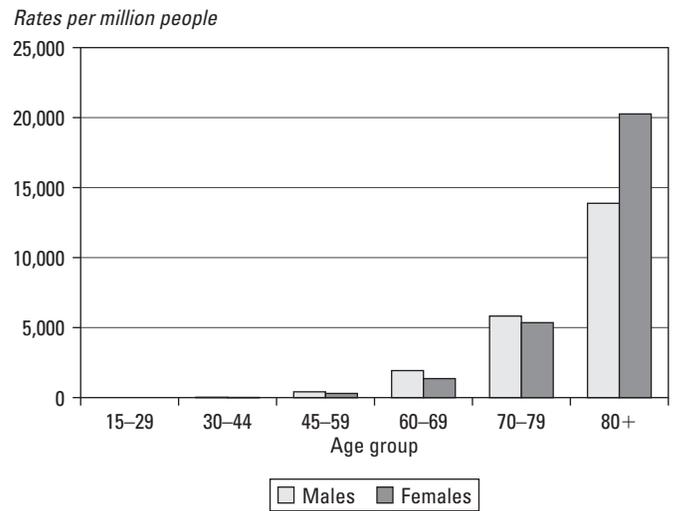
Source: WHO 2000.

**Figure 35.1** Chronic Respiratory Diseases DALYs as a Percentage of World Totals

undertake the training in its use and in the interpretation of results from the tests, diagnostic uniformity will improve. Unfortunately, as pointed out by Ait-Khaled, Enarson, and Bousquet (2001), the applicability of these guidelines has not been effectively tested in developing countries.

In adults, COPD dominates all other chronic respiratory diseases in accounting for 2 percent to more than 10 percent of lost disability-adjusted life years (DALYs) on a worldwide basis. Its incidence increases dramatically with age (figures 35.1a and 35.1b). Of note, mortality from COPD is low before age 45. Over age 45, death rates increase from 50 to 200 per 10,000 individuals and are consistent across age groups in men and women, with the exception of death rates in women over age 80, which exceed those in men in that age group (figure 35.2).

Much of COPD in the developed world is related to cigarette smoking, and there is no question that progression of the disease is related to the number of cigarettes smoked and the years of smoking. Smoking cessation has been associated with



Source: WHO 2000.

**Figure 35.2** COPD by Age and Sex, Worldwide

reduced mortality from COPD, presumably through a mechanism that results in a modest improvement in pulmonary function that appears to be related primarily to the extent of chronic bronchitis and mucus hypersecretion (Scanlon and others 2000; Speizer and others 1989). Within a few years of stopping smoking, smokers' rate of decline of pulmonary function (that is,  $FEV_1$ ) returns to the rate found in nonsmokers, although little of the lost pulmonary function is regained (Fletcher and others 1976). Similar effects are seen in the developing world. However, because smoking is far less prevalent in developing countries, especially among women, other exposures are related to the development of disease (see also chapter 46). One of the most important exposures, particularly for women, is to unvented coal-fired cooking stoves, starting during childhood and continuing into adult life (see chapter 42).

Because the interventions and treatments for COPD overlap with those for asthma, they will be treated together.

The diagnosis of asthma has been debated for centuries. Health care providers can generally agree on the diagnosis in the individual patient who is wheezing and in whom other etiologic factors are ruled out. They would also agree on the definition of the disease as an inflammatory response in the airways that results in variable and generally reversible airflow obstruction with or without treatment. However, depending on the training of health care providers, the nature of surveillance, the characteristics of a given community, and the particular environment of the community, the accuracy of the estimate of the prevalence of asthma in a community may vary much more. The reported prevalence of the disease may be based on no more than an answer to this question: "Has a

provider ever told you that you (or your child) has had asthma?" The response to this question has been validated in a number of studies. In contrast, the diagnosis may depend on examination of the patient's chest, physiological testing, responsiveness to provocative stimuli to the airways, and specific response to therapy. Thus, estimates of community burden from asthma may depend on the threshold used in making the diagnosis.

Despite variations in diagnostic criteria, worldwide estimates of the asthma burden among adults have generally come from surveys within selected communities. In contrast to other adult respiratory diseases, the prevalence of asthma is relatively low (figures 35.1a and 35.1b). In adults, the DALYs for asthma are at a peak of about 2 percent of the total worldwide in people age 15 to 29, and they decline in each older age group. This pattern is also reflected in mortality rates, with the highest rates occurring in young people and equal rates in men and women about age 60. After age 60, reported rates of death caused by asthma in men begin to exceed those in women, and both become substantial. That shift reflects primarily either increasingly questionable diagnostic accuracy or misclassification of other obstructive respiratory diseases such as COPD.

### **Economic Impact of Asthma and COPD in the Developed World**

In the United Kingdom (where asthma rates are particularly high), respiratory disease accounts for 6.5 percent of hospital admissions. Fifteen percent of the working population report work-limiting health problems caused by respiratory disease, and 18.3 million workdays were lost to asthma problems in 1995–96 (Chung and others 2002).

In the Netherlands, annual costs associated with asthma and COPD (direct and indirect) were estimated to exceed US\$500 million for a population of about 14 million (data for the 1980s). Asthma or COPD was responsible for 3 percent of absenteeism caused by illness, and asthma was also the main reason for absence from school among children age 4 to 12 (Rutten–van Mólken and others 1992).

In the United States in the early 1990s, health care costs attributable to respiratory disease were US\$11 billion (about 2 percent of total health care costs), and an estimated 3 million workdays and 10 million schooldays were lost to respiratory disease (Stoloff, Poinsett-Holmes, and Dorinsky 2002).

Another survey (Weiss and Sullivan 2001) estimated the costs of asthma in 1991 US dollars for four developed countries (Australia, Sweden, the United Kingdom, and the United States) and one state (New South Wales in Australia). Per patient costs of asthma ranged from US\$326 (Australia) to US\$1,315 (Sweden) annually, with direct costs accounting, in most cases, for more than half of total costs.

### **Economic Impact of Asthma in the Developing World**

Data for developing countries are much scarcer. For Estonia, Kiiwet and others (2001, cited in Lee and Weiss 2002) estimated the direct annual costs of asthma to be US\$104 per year per asthma patient, equivalent to 1.4 percent of direct health care costs. In Singapore, medical costs for asthma constitute 1.3 percent of total health care costs (Chew, Goh, and Lee 1999, cited in WHO 2001).

One study (Ait-Khaled, Enarson, and Bousquet 2001, cited in Weiss and Sullivan 2001) found that asthma drugs cost between 3.8 and 25 percent of the patient's monthly income in 24 developing countries in Asia and Africa. K. R. Smith (2000) estimates the burden of respiratory disease in India that is attributable to indoor air pollution (only a fraction of all respiratory disease) as 1.6 billion to 2 billion sick days per year. Of that total, asthma is responsible for about one-third, acute respiratory infection is responsible for about one-third, and the remainder is attributable to COPD, tuberculosis, and ischemic heart disease. Asthma and COPD combined account for 44 percent of the burden.

### **Cost Effectiveness of Interventions for COPD and Asthma in Developed Countries**

Five recent overviews of the economics of chronic respiratory disease, COPD, and asthma (Friedmann and Hilleman 2001; Lee and Weiss 2002; Ruchlin and Dasbach 2001; Sullivan and Weiss 2001; Weiss and Sullivan 2001), in addition to many individual studies, focus on developed countries.<sup>1</sup> Only a limited number of studies use cost- or quality-adjusted life years (QALYs) saved as the outcome (others use life years saved). (Studies focusing on intermediate health outcomes and on cost minimization are not discussed here.) In general, costs in developing countries would be about 20 percent of those reported here, according to detailed unit cost data by region from WHO-CHOICE (Choosing Interventions That Are Cost-Effective) and on comparisons of respiratory drug prices from online pharmacies in the United States and from the International Drug Price Indicator Guide (<http://erc.msh.org>). The exceptions are interventions involving nondiscounted drugs that are still under strictly enforced patents, for which the costs in developing countries would be closer to those in the United States. Table 35.2 summarizes the results.

Inhaled salbutamol (short-acting beta-2 agonist) is the first line of treatment for both intermittent asthma (daytime symptoms less than once per week, nocturnal symptoms less than twice per month, and normal spirometry between episodes) and COPD (mild to severe) in both developed and developing countries. This treatment became standard practice beginning in the 1970s, so there are no cost-effectiveness studies of salbutamol compared with placebo. This medical intervention is likely the most cost-effective one, but it is still likely to cost

**Table 35.2** Cost-Effectiveness of Interventions for Asthma and COPD in 2001

Reference	Intervention	Alternative	Cost-effectiveness
<i>Pharmacological</i>			
Authors' estimates	Inhaled ipratropium bromide	Placebo	US\$6,700–US\$8,900/QALY for moderate COPD
Paltiel and others 2001	Quick relievers <sup>a</sup> and inhaled corticosteroids	Quick relievers only	US\$13,900/QALY in adults with mild to moderate asthma: US\$10,600 for moderate only
Van den Boom and others 2001	Inhaled corticosteroid (fluticasone propionate)	Placebo	US\$13,400/QALY COPD treatment
Akins and O'Malley 2000	A-1 antitrypsin augmentation therapy	Standard care <sup>b</sup>	US\$14,400/QALY, severely deficient individuals
Hay and Robin 1991, in Ruchlin and Dasbach 2001	A-1 antitrypsin augmentation therapy	Standard care <sup>b</sup>	US\$45,000–US\$215,000/life year, depends on age, efficacy, and so forth
<i>Education</i>			
Toeve, Kaplan, and Atkins 1984, in Ruchlin and Dasbach 2001	Education and exercise program	Exercise program only	US\$71,500/QALY
<i>Long-term oxygen</i>			
Authors' estimate	Home oxygen therapy for COPD	No oxygen	US\$19,000/life year (US\$26,700–US\$38,000/QALY)
<i>Mechanical ventilation</i>			
Schmidt and others 1983, in Rutten–van Mölken	Mechanical ventilation	Standard hospital care <sup>c</sup> (excluding ventilation)	US\$6,400–US\$23,600/life year (COPD, asthma, cardiac patients) excluding physician costs
Anon and others 1999 in Ruchlin and Dasbach 2001	Mechanical ventilation in intensive care unit, asthma, and COPD patients	Standard hospital care <sup>c</sup> (excluding ventilation)	US\$35,000–US\$60,700/QALY
<i>Surgery</i>			
Al and others 1998, in Ruchlin and Dasbach 2001	Lung transplant in end-stage disease	No transplant	US\$464,000/QALY
Ramsey and others 1995, in Ruchlin and Dasbach 2001	Lung transplant in those eligible	No transplant	US\$238,200/QALY

a. *Quick relievers* refer to rapid-acting bronchodilators (for example, salbutamol) that act to relieve bronchoconstriction and accompanying acute symptoms of wheeze, chest tightness, and cough.

b. Standard care includes medical management (ipratropium bromide, beta-2 agonist, steroid) and home oxygen as needed.

c. Standard care includes medical management and oxygen.

some thousands of dollars per life year saved in the United States.

The next line of treatment currently recommended for developing countries is inhaled corticosteroids (for example, beclomethasone) for mild to severe persistent asthma (disease ranging from daytime symptoms greater than once per week, nocturnal symptoms more than twice a month, and normal spirometry between episodes to daily frequent symptoms associated with severe obstruction) and inhaled ipratropium bromide for COPD. Both first-generation corticosteroids and ipratropium bromide are off patent. However, as pointed out by Chan-Yeung and others (2004), the use of corticosteroids either intermittently or chronically is commonly recommended in developed countries, where the background level of tuberculosis among patients is considerably lower. In developing countries with higher tuberculosis rates, corticosteroids must be used with greater caution.

Inhaled steroids cost about US\$13,900 per QALY for mild to moderate asthma or when used in early treatment of

COPD. The cost per QALY is likely to be lower for severe asthma, but ethical considerations render random controlled trials unfeasible.

No cost-effectiveness study could be found for ipratropium bromide compared with placebo. We estimate that the cost per QALY saved would be between one-half and two-thirds of that for a new-generation inhaled steroid such as fluticasone propionate. This estimate, which is based on the relative cost of the two drugs in the United States and assumes similar effectiveness of the two drugs, would put the cost of ipratropium bromide between US\$6,700 and US\$8,900 per QALY.

Most of the other interventions summarized in table 35.2 have a higher cost per QALY. For individuals who develop COPD related to a severe deficiency in alpha-1 antitrypsin, alpha-1 antitrypsin therapy is sometimes considered, at a cost of between US\$45,000 and US\$215,000 per life year.<sup>2</sup> The use of long-acting beta-2 agonists and leukotriene modifiers is now an accepted and integrated component of the treatment of moderate to severe asthma in the developed world. However,

the cost savings for the developing world are difficult to demonstrate because the endpoints of studies using those drugs are often changes in spirometric testing, improved quality-of-life measures, steroid-sparing effects, or altered hospital admission rates.

Likewise, oral or intravenous steroids play a crucial role in the treatment of acute exacerbations in both asthma and COPD, but endpoint assessments in studies typically address decreases in the duration of hospital stays and increases in the use of emergency department facilities, which result in decreases in health costs in the developed world. Oral steroids are inexpensive, even by standards in developing countries, and in the short term might appear to be cost-effective, but they are associated with major medium- to long-term consequences and are not recommended as standard therapy.

Educational programs tend to be cost saving in developed countries, where uncontrolled exacerbations are extremely costly in terms of hospital care (six such programs are surveyed in Van Mólken and others 1992 and one in Ruchlin and Dasbach 2001). Similarly, exercise rehabilitation programs (six surveyed in Ruchlin and Dasbach 2001) can also be cost saving. WHO (2001) has commented on cost savings achieved by education programs for asthma from four different U.S. studies. Only one of these studies addressed cost per well year, which was estimated at US\$71,500 in 2001 (Toevs, Kaplan, and Atkins 1984, cited in Ruchlin and Dasbach 2001). However, there are likely to be monetary savings from fewer workdays lost, which are not factored into this analysis.

WHO (2001) surveyed one self-management training program for chronic asthma in India (Ghosh and others 1998), which resulted in improvements in health status, reduced use of emergency departments and hospitals, and savings on health costs. Sudre and others (1999) pointed out that studies of education programs tend not to provide a good description of the actual program content and that a more systematic description of these interventions needs to be promoted to replicate best practice.

Long-term oxygen therapy is a life-prolonging intervention in advanced stages of COPD. Recent studies do not quantify the cost per QALY but instead compare different methods of oxygen delivery (cylinder or concentrator). These authors' crude estimate for long-term oxygen use is US\$19,000 per life year saved.<sup>3</sup> If the quality-of-life scores of patients on long-term oxygen were 0.8 or 0.6, the cost per QALY would be US\$22,750 or US\$31,700, respectively. (K. J. Smith and Pesce 1994, cited in the Harvard Catalogue of Preference Scores, assign a median score of 0.4 to quality of life for patients with severe COPD with high supportive care needs and poor functional status.)

In hospitals, mechanical ventilation in the intensive care unit has been estimated to cost US\$35,000 to US\$60,700 per QALY in 2001 (Anon and others 1999, cited in Ruchlin and Dasbach 2001). Studies suggest that noninvasive positive

pressure ventilation, where it is feasible, is less costly than invasive mechanical ventilation for specific indications. Finally, costs of lung transplants are at a level scarcely affordable even in developed countries; Al and others (1998, cited in Ruchlin and Dasbach 2001) estimated costs at US\$464,000 per QALY, and Ramsey and others (1995, cited in Ruchlin and Dasbach 2001) estimated costs at US\$238,000 per QALY (in 2000 U.S. dollars).

All those interventions compare unfavorably with the cost-effectiveness of smoking prevention for preventing COPD (discussed in chapter 46). Smoking prevention is one of the most cost-effective health interventions that exists, and there is a strong case for moving resources from expensive curative interventions to that intervention. Likewise, prevention of COPD by switching the cooking source from unventilated stoves that burn biomass to either improved stoves or kerosene stoves is more cost-effective than treatment (see chapter 42).

### **Cost-Effectiveness of Interventions for COPD and Asthma in Developing Countries**

It is difficult to transfer the costs per QALY saved in developed countries to developing countries. The cost of patented drugs in developing countries should be the same as that in developed countries, whereas the costs of education and of the time of medical personnel should be substantially lower (on the order of 20 percent of U.S. levels). In practice, the costs of off-patent drugs also vary considerably. Beclomethasone dipropionate (one of the older, off-patent inhaled steroids) is available for about US\$15 per 200-dose inhaler in Canada in online pharmacies but is quoted at US\$1 to US\$3 by agencies and suppliers on the International Drug Price Indicator Guide (<http://erc.msh.org>). A similar price difference exists for salbutamol inhalers. Hence, the most cost-effective therapies in developed countries (inhaled salbutamol and first-generation corticosteroids for asthma and ipratropium bromide for COPD) are also likely to be cost-effective in the wealthier developing countries—or more broadly if inexpensive drug supplies are available. Those drugs are likely to be particularly cost-effective for those with severe and moderately severe asthma or COPD but less cost-effective for those with mild disease. Recent practice suggests that a combination of long-acting beta agonists and inhaled corticosteroids can control moderate to severe disease more rapidly. However, to make this form of therapy cost-effective, the patient needs to be reevaluated to determine whether one or the other drug can be removed. Because of cost considerations, that may not be feasible in the developing world.

Once control has been obtained, education alone appears to be ineffective when only respiratory outcomes are considered (although education on the benefits of exercise has other health benefits: see chapter 44 on lifestyles). However, education

addressing the appropriate use of medication is extremely important, particularly in developing countries, where timely emergency care for severe exacerbations may not be readily available. Although the cost of educational efforts would be expected to be considerably lower in developing countries, this area requires more systematic research.

Long-term oxygen is also an option for high-income households in middle-income developing countries. The costs are likely to be lower than in developed countries. In Brazil the monthly cost for supplemental home oxygen therapy is close to US\$150 (Sant'Anna and others 2003), compared with US\$400 per month paid by Medicare, which would bring the cost-effectiveness to US\$7,000 per life year by these authors' crude estimates, or between US\$8,750 and US\$11,700 per QALY. Publicly funded systems are unlikely to be able to pay this rate, although private insurers and wealthy households might pay because such therapy prolongs life.

The other interventions in table 35.2 are likely to be too expensive for most developing countries to use at present.

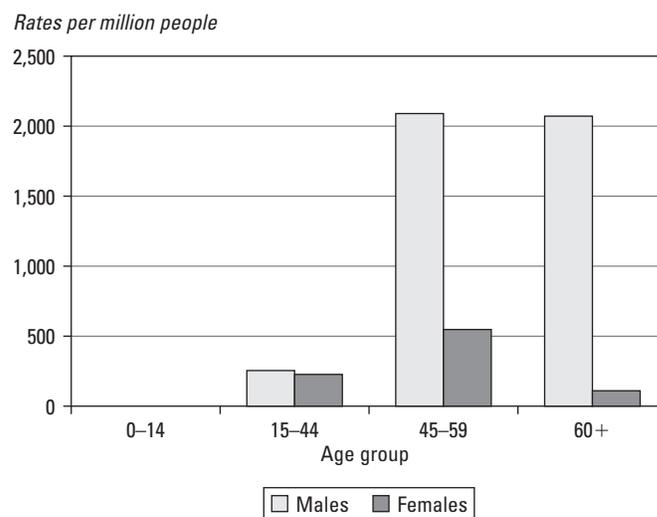
## OCCUPATIONAL LUNG DISEASE AND OTHER RESPIRATORY DISEASES

Although occupational lung diseases are often considered diseases of the industrial world, they are occurring with increased frequency in the developing world, where guidelines for worker safety are generally more lax or nonexistent. In addition, because of increased migration from rural areas to more urbanized centers and the transfer of major manufacturing activities from the developed market economy countries to the less developed countries, the number of employees with potentially harmful occupational exposures has increased exponentially in the past 30 years. The general discussion of occupation-related diseases is reviewed in chapter 60. We focus here on specific occupation-related lung diseases.

Occupational lung diseases are, for the most part, characterized as related to particular occupational exposures and generally fall into two broad pathophysiological types. One type may result in pulmonary fibrosis, which is manifested by restricted lung volume and decreased diffusion capacity on pulmonary function testing and increased interstitial pulmonary markings on chest x-ray. Certain occupational lung diseases, such as silicosis, are complicated by a substantially increased risk of tuberculosis, which contributes to the overall burden of respiratory disease in the developing world. The second pattern of occupational lung disease is that of obstructive airways disease, which may be reversible (occupational asthma) or irreversible (chronic bronchitis with or without obstruction or emphysema or COPD), in which the chest x-ray often is negative and the diagnosis is dependent largely on reported histories of exposures, symptoms, and pulmonary function testing.

There are few reliable estimates of the global burden of occupation-related respiratory diseases. Because of the lack of systematic surveillance in most developing countries, the few published estimates of occupation-related respiratory diseases have relied on selected studies involving particular industries that investigators have had unique opportunities to explore. For example, Trapido and others (1996) conducted a survey in a relatively small group of former mineworkers and found that approximately 55 percent had pneumoconiosis with or without tuberculosis. They estimated that about 25 percent of migrant and former mineworkers in South African gold mines with 15 to 25 years of exposure had occupational lung diseases. Loewenson (1999) pointed out the difficulties in making assessments of occupational risk throughout the African countries and suggested a series of methodological issues that need to be considered.

Leigh and others (1999) estimated the global burden of diseases related to occupational factors at 4.2 million to 10.0 million cases per year. If one subtracts the rates for established market economy countries, the total burden for the rest of the world is approximately 3.4 million to 9.1 million cases per year. Using limited data and applying rates from individual nations and regional groups of countries, the authors made an indirect calculation for the expected number of cases of occupation-related diseases globally. Figure 35.3 summarizes their estimates for pneumoconiosis and other chronic respiratory diseases by age and gender. Notably, these two categories of disease account for approximately 30 percent of all occupational diseases. The prevalence of these diseases increases with age and is higher among men.



Source: Leigh and others 1999.

**Figure 35.3** Estimated Combined Pneumoconiosis and Other Occupation-Related Chronic Respiratory Diseases

Asbestosis and asbestos-related cancers present a particular problem in developing countries. Asbestosis can manifest both as other interstitial lung disease, as described above, and as obstructive airways disease. In addition, occupational exposure is associated with the occurrence of lung cancer, and according to studies in developed countries, the rate of occurrence is synergistically associated with smoking. Because the cost of health care compensation in the developed world exceeds the potential profit from mining and manufacturing of asbestos products, much of the industry has moved to the developing world.

LaDou (2004) has recently summarized the status of the potential for reducing occupational exposure on a worldwide basis and suggests that upward of 10 million lives will be lost if the current lack of controls and continued increases in mining and manufacturing are not changed. In 2000, more than 2 million tons of asbestos products were produced, whereas 25 years earlier the total production was 350,000 tons each year. Except for the Russian Federation and Canada, virtually all the larger producers are in the developing world, where the recognition and reporting of health effects are less well established. The likelihood of reversing this trend and developing an international ban on asbestos use is small, particularly because it is the nations that produce more asbestos products that are, in fact, increasing consumption.

The economic burden of occupational lung diseases is surprisingly difficult to document. Most developed countries and some developing countries (for example, South Africa) have legislation protecting workers from exposure and compensating those who have contracted chronic conditions. In the United States, compensation payments from the Social Security Administration and the Department of Labor for black lung disease totaled US\$1.6 billion in 1996 (NIOSH 1999). Data exist on compensation for claims for various occupational lung diseases for the United States and the European Union countries. However, claims data represent only a small fraction of the true economic cost (for example, not all workers make claims; compensation payments lag considerably). For the United States, the annual costs of complying with the revised respirator standards for 1993 were US\$111 million for about 5 million workers needing to use a respirator (presumably these costs of prevention were far lower than the economic cost of unprotected work) (OSHA 1998). The primary treatment for affected workers is to remove them from the inciting exposures. (See chapter 60 for discussion of preventive strategies that need to be considered to reduce the risk of occupational disease.)

Some of the other major classes of adult respiratory diseases are discussed in other chapters: tuberculosis, in chapter 16; AIDS-related lung disease, in chapter 18; and lung cancer, in chapter 29. Other diseases that have been studied, particularly in the developed world, include the hypersensitivity or

immunologically related pulmonary diseases most often associated with environmental exposures to specific inhaled antigens or interstitial inflammation and fibrosis, often of unknown origin. In the developing world, little systematic work has been done on these diseases to assess incidence or prevalence. These conditions probably occur considerably less frequently than asthma and COPD. However, they are likely to have a higher prevalence in developing countries than is reported in the developed world simply because of the presumed associations with exposures to organic dusts and the increased prevalence of malnutrition (see chapter 56), both of which are likely to occur in more rural and less developed areas of the world.

See chapters 16, 18, and 29 for interventions for tuberculosis, AIDS-related lung disease, and lung cancer, respectively. Managing immunologic and fibrotic respiratory diseases with medication is extremely difficult and expensive. Therapeutic trials often fail, presumably because the treatments are not aimed at a particular antigen. The most effective way of managing these respiratory diseases is to reduce exposure to the inciting agents, an approach that hinges on two strong premises, which are not always applicable in the developed world. First, the disease must be recognized as related to a common environmental contaminant encountered in an occupational or avocational exposure—for example, exposure to thermophilic actinomycetes in moldy hay or sugarcane results in farmer's lung, and exposure to bird feathers or droppings results in bird fancier's disease. Second, community resources must be directed toward educating the public about the importance of limiting exposure to these agents.

## GENERAL APPROACH TO LOWERING RISK OF ADULT RESPIRATORY DISEASE

Although interventions of various sorts are indicated for each of the disease categories discussed, these interventions are often costly and sometimes ineffective in lowering or preventing premature mortality. Thus, from an operational perspective, it is important to consider preventive and therapeutic strategies that will have greater societal effect than will the management of the manifestations of diseases as they arise in individuals. This approach applies to acute diseases (vaccination schemes to reduce the burden of influenza, in contrast to individual management of community-acquired pneumonia) and chronic diseases (smoking prevention and reduction programs, compared with availability of routine asthma medication). Primary prevention strategies should include efforts by multiple agencies of government and the community coming together to establish appropriate priorities for action. Four sources of exposure stand out: tobacco smoke, indoor smoke, outdoor air pollutants, and occupational exposure (see chapters 46, 42, 43,

and 60, respectively). Of these, the most pressing and cost-effective is a cohesive policy to control tobacco smoking.

In conjunction with the International Union against Tuberculosis and Lung Disease (IUATLD) and selected universities and health institutions in various countries, WHO is developing the Practical Approach to Lung Health (PAL, previously known as the Adult Lung Health Initiative). The program is focused on improving primary care services, as well as appropriate referral to secondary health care facilities, for individuals with tuberculosis, acute respiratory infections (especially pneumonia), asthma, and COPD. Four countries (Chile, Morocco, Nepal, and South Africa) are serving as the pilot implementation sites (WHO 2003).

In Chile, where respiratory symptoms account for one-third of primary health care visits, a respiratory disease program was initiated in 2001 as part of ongoing efforts to strengthen primary health care. The pilot program was implemented in 15 centers. Standard formats are used to devise scores to determine follow-up for asthma and COPD. Sentinel centers are used to provide epidemiologic information. Influenza immunization coverage of the elderly and at-risk population has reached 85 percent (WHO 2003).

In Morocco, survey work done before establishing a PAL strategy showed that 31 percent of patients who consult primary health care centers present with respiratory symptoms. Of those patients, 85 percent have acute respiratory infections, 14 percent have chronic conditions, and 1 percent have tuberculosis. In Mexico, an IUATLD study implementing asthma control measures was shown to be cost-effective. Control of asthma improved, and the majority of patients experienced a decrease in the severity of asthma. The cost of asthma management decreased because of lower costs for emergency services and hospitalizations (WHO 2003).

## FUTURE RESEARCH NEEDS

One of the difficulties in quantifying the burden of respiratory diseases in adults is the inability to apply uniform methods of diagnosis across economies in which sophisticated diagnostic procedures are possible, let alone across less developed economies. The problems relate in part to differences in the language describing the same symptoms, levels of registration of census and disease reporting, availability of diagnostic procedures, and reluctance to make accurate estimates because of the cost of intervention strategies. Furthermore, unless controls on cigarette smoking are initiated, little progress in stemming the increasing burden of chronic respiratory diseases can be expected.

There are still a number of unanswered questions related to COPD, which remains the dominant respiratory disease in adults. The developing world provides some unique opportu-

nities for research that go beyond the primary prevention that would result from better smoking control policies. Because not all smokers are at increased risk, the interaction of smoking with nutritional status (including micronutrient status), with genetic factors that determine susceptibility, and with respiratory infections may act as a precursor of susceptibility to environmental (ambient or occupational) pollution and personal (smoking) pollution. Similarly, the role of immunologic stimulation or immunocompetence needs further exploration as it relates to the development of asthma. Synergies between the conditions discussed in this chapter and other infections (particularly tuberculosis, but possibly others) may be especially important in the developing world. Finally, specific environmental conditions—such as altitude, heat and cold stress, and increased ambient pollution from rapid urbanization—and their effects on asthma and COPD should be explored.

Acute respiratory infections, specifically bacterial pneumonia, have not been addressed nearly as well for adults as they have been for children. For example, simple data on the prevalence of infecting organisms, typical susceptibilities, the ability to train ancillary workers in clinical diagnosis, and the correlation of clinical assessment with verified disease would be helpful in establishing the feasibility of assessment and treatment at home versus at a clinic or hospital, specifically in the developing world. Common etiologic agents in North America are common elsewhere; therefore, treatment of disease would be relatively inexpensive. Most community-acquired acute disease responds relatively well. Certainly, penicillin should be recommended as a first-line drug for community-acquired pneumonia. Educating local healers on the importance of initiating treatment earlier in the course of disease would translate into savings with respect to decreased days of work lost and reduced case-fatality rates. Follow-up monitoring and the development of hospital-based bacteriologic testing should be expanded to identify and control for the emergence of resistant bacterial strains.

Studies of asthma in the developed world have been extensive and of extremely high quality but are directed specifically toward the health care structures in which they are tested. Specific cost-effectiveness studies in the developing world should be done to see, for example, whether a focus on disease education and modification of risk factors in addition to medications outweighs simple administration of medications (with instructions on use). In the developed world, there is no question that an approach that is multitiered and involves multiple health care providers is the best, but we still do not have concrete evidence of where monies are best spent in the developing world. Another possible fruitful area of research is on education programs. Most of the literature relates to education programs for specific entities (for example, “asthma triggers”) and their costs in developed countries. Education programs in developing countries that are multidimensional (smoking

cessation, indoor air quality, vaccination) are likely to be relatively inexpensive and cost-effective. Better methods of educating local healers through the use of demonstration projects should be tested, as should more efficient distribution systems to make relatively inexpensive medication available. General increased awareness of the impact of symptoms on adults and of the potential for earlier intervention in a disease should also be explored and tested for their effects on reducing respiratory disease burdens.

## NOTES

1. The survey of the cost-effectiveness of interventions below is based on a review of the University of York database (<http://www.york.ac.uk/inst/crd>), combined with a Medline search (focusing mainly on data after 1996).

2. According to Hay and Robin (1991), cited in Ruchlin and Dasbach (2001). Akins and O'Malley (2000) have a much lower estimate, which probably does not include all the costs of screening and the like.

3. This estimate was calculated as follows: the MRC (1981) trials suggest that over five years the mortality in a randomized trial for patients with severe hypoxemia is 667 per 100,000 for those not treated with long-term oxygen, compared with 548 per 100,000 for those treated with long-term oxygen (reviewed in Crockett and others 2001). The cost per month of home oxygen is taken as US\$400 (based on U.S. Medicare reimbursements in the early 1990s).

## REFERENCES

- Ait-Khaled, N., D. Enarson, and J. Bousquet. 2001. "Chronic Respiratory Diseases in Developing Countries: The Burden and Strategies for Prevention and Management." *Bulletin of the World Health Organization* 79 (10): 971–79.
- Akins, S. A., and P. O'Malley. 2000. "Should Health-Care Systems Pay for Replacement Therapy in Patients with Alpha(1)-Antitrypsin Deficiency? A Critical Review and Cost-Effectiveness Analysis." *Chest* 117 (3): 875–80.
- Al, M. J., M. A. Koopmanschap, P. J. van Enckevort, A. Geertsma, W. van der Bij, W. J. de Boer, E. M. Ten Vergert. 1998. "Cost-Effectiveness of Lung Transplantation in the Netherlands." *Chest* 113: 124–40.
- Anon, J. M., A. Garcia de Lorenzo, A. Zarazaga, V. Gomez-Tello, and G. Garrido. 1999. "Mechanical Ventilation of Patients on Long-Term Oxygen Therapy with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Prognosis and Cost-Utility Analysis." *Intensive Care Medicine* 25 (5): 452–57.
- Bell, D. M. 2004. "World Health Organization Working Group on Prevention of International and Community Transmission of SARS. Public Health Interventions and SARS Spread, 2003." *Emerging Infectious Diseases* 10 (11). <http://www.cdc.gov/ncidod/EID/vol10no11/04-0729.htm>.
- Buist, A. S. 2002. "Guidelines for the Management of Chronic Obstructive Pulmonary Disease." *Respiratory Medicine* 96 (Suppl. C): S11–16.
- Chan-Yeung, M., N. Ait-Khaled, N. White, K. W. Tsang, and W. C. Tan. 2004. "Management of Chronic Pulmonary Disease in Asia and Africa." *International Journal of Tuberculosis and Lung Disease* 8 (2): 159–70.
- Chew, F. T., D. Y. Goh, and B. W. Lee. 1999. "The Economic Cost of Asthma in Singapore." *Australian and New Zealand Journal of Medicine* 29 (2): 228–33.
- Chung, F., N. Barnes, M. Allen, R. Angus, P. Corris, A. Knox, and others. 2002. "Assessing the Burden of Respiratory Disease in the U.K." *Respiratory Medicine* 96: 963–75.
- Crockett, A. J., J. M. Cranston, J. R. Moss, and J. H. Alpers. 2001. "A Review of Long-Term Oxygen Therapy for Chronic Obstructive Pulmonary Disease." *Respiratory Medicine* 95: 437–43.
- Demicheli, V., T. Jefferson, D. Rivetti, and J. Deeks. 2000. "Prevention and Early Treatment of Influenza in Healthy Adults." *Vaccine* 18: 957–1030.
- Dolin, P. J., M. C. Raviglione, and A. Kochi. 1994. "Global Tuberculosis Incidence and Mortality during 1990–2000." *Bulletin of the World Health Organization* 72: 212–20.
- Fitzner, K. A., K. F. Shortridge, S. M. McGhee, and A. J. Hedley. 2001. "Cost-Effectiveness Study on Influenza Prevention in Hong Kong." *Health Policy* 56: 215–34.
- Fletcher, C. M., R. Peto, C. M. Tinker, and F. E. Speizer. 1976. *The Natural History of Chronic Bronchitis: An Eight Year Follow-up Study of Working Men in London*. New York: Oxford University Press.
- Friedmann, M., and D. E. Hilleman. 2001. "Economic Burden of Chronic Obstructive Pulmonary Disease: Impact of New Treatment Options." *Pharmacoeconomics* 19 (3): 245–54.
- Ghosh, C. S., P. Ravindran, M. Joshi, and S. C. Stearns. 1998. "Reductions in Hospital Use from Self Management Training for Chronic Asthmatics." *Social Science and Medicine* 46 (8): 1087–93.
- GOLD (Global Initiative for Chronic Obstructive Lung Disease). 2001. "Global Strategy for the Diagnosis, Management and Prevention of GOLD." National Heart, Lung, and Blood Institute–WHO Workshop Report, NHLBI Publication 2701, National Institutes of Health, Bethesda, MD.
- Hay, J. W., and E. C. Robin. 1991. "Cost-Effectiveness of Alpha-1 Antitrypsin Replacement Therapy in Treatment of Congenital Chronic Obstructive Pulmonary Disease." *American Journal of Public Health* 81: 427–33.
- Hooi, L. N., I. Looi, and A. J. Ng. 2001. "A Study on Community Acquired Pneumonia in Adults Requiring Hospital Admission in Penang." *Medical Journal of Malaysia* 56: 275–84.
- Hui, K. P., N. K. Chin, K. Chow, A. Brownlee, T. C. Yeo, G. Kumarasinghe, and others. 1993. "Prospective Study of the Etiology of Adult Community Acquired Bacterial Pneumonia Needing Hospitalisation in Singapore." *Singapore Medical Journal* 34: 329–34.
- Kiivet, R. A., I. Kaur, A. Lang, A. Aaviksoo, and L. Nirk. 2001. "Costs of Asthma Treatment in Estonia." *European Journal of Public Health* 11: 89–92.
- LaDou, J. 2004. "The Asbestos Cancer Epidemic." *Environmental Health Perspectives* 112: 285–90.
- Lee, P. Y., D. V. Matchar, D. A. Clements, J. Huber, J. D. Hamilton, and E. D. Peterson. 2002. "Economic Analysis of Influenza Vaccination and Antiviral Treatment for Healthy Working Adults." *Annals of Internal Medicine* 137: 225–31.
- Lee, T. A., and K. B. Weiss. 2002. "An Update on the Health Economics of Asthma and Allergy." *Current Opinion in Allergy and Clinical Immunology* 2: 195–200.
- Leigh, J., P. Macaskill, E. Kuosma, and J. Mandryk. 1999. "Global Burden of Disease and Injury Due to Occupational Factors." *Epidemiology* 10: 626–31.
- Lieberman, D., F. Schlaeffer, I. Boldur, D. Lieberman, S. Horowitz, M. G. Friedman, and others. 1996. "Multiple Pathogens in Adult Patients Admitted with Community-Acquired Pneumonia: A One Year Prospective Study of 346 Consecutive Patients." *Thorax* 51: 179–84.
- Loewenson, R. 1999. "Assessment of the Health Impact of Occupational Risk in Africa: Current Situation and Methodological Issues." *Epidemiology* 10: 632–9.

- Low, D. E., and A. McGeer. 2004. "SARS—One Year Later." *New England Journal of Medicine* 349: 2381–2.
- MRC (Medical Research Council Working Group). 1981. "Long-Term Domiciliary Oxygen Therapy in Chronic Hypoxic Cor Pulmonale Complicating Chronic Bronchitis and Emphysema." *Lancet* 1 (8222): 681–86.
- Murray, C. J. L., and A. D. Lopez, eds. 1996. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press.
- NIOSH (National Institute of Occupational Safety and Health). 1999. *Work-Related Lung Disease Surveillance Report 1999*. NIOSH Publication 2000-105. <http://www.cdc.gov/niosh/docs/2000-105/2000-105.html>.
- OSHA (Occupational Safety and Health Administration). 1998. *Respiratory Protection Regulations. Section 6: Summary of the Final Economic Analysis*. [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_id=1052&p\\_table=PREAMBLES](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=1052&p_table=PREAMBLES).
- Paltiel, A. D., A. L. Fuhlbrigge, B. T. Kitch, B. Liljas, S. T. Weiss, P. J. Neumann, and K. M. Kuntz. 2001. "Cost-Effectiveness of Inhaled Corticosteroids in Adults with Mild-to-Moderate Asthma: Results from the Asthma Policy Model." *Journal of Allergy and Clinical Immunology* 108 (1): 39–49.
- Postma, M. J., P. Jansema, M. L. L. van Genugten, M.-L. A. Heijnen, J. C. Jager, and L. T. W. de Jong-van den Berg. 2002. "Pharmacoeconomics of Influenza Vaccination for Healthy Working Adults." *Drugs* 62 (7): 1013–24.
- Ramsey, S. D., D. L. Patrick, R. K. Albert, E. B. Larson, D. E. Wood, and G. Raghu. 1995. "The Cost-Effectiveness of Lung Transplantation: A Pilot Study." *Chest* 108: 1594–601.
- Ruchlin, H. S., and E. J. Dasbach. 2001. "An Economic Overview of Chronic Obstructive Pulmonary Disease." *Pharmacoeconomics* 19 (6): 623–42.
- Rutten-van Mólken, M. P., E. K. Van Doorslaer, and F. F. Rutten. 1992. "Economic Appraisal of Asthma and COPD Care: A Literature Review 1980–1991." *Social Science and Medicine* 35 (2): 161–75.
- Sant'Anna, C. A., R. Stelmach, M. I. Zanetti Feltrin, W. J. Filho, T. Chiba, and A. Cukier. 2003. "Evaluation of Health-Related Quality of Life in Low-Income Patients with COPD Receiving Long-Term Oxygen Therapy." *Chest* 123 (1): 136–41.
- Scanlon, P. D., J. E. Connett, L. A. Waller, M. D. Altose, W. C. Bailey, A. S. Buist, and D. P. Tashkin. 2000. "Smoking Cessation and Lung Function in Mild-to-Moderate Chronic Obstructive Pulmonary Disease: The Lung Health Study." *American Journal of Respiratory and Critical Care Medicine* 161: 381–90.
- Schmidt, C. D., C. G. Elliott, D. Carmelli, R. L. Jensen, M. Gengiz, J. C. Schmit, and others. 1983. "Prolonged Mechanical Ventilation for Respiratory Failure: A Cost-Benefit Analysis." *Critical Care Medicine* 11: 407.
- Scott, J. A. G., A. J. Hall, C. Muyodi, B. Lowe, M. Ross, B. Chohan, and others. 2000. "Aetiology, Outcome, and Risk Factors for Mortality among Adults with Acute Pneumonia in Kenya." *Lancet* 355: 1225–30.
- Scuffham, P. A., and P. A. West. 2002. "Economic Evaluation of Strategies for the Control and Management of Influenza in Europe." *Vaccine* 20: 2562–78.
- Smith, K. J., and R. R. Pesce. 1994. "Pulmonary Artery Catheterization in Exacerbations of COPD Requiring Mechanical Ventilation: A Cost-Effectiveness Analysis." *Respiratory Care* 39: 961–7.
- Smith, K. R. 2000. "National Burden of Disease in India from Indoor Air Pollution." *Proceedings of the National Academy of Sciences of the United States of America* 97 (24): 13286–93.
- Speizer, F. E., M. E. Fay, D. W. Dockery, and B. G. Ferris Jr. 1989. "Chronic Obstructive Pulmonary Disease Mortality in Six U.S. Cities." *American Review of Respiratory Disease* 140: S49–55.
- Stoloff, S., K. Poinsett-Holmes, and P. M. Dorinsky. 2002. "Combination Therapy with Inhaled Long-Acting  $\beta_2$ -Agonists and Inhaled Corticosteroids: A Paradigm Shift in Asthma Management." *Pharmacotherapy* 22 (2): 212–26.
- Sudre, P., S. Jacquemet, C. Uldry, and T. V. Perneger. 1999. "Objectives, Methods, and Content of Patient Education Programmes for Adults with Asthma: Systematic Review of Studies Published between 1979 and 1998." *Thorax* 54: 681–7.
- Sullivan, S. D., and K. B. Weiss. 2001. *Health Economics of Asthma and Rhinitis: II. Assessing the Value of Interventions*. *Journal of Allergy and Clinical Immunology* 107: 203–10.
- Toeys, C. D., R. M. Kaplan, and C. J. Atkins. 1984. "The Costs and Effects of Behavioral Programs in Chronic Obstructive Pulmonary Disease." *Medical Care* 22: 1088–100.
- Trapido, A. S., N. P. Mqoqi, C. M. Macheke, B. G. Williams, J. C. Davies, and C. Panter. 1996. "Occupational Lung Disease in Ex-Mineworkers—Sound a Further Alarm!" *South African Medical Journal* 86 (5): 559.
- Van den Boom, G., M. P. Rutten-van Mólken, J. Molema, P. R. Tirimanna, C. van Weel, and C. P. van Schayck. 2001. "The Cost Effectiveness of Early Treatment with Fluticasone Propionate 250 Microg Twice a Day in Subjects with Obstructive Airway Disease. Results of the DIMCA Program." *American Journal of Respiratory and Critical Care Medicine* 164 (11): 2057–66.
- Weiss, K. B., and S. D. Sullivan. 2001. "The Health Economics of Asthma and Rhinitis: I. Assessing the Economic Impact." *Journal of Allergy and Clinical Immunology* 107: 3–8.
- WHO (World Health Organization). 2000. "Global Burden of Disease 2000: Deaths by Age, Sex and Cause for the Year 2000." WHO, Geneva.
- . 2001. "Innovative Care for Chronic Conditions: Building Blocks for Action." WHO/MNC/CCH/02.01. WHO, Geneva.
- . 2002a. "Influenza." *Weekly Epidemiological Record* 77.28 (July 12): 229–40.
- . 2002b. "Outbreak of Influenza, Madagascar, July–August 2002." *Weekly Epidemiological Record* 77.46 (November 15): 381–88.
- . 2003. "Report of the First International Review Meeting, Practical Approach to Lung Health (PAL) Strategy." [http://whqlibdoc.who.int/hq/2003/WHO\\_CDS\\_TB\\_2003.324.pdf](http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.324.pdf).
- . 2005a. "Strengthening Pandemic Influenza Preparedness and Response." Report by the Secretariat. 58th World Health Assembly, A58/13, April 7.
- . 2005b. "Communicable Disease Surveillance & Response." Confirmed Human Cases of Avian Influenza A (H5N1). <http://www.who.int/csr/don/en/>. (This site provides weekly updates "Disease Outbreak News" of reported cases to WHO by specific countries and latest assistance with regard to potential pandemic status and preparedness. (Last accessed August 19, 2005, Updated 28<sup>2</sup>).
- . 2005c. "WHO Global Influenza Preparedness Plan." The Role of WHO and Recommendations for National Measures before and during Pandemics. WHO/CDS/CSR/GIP/2005.5, pp. 1–49.

