

The Global Impact of Respiratory Disease

THIRD EDITION



**Forum of
International
Respiratory
Societies**

ACKNOWLEDGMENTS

WRITING COMMITTEE

Stephanie Levine (co-chair)

UT Health- San Antonio and South Texas
Veterans Health Care System
San Antonio, Texas, USA

Darcy Marciniuk (co-chair)

University of Saskatchewan
Saskatoon, SK, CANADA

Amro Aglan

Beth Israel Deaconess Medical Center
Boston MA, USA

Juan C. Celedón

University of Pittsburgh
Pittsburgh, Pennsylvania, U.S.A.

Kwun Fong

The Prince Charles Hospital, Brisbane
QLD AUSTRALIA
UQ Thoracic Research Centre Brisbane
QLD AUSTRALIA

Robert Horsburgh

Boston University School
of Public Health, Boston MA, USA

Atul Malhotra

Pulmonary, Critical Care and
Sleep Medicine, UC San Diego
La Jolla, CA, USA

Refiloe Masekela

University of KwaZulu Natal
Durban, South Africa

Kevin Mortimer

Liverpool School of Tropical Medicine
Liverpool, UK

Hellen Redde

The Woolcock Institute of Medical
Research and the University of Sydney,
Sydney, AUSTRALIA

Mary Rice

Beth Israel Deaconess Medical Center
Boston MA, USA

Anita Simonds

Royal Brompton and Harefield Hospital,
NHLI, London UK

Lynn Tanoue

Yale School of Medicine
New Haven, CT, USA

Heather Zar

Red Cross Childrens Hospital
University of Cape Town, South Africa

CONTRIBUTING CONSULTANTS AND EXTERNAL REFEREES

Chris Brightling

University of Leicester
Leicester, UK

Joanna Chorostowska

National Institute of Tuberculosis and
Lung Diseases, Warsaw, Poland

Clayton Cowl

Mayo Clinic, Rochester,
Minnesota, USA

David Lam

Department of Medicine, University of
Hong Kong, Hong Kong SAR, China

David Lewinsohn

Oregon Health & Science University,
Portland, OR, USA

Giovanni Battista Migliori

Servizio di Epidemiologia Clinica delle
Malattie Respiratorie, Istituti Clinici
Scientifici Maugeri IRCCS, Tradate, Italy

Yoichi Nakanishi

Kitakyushu City Hospital Organization,
Kitakyushu, Japan

Patrick Nana-Sinkam

Virginia Commonwealth University,
Richmond Virginia, USA

Uju Ozoh

Department of Medicine, College of
Medicine, University of Lagos, Lagos,
Nigeria

Rogelio Padilla

Instituto Nacional de Enfermedades
Respiratorias, Mexico City

Mariëlle Pijnenburg

Department of Paediatrics/ Paediatric
Respiratory Medicine and Allergology,
Erasmus University Medical Centre –
Sophia Children's Hospital, Rotterdam,
the Netherlands

Eva Polverino

Hospital Universitari Vall d'Hebron
(HUVH), Institut de Recerca Vall d'Hebron
(VHIR), Barcelona, Spain

Marcos Restrepo

South Texas Veterans Health Care System
and University of Texas Health, San
Antonio, TX, USA.

Nicolas Roche

Hôpital Cochin, AP-HP.Centre –
Université de Paris, Paris, France

Gerard Silvestri

Medical University of South Carolina,
Charleston, South Carolina, USA

Peter Sly

The University of Queensland, Brisbane,
Qld, Australia

Tobias Welte

Department of Pulmonary and Infectious
Diseases at Hannover University School
of Medicine, Hannover, Germany

EXECUTIVE DIRECTORS

Werner Bill

European Respiratory Society

Karen Collishaw

American Thoracic Society

Robert Musacchio

American College of Chest Physicians

Editorial support was provided by Sherri Damlo, ELS, of Valid Point, Inc.

Cite this publication as: Forum of International Respiratory Societies. The global impact of respiratory disease. Third Edition. European Respiratory Society, 2021. Accessed 22 September, 2021. firsnet.org/images/publications/FIRS_Master_09202021.pdf



TABLE OF CONTENTS

Acknowledgements	2
Foreword	4
Executive summary	5
Introduction	6
The Big Five	
COPD	8
Asthma	11
Acute lower respiratory tract infection	15
Tuberculosis	19
Lung cancer	23
Other important respiratory conditions and concerns	28
What can be done to combat respiratory disease?	31
Summary	35
Recommendations	36
References	37
About FIRS	45
FIRS member societies	46
Appendix - GARD	51



FOREWORD

by Arzu Yorgancioglyu

Noncommunicable diseases, including heart disease, stroke, cancer, diabetes, and chronic lung disease, are collectively responsible for almost 70% of all deaths worldwide. Almost three-quarters of all deaths related to noncommunicable diseases and 82% of the 16 million premature deaths (ie, death <70 years of age) occur in low- and middle-income countries. Most of these diseases—especially chronic respiratory diseases—are preventable. Rather than solely dealing with a biomedical approach in diagnosis and treatment, focusing on social determinants of health such as tobacco use, air pollution, physical inactivity, the harmful use of alcohol, unhealthy diets, poverty, occupational exposure, and gender inequalities can help prevent these diseases.

The COVID19 pandemic has showed us the vital importance of lungs; it mostly affects the lungs; death is most commonly caused by lung involvement; and healthy lungs are able to fight COVID better. We have seen how a tiny virus can pose a threat to life when we disrupt the world's natural life balance, resulting in millions of casualties. Undoubtedly, SARS-CoV-2 not only caused deaths but also displaced many people globally with its economic, political and sociologic effects. The owner of nature alone is not human, and any attempt to disrupt the health and harmony of the environment in which humans live will directly affect the health of humankind and other creatures.

The only gain we can achieve from COVID-19 should be to change our perspective, our values, and, ultimately, our mentality.

Let us change, change for a new world, for another world, for our future...

The Global Alliance against Chronic Respiratory Diseases (GARD) is a voluntary alliance of national and international organizations, institutions, and agencies committed to the vision of a *"world where all people breathe freely,"* established by the World Health Organization (WHO) with the goal to reduce the global burden of chronic respiratory diseases.

GARD had a new governmental structure in 2019 and invited all international societies to liaise with GARD, with the strong branding of the WHO and the motto, *"If we work together to achieve our common goals, WE CAN MAKE A REAL DIFFERENCE."*

It is my great pleasure and opportunity to have the Forum of International Respiratory Societies (FIRS) representative act as an advisor to the GARD chair and Global Initiative for Asthma (GINA) & Global Initiative for Chronic Obstructive Lung Disease (GOLD) representatives in the GARD Executive Committee.

I would like to congratulate FIRS for this very important and comprehensive report, which shows the global impact of major respiratory diseases. We need advocacy and wide dissemination of this report to increase awareness and hopefully reduce the burden of these diseases.

"Live a life that leaves the world a better place because you made a difference."

—Janet N. Spriggs

"I believe FIRS is leading us to make a difference."

—Arzu Yorgancioglu, GARD Chair



EXECUTIVE SUMMARY

We take our breathing and our respiratory health for granted, but our lungs enable us to live, laugh, love, and enjoy activities. The lungs are vital organs and are vulnerable to airborne infection and injury. Respiratory diseases are leading causes of death and disability in the world. Nearly 200 million people, or 4% of the world's population, have COPD and 3.2 million die of it each year [1-3], making it the third-leading cause of death worldwide. Asthma affects more than 350 million people worldwide [4] and is the most common chronic disease of childhood worldwide. Pneumonia kills more than 2.4 million people annually [5] and is a leading cause of death among children younger than 5 years outside the neonatal period and adults older than 65 years [6]. More than 10 million people develop TB and 1.4 million die of it each year, making it the most common lethal infectious disease next to the COVID-19 pandemic [7]. The current pandemic has claimed the lives of more than 4.5 million people, largely all from respiratory causes [8]. Lung cancer kills 1.8 million people each year and is the deadliest of all cancers [9]. In 2019, respiratory disease comprised three of the top 10 causes of death according to the World Health Organization (WHO), leading to more than 8 million deaths annually [10]. Moreover, at least 2.4 billion people are exposed to indoor air pollution [11], and 90% of all people breathe outdoor air that exceeds WHO guideline limits, especially in low- and middle-income countries [12], and more than 1.3 billion are exposed to tobacco smoke [13]. The truth is that many of us are naïve to these stark realities, but the numbers do not lie.

Fortunately, most respiratory diseases are preventable by improving the quality of the air we breathe. Common sources of unhealthy air are tobacco smoke, indoor and outdoor air pollution, and air containing microbes, toxic particles, fumes, or allergens. Reducing tobacco consumption is the most important first step. Controlling unhealthy air in the workplace will prevent occupational lung disease. Strengthening vaccination programs can prevent many types of pneumonia, including those caused by SARS-CoV-2. Improving respiratory health also entails strengthening health-care systems, using established guidelines for health promotion and disease prevention and management, training medical personnel, research, and informing the public about the importance of lung health.

Prevention, control, and cure of these diseases and promotion of respiratory health must be a top priority in global decision-making and action in the health-care sector. These goals are achievable, and the control, prevention, and cure of respiratory diseases are among the most important and cost-effective health interventions available. The Forum of International Respiratory Societies (FIRS) asserts that alleviating the burden of respiratory disease must be a leading strategy to achieve its Sustainable Development Goals by 2030 and a willing obligation for nations to achieve [14,15].

The world is focused, most appropriately, on the current COVID-19 pandemic. Vaccinations have proven exceedingly effective and offer significant hope, and we need to enable the global distribution and administration of effective vaccines for all. It seems probable that a long-term vaccination strategy will include regular vaccine boosters to protect against variants. However, much more work must be done before the current pandemic abates and, perhaps even more importantly, for the world to be prepared for and potentially prevent future pandemics.

The purpose of this report is to call attention to the importance of overall respiratory health in the world and to raise it to be a top priority in global decision-making. Let us not take our breathing and respiratory health for granted.



INTRODUCTION

The lung is the internal organ most vulnerable to infection and injury from the external environment because of its constant exposure to particles, chemicals, and infectious organisms in ambient air. Globally, at least 2.4 billion people are exposed to the toxic smoke of biomass fuel, typically inefficiently burned in poorly ventilated indoor stoves or fireplaces [11]. Air pollution levels remain dangerously high in many parts of the world. Recent data from WHO show that nine of 10 people breathe air containing high levels of pollutants and that 7 million people die every year from exposure to polluted air [12]. More than 1.3 billion people worldwide use tobacco, exposing many others via secondhand exposure [13]. Tobacco use causes 8 million avoidable deaths per year, mostly from cardiovascular or respiratory diseases [14]. Although respiratory impairment causes disability and death in all regions of the world and among all social classes, poverty, overcrowding, environmental exposures, and generally poor living conditions increase vulnerability to this large group of disorders.

Respiratory diseases impose an immense worldwide health burden, with five of these being the most common causes of severe illness and death worldwide [10, 11, 16-18]:

1

An estimated 200 million people have COPD, from which about 3.2 million die each year, making it the third-leading cause of death worldwide [1-3].

2

Asthma afflicts more than 350 million people worldwide and is the most common chronic disease of childhood [4]. The prevalence of asthma has been rising for the past three decades [4].

3

For decades, acute lower respiratory tract infections have been among the top causes of death and disability among children and adults. Although its burden is difficult to quantify, lower respiratory tract infection causes more than 2.4 million estimated deaths annually and is a leading cause of death among children younger than 5 years outside the neonatal period and adults older than 65 years [6]. Moreover, acute lower respiratory tract infection in children predispose them to chronic respiratory disease later in life. Worldwide, annual epidemics of influenza are estimated to result in about 3 million to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths [19]. At the time of this writing, the COVID-19 pandemic has affected nearly 140 million worldwide and resulted in the deaths of more than 4.5 million people [8,20].

4

In 2019, 10 million people developed TB and 1.4 million people died from it [7].

5

The most common lethal neoplasm in the world is lung cancer, which resulted in the deaths of 1.8 million people in 2020 [9].

Leading causes of death globally



Source: WHO Global Health Estimates

REPRINTED FROM WHO.10

In addition to these top five, there are several respiratory disorders whose burden is also great.

- More than 1 billion people experience sleep-disordered breathing [21].

- Millions live with pulmonary hypertension [22].

- Millions are affected by occupational lung diseases.

In 2019, respiratory disease comprised three of the top 10 causes of death according to the WHO, leading to more than 8 million deaths annually, with COPD being the third-leading cause of death, lower respiratory tract infections being the fourth, and cancers of the trachea, bronchi, and lungs being sixth [10].

However, the impact on society is even greater. In the 2020 Global Burden of Disease Report, four of the “big five” lung diseases are among the top 20 causes of disability-adjusted-life-years after analyzing all ages and all levels of country income [18]. Lower tract respiratory infection is the fourth cause, COPD is the sixth, TB is the 12th, and lung cancer is the 17th-leading cause.

Even more distressing is the enormous disability and suffering that living with these illnesses can cause. Those who are most disadvantaged suffer most from poor health. With this awareness, the United Nations created the sustainable development goals to raise living standards globally [14,15,24]. Goal 3 of the sustainable development goals is to “ensure healthy lives and promote well-being for all at all ages.” FIRS is part of a global effort to call for action to address the huge burden of respiratory diseases. FIRS asserts that alleviating this burden should be a leading strategy of the sustainable development goals and a requirement for nations to achieve these goals [14,15]. FIRS has previously published reports, including prior editions of this ‘Global Impact of Respiratory Diseases’ report calling for improvements in health-care policies, systems, and care delivery, as well as providing direction for future research [24,25]. This report aims to provide an update on what has happened in the intervening years. Although some progress has been made, three of the big five areas of respiratory disease discussed in this report remain among the top 10 causes of global mortality, and all are among the leading causes of morbidity. These truths confirm the stark reality that far more work must be done to reduce the global burden and consequences of respiratory diseases.

COPD



SCOPE OF THE DISEASE

COPD is the most prevalent noncommunicable respiratory disease, affecting approximately 300 million people, or 4% of the world's population [1,2]. Worldwide, it is the third most common cause of death. In 2017, 3.2 million people died from COPD, accounting for an astounding 81.7% of the total number of deaths from chronic respiratory diseases [3]. Underdiagnosis and misdiagnosis are both common, especially in low-resource settings where access to basic effective care for COPD is limited [1,26,27]. The high prevalence and severity of illness make its economic cost high. For example, the direct cost of COPD is 6% of total health-care spending (€38.6 billion annually) in the European Union and accounts for 56% of the total cost of treating respiratory diseases [28].

The most important risk factor for developing COPD is tobacco smoking. Tobacco smoke destroys lung tissue (emphysema) and obstructs the small airways with inflammation and mucus, leading to the cardinal symptoms of COPD, namely shortness of breath, cough, and sputum production (chronic bronchitis). Household and outdoor air pollution, second-hand tobacco smoke, occupational dust, genetic causes (eg, α -1-antitrypsin deficiency), childhood pneumonia, other diseases that involve the airways (eg, uncontrolled asthma, TB), and markers of social deprivation (eg, poor education, low body mass index) are also associated with an increased risk of COPD [29,30].

PREVENTION

Discouraging individuals from starting to smoke tobacco and enabling those who already smoke tobacco to reduce and quit smoking are the most important priorities for preventing COPD. Clinically and cost-effective approaches to addressing household air pollution from use of dirty-burning fuels in low- and middle-income countries are needed to help reduce the burden of COPD and other respiratory diseases associated with this exposure. Childhood vaccines and prompt recognition and treatment of lower respiratory tract infections will minimize the airway injury that predisposes people to COPD in adulthood. COPD may begin in childhood, and management of childhood asthma, controlling occupational and domestic exposure to dust and fumes, eliminating second-hand tobacco exposure, and controlling for other environmental factors could have substantial benefits in reducing the burden of COPD.

Widespread population screening for COPD in asymptomatic adults is not recommended [30], although performing targeted testing with spirometry in populations with certain risk factors and respiratory symptoms (breathlessness, cough, sputum production, wheezing, recurrent lower respiratory tract infections) is advised [31]. For example, clinicians should pursue a diagnosis for symptomatic people exposed to smoke from cigarettes, biomass fuels, occupational dusts, and certain chemicals, as well as those with a family history of α -1-antitrypsin deficiency.

DIAGNOSIS AND TREATMENT

Spirometry is required to establish a diagnosis of COPD and is a key step toward appropriate treatment. Using spirometry confirms diagnosis and avoids misdiagnosis, yet its availability is poor in low- and middle-income countries as well as in some other settings [1]. In settings where spirometry is not readily available, therapy may be proposed based on a clinical suspicion of COPD, awaiting diagnostic confirmation.

Identification and reduction of exposure to risk factors are essential to prevent and treat the disease. All individuals who smoke should be identified and provided with assistance to enable them to quit. Vaccination against seasonal influenza can reduce the risk of severe exacerbations triggered by influenza [32]. Vaccinations against COVID-19, *Streptococcus pneumoniae* infection, and pertussis are also recommended [33].



Along with removal of respiratory irritants or triggers and early treatment of respiratory infections, inhaled bronchodilators are basic medicines that may help these patients. Treatment with long-acting bronchodilators, sometimes together with inhaled corticosteroids and other pharmacologic and nonpharmacologic measures, can significantly help patients with frequent exacerbations and severe airflow obstruction [33].

Patients with low blood oxygen levels may require supplemental oxygen. Long-term oxygen therapy can increase survival and improve the quality of life in patients with very low oxygen levels. Maintaining physical fitness and activity is important because difficulty breathing may lead to a decreased activity and subsequent deconditioning. Therefore, exercise-based pulmonary rehabilitation is important for many people with COPD [34], although access and participation remain very limited [35]. Treating comorbidities can extend the life of many people.

Evidence-informed clinical strategies are available that outline the appropriate management of COPD [33]. Despite the availability of clinical practice guidelines in high-resource settings [31,36], several studies have shown that COPD is undertreated in its early as well as its advanced stages. There is much more limited availability of relevant clinical practice guidelines in low- and middle income-countries [34].



CONTROL AND ELIMINATION

The key element of reducing and controlling COPD is abolishing tobacco use. This is best addressed through effective political and public health initiatives. Public health and societal efforts are also needed to reduce indoor smoke exposure and other COPD-related risk factors as well as to develop cost-effective management protocols for COPD, especially in low-income settings. Although age-specific mortality rates from COPD are now declining, the world's ageing population makes this a huge problem for decades to come that will not abate by itself. Research should lead to better understanding of how risk factors and comorbidities interact to affect the severity of disease and which other factors cause COPD in those who smoke and never-smokers. Increasing awareness of COPD in the population and among health-care professionals in low- and middle-income countries is needed [37].

RESEARCH QUESTIONS

The need is great to prevent the development of COPD, and diagnostic strategies to diagnose early COPD are urgently needed. Uncertainties exist regarding how best to identify and treat mild COPD and non-smoking-related COPD, as well as how to best manage COPD in the context of concomitant conditions (eg, sleep apnea, cardiovascular disease, depression, osteoporosis, diabetes, lung cancer, aging, frailty). Also unknown is the best approach outside of exposure avoidance to treat the large number of individuals exposed to smoke or other pollutants, with chronic bronchitis, emphysema, or abnormal lung function but without airflow obstruction.

ASTHMA





SCOPE OF THE DISEASE

Asthma afflicts more than 350 million people worldwide and its incidence has been increasing for the past three decades [4]. It affects all ages, races, and ethnicities, although wide variation exists between different countries and in different groups within the same country. It is the most common chronic disease in children and is more severe in children living in nonaffluent countries [38]. In nonaffluent countries, underdiagnosis and undertreatment are common, and effective medicines may not be available or affordable. Asthma is characterized by symptoms of breathlessness, cough, wheezing, and variable expiratory airflow limitation, usually associated with underlying airway inflammation. At times, acute worsening of symptoms and airflow limitation known as exacerbations or severe attacks can occur.



The burden of asthma is high [4,39]. It is not widely realized that asthma causes nearly 500,000 deaths per year or more than 1,300 deaths per day [19]. It is one of the most frequent reasons for preventable hospital admissions among children in high-income countries, but less information is available on children from low- and middle-income countries [4]. In some pediatric studies, asthma accounts for more than 30% of all hospitalizations and nearly 12% of readmissions within 180 days of discharge [40]; in the United States, up to 36% of children with asthma aged 17 years or younger were reported to have had an emergency department visit for asthma in the previous year [41]. Recent evidence indicates that some children with asthma are born with reduced lung function and may have abnormal lung growth during early childhood [42]. Some are at risk for developing persistent airflow limitation [43], although the impact of treatment on preventing this is uncertain.

The causes of the increase in global prevalence of asthma are not completely understood. In high-income countries, persistent asthma is associated with early allergic sensitization, whereas the role of atopy in low-income settings is less clear. Genetic predisposition, gene-by-environment interactions, epigenetic mechanisms, exposure to environmental allergens, indoor and outdoor air pollution, lower respiratory tract infection early in life, airway microbiome makeup and disbalance, dietary factors,

obesity, preterm birth, and abnormal immunologic responses may promote the development of asthma. The timing and level of exposure to allergens, infection, or irritants may also be major factors leading to the development of disease. Early viral infection, maternal smoking during pregnancy, and passive tobacco smoke exposure have been associated with the development of asthma in young children. Airborne allergens and irritants associated with asthma occur in the workplace and can lead to chronic and debilitating disease among workers if the individual is not promptly removed from exposure.

PREVENTION

The cause of most asthma cases is unknown, and no effective strategy exists yet for primary prevention. However, potentially modifiable risk factors for development of asthma include smoking during pregnancy and infant diet [44]. A Mediterranean diet containing fresh fruit and vegetables, unprocessed foods, and food rich in antioxidants has been associated with lower rates of asthma and fewer asthma exacerbations in some, but not all, studies. Correction of vitamin D deficiency in women who are pregnant or those planning pregnancy may reduce the risk of early childhood wheezing illness, although not childhood asthma [45]. Early initiation of inhaled corticosteroids in preschool children considered to be at high risk did not reduce asthma prevalence by school age [46].

Once asthma has developed, avoidance of smoking may prevent rapid decline in lung function. Avoiding smoking during pregnancy and avoiding passive smoke exposure after birth, especially in the home and car, can reduce the severity of asthma in children. Epidemiologic interventions involving work-related asthma show that early removal of allergens or irritants in adulthood may lead to better control of the disease, although the burden and cost of the intervention must be considered. Evidence is scarce for effective, single-strategy indoor allergen avoidance interventions in adults outside the occupational context, except for remediation of dampness and mold [47]. Inhaled corticosteroids do not appear to prevent lung function decline [43], except in people who have experienced a serious exacerbation [48].



TREATMENT

Making a correct diagnosis is essential for treatment, and improving access to spirometry will help to reduce misdiagnosis in older children [49] and adults [50]. Asthma is generally an incurable lifelong disease, but treatment with quality-assured essential asthma medicines can effectively control the disease and lead to a near-normal life. Inhaled corticosteroids are the cornerstone of effective asthma control. When they are used appropriately (ie, taken regularly with optimal technique), inhaled corticosteroids can decrease the severity and frequency of symptoms of asthma. They can also reduce the need for reliever inhalers (short-acting bronchodilators) and the frequency of exacerbations requiring urgent medical care, emergency department visits, hospitalizations, or death. Inhaled bronchodilators are important for providing rapid relief from asthma-related symptoms.



In preschoolers with recurrent wheeze, inhaled corticosteroids do not prevent acute asthma exacerbations, perhaps because approximately one-third of such children will develop persistent asthma. Unfortunately, no current method can accurately predict which of these children will go on to develop persistent asthma.

Adherence to inhaled corticosteroid monotherapy is extremely poor, leading to studies of alternative therapies. In adults and adolescents with mild asthma, taking low-dose budesonide/formoterol as a reliever markedly reduces the risk of exacerbations versus short-acting β_2 -agonists alone, and, to a similar or greater extent, as maintenance inhaled corticosteroid with as-needed short-acting β_2 -agonist reliever [51]. No evidence supports these strategies in children aged 5 years and younger, so their use is not recommended in this age group [51].

Unfortunately, many people with asthma do not have access to effective quality-assured asthma medicines. Even though inhaled corticosteroids, inhaled bronchodilators, and budesonide/formoterol are on the essential drug list of the WHO, they are regrettably either unavailable or unaffordable in many settings [4,52].

Lack of availability of medication is not the only reason people with asthma do not receive effective care. Widespread misconceptions about the nature of the disease and its treatment often prevent people from accessing and using appropriate treatments. Educational campaigns to encourage appropriate use of inhaled corticosteroids for control (either regularly or in combination with formoterol for use as a reliever by patients with mild asthma), avoidance of exposures that trigger asthma attacks, training in inhaler technique, and provision of written asthma action plans (so that the patient can respond to worsening asthma) are important parts of effective asthma control programs.

CONTROL AND ELIMINATION

Additional research is needed to better understand the earliest origins of asthma, the causes of exacerbations, and reasons for its rising prevalence in many countries [53]. Elimination is a distant vision. The International Study of Asthma and Allergies in Childhood and the Global Asthma Network have provided insights into the disease and facilitated standardized research on asthma in children that has helped to define the worldwide prevalence, trends, and determinants of asthma and allergies. Their work and other research findings are being incorporated into evidence-based strategies for the management of asthma [54]. Effective dissemination and implementation of these strategies will improve asthma control. Making quality-assured inhaled corticosteroids or combination inhaled bronchodilators/corticosteroids, bronchodilators, and spacer devices widely available at affordable prices and educating people with asthma about the disease and its management are key steps to improve outcomes for people with asthma. Strategies to reduce indoor and outdoor air pollution, smoke exposure, and respiratory infections will improve asthma control and importantly reduce the need for health-care utilization.

Acute Lower Respiratory Tract Infection





SCOPE OF THE DISEASE

Lower respiratory tract infection is a leading cause of mortality, accounting for more than 2.4 million deaths every year, particularly among those in low- and middle-income countries [5]. Lower respiratory tract infection kills more people than HIV infection, TB, and malaria combined [6]. It is the leading cause of death in children younger than 5 years of age outside the neonatal period and adults older than 65 years [6]. In 2019, pneumonia-related deaths occurred in approximately 650,000 children younger than 5 years, making up almost 15% of the deaths in this age group [55]. In addition, lower respiratory tract infections caused more than 1 million deaths in adults older than 70 years [56]. It is also the second-leading cause of years of life lost due to premature mortality and one of the most frequent reasons for hospitalization [5]. In addition to death and hospitalization, pneumonia has potential long-term consequences leading to impaired lung health and progression to chronic respiratory disease, such as bronchiectasis or chronic cardiovascular conditions (eg, heart failure, cardiac arrhythmias, coronary syndromes). COVID-19–associated pneumonia has increased the burden of pneumonia, particularly in adults, with potential long-term consequences, including neurologic, cardiovascular, mental health, and respiratory sequelae.



Risk factors for pneumonia include very young and very old age, residing in crowded conditions, malnutrition, HIV infection, lack of breastfeeding in infants, lack of immunization, chronic health conditions (eg, immunosuppression, chronic heart conditions, chronic lung disease, diabetes, exposure to tobacco smoke or indoor /outdoor air pollutants). However, for COVID-19, specific risk factors include very old age and the presence of comorbidities, especially diabetes, obesity, chronic lung or heart disease, and immunosuppression. Uncommonly, children and infants have been relatively spared in the COVID-19 pandemic, predominantly by developing asymptomatic or mild illness. Adults have been predominantly affected by COVID-19, and most of COVID-19–related deaths occur among adults older than 45 years.

CAUSES

Pneumonia, especially severe illness, is often caused by host–pathogen interactions. With strengthened global immunization programs, improved living conditions, and control of the HIV pandemic, bacteria have declined as a cause of pneumonia and viruses predominate. In young children, respiratory syncytial virus (RSV) is the most common cause, responsible for almost 34 million episodes each year. More than 90% of deaths from RSV infection in children occur in low- and middle-income countries [57]. Every year, influenza leads to respiratory tract infections in 5% to 15% of the population and severe illness in 3 million to 5 million people [58]. Respiratory viruses can spread quickly because of their ease of transmission, as has been seen in past influenza pandemics as well as in the COVID-19 global pandemic.

Among bacteria, *S. pneumoniae* remains the most frequent bacterial cause. *S. pneumoniae* was the worldwide leading cause of lower respiratory infection morbidity and mortality, contributing to more deaths than all other etiologies combined in 2016 [56]. However, increased global uptake of the pneumococcal conjugate vaccine has substantially reduced pneumonia in children as well as in unvaccinated groups such as the elderly due to reduced transmission of disease-causing serotypes. HIV infection increases the risk of pneumonia, although the incidence of severe disease has declined with use of antiretroviral therapy.

TB may present as acute pneumonia in children in areas with high TB prevalence and thus be frequently undiagnosed and untreated.

TREATMENT

The success of prevention or treatment of many respiratory infections depends on the quality of the health-care system. Most bacterial infections are treatable with antibiotics and most viral infections are self-limited, requiring only supportive care. Yet millions of children and people still die of pneumonia. Failure to prevent these deaths may be due to lack of access to quality health care and limited availability of effective treatment or preventive interventions, including immunization. Comorbidities, such as HIV infection and malnutrition, and lack of awareness, education, and access may lead to advanced disease before affected people seek medical attention, resulting in greater treatment failure.

Early diagnosis of lower respiratory tract infection is essential to prevent death and disability and includes the need for community engagement and education. Better diagnostic tests, with improved sampling procedures and methods for rapid detection of infectious agents that distinguish bacterial, viral, and mycobacterial pathogens are needed. Cost-effective, rapid, and low-technology solutions for accurate detection of infectious agents are required to reduce morbidity and mortality even in the most remote locations.

The most effective way to manage pneumonia is through standard case management. For childhood pneumonia, a standard approach to diagnosis and treatment has been developed by the WHO in the Integrated Management of Childhood Illness program. The cornerstone of management is appropriate diagnosis, referral, and use of antibiotics. Supplemental oxygen is essential for treatment of severe pneumonia but is unavailable in many low- or middle-income country settings. Greater availability of pulse oximeters to guide supplemental oxygen therapy coupled with better access to reliable oxygen delivery systems must be a priority for effective treatment of severe respiratory infections [52]. Treatment of TB is addressed elsewhere (see TB below).

In the management of pneumonia in adults, several national guidelines have been developed and many studies have documented that adherence to these guidelines is associated with better patient outcomes [59]. For the treatment of COVID-19, high-flow oxygen, noninvasive ventilatory support, and use of corticosteroids and antivirals have been key effective interventions [60].





PREVENTION, CONTROL, AND ELIMINATION

Childhood respiratory disease can be prevented or ameliorated by several measures: improving childhood nutrition and promoting breastfeeding; ensuring comprehensive immunization; improving living conditions to prevent crowding; avoiding exposure to tobacco smoke and air pollution across the life course; treating or preventing HIV infection; giving prophylactic antibiotics to immunosuppressed children; and preventing vertical HIV transmission. Several of these measures are also appropriate for respiratory disease prevention in adults.

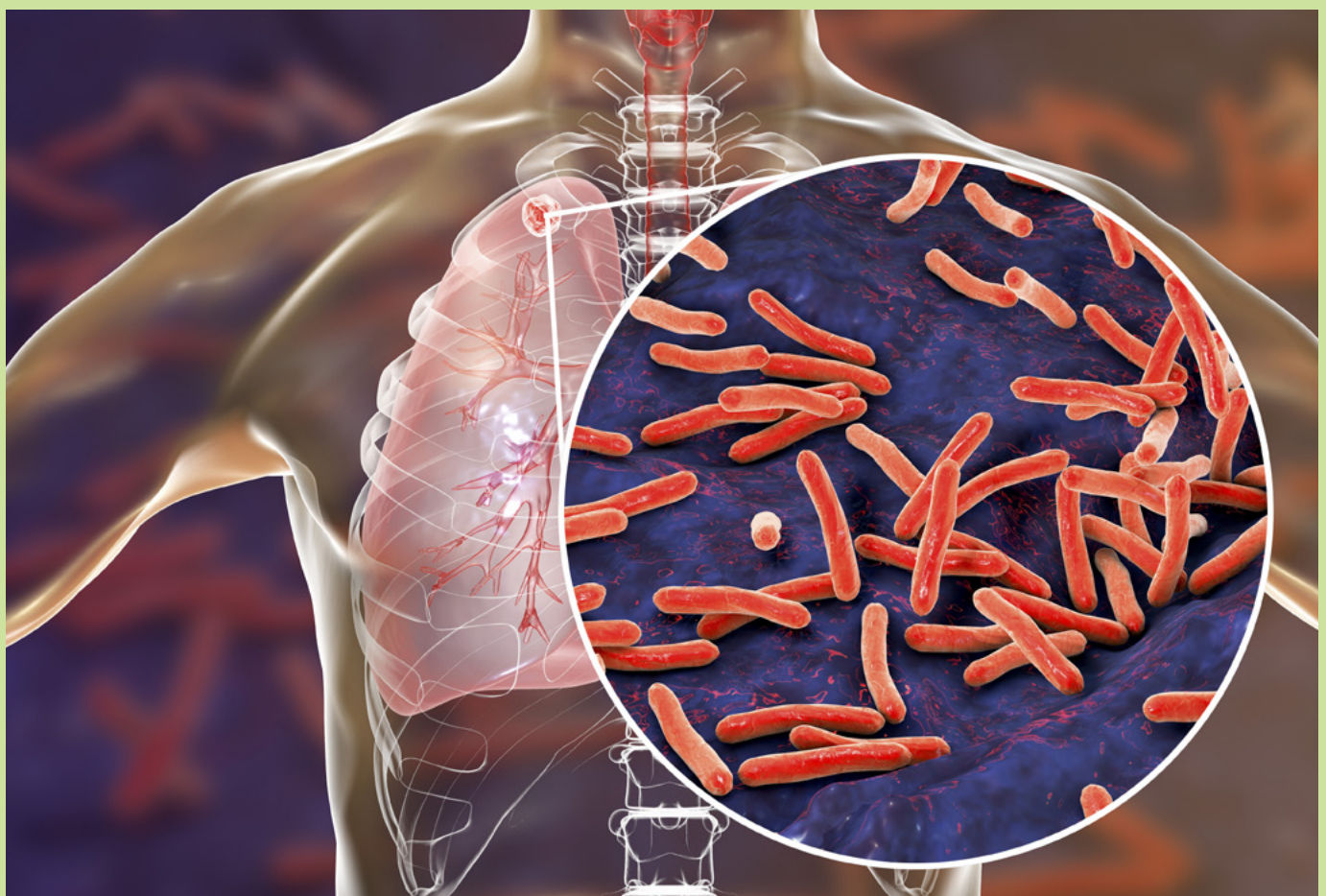
When they are used widely as public health measures, nonpharmacologic interventions are effective for prevention of viral transmission and TB in children and adults. Measures include social distancing, hand hygiene, and universal wearing of masks. Such interventions have been effective at reducing transmission of and decreasing cases of COVID-19 and have also reduced viral infections such as RSV and influenza. However, lack of access to running water, crowded living conditions, an inability to social distance, and poverty make implementation of such measures challenging.

Vaccination is one of the greatest public health advances, yet many children are unimmunized against preventable infections, particularly those living in low- and middle-income countries. Countries with the lowest immunization rates account for more than two-thirds of the vaccine-preventable disease burden and have the highest rates of childhood mortality. Development of new conjugate vaccines against *S. pneumoniae* (pneumococcus), *Haemophilus influenzae* type b, and pertussis (whooping cough) have been important advances in prevention of pneumonia. The influenza vaccine is effective in preventing seasonal influenza. Vaccines against other viruses, such as measles, are so effective that they are essentially eradicating the diseases. Adolescent and adult vaccination programs, which are also effective, have frequently been neglected. New conjugate vaccines must be available as part of expanded programs for immunization in all countries. Furthermore, new preventive interventions are needed for common pathogens such as RSV and influenza.

Several effective vaccines against COVID-19 have been rapidly developed and implemented; however, COVID-19 vaccine inequity is one of the most pressing current global issues. Vaccines are being distributed in many countries, predominantly in high-income settings. In many low- and middle-income countries, vaccination is occurring in very small numbers. For example, only 1.1% of people in low-income countries have received at least one vaccination dose [61]. At current rates, widespread access to vaccination in African countries is only predicted to occur between April 2022 and 2023. To attain ultimate global control of the pandemic, high coverage of populations is needed.

Inequities in global access to vaccination has exposed and worsened large disparities between countries. Countries with the lowest rates of vaccination are also those with the most fragile health-care systems, lack of infrastructure for widespread vaccination programs, lack of access to oxygen and other life-saving interventions, and more economically disadvantaged populations. Greater cooperation and collaboration between high-income countries and low- and middle-income countries are needed to ensure equitable distribution of vaccines as well as sustained programs to enable vaccination.

TUBERCULOSIS





SCOPE OF THE DISEASE

Ten million new cases of TB occurred in 2019, with an estimated 500,000 new cases of rifampicin-resistant or multidrug-resistant TB [7]. Among new cases of TB, 8.2% of people were coinfecting with HIV. TB was responsible for the deaths of 1.4 million people in 2019, making it the greatest single infectious agent to cause death at the time and the 10th-leading cause of overall deaths in the world. Thirty countries accounted for 8% of the cases of TB [7]. In addition, there are negative consequences for those who survive TB, because post-TB carries a high burden of morbidity and mortality [62].

The incidence of TB fell by more than 2% per year between 2015 and 2019, which is insufficient to end TB by the WHO's stated goal of 2035. The absolute number of TB-related deaths among HIV-negative people fell 31% between 2000 and 2019, from a best estimate of 1.7 million in 2000 to 1.2 million in 2019, and the mortality rate decreased by 45%. Among people with HIV infection, the number of TB deaths decreased faster, from 678,000 in 2000 to 208,000 in 2019 (69% reduction), and the mortality rate fell by 76% (from 11 to 2.7 per 100,000 population). [7].

In 2019, 7.1 million people worldwide were newly diagnosed with TB and notified, up from 6.4 million in 2017 and 5.7 million to 5.8 million annually in the period between 2009 and 2012. Despite increases in TB notifications, a gap of 2.9 million remained between the number of people newly diagnosed and reported and the 10 million people estimated to have developed TB in 2019 [7].

PREVENTION

Three methods are used to prevent TB disease: reducing transmission, treating infection so it does not progress to disease, and vaccination to prevent infection/disease progression. Reducing transmission requires prompt identification and treatment of people with infectious pulmonary TB. Given the estimated 2.9 million people with incident TB who went undiagnosed in 2019, awareness is increasing that active case-finding strategies will be required to reduce infection in high-burden TB communities. Targeted screening has focused on household contacts, clinic attendees, people living with HIV, people with clinical or structural risk factors (eg, diabetes, homeless, incarcerated people, miners), and high-incidence communities. The most common active case-finding strategies included door-to-door visits and mobile chest radiography. Active case-finding was shown to be cost effective in most studies among people with HIV infection [63,64].

Cost effectiveness of active case-finding among the general population ranged from \$31 to \$1,626 per case detected; cost effectiveness for children ranged from \$18 to \$28 per case detected; and cost effectiveness for household contacts ranged from \$36 to \$2,693 per case detected [65,66]. Key drivers of cost effectiveness are underlying TB prevalence, false-positive screen rates, downstream treatment costs, and inclusion of programmatic costs.

Antibiotic treatment of latent TB infection (LTBI) to prevent progression to disease has become a more prominent strategy over the past decade. This strategy has long been recommended for low-incidence countries and people co-infected with HIV and LTBI. With the advent of rifamycin-based treatment regimens of 3 months or shorter for LTBI, recommended target populations have expanded. These target populations now include household contacts of a person with infectious pulmonary TB, people with HIV infection living in high TB-incidence regions without regard to latent infection status, patients initiating antitumor necrosis factor treatment, those receiving dialysis, people preparing for organ or hematologic transplantation, and those with silicosis, regardless of the background TB epidemiology. Implementing LTBI screening and treatment are not recommended in areas with high TB incidence because the likelihood of prompt reinfection is substantial.

Although the combination of active case-finding and treatment for LTBI dramatically reduce the burden of TB in well-resourced settings, modeling suggested that elimination of TB will also depend on the development of a vaccine that prevents disease and, hence, transmission [67,68]. The Bacille-

Calmette–Guérin vaccine offers only partial protection against TB but does reduce the risk of disseminated TB and tuberculous meningitis in children. A recent phase 2 vaccine trial demonstrated that, among people with LTBI, the M72 vaccine, when administered with the AS01E adjuvant, elicited an immune response and provided protection against to pulmonary TB disease progression for at least 3 years [69]. This is now being examined in a phase 3 trial; if these promising results can be replicated, then this will provide an important new tool for preventing TB. However, it should be noted that the preclinical development of this vaccine occurred during the 1990s, highlighting the delayed timeline



in the development and potential deployment of TB vaccines. It is estimated that the earliest the M72AS01E vaccine could be available would be 2028, but recent experiences with vaccine development and deployment increase hope for potentially accelerated availability. At present, it seems likely that multiple vaccines will be needed to serve disparate populations (eg, infants vs uninfected adults vs infected adults) [70]. As a result, renewed investment in the rapid development and evaluation of diverse vaccine candidates is needed. Recent progress seen in the development of successful SARS-CoV-2 vaccines highlight the power of public private partnerships in evaluating and ultimately purchasing vaccines prior to their demonstrated effectiveness. As TB remains a leading cause of infectious disease morbidity and mortality worldwide, these public investments are both necessary and achievable [70].

DIAGNOSIS

The global rollout of DNA-based testing has improved the diagnosis of TB, but important gaps remain. Improved sensitivity of such tests may provide sensitivity equal to culture [71], and development of sensitive and specific point-of-care diagnostic tests is a high priority. Current DNA-based testing still requires a centralized laboratory, so this means that patients living some distance from laboratories often fail to receive their test results. Tests that do not require sputum for diagnosis are also important for diagnosing TB when sputum cannot be obtained or when disease is extrapulmonary. Recent studies have suggested promise with urine-based testing [72].

Global TB drug-resistance testing capacity is limited, with the result that, in 2019, only 61% of people with bacteriologically confirmed TB were tested for rifampicin resistance. Although this rate has improved from 2017 when only 51% were tested, it is still far below what is needed [7]. The movement toward sequence-based drug-susceptibility testing has made substantial progress but is not yet available in most localities [73,74].

The potential for using biomarkers to identify patients with TB, possibly even before they become infectious, was the subject of a WHO-sponsored Targeted Product Profile for predicting progression from infection to active disease. At present, such products are not commercially available and would need to be carefully integrated into the active case-finding strategies outlined in the previous section [75].



TREATMENT

Most cases of TB can be cured if diagnosed early and appropriately treated using standardized approaches based on evidence derived from clinical trials. In 2019, the rates of treatment success were 83% for drug-sensitive TB, 52% for multidrug-resistant TB, and 28% for extensively drug-resistant TB [7]. The lengthy duration of therapy (usually 6 months, starting with four drugs in uncomplicated cases) makes adherence to treatment challenging, especially in individuals who are taking other medications for chronic diseases such as HIV infection. Failure to take the full course of prescribed drugs may result in relapse with drug-resistant disease, which is more difficult to treat and poses a risk to others. The recent identification of an effective 4-month regimen for drug-susceptible TB disease is a major step forward and will hopefully soon be incorporated into global practice [76].

Treatment of patients with multidrug-resistant TB is a more complicated issue. Such treatment requires a course of second-line drugs for at least 9 months and up to 20 months. WHO now recommends expanded access to all-oral regimens, an important step forward in improving the tolerability of these regimens [77]. Globally, 177,099 people were enrolled in treatment for drug-resistant TB in 2019, a number up from 156,205 in 2018. Despite these improvements, the number of people receiving multidrug- and rifampicin-resistant treatment in 2019 was equivalent to only 38% of the estimated number of people who developed multidrug- and rifampicin-resistant TB [7].

CONTROL AND ELIMINATION

The World Health Assembly approved the End TB Strategy in 2014, a comprehensive set of principles and activities developed by WHO's Global Tuberculosis Program over 2 years with broad global consultative input [78]. More than 5 years later, TB incidence is falling but not fast enough to reach the 2020 milestone of a 20% reduction between 2015 and 2020—only a 9% reduction was achieved. The milestone of a 35% reduction in TB-related deaths between 2015 and 2020 has also not been achieved; only a 14% reduction was accomplished. Moreover, in 2019, 49% of people with TB and their households faced catastrophic costs (defined as total costs equivalent to >20% of annual household income). The target for this metric was 0%. Funding for TB prevention, diagnosis, treatment, and care was \$6.5 billion in 2020—only 50% of the target of at least \$13 billion per year by 2022 [7]. Thus, while funding for the provision of TB prevention and diagnostic and treatment services has doubled since 2006, it still sadly falls far short of what is needed.



Moreover, in 2019, 49% of people with TB and their households faced catastrophic costs (defined as total costs equivalent to >20% of annual household income). The target for this metric was 0%. Funding for TB prevention, diagnosis, treatment, and care was \$6.5 billion in 2020—only 50% of the target of at least \$13 billion per year by 2022 [7]. Thus, while funding for the provision of TB prevention and diagnostic and treatment services has doubled since 2006, it still sadly falls far short of what is needed.

In 2018, the 71st World Health Assembly delegates agreed on the Organization's 13th General Program of Work, which is designed to help the world achieve the Sustainable Development Goals with a particular focus on ensuring healthy lives and promoting wellbeing for all at all ages by 2030 [15]. The plan includes key milestones toward ending TB, aiming by 2023 to reduce TB-related deaths by 50% compared with numbers from 2018, increase coverage of treatment for drug-resistant TB to 80% of estimated incidence, and ensuring no TB-affected families face catastrophic costs due to TB [7]. Whereas the COVID-19 pandemic that began in 2020 has delayed realization of these goals [79], it is hoped that, once COVID-19 is under control, these will be appropriately readdressed with renewed vigor and resources.

The potential for using biomarkers to identify patients with TB, possibly even before their becoming infectious, was the subject of a WHO sponsored Targeted Product Profile for predicting progression from infection to active disease. At present, such products are not commercially available and would need to be carefully integrated into the ACF strategies outlined above [74].

LUNG CANCER





SCOPE OF THE DISEASE

Lung cancer is the leading cause of cancer death worldwide. The International Agency for Research on Cancer GLOBOCAN estimated a global lung cancer burden of 2.2 million new cases and 1.8 million deaths in 2020 [1]. Despite many remarkable advances in evaluation and treatment, lung cancer remains a highly fatal disease, with a global mortality incidence ratio of 0.85 in 2016 [80]. Five-year survival rates remain only 10% to 20% in most countries, with improvement observed predominantly in countries with higher health development index [1].

Lung cancer is caused by modifiable risk factors, predominantly tobacco smoking. Multiple carcinogens in tobacco smoke cause mutations of both protective and tumor-promoting genes that accumulate over time. The risk of lung cancer correlates with intensity and duration of smoking. Presently, the incidence and mortality rates of lung cancer are higher in high-income countries, reflecting a longer duration of the cultural tolerance of smoking [17]. Evolution of the global tobacco epidemic will likely change this distribution, as more than 80% of the individuals worldwide who smoke live in low- and middle-income countries [81].



Although tobacco is implicated as causal in most lung cancer cases, other carcinogens contribute to increased risk in both individuals who have ever smoked and those who have never smoked. An estimated 5% to 10% of deaths related to lung cancer worldwide are attributable to occupational carcinogens, including asbestos, vinyl chloride, and beryllium, among others [82-85]. Domestic carcinogens include radon and indoor emissions from combustion of biomass fuels [86-88]. Outdoor air pollution related to industrialization and climate change increases exposure to carcinogens such as particulates and diesel exhaust [90-92]. Genetic factors may influence individual susceptibility to mutagenicity of carcinogenic agents as well as individual capability of DNA repair [92-94].

The human cost inflicted by lung cancer is immeasurable, and the global economic cost of lung cancer is immense. US and EU economic studies identified lung cancer as having the highest cost related to lost earnings among all cancers, estimated at \$21.3 billion in the United States in 2015 and €18.8 billion in the European Union in 2009 [95,96]. Although worldwide data are limited, a 2010 American Cancer Society study using WHO data estimated the annual global economic toll related to lung cancer at \$180 billion [97,98].

WOMEN

The incidence of lung cancer in women is increasing worldwide, largely attributable to increases in smoking prevalence [99]. One modeling study in the United States found that, although more men than women died of lung cancer in 2015, current smoking trends predict that this gender gap will close by 2045 [100]. Increasing rates of lung cancer in women have also been attributed to genetic differences and environmental exposures such as cooking fumes in poorly ventilated enclosures, among others.

Although approximately 10% to 20% of lung cancers occur in individuals who have never smoked, the incidence of lung cancer in those who have never smoked is much higher in women compared with men. Adenocarcinoma is the most common histologic subtype in both sexes, but women have an even higher predominance of this cell type. EGFR mutations, which are identified in approximately one-half of those who have never smoked with lung cancer, are more prevalent in women, particularly in women who do not smoke [101].

Irrespective of smoking and EGFR mutational status, women with lung cancer have better survival rates than men, even after controlling for age, stage, and treatment type [102-104]. This sex-related advantage may also be true for lung cancer screening using low-dose computed tomography, as the two largest randomized controlled lung cancer screening trials suggested a trend toward better outcomes for women [105,106].

PERSPECTIVE FROM ASIA

Approximately 59% of the global population resides in Asia [107]. If the current trend of an increasing number of individuals who smoke in the region persists, lung cancer rates will inevitably also rise. Many lung cancers in Asia occur in individuals who have never smoked; 60% to 80% of women in Asia with lung cancer have never smoked compared with 15% to 20% of those in the United States and Europe [108].

Preliminary reports from the TALENT lung cancer screening study of high-risk individuals who have never smoked in Taiwan, of which 73.8% were women, identified a positive family history of lung cancer as the most significant risk factor [109]. Epidemiologic and clinicomolecular patterns are distinctive (eg, prevalence of EGFR mutations is higher than in western populations), emphasizing the importance of molecular profiling to guide therapies [110,111]. Research is needed to better understand ethnic and regional factors that could be targeted for prevention.

PREVENTION

Lung cancer is a disease that should be rare; nearly all risk factors are modifiable and preventable. The most consequential is tobacco smoking. The WHO estimates that 1.3 billion people are current tobacco users [13]. International heterogeneity in the incidence and mortality rates of lung cancer largely reflect variation in the maturity of the tobacco epidemic and are several-fold higher in countries with a high or very high health development index compared with a medium or low health development index [9,112]. An encouraging global reduction of 28.6 million individuals who currently smoke was observed from 2000 to 2015 [81]. However, this net reduction reflects a decrease of 82.5 million individuals who smoke predominantly in the Americas and Europe, offset by an increase of 53.9 million individuals who smoke in the WHO African, Eastern Mediterranean, South-East Asian, and Western Pacific regions [81]. Current tobacco use rates are highest in the South-East Asian, Western Pacific, and European regions (27.9%, 25.7%, and 25.6%, respectively); are lower in the Eastern Mediterranean and Americas regions (18.6% and 17.5%, respectively); and lowest in African regions (12.3%) [81].



Tobacco control efforts are a global imperative. Much of the momentum curtailing tobacco use dates to the 2003 WHO Framework Convention on Tobacco Control [113], which outlined a global approach to reducing tobacco consumption [114-117]. The 168 countries signing the treaty committed to develop and implement public health policies with measures to reduce tobacco demand; decrease tobacco smoke exposure; regulate packaging, labeling, and advertising; and educate the public. Subsequent research has shown that multiple approaches are needed. Tax and price increases are more effective among younger adults [118,119], as are tobacco packaging warnings and education [120-122]. Smoke-free mandates have a modest effect in decreasing social acceptability of smoking [120,123,124].

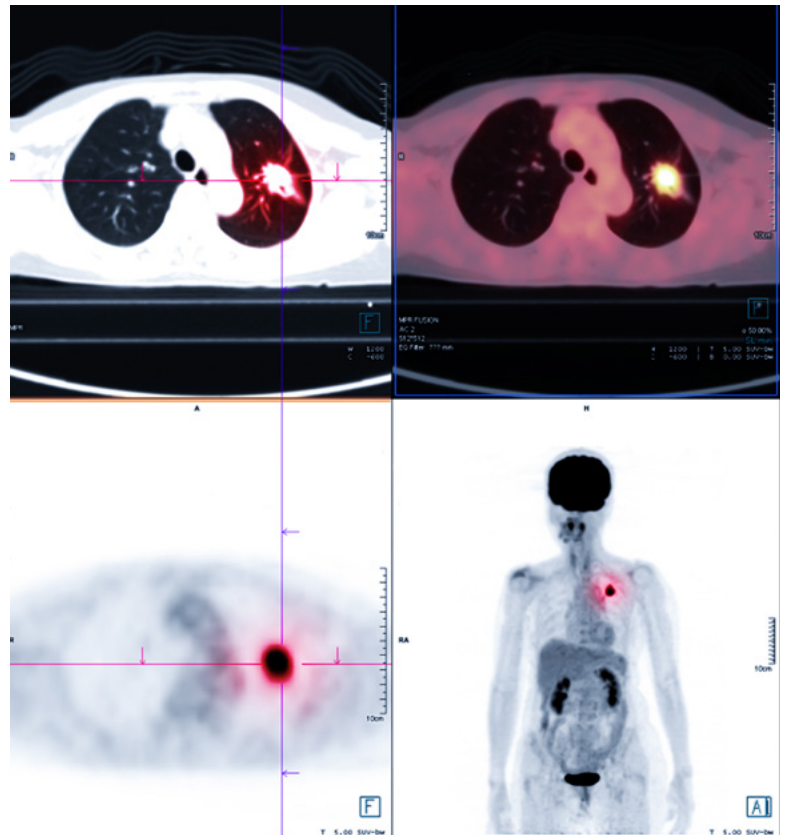
Environmental causes of lung cancer are also modifiable. Occupational regulatory policies should govern safe production, sale, and use of known carcinogens. Research is needed to understand how domestic carcinogens can be kept out of home environments, particularly in regions that depend on biomass fuels for heating and cooking. Further study is required to inform and implement health policies that will effectively prevent exposure to lung carcinogens.

TREATMENT

Care for lung cancer is optimally provided by an expert multidisciplinary team to ensure access to clinically and cost-effective treatment. Diagnostic and staging processes are key to characterize tumor pathomolecular characteristics and extent of disease, all of which determine intent and type of treatment. Computed tomography–positron emission tomography has revolutionized staging but is not universally accessible.

Unfortunately, most new cases are diagnosed at advanced incurable stages, emphasizing the need for early detection by low-dose computed tomography screening [105,106]. However, screening implementation has been relatively slow and is inconsistent around the world. Early-stage lung cancer is potentially curable by surgery or ablative therapy, including stereotactic radiotherapy. Select patients may benefit from chemotherapy after resection. The approach to locally advanced disease includes chemoradiotherapy and adjuvant immunotherapy; occasionally, surgery is an additional option.

Although metastatic lung cancer is incurable, many patients can gain meaningful symptom improvement and survival prolongation with systemic treatments. Chemotherapy remains a useful option for those with good performance status. Targeted therapies, often oral formulations, block key oncogenic pathways activated by driver gene aberrations (eg, EGFR, ALK, ROS1). Targeted angiogenesis inhibitors prevent new blood vessel formation, a hallmark of neoplasia. Immunotherapies, particularly



immune checkpoint inhibitors, enhance intrinsic, immune-mediated killing of cancer cells by abrogating their ability to escape immune surveillance. Use of biomarkers is a developing strategy to identify subpopulations of patients for whom specific therapies may be particularly effective. Palliative care is key to relieve distressing symptoms such as dyspnea or airway obstruction. Early referral can improve both quality of life and survival.

CONTROL AND ELIMINATION

Control of the global lung cancer epidemic will require concerted efforts at achieving primary prevention, promoting early detection through screening, addressing the drivers of disparities that exist in both early detection and treatment, and ensuring access to effective treatment for all, including novel therapies. The most powerful strategy is tobacco control and elimination. Effective public policies to reduce and eliminate the production and promotion of cigarettes, other tobacco products, and alternative nicotine delivery products are needed at local, national, and global levels. These should be informed by research focusing on successful approaches to reducing tobacco use. Examples of policies that have proven effective include banning smoking in public areas, raising taxes on tobacco products, and supporting programs to educate the public, including children, on the health hazards of smoking [118-124]. These policies must be culturally appropriate and relevant and are particularly important in regions of the world where tobacco control has been less successful and smoking rates are persistently high. Reduction of risk related to other factors, including decreasing exposures to domestic and occupational carcinogens, should also be prioritized.

Control of lung cancer beyond primary prevention must build on scientific and technologic advances. More research is needed on early detection and treatment of both early and advanced stage disease. Screening implementation, development of improved molecular diagnostics, and translation of scientific discovery to patient treatment can all improve lung cancer outcomes and should be undertaken with the goal of equitable access to effective and affordable universal health care worldwide.



Other Important Respiratory Conditions and Concerns



In addition to the five respiratory diseases described, other important respiratory conditions also impact global health. Occupational lung disease is a common health hazard that harms thousands of workers worldwide with death, disability, and absenteeism, as well as lost productivity affecting businesses, industries, and economies. Exposure to asbestos can cause lung fibrosis (asbestosis) and mesothelioma (cancer of the pleura surrounding the lungs). Exposure to other mineral dusts is associated with silicosis or coal worker's pneumoconiosis, and exposure to organic antigens triggers hypersensitivity pneumonitis and environmental-related asthma. Inhalation of toxic material inside and outside the workplace can cause acute and large-scale health problems. More recently, research has confirmed that not only lung disease but also multiple organ systems—from the liver and kidney to the neurologic system—are affected by air pollutants inhaled by populations across the globe. Importantly, these diseases may be preventable by ensuring clean air in the workplace and reducing emissions in the ambient atmosphere.

SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (or sleep apnea) is a common condition affecting up to 1 billion people worldwide [21]. Sleep apnea is more common in middle-age to older individuals: one study reported up to 50% of men and 23% of women had clinically important sleep apnea [125]. Sleep apnea causes fragmented sleep and hypoxemia, both of which have long been recognized to cause daytime somnolence and increased road collisions. Sleep apnea has also been associated with many other illnesses such as hypertension, cardiovascular disease, stroke, diabetes, poor cognitive function, and neuropsychiatric disorders, not to mention effects on alertness causing problems with safety sensitive activities. Improvements in technology are facilitating opportunities to address the global burden of disease. For example, wearable technology and mobile phone applications are being developed and may have a role in the diagnosis and management of sleep apnea in the future. Pediatric sleep

disorders are also increasingly recognized as causes of morbidity and mortality. The obesity pandemic has affected adults as well as children. Obstructive sleep apnea syndrome has been described in 5% of children tested but exceeds 10% in some pediatric populations. The best preventive measures for sleep apnea are maintaining a healthy bodyweight and physical exercise. Continuous positive airway pressure is the treatment of choice for sleep apnea. Advances in therapy are ongoing to further improve adherence. Positive pressure therapy with noninvasive ventilation has an important role for patients, with benefit documented in chronic respiratory failure associated with obesity hypoventilation syndrome, neuromuscular/chest wall disorders, and hypercapnic COPD.

PULMONARY HYPERTENSION

Pulmonary hypertension occurs in approximately 1% of the world's population (affecting 50 million to 70 million adults) and up to 10% of those aged older than 65 years. Pulmonary hypertension is often associated with left ventricular failure (WHO group 2) and lung disease (WHO group 3), but schistosomiasis, HIV infection, rheumatic heart disease, and sickle cell disease are other prominent causes [22]. Treatment and prevention of pulmonary hypertension vary depending on the cause and can often be managed by alleviation or optimal management of the underlying conditions.

PULMONARY EMBOLISM

Pulmonary embolism is a common life-threatening disease estimated to occur in 6 to 20 per 10,000 European inhabitants every year [126], but the number is likely much higher because both mild and severe cases frequently go undiagnosed and often are a diagnostic challenge. Some estimates of the worldwide burden of disease due to pulmonary embolism suggest approximately 10 million cases occur every year with substantial associated morbidity and mortality [127]. Mild cases may be self-limited and not reported, and end-of-life cases associated with other severe diseases typically erroneously report the cause of death attributable only to the underlying condition instead of concurrent pulmonary embolism. Pulmonary embolism is associated with age, many different health conditions such as malignancy, genetic predisposition, and surgery, and other causes of physical inactivity. Treatment is generally with anticoagulants and is effective.

INTERSTITIAL LUNG DISEASE

Interstitial lung diseases (ILDs) comprise more than 100 conditions that affect the alveolar structures, pulmonary interstitium, and/or small airways. The most prevalent are idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis, and ILD related to collagen vascular diseases (eg, rheumatoid arthritis, certain drug use, pneumoconiosis); however, only one-third of cases have an identifiable etiology [128]. A Global Burden of Disease Study suggested an 86% increase in ILD-related years of life lost; as a consequence, between 1990 and 2013, it was among the top 50 causes of global years of life lost [129]. In addition, the age-standardized incidence rates of ILD and sarcoidosis have increased from 1990 to 2017 [130].



BRONCHIECTASIS

Bronchiectasis is a pulmonary disorder characterized by permanently and pathologically dilated bronchi and clinically by productive cough, recurrent infection, and obstructive lung disease. Although associated with the genetic disorder of cystic fibrosis, non-cystic fibrosis bronchiectasis can be due to infection, other genetic disorders, and inflammatory, environmental, or allergic causes. The global presence of non-cystic fibrosis bronchiectasis ranges from 67 to 566 per 100,000 inhabitants in Europe and North America and from 1,200 per 100,000 inhabitants in China in those 40 years or older [131]. The disease is associated with significant economic burden.



CLIMATE CHANGE AND TERRORISM

The respiratory system is also at the forefront of two additional global health concerns, namely climate change and terrorism. Climate change affects respiratory diseases by several means. Temperature is closely associated with air pollution, which affects many respiratory conditions. Ozone production increases with higher temperatures, because higher temperature speeds the reactions of volatile organic compounds and nitrogen oxides to produce ozone. Political debate over climate change has obscured to some extent the major cardiopulmonary toxicity of air pollution. However, climate change may affect the incidence and severity of respiratory infections by their affecting vectors and habitats as well as changing the transmission patterns of viruses [132]. Weather events may also alter human-host response and susceptibilities to infectious and noninfectious diseases.

Deliberate use of biologic agents or chemicals to inflict casualties has been globally outlawed since 1925. In 1972, the United Nations Biological and Toxin Weapons Convention prohibited the development, production, accumulation, acquisition, and retention of biological agents or toxins. [133] Unforgivably, they have been used in conflicts since then. The lungs are particularly vulnerable to biologic or chemical terrorism because the causative agents are most often disseminated through the air. Preventing attacks is paramount but defending against such attacks requires further research to understand how to best protect the lungs.



What can be done to combat respiratory disease



Because respiratory illnesses are either caused or worsened by what we breathe, tobacco smoke, air pollution, occupational toxicants, and infectious agents disproportionately impact respiratory diseases. Thus, strategies to reduce these exposures and preserve lung health are cost effective and must be a top priority in a global health agenda [134].

TOBACCO USE

Tobacco use causes 8 million avoidable deaths per year, mostly from cardiovascular or respiratory disease [13]. In the United States, individuals who smoke are 25 times more likely to die of lung cancer and three times as likely to die of any cause than individuals who have never smoked [135,136]. In Europe, total health-care costs from tobacco use are ~€544 billion annually, or ~5% of the EU gross domestic product [137].

Tobacco can also harm individuals who do not smoke. Second-hand smoke is an indoor pollutant that contains at least 250 carcinogenic or toxic chemicals [138]. Second-hand smoke has been estimated to cause 1.2 million deaths per year worldwide [13], including 7,300 lung cancer-related deaths in the United States [138]. Globally, nearly one-half of all children breathe second-hand smoke, and 65,000 children die each year due to illnesses related to second-hand smoke [13]. Because no level of exposure is safe to second-hand smoke, eliminating all smoking from indoor environments is the only effective measure to tackle this public health threat [139]. For example, local and national governments are increasingly implementing smoke-free policies in public places and public housing to protect nonsmokers from exposure to second-hand smoke [140].



Electronic cigarettes (e-cigarettes) are devices that heat a liquid to create an aerosol that is then inhaled by the users. E-cigarette use, also known as vaping, impairs respiratory health [141]. Vaping at a younger age is particularly risky, because addictive nicotine exposure can lead to long-term tobacco use that also has damaging effects on brain development [142] and can cause e-cigarette- or vaping-associated lung injury [143]. The WHO recommends regulation of e-cigarettes to prevent vaping initiation by nonsmokers, particularly minors and vulnerable groups [144]. Moreover, e-cigarettes should not be advertised as a smoking cessation aid in the absence of compelling evidence of their effectiveness [145].

Reducing and eliminating tobacco use is a high-priority and cost-effective public health intervention. The WHO Framework Convention on Tobacco Control, adopted in 2003, is an essential mechanism by which governments can control the tobacco industry using laws, regulations, administrative decisions, and enforcement measures such as bans on tobacco advertising [113]. Other effective strategies include educational campaigns and high tobacco tax policies [146].

AIR POLLUTION

Worldwide, air pollution leads to 7 million deaths per year from such causes as COPD, lung cancer, and respiratory infections [147]. Ninety percent of all people breathe outdoor air that exceeds WHO guideline limits, especially those living in low- and middle-income countries [147]. Pollutants that cause adverse health effects include particulate matter, ozone, nitrogen dioxide, and sulfur dioxide, all of which originate from fuel combustion [148]. No known safe exposure level exists for any of these pollutants. Moreover, indoor air pollution is a leading cause of premature death in the developing world, primarily among women and children [147]. Unfortunately, approximately 50% of all households and nearly 90% of rural households worldwide rely on solid fuels for domestic energy, leading to indoor air pollution [149].

CLIMATE CHANGE

Most outdoor air pollutants are emitted by the same sources that emit greenhouse gases, likely contributing to climate change [150]. Global warming and related climate emissions can affect respiratory health directly (heat waves and extreme weather events such as hurricanes and cyclones) or indirectly (increasing air pollutants, wildfire activity, pollens, and molds, as well as by promoting vectors for transmission of infectious diseases). Between 2030 and 2050, climate change is expected to cause nearly 250,000 additional deaths every year as result of malnutrition, malaria, diarrhea, and heat stress [151]. Policies that reduce air pollution from fossil fuel combustion offer a “win-win” strategy for both climate and health, immediately lowering disease burden from air pollution while also mitigating climate change.



In response to pollution-related health effects, the first WHO Global Conference on Air Pollution and Health set an aspirational goal of reducing the number of deaths from air pollution by two-thirds by 2030 [152]. Reaching this target requires scaling up global efforts for cities to reach the WHO air quality guidelines. Policies are needed to promote sustainable land use, cleaner household energy and transportation, energy-efficient housing, power generation, better municipal waste management,

and access to clean energy technologies in resource-poor settings. Interactions between public and private stakeholders are key to ensure national and local policies that effectively address both air pollution and climate change.

OCCUPATIONAL HAZARDS

Occupational hazards can lead to respiratory diseases under certain working conditions. For example, exposure to asbestos can cause lung fibrosis and mesothelioma; exposure to mineral dust can cause silicosis and coal workers' pneumoconiosis; and exposure to organic antigens in agricultural settings can cause hypersensitivity pneumonitis and occupational asthma [153].

Exposure to occupational hazards is much higher among economically disadvantaged individuals living in low-income countries, thereby leading to a greater burden of occupational diseases that are often unrecognized or inadequately addressed through occupational safety and health programs. If not prevented or diagnosed at early stages, this continued occupational exposure can lead to severe respiratory disease.

Occupational lung diseases can be avoided by setting exposure limits based on scientific evidence and implementing preventive interventions to reduce exposure, particularly to carcinogens and sensitizing agents [154]. Implementing effective workplace preventive measures also requires up-to-date knowledge about occupational respiratory hazards and periodic surveillance of exposed workers (eg, routine chest clinic visits, lung function testing, chest radiographs) to identify any early signs of adverse respiratory effects.

RESPIRATORY INFECTIONS

Respiratory infections are a major public health threat worldwide. Indeed, acute lower respiratory infections such as bacterial pneumonia and influenza are among the top global causes of death and loss of disability-adjusted life years in adults.

Pneumonia is the worldwide leading cause of death in children younger than 4 years [155]. Although prevention and control policies have reduced deaths from childhood pneumonia from 4 million in 1981 to 808,000 in 2017, pneumonia still accounts for one-fifth of childhood deaths in the world. Because such mortality is linked to malnutrition, poverty, and inadequate health care, more than 98% of pneumonia-related deaths in children occur in 68 under-resourced countries [156]. The Global Action Plan for the Prevention and Control of Pneumonia developed by WHO and the United Nations Children's Emergency Fund has proposed feasible low-cost interventions that aim to reduce deaths from childhood pneumonia to fewer than three per 1,000 live births by 2025 [156]. As part of this global plan, prevention strategies include promoting adequate nutrition (eg, breast feeding, good zinc intake), reducing indoor pollution, and increasing immunization rates against *H. influenzae* type b, pneumococcus, measles, and pertussis. Moreover, evidence-based guidelines are available for early detection and appropriate antibiotic treatment of pneumonia [157].

In 2020, the COVID-19 pandemic claimed the lives of more than 2 million people worldwide, and total deaths to date exceed 4.5 million [20]. Many of these deaths could have been prevented through better public health infrastructure and preparedness. Moreover, the ongoing pandemic has exposed lack of vital resources such as personal protective equipment and ventilators around the globe [158]. Alternatively, the COVID-19 pandemic has also shown the key role of science-based approaches to global health threats, and scientists have developed multiple vaccines shown to be safe and protective against COVID-19. However, inequitable distribution of available vaccines threatens global control of COVID-19 [159]. To address this, a global alliance (COVAX) is working to ensure access to SARS-CoV-2 vaccines for all countries, regardless of their wealth [160].



TB is one of the top 10 causes of death worldwide, killing 1.4 million people in 2019. In 2014, the World Health Assembly approved the post-2015 Global TB Strategy, which provides a global framework for TB control and elimination with a focus on the most vulnerable populations [161]. This strategy, known as End TB, aims to reduce TB-related deaths by 95% and the incidence rate of new cases by 90% between 2015 and 2035. The three main pillars of End TB are (1) integrated, patient-centered TB care and prevention, (2) bold policies and supportive systems, and (3) intensified research and innovation. Achieving its 2035 targets will require more coordinated global efforts to address social determinants of TB and provide better diagnostics focusing on early detection, easier and shorter treatment regimens, and effective pre- and post-exposure vaccines.

Controlling common respiratory diseases requires availability and optimal use of public health tools and vigorous advocacy for sound health policies to reduce or eliminate key risk factors such as tobacco use, air pollution, occupational hazards, and respiratory infections [1]. To be most effective, such efforts must be accompanied by continued innovation and discovery and access to quality health care. Indeed, basic, clinical, and population-based research are critical to improve the prevention, diagnosis, and management of respiratory diseases. Moreover, patients with respiratory diseases need, and deserve, proper and compassionate care.



Those who are economically disadvantaged and those from other vulnerable populations (eg, racial/ethnic minorities, migrants, refugees) share a disproportionate burden of respiratory disease, because these populations are often exposed to major risk factors and lack adequate health care [162,163]. Such health disparities are not only unethical but also pose tremendous costs to health-care systems around the world. Thus, global prevention and treatment of respiratory disease moves us closer to the laudable, cost effective, and shared goal of health equity.

We must be encouraged by our progress in reducing the worldwide impact of respiratory diseases over the last few decades. Indeed, investments in research and public health have paid substantial dividends, as evidenced by decreasing rates of pneumonia and TB, as well as reduced tobacco use in certain nations. However, the dire toll of the COVID-19 pandemic is awakening us to the need to strengthen and expand global public health, research, and health-care systems. Moving forward, we must build the capacity, infrastructure, and resources needed to confront, and hopefully prevent, the next worldwide emergency, be it a pandemic or a climactic catastrophe, while also addressing the existing and terrible burden of respiratory diseases.



SUMMARY

Lung health is vital for life, whereas respiratory diseases are a clear threat to life, health, and productive human activity. Prevention, control, and cure of these diseases and promotion of respiratory health must be a top priority in global decision-making in the health sector. The control, prevention, and cure of respiratory diseases are among the most cost effective health interventions available—a “best-buy” in the view of the WHO [164]. Genuine investment in respiratory health will pay exponential dividends in longevity, healthy living days, and national economies.

Public awareness and control of the environment are important steps to preventing respiratory diseases. The key controllable factors are reduction in tobacco smoking and improvement in air quality, which includes reduction in second-hand tobacco smoke, indoor air pollution, and unhealthy public and workplace air. Strengthening childhood immunization programs and providing greater availability of the pneumococcal conjugate vaccine and SARS-CoV-2 vaccines must be a priority in low-income countries. Prevention and timely treatment of HIV infection can have major impact in reducing the burden of respiratory illness. Effective training of health-care professionals and ensuring the availability of medications and appropriate diagnostic tools are keys to better lung and respiratory health. A vital need exists for better access to basic and effective affordable medicines, including oxygen and WHO-essential inhaled medicines, for people in living in low- and middle-income countries with respiratory diseases.

FIRS calls on all governments, communities, health-care professionals, and individuals to promote the achievable and effective preventive measures that have reduced tobacco consumption in many countries.

The health benefits of clean air policies are far reaching. It is well known that improvement in air quality has reduced deaths and hospitalizations for cardiovascular and pulmonary diseases. Legislation and political action on clean air make a difference. The respiratory societies of the world believe that everyone has the right to breathe clean air [165], and we ask lawmakers to enact and enforce clean air standards in all countries.

Finally, research in respiratory diseases is the hope for today and the promise for tomorrow. The advances we enjoy today are the direct result from research undertaken in the past. Research must still answer many questions, to name a few: how lung diseases arise, how do they spread, who is most vulnerable, and what are the best actions that can be used to control or cure them. Research must also help us understand and adopt what keeps people healthy. Measures developed from the research must be cost effective and widely applicable. Increased funding to support respiratory research is needed to ensure our children’s lung health is preserved in the future.



RECOMMENDATIONS

FIRS calls for these essential actions to reduce the burden of respiratory disease and improve global health:

- 1** Improve awareness among the public as well as policy makers that respiratory health is vital to global health and that childhood respiratory disease has long-term negative consequences on adult health.
- 2** Reduce, and then eliminate, use of all tobacco and smoking products.
- 3** Adopt and adhere to WHO standards, at a minimum, to reduce ambient, indoor, and occupational air pollution for all countries.
- 4** Implement universal access to quality health care, including the availability of affordable, quality-assured, essential medicines and universal coverage for all effective childhood and adult immunizations.
- 5** Improve the prevention and early diagnosis of respiratory diseases.
- 6** Increase education and training of health-care professionals in respiratory disease worldwide.
- 7** Standardize the monitoring and reporting of the prevalence, severity, and management of respiratory diseases to enable development of better-informed national strategies through programs of the WHO and governmental and nongovernmental organizations.
- 8** Boost funding for respiratory research to develop programs, tools, and strategies to better prevent and treat respiratory diseases

Significant progress on these essential actions will help to eliminate respiratory diseases from the top 10 leading causes of death in the world.





REFERENCES

1. Meghji J, Mortimer K, Agusti A, et al. Improving lung health in low- and middle-income countries: from challenges to solutions. *Lancet*. 2021;397(10277):928-940.
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med*. 2020;8(6):585-596.
3. Li X, Cao X, Guo M, Xie M, Liu X. Trends and risk factors of mortality and disability adjusted life years for chronic respiratory diseases from 1990 to 2017: systematic analysis for the Global Burden of Disease Study 2017. *BMJ*. 2020;368:m234. Published correction appears in *BMJ*. 2020;370:m3150
4. Global Asthma Network. Global Asthma Report 2018. 2018. Accessed June 24, 2021. <http://globalasthmareport.org/burden/burden.php>
5. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128. Published correction appears in *Lancet*. 2013;381(9867):628.
6. Wardlaw TM, Johansson EW, Hodge M; World Health Organization; United Nations Children's Fund. Pneumonia: The Forgotten Killer of Children. 2006. Accessed April 16, 2021. http://www.who.int/maternal_child_adolescent/documents/9280640489/en/
7. World Health Organization Global Tuberculosis Program. Global Tuberculosis Report 2020. World Health Organization; 2020.
8. Johns Hopkins Coronavirus Resource Center. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Accessed April 16, 2021. <https://coronavirus.jhu.edu/map.html>
9. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
10. World Health Organization. The top 10 causes of death. December 2020. Accessed April 16, 2021. <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>
11. World Health Organization. Indoor air pollution and household energy. 2021. Accessed April 16, 2021. <https://www.who.int/heli/risks/indoorair/indoorair/en/>
12. World Health Organization. Air pollution. 2021. Accessed April 16, 2021. <https://www.who.int/health-topics/air-pollution>
13. World Health Organization. Tobacco. May 2020. Accessed April 16, 2021. <https://www.who.int/news-room/fact-sheets/detail/tobacco#:~:text=The%20tobacco%20epidemic%20is%20one,exposed%20to%20second%2Dhand%20smoke>
14. United Nations Department of Economic and Social Affairs. Transforming Our World: The 2030 Agenda for Sustainable Development. Publication A/RES/70/1. United Nations; 2015.
15. Bennett JE, Kontis V, Mathers CD; NCD Countdown 2030 collaborators. NCD Countdown 2030: pathways to achieving Sustainable Development Goal target 3.4. *Lancet*. 2020;396(10255):918-934. Published correction appears in *Lancet* 2020;396(10264):1736.
16. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023-1075.
17. Vos T, Lim SS, Abbafati C, et al; GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):P1204-1222.



18. Wang H, Naghavi M, Allen C, et al; GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544.
19. World Health Organization. Influenza (seasonal). November 2018. Accessed April 16, 2021. [https://www.who.int/en/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal))
20. World Health Organization. WHO coronavirus (COVID-19) dashboard. Accessed April 17, 2021. <https://covid19.who.int/>
21. Benjafield AV, Ayas NT, Eastwood PE, et al. Estimation of global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):P687-698.
22. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Respir Med*. 2016;44(4):306-322.
23. United Nations. Sustainable development goals: 17 goals to transform our world. Accessed June 3, 2021. <https://www.un.org/en/exhibits/page/sdgs-17-goals-transform-world>
24. Forum of International Respiratory Societies. Respiratory diseases in the world. Realities of today—opportunities for tomorrow. European Respiratory Society, 2013. Accessed April 20, 2021. <https://firsnet.org/images/firs/FIRS-report-for-web.pdf>
25. Forum of International Respiratory Societies. The Global Impact of Respiratory Disease. Second Edition. European Respiratory Society, 2017. Accessed June 3, 2021. https://www.firsnet.org/images/publications/The_Global_Impact_of_Respiratory_Disease.pdf
26. Casas Herrera A, Montes de Oca M, Lopez Varela MV, et al. COPD underdiagnosis and misdiagnosis in a high-risk primary care population in four Latin American countries. A key to enhance disease diagnosis: the PUMA study. *PLoS One*. 2016;11(4):e0152266.
27. Talamo C, de Oca MM, Halbert R, et al. Diagnostic labeling of COPD in five Latin American cities. *Chest*. 2007;131(1):60-67.
28. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010;182(5):693-718.
29. Burney P, Patel J, Minelli C, et al. Prevalence and population attributable risk for chronic airflow obstruction in a large multinational study. *Am J Respir Crit Care Med*. Published online November 10, 2020. doi:10.1164/rccm.202005-1990OC
30. Montes de Oca M, Lopez Varela MV, Acuna A, et al. ALAT-2014 chronic obstructive pulmonary disease (COPD) clinical practice guidelines: questions and answers. *Arch Bronconeumol*. 2015;51(8):403-416.
31. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147(4):894-942.
32. Global Initiative for Chronic Obstructive Lung Disease. 2021 Global Strategy for Prevention, Diagnosis and Management of COPD. 2021 Report. Accessed June 1, 2021. <https://goldcopd.org/2021-gold-reports/>
33. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64.
34. Tabyshova A, Hurst JR, Soriano JB, et al. Gaps in COPD guidelines of low- and middle-income countries. A systematic scoping review. *Chest*. 2021;159(2):575-584.
35. Rochester CL, Vogiatzis I, Holland AE, et al. An official American Thoracic Society/European Respiratory Society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2015;192(11):1373-1386.
36. Nici L, Mammen MJ, Charbek E. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;201(9):e56-e69.
37. Ozoh OB, Awokola T, Buist SA. A survey of the knowledge of general practitioners, family physicians and pulmonologists in Nigeria regarding the diagnosis and treatment of chronic obstructive pulmonary disease. *West Afr J Med*. 2014;33(2):100-106.

38. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis.* 2014;18(11):1269-1278.
39. Kassebaum NJ, Arora M, Barber RM, et al; GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1603-1658.
40. Wallace JC, Denk CE, Kruse LK. Pediatric hospitalizations for asthma: use of a linked file to separate person-level risk and readmission. *Prev Chronic Dis.* 2004;1(2):A07.
41. Gushue C, Miller R, Sheikh S, et al. Gaps in health insurance coverage and emergency department use among children with asthma. *J Asthma.* 2019;56(10):1070-1078.
42. Sly P. Predicting which children have asthma: are we any closer to finding the Holy Grail? *Respirology.* 2019;24(6):510-511.
43. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med.* 2016;374(19):1842-1852.
44. Garcia-Larsen V, Del Giacco SR, Moreira A, et al. Asthma and dietary intake: an overview of systematic reviews. *Allergy.* 2016;71(4):433-442.
45. Wolsk HM, Chawes BL, Litonjua AA, et al. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: a combined analysis of two randomized controlled trials. *PLoS One.* 2017;12(10):e0186657.
46. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med.* 2006;354(19):1985-1997.
47. Sauni R, Uitti J, Jauhianen M, Kreiss K, Sigsgaard T, Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma (review). *Evid Based Child Health.* 2013;8(3):944-1000.
48. O'Byrne PM, Pedersen S, Lamm CJ, et al. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med.* 2009;179(1):19-24.
49. Gaillard EA, Kuehni CE, Turner S, et al. European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years. *Eur Respir J.* 2021;19:2004173.
50. Aaron SD, Boulet LP, Reddel HK, et al. Underdiagnosis and overdiagnosis of asthma. *Am J Respir Crit Care Med.* 2018;198(8):1012-1020.
51. Hatter L, Bruce P, Braithwaite I, et al. ICS-formoterol reliever versus ICS and short-acting β_2 -agonist reliever in asthma: a systematic review and meta-analysis. *ERJ Open Res.* 2021;7(1):00701-2020.
52. Beran D, Zar HJ, Perrin C, et al; Forum of International Respiratory Societies working group. Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries. *Lancet Respir Med.* 2015;3(2):159-170.
53. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* 2007;62(9):758-766.
54. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Accessed June 1, 2021. www.ginasthma.org/reports
55. Cilloniz C, Martin-Loeches I, Garcia-Vidal C, San Jose A, Torres A. Microbial etiology of pneumonia: epidemiology, diagnosis and resistance patterns. *Int J Mol Sci.* 2016;17(12):2120.
56. Troeger C, Blacker B, Khalil IA, et al; GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis.* 2018;18(11):1191-1210.
57. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet.* 2010;375(9725):1545-1555.
58. Case Management Society of America. Standards of Practice for Case Management. Case Management Society of America; 2010.



59. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67.
60. World Health Organization. Coronavirus disease (COVID-19) technical guidance: patient management. Accessed June 16, 2021. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management>
61. Our World in Data. Coronavirus (COVID-19) vaccinations. Accessed August 2, 2021. <https://ourworldindata.org/covid-vaccinations>
62. Allwood BW, van der Zalm MM, Amaral AFS, et al. Post-tuberculosis lung health: perspectives from the First International Symposium. *Int J Tuberc Lung Dis*. 2020;24(8):820-828.
63. Fox GJ, Johnston JC, Nguyen TA, et al. Active case-finding in contacts of people with TB. *Int J Tuberc Lung Dis*. 2021;25(2):95-105.
64. Sohn H, Sweeney S, Mudzengi D, et al. Determining the value of TB active case-finding: current evidence and methodological considerations. *Int J Tuberc Lung Dis*. 2021;25(3):171-181.
65. Alsdurf H, Empringham B, Zwerling A. Economic evaluations of active case finding for tuberculosis among high-risk groups: a systematic review. Presented at: 2021 Annual Meeting of the Union–North America Region, February 26, 2021 (virtual).
66. Empringham B, Alsdurf H, Zwerling A. Economic evaluations of active case finding for tuberculosis: children, contacts and general population screening; a systematic review. Presented at: 2021 Annual Meeting of the Union–North America Region, February 26, 2021 (virtual).
67. Abu-Raddad LJ, Sabatelli L, Achterberg JT, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proc Natl Acad Sci U S A*. 2009;106(33):13980-13985.
68. Harris RC, Sumner T, Knight GM, Zhang H, White RG. Potential impact of tuberculosis vaccines in China, South Africa, and India. *Sci Transl Med*. 2020;12(564):eaax4607.
69. Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01(E) vaccine to prevent tuberculosis. *N Engl J Med*. 2019;381(25):2429-2439.
70. White RG, Hanekom WA, Vekemans J, Harris RC. The way forward for tuberculosis vaccines. *Lancet Respir Med*. 2019;7(3):204-206.
71. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018;18(1):76-84.
72. Broger T, Nicol MP, Sigal BG, et al. Diagnostic accuracy of 3 urine lipoarabinomannan tuberculosis assays in HIV-negative outpatients. *J Clin Invest*. 2020;130(11):5756-5764.
73. Allix-Béguec C, Arandjelovic I, Bi L, et al; The CRYPTIC Consortium and the 100,000 Genomes Project. Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing. *N Engl J Med*. 2018;379(15):1403-1415.
74. Hunt M, Bradley P, Grandjean Lapierre S, et al. Antibiotic resistance prediction for *Mycobacterium tuberculosis* from genome sequence data with Mykrobe. *Wellcome Open Res*. 2019;4:191.
75. World Health Organization. Consensus Meeting Report: Development of a Target Product Profile (TPP) and a Framework for Evaluation for a Test for Predicting Progression From Tuberculosis Infection to Active Disease. WHO/HTM/TB/2017.18. World Health Organization; 2017.
76. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med*. 2021;384(18):1705-1718.
77. Global Tuberculosis Program, World Health Organization. WHO Operational Handbook on Tuberculosis. Module 4: Treatment. Drug-Resistant Tuberculosis Treatment. World Health Organization; 2020.
78. World Health Organization. The End TB Strategy. 2015. Accessed June 4, 2021. <https://www.who.int/tb/strategy/en/>
79. Migliori GB, Thong PM, Akkerman O, et al. Worldwide effects of coronavirus disease pandemic on tuberculosis services, January–April 2020. *Emerg Infect Dis*. 2020;26(11):2709-2712.

80. Rafiemanesh H, Mehtarpour M, Khani F, et al. Epidemiology, incidence and mortality of lung cancer and their relationship with the development index in the world. *J Thorac Dis.* 2016;8(6):1094-1102.
81. World Health Organization. WHO Global Report on Trends in Prevalence of Tobacco Use 2000-2025, Third Edition. World Health Organization; 2019.
82. Fingerhut M, Nelson DI, Driscoll T, et al. The contribution of occupational risks to the global burden of disease: summary and next steps. *Med Lav.* 2006;97(2):313-321.
83. Nielsen LS, Baelum J, Rasmussen J, et al. Occupational asbestos exposure and lung cancer—a systematic review of the literature. *Arch Environ Occup Health.* 2014;69(4):191-206.
84. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 suppl):e1S-e29S.
85. Loomis D, Guha N, Hall AL, Straif K. Identifying occupational carcinogens: an update from the IARC Monographs. *Occup Environ Med.* 2018;75(8):593-603.
86. Krewski D, Lubin JH, Zielinski JM, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology.* 2005;16(2):137-145.
87. Hosgood HD 3rd, Boffetta P, Greenland S, et al. In-home coal and wood use and lung cancer risk: a pooled analysis of the International Lung Cancer Consortium. *Environ Health Perspect.* 2010;118(12):1743-1747.
88. National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation. BEIR VII Phase 2. The National Academies Press; 2006
89. Pershagen G. Air pollution and cancer. *IARC Sci Publ.* 1990;(104):240-251.
90. Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med.* 1993;329(24):1753-1759.
91. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet.* 2017;389(10082):1907-1918.
92. Spitz MR, Wei Q, Dong Q, Amos CI, Wu X. Genetic susceptibility to lung cancer: the role of DNA damage and repair. *Cancer Epidemiol Biomarkers Prev.* 2003;12(8):689-698.
93. McKay JD, Hung RJ, Han Y, et al. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nat Genet.* 2017;49(7):1126-1132.
94. Lissowska J, Foretova L, Dabek J, et al. Family history and lung cancer risk: international multicentre case-control study in Eastern and Central Europe and meta-analyses. *Cancer Causes Control.* 2010;21(7):1091-1104.
95. Islami F, Miller KD, Siegel RL, et al. National and state estimates of lost earnings from cancer deaths in the United States. *JAMA Oncol.* 2019;5(9):e191460.
96. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol.* 2013;14(12):1165-1174.
97. American Cancer Society. The American Cancer Society and LIVESTRONG Launch First Global Economic Cost of Cancer Report [press release]. American Cancer Society; 2010.
98. John R, Ross H. The Global Economic Cost of Cancer. American Cancer Society and LIVESTRONG; 2010.
99. North CM, Christiani DC. Women and lung cancer: what is new? *Semin Thorac Cardiovasc Surg.* 2013;25(2):87-94.
100. Jeon J, Holford TR, Levy DT, et al. Smoking and lung cancer mortality in the United States from 2015 to 2065: a comparative modeling approach. *Ann Intern Med.* 2018;169(10):684-693.
101. Goizueta A, Estrada-Y-Martin R, Cherian S. Lung cancer in women: a review. *Curr Pulmonol Rep.* Published online March 22, 2021. doi:10.1007/s13665-021-00270-6
102. Fu JB, Kau TY, Severson RK, Kalemkerian GP. Lung cancer in women: analysis of the national Surveillance, Epidemiology, and End Results database. *Chest.* 2005;127(3):768-777.



103. Sagerup CM, Smastuen M, Johannesen TB, Helland A, Brustugun OT. Sex-specific trends in lung cancer incidence and survival: a population study of 40,118 cases. *Thorax*. 2011;66(4):301-307.
104. Kinoshita FL, Ito Y, Morishima T, Miyashiro I, Nakayama T. Sex differences in lung cancer survival: long-term trends using population-based cancer registry data in Osaka, Japan. *Jpn J Clin Oncol*. 2017;47(9):863-869.
105. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.
106. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382(6):503-513.
107. World Health Organization. The Global Health Observatory. Global Health Estimates: Life expectancy and leading causes of death and disability. Accessed January 8, 2021. <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates>
108. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers – a different disease. *Nat Rev Cancer*. 2007;7(10):778-790.
109. Yang P-C. National Lung Cancer Screening Program in Taiwan: the TALENT study. Plenary Presentation at: International Association for the Study of Lung Cancer World Conference on Lung Cancer 2020; January 28-31, 2021; Singapore.
110. Planchard D, Besse B. Lung cancer in never-smokers. *Eur Respir J*. 2015;45(5):1214-1217.
111. Chen YJ, Roumeliotis TI, Chang YH, et al. Proteogenomics of non-smoking lung cancer in East Asia delineates molecular signatures of pathogenesis and progression. *Cell*. 2020;182(1):226-244.e217.
112. Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century. *Tob Control*. 2012;21(2):96-101.
113. World Health Organization. WHO Framework Convention on Tobacco Control. World Health Organization; 2003.
114. Flor LS, Reitsma MB, Gupta V, Ng M, Gakidou E. The effects of tobacco control policies on global smoking prevalence. *Nat Med*. 2021;27(2):239-243.
115. Dubray J, Schwartz R, Chaiton M, O'Connor S, Cohen JE. The effect of MPOWER on smoking prevalence. *Tob Control*. 2015;24(6):540-542.
116. Anderson CL, Becher H, Winkler V. Tobacco control progress in low and middle income countries in comparison to high income countries. *Int J Environ Res Public Health*. 2016;13(10):1039.
117. Gravely S, Giovino GA, Craig L, et al. Implementation of key demand-reduction measures of the WHO Framework Convention on Tobacco Control and change in smoking prevalence in 126 countries: an association study. *Lancet Public Health*. 2017;2(4):e166-e174.
118. Chaloupka FJ, Straif K, Leon ME; Working Group, International Agency for Research on Cancer. Effectiveness of tax and price policies in tobacco control. *Tob Control*. 2011;20(3):235-238.
119. Kalousova L, Levy D, Titus AR, et al. Cigarette taxes, prices, and disparities in current smoking in the United States. *SSM Popul Health*. 2020;12:100686.
120. Hoffman SJ, Tan C. Overview of systematic reviews on the health-related effects of government tobacco control policies. *BMC Public Health*. 2015;15:744.
121. Saffer H, Chaloupka F. The effect of tobacco advertising bans on tobacco consumption. *J Health Econ*. 2000;19(6):1117-1137.
122. Noar SM, Francis DB, Bridges C, Sontag JM, Ribisl KM, Brewer NT. The impact of strengthening cigarette pack warnings: systematic review of longitudinal observational studies. *Soc Sci Med*. 2016;164:118-129.
123. Frazer K, McHugh J, Callinan JE, Kelleher C. Impact of institutional smoking bans on reducing harms and secondhand smoke exposure. *Cochrane Database Syst Rev*. 2016(5):CD011856.
124. Vuolo M, Kelly BC, Kadowaki J. Independent and interactive effects of smoking bans and tobacco taxes on a cohort of US young adults. *Am J Public Health*. 2016;106(2):374-380.
125. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep disordered breathing in the general population: the HypnoLaus Study. *Lancet Respir Med*. 2015, 3:310-318.

126. European Respiratory Society. European Lung White Book. European Respiratory Society; 2013. Accessed June 22, 2021. <http://www.erswhitebook.org/>
127. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Semin Thromb Hemost*. 2014;40(07):724-735.
128. Rivera-Ortega P, Molina-Molina M. Interstitial lung diseases in developing countries. *Ann Glob Health*. 2019;85(1):4.
129. Naghavi M, Wang H, Lozano R, et al; GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385(9963):117-171.
130. Xie M, Liu X, Cao X, Guo M, Li X. Trends in prevalence and incidence of chronic respiratory diseases from 1990 to 2017. *Respir Res*. 2020;21(1):49.
131. Guan W-J, Han X-R, de la Rosa D, Martinez-Garcia MA. The significant global economic burden of bronchiectasis: a pending matter. *Eur Respir J*. 2019;53(2):1802392.
132. Mirsaeidi M, Motahari H, Taghizadeh Khamesi M, Sharifi A, Campos M, Schraufnagel DE. Climate change and respiratory infections. *Ann Am Thorac Soc*. 2016;13:1223-1230.
133. International Committee of the Red Cross. 1972 Convention on the Prohibition of Biological Weapons. May 21, 2021. Accessed August 2, 2021. <https://www.icrc.org/en/document/1972-convention-prohibition-bacteriological-weapons-and-their-destruction-factsheet>
134. World Health Organization, World Economic Forum. From Burden to “Best Buys”: Reducing the Economic Impact of Non-Communicable Disease in Low- and Middle-Income Countries. World Health Organization, 2011. Accessed July 23, 2021. https://www.who.int/nmh/publications/best_buys_summary.pdf134.
135. Thun MJ, Carter BD, Feskanich D, et al. 50-Year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013;368(4):351-364.
136. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-Century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013;368(4):341-350.
137. Jarvis A, Péter Vincze M, Falconer B, et al; GHK. A study on liability and the health costs of smoking. 2012. Accessed April 16, 2021. https://ec.europa.eu/health/sites/health/files/tobacco/docs/tobacco_liability_final_en.pdf
138. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Centers for Disease Control and Prevention; 2014. Accessed April 16, 2021. <https://www.hhs.gov/sites/default/files/consequences-smoking-exec-summary.pdf>
139. Barnoya J, Navas-Acien A. Protecting the world from secondhand tobacco smoke exposure: where do we stand and where do we go from here? *Nicotine Tob Res*. 2013;15(4):789-804.
140. US Department of Housing and Urban Development. Implementing HUD’s Smoke-free Policy in Public Housing. 2017. Accessed April 16, 2021. <https://www.hud.gov/smokefreepublichousing>
141. Gotts JE, Jordt SE, McConnell R, et al. What are the respiratory effects of e-cigarettes? *BMJ*. 2019;366:l5275
142. Yuan M, Cross SJ, Loughlin SE, et al. Nicotine and the adolescent brain. *J Physiol*. 2015;593(16):3397-3412.
143. Centers for Disease Control and Prevention. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. 2020. Accessed April 16, 2021. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
144. Pisinger C. A Systematic Review of Health Effects of Electronic Cigarettes. World Health Organization. 2015. Accessed April 16, 2021. https://www.who.int/tobacco/industry/product_regulation/BackgroundPapersENDS3_4November-.pdf
145. Perez MF, Crotty Alexander LE. Why is vaping going up in flames? *Ann Am Thorac Soc*. 2020;17(5):545-549.
146. World Health Organization. WHO Technical Manual on Tobacco Tax Administration. 2010. Accessed April 16, 2021. https://www.who.int/tobacco/publications/tax_administration/en/



147. World Health Organization. Air pollution. 2021. Accessed April 16, 2021. <https://www.who.int/health-topics/air-pollution>
148. World Health Organization. Ambient Air Pollution: A Global Assessment of Exposure and Burden of Disease. 2016. Accessed April 16, 2021. <https://www.who.int/phe/publications/air-pollution-global-assessment/en/>
149. Rehfuess E. Fuel for life. Household Energy and Health. World Health Organization, 2006. Accessed April 16, 2021. <https://www.who.int/airpollution/publications/fuelforlife.pdf>
150. Environmental Protection Agency. Sources of greenhouse gas emissions. 2020. Accessed April 16, 2021. <https://www.epa.gov/ghgemissions/sources-greenhouse-gas-emissions>
151. World Health Organization. Climate change. 2021. Accessed April 16, 2021. <https://www.who.int/health-topics/climate-change>
152. First WHO Global Conference on Air Pollution and Health, 30 October – 1 November 2018. Accessed April 16, 2021. <https://www.who.int/airpollution/events/conference/en/>
153. Suganuma N, Natori Y, Kurosawa H, et al. Update of occupational lung disease. *J Occup Health*. 2019;61(1):10-18.
154. De Matteis S, Heederik D, Burdorf A, et al. European Respiratory Society Environment and Health Committee. Current and new challenges in occupational lung diseases. *Eur Respir Rev*. 2017;26(146):170080.
155. UNICEF, World Health Organization, World Bank Group, United Nations. Levels and Trends in Child Mortality 2020. Accessed April 17, 2021. <https://www.who.int/publications/i/item/levels-and-trends-in-child-mortality-report-2020>
156. World Health Organization, UNICEF. Global Action Plan for Prevention and Control of Pneumonia (GAPP). 2020. Accessed April 17, 2021. https://www.who.int/maternal_child_adolescent/documents/fch_cah_nch_09_04/en/
157. World Health Organization. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities. 2014. Accessed April 17, 2021. https://www.who.int/maternal_child_adolescent/documents/child-pneumonia-treatment/en/
158. Ranney ML, Griffeth V, Jha AK. Critical supply shortages – the need for ventilators and personal protective equipment during the Covid-19 pandemic. *N Engl J Med*. 2020;382(18):e41.
159. Wouters OJ, Shadlen KC, Salcher-Konrad M, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *Lancet*. 2021;397(10278):1023-1034.
160. World Health Organization. COVAX: The Vaccines Pillar of the Access to COVID-19 tools (ACT) Accelerator. Structure and Principles. 2020. Accessed April 17, 2021. <https://www.who.int/publications/m/item/covax-the-vaccines-pillar-of-the-access-to-covid-19-tools-act-accelerator>
161. World Health Organization. WHO End TB Strategy. Global Strategy and Targets for Tuberculosis Prevention, Care and Control After 2015. 2015. Accessed June 21, 2021. https://www.who.int/tb/strategy/End_TB_Strategy.pdf
162. Thakur N, Lovinsky-Desir S, Bime C, et al. The structural and social determinants of the racial/ethnic disparities in the U.S. COVID-19 pandemic. What's our role? *Am J Respir Crit Care Med*. 2020;202(7):943-949.
163. Roman J, Viegi G, Schenker M, et al. Research needs on respiratory health in migrant and refugee populations. An official American Thoracic Society and European Respiratory Society Workshop Report. *Ann Am Thorac Soc*. 2018;15(11):1247-1255.
164. World Health Organization. 'Best Buys' and Other Recommended Interventions for the Prevention and Control of Noncommunicable Diseases. Updated (2017) Appendix 3 of the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020. Accessed April 17, 2021. https://www.who.int/ncds/management/WHO_Appendix_BestBuys_LS.pdf
165. Brunekreef B, Annesi-Maesano I, Ayres JG, et al. Ten principles for clean air. *Eur Respir J*. 2012;39(3):525-528.



ABOUT FIRS

ABOUT THE FORUM OF INTERNATIONAL RESPIRATORY SOCIETIES (FIRS)

Formed in 2001, the Forum of International Respiratory Societies (FIRS) is composed of the leading international respiratory societies.

In total, FIRS's organizations have more than 100,000 professional members working in the broad field of respiratory health. These specialists advise and set standards for other specialists and primary care health providers who manage patients with respiratory illnesses around the world, thus magnifying the effects of the societies.

The journals of these societies publish most respiratory scientific breakthroughs in the world. Their annual meetings provide a forum for nearly all-important research in the field. Their educational venues teach or train most respiratory specialists in the world.

The members of these societies are distributed across the globe and interact and impact on the lives of many, or most, people with serious respiratory disease.

The goal of FIRS is to promote respiratory health worldwide. FIRS speaks with one voice to communicate the importance of respiratory health for global health and prosperity. FIRS, its societies, their members and the patients they serve, with millions of voices harmonized, call for action to reduce, prevent, cure, and control the terrible burden of respiratory disease.

Website: www.firsnet.org

Contact: Alexandra.alexandropoulou@firsnet.org



FIRS MEMBER SOCIETIES

AMERICAN COLLEGE OF CHEST PHYSICIANS (CHEST)



Founded in 1935, CHEST is the global leader in the prevention, diagnosis, and treatment of chest diseases. Its mission is to champion advanced clinical practice, education, communication, and research in chest medicine. It serves as an essential connection to clinical knowledge and resources for its 19,000+ multidisciplinary members from over 100 countries who provide patient care in pulmonary, critical care, and sleep medicine. CHEST's premier publication, the journal CHEST®, features outstanding peer-reviewed, cutting-edge original research in multidisciplinary chest medicine specialties through print and online editions. CHEST Podcasts address controversial issues, fostering discussion among physicians. CHEST also publishes CHEST Physician® (a monthly newspaper), CHEST NewsBrief® (a weekly e-newsletter) and CHEST Today® (a daily publication), which offer varied resources for continuing education and practice management. Clinicians also know CHEST for its clinical guidelines in antithrombotic therapy, cough, lung cancer, and more. In addition to its annual meetings, CHEST provides preparation for certification or accreditation and live and e-learning education in pulmonary, critical care, sleep, and pediatric pulmonary medicine, all designed to enable clinicians to provide the best care for their patients. The CHEST Foundation, the charitable foundation of the American College of Chest Physicians founded in 1996, champions lung health by providing support for clinical research, community service, and patient education. By forming strategic relationships with public and private sector organizations around the world, the CHEST Foundation makes an impact on world health, one community at a time.

Website: www.chestnet.org

Headquarters:
2595 Patriot Boulevard
Glenview, Illinois 60026, USA

Contact: helpteam@chestnet.org

Number of members: >19,000

Publications: CHEST®, CHEST Physician®, CHEST SEEK™

AMERICAN THORACIC SOCIETY (ATS)



Created in 1905, the American Thoracic Society (ATS) is the oldest respiratory society in the world. Its founding philosophy "that disease and suffering can be eliminated faster when discoveries and knowledge are shared" encompass all aspects of pulmonary, critical care, and sleep medicine. Over time, the Society's membership has become increasingly diverse, and nearly one-third of the Society's members are non-US based. The mission is to improve health worldwide by advancing research, clinical care and public health in respiratory diseases.

ATS publishes four premier journals that meet the needs of basic, translational, and clinical scientists as well as medical educators, produces clinical care guidelines, advocates for clean air and tobacco control, works to defeat tuberculosis in developing countries, and trains physicians in low- and middle-income countries to become researchers through its Methods in Epidemiologic, Operations and Clinical Research program. Each year, through its International Conference the Society also convenes the world's leading experts in pulmonary, critical care and sleep medicine to present and discuss the latest research and advances in patient care in these fields.

Website: www.thoracic.org

Headquarters:
25 Broadway, 4th Floor
New York City, New York 10004
USA

Contact: atsinfo@thoracic.org

Number of Members: 16,000

Publications: American Journal of Respiratory and Critical Care Medicine, American Journal of Respiratory Cell and Molecular Biology, Annals of the American Thoracic Society, ATS Scholar

ASIAN PACIFIC SOCIETY OF RESPIROLOGY (APSR)



The Asian Pacific Society of Respiratory (APSR) was established in 1986. It is composed of national societies from the Asia-Pacific region. Its objectives are the advancement and promotion of knowledge of the respiratory system in health and disease. It promotes and coordinates activities in the field of respiratory medicine, fosters research activities in respiratory medicine, and organizes and coordinates regular congresses and meetings. Its publications include the flagship journal, *Respirology*, as well as *Respirology Case Reports*, *APSR Respiratory Updates*, and the *APSR Newsletter*. The APSR has many educational programs administered through the Educational Seminar of the APSR program. Its scholarships, Teaching Library, research awards and travel awards promote the careers of young doctors and scientists by encouraging involvement with other researchers in an international forum.

Sixteen APSR assemblies and three sections are specialized scientific and clinical activity groups. Their purpose includes education and training with guidance/position statements, improving clinical practice and fostering research innovations for the future.

Website: www.apsresp.org

Headquarters:
2F UK's Bldg., 2-29-3,
Hongo, Bunkyo-ku,
Tokyo 113-0033, Japan

Contact: apsrinfo@theapsr.org
(APSR secretariat office)

Number of Members: 17,700

Publications: *Respirology*,
Respirology Case Reports, *APSR*
Respiratory Updates, *APSR*
Bulletin, *APSR Newsletter*

ASOCIACIÓN LATINOAMERICANA DE TÓRAX (ALAT)



The Asociación Latinoamericana de Tórax (ALAT) was founded in 1996. It comprises specialists in respiratory medicine from Latin America and works closely with the national medical associations of the region. ALAT's mission is to alleviate the suffering of respiratory disease and promote lung health through research, knowledge exchange and continuing medical education. One of ALAT's priorities is tuberculosis control, which remains a prevalent disease in large areas of Latin America. ALAT promotes development in the treatment of chest diseases in Latin America through many activities, including the publication of its journal *Revista Respirar y Archivos de Bronconeumología* in collaboration with *Sociedad Española De Neumología y Cirugía Torácica*. It holds an annual congress of specialists in respiratory medicine in Spanish and Portuguese and supports many other national and regional events. It offers training scholarships for young specialists and continuing medical education courses for specialists and primary care physicians. It has developed many manuals and guidelines for respiratory health professionals in Latin America.

Website: www.alatorax.org

Headquarters: Libertad 2848,
11300 Montevideo, Uruguay

Contact: secretaria@alatorax.org
(ALAT Secretary)

Number of members: 9,713

Publication: *Revista Respirar* and
Archivos de Bronconeumología



EUROPEAN RESPIRATORY SOCIETY (ERS)



ERS

EUROPEAN
RESPIRATORY
SOCIETY

The European Respiratory Society (ERS) is an international membership organization that

brings together physicians, health-care professionals, scientists and other experts working in respiratory medicine. We are one of the leading medical organizations in the respiratory field, with a growing membership representing over 160 countries. Our mission is to promote lung health to alleviate suffering from disease and drive standards for respiratory medicine globally.

Science, education and advocacy are at the core of everything we do; we promote scientific research, provide access to high-quality educational resources and play a key role in raising awareness of lung disease to politicians. We work closely with the European Lung Foundation to extend that reach to the public and patients.

Website: www.ersnet.org

Headquarters:
4 Avenue St-Luce, 1003
Lausanne, Switzerland

Contact: info@ersnet.org

Number of Members: >35,000

Publications: European
Respiratory Journal, ERJ Open
Research, European Respiratory
Review, ERS Monograph,
Breathe, ERS Handbooks

INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE (THE UNION)



The International Union Against Tuberculosis and Lung Disease (The Union) is a membership organization, a

technical organization and a scientific organization. Established in 1920, its vision is a healthier world for all, free of tuberculosis and lung disease.

The Union strives to end suffering due to tuberculosis and lung disease by advancing better prevention and care. It aims to ensure that no one is left behind and everyone is treated equally, especially those in vulnerable and marginalized populations and communities. The Union seeks to achieve this by the generation, dissemination, and implementation of knowledge into policy and practice.

Its members are organizations and individuals from all parts of the world. The Union brings together clinicians, managers, policy makers, front-line workers and implementers, scientists, patients and survivors, advocates, and civil society.

The organization develops solutions for tuberculosis, HIV, and other lung diseases, and policies to reduce tobacco use and prevent noncommunicable diseases. The Union's annual World Conference on Lung Health is globally renowned and its publications have subscribers from around the world. The Union has its headquarters in Paris and offices worldwide in Africa, the Asia Pacific region, Europe, Latin America, North America, and Southeast Asia.

Website: www.theunion.org

Headquarters: REGUS Business
Center, 2 Rue Jean Lantier, 75001
Paris, France

Contact: [www.theunion.org/
contact](http://www.theunion.org/contact)

Publications: The International
Journal of Tuberculosis and Lung
Disease, Public Health Action,
and many technical manuals and
other educational and scientific
works

PAN AFRICAN THORACIC SOCIETY (PATS)



The Pan African Thoracic Society (PATS) was formed in 2003 to create a representative African respiratory society for the region and to address the high burden of respiratory illness in Africa, and members originate from 43 different African countries. The overall aim of PATS is to promote lung health in Africa through education, training, research and advocacy. PATS has developed several sentinel activities to achieve its aims.

The Pan African Thoracic Society program in Methods in Epidemiologic, Clinical and Operations Research began in 2007 with the aim of developing research capacity in Africa. Highly successful courses have been held annually for trainees from several African countries. The Journal of the Pan African Thoracic Society is an open-access, peer-reviewed journal which aims to be the leading voice in respiratory-related research in Africa through the publication of high quality globally relevant research. PATS hosts several spirometry training courses across the continent to increase knowledge and awareness of spirometry. PATS also supports the recently established African Infant and Preschool Lung Function Working Group. PATS hosts a biennial congress to connect researchers from across the continent and has been hosting webinars to provide information and updates to health-care professionals.

Website: www.panafricanthoracic.org
Headquarters: Virtual society
Contact: info@panafricanthoracic.org
Number of members: 1287
Publication: Journal of the Pan African Thoracic Society

GLOBAL INITIATIVE FOR ASTHMA (GINA)



The Global Initiative for Asthma (GINA) was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute of the US National Institutes of Health and the World Health Organization. By publishing resources such as evidence-based strategy documents for asthma management, and hosting events such as the annual celebration of World Asthma Day, GINA is working to improve the lives of people with asthma in every corner of the globe. We support health-care professionals and public health officials around the world to reduce asthma prevalence, morbidity, and mortality by providing annual updates to asthma diagnosis and management. The GINA global strategy reports are freely available on the GINA Website; the GINA committees are made up of leading asthma experts from around the world.

Website: www.ginasthma.org
Contact: goldandgina@gmail.com
Headquarters: PO Box 558
Fontana, WI 53125
Publications: Annual reports for asthma strategy (Reports - Global Initiative for Asthma - GINA [ginasthma.org])



GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)



The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was created in 1998, with the cooperation of the National Heart, Lung, and Blood Institute of the US National Institutes of Health and the World Health Organization. When the GOLD program was initiated, the goal was to produce management recommendations for COPD based on the best available evidence.

Website: www.goldcopd.org

Contact:

k.langefeld@goldcopd.org

Headquarters: Virtual society

The first Global Strategy for Diagnosis, Management and Prevention of COPD was issued in 2001. Since its start, the aim of the GOLD report is to provide a nonbiased review of the current evidence for the assessment, diagnosis, and treatment of COPD that can aid the practicing clinician faced with managing this chronic disease.

Since the creation of the first GOLD report, the burden of chronic respiratory diseases is generally increasing worldwide, with COPD among the main causes of mortality and morbidity. GOLD works with health-care professionals and public health officials around the world to raise awareness of COPD and to improve prevention and treatment of this lung disease. Through the development of evidence-based strategy documents for management of both COPD, and events such as the annual World COPD Day and the yearly GOLD International COPD Conference, GOLD is working to improve the lives of people with COPD in every corner of the globe.



APPENDIX

ABOUT GLOBAL ALLIANCE AGAINST CHRONIC RESPIRATORY DISEASES (GARD)



GLOBAL ALLIANCE AGAINST CHRONIC RESPIRATORY DISEASES

The Global Alliance against Chronic Respiratory Diseases (GARD) is a voluntary alliance of national and international orga-

nizations, institutions and agencies committed to the vision of “a world where all people breathe freely,” established by WHO with the goal to reduce the global burden of chronic respiratory diseases.

Founded almost a decade ago, GARD has had many successes, particularly at country level. GARD has four strategic objectives: advocacy; partnership; national plans; and surveillance. Current projects vary in different countries according to country-specific needs and the level of engagement of government health departments. The WHO has a dual role in the alliance: it provides technical leadership and secretariat support. GARD is supporting the implementation of the WHO’s Global Action Plan.

In alignment with Sustainable Development Goals (SDG), especially SDG goal 3, countries are struggling to reduce premature mortality from noncommunicable diseases by one-third by the year 2030.

At the last General Meeting, in 2019 in Beijing, GARD adopted the “Beijing Call to Action for Lung Health Promotion,” with four key priority areas that conform with the UN’s Sustainable Development Goal (SDG) 3.4:

1. Advocating for action on chronic respiratory diseases
2. Fostering multisectoral action to reduce risk factors for chronic respiratory diseases
3. Strengthening primary health care for chronic respiratory diseases to achieve universal health-care coverage
4. Supporting research.

GARD aims to engage with multiple stakeholders to prioritize sustainable and long-term actions against chronic respiratory disease through “whole-of-government” and “whole-of-society” initiatives. These would “mainstream” prevention of chronic respiratory disease in all policies and promote intersectoral action to address indoor and outdoor air pollution. GARD seeks to engage a range of sectors of society and identify clean-energy strategies to shift away from kerosene, biomass and biofuel burning, and reduce carbon dioxide emissions.

GARD will ensure that national universal health coverage benefit packages include chronic respiratory disease services, including respiratory health promotion and prevention, as well as access to essential medicines and technologies, through the adaptation of the WHO Model Lists of Essential Medicines and Essential In Vitro Diagnostics, and investigate the intersection between social and environmental determinants of health and their impact on the management of chronic respiratory disease, with emphasis on the role of populations in conflict.

GARD’s greatest achievement has been its ability to forge collaborative partnerships and develop a shared vision with many parties. Preventing and controlling chronic respiratory diseases, and keeping them on the global health agenda, will require the ongoing energies of all involved in GARD and is a step toward allowing all people to breathe more freely.

