

## Prioritized Research Agenda for Prevention and Control of Chronic Respiratory Diseases

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## **Abbreviations and acronyms used in this document**

COPD: chronic obstructive pulmonary disease  
CPAP: continuous positive airway pressure  
CRD: chronic respiratory disease  
CVD: cardio-vascular disease  
GARD: Global Alliance against Chronic Respiratory Diseases (WHO)  
HCP: health care provider  
HIV: Human Immunodeficiency Virus  
ICS: inhaled corticosteroid  
IMAI: Integrated Management of Adolescent and Adult Illnesses  
IMCI: Integrated Management of Childhood Illnesses  
ISH: International Society of Hypertension  
LMIC: low- and middle-income country  
NAEPP: National Asthma Education and Prevention Program (NHLBI)  
NCD: noncommunicable diseases  
OSAS: obstructive sleep apnea syndrome  
PAL: Practical Approach to Lung Health (WHO)  
PALSA Plus: Practical Approach to Lung Health and HIV/AIDS in South Africa (GARD)  
PRO: patient-reported outcome  
SDB: sleep-disordered breathing  
TB: tuberculosis  
The Union: International Union Against Tuberculosis and Lung Disease  
WHA: World Health Assembly  
WHO: World Health Organization

## **Abstract**

The 2008-13 WHO Action Plan on noncommunicable diseases includes chronic respiratory diseases as one of the four priorities. Major chronic respiratory diseases (CRD) include asthma and rhinitis, chronic obstructive pulmonary disease (COPD), occupational lung diseases, sleep-disordered breathing (SDB), pulmonary hypertension, bronchiectasis and pulmonary interstitial diseases. One billion people suffer from chronic respiratory diseases, the majority being in developing countries. Chronic respiratory diseases have major adverse effects on the life and disability of patients. Effective intervention plans can prevent and control chronic respiratory diseases, thus reducing morbidity and mortality. A prioritized research agenda should encapsulate all of these considerations in the frame of the global fight against noncommunicable diseases. It requires both chronic respiratory diseases-targeted interventions as well as transversal noncommunicable disease programs which include chronic respiratory diseases with emphasis on health promotion and disease prevention.

**Key words:** Asthma, COPD, chronic respiratory diseases, noncommunicable diseases, control, prevention, research

## Introduction

Major chronic respiratory diseases (CRD) include asthma and rhinitis, chronic obstructive pulmonary disease (COPD), occupational lung diseases, sleep-disordered breathing (SDB), pulmonary hypertension, bronchiectasis and pulmonary interstitial diseases (1).

Over one billion people of all ages suffer from CRDs (Table 1). Over 500 million of these live in low- and middle-income countries (LMICs). CRDs are increasing in prevalence and severity (1).

**Table 1 – Estimated prevalence of chronic respiratory diseases**

Asthma	300 million
COPD	210 million
Rhinitis (excluding asthma)	400 million
Sleep-disordered breathing	> 100 million
Other CRDs	> 50 million

2007 WHO estimates, from (1)

CRDs have major adverse effects on the life and disability of patients (1). It is estimated that 4.0 million people died prematurely from CRDs in 2005, and it is projected that globally, the CRD death rate and burden will considerably increase in the future (2).

Everyone in the world is exposed to CRD risk factors, and effective preventive measures are available to reduce the deleterious impact of CRD risk factors: tobacco smoking in all countries, indoor air pollution and particularly biomass fuel combustion in LMICs, outdoor air pollution, unhealthy diet, lack of physical activity and obesity, allergens and occupational agents (1, 3, 4). The consequences of these factors start before birth, and continue throughout life (5-7). Many of them are common to other noncommunicable diseases (NCDs) (2). Furthermore, in some countries, infectious diseases (including TB and HIV/AIDS) add to the burden of CRD morbidity.

Effective interventions can control CRD, and reduce morbidity and mortality.

Most CRDs occur in LMICs, however:

- Data on CRD burden and risk factors are scarce, and surveillance on CRDs is unavailable in most LMICs. Consequently the true CRD burden on health services and society is unknown.
- Infrastructure and programs for the management of CRDs in many LMICs are not available or poorly developed because of competing priorities. Resources are limited and fragmented.
- Facilities for diagnosis and monitoring, and essential medicines for treating CRDs are not available and/or affordable in many LMICs (8, 9).
- Strategies for CRD prevention and health promotion are often absent or rudimentary.

- Programs for educating health care providers (HCPs) in the care and management of patients with CRDs require strengthening.
- Patient involvement in health promotion programs is rare or non-existent.

A prioritized research agenda should encapsulate all of these considerations in the frame of the global fight against NCDs, and requires both CRD-targeted interventions as well as transversal NCD programs which address CRDs and health promotion to prevent them.

Among the CRDs, there are currently four major topics for which more research is needed:

- Severe/uncontrolled asthma and co-morbidities.
- COPD and co-morbidities.
- Sleep-disordered breathing, links with obesity and other NCDs
- Early determinants of respiratory diseases.

## **1- Review of successful interventions**

### **1.1 - Asthma**

#### **Successful interventions in developed countries:**

- The implementation of clinical practice guidelines has led to improvements in the quality of care and reductions in the burden of disease (10, 11).
- Patient education improves asthma control, reduces urgent care visits, and improves quality of life (12, 13).
- Environmental control may improve asthma control (14) but single intervention measures are not effective (15).

#### **Successful interventions in LMICs:**

- Outdoor air pollution may be controlled and reduce asthma severity (16).
- For LMICs, The Union has developed a guide for asthma management focusing on the WHO list of essential medicines (17). A study in a limited number of patients in LMICs showed benefits (18), and a systematic approach to the organization of standard case management has been proposed (19).

**Community-wide programs:** There are limited data on the effectiveness of asthma care in whole populations at the community level. However, there was a cost-effective considerable reduction of hospitalizations and deaths in Finland (20). In middle-income countries and deprived populations, availability of effective drugs and education reduced hospitalizations and was cost-effective (21-23).

### **1.2 - COPD and co-morbidities**

#### **Successful interventions in developed countries:**

- Several guidelines are available for COPD management (24, 25). However, they should be adapted for LMICs (26).
- Environmental control is essential, in particular for tobacco (active and passive smoking and other forms of tobacco) (27-30). There are several key actions targeting tobacco control such as the WHO Framework Convention on Tobacco Control (FCTC) and the MPOWER package of interventions (**M**onitor tobacco use and prevention policies; **P**rotect people from tobacco smoke; **O**ffer help to quit tobacco use; **W**arn about the dangers of tobacco; **E**nforce bans on tobacco advertising, promotion and sponsorship, and; **R**aise taxes on tobacco) (31).
- Reducing air pollution exposure results in lower CRD morbidity and mortality .
- Educational interventions have not been fully studied (32).
- Pulmonary rehabilitation is effective in COPD (33). Regular physical activity should be encouraged in these patients.
- Influenza and pneumococcal vaccinations are recommended for the prevention of COPD exacerbations (25).

**Successful interventions in LMICs:** Preventive measures reducing biomass fuel combustion were found to reduce the risk of COPD (3, 34).

**Community-wide programs:** Community-wide programs on COPD control have been started in many countries, but definitive results are not yet available (35).

### 1.3 – Sleep-disordered breathing

**Successful interventions in developed countries:**

- Active education programs on diet and exercise are an important component of SDB management (36).
- Continuous positive airway pressure (CPAP) is highly effective in OSAS and decreases cardiovascular comorbidities (37, 38).

**Community-wide program:** A Finnish national program has been started for the prevention and treatment of sleep apnea (2002-2012) (39).

### 1.4 - Occupational chronic respiratory diseases

**Pneumoconiosis:** Improvement in ventilation and government legislation has dramatically reduced the prevalence of pneumoconiosis in many countries (1) but more data are needed in LMICs.

**Occupational asthma in developed countries:** Control of exposure by noxious agent substitution, improvement of ventilation, change in process and enclosure is effective in the primary and secondary prevention of occupational asthma (40, 41).

### 1.5 - Early determinants of chronic respiratory diseases

**Successful interventions in developed countries:**

- In respiratory distress syndrome of premature infants, surfactant and antenatal steroids (42) have dramatically decreased deaths.
- Primary prevention of allergy and asthma is still a matter of debate, as only multifaceted interventions showed some efficacy (43, 44). A Finnish national program associated with GARD has been started for the prevention and treatment of allergy and asthma (2008-2018) (45).

**Successful interventions in LMICs:** Reduction of indoor air pollution exposure from biomass fuel use is a potentially important intervention for the prevention of acute respiratory infection in children (46, 47) but evidence for its impact is lacking (48).

### **1.6 - Transversal NCD prevention and control programs with chronic respiratory disease components**

Health care providers face considerable and diverse challenges in LMICs. These include separate disease-specific interventions fragmenting and duplicating efforts, and limiting resources across a range of priorities as well as competition with programs against communicable diseases. However, such transversal programs:

- May face difficulties in the evaluation of their effectiveness.
- Do not usually provide for adaptation to national, regional and local needs and resources, resulting in non-feasibility or non-sustainability or both.
- Do not usually develop a partnership between policy makers and HCPs in the field, consequently fail to transform evidence into policies and policies into practice.
- Do not usually develop and implement affordable educational methods that can be sustained in resource-poor settings of LMICs.

There are few examples of successful programs incorporating several NCDs, in some cases with infectious diseases in children and adults (49, 50, 51). Lessons learnt from these initial efforts confirm that such methods may be extended in many LMICs to address priority needs in NCD prevention and management.

### **1.7- Models of risk factor effect and avoidance on chronic respiratory diseases**

There is little systematically collected evidence on the overall contribution of environmental risk factors to the global burden of disease. WHO recently completed a comprehensive, systematic, and transparent estimate of the disease burden attributable to the environment and 24% of the global burden of disease was estimated to be due to environmental risk factors (52).

The WHO Comparative Risk Assessment (CRA) methodology (53) enabled the assessment of world mortality and morbidity in the year 2000 resulting from exposures to selected occupational hazards. Occupational risk factors were responsible for 13% of COPD, 11% of asthma, 9% of lung cancer, and 100% of pneumoconioses and mesothelioma (54).

Health gains that environmental interventions could achieve are main questions when choosing environmental health actions to prevent disease. WHO has released profiles of environmental burden of disease for 192 countries (55). 13 to 37% of the countries' disease burden could be prevented by environmental improvements, resulting in a reduction of about 13 million deaths per year (56).

For successful NCD prevention and control strategies, a focus on individuals needs to complement population-wide strategies. Strategies that focus on individuals are cost effective only when targeted at high-risk groups. Risk prediction tools predicting an individual's absolute NCD risk are key to targeting limited resources at high-risk individuals who are likely to benefit the most (57). The WHO/ISH charts, already available, enable the prediction of future risk of heart attacks and strokes in people living in LMICs (57, 58). Risk charts also put cancer in context (59).

## **2- Prioritized Research Agenda for CRDs**

Research opportunities vary between high-income countries where diagnostic methods and treatments are usually available and LMICs. The priorities should be flexible enough in harmonizing the specific needs and conditions of the countries. Standardized methods, in particular for epidemiologic studies, should be made available and tailored for LMICs. Redefining (phenotyping) of CRDs is ongoing and will influence the program in coming years as well as the transition of disease burden in different regions and climate changes. Dissemination of the relevant information and training of PHCs should be part of the research program.

**Five topics have been prioritized according to short-, medium- or longer-term deliverables** (Table II) and depending on burden, perceived need in LMICs, potential impact on health and gaps in knowledge as well as cost-effectiveness and applicability to LMICs:

- Severe/uncontrolled asthma is a major health problem and interventions seem to be cost-effective, reducing considerably burden and mortality. They should be tested in various settings and co-morbidities should be considered.
- Modeling for estimates of the impact of interventions for prevention of NCD should be envisaged and risk charts for COPD and OSAS can be developed.
- The impact of reduction in obesity on the prevention of SDB should be studied as part of the NCD prevention plan.
- Assessment of patterns of disease and symptoms in adults presenting to first-level facilities in LMICs to serve as a guide to the development of transversal programs.
- Development and evaluation of transversal (integrated) programs of prevention and care in selected LMICs with different resources and needs employing methods used in PAL (51) and PALS Plus (50, 60) and other similar programs. A dominant feature of this program is the strengthening of health systems through education and optimal use of resources.

A global fund for CRD research in LMICs should be developed.

Other interventions should be discussed. Research should be conducted to better appreciate definition, risk factors, burden, prevention and control, and a program started when sufficient knowledge becomes available.

**Table II: Research priorities in CRDs from the public health perspective**

Proposed to focus on low- and middle-income countries (LMICs), but recommended for all countries

Topic	Short term	Medium term	Longer term
<p><b>1- Severe / uncontrolled asthma and co-morbidities</b></p> <p>Gaps in knowledge and gaps in knowledge translation into policies</p>	<p>(i) To reach consensus on a universal definition of severe / uncontrolled asthma in adults and children with identification of gaps in the knowledge.</p> <p>(ii) To estimate (and monitor yearly) the number of countries with access to spirometry, essential medicines for CRDs and adequate care (common to Topics 1, 3, 4 and 5).</p>	<p>(iii) To develop and validate, in pilot studies, a protocol to estimate the prevalence, case fatality rate and co-morbidities of severe/uncontrolled asthma.</p> <p>(iv) To implement studies in LMICs to confirm the impact of access to ICS on morbidity and case fatality of severe/uncontrolled asthma in children and adults.</p>	<p>(v) To characterize the phenotypes of patients with severe/uncontrolled asthma and search for specific risk factors and co-morbidities.</p> <p>(vi) To investigate genomics.</p> <p>(vii) To redefine severe asthma phenotypes according to latest research.</p>
<p><b>2- Impact of primary and secondary prevention of CRDs</b></p>	<p>(i) To develop models to estimate the regional and global attributable fraction of risk of CRD related to tobacco smoke, solid fuel combustion, outdoor air pollution and allergens; and the potential impact of interventions for their reduction.</p> <p>(ii) To develop models to estimate the impact of healthy diet and physical activity on prevention and control of obesity and its major co-morbidities, such as CVDs, type II diabetes and SDB.</p> <p>(iii) To develop models to estimate the impact of early detection of occupational CRDs and subsequent intervention on the prevention of disability due to occupational CRDs.</p>	<p>(iv) To develop risk charts for COPD and OSAS using the methodology of WHO CVD risk charts, and to test its usefulness as a tool to change behavior of health professionals, users of health services and the community.</p> <p>(v) To develop and validate in pilot studies, simple protocols (including questionnaires and spirometry) to assess the CRD risks.</p>	<p>(vi) To review risk charts and assess impact of its adoption on tangible health outcomes.</p>
<p><b>3- Effectiveness of integrated prevention and management of chronic diseases in PHC in low resource settings</b></p>	<p>(i) To investigate the feasibility, effectiveness and affordability of integrated prevention and management strategies for CRDs, CVDs, diabetes and other priority diseases in PHC in pilot countries. Based on PAL and PALS-Plus, IMAI, IMCI and other programs.</p> <p>(ii) To investigate the outcomes of a tailored syndromic approach to case management of chronic diseases in PHC by trained nurses with the supervision of physicians in pilot countries using an implementation plan based on PAL, PALS-Plus, IMAI, IMCI and other programs.</p> <p>(iii) To estimate (and monitor yearly) the number of countries with access to spirometry, essential medicines for CRDs and adequate care (common to Topics 1, 3, 4 and 5).</p>	<p>(iv) To assess CRD burden on emergency services and PHC facilities</p> <p>(v) To develop methods for measurement of the impact of the interventions (e.g. indicators and outcomes for audit and pragmatic randomized controlled trials)</p>	<p>(vi) To evaluate benefit of large-scale community education campaigns and community participation in the prevention and control of NCDs (including CRDs) in different cultural and economical settings.</p>
<p><b>4- COPD and co-morbidities</b></p> <p>Planning management of a</p>	<p>(i) To reach consensus on a universal definition of COPD, COPD exacerbations and risk factors for</p>	<p>(iv) Surveys to assess the COPD prevalence, risk factors and co-morbidities (CVDs, cancer</p>	<p>(vi) Evaluate benefits of treatment on both COPD and all NCDs over treatment of</p>

person with COPD and concomitant co-morbidities (CVDs, diabetes and others)	<p>exacerbations, and to address gaps in knowledge to understand mechanisms of exacerbations.</p> <p>(ii) To propose essential patients' reported outcomes (PROs) acceptable in all countries.</p> <p>(iii) To estimate (and monitor yearly) the number of countries with access to spirometry, essential medicines for CRDs and adequate care (common to Topics 1, 3, 4 and 5).</p>	and diabetes) in population based studies (BOLD initiative)	individual diseases, on PROs, specific and general health outcomes, as well as in costs.
<p><b>5- Early determinants of chronic respiratory diseases</b></p> <p>Indoor and outdoor air pollution, infections, allergens, lack of awareness and demand to health services, lack of access to proper care.</p>	<p>(i) To reach consensus on the definition of major CRDs by age groups, risk factors and identify gaps in knowledge.</p> <p>(ii) Develop methodology for a survey in LMICs to study prevalence of CRD and high risk patients in children under 5.</p> <p>(iii) To estimate (and monitor yearly) the number of countries with access to spirometry, essential medicines for CRDs and adequate care (common to Topics 1, 3, 4 and 5).</p>	<p>(iv) Surveys using spirometry and other case finding strategies to determine CRD prevalence (including asthma) in children and adolescents and to identify risk factors in early life.</p> <p>(v) To develop and validate strategies for the management of acute respiratory diseases and asthma in LMICs for children under 5</p>	<p>(vi) Birth cohort studies and other longitudinal studies to assess genetic and early environmental determinants on CRD causality (especially asthma).</p> <p>(vi) Develop and evaluate efficacy of preventive interventions worldwide and particularly in LMICs.</p>

### 3- Topics for future research

Some CRDs are known to be of great importance, but further studies are needed to fully define their burden and / or methods needed to be established/validated for their assessment in population-based surveys in LMICs. There is a need for operational research, better surveillance of vital statistics, standardization of lung function testing in LMICs and estimation of costs of improving management of CRD. Once these methods are clarified, research should start. These include SDB, bronchiectasis and pulmonary hypertension.

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