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REVIEW

The complications of treating chronic obstructive pulmonary disease in low income countries of sub-Saharan Africa

Frederik A. van Gemert [a,b], Bruce J. Kirenga[a,b,c], Tewodros Haile Gebremariam[d], George Nyale[e,f], Corina de Jong[a] and Thys van der Molen [a,b]

[a]Groningen Research Institute for asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [b]Makerere University Lung Institute (MLI), Mulago Hospital, Kampala, Uganda; [c]Department of Medicine, Makerere University, Kampala, Uganda; [d]Department of Internal Medicine, Division of Pulmonary & Critical Care Medicine, Addis Ababa University, College of Health Science, Addis Ababa, Ethiopia; [e]Respiratory and Infectious Disease Unit, Kenyatta National Referral & Teaching Hospital, Nairobi, Kenya; [f]Kenya Association of Physicians for Tuberculosis and other Lung Disease (KAPTLD), Nairobi, Kenya

ABSTRACT

Introduction: In most low and middle-income countries, chronic obstructive pulmonary disease (COPD) is on the rise.

Areas covered: Unfortunately, COPD is a neglected disease in these countries. Taking sub-Saharan Africa as an example, in rural areas, COPD is even unknown regarding public awareness and public health planning. Programs for the management of COPD are poorly developed, and the quality of care is often of a low standard. Inhaled medication is often not available or not affordable. Tobacco smoking is the most common encountered risk factor for COPD. However, in sub-Saharan Africa, household air pollution is another major risk factor for the development of COPD. Communities are also exposed to a variety of other risk factors, such as low birth weight, malnutrition, severe childhood respiratory infections, occupational exposures, outdoor pollution, human-immunodeficiency virus and tuberculosis. All these factors contribute to the high burden of poor respiratory health in sub-Saharan Africa.

Expert commentary: A silent growing epidemic of COPD seems to be unravelling. Therefore, prevention and intervention programs must involve all the stakeholders and start as early as possible. More research is needed to describe, define and inform treatment approaches, and natural history of biomass-related COPD.

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1. Introduction

1.1. Noncommunicable diseases in sub-Saharan Africa

After Asia, Africa is the world's second-largest and second-most-densely populated continent. With a 1.2 billion people (as of 2017), it accounts for about 16.4% of the world's human population. Africa is often spoken of as if it were one country. With 54 different countries and more than 2000 languages and cultures, it is misleading to treat the countries of Africa as one and the same.

Until the last decade, noncommunicable diseases (NCDs) have been neglected by development agencies, foundations, and global health organizations [1]. In September 2011, at the United Nations high-level meeting on NCDs, the world's leaders recognized the increasing human, social, and economic threat caused by NCDs and committed to tackling this emerging global epidemic [2]. The need was urgent, given that the combined burden of NCDs was increasing fastest among most low- and middle-income countries (LMICs). Of the 56 million deaths that occurred globally in 2015, almost 70% were due to NCDs, of which over three-quarters took place in LMICs [3].

Sub-Saharan Africa, a geographic term to describe countries which are fully or partially located south of the Saharan desert, represents a relatively comparable group of LMICs with similar health problems. Sub-Saharan Africa has a very high prevalence of communicable diseases, such as the three pandemics of tuberculosis (TB), AIDS/HIV and malaria, as well as infections in young children, causing more deaths from communicable diseases than NCDs [4]. It is estimated, however, that the NCDs will overtake communicable diseases as the leading cause of death in sub-Saharan Africa by 2030 [4]. Not only does this region have the highest burden of disease, but it also has the weakest health systems, including poor public health leadership and management, lack of qualified personnel, and lack of resources for the diagnosis of NCDs. In almost all the countries of sub-Saharan Africa the governments' health expenditure are insufficient or are often cut down by corruption [5]. The poorest people in resource-poor settings have the highest risk of developing chronic diseases and are the least able to cope with these conditions [6].

1.2. Chronic respiratory diseases

Chronic respiratory diseases (CRDs) i.e. chronic diseases of the airways and other structures of the lungs, represent a broad group of serious diseases. CRDs include asthma and

CONTACT Frederik A. van Gemert frgemert@xs4all.nl Department of General Practice and Elderly Care, University Medical Center Groningen, Huispostcode FA21, P.O. Box 196, Groningen 9700 AD, The Netherlands

respiratory allergy, chronic obstructive pulmonary disease (COPD), allergic rhinitis, sleep apnea syndrome, occupational lung diseases, and pulmonary hypertension. Throughout the world, hundreds of millions of people of all ages are affected by preventable CRDs, and more than 50% of them live in LMICs or deprived populations [5,7]. The prevalence of preventable CRDs is increasing everywhere and, in particular, among children and elderly people [8]. Three hundred thirty-four million have asthma, 210 million have COPD, and 600 million suffer from allergic rhinitis; millions of others have other CRDs. In 2015, 383,000 people died of asthma, and 3 million died of COPD; 90% of all COPD deaths were in LMICs [9,10]. In 2010, the World Health Organization reported that COPD was the fourth-leading cause of death globally, and was expected to be the third by 2030. Unfortunately, this prediction has been overtaken by reality; currently, COPD is the third-leading cause of mortality worldwide, surpassing the combined mortality of AIDS/HIV, TB, and malaria [11,12].

In many countries of sub-Saharan Africa, programs for the management of respiratory diseases are poorly developed or limited, and the quality of care offered is often of a low standard. Asthma and COPD guidelines are rarely (and sometimes not at all) implemented in most sub-Saharan Africa countries, except for South Africa which can be classified in the middle-income country group. CRDs pose a serious public health threat in sub-Saharan Africa, particularly among the poor and deprived population [13,14].

1.3. Chronic obstructive pulmonary disease

The Global Initiative for chronic Obstructive Lung Disease (GOLD) guidelines of 2017 has a working definition of COPD as '*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. COPD, a preventable and treatable disease with some significant extrapulmonary effects, is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.*'[15]

COPD leads to slowly progressive respiratory symptoms of breathlessness, chronic cough, or sputum production, as well as wheezing or chest tightness. These symptoms can vary from day to day and from person to person [15]. Additional features of (very) severe COPD are fatigue, weight loss, ankle swelling, and symptoms of depression and/or anxiety [15]. Worldwide, tobacco smoking is recognized as the most important risk factor for COPD. There is growing evidence, however, that the development of COPD occurs among nonsmokers as well, especially younger persons and individuals living in LMICs [16,17]. Other relevant risk factors suggesting a possible influence in the development of COPD are exposure to indoor and outdoor air pollution, occupational exposures, history of acute lower tract infections among young children, previous TB, poor lung growth and development, malnutrition, chronic asthma, and genetic predisposition [17–20]. Smoke caused by biomass fuel use (such as wood, animal dung, crop residues, straw and charcoal) for domestic cooking and heating, has shown to be a major independent risk factor for the development of COPD, particularly in rural areas of LMICs [15–20]. Unfortunately, in the last decade, most of the international health authorities still did not consider household air pollution to be a serious global public health concern. COPD seemed to be a neglected disease in LMICs.

1.4. Prevalence of COPD

The existing global COPD prevalence data, based on large-scale epidemiological studies, such as the Burden of Obstructive Lung Diseases (BOLD) and the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO), have all been conducted in those ≥40 years and mainly in urban areas [21,22]. Data on spirometry- and population-based COPD and related risk factors are scarce in sub-Saharan Africa [23–25].

The BOLD study in South Africa (Johannesburg, 2007) showed a COPD prevalence of 22.2% among men and 16.7% among women (aged ≥40 years), probably caused by a combination of high levels of TB, occupational exposure, and smoking habits [26]. In Malawi (2011), a COPD prevalence of 13.6% was found among adults above the age of 30 years living in urban and rural areas, and showing poverty to be a risk factor for COPD [27]. In Rwanda (2011), a COPD prevalence of 9.6% was found among adults aged ≥45 years; exposure to biomass smoke was minor since many Rwandans cook outdoors [28]. The BOLD study in Nigeria (2015), performed in a suburban community, showed a COPD prevalence of 7.7% (aged ≥40 years) with poor education, a previous diagnosis of TB, and asthma as key independent predictors [29]. The *FRESH AIR Uganda* survey (2015), performed in a rural district, found a COPD prevalence of 16.2% (participants were aged ≥30 years); of these, more than 90% were exposed to biomass smoke [30]. Another survey was conducted in an urban area of Malawi (2016) among adults above the age of 18 and showed a COPD prevalence of 4.2%; increasing age was the only associated factor [31]. In Cameroon (2016), in the capital city Yaounde, a COPD prevalence among adults aged ≥19 years was 2.4%; 47.6% were exposed to smoke caused by a mix of biomass and clean fuels, and only 7.9% were exposed to biomass smoke [32].

The limited surveys focusing on the prevalence of COPD in sub-Saharan Africa show great diversity, and is reflected in differences in age, criteria for COPD and methodology, as well as different risk factors. Most of the surveys have been conducted in urban areas. It is known that 56% of this population (and 70% of East African people) lives in rural areas. This suggests a hidden health problem and the potential for significant consequences in the future [25,30]. Adults under the age of 40 years, mainly living in rural areas of sub-Saharan Africa, are an entirely overlooked group in countries with a high COPD burden.

2. COPD management in Uganda, Ethiopia, and Kenya

2.1. A patient with respiratory problems

We compared three countries in East Africa, i.e. Uganda, Ethiopia, and Kenya, focusing on their knowledge, treatment

and management of COPD. Uganda is one of the countries in east Africa covering a surface area of 241,038 km^2. According to the 2014 national census, the population is estimated to be 41.4 million people [33]. Approximately 82% of the population lives in rural areas [33]. Ethiopia is located in the Horn of Africa and covers an area of 1,104,300 km^2. Ethiopia is the second most-populated nation in Africa, home for 102.4 million people. Approximately 80.5% of the population lives in rural areas [33]. Kenya is a country with coastline on the Indian Ocean, surfacing an area of 580,267 km^2. The country is populated by 48.4 million people, of which 74% are living in rural areas [33].

In addition to the FRESH AIR survey in Uganda, another survey has been conducted in rural Mbarara district among adults above 18 years, showing a COPD prevalence of 10% [34]. Little is known about COPD in Ethiopia; only limited data are available on prevalence and mortality rates. The few studies in rural Ethiopia have used physician-diagnosed COPD without spirometric confirmation. In Kenya, the current prevalence of COPD is unknown since there has not been any study in the communities. However, there have been a few hospital-based studies looking at COPD: the estimated prevalence was about 200 per 100,000 population.

A 60-year old patient was presented at the university hospital with progressive breathlessness and leg swelling of 3 months duration. He also had cough, productive sputum and wheezes. He lives in a rural village and is a farmer. He smokes tobacco for 40 years, about 5-10 a day (30 pack years).

The last three years he visited the health center several times due to his breathlessness, often in combination with coughing. He was tested on TB: this was negative. No treatment was given. Recently, the symptoms worsened and he went to the local hospital. They treated him with salbutamol inhalers as a case of asthma, but he did not show any significant improvement. Eventually he was referred to the university hospital.

The knowledge of COPD is low in all three countries. The Uganda Clinical Guidelines 2014, published by the Ministry of Health, did not even mention COPD [35]. Most professional health workers are uncomfortable managing COPD. In Uganda, most respiratory care is provided by general internal medicine physicians and general practitioners. There are five pulmonologists in Uganda, and all are based in the capital city of Kampala. Although most medical training curricula have aspects of asthma and COPD, providers lack hands on practice post training to help them gain competence in COPD diagnosis and management. In Ethiopia, there are currently only nine physicians with formal pulmonary and critical care training, a majority through the East African Training Initiative based in Addis Ababa University. This small number of physicians is unable to provide specialized respiratory medical service to the whole country. Consequently, the level of COPD knowledge among general practitioners, notably those in rural areas, is often limited and leads to misdiagnosis and inadequate treatment. Kenya has 16 pulmonologists, mostly based in the Nairobi and Mombasa.

In the rural areas, COPD is completely unknown by the clinicians and other healthcare workers. A frequently mentioned diagnosis at a health center is 'TB-negative'; this indicates that no cause is found for a person with respiratory symptoms and, therefore, there is no possibility to offer therapeutic options. Spirometry and inhaled medication are hardly available in the rural areas [36].

The disease COPD is unfamiliar in the general population. This lack of awareness on the part of the patients leads to delayed presentation to diagnostic services and delayed reduction of risk factors. Uninformed patients are also unable to anticipate the prognosis of their conditions. In most patients that we see, the diagnosis of COPD is new and the patients are hearing this for the first time. It requires a lot of time and resources to educate the patients on what the disease is, what caused it, how it can be treated, and what the patients should expect their life to be now that they have such a diagnosis. With limited personnel and lack of educational materials the clinicians always find themselves constrained on how much information they can offer. In the current situation, if a person in a rural area did in fact have COPD, the diagnosis would not be known and that individual would accept the symptoms as 'part of life'. The person would have no idea about the various risk factors and would probably use some form of treatment with local herbs or ask help from the traditional healers; medication from a private dispensary would often be too costly to purchase [36].

At the university hospital, on examination he was in moderate distress. He could not speak in full sentences, and used accessory muscles of respiration. His blood pressure was 130/80, pulse 92 (regular), respiratory rate of 28, temperature 36.5 C and SaO_2 was 70%. On his chest scattered wheezes were heard. The abdomen showed no signs of hepatomegaly, splenomegaly or ascites. The lower extremities: pedal edema. The chest X-ray showed hyperinflated lungs. The working diagnosis was an exacerbation of asthma, and he was treated with prednisolone, salbutamol nebulizer, diuretics and oxygen.

The issue that represents a major challenge to COPD management in sub-Saharan Africa is capacity to diagnose and management comorbidities. COPD is a disease that is highly associated with many and more severe comorbidities than other diseases, such as cardiovascular diseases, skeletal muscle dysfunction, metabolic syndrome and diabetes mellitus, osteoporosis, depression and anxiety, malnutrition, anemia, and lung cancer [37,38]. In resource-limited settings, it is almost impossible to investigate all these comorbidities while they have a big impact on treatment outcomes.

His SaO_2 improved to 84%. The electrocardiogram showed signs of severe pulmonary hypertension. The chest CT showed signs of emphysematous changes. After improvement, spirometry was performed: FVC 3.2lt, FEV_1 1.8lt and FEV_1/FVC ratio 0.56. His diagnosis was changed to severe COPD with cor pulmonale.

Spirometry still forms the cornerstone in the diagnosis of COPD [15]. Although presence of symptoms and exposure to risk factors are important in the diagnosis of COPD, these symptoms and risk factors occur in many other diseases. In Uganda, Ethiopia, and Kenya, spirometry only became available a few years ago as automated portable machines were used in scarcely performed COPD surveys. Currently, spirometry of good quality is only available in a few health facilities. This makes the diagnosis of COPD quite difficult. This forces physicians to make a symptom-based diagnosis of COPD, which can underestimate disease prevalence, especially in

women who are less often cigarette smokers and in those living in rural areas where medical knowledge about COPD is frequently lacking.

The diagnosis of COPD in East Africa faces other challenges besides lack of spirometry. Because of the high burden of TB, the diagnostic work up for COPD needs to happen alongside that for TB and other lung infections. For example, in the chest clinics in the three countries, patients need to have at a minimum a chest X-ray and sputum tests for TB before the consultation is concluded. This is important not only to ensure that a TB diagnosis is not missed, but also to ensure that patients with active TB do not perform spirometry for their and the spirometry technician' safety. This increases cost of COPD diagnosis and introduces delays that may result in patients missing the diagnosis.

> After 10 days he left the hospital with a combination of inhaled corticosteroids/long-acting beta-agonists combination inhaler (combination inhalers of long-acting beta-agonists and long-acting muscarinic receptor antagonists were not available) and a salbutamol inhaler if necessary. Home oxygen and influenza vaccine were not possible because of inaccessibility issues in his rural district. Tobacco smoking cessation counselling was done, but no other risk factors were discussed, and no follow-up was planned.

There are several barriers to the optimal management of COPD in East Africa. The first is a lack of a national protocol for assessing and managing COPD, which could help lessen the existing knowledge gap in primary care providers. Secondly, healthcare resources in general are limited in Ethiopia, Kenya, and Uganda, further challenging the care of noninfectious chronic diseases like COPD. Rural communities experience inequities in access to needed health care as compared to urban populations due to poor infrastructure, lack of medicines and other health supplies. The availability of inhaled medication is low, particularly in the rural communities (Table 1). Furthermore, inhalers are often unaffordable when assessed from the private sector [7,39,40]. And finally, ongoing exposure to household biomass fuel and tobacco smoke continue to increase the development and severity of COPD in these countries.

2.2. Interpretation of the findings

In sub-Saharan Africa, CRD and its risk factors, such as household air pollution, tobacco smoking, occupational exposure, severe childhood respiratory infections, and TB, receive insufficient attention from the healthcare community, government officials, patients and their families, as well as the media [23]. Diagnostic tests such as handheld spirometry and even peak flow measurements are only scarcely available. Inhaled medication, which is included in the World Health Organization's (WHO) Model List of Essential Medicines, is often limited available or not affordable, particularly in rural areas. Treatment for chronic conditions (like COPD) is focused on the ad hoc treatment of acute exacerbations instead of long-term disease management, including adjustment of lifestyle factors and prevention of exacerbations [36]. Thus, COPD seems to be a neglected disease in many sub-Saharan countries. The framework of the Package of Essential Noncommunicable (PEN) disease interventions, and the Practical Approach to Lung Health (PAL), both developed by the WHO, did not work out for CRDs in Uganda, Ethiopia, and Kenya [41].

2.3. Tobacco smoking

In Uganda (data published in 2014), 7.9% of adults aged 15 years or older were using tobacco products (11.6% of men and 4.6% of women). An estimate 20.4% of adult who worked indoors had been exposed to second-hand smoke in their workplace and 13.1% of adults were exposed to second-hand smoke at home [42]. Demographic data showed that 6.6% of current smokers lived in urban areas and 10.1% in rural homes [43]. In Masindi district, a tobacco-growing area, 34.4% of men (particularly young men) and 7.4% of women (mostly the elderly) were current smokers [30]. Smoking cessation services are hardly available in Uganda. Tobacco dependency treatment medicines are not widely available especially in public health hospitals [44]. Recently, very brief advice (VBA) has been introduced to healthcare workers in Kampala. In Uganda, smoking is now prohibited in indoor public spaces. The legislation also regulates tobacco advertising, promotion and sponsorship, and protection against tobacco industry interference.

In Ethiopia, data on smoking prevalence are scarce. According to the WHO, 3.1% of adults aged 15 years or older smoke tobacco (8.9% of men and 0.5% of women [45]. A survey conducted in eastern Ethiopia reported the proportion of current smoking men of 21.6% in rural areas vs. 10.3% in urban areas [46]. The exposure to second-hand smoke was 52% [46,47]. Smoking cessation programs are limited to two hospitals in Addis Ababa. Services rendered in the clinics include behavioral counseling on smoking cessation and nicotine replacement therapy. But pharmacotherapy like varenicline is not readily available. Legislative actions have been taken recently in Ethiopia regarding tobacco smoking, like banning smoking in public areas, and prohibiting the sale of tobacco products to minors. Tax increment on tobacco has also been implemented to minimize access of the youth to cigarette smoking.

In Kenya (data published in 2014), 7.8% of adults aged 15 years or older were using tobacco products (15.1% of men and 0.8% of women). The survey found that 17.6% of adults who worked indoors were exposed to tobacco smoke at the workplace and 14.3% of adults were exposed at home [48]. A recent report by the Ministry of Health on risk factors of NCDs, found that 13.3% of Kenyans consumed some form of tobacco products (23% of men and 4.1% of women [49]. The demographic characteristics were not different: urban 13.2% and rural 13.4%. About 20.9% were exposed to second-hand smoke [49]. Behavioral counseling and smoking cessation programs are lacking or unorganized in the public sector [49,50]. Only nicotine replacement therapy is available. Smoking is allowed in designated areas in most public places and workspaces. It is unclear whether smoking is prohibited in most means of public transport. The law prohibits virtually all forms of advertising and promotion of tobacco products [51]. In 2017, the Court of Appeal ruled that the Ministry of Health had an obligation in safeguarding the health interest of Kenya by implementing regulations under the Tobacco Control Act.

Table 1. The availability of inhaled respiratory medication in Uganda, Kenya, and Ethiopia.

Uganda [40]	Kenya[a]	Ethiopia[a]
SABA are available in 26% of public hospitals, 77% of private hospitals and 88% of pharmacies[b]. SAMA are only available in pharmacies[b]. SABA/SAMA are available in 4.6% private hospitals and 15.3% pharmacies[b], and not in public hospitals.	SABA are mostly available in public hospitals and all the private hospitals and pharmacies[b]. SAMA and SABA/SAMA are not available in public hospitals, mostly available in private hospitals and available in pharmacies[b].	SABA are available in most public hospitals and all the private hospitals and pharmacies. SAMA are not available. SABA/SAMA are only available in few pharmacies[b] in Addis Ababa.
LABA are available in 15.3% pharmacies[b]; LAMA and LABA/LAMA are not available.	LABA are only rarely available in pharmacies[b]. LAMA are rarely available in public hospitals, and mostly available in private hospitals and pharmacies[b]. LABA/LAMA are rarely available in private hospitals and pharmacies[b]	LABA, LAMA and LABA/LAMA are not available.
ICS are available in 4% of public hospitals, 50% of private hospitals and 55% of pharmacies[b]. ICS/LABA are not available in public hospitals, but available in 40% of private hospitals and 61% of pharmacies[b]. ICS/LAMA are not available.	ICS are mostly available in public hospitals and private hospitals, and available in pharmacies[b]. ICS/LABA are at times available in public hospitals, mostly available in private hospitals and available in pharmacies[b]. ICS/LAMA are rarely available.	ICS are available in big private hospitals in Addis Ababa, in some private hospitals and pharmacies[b] in big cities. ICS/LABA are not available in public hospitals, but available in some private hospitals and pharmacies[b] in big cities. ICS/LAMA are not available.
Oral methylxanthines are available in 4% of public hospitals and 18% of private hospitals and 20% of pharmacies[b].	Oral methylxanthines are available.	Oral methylxanthines are available.
Adult spacer devices only 28.2% available in pharmacies[b].	Adult spacers devices are only mostly available in private hospitals and available in pharmacies[b].	Adult spacer devices not available.

[a]Unpublished data from the local physicians and pharmacists; [b]pharmacies are private pharmacies

SABA: short-acting beta-agonists; SAMA: short-acting antimuscarinic agents; SABA/SAMA: combination of SABA and SAMA; LABA: long-acting beta-agonists; LAMA: long-acting antimuscarinic agents; LABA/LAMA: combination of LABA and LAMA; ICS: inhaled corticosteroids; ICS/LABA: combination of ICS and LABA

2.4. Indoor air pollution

Although tobacco smoking is an established risk factor worldwide, exposure to biomass smoke may even be greater; moreover, their effects may be additive [52]. Worldwide, almost three billion people (mostly from LMICs) rely on the use of open fires and simple burning of biomass fuels (wood, animal dung, crop residues, straw, and charcoal) for cooking and heating [52,53]. In sub-Saharan Africa, most rural communities cook indoors, using the traditional cooking fireplace with three rocks to support the pot or griddle. Biomass fuels are burned with inefficient combustion and poor ventilation, leading to extremely high levels of indoor pollution [54,55]. Biomass fuels account for more than 50% of household energy in many LMICs of sub-Saharan Africa, and up to 95% in some lower-income countries, particularly for the rural population [54,55]. People living in poverty are unable to afford clean, efficient cooking practices, and have the greatest exposure to household air pollution [14,18,56].

Exposure to household air pollution is associated with a wide range of health-damaging outcomes [54,55,57]. The smoke from biomass fuel use contains more than 250 health-damaging pollutants (including carbon monoxide, nitrogen, and sulfur oxides) as well as a variety of pollutants, irritants, carcinogens, co-carcinogens and free radicals [54,55,57]. These include significant amounts of particulate matter (PM), of which the smallest particles (mean aerodynamic diameter of particles <2.5 μg, $PM_{2.5}$) can penetrate deep into the lungs to the alveolar spaces. There is evidence that biomass smoke increases the risk of pneumonia in children under age 5 years, and COPD in adults aged over 30 years, as well as the risk of heart disease, eye disease (e.g. cataract), low birthweight and lung cancer (in relation to coal use [54,55,58].

2.5. Reducing the risk factors

Exposure to biomass smoke and tobacco smoke is largely determined by cultural tradition, gender, and socioeconomic factors. For example, in most countries of sub-Saharan Africa, women have the responsibility for domestic cooking and are exposed to biomass smoke every day; this exposure also applies to young children and sick persons who generally spend more time indoors and around the fires [59]. However, women cannot change their cooking tradition themselves, as they are in the lowest societal position. In contrast, men are head of the family and smoke tobacco most of the time and wherever they want, even inside the house [36].

Intervention programs to reduce exposure to household air pollution have been conducted in sub-Saharan Africa over the past three decades. Initially, the drive behind these programs was deforestation and encouraging local economic development, rather than health risks from household air pollution [55,56,60]. Several national programs did make a transition to cleaner fuels including liquefied petroleum gas (LPG) as their socioeconomic circumstances improved [60]. But for the next decade, the majority of the poorest people in rural areas will have limited opportunities to switch to clean fuels, and will depend on 'clean' and 'efficient' cookstoves [60–62].

Preventive actions are needed to combat the burden of COPD and other CRDs in LMICs. Awareness-raising activities related to the adverse effects of biomass fuel use and tobacco smoking in all communities should be promoted. It is essential to provide key policymakers in sub-Saharan Africa with convincing evidence about the prevalence and impact of COPD in local communities and the implementation of culturally appropriate interventions to control the development of COPD and its risk factors. COPD is a chronic disease that will continue to become more frequent with the aging of the global population, combined with the rapidly expanding population of sub-Saharan Africa [25].

2.6. Reference values for spirometry in sub-Saharan Africa

In most epidemiological surveys, a COPD diagnosis is based on spirometry. This is fundamentally different from the clinical diagnosis of COPD that is based on the clinician's evaluation of exposure to risk factors, symptoms, limitations, quality of life, exacerbation assessment and spirometry [63]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 0.7 measured after administration of an inhaled bronchodilator confirms the presence of persistent airflow obstruction. In healthy subjects the FEV_1/FVC ratio declines with increasing age and height; therefore, the use of the fixed ratio of less than 0.7 after administration of an inhaled bronchodilator naturally leads to over-diagnosis in elderly people, and under-diagnosis in young people. Thus, the use of the lower limit of normal (LLN), i.e. below the fifth centile of the predicted FEV_1/FVC ratio, has been introduced by the Global Lung Function Initiative (GLI) to define COPD [64,65].

Using the post-bronchodilator FEV_1/FVC < LLN to define an airflow obstruction, data from *FRESH AIR Uganda* showed a prevalence of airflow obstruction of 16.2% (53% women), of whom 37% of men and 40% of women were 30–39 years old [30]. These findings also showed that 7.3% of the participants with an airflow obstruction were aged over 70 years. Using the fixed ratio of FEV_1/FVC <0.7, data from *FRESH AIR Uganda* showed a lower prevalence of airflow obstruction of 12.5% (44% women), of whom only 17% of men and 25% of women were 30–39 years old; 36% of the participants with airflow obstruction were over 70 years of age. The fixed ratio for defining airway obstruction would have missed many of the younger adults with airflow obstruction and falsely identify elderly subjects as having an obstructive lung disease. The GLI has provided us with a worldwide diagnostic standard using the LLN as criterion, free of bias due to age, height, gender and ethnic group, and making it possible to identify (globally) younger people with airflow obstruction. Only then can the true burden of COPD in LMICs be understood.

In contrast with the FEV_1 and FVC, which are affected by race and ethnic origin, the FEV_1/FVC ratio is generally independent of ethnic origin and therefore does not require specific reference values [65,66]. Unfortunately, reference values for sub-Saharan Africa do not exist and underlines the urgent need to derive reference values equations and thus the severity of airflow limitation.

3. The challenge for healthy lungs in sub-Saharan Africa

3.1. Risk factors of COPD

In recent years, more understanding has been developed in the significance of early origins of COPD [67]. In normal lung development, airway branching is complete by the first trimester of pregnancy [19]. Alveoli develop by a different process and are present at birth, increasing during childhood [68]. Lung volume and airflow continue to increase as the thorax grows; lung growth ceases in young adulthood (by the end of adolescence in women and around the mid-20s in men), and lung function remains constant for about 10 years (plateau phase); after that lung function slowly decreases [19,68,69]. When a pregnant woman is cooking with biomass fuels, the exposure to biomass smoke affects the unborn: this is associated with low birth weight, reduced lung function soon after birth, and pre-term births [14,70]. It is known that other early-life events leading to low birth weight increase the risk of developing COPD [70]. Thereafter, young children are exposed to these high levels of biomass smoke in the first years of their lives, as they remain close to their mother during cooking (infants are often carried on the mother's back), causing poor lung growth and reduced lung development during childhood [70]. Biomass smoke also induces respiratory infections among young children, strongly associated with a decline in lung function in later life [71]. Exposure in children to household air pollution accounts for more than half of deaths to childhood pneumonia in children under 5 years of age [54,58]. The children are also exposed to other risk factors, such as childhood asthma, occupational exposure, second-hand smoking, poor nutrition and the use of kerosene lamps (e.g. to do their homework). The reduced lung function continues during life and could result in a lower plateau at young adulthood, having a lasting effect into adulthood and, thus, substantially increasing COPD risk [69]. Most recently, it was highlighted that low lung function in early adulthood is associated with an increased prevalence and earlier incidence of cardiovascular and metabolic comorbidities [72].

The adult is exposed to a combination of traditional and less traditional factors for the development of COPD, including: occupational exposures, agricultural smoke, indoor biomass smoke, cigarette smoking, second-hand smoking, kerosene lamps, and outdoor air pollution. Tobacco smoke also potentiates the detrimental effect of biomass smoke. There is an inverse relationship between socioeconomic status and male smoking prevalence: in the poorest households, about 10% of the household expenditure goes to tobacco use [73,74]. Ambient air pollution is a growing problem, especially in the urban areas of many LMICs, mainly caused by vehicle emission, industrial facilities and diesel generators, as it is linked to rising industrial expansion, and causing a major threat to human health [75,76]. In summary, communities in sub-Saharan Africa are not only lifelong exposed to biomass smoke and tobacco smoking, but also to a variety of other risk factors for the development of COPD.

Population attributable fraction (PAF) or the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario, has not been measured by any of the studies mentioned in our paper. Studies measuring PAF would be very welcome in order to understand the proportional attribution of risk factors in developing COPD in both rural and urban circumstances.

3.2. Socioeconomic status as a risk factor for the development of COPD

Socioeconomic factors (such as poverty) are associated with poor access to health care, poor nutrition, low birth weight,

exposure to indoor and outdoor air pollution, lower education, lower household income, poor living conditions and water supply/sanitation, causing ill health effects, and increasing the risk of developing COPD [13,75,77]. Nevertheless, the mechanisms of these associations remain complex [78]. Previous treatment for TB is associated with both airflow obstruction and low lung function, and gives an adjusted odd ratio for the development for COPD of more than three [79,80]. The human immunodeficiency virus (HIV) is known to be a risk factor for COPD (poorly controlled HIV infections worsen lung function [81,82]. TB and HIV are also strongly linked to poverty [83,84]. Exposures from tobacco and biomass smoke are also strongly associated with poverty and clearly have a detrimental effect on both TB and HIV, causing colliding epidemics in sub-Saharan Africa. Occupational exposures, such as respirable dusts, smoke, vapors and fumes (for both adults and children), are also emerging as important risk factors for COPD in LMICs, as there is a lack of government capacity to inspect workplaces [75,85]. Although the damaging effects of exposure to biomass smoke in early life on lung development are not yet fully described, a silent growing epidemic of COPD, starting at younger age, seems to be unfolding in sub-Saharan Africa. Health disparities will result in a high prevalence among the poorest people [13]. Therefore, prevention must start as early as possible.

Although tobacco smoke is still considered the major risk factor for the development of COPD, there is a growing understanding that the development of COPD in LMICs is often multifactorial [27]. It is known that exposure to household air pollution is associated with an increased risk of developing COPD [52]. However, the combinations of other risk factors are likely to be highly prevalent in the poor communities of sub-Saharan Africa, and may account for a greater burden of COPD [18]. The question is whether these risk factors cause a different COPD phenotype with its related treatment, the rate of decline and outcomes. Our knowledge on the pathophysiology, diagnostics, and treatment of COPD is based on extensive research on the effects of tobacco smoke on the lungs, mostly conducted in developed countries [18,58]. However, differences in characteristics have been observed between COPD from biomass smoke and COPD from tobacco smoke [57,86,87]. Patients with biomass-related COPD have more chronic bronchitis and greater hyperresponsiveness, show worse air trapping, less pulmonary emphysema, and a slower FEV_1 decline [57,87,88]. The underlying mechanisms of the pulmonary response to biomass smoke are not yet fully understood. The mechanism of TB-associated COPD is uncertain and the mechanisms behind HIV-associated COPD are unknown [18]. Thus, uncertainty still remains as to how patients in sub-Saharan Africa will respond to treatment. Therefore, in sub-Saharan Africa, more research is needed to describe, define and inform treatment approaches, and natural history of COPD.

3.3. Prevention and intervention programs

Of all the interventions, the key ones are sharing the knowledge of CRDs among physicians and other healthcare workers, and raising awareness about the health effects of tobacco smoke and biomass fuel use among the communities. The use of biomass fuel is not only determined by cultural traditions but also by socioeconomic factors, such as poverty and living conditions. The general lack of knowledge leads to failure to take simple steps to avoid exposure and to link respiratory symptoms to a smoke-related condition [53]. The nature of the communities also determines healthcare-seeking behavior – both traditional (local herbs) and western (dispensaries and health centers) – generally with a lack of successful results, and not addressing the problem of exposure [36]. As a consequence, the necessary steps to prevent the detrimental effects of smoke have never been taken. Furthermore, for low-income households, purchasing a new cooking device is generally beyond their means and, therefore, they are trapped into using biomass as their main domestic fuel. Purchasing cooking fuel is not given a priority in places where biomass fuel is collected free. However, once people are aware of the dangers of biomass and tobacco smoke, their desire to alleviate it goes up their list of priorities. The community takes ownership of both the problem and its solution, and alleviating smoke becomes a part of the normal pattern of life [89]. Therefore, community participation is essential from the start.

The key controllable factors are the reduction of tobacco smoking and improvement of air quality, which includes the reduction in second-hand tobacco smoke, smoke from biomass fuel use, smoke from kerosene lamps, and unhealthy public and workplace air. Lung health education programs offer the potential to teach people about the problem of biomass smoke exposure and allow those at greatest risk (including pregnant women and young children) to change their cooking tradition and apply behavioral changes to the exposure of household air pollution [67]. An example of a promising educational program is the *FRESH AIR* Global Bridges project in a rural district of Uganda where healthcare workers and community health workers were educated about lung health, and trained to develop educational materials for them to use in raising awareness, intervening to stop tobacco smoking and promoting other actions to improve lung health in their local communities. The community health workers are people working at village level and who offer health education on basic health issues; they have no clinical training and are often chosen by the village themselves.

A mix of these potent risk factors contributes to the high burden of poor respiratory health in more than half billion biomass-exposed individuals in sub-Saharan Africa. A number of disease processes and exposures will have to be addressed to reduce the burden of COPD in sub-Saharan Africa: reducing tobacco consumption, combatting infectious diseases (childhood lung infections, TB, and HIV), reducing outdoor and occupational pollution, reducing indoor air pollution and, most important, uplifting of socioeconomic circumstances [27,90]. Implementation of clean and efficient cooking practices (interventions at the source of the smoke, interventions directed toward the living environment, and interventions aimed at the user) may offer many health and environmental

advantages for the individual in sub-Saharan Africa: however, they should not be seen as the sole solution to prevent the development of COPD in Africa [27,56].

3.4. Conclusion

COPD is an NCD that will be more frequent in low and middle-income countries, including sub-Saharan Africa. Unfortunately, the knowledge of COPD is limited, and people are not aware of the risk factors, such as tobacco smoking and household air pollution, among others. A silent growing epidemic of COPD seems to be unfolding in sub-Saharan Africa. Reducing the burden of COPD will be an enormous challenge, and has to involve all the stakeholders, including the community.

4. Expert commentary

COPD is a neglected disease in many countries of sub-Saharan Africa: in most of the rural areas, COPD is completely unknown, both regarding public awareness and public health planning. Early detection, diagnosis, and control are limited due to inadequate knowledge and skills of the primary care health workers and physicians. Inhaled medication, influenza vaccination, oxygen therapy, pulmonary rehabilitation among others are not available or not affordable, particularly in the rural areas. Tobacco smoking interventions are commencing, although nicotine replacement therapies are scarcely available.

While studies on the effects of biomass smoke are increasing, more research is needed on the benefits of prevention and reductions in exposure at a community level. Researchers, policymakers and government, stakeholders, health professionals and communities will have to work together to control the growing burden of COPD, and start prevention and intervention programs as early as possible.

Prevention of COPD is the ultimate goal. This can be achieved to a large extent by reduction of the exposure of household air pollution and other risk factors such as tobacco smoking. This should be a major public health goal for sub-Saharan Africa, and should start early in life. Socioeconomic factors (such as poverty) are associated with poor access to health care, poor nutrition, low birth weight, exposure to indoor and outdoor air pollution, lower education, lower household income, poor living conditions and water supply/sanitation, causing ill health effects, and increasing the risk of developing COPD as well.

Apart from an improvement of socioeconomic circumstances in these countries research should be focused on implementation of preventive strategies for COPD, taking into account the massive challenges to implement these strategies in low and middle-income countries with a mainly illiterate population. Furthermore, more research is needed to describe, define and inform treatment approaches, and natural history of biomass-related COPD.

In November 2015, the inauguration of Makerere University Lung Institute (MLI) in Uganda has taken place. The MLI will act as a center of excellence for education and research into prevention, diagnosis and care of CRDs in Uganda. In the near future, the institute will act as a sub-Saharan Africa's center of excellence in lung health. This encouraging initiative may stimulate implementation research directed to low and middle-income countries.

5. Five-year view

In most low- and middle-income countries, COPD is on the rise. In the coming five years, with a growing population and increasing life expectancy in sub-Saharan Africa, COPD will become a more frequent NCD, posing a serious public health threat for the individuals, families, and communities, and a very high burden for the health system.

Effective prevention by reducing risk factors will only provide reduction of COPD prevalence after many years. Moreover, the reduction of risk factors for COPD is difficult to grasp. Recent data indicate that smoking rates are rapidly increasing in sub-Saharan Africa, particularly among the (male) youth. Household air pollution is a major public health concern, and affects the poorest and most vulnerable communities. Unfortunately, there is no 'one-size-fits-all' solution for this problem. Ambient air quality is worsening by the day because of the rapid urban transition and industrial expansion in the cities. The local authorities will need more legislative actions to minimize the exposure of unhealthy air and should facilitate the use of other affordable energy sources.

Little is known about the natural history and the response to treatment of biomass-related COPD. Sub-Saharan Africa has a great opportunity for sound scientific research to describe, define and inform treatment approaches as well as the natural history of COPD. In this regard, the establishment of the Makerere Lung Institute with a focus on capacity building for lung healthcare in primary care settings, will be a great opportunity to improve respiratory research, training and care of CRDs in sub-Saharan Africa.

New multidisciplinary approaches toward prevention must involve not only health professionals and researchers, but also health policymakers, local governmental bodies, and the communities, as well as international partners, including foundations and global health agencies.

Key issues

- COPD is a chronic disease that will continue to become more frequent with the ageing of the global population, combined with the rapidly expanding population of sub-Saharan Africa.
- COPD is a neglected disease in many countries of sub-Saharan Africa; in most of the rural areas, COPD is completely unknown, both regarding public awareness and public health planning.
- Communities in sub-Saharan Africa are not only lifelong exposed to biomass smoke and tobacco smoking, but also to a variety of other risk factors for the development of COPD, such as low birth weight, malnutrition, severe childhood respiratory infections, (untreated) asthma, occupational exposures, second-hand smoking, outdoor pollution, HIV and previous treatment of TB.

- In sub-Saharan Africa household air pollution is the biggest risk factor for the development of COPD.
- People in sub-Saharan Africa (stakeholders, policy-makers, healthcare professionals and communities) are unaware of damage to respiratory and non-respiratory health caused by tobacco and biomass smoke.
- A silent growing epidemic of COPD, starting at younger age, seems to unfold in sub-Saharan Africa.
- In sub-Saharan Africa, reference values for spirometry do not exist and underlines the urgent need to derive reference values equations and thus the severity of air flow limitation.
- It is essential to provide key policymakers in sub-Saharan Africa with convincing evidence about the prevalence and impact of COPD in local communities and the implementation of culturally appropriate interventions to control the development of COPD and its risk factors.
- In sub-Saharan Africa, more research is needed to describe, define and inform treatment approaches, and natural history of biomass-related COPD.

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ORCID

Frederik A. van Gemert http://orcid.org/0000-0002-0287-1016
Thys van der Molen http://orcid.org/0000-0002-6606-8804

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