

Review Article

The epidemiology of noncommunicable respiratory disease in sub-Saharan Africa, the Middle East, and North Africa

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Abstract

Noncommunicable diseases (NCDs) are a major and increasing global health issue. The World Health Organization (WHO) estimates that NCDs represent 63% of all global deaths of which 3.9 million are due to chronic respiratory diseases (CRDs) and Chronic Obstructive Pulmonary Disease (COPD) in particular. COPD is now the third most common cause of death globally; 90% of these deaths occur in Low and Middle Income Countries (LMICs). COPD affects 329 million people, almost 5% of the world's population. In addition, asthma affects 334 million people, again representing almost 5% of the world's population. There is limited literature published on the epidemiology of COPD and Asthma from Sub-Saharan Africa (SSA) and Middle East and North Africa (MENA). Both diseases are under-diagnosed and underestimated in both SSA and MENA regions. The burden of COPD in sub-Saharan Africa is disputed and reports offer variable prevalence estimates, ranging from 4.1% to almost 22.2%. SSA and MENA countries report similar mortality rates from COPD of 18 per 100,000 population (2001 data). Asthma is a less common cause of death than COPD but is a major cause of morbidity; WHO estimates that there are 250,000 deaths per year from asthma, mainly in LMICs and it remains in the top twenty causes of disability in children globally. Risk factors for CRD are genetic and environmental; the latter dominated by air pollution exposures including tobacco smoke, household air pollution, outdoor air pollution and occupational exposures.

Introduction

Noncommunicable diseases (NCDs) are a major and increasing global health issue. According to the Global Burden of Diseases (GDB) 2015 report, there are between 39.8 and 40.5 million deaths per year from the four main categories of NCDs, namely cardiovascular diseases, diabetes, cancer, and chronic respiratory diseases (CRDs), representing 63% of all global deaths.¹ Of these, 3.9 million were due to CRDs. In 2008, the World Health Organization (WHO) estimated that over the following decade respiratory diseases would be responsible for the largest increase in global mortality.^{2,3} Low- and middle-income countries (LMICs) shoulder 80% of the deaths from NCDs, of which an estimated 12% are due to respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD).^{1,2} Respiratory diseases also have a significant economic impact, causing 4-7% of global disability-adjusted life-years (DALYs), two-thirds of which are due to COPD and one-fifth due to asthma.¹

The impact of CRDs in the developing world is a growing problem. COPD jumped from the fourth to the third most common cause of death between 1990 and 2010.⁴⁻⁶ Ninety per cent of COPD deaths now occur in LMICs.⁷⁻¹⁰ However, in many of these countries, governments and medical professionals have not historically given CRDs the attention they deserve. We set out to review the literature on the epidemiology of CRDs in sub-Saharan Africa (SSA), the Middle East and North Africa (MENA) with a focus on asthma and COPD.

COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), established in 1998, standardised the definition of COPD as a “preventable and treatable disease categorised

by persistent airflow limitations which is mostly increasingly related and enhanced by chronic inflammatory responses of the airways and lung to harmful elements or smokes”. Despite this, varying definitions of COPD are used globally.¹¹ The ATS and ERS define COPD as a “preventable and treatable disease state characterised by airflow limitation that is not fully reversible”.¹² COPD is mainly caused by cigarette smoking and leads to symptoms of cough, excessive sputum production, and breathlessness, causing considerable disability as the illness progresses.¹³ GOLD requires COPD diagnosis to be dependent on spirometry and specifically the documentation of a post-bronchodilator ‘forced expiratory volume in one second’ (FEV1) to ‘forced vital capacity’ (FVC) ratio (FEV1/FVC) of <0.7.

Asthma

The Global Initiative for Asthma (GINA) defines asthma as “heterogeneous disease, usually characterised by chronic airway inflammation. Its defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with expiratory airflow limitation”.¹⁴ However, asthma lacks a gold standard definition with other definitions also in use. Nevertheless, bronchial hyper-responsiveness, airway inflammation, and obstruction which may be reduced spontaneously or with medication are widely accepted features.¹⁵ There can be a chronic reduction in FEV1 and peak expiratory flow (PEF), with the degree of reduction being one marker of disease severity.¹⁶

Disease management and global initiatives

Several guidelines, such as GOLD, GINA, and the ‘Allergic Rhinitis and its Impact on Asthma’ (ARIA) guidelines were developed to improve the management of CRDs.

CRDs

In 2002, the WHO developed 'The Global Strategy for the Prevention and Control of NCDs'. Clear objectives were drawn to provide better surveillance and monitor CRD trends, and lower the level of exposure to recognised risk factors. Moreover, it aimed to strengthen the available health care systems.¹⁷ In addition to general guidelines for CRDs, asthma and COPD action plans for 2013 up to 2020 were developed to follow the WHO treatment guidelines, and provide influenza vaccination for patients with COPD.^{3,18} In 2002 and 2003, the WHO conducted the World Health Survey as a standardised survey tool measure to allow comparability of diseases findings, including asthma within and between countries to inform policy in a wide range of countries.^{19,20}

COPD

In 1998, GOLD was initiated to produce recommendations for management of COPD based on best evidence and was last updated in January 2014.^{21–23,24} These guidelines stated that the use of spirometry is mandatory to diagnose COPD.^{5,21,22,24} Other guidelines for COPD definition and diagnosis have been developed including the European Respiratory Society (ERS) and ATS.^{25,26} In 2015, the ERS/ATS published an official statement of update comparing the recognised COPD diagnostic standards and recommended further study to evaluate the long-term prognosis of patients diagnosed based on different COPD definitions.¹² The BOLD initiative was established to further develop standardised methods for estimating COPD prevalence and associated risk factors in the 40 years and above population.^{27,28} In addition, it aims to measure its influence on quality of life, activity limitation, respiratory symptoms, and usage of healthcare services.^{28,29} BOLD studies have provided a solid base for assessing the economic burden of COPD by developing the 'BOLD Health Economic Model'^{27,29} and the distribution of the disease in relation to age, sex, and smoking status across a range of countries and settings.^{28,30}

Asthma

In the 1990s, GINA proposed strategies and guidelines for asthma management, and standardised the definition so it can be clearly distinguished from other respiratory diseases.³¹ In 1996, the International Union Against Tuberculosis and Lung Disease adopted these guidelines to control asthma in developing countries.³² However, as demonstrated by Ait-Khaled et al., there is a need to effectively utilise these guidelines especially in rural areas in Africa.³³

COPD and asthma disease burden

WHO estimates that COPD affects almost 329 million people (4.8% of the world's population), however it is under-recognised and undertreated in most populations.³⁴ Asthma is estimated to affect 334 million people, 4.9% of the world's population. 635 million people are reported to be living with some level of asthma-like symptoms.¹⁹

Worldwide, males and females are affected by COPD to a similar extent (4.9% and 4.7%, respectively).³⁵ The gender distribution of asthma varies with age; in childhood males are more frequently affected, however after adolescence the prevalence is higher among females.³⁶ Overall asthma is estimated to affect slightly more females than males (5.1% and 4.6%, respectively).³⁵

WHO estimates that 65 million people have moderate to severe COPD and three million people die as a direct cause
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of it annually. This corresponds to 5% of all global deaths, the majority of which occur in LMICs. Deaths from COPD are on an upward trajectory.^{37,38} The number of affected individuals with asthma is predicted to increase to 400 million by 2025.^{19,39}

In Africa, mortality from COPD was estimated to be 18.1 per 100,000 in 2001 with a similar rate, 18.3 per 100,000, seen in East Mediterranean countries.²⁶ While deaths are less commonly seen in asthma than COPD, WHO estimates that there are 250,000 deaths per year from asthma, mainly in LMICs.⁴⁰ Asthma is in the top twenty causes of disability in children globally.³³

COPD burden in SSA

The burden of COPD in SSA is disputed and reports offer variable prevalence estimates.^{41,42} Finney et al. conducted a systematic review of nine cross-sectional studies (five from South Africa, two from Nigeria, one from Malawi, and one from Cape Verde) reporting a prevalence ranging from 4.1% to 24.8%, based on the diagnostic method used.⁴³ Chan-Yeung et al. estimate a prevalence of 179 per 100,000 in Africa and 301 per 100,000 in Eastern Mediterranean countries, less than that of America and Europe.^{7,44} However, a recent systematic analysis by Adeolaye et al. reported the estimated median prevalence of COPD in persons aged 40 years or older as 13.4% (range 9.4% to 22.1%), translating into 26.3 million (18.5 to 43.4 million) cases of COPD in SSA.⁴⁵ Within the SSA region, Cape Town in South Africa had the highest prevalence estimates published within the international BOLD study, as GOLD stage II prevalence was 22.2% in men above 40 years.^{46–48}

There are several possible explanations for the variation in COPD prevalence estimates. Firstly, relevant epidemiological data is lacking because of a paucity of data from population representative samples.²⁷ Secondly, the studies that do exist are limited by the lack of a standardised definition of COPD with marked variation in the diagnostic methods used.³³ In particular, there is a widespread shortage of good quality post-bronchodilator spirometry.^{41,49} Diagnosis frequently depends on clinical judgment, and knowledge about COPD is often limited. Many people, including health workers, are not well informed about the effects of cigarette smoking and smoke from the burning of biomass fuels on their respiratory health.⁵⁰

Asthma burden in SSA

There is a similar wide variation in reported asthma prevalence in Africa. Available published data gives estimates of asthma prevalence in sub-Saharan Africa between 6 and 20%.⁵¹ The International Study of Asthma and Allergies in Childhood (ISAAC) has been the most widely used prevalence research methodology in Africa,⁴⁰ where its diagnostic criteria have been shown to be reproducible, and able to discriminate children with allergic diseases in different areas of the world.⁵² Another review reported that prevalence rates in Africa varied according to the ISAAC study results (Ethiopia 9.1%, Kenya 15.8%, Nigeria 13.0%, and South Africa 20.3%) while rural areas reported lower prevalence than urban areas.^{7,53} In 2011, Musafiri et al. reported an increase in asthma prevalence in Africa over the past two decades, with 50 million people currently living with asthma.⁵⁴ In 2013, a systematic review by Adeolaye et al. reported a similar prevalence to that of high-income countries. In 1997, the aggregated prevalence was highest in South Africa (53% of 5-12 year olds) and lowest in The Gambia (1.9% of >15 years).³³ Adeolaye et

al. estimated asthma increased in prevalence from 11.7% in 1990 to 12.8% in 2010 in the general population. This rise is further supported by the Global Burden of Asthma Report, which corroborates the highest levels being in South Africa.¹⁶ ISAAC phase three reported that Africa, the Indian sub-continent, and East Mediterranean had the highest proportion of severe asthmatics.⁵⁵

COPD burden in MENA countries

As in SSA, the burden of COPD is increasing in MENA countries. Although there is a paucity of good epidemiological data, there appears to be substantial differences in prevalence estimations between countries in the region.^{44,49} Tunisia reportedly has a prevalence of 3.8% compared to 125 per 100,000 people in Algeria and 5.6% in Lebanon.⁴⁴ A recent study from Saudi Arabia estimated COPD prevalence to be 2.4% in the general population and 14.2% among smokers (56). United Arab Emirates reports a prevalence of 3.7% in 40 to 80 year olds in Abu Dhabi.⁵⁷ The BREATHE study, a large observational population-based survey, completed in ten countries in MENA, and Pakistan, reports that the available data from the region does not represent national COPD prevalence accurately as there are infrequent community-based prevalence surveys in the region and available epidemiological data are either incomplete or restricted to small region.^{44,49,58} The estimated overall COPD adjusted prevalence according to symptoms or diagnosis and 10-pack/year smoking was 3.6%, and is higher in men than in women (5.2% and 1.8%, respectively)⁵⁸

Asthma burden in MENA countries

There is substantial variability in the reported prevalence of asthma in the MENA region. In 1998 the ISAAC study reported an overall prevalence of 16.5% in North Africa and 10.7 % in the East Mediterranean.⁴⁴ The study showed prevalence in children between 5%-12% in rural and urban Sudan, respectively,⁵⁹ and ranging from 8.8% to 9.5% in rural and urban Jordan.⁴⁴ The World Health Survey published the global asthma prevalence from 70 countries in 2012. The overall prevalence in the East Mediterranean region was 2.9%, 3.0%, and 7.9% for 'doctor diagnosed', 'clinical', and 'wheezing symptoms asthma', respectively.¹⁹ In contrast the 'Asthma Insights and Reality in the Maghreb' (AIRMAG) study reported an overall prevalence of 3.6% in the general population of Maghreb, with no significant disparity between the three countries (Algeria, Morocco, and Tunisia).^{44,60,61} Egypt reported a prevalence of 14.7% for wheezing in that year and 9.4% of physician-diagnosed asthma.⁶² There was a varying prevalence in Saudi Arabia ranging from 8% to 25% in children, with 19.6% of adolescents having doctor diagnosed asthma⁶³ and 4.1% of adults self-reporting asthma.⁶⁴ Iran also reported a similarly varying prevalence ranging from 1.4% to 5.9% in the adult population.⁶⁵

Risk factors for CRD in SSA and MENA

There are several common environmental risk factors for CRD including; tobacco smoking, household and outdoor air pollution, and exposure to dust, gases, or fumes in occupational settings.³⁶ Genetic factors are also implicated; this is beyond the scope of this review. It has, however, been recently acknowledged that for both asthma and COPD burden in LMICs, other causes are also contributing, particularly tuberculosis (TB), HIV and rapid urbanisation.

Tobacco

Tobacco smoking, alongside the aging of the population, are widely regarded as the most important risk factors for COPD globally.^{45,30,27} The WHO reports that smoking alone causes about 42% of CRD.⁶⁷ Environmental tobacco smoke exposure is a risk factor for asthma in paediatric patients.¹⁴ The rapid increase in smoking rates in LMICs reflecting the 'success' of intensive efforts by the Tobacco Industry to expand African markets will see the global prevalence of COPD increasing over coming decades.^{54,30,68,69}

The burden of tobacco use in African countries is estimated to be between 8 and 43% for men and between 5 and 30% for women.⁵⁴ COPD prevalence in current smokers in men ranges from 9.4% to 56.9%, with comparable broad ranges seen in other risk factors such as history of tuberculosis, exposure to biomass smoke, or occupational fumes.^{42,70} Smoking is also increasing in the MENA region. An epidemiological study in Turkey reported that COPD prevalence in current male smokers above 40 years of age was 18.1%, and 4.5% amongst younger smokers; 25.5% of the women and 57.2% of the men were current smokers. The rate of smoking varies greatly within the region, from 20% of men in Iran to 63% in Turkey.⁴⁴ The Burden of Obstructive Lung Disease (BOLD) study analysed COPD prevalence and mortality in association with smoking and poverty, and reports that tobacco and exposure to environmental tobacco smoke remain the greatest risk factors for airflow obstruction.⁵ However, many areas with high COPD mortality rates have a low consumption of tobacco.^{5,34} Tobacco alone, therefore, does not fully illuminate the varying prevalence globally, and other factors need to be explored in LMICs.^{5,42,50,30,71}

Household air pollution

Exposure to household air pollution from biomass fuel smoke is a recognised risk factor for CRD, particularly COPD and mostly among women.^{72,73} Biomass fuel contains material from plants or animals burnt by humans such as wood, animal dung, crop residues, and grass.⁷ It is estimated that over 80% of homes in sub-Saharan Africa and 90% of rural houses use biomass fuel.^{17,71} A Malawian study, found women and people of lower socioeconomic status in SSA are particularly affected by biomass smoke exposure.⁷⁴ In MENA countries, household air pollution from biomass fuel smoke is also considered a factor for CRD but to a lesser extent.^{26,49} The link between asthma and biomass exposure is less clear^{75,76}; however, a recent systematic review reported a relationship between these fuels and asthma symptoms.⁷⁷ In the MENA region, 25 to 45% of patients with COPD were known to have been exposed to biomass fuel and were reported non-smokers.⁴⁴ Ben Abdallah et al. estimates 54.5% of female patients in turkey's study with COPD in rural areas were exposed to biomass. The same study reports, however, that the relative risk from smoking was 3.4 times greater than biomass exposure and 3.3 times greater than occupational exposure.^{44,78}

Outdoor air pollution

Outdoor air pollution is variable, differing greatly between urban and rural environments and with the degree and nature of local industry. The main contributors to the outdoor air pollution are combination of wood smoke and vehicle exhausts⁷⁹ with higher levels of nitrogen dioxide, ozone, particulate matter and sulphur dioxide in urban areas.⁸⁰ There has been a rise in the prevalence of asthma that corresponds with increasing urbanisation over the last

three decades.⁸¹ There is evidence that high levels of vehicle emissions and living in the urban environment is correlated with the rising trend in allergic respiratory diseases.⁸⁰ Air pollution has a quantifiable impact on COPD mortality and morbidity and is also recognised to have a negative influence on lung development in children.^{38,82} Research on outdoor air pollution and CRD in SSA and MENA regions is limited, and the majority of the data in these regions is extrapolated from studies observing other risk factors.

The global population in urban areas is predicted to increase from 45% to 59% by 2025. Africa's urban population in particular is growing rapidly and predicted to increase from 40% to 56% by 2050. The impact of air pollution on CRD can therefore also be expected to increase.⁸³ Studies looking at wheezing, asthma, and COPD in Africa illustrate rural-urban gradients, with generally low levels in the villages and increasing prevalence with urbanization.^{7,84}

Occupational exposures

There is little evidence regarding the burden of asthma due to occupational exposure in LMICS, in particular Africa outside South Africa.⁸⁵ Hoy et al. estimates 15 to 20% of asthma cases are caused by occupational exposure. However, this is only valid to developed countries which have strong occupational health data.⁸⁵ Similarly, the American Thoracic Society (ATS) reported occupational exposure as the main cause of 15% of COPD and asthma and was associated with an increased mortality rate in the COPD population.⁸⁶ GINA also reported that occupational exposure can trigger asthma in 5 to 20% of adults.³¹ These findings have been replicated by a study in a 'never-smoked population' in two industrialised areas of Sweden, where 24% of the study population was found to have relevant occupational exposure.⁴ A Nigerian study reported a high prevalence of occupational asthma (6.5%) and rhinitis (78%) in woodworkers, which increased with duration of employment.⁸⁷ As reported by Finney et al., COPD was prevalent in 13.4% of South African gold miners and 33.1% of Nigerian shoe factory workers.⁴³

In the MENA region, there are variable reports regarding occupational exposure. A study from Sudan reported that 26% of miners had symptoms of chronic bronchitis and mine dust as the leading cause.^{88,89} The non-smoker BOLD study in Tunisia reported 92% of those exposed to occupational pollutants suffered from chronic bronchitis and a significant association (OR 1.87, 95%CI 1.14 - 12.86) between occupational exposure and COPD as well as having more respiratory symptoms.⁹⁰ This is further evidenced by a recent study in Dubai which showed a significant association between occupational exposure to dust and airflow limitation (OR 2.07, 95% CI 1.20 - 3.59).⁹¹

Pulmonary tuberculosis (TB)

According to the WHO stop TB partnership, there are more than 2.4 billion people infected with TB globally and 9.6 million new cases are diagnosed every year, with the majority occurring in LMICS. TB is known to cause inflammation of the airways and changes characteristic of COPD. TB patients often have airflow obstruction; studies have found a prevalence varying from 28% to 68%.^{92,93} A large study based in South Africa in 2004 reported that the strongest predictor of COPD was previous TB (OR 4.9, 95% CI 2.6 - 9.2) in men and (OR 6.6, 95% CI 3.7 - 11.9) in women, an association stronger than both smoking and biomass exposure.⁹⁴

The ISAAC study found an inverse relationship between

asthma symptom prevalence and estimated TB incidence.⁹⁵ It has been hypothesized that exposure to mycobacterium tuberculosis may reduce the risk of developing asthma through the induction of a Th1-like immune response.⁵² Research is however lacking and this requires more study.

HIV

The link between HIV and chronic respiratory disease is unclear, however in both children and adults, HIV patients are reported to have a higher risk of respiratory disease.^{96,97} Countries with a high reported prevalence of HIV also have high reported prevalence of asthma⁷ and children with HIV on anti-retroviral therapy have more recurrent wheeze.⁹⁶ Similarly, a study in Cameroon reported a positive association between COPD and HIV infection (OR 2.85, CI 1.20-6.74, $p=0.017$). This study found a COPD prevalence of 2.2% in HIV positive patients compared to 0.7% in HIV negative participants. It did, however, note the main determinants of COPD to be TB, weight and chronic respiratory symptoms.⁶⁶ Similar studies in South Africa and Nigeria have also found an association between HIV and airflow obstruction.⁹⁶ The pathophysiology of the link between obstructive lung disease and HIV is not understood but thought to involve the development of lung inflammation and a low lung diffusing capacity.⁹⁷ A rapid decline in lung function, obliterative bronchiolitis and severe airflow limitation in children with HIV has also been reported.⁹⁶

Socioeconomic status

Poor socioeconomic status is an independent risk factor for COPD and there is a significant correlation with lung function even after adjustment for smoking, occupational exposure and ethnicity.^{71,98} The interplay of several risk factors is complex but thought to include low birth weight, recurrent respiratory infections, poor nutrition, housing conditions and air pollution.⁹⁹ A similar pattern of exposure to risk factors and an impact on health care access may also influence the development of asthma. A study by Pallasaho et al. in Finland, Sweden and Estonia interviewed 44,483 participants and reported a significant link between low socio-economic status and asthma-like symptoms.¹⁰⁰ These issues need to be further explored in SSA and MENA.

Chronic asthma

Chronic airway inflammation and obstruction from uncontrolled asthma has been hypothesized as a cause of lung re-modelling, leading to fibrosis and the irreversible airflow obstruction of COPD.¹⁵ Globally the increasing prevalence and on going lack of access to effective treatment (such as inhaled corticosteroids) will likely be contributing to the development of COPD in asthma patients.

Other risk factors that have been implicated globally for asthma

Allergen inhalation

Indoor allergens such as house dust, cockroach and hairy pets can sensitize asthmatic patients and are considered important risk factors for the emergence of the disease in SSA.^{101,89} The risk of developing asthma is higher in children than in adults.¹⁰¹ In polluted urban areas, the prevalence of allergic respiratory diseases could be increased by exposure to inhaled allergens, which foster the airway sensitization and cause a more severe immunoglobulin mediated reaction to further aeroallergens and airway inflammation.⁸² A rapid asthmatic reaction can be triggered by allergen inhalation. These create immunoglobulin mediated mast

cell degranulation and downstream inflammation and also a late asthmatic reaction, including activation of T-helper 2 lymphocytes.¹⁰² In many African countries, asthma and allergic sensitization are becoming more widespread, a trend supported by studies in Ghana, Kenya, Ethiopia and Rwanda. This rising tendency is mostly associated to sensitization to house dust mite, tobacco smoking, and living in urbanised areas.¹⁰³ Other specific allergic sensitizers in Africa are span trees, grasses, and weeds as well as airborne mould spores. In MENA countries, increased asthma prevalence has been shown to be associated with increased rates of sandstorms.¹⁰³

Infections

In SSA, the incidence of acute respiratory infections is one of the highest in the world. Household air pollution is considered to be a risk factor for acute respiratory tract infections in children, which in turn may increase the risk of asthma.²⁶ Several viral infections can progress to asthma in children by causing wheezy bronchitis.¹⁰² Children who experience severe respiratory infections in early childhood have up to a 50% risk of developing asthma in subsequent years of childhood and COPD in future life.^{101,104}

Other important factors implicated in asthma include drugs, exercise and diet. In particular cow's milk, egg, nuts, fish, and shellfish are the most allergenic foods, causing an IgE-mediated reaction.^{101,102} About 40% of allergic children have asthma and 30% will have allergic rhinitis.¹⁰¹ Food induced asthma appears to be less frequent in SSA than in the developed world although data are limited.¹⁰² In a Zimbabwean study, tropical dietary lifestyles considered a probable cause of allergen sensitization in Africa included grains, plants, fruits and even insects.¹⁰³

Conclusions

CRD is a very real present and growing problem across SSA and the MENA region. There is, however, limited epidemiological evidence currently representing an important gap in the evidence base and need for further research. Across both regions, asthma and COPD are likely to be under-estimated, under-diagnosed, under-treated as well as inadequately prevented.^{7,51,105} Although there have been many global strategies for management and control put forward, the implementation of these guidelines is limited and is logistically challenging, especially in LMICs. In these areas, which are facing threats from the tobacco epidemic, household and outdoor air pollution and urbanisation, there is often limited adoption of international guidelines within resource-limited health systems. There are important challenges regarding the lack of diagnostic equipment, treatment and trained and experienced health care providers which need to be addressed through strengthening of health systems.^{89,106}

Competing interests

All authors declare that they have no competing interests related to this work.

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