Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries

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Demographic and epidemiological transitions are changing the age structure of the population and the most common diseases. Non-communicable respiratory diseases are an increasing problem at both ends of the age range in low-income and middle-income countries. In children, who represent a large proportion of the total population, the increasing problem of asthma is a strain on health services. Improved survival of the older population is increasing the proportion of morbidity and mortality attributable to chronic lung diseases. Health services in low-resource countries are poorly adapted to treating chronic diseases. Designed to respond episodically to acute disease, almost all historical investment has focused on infectious diseases. Crucial to the successful management of chronic diseases is an infrastructure designed to support pro-active management, providing not only an accurate diagnosis, but also a secure supply of cost effective drugs at an affordable price. The absence of such an infrastructure in many countries and the market failure that makes drugs generally more expensive in low-resource regions means that many people with chronic non-communicable lung diseases are not given effective treatment. This has damaging economic consequences. The common causes of poor lung health in low-income countries are not the same as those in richer countries, and there is a need to study why they are so common and how best to manage them.

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Introduction

With the reduction of deaths from many common infectious diseases and the related improvement in life expectancy, the worldwide burden from non-communicable diseases (NCDs) is increasing. Respiratory diseases constitute a major proportion of the burden of NCDs in both children and adults.

The main non-communicable lung diseases are generally classified as either obstructive or restrictive. Obstructive disease is classified as reversible (asthma) and irreversible (chronic obstructive lung disease), although the distinction might be less clear in practice. The restrictive respiratory diseases are generally rare, but the prevalence of a low forced vital capacity (FVC) without a specific diagnosis is very common in some countries and might be associated with high mortality. Malignancies of the lower respiratory tract are now ranked the fifth most common cause of death worldwide after ischaemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), and lower respiratory tract infections. Other causes of chronic lung disease, such as bronchiectasis, are generally less well documented and are rare or of clinical significance only in particular regions. This Review will focus on asthma and COPD as the most common respiratory NCDs.

Respiratory NCDs need continuity in the delivery of care, which includes both access to health care and a reliable supply of accessible and affordable drugs. Continuity of health-care delivery is difficult to achieve in many low-income and middle-income countries (LMICs), where health care is still designed largely to cope with episodic illness.

Childhood asthma

Children constitute a greater proportion of the population in LMICs than in high-income countries, and childhood chronic respiratory diseases impose a large burden on health services. However, accurate diagnosis of childhood asthma can be difficult in these settings because asthma symptoms are not easily expressed in a local language,

Key messages

- With the increase in size of the older population and the rapid decline in some other causes of poor health, non-communicable respiratory diseases are becoming relatively more important; chronic obstructive pulmonary disease is now the third most common cause of death and asthma is the most common non-communicable disease in children worldwide
- Little is known about the epidemiology of non-communicable respiratory disease in low-income countries, but this is markedly different from high-income countries and strongly influenced by environmental factors, including material deprivation
- Unlike the other four non-communicable diseases prioritised by WHO's Global Monitoring Framework, no target has been set for non-communicable respiratory diseases
- Both affordability and availability of drugs vary widely, with absolute costs and costs relative to wages being highest in low-income and middle-income countries; the Asthma Drug Facility, the principal initiative aimed at improving purchasing standards, has been abandoned and not yet replaced

access to health care may be poor, and testing of lung function may not be available.[1] Questionnaire-based studies must be interpreted with caution because they often rely on an understanding of words like "wheezing" or "asthma" and are prone to recall bias.[1]

Despite these limitations, the International Study of Asthma and Allergies in Childhood (ISAAC) has provided the most reliable worldwide comparative data for the prevalence of asthma and other allergic conditions in children, using standard written and video-presented questionnaires. ISAAC Phase One (ISAAC-1) and ISAAC Phase Three (ISAAC-3) studies using identical questionnaires were carried out about 7 years apart.

The prevalence of current asthma worldwide, according to reported symptoms in ISAAC-3[2] in children aged 6–7 years and 13–14 years, was 11·5% and 14·1%, respectively. However, wide variability in the prevalence and severity of asthma between regions was found (table 1). Even within countries, and in some cases within cities, there was substantial variability in prevalence rates.[2–6] The reported association between asthma and per capita gross national income has varied widely, with studies reporting an inverse association, no association, or a modest positive association.[2,7,8] These ecological associations do not necessarily imply a direct causal association between poverty and asthma, and in several sites in LMICs, the prevalence of asthma was similar to that in high-income countries.[2–4,6] For example, analysis of the prevalence of asthma in African children found that the prevalence in 13–14 year old children was higher than the worldwide average,[5,6] whereas in children in Latin American countries, the prevalence was substantially higher than the average in both 6–7 and 13–14 year old children (table 1).[9] The prevalence of childhood asthma in several LMICs is increasing, by contrast with that in many high-income settings, where prevalence has stabilised or is decreasing.[3,4]

Results of studies have shown consistently higher asthma prevalence in urban settings than in rural settings in LMICs,[10–14] and urban populations in LMICs are predicted to expand rapidly in the next decades. Furthermore, children in LMICs with asthma have more severe symptoms than children with asthma in high-income countries, which might relate to factors such as absence of diagnosis, access to care, affordability of therapy, environmental irritants, genetic susceptibility to severe disease, or a combination of these.[15] In many LMICs, about 50% of children who reported asthma in ISAAC-3 had severe symptoms, and more than 30% of children with severe asthma symptoms had never been diagnosed with asthma.[15] More than 80% of asthma-related deaths worldwide occur in LMICs, suggesting that absence of appropriate diagnosis, treatment, or access to care are important considerations in these areas.[1]

Significant differences exist between the epidemiology of asthma in low-income and high-income settings. For instance, unlike in high-income countries, there is no evidence that rural life and exposure to bacteria in low-income countries reduce the risk of sensitisation, as assessed by specific IgE,[14,16,17] but rural children in low-income countries are less likely to have positive skin tests and atopic symptoms. Positive skin tests and asthma symptoms are associated with greater body-mass index[14] and independently with the quality of diet.[18] Further research, particularly in LMIC settings with transitioning populations, is needed to investigate the factors associated with asthma inception and exacerbations so as to develop novel and improved preventative and management strategies.

	6–7 years			13–14 years		
	N	n	%	N	n	%
Africa	5865	589	10·0	66 308	10 168	15·3%
Asia-Pacific	59 979	5719	9·5	99 634	8731	8·7%
Eastern Mediterranean	40 573	3824	9·4	51 705	4801	9·2%
Indian sub-continent	50 092	3392	6·8	55 783	3884	7·0%
Latin America	93 774	16 256	17·3	165 900	26 350	15·9%
North America	4012	767	19·1	141 009	30 427	21·6%
Northern and eastern Europe	42 548	3715	8·7	72 057	7009	9·7%
Oceania	13 888	3020	21·7	36 299	6301	17·4%
Western Europe	77 722	7487	9·6	107 673	15 483	14·4%
Global total	388 811	44 799	11·5	798 685	112 630	14·1%

N=sample size. n=number of symptomatic children.

Table 1: **Prevalence of asthma symptoms by world region in children age 6–7 years and 13–14 years (International Study of Asthma and Allergies in Childhood Phase 3)[2]**

Asthma in adults

Mortality from asthma rises exponentially with age and predominantly occurs in later adult life. Worldwide, about 346 000 people died from asthma in 2010, and this represented a 42% decrease in age-adjusted mortality rates over 20 years since 1990,[19] although this decrease in age-adjusted mortality was offset by the ageing of the population. Asthma ranks 42nd in the causes of years of life lost, but is relatively more important in many low-income and middle-income regions, including Oceania (16th), south-east Asia (25th), south Asia (26th), Middle East and North Africa (30th), and most of the regions of sub-Saharan Africa.

There is much less information about the prevalence of asthma in adults in LMICs compared with children, and the only consistent source using a standard method is the World Health Survey,[20] which used questions based on those used in the European Community Respiratory Health Survey to assess the prevalence of wheeze and diagnosed asthma. Mean prevalence was lowest in middle-income countries (gross national income US$3000–8000 per year), although the countries with the lowest gross national income had a smaller range of prevalence than the middle-income countries. Because asthma begins early in life, it contributes substantially to

the loss of life in full health. It ranks as the 28th most common cause of disability-adjusted years of life lost, but 8th in Oceania (Fiji, Kiribati, Marshall Islands, Micronesia, Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu).[21]

Asthma in adults is an increasing burden on health services in LMICs, with many patients being seen in emergency rooms, with no continuity of care and very poor management compared with current guidelines. Suboptimal treatment causes substantial loss of earnings and productivity. Of those patients who receive less than the recommended dose of inhaled steroids, 47% of those seen in the emergency rooms in one study had missed work at least 1 day each week for the previous 4 weeks, compared with 18% of those who were taking the recommended dose.[22]

The high and increasing burden from asthma in low-income populations in adults is probably related to both increasing prevalence and poor control. As with children, the prevalence could be increasing with migration to urban areas. The mechanism behind this change is not understood, but it is probably not related to pollution, which can be very high in populations with little or no asthma.[23] As in children, in addition to increasing prevalence, severity of disease is also higher in adults in low-income settings. This, in turn, might indicate poor access to care,[22] under diagnosis, or low availability of inhaled asthma controller or reliever therapy, but might also indicate increased vulnerability and exposure to risk factors.

COPD

Worldwide mortality from COPD was about eight times more common in 2010 than mortality from asthma after adjustment for age.[19] Age-adjusted mortality rates from COPD fell by about 43% between 1990 and 2010, although this was largely offset by the increasing age of the population. COPD now ranks as the third most common cause of death in east Asia and the fifth most common cause of death in south Asia. COPD mortality is most common in low-resource regions and is particularly high in countries with a yearly gross national income of less than US$20 000 per capita (figure 1).[24]

COPD is generally defined by measures of chronic airflow obstruction (post-bronchodilator forced expiratory volume in 1 s/FVC). However, well standardised data have been difficult to obtain, particularly from low-resource areas.[25] Now the Burden of Obstructive Lung Disease (BOLD) and the Latin American Project for Research in Pulmonary Obstruction (PLATINO) studies have provided standardised information using the same protocol.[26,27]

Smoking is the strongest risk factor for chronic airflow obstruction in LMICs.[27–30] Other independent risk factors identified in both a large Chinese study based on the BOLD protocol (Chinese Epidemiological Survey of COPD)[29] and in the international BOLD study[30] include male sex, increasing age, poor education, a family history of respiratory disease, and a history of childhood respiratory problems. The Chinese Epidemiological Survey of COPD also found an association with biomass use, although this association was not found in the BOLD study[30] or in the even larger Kedourie cohort in China.[31] A consistent association between a history of tuberculosis and chronic airflow obstruction could not be explained by a common exposure to cigarette smoking.[30,32,33] Zhong and colleagues[29] reported a small

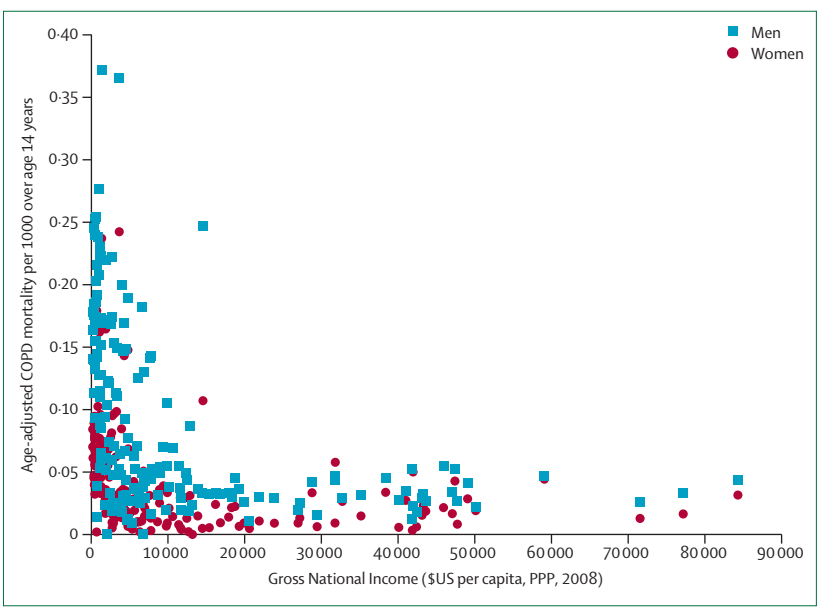

Figure 1: **National COPD mortality (age 15+ years) by gross national income and sex[24]**
COPD=chronic obstructive pulmonary disease. PPP=purchasing power parity.

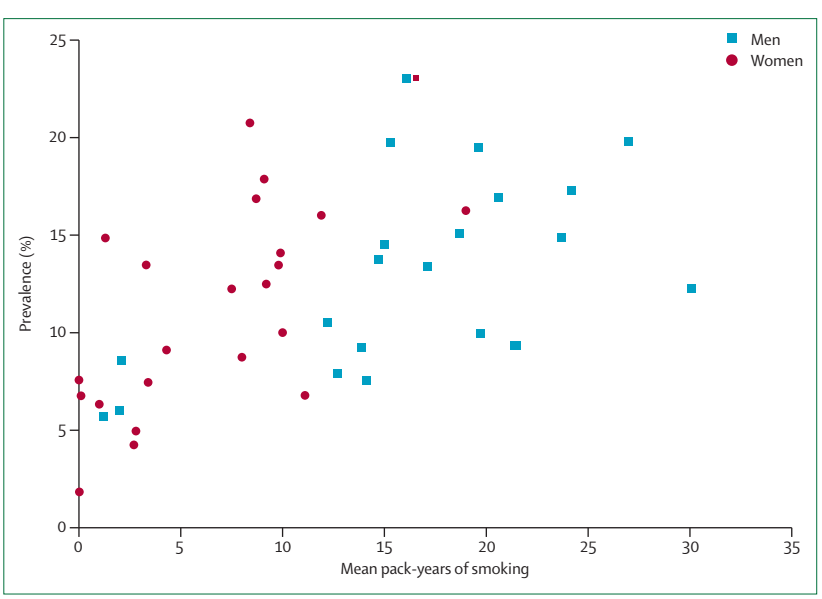

Figure 2: **Prevalence of chronic airflow obstruction (FEV1/FVC < lower limit of normal) in the BOLD study sites by mean pack-years smoked[24]**
FEV1=forced expiratory volume in 1 s. FVC= forced vital capacity.

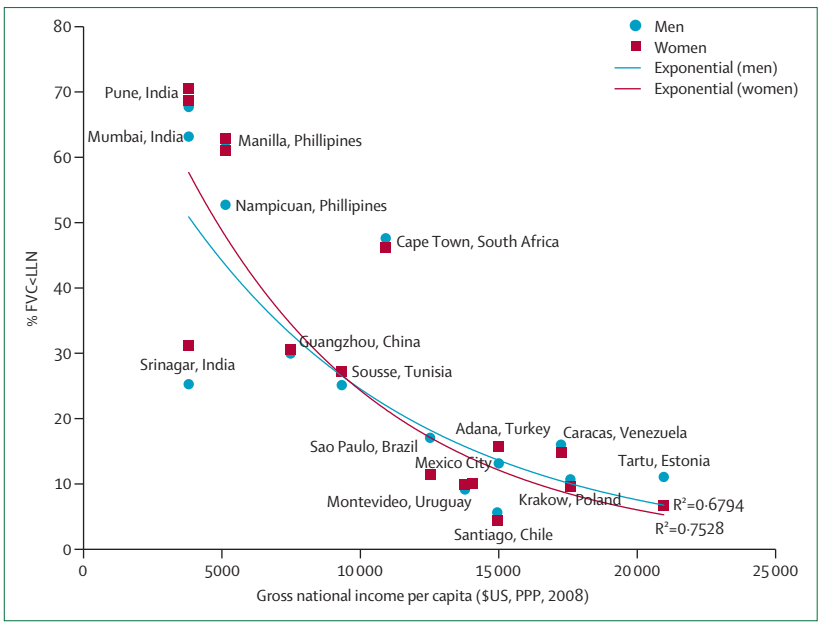

Figure 3: **Prevalence of low FVC (less than the lower limit of normal for white Americans) by gross national income per capita in US dollars, adjusted for purchasing power parity in the BOLD and PLATINO sites in low-income and middle-income countries[27,30]**

FVC=forced vital capacity. LLN=lower limit of normal. PPP= purchasing power parity.

but significant association between chronic airflow obstruction and occupational exposure to dusts, gas, or vapours (OR 1·2; 95% CI 1·04–1·39). Hooper and colleagues[30] were unable to replicate this finding, but reported an association between chronic airflow obstruction and the number of years exposed to dust in the workplace.

Taken together, the results from the BOLD and the PLATINO studies in LMICs show an association between the prevalence of chronic airflow obstruction and the mean pack-years smoked in the population, although there is substantial variation in prevalence that is not explained by smoking habits (figure 2).[24] Analyses combining information about exposure to different particle sources, including ambient air pollution, passive smoking, active smoking, and household air pollution, provide consistent evidence of a similar effect on the risk of COPD from all sources.[34] However, apart from the negative findings from very large studies, such as the Kedourie cohort,[31] many low-income areas with reliance on biomass and coal, such as Pune in India, have a very low prevalence of obstruction in both men and women.[24] The prevalent view that household air pollution is a major cause of the excess prevalence of chronic airflow obstruction in non-smokers in low-income countries needs further investigation.

Because COPD is unreliably diagnosed and reported, knowledge of its prevalence depends on population surveys. These have been uncommon, and the few studies that exist generally reported symptoms only. Relatively few studies have reported results from spirometry,[35,36] and for those studies where spirometry was used, methods of reporting have been very variable, making comparisons difficult.[25] A change in this situation will need substantial investment in infrastructure,[36] and little priority has been given to the area of chronic lung diseases. The first attempt to obtain high quality and well standardised spirometry from all regions worldwide is only now reaching completion.[26,27]

Restrictive lung disease

The finding of a high mortality from COPD in poor regions, such as south and south-east Asia, east Asia, and sub-Saharan Africa,[19] where the intensity of tobacco use[37] and the prevalence of chronic airflow obstruction[24] are generally low, needs some alternative explanation. In the USA, FVC and total lung capacity are more powerful predictors of mortality in the general population than airflow obstruction.[38–40] In the BOLD and PLATINO studies,[26,27] the prevalence of a low FVC is strongly correlated with the gross national income per capita (figure 3), although there seems to be a threshold effect that only begins when the gross national income falls below around US$20 000 per year.[24]

The causes of the low FVC found in low-resource regions are largely unexamined. A consistent association between low FVC and low birthweight has also been reported from low-income countries.[41,42] Evidence from family studies strongly suggests that around 50% of the variance in lung volumes can be explained by inheritance,[43] but so far very little of this variance has been explained by specific genetic polymorphisms. To evaluate the separate contributions of genetics and social conditions to lung volumes will need improved understanding of the genetic determinants of lung volumes. Nevertheless, the association between FVC and mortality seems to be the same for both white and African Americans; whatever the explanation for the low FVC in African Americans is, the condition is not benign.[44]

Low FVC discussed above needs to be distinguished from the relatively small number of cases of the more clearly recognised restrictive lung diseases. Restrictive lung diseases are a mixed group of conditions associated with exposure to occupational dusts, particularly silica dusts and asbestos, or several systemic inflammatory conditions that might affect the lungs. Although these disorders mostly have a poor prognosis, they are rare, and mortality rates (1·7 per 100 000 per year in 2010) are low compared with COPD (43·8 per 100 000 per year).[19] Restrictive lung diseases are, however, the only category of chronic respiratory disease for which the age-standardised rates might be increasing rather than falling.[19]

The burden of disease

In the past two decades, an improved understanding about the distribution of chronic lung disease in LMICs has been reached. In urbanising societies, asthma is a common cause of disability in childhood, and in ageing

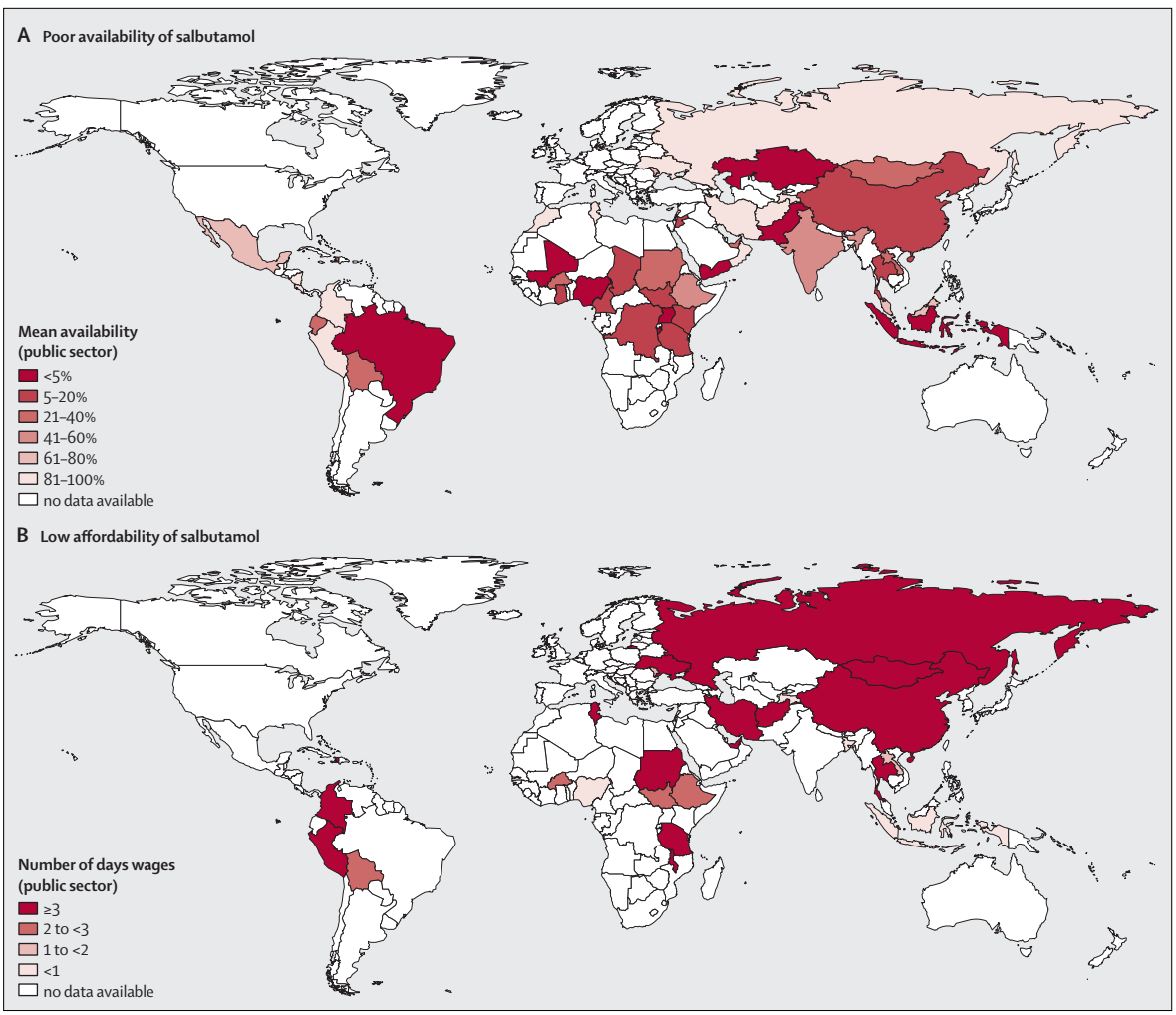

Figure 4: **Maps showing countries in which there is poor availability or low affordability of inhaled salbutamol in public health facilities**[53]

societies, COPD is now the third most common cause of death and an important cause of disability. Beyond this, still very little is known about the epidemiology of these conditions in low-income countries. There are important differences in the risk factors for atopic disease in low-income and high-income settings, but these have been explored almost entirely in high-income countries. As more has been learnt about chronic diseases in low-income countries, discrepancies have emerged between commonly held assumptions and observed facts. High levels of sensitisation to allergens in rural areas are not matched by high levels of atopic disease and are found despite high exposure to bacteria. The high recorded mortality from COPD in low-income countries is at odds with the low prevalence of chronic airway obstruction and the low consumption of tobacco. To understand the emerging epidemic in LMICs, more research is needed.

A major obstacle to both understanding of the burden of disease and identification and management of patients is the poor access to diagnostic technology in low-resource regions. Accurate diagnosis of airway disease needs at least spirometry, and this is not available in most primary or even secondary care settings. Diagnosis is therefore necessarily based on symptoms, and is therefore prone to both substantial false-positive and false-negative results. Some suggestions to improve this situation are based on low cost technology,[45] but implementation is inappropriate without improvement of access to appropriate care.

Access to drugs for non-communicable respiratory diseases

Following the UN High Level Meeting on NCD in September, 2011, WHO developed the Global Monitoring Framework for the implementation of measures to prevent and control NCDs.[46] This framework includes nine general NCD targets, with the overall goal of a 25% relative reduction in premature mortality from NCDs by 2025. One of these targets is to achieve "80% availability of the affordable basic technologies and

essential medicines, including generics, required to treat major NCDs in both public and private facilities."[46]

The concept of essential medicines emerged from WHO in 1975 with the objective of providing a limited range of carefully selected drugs that are viewed as indispensable. This concept led to improved health care, improved drug management, and reduced overall costs. Essential medicines are defined as those that satisfy the priority health-care needs of the population and are selected with respect to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness.[47] For non-communicable respiratory diseases, the present WHO Essential Medicines List (EML) includes beclometasone (aerosol), budesonide (aerosol), epinephrine (injection), ipratropium bromide (aerosol), and salbutamol (aerosol, injection, and respirator solution for nebulisers). However, some drugs that might be essential for management of acute asthma and for effective control, including oral corticosteroids, oxygen, and spacer devices, are not included on the WHO EML. Although several cancer drugs that can be used to treat lung disease are also present on the WHO EML, the present version does not include the most recent treatments for lung cancer. This might be addressed in the planned revision of the section on cancer in the WHO EML in 2015. Oxygen for the management of hypoxia in severe disease is not included in the WHO EML because this list focuses on drugs, but this technology is included in the Package of Essential Non-communicable disease interventions for primary health care in low income countries.[48] Nicotine replacement therapy, in the form of nicotine gums and patches, was added to the WHO EML in 2009. The inclusion of these elements for the management of chronic respiratory diseases in different guidelines from WHO emphasises the availability of efficacious, safe, and cost-effective interventions. Data for cost-effectiveness for all these drugs in LMICs are scarce, but Stanciole and colleagues[49] built a model of cost-effective strategies for COPD and asthma in sub-Saharan Africa and Asia, which showed that the use of low-dose inhaled corticosteroids for mild persistent asthma was cost-effective, with an average cost per DALY of INT$2500.

For the **WHO Essential Medicines List**, see http://www.who.int/medicines/publications/essentialmedicines/en/

Panel: Use of long-acting β_2 agonists in low-income and middle-income countries (LMICs)

In LMICs, where pharmacovigilance capacities and training of health staff for proper asthma care are almost non-existent, there is a reasonable fear that issues faced during the introduction of long-acting β_2 agonists in high-income countries might lead to safety concerns. The US Food and Drug Administration has raised the issue of severe exacerbation of asthma symptoms in some patients with asthma who use long-acting β_2 agonists compared with patients who do not.[57] This explains why institutions, such as the International Union Against Tuberculosis and Lung Disease, which provide technical support in LMICs for chronic respiratory diseases, recommend the use of quality-assured single inhalers. The Global Asthma Network has taken a similar approach. Pilot projects introducing long-acting β_2 agonists in LMICs are under consideration by several entities so national asthma guidelines and health staff training can be developed to allow a smooth transition to long-acting β_2 agonists. While no reports are available on the issue, it is not yet appropriate to refer to the need for long-acting β_2 agonists in LMICs.

An additional problem for long-acting β_2 agonists and long-acting muscarinic antagonists is their unaffordable prices for most patients with asthma in LMICs. Mostly novel, long-acting β_2 agonists and long-acting muscarinic antagonists are marketed in LMICs, with prices approaching a yearly treatment cost that is 10 times higher compared with single inhalers. The first generic quality-assured long-acting β_2 agonists and long-acting muscarinic antagonists are just beginning to be filed for registration. It will take some time before affordable long-acting β_2 agonists and long-acting muscarinic antagonists become available.

More information about safety, appropriate guidelines, training, and how new drugs can be made affordable are needed in LMICs before the introduction of a new drug.

The responsibility for assessing the quality, safety, and efficacy of available drugs, whether originator brands or generic products, relies on national medicine regulatory agencies. Inhalers are among the most complex medical devices manufactured by the pharmaceutical industry and, consequently, it is difficult to guarantee that inhalers reliably deliver a known dose of active drug to the lower airway. This poses a problem in terms of capacity of the national medicine regulatory agencies to ensure the quality of the drugs dispensed and renders access to quality-assured inhalers on the international market uneven.[50]

The Global Monitoring Framework target on drugs summarises availability and affordability as the barriers to access for essential medicines.[51] Availability is the presence of the drug when the person needing it goes to a facility or pharmacy to gain access to it. Affordability is the absence of a financial barrier to an available drug. Ideally, drugs should be widely available and affordable (if not provided for free) to all, but for this to be possible, various factors need to be met at both international and national levels.[51] Most data for the availability and affordability of drugs for chronic respiratory diseases in LMICs focuses on the use of beclometasone and salbutamol for patients with asthma.

Availability of drugs for respiratory NCDs

Much overlap exists in the drugs used to treat asthma and COPD. In 36 countries surveyed in different WHO Regions,[52] the mean availability of the generic salbutamol 0·1 mg/dose inhaler was 29% in the public sector and 61% in the private sector. Mean availability was lowest in

the public sector in the WHO southeast Asian region at 5% (range 0–30%; figure 4). This low availability was also found in another study[50] in 52 LMICs, with availability in public hospitals of generic beclometasone 100 mg/puff being 19% and that of generic budesonide being 16%. In the Hubei province in China, beclometasone was not available in the public or private sectors.[54] The availability of beclometasone inhalers was also poor in the private sector (10–65%) in four Indian states.[55] However, the availability of salbutamol inhalers ranged from 20% to 95% for innovator brands and 83% to 100% for the generic versions. In a study[56] of eight countries, four countries could not provide ipratropium inhalers, a key treatment for COPD which should be available at primary health-care centres. The highest availability was found in Sri Lanka, but only 30% of facilities were able to provide this drug.[56]

The appropriateness of using newer medications, including longer-acting medications, in low-income and middle-income settings requires further investigation (panel). Spacer devices are essential for children given asthma treatment through a metered dose inhaler for prevention and treatment of acute exacerbations.[58] Spacers should therefore be regarded as part of the essential requirements for delivery of appropriate asthma care for children. However, commercially produced spacer devices might be unaffordable or unavailable in many LMICs. A low cost, homemade spacer made from a 500 mL plastic soda bottle has been shown to be effective for children with asthma.[59]

Affordability of drugs for respiratory NCDs

A 1 month combination asthma treatment for a lowest-paid government worker ranged in price from 0·3 days' wages in Bangladesh to 9·2 days' wages in Malawi (figure 4).[52] In India, one inhaler of salbutamol and one inhaler of beclometasone costs 1·6–2·3 days' wages for a lowest-paid government worker.[55] In this study, Kotwani and colleagues noted that 80% of the population earn less than this amount each day. Availability of these drugs in different sectors (public *vs* private) and presentations (originator brand *vs* branded generic *vs* generic) also has an effect on affordability.

In Bangladesh's private sector, a lowest-paid government worker would need to spend 1·3 days' wages for 1 month of treatment, compared with 9·2 days' wages in Malawi, 5·4 in Nepal, 2·5 in Pakistan, and 2·3 in Sri Lanka.[60] In Brazil, a 30 day treatment for asthma with an originator brand drug (salbutamol inhaler) would cost 2·1 days' wage compared with 1·6 days' wage for the branded generic drug.[61] Cameron and colleagues[52] emphasise the differences in affordability in different sectors and for different presentations in various WHO regions (table 2). In Africa, for example, a course of originator brand salbutamol would cost a lowest-paid government worker 4·4 days' wages in the private sector, whereas the cheapest generic brand drug would cost 2·5 days' wages in the private sector and 1·6 days' wages in the public sector. If the drugs were not available in the public sector, the cost to the patient would increase by 1·6–2·8 times.

Babar and colleagues[50] reported that in 40% of the 52 countries they studied, it cost an individual more than 1 day of work to purchase a standard monthly course of generic salbutamol from a private sector pharmacy, and more than 4·5 days' wages in several other countries. A single beclometasone 100 mg inhaler cost between about a half day's wages in Afghanistan and almost 14 days' wages in Madagascar. The cost of a budesonide inhaler ranged from half a day's wages in Jordan to 107 days' wages in Guinea. No data for affordability of ipratropium inhalers was found in the scientific literature.

What are the causes of poor availability and affordability?

The median number of drugs included on the national EMLs for COPD and asthma in LMICs is seven (range 0–22),[62] and these are not always the same drugs as listed on the WHO EML. The authors of the Global Asthma Report[63] also found that rather than using drugs with proven cost benefit, such as inhaled corticosteroids, which are included on the WHO EML, prescribers often selected other less effective drugs. According to the Global Asthma Report,[63] only 12% of children with asthma and 10% of adults with asthma were treated according to international guidance. Additionally, pharmaceutical funding was used to develop asthma guidelines for children in 15% of countries and for adults in 19% of countries surveyed.

In explaining high prices for these drugs, one element to consider is the purchasing price against some international price standard. The median price ratio is the ratio of the price of a local drug to an international reference price. For example, a median price range of 3·5 means that the price

	Africa	Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
Private sector, originator brand	4·4 (n=8)	2·0 (n=3)	1·6 (n=11)	3·6 (n=4)	1·2 (n=9)	1·4 (n=5)
Private sector, lowest priced generic	2·5 (n=6)	1·0 (n=2)	0·8 (n=10)	5·0 (n=5)	0·6 (n=7)	0·7 (n=6)
Public sector, lowest priced generic	1·6 (n=2)	0·6 (n=1)	0·7 (n=3)	15·0 (n=1)	..	1·1 (n=2)

n=number of surveys.

Table 2: **Mean number of days' wages of lowest-paid government worker for a course of treatment with salbutamol (0·1 mg/dose inhaler) by WHO Region[52]**

of the local drug is 3·5 times higher than the international reference price. In some countries the public sector's median price ratio for drugs to treat NCDs was lower than 1, showing that some countries, through good purchasing practices, were able to decrease the price of these drugs.[52,55] In five Indian states, the median price range for generic beclometasone inhalers ranged from 0·87 to 1·49, the median price ratio of the original brand salbutamol inhaler ranged from 0·86 to 1·12, and the median price ratio for generic brand salbutamol ranged from 0·82 to 0·96.[55] In a Chinese study,[54] the median price ratio for salbutamol in the public sector was up to five times higher than in the private sector. There is wide variation depending on the sector, presentation of the drug, and region, ranging, for example, from 1·82 for the lowest priced generic brand in the public sector in the WHO Americas region to 14·26 for the originator brand in the private sector in the Africa region (table 3).

The challenges of studying availability and affordability

The literature on availability and affordability of drugs uses a standardised method developed by WHO and Health Action International. Availability is measured at one time point and as drugs become available at pharmacies or facilities. The authors of these studies do not describe why the drugs are unavailable or to what extent different elements, such as logistics of production, orders, shipping, storage, distribution, and prescription, determine the availability of the drug to the end user.[64]

The number of days' wages the lowest-paid government worker has to pay for 1 month of treatment is a useful and easily understood benchmark. However, no cutoff is used to indicate when a drug is affordable or not. Assessment of affordability needs an explicit cutoff to define when a drug is to be regarded as unaffordable for a given population.[65] This cutoff could be the price at which a drug exceeds either the total budget that an individual has at their disposal or a proportion of income that is seen as the limit of how much an individual could spend on drugs. Table 4 shows how many millions of people would be pushed into poverty or could not afford a salbutamol inhaler in 16 LMICs.[66] The authors assessed affordability by the population that would be pushed into poverty (earning less than US$1·25–2·0 each day) because of their need to purchase an asthma inhaler. The aim was to assess the so-called impoverishing effect of drug expenses on disadvantaged people who need to purchase drugs out of pocket and how many people this expense might push into poverty. According to the results of this analysis,[66] up to 86% of the population in the countries studied would be pushed into poverty as a result of purchasing drugs.

For nicotine replacement therapy, there are additional issues about who will pay for the therapy and how the therapy is integrated into an overall tobacco control strategy. Knowledge of this therapy in LMICs is poor,[67] and affordability is an issue. For example, 3 months of nicotine replacement therapy costs as much as 7 years supply of cigarettes in Indonesia.[68]

The way forward

Lessons from HIV/AIDS show that delivery of care and drugs for a complex chronic disease is possible in LMICs.[69] However, although the WHO Prequalification Programme and the Global Fund have improved the quality assessment and supply of HIV/AIDs treatments, respectively, no comparable initiatives for NCDs exist. Drugs for NCDs fall into four distinct categories.[70] Some oral drugs are available in generic form (eg, metformin, aspirin, hydrochlorothiazide, tamoxifen) and are available on the international market at a low price, but are still not widely available in low-resource countries and are often of uneven quality. More complex products, such as inhalers and insulin, are available at a high cost, are often less readily accepted by patients, and their quality assurance is both important and challenging to provide in low-resource settings. There are usually high costs for new suppliers of these products wishing to enter the market. Some NCD drugs are still under patent and are only accessible via expanded access programmes of individual companies, which leads to varied accessibility. Local regulation might limit access to some drugs, such as opioid analgesics, that might be necessary for palliative care. Some countries have been able to decrease the price of asthma drugs, such as beclometasone, with the use of generics.[71] For example, in Poland, beclometasone costs US$20 for 1 year of treatment, which is ten times cheaper than in Burkina Faso.

	Africa	Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
Private sector, originator brand	14·26 (n=8)	9·05 (n=2)	6·00 (n=11)	5·58 (n=4)	6·47 (n=9)	8·60 (n=5)
Private sector, lowest priced generic	7·19 (n=6)	5·58 (n=2)	3·28 (n=10)	4·05 (n=5)	4·56 (n=7)	4·32 (n=6)
Public sector, lowest priced generic	3·58 (n=2)	1·82 (n=1)	3·02 (n=3)	3·73 (n=1)	..	4·64 (n=2)

n=number of surveys.

***Table 3*: Median price ratios (compared with international reference price) across sectors, by types of drugs and by WHO Region, for salbutamol 0·1 mg/dose inhaler[52]**

	Originator brand		Lowest priced generic	
	Impoverished	Unaffordable	Impoverished	Unaffordable
Less than US$1·25/day	64 000 000	190 000 000	16 000 000	142 000 000
Less than US$2·00/day	71 000 000	280 000 000	23 000 000	233 000 000

People are impoverished if their wages are above the poverty line before but not after purchasing the drug. Unaffordable includes people who are below the poverty line either before or after purchasing the drug.

***Table 4*: Numbers of people pushed into poverty and numbers of people who cannot afford a salbutamol inhaler from the private sector from 16 low-income and middle-income countries[66]**

The Asthma Drug Facility, which was established and was run by the International Union Against Tuberculosis and Lung Disease, has helped LMICs obtain quality-assured asthma inhalers at affordable prices. Because asthma inhalers are not yet prequalified by WHO, the Asthma Drug Facility has developed its own quality assurance system to select manufacturers and products on the basis of WHO norms and standards. The Asthma Drug Facility lowered the drug prices by organising yearly tenders for generic asthma inhalers from manufacturers who complied with WHO Good Manufacturing Practices and had product dossiers compliant with WHO quality standards.[72] Additionally, the prices arranged by the Asthma Drug Facility were kept low by limiting the competitive process between selected manufacturers on the basis of estimated yearly volumes and pooled procurement.[73] The incentives for the generic companies were the new markets that opened up in countries where innovator companies dominate. This facility lowered the cost of treatment for an individual with severe asthma to a yearly cost of about US$40, compared to US$79, with inhalers marketed in Benin, for instance.[72] The approach and success of this mechanism makes it a possible solution for lowering the price of other NCD drugs.[70,73–75] Funding of the management of the Asthma Drug Facility came from the International Union Against Tuberculosis and Lung Disease with Ministries of Health, National Lung foundations, and other non-governmental organisations purchasing drugs from this facility. The Asthma Drug Facility also provided standardised asthma management guidelines and therefore went beyond only providing drugs. At the time of writing this Review, this work has been suspended due to lack of funding, and an alternative service is yet to be established.

For people with NCDs, the aim of the health-care system is to prevent complications and the negative physical, psychosocial, and economic effect of the disease on the individual.[74] Consideration of the availability and affordability of drugs in isolation would overlook the complex requirements for delivery of effective care for chronic NCDs (figure 5). Drugs are only one of the six key elements of the health-care system, with service delivery, a well trained workforce, information systems, finance, leadership, and governance being crucial.[75] To achieve effective delivery of care, non-communicable respiratory diseases need to be managed in primary health-care facilities that are geographically close to the individual. These facilities need the appropriate infrastructure and tools to diagnose and manage non-communicable respiratory diseases, as well as referral pathways when necessary. Trained health-care personnel are also essential, and appropriate staffing with appropriate treatment guidelines needs to be combined with control of the drug costs, improvement in patient education, and empowerment adapted to the local context to improve adherence. One approach would be to involve the community, be it patient associations, expert patients, peer educators, or even traditional healers. These elements are often left out of disease responses and can have an important role, not only in disease management, but also in addressing other social aspects, such as the stigma linked to disease. Community services and organisations can also have an important role in prevention. Just as with education and empowerment, these need to be adapted to local social and cultural perspectives. These preventive measures need to be accompanied by comprehensive government policies. All these elements need to be supported by data and, as this Review highlights, data relevant to LMICs does not exist.

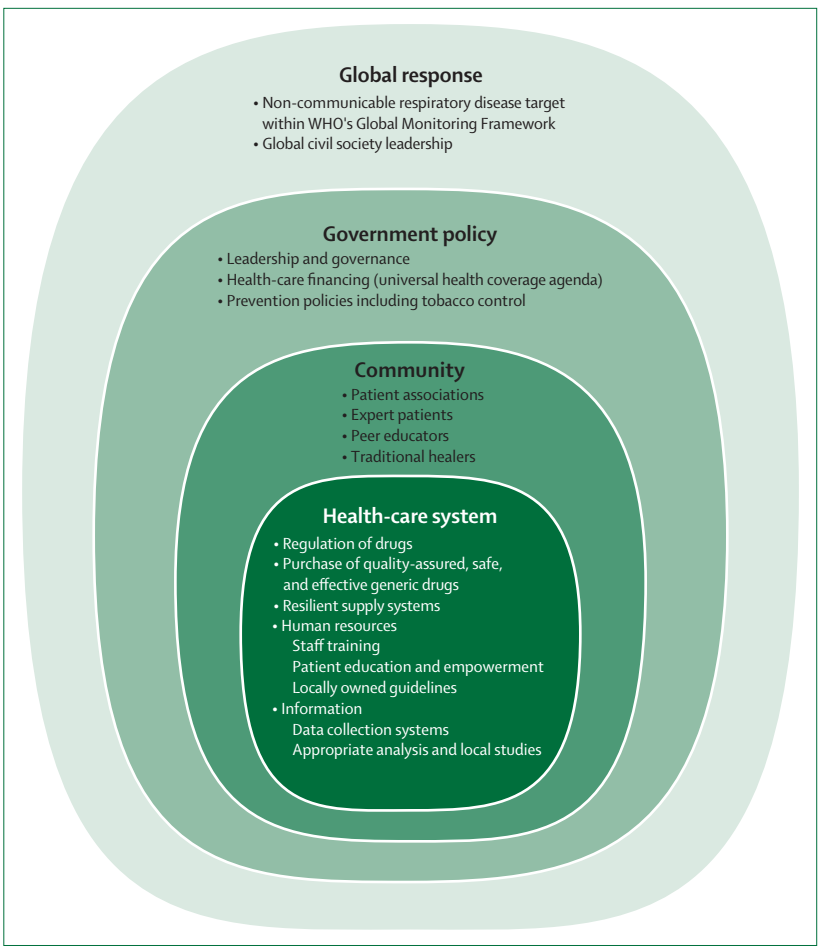

Figure 5: **Requirements for an adequate health-care response to non-communicable chronic respiratory disease**

The absence of a global response to non-communicable respiratory diseases might explain the inaction at a local level. Unlike the other four NCDs prioritised by WHO (heart disease, stroke, cancer, and diabetes), there is no specific target for non-communicable respiratory diseases in WHO's Global Monitoring Framework. This absence of general attention results in a failure to assemble national attention, and the inclusion of a target relevant for non-communicable respiratory diseases

within the general NCD agenda is necessary. In 2010, the Global Initiative for Asthma proposed the target of reduction of hospital admissions due to asthma by 50% over 5 years.[76] This target is important because asthma-related hospital admissions are preventable through an integrated health-care system response that includes available and affordable drugs. The general community should therefore endorse such a target to ensure improved outcomes for people with non-communicable respiratory diseases worldwide.

Conclusions

Chronic respiratory diseases are responsible for a substantial burden of morbidity and mortality on both health-care systems and individuals in low-resource countries. The large proportion of children in low-income countries and the high prevalence of asthma in this age group contribute to the burden. Despite falling age-specific mortality rates from chronic respiratory diseases, the relative burden is increasing because of the increasing size of the older population.

In management of this problem, there is a high priority to prevent a tobacco epidemic from occurring in countries that still have relatively low consumption levels of tobacco, and a very high priority to lower tobacco consumption in countries where the epidemic is already established. Other preventive policies are currently difficult to recommend in view of the epidemiology of these diseases differing between low-resource countries and still being poorly understood.

Established and cost-effective treatments exist for asthma, although fewer treatments are available for COPD.[49] Apart from making drugs available at economic costs, which is an essential component of effective health care, health infrastructure also needs to facilitate continuity of care, which is a much more cost-efficient way of providing care for these chronic conditions. Consideration of the availability and affordability of drugs in isolation overlooks the complexity of NCD management. Stronger health-care systems are needed to achieve better health for populations,[77] and chronic non-communicable respiratory diseases need an integrated health-care system response that brings together these different elements in a sustainable way.[78]

A comprehensive health-care package is needed to improve outcomes for people with non-communicable respiratory diseases. This package includes guidelines, access to drugs, training of health-care workers, appropriate services for people with chronic conditions, appropriate paediatric formulations and devices (including spacers), patient education, data for the burden, and comprehensive international and national policy and programme responses. International and national responses to the challenge of non-communicable respiratory diseases are absent, which is emphasised by the absence of a specific target in the Global Monitoring Framework. In view of the burden of non-communicable respiratory diseases, there is a gap in the worldwide response to NCDs that needs to be addressed by the global community worldwide.

Contributors

Each author wrote part of the initial draft. All authors read and approved the final version.

Declaration of interests

AMM declares personal fees from GlaxoSmithKline, outside of the submitted work; PB reports personal fees from Novartis, outside of the submitted work; all other authors declare no competing interests.

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