Improving lung health in low-income and middle-income countries: from challenges to solutions

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Low-income and middle-income countries (LMICs) bear a disproportionately high burden of the global morbidity and mortality caused by chronic respiratory diseases (CRDs), including asthma, chronic obstructive pulmonary disease, bronchiectasis, and post-tuberculosis lung disease. CRDs are strongly associated with poverty, infectious diseases, and other non-communicable diseases (NCDs), and contribute to complex multi-morbidity, with major consequences for the lives and livelihoods of those affected. The relevance of CRDs to health and socioeconomic wellbeing is expected to increase in the decades ahead, as life expectancies rise and the competing risks of early childhood mortality and infectious diseases plateau. As such, the World Health Organization has identified the prevention and control of NCDs as an urgent development issue and essential to the achievement of the Sustainable Development Goals by 2030. In this Review, we focus on CRDs in LMICs. We discuss the early life origins of CRDs; challenges in their prevention, diagnosis, and management in LMICs; and pathways to solutions to achieve true universal health coverage.

Introduction

Non-communicable diseases (NCDs) are a major cause of morbidity and mortality, accounting for approximately 70% of global deaths, with the highest risks of dying from NCDs observed in low-income and middle-income countries (LMICs).[1] The United Nations' Sustainable Development Goals (SDGs) aim to reduce the risk of premature mortality from NCDs by a third by 2030.[2] Chronic respiratory diseases (CRDs), such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and post-tuberculosis lung disease (PTLD) are common and frequently neglected NCDs that span the life course. They are frequently associated with high levels of patient and health care costs, morbidity, and risk of mortality due to persistent symptoms, activity limitation, and intermittent exacerbations requiring acute care. They disproportionately affect poor people in all countries, but especially in LMICs where resources for research, prevention, and management are scarce.[3] The recent *Lancet* Commission on NCDs and Injuries has helped to highlight and frame this issue as a matter of justice and equity for the world's poor.[4]

This Review focuses on CRDs in LMICs. Although we recognise that poverty and social deprivation are global issues, people living in LMICs face a particularly difficult combination of damaging early life and environmental exposures, challenging social and political contexts, and poor access to high-quality health services. We discuss the early life origins of CRDs in LMICs, and potential approaches to the prevention of disease. We address the clinical and health system challenges faced in the management of established disease. We suggest strategies for research and clinical capacity strengthening, for both the prevention and management of CRDs, and propose pathways to solutions that would contribute to achieving international targets for health, including reducing morbidity and premature mortality, and achieving universal health coverage.

Search strategy and selection criteria

We did not do a formal literature search for this Review. Studies included in this Review were identified by the authors based on their knowledge of non-communicable respiratory disease in low-income and middle-income countries; the studies referenced were selected by the authors, as most relevant to this field.

Early life origins of chronic respiratory disease

Evidence that has mainly been acquired in high-income countries (HICs) indicates that the in-utero, infant, child, and adolescent environment is crucial for lung development, with pre-school lung function tracking and predicting early adult lung function, into at least the seventh decade of life.[5,6] Although comparable data from LMICs are scarce, the same association probably holds true in these countries.[7] Common to both settings are detrimental in utero and early childhood exposures, which can disturb lung development such that individuals fail to reach an optimal peak in early adulthood, with increased risk of CRDs later in life. The increased prevalence and severity of many of these harmful early life exposures in LMICs might explain the lower lung volumes observed in asymptomatic non-smoking adults in many sub-Saharan African settings, compared with age-matched and height-matched adults in HICs.[8] Reduced forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in early adulthood have been associated with cardiovascular and metabolic morbidity in both HICs and

LMICs.[6,9–11] Given the likely importance of in-utero and early childhood exposures to adult lung health and wellbeing, and the high prevalence of these adverse exposures in LMICs, interventions to mitigate early life exposures might be crucial for the prevention of CRDs in LMICs.

In-utero exposures

Tobacco and air pollution

In-utero exposure to tobacco smoking alters lung structure and function, and affects immune responses in the developing fetus.[5] Data from the Drakenstein child health study in South Africa—one of the first birth cohorts in sub-Saharan Africa—showed that infants of the third of mothers who smoked during pregnancy had lower tidal volumes and higher lung clearance indices at age 6 weeks than infants of non-smoking women, suggesting impaired lung and airway development.[12] Similar outcomes have been seen in relation to other forms of air pollution exposure, including atmospheric pollution.[13]

Social deprivation

Maternal stress, depression, adverse living conditions, and intimate partner and neighbourhood violence are issues faced by women around the world. In LMICs, these challenges are often faced on a background of structural inequality, notable gender divisions, and the absence of universal health coverage, such that women here are especially vulnerable to these issues.[14,15] Maternal psychological distress is negatively associated with measures of neonatal health, including weight for age and head circumference,[14] and positively associated with ongoing respiratory morbidity in children.[7,16,17] Maternal alcohol exposure during pregnancy adversely impacts lung function at 6 weeks, but this effect disappears by 1 year.[7,12] Better maternal nutrition might protect against childhood wheeze.[18]

HIV infection

The prevalence of HIV in women of childbearing age is high in many LMICs but the introduction of test and treat approaches to combination antiretroviral treatment (cART), strengthened provision of cART, and dedicated programmes to prevent maternal-to-child transmission have dramatically decreased rates of perinatal infection.[19] Although HIV-exposed but uninfected infants might have reduced early lung function, by the age of 2 years impairment is seen only in those children whose mothers had poorly controlled HIV disease during pregnancy.[20]

Premature birth

Premature births occur in 10% of all livebirths globally, but 80% of these are in LMICs.[21] Preterm birth is associated with increased respiratory symptoms, airway obstruction, abnormal lung structure, and poor cardiovascular health in childhood and early adulthood.[22,23]

Childhood exposures

Acute lower respiratory infection

Early childhood bacterial and viral infections are common in LMICs and are a risk factor for ongoing respiratory illness. Respiratory syncytial virus, rhinovirus, adenovirus, and influenza A are some of the most common viral pathogens detected in children with acute lower respiratory tract infections in LMICs.[24,25] Wheezing illnesses associated with rhinovirus and respiratory syncytial virus in early life are strong predictors of childhood asthma by 6 years of age,[26] and adenovirus-related lower respiratory tract infections have been associated with subsequent obliterative bronchiolitis or bronchiectasis.[27] Pneumonia is a major cause of mortality in children with an estimated incidence of 0·2–0·3 episodes per child-year in LMICs.[28] Contrary to previous findings in HICs, lower respiratory tract infections in early childhood in sub-Saharan Africa have been shown to be an independent risk factor for reduced lung function by 1 year of age.[12,29] However, the pneumococcal conjugate vaccine is still only available to approximately 50% of children globally, despite having been introduced two decades ago.[30]

Pulmonary tuberculosis

Children younger than 15 years of age account for 11% of incident tuberculosis disease globally[31] and paediatricians in LMICs routinely report a high burden of post-tuberculosis sequelae, including bronchiectasis and lung destruction, in those children successfully completing treatment.[32]

Chronic HIV infection

Large numbers of children previously infected with vertically acquired HIV in LMICs are now reaching adolescence.[33] These long-term survivors experience a high burden of CRDs, including bronchiectasis, bronchiolitis obliterans, and impaired lung function.[32,33] Deficits are more severe in those with delayed diagnosis and late initiation of antiretroviral therapy.[34]

Nutrition

LMICs increasingly face a dual burden of maternal and childhood malnutrition,[35] which results in fetal growth restriction, stunting, wasting, and isolated nutrient deficiencies, but also children who are overweight or obese.[36,37] The scarce available data suggest that in-utero and early childhood starvation have adverse effects on lung development that persist into adult life. Childhood obesity is also thought to cause long-term airway disease and has been associated with asthma in LMICs and in HICs.[38]

Air pollution

Both indoor and outdoor air exposures could be relevant to child lung health. The association between biomass fuel exposure in early childhood and lung

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development is unclear: delayed introduction of clean burning stoves into Guatemalan households (child age 18–57 months vs younger than 6 months) was associated with lower, but not significantly different, rates of lung growth,[39] and data from a clean stoves intervention study in rural Malawi showed a small but statistically significant difference (0·2 Z scores) in the FVC of children from households who had previously been provided with a clean burning stove compared with those who had not.[40] In HICs, reductions in outdoor air pollution over time have been associated with better lung function in children from serial birth cohorts.[41] Diesel exposure has been associated with poor asthma outcomes, and this could be particularly relevant in LMICs where trucks are often poorly maintained, use unregulated fuel, and drive in close proximity to habitations.[42–44]

Towards solutions

Prevention of CRDs in LMICs will require attention to in-utero and early childhood exposures, which determine the trajectory of lung development and health over the course of an individual's lifespan.

Many of these exposures are amenable to public health interventions and are rooted in poverty among mothers and children. Existing programmes for maternal care must be strengthened to protect the physical and mental health of women of childbearing age and mothers, improve access to high-quality antenatal care, and support maternal education about childhood nutrition and vaccination. Programmes that support HIV-infected mothers to prevent perinatal transmission and provide early childhood HIV testing must be maintained. We suggest that programmes to support early child health should be strengthened and should include secure access to high-quality nutrition and effective immunisation. Given the likely detrimental effects of air pollution on lung development, we suggest that efforts to promote behaviour change in cooking and ventilation practices should continue, as a potentially low-cost strategy to improve child health.[45] Political action including taxation and effective legislation to regulate advertising will likely be needed to minimise exposure to smoking and e-cigarettes, alcohol, and household and atmospheric air pollution.[46] Such efforts might be particularly relevant in LMICs, given increasing marketing and interference with public health efforts by tobacco, alcohol, food, and beverage companies, and inadequate national regulatory frameworks.[3] Many of these health system and political interventions are broad in their scope, and stand to benefit health beyond CRDs. However, without them, it is likely that the substantial burden of CRDs in LMICs will remain.

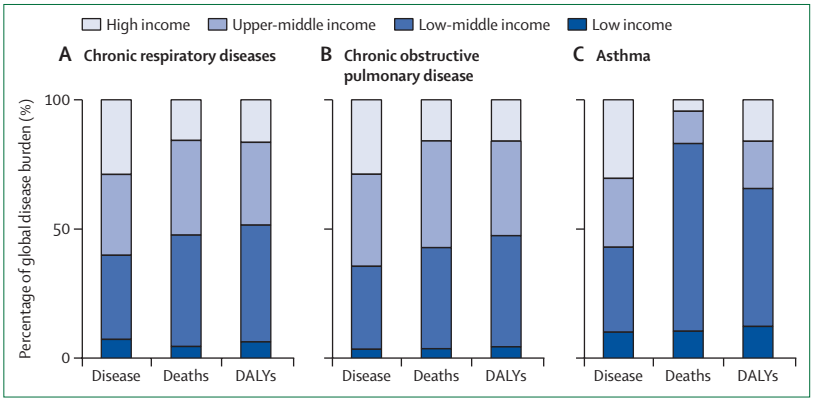

Figure 1: **Distribution of the global burden of disease, deaths, and DALYs from (A) chronic respiratory diseases, (B) chronic obstructive pulmonary disease, and (C) asthma, by World Bank-defined country income strata, using Global Burden of Disease 2019 estimates[47]**
DALY=disability-adjusted life-year.

Asthma

Asthma is the most common CRD globally, affecting 262·4 million people in 2019,[47] with LMICs contributing 96% of global asthma-related deaths and 84% of global disability-adjusted life-years (DALYs; figure 1).[47] However, morbidity and mortality from asthma is largely preventable.[48]

Diagnosis

The Global Initiative for Asthma (GINA) suggests a syndromic approach for asthma diagnosis in LMICs, but emphasises the importance of measuring variability in airflow for confirmation, using peak flow monitoring or spirometry with reversibility testing.[49] Access to these devices is poor in LMICs, such that diagnostic capacity is severely constrained.[50] Asthma is frequently underdiagnosed in children and adults in LMICs, and is often more severe when eventually identified.[51,52]

Management

Management of chronic asthma requires the use of inhaled corticosteroid (ICS) to improve symptom control and reduce hospital admissions and mortality.[53] GINA now recommends as-needed use of inhalers combining ICS with the rapid-onset long-acting bronchodilator (LABA) formoterol for adolescents and adults at treatment steps 1 and 2.[49,54] Data from large clinical trials indicate that this approach is equivalent or superior to use of regular ICS with as-needed short-acting β_2 agonists (SABAs) for reducing the risk of severe exacerbations, and uses a much lower dose of ICS with no clinically important difference in symptom control, at least in adolescents older than 12 years of age and adults.[55–58] Similarly, in moderate-to-severe asthma, use of maintenance and reliever therapy with combination ICS and formoterol reduces severe exacerbations compared with conventional regular ICS and LABA therapy with a SABA reliever.[59] For mild asthma, if combination ICS and bronchodilator preparations are not available or affordable, separate ICS may be used whenever a SABA is taken.

Despite these guidelines and although ICS are crucial to disease management, they are frequently

under-prescribed, unavailable, or unaffordable to people with asthma in LMICs, who consequently rely heavily on inhaled bronchodilators alone, or oral preparations of salbutamol, theophylline, or prednisolone instead.[50,60–62] Health system capacity for long term follow-up with titration of medication for symptom control is insufficient, and patient and clinician understanding of the need for chronic treatment might be incomplete, with 52–76% loss to follow-up seen within 1-year in pilot projects in China, Benin, and Sudan.[60–62]

Towards solutions

Global strategies for asthma care in LMICs can be adapted for national use.[49] Implementation will require guidance and training for health-care workers of multiple cadres to improve the clinical recognition of asthma, to promote the use of syndromic diagnosis, and to ensure appropriate prescription of effective preventer medication. A major need exists for improved access to diagnostic tools (peak flow meters and spirometry) and training in their use. Similarly, access to affordable quality-assured asthma medicines listed on the WHO Essential Medicines list (panel 1) is needed. Education of both patients and providers will be required to ensure appropriate use of inhalers, with emphasis on the importance of ICS, and training in inhaler technique using spacers will be needed to optimise drug delivery in both children and adults. Health services with capacity for follow-up of patients with asthma are rare in LMICs, but are essential for preventing over-reliance on emergency services, improving long-term symptom control, and minimising morbidity and mortality.

COPD

Global burden of disease estimates suggest that 212·3 million adults were affected by COPD in 2019.[47] However, primary data on the global burden of disease show widespread variability in the prevalence, causes, clinical presentation, and mortality between and within LMICs.[64] These differences are mainly related to poor access to spirometry and scarce epidemiological data, but are compounded by controversy in the definition of COPD—for example, it is unclear whether fixed ratios and percent predicted cutoffs or lower limit of normal boundaries should be used to identify abnormal results, which reference ranges to use for standardisation of measurements, and whether to consider all patients with fixed airflow limitation as having COPD.[8] Notwithstanding this problem, community-based data indicate that the prevalence of airway obstruction is between 6 and 20% in Latin America,[65–67] and 5–24% in sub-Saharan Africa.[68–71] LMICs are believed to contribute to 71% of the global COPD burden, 84% of global COPD deaths, and 84% of the global COPD DALYs (figure 1).[47] Although tobacco smoking remains an important risk factor for airway obstruction in LMICs, between a third to a fifth of cases in LMICs occur in people who have never smoked, and a substantial proportion of these cases are probably related to biomass use for cooking and heating, especially in women.[72–76]

Diagnosis

High levels of under-diagnosis and misdiagnosis of COPD are observed in LMICs,[77,78] and data from national and international COPD surveys suggest that more than 80% of COPD cases identified on spirometry are undiagnosed within routine clinical care.[79] Unsurprisingly, individuals with mild disease and without a history of exacerbations or admissions are less likely to have a diagnosis, but ethnicity, educational status, and absence of contact with health services also emerge as risk factors for under-diagnosis, suggesting that broader socioeconomic determinants are also important.[77–79] As noted previously, poor access to spirometry for diagnosis globally is probably a key constraint.

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Panel 1: **Medications for chronic respiratory disease management, from the WHO Model List of Essential Medicines[63]**

Respiratory medications—inhaled or nebulised*
- Beclomethasone (inhaled)
- Budesonide (inhaled)
- Budesonide plus formoterol (inhaled)
- Ipratropium bromide (inhaled)
- Salbutamol (inhaled and nebulised)
- Tiotropium (inhaled)

Respiratory medications—oral or intravenous
- Epinephrine (adrenaline; injectable)
- Prednisolone (oral)
- Hydrocortisone (injectable)

Medical gases
- Oxygen

Pain and palliative care medications
- Opioid preparations (codeine, fentanyl, morphine)

Antibiotics for respiratory infection (to be adapted as per local guidelines)
- Beta lactams: amoxicillin, amoxicillin plus clavulanic acid, cefalexin, cefixime†, cefotaxime†, ceftriaxone†
- Tetracyclines: doxycycline
- Macrolides: azithromycin†, clarithromycin†
- Quinolones: ciprofloxacin†
- Aminoglycosides: amikacin, gentamicin
- Other: sulfamethoxazole plus trimethoprim, metronidazole, chloramphenicol

Vaccines
- Childhood vaccines: pertussis, measles, diphtheria, and *Haemophilus influenzae* type B
- Influenza vaccine (seasonal)
- Pneumococcal vaccine (conjugate and polysaccharide)

*All metered-dose inhalers to be provided with spacer device. †Antibiotics on the WHO watch list due to high resistance potential—for limited use, with guidance from local antibiotic stewardship programmes.

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Management

Standard management of smoking-related COPD includes non-pharmacological interventions (supported smoking cessation, pneumococcal and influenza vaccination, and pulmonary rehabilitation) and pharmacological treatment with inhaled therapies (SABAs, LABAs, short-acting and long-acting muscarinic antagonists, and ICS according to disease severity). These interventions are under-utilised in LMICs. In Latin America, population-based surveys show that only half of smokers had physician counselling, a quarter received any respiratory medication, and access to influenza vaccination was poor.[80,81] Results from the PUMA study showed that in primary care, the most widely used inhaled therapy was SABAs, with long-acting bronchodilators and ICS relatively less used.[82] No clinical trials have investigated the appropriate pharmacotherapy for non-smoking-related COPD, including disease related to biomass pollutant exposure in LMICs, which might differ from that recommended for smoking-related COPD.

Towards solutions

There is an urgent need for better epidemiological data, accurate diagnosis, and appropriate clinical care for COPD in LMICs.[83,84] Some of the approaches required might be similar to those outlined for asthma, including raising awareness among patients and providers, use of approved standardised guidelines for diagnosis and management, better access to spirometry, increased availability of inhaled therapies, improved education for both patients and health-care providers, and better access to long term follow-up. However, COPD in HICs has been associated with systemic sequelae including cardiovascular disease, malignancy, osteoporosis, depression, and anxiety.[85] Consequently, there is a need to determine whether the same outcomes are seen in LMICs, and if the data are similar, programmes designed to address this multi-morbidity will likely be needed. Broader access to cost-effective non-pharmacological interventions including smoking cessation and pulmonary rehabilitation should be prioritised and adapted for use in specific cultural contexts.[86] Smoking remains the key driver of COPD worldwide, and ongoing efforts to translate lessons learnt in HICs about public health and policy approaches to regulation across to LMICs, to reduce both direct and passive exposure, will require sustained long-term support. Data about the risks, nature, outcomes, and management of non-smoking related airway obstruction are needed in both high-income and low-income settings.

Bronchiectasis

The reported population prevalence of non-cystic fibrosis bronchiectasis in HICs has increased in recent years to 566 per 100 000,[87] with disease prevalence and severity associated with increasing age[88] and female gender. Epidemiological data on bronchiectasis in LMICs are scarce,[89] but the few data that are available suggest that the prevalence, causes, and risk factors for bronchiectasis might differ substantially to those in most HICs, with more post-infectious disease, an association with HIV infection, a higher burden of severe disease in younger adults, and differences in colonising or infecting microbiology.[87,90,91]

Diagnosis

The diagnosis of bronchiectasis in LMICs is challenging. The clinical presentation is similar to that in patients in HICs, with chronic cough and sputum production in adults, and failure to thrive in children, often associated with chronic, severe respiratory symptoms and recurrent infections. However, in many low-resource settings with high tuberculosis incidence, patients presenting with these symptoms are managed primarily as tuberculosis suspects and not evaluated for underlying CRDs. International guidelines for the diagnosis of bronchiectasis rely heavily on the use of CT imaging as the gold standard diagnostic tool, but this is unavailable to the majority of people living in LMICs. Little evidence exists to support the use of plain chest x-ray for the diagnosis of bronchiectasis specifically, and few guidelines support the use of chest x-ray for the investigation of chronic respiratory symptoms in LMICs, in general.

Management

Management of bronchiectasis in HICs is increasingly individualised and focused on addressing so-called treatable traits with the use of airway clearance tools, pneumococcal and influenza vaccination, appropriate treatment of infecting or colonising organisms, and early diagnosis and active management of intercurrent fungal and non-tuberculous mycobacterial disease.[92] These individualised approaches are not widely available in LMICs and, to our knowledge no guidelines have yet been developed for the diagnosis and management of bronchiectasis in resource-poor settings.

Towards solutions

Improved investigation and management approaches for chronic productive cough in children and adults in LMICs are required. Standardised guidelines for decentralised care are needed, and should focus on feasible and scalable programmatic approaches.[87] In settings with a high tuberculosis burden, these guidelines must include appropriate investigation for active tuberculosis disease, but with consideration of underlying CRD when tuberculosis is excluded. This will require better integration between tuberculosis services and broader respiratory or medical services. Education of health workers about bronchiectasis as a cause of chronic productive cough, and accessible and affordable approaches to diagnosis in the absence of CT imaging are required to facilitate this. Patient-centred, low-cost tools, such as airway clearance, have been shown to be acceptable and effective in children in South Africa and should be optimised for use in

LMICs.[93] An improved understanding of the microbiology of bronchiectasis in both children and adults is needed to inform population-level antibiotic recommendations.

Post-tuberculosis lung disease

Pulmonary tuberculosis survivors, estimated at 58 million globally so far,[31] have two-to-four fold odds of persistently abnormal spirometry (airway obstruction and low FVC patterns) after completion of tuberculosis treatment, compared to those who have never had tuberculosis disease. Bronchiectasis, parenchymal cavitation and destruction, and fibrotic change are widely seen on imaging.[94–97] Much heterogeneity exists in the prevalence, patterns, and severity of residual pathology, but bronchiectasis or abnormal spirometry are thought to occur in more than a third of pulmonary tuberculosis survivors.[97–99] Those with PTLD are at risk of long-term chronic respiratory symptoms, recurrent respiratory exacerbations, and accelerated lung function decline.[98] Tuberculosis survivors are at high risk of recurrent tuberculosis disease, whether re-activation or re-infection.[100] However, chronic respiratory symptoms also place them at risk of empirical and unnecessary tuberculosis retreatment,[101] exposing them to further drug side-effects, stigma, and health-care costs.[102] Mortality in adult survivors of tuberculosis is almost three-times greater than that in the general population, but the direct association between PTLD and mortality is unclear.[103] Of the 10 million annual cases of incident pulmonary tuberculosis globally, more than 1 million occur in children,[31] yet very little is known about the burden and impact of PTLD in this population.

Diagnosis

Abnormal spirometry or chest x-ray imaging can suggest a diagnosis of PTLD, but these tests are not routinely performed at successful completion of tuberculosis treatment and might not be available at the point of care within decentralised tuberculosis treatment programmes. Most individuals with residual PTLD are therefore discharged without a diagnosis and without ongoing care in LMICs.[98] The diagnosis of recurrent tuberculosis in those with existing PTLD can be challenging: the specificity of nucleic acid amplification tests is reduced in tuberculosis survivors, and the performance of screening tools, including the WHO symptom screen and chest radiography, in those with PTLD is unclear.[104,105]

Management

There is little attention paid to post-tuberculosis morbidity in existing international and national tuberculosis guidelines, with no evidence-based guidelines available for the diagnosis and management of PTLD in LMICs.[106,107] Existing approaches are based on models of COPD and bronchiectasis care, and include education about avoiding cannabis and smoking, which are common co-exposures in patients with tuberculosis; airway clearance exercises; vaccinations as per national guidelines; and use of inhaled bronchodilators for reversible airway obstruction.[108] The use of ICS is not recommended given the associated increased risk of recurrent mycobacterial disease and other respiratory infections.[109–111] Pulmonary rehabilitation can help to improve quality of life.[112] Although sputum culture is the gold-standard tool for the diagnosis of recurrent tuberculosis disease and drug susceptibility testing in this group, culture is frequently not available in LMICs, and is not feasible in young children. Further work is needed to explore the performance of tuberculosis screening and diagnostic tools in pulmonary tuberculosis survivors and those with PTLD.

Towards solutions

Tuberculosis treatment completion provides an opportunity to screen pulmonary tuberculosis survivors for residual lung pathology, with a view to ongoing follow-up and intervention. However, given resource constraints in LMICs, further evidence is required to inform decisions about how this should be done, which patients would benefit from ongoing follow-up, and the impact and cost-effectiveness of clinical interventions for this group, before implementation of this approach. Clear evidence-based guidelines are also required for the diagnosis and management of those who are not identified at treatment completion but re-present with chronic respiratory symptoms several years later. Integration of tuberculosis and CRD services will be required to optimise PTLD diagnosis and management,[113] with improved approaches to the diagnosis of recurrent tuberculosis disease. We suggest that the broader cardiovascular, psychological, and socioeconomic morbidities faced by tuberculosis survivors should also be addressed within any packages of post tuberculosis care.[114]

Health systems strengthening

Strong health systems that are capable of providing effective and efficient services across the life-course will be key to the prevention and management of CRDs and NCDs in LMICs, and must include the provision of comprehensive maternal care. Development of these systems will require attention to the six key building blocks specified by the WHO: service delivery; health workforce; health information systems; access to essential medicines and vaccines; financing; and leadership or governance (figure 2).[115]

Several key weaknesses have been identified in these areas, with respect to respiratory care in LMICs. Health system surveillance data for respiratory diseases other than tuberculosis are scarce,[116] limiting the capacity of countries to identify and plan for the health-care needs of their populations. Robust indicators for the monitoring and evaluation of priority CRD programmes are missing. National guidelines for the management of CRDs are also sparse, and were identified in only 64% of countries in the seventh NCD country capacity survey 2019.[117]

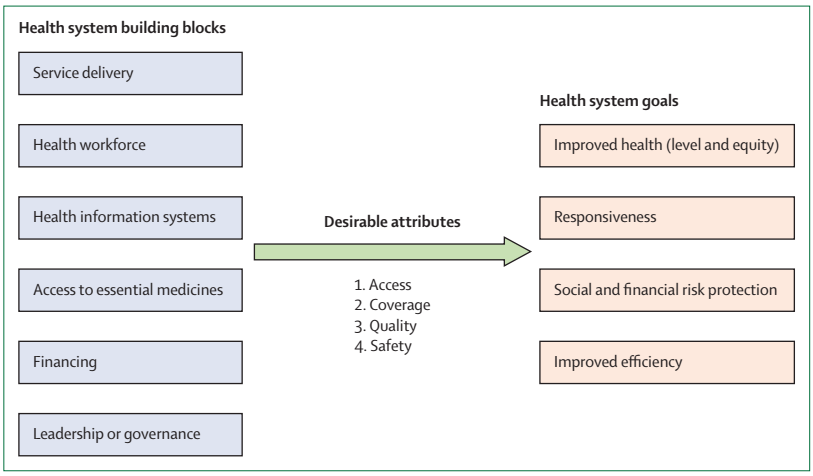

Figure 2: **World Health Organization six building blocks of health systems, together with aims and desirable attributes[135]**

Access to key diagnostic tools including spirometry and imaging is inadequate, and in 2019 peak flow or spirometry were available in only 45% of primary care facilities, compared with 88% for blood glucose measurement.[118] Access to preventive measures including vaccination, nutritional support, and smoking cessation services is poor.[119] Crucially, the health workforce is poorly equipped to deliver respiratory care, with low numbers of respiratory specialists,[120–123] and most care is delivered at the primary care level by nursing staff with little training.[124] Solutions to some of these challenges are explored in the following paragraphs.

Integrated delivery of CRD care

Front-line primary care staff in LMICs have a broad remit and are expected to provide preventive and curative care, for infectious and non-infectious diseases, to both children and adults. As such, CRD services must be efficiently integrated within broader services and customised to local needs. Several approaches to integrated care have been developed for use in LMICs, to this end.[125,126] Early models, such as the WHO Practical Approach to Lung Disease (PAL), which was developed in part to improve case finding for tuberculosis, were focused only on respiratory diseases. These have been followed by tools with more comprehensive scope including the WHO Package of Essential Noncommunicable disease interventions (PEN),[127] WHO Integrated Management of Adolescent and Adult Illness (IMAI),[128] and Package of Care Kit (PACK) for children, adolescents and adults.[129] As an example, PACK includes a decision support tool for use across a range of clinical presentations and is available in both paper and electronic forms.[130–133] It integrates local management guidelines and evidence, is regularly updated, and is supported by on-site, case-based, interactive training.[134,135] Qualitative data confirm the effectiveness of this integrated care approach in improving CRD services, including the treatment of asthma, diagnosis of tuberculosis, and appropriate referral to hospital.[134–136]

We suggest that respiratory and tuberculosis services should be closely linked in LMICs. Patients with acute and chronic respiratory disease frequently present with worsening respiratory symptoms and in settings with a high tuberculosis burden will usually require investigation for active tuberculosis disease. However, if these investigations are negative, it is important that alternative respiratory diagnoses are considered. Similarly, patients with PTLD at completion of tuberculosis treatment would benefit from clear and efficient integrated care pathways.

Lastly, NCD programmes in LMICs should consider including palliative care support within their services. This concept is particularly important for CRDs that are frequently irreversible, progressive, and can be associated with distressing symptoms such as severe breathlessness. Such integration will require cultural awareness, education of staff and patients, development of symptom management approaches, and access to opioid medications.[137]

Improving access to diagnostic devices

Specific challenges to accessing diagnostic devices, including spirometry and imaging, at the primary care level include the funding of these services, and training of clinical staff in how to perform tests, maintain quality control, and accurately interpret results.[138] Advances in the development of reliable and portable spirometry, ultrasound, and chest x-ray equipment for community-based diagnosis might facilitate decentralisation, but services could potentially prove more sustainable if accompanied by education and access to equipment maintenance services.[139] More sophisticated diagnostics such as CT imaging, complex lung function testing, and bronchoscopy will probably remain the purview of tertiary centres in LMICs, but these tools are of value in the training and retention of specialist physicians, and building research capacity, such that some investment in their centralised use may be of benefit.

Improving access to treatment

Although many key respiratory medications are included in the WHO essential medicines list (panel 1),[63] access to these drugs varies widely: in 2019, ICS were generally available in 19% of low-income compared with 96% of HICs, and bronchodilators in 55% and 100%, respectively.[118] Even where available, these medications were often unaffordable to patients in LMICs. Access to non-pharmacological interventions including pulmonary rehabilitation and smoking cessation services is also insufficient in LMICs, despite these being among the most cost-effective interventions for CRDs, and relevant to the prevention and management of other NCDs including cardiovascular disease and cancer. Educational programmes to

Panel 2: **Suggested research and clinical care priorities, for the delivery of chronic respiratory care in low-income and middle-income countries (LMICs)**

Lung health over the life course

- Development of birth cohorts in diverse settings in LMICs, to obtain prospective data on how genetic parameters, and in-utero and early childhood exposures affect lung development
- Investigation of the long-term impact of nutrition, lower respiratory tract infections (LRTIs) and tuberculosis in children, and mechanisms for development of chronic respiratory disease (CRD)
- Investigation of the origins, nature, and outcomes associated with the low forced vital capacity phenomenon seen in LMICs
- New vaccine development to reduce childhood LRTIs

Asthma

- Investigation of the determinants of asthma-related morbidity and mortality in LMICs
- Development of feasible and scalable models for long-term asthma care, which include access to regular clinical review, and access to education about the use of inhaled corticosteroid (ICS) medications
- Investigation of the pragmatic use of Global Initiative for Asthma recommendations for as-required ICS–formoterol for steps 1 and 2 of asthma treatment, given challenges in making a definitive diagnosis of asthma and the potential overlap with other diagnoses, including bronchiectasis and tuberculosis

Chronic obstructive pulmonary disease (COPD)

- Longitudinal data on patient outcomes associated with airway obstruction in smokers and non-smokers in LMICs, and risk factors for morbidity and mortality
- Investigation of the efficacy of pharmacological and non-pharmacological therapies for non-smoking related COPD in LMICs

Bronchiectasis

- Development and validation of feasible and accessible tools for the diagnosis of bronchiectasis in LMICs (eg, using questionnaires and chest x-ray), against gold standard CT-based diagnostics
- Longitudinal data on patient outcomes associated with bronchiectasis in LMICs, with assessment of risk factors for morbidity and mortality
- Data on the microbiology of bronchiectasis in LMICs, including colonising organisms and those associated with exacerbations, to inform antibiotic guidelines

Post-tuberculosis lung disease (PTLD)

- Investigation of host, pathogen, and environmental risk factors for PTLD
- Longitudinal data on patient outcomes associated with PTLD in LMICs, with assessment of risk factors for morbidity and mortality
- Investigation of the performance of tuberculosis diagnostic tools in those with PTLD being investigated for recurrent tuberculosis disease
- Investigation of the pathology underlying chronic respiratory symptoms in pulmonary tuberculosis survivors re-presenting to health services, after recurrent tuberculosis disease has been excluded

CRD diagnosis

- Consensus guidelines for the use of spirometry in routine clinical practice in LMICs settings, including approaches to quality control, and use of reference ranges for standardisation
- Development and validation of simple screening tools for CRDs in decentralised care settings
- Development and validation of syndromic based diagnostic pathways, for individual CRDs including asthma, COPD, bronchiectasis, and PTLD

CRD management

- Investigation of pathogens causing respiratory exacerbations of CRDs in LMICs, to inform antibiotic guidelines and vaccine use
- Optimisation of non-pharmacological CRD management tools for use in LMICs, including self-management tools, pulmonary rehabilitation, airway clearance tools, and smoking cessation programmes
- Investigation of effect of ICS on risk of tuberculosis disease, in settings with a high incidence of tuberculosis
- Inclusion of epidemiological data on CRD in LMICs into international registries and consensus statements, so that LMIC needs are prioritised within global CRD research agendas

Health systems

- Development of methods for programmatic data capture, to contribute data on the burden and nature of CRDs in LMICs, and to allow for local service planning and evaluation
- Development of models of integrated CRD care in LMICs, which are co-developed with patients and responsive to patient needs, integrated with tuberculosis and palliative care services, and integrated with the management of other non-communicable diseases (eg, cardiovascular disease services), with tools for the evaluation of clinical impact and health system and patient costs
- Development of key programme indicators for the planning, monitoring, and evaluation of CRD interventions

Training

- Development of a core curriculum for clinical respiratory training in LMICs, for multiple health professionals including nurses, physiotherapists, and non-specialist and specialist doctors
- Broader access to clinical and research-focused respiratory education and training platforms including journals, online courses, and in-person workshops

improve self-management, promote health literacy, and combat stigma are scarce.

Advocacy around access to these interventions is urgently needed. Key evidence gaps exist for the cost-effectiveness of newly recommended treatments for respiratory diseases, including ICS–formoterol treatment as needed (and regularly and as needed) in asthma, and dual LAMA and LABA treatment in COPD, in LMICs. Quality pharmacoeconomic analysis should inform strategies for expanding the options and strategies promoted as essential drugs for respiratory diseases in LMICs, rather than assuming unaffordability. Strategies to facilitate the affordable delivery of quality-controlled supplies of these medications will then be needed,[140] and efforts to adapt and integrate non-pharmacological interventions into programmes of care will be required. The development of a health workforce that can provide CRD services competently and compassionately is at the core of improving access.

Research priorities and research capacity strengthening

This Review has highlighted several areas of uncertainty that we have formulated into research priorities for CRDs in LMICs (panel 2). However, these issues cannot be addressed without a thriving critical mass of LMIC investigators. The Structured Operational Research Training Initiative (SORT-IT) course, and the American Thoracic Society/Pan African Thoracic Society's Methods in Epidemiological, Clinical and Operational Research (PATS-MECOR) course are examples of successful respiratory-focused programmes that provide training and networking opportunities for research-interested clinicians from LMICs, in order to build this capacity. Both SORT-IT and PATS-MECOR focus on clinical, epidemiological, and operational research, or the so-called science of doing better.[141,142] Each course also offers modules that cover concept development, grant and protocol writing, quality-assured data capture and analysis, and manuscript writing. Participants are required to achieve various targets in order to progress, and strong, hands-on mentorship is offered throughout. Collectively, more than 1000 participants from 90 countries have produced a large body of published literature that has contributed to changes in policy and practice in LMICs.[141,143–146] Graduates have a strong track record of staying in research after course completion,[147–150] or continuing on to become course faculty.[147–149,151]

Conclusions

CRDs contribute substantially to the burden of disease in LMICs. Achieving the SDGs will require action to address this burden of disease through improvements in prevention and care. Poverty reduction measures must be at the core of efforts for prevention, with a specific focus on improving maternal nutrition and health, reducing exposure to airborne contaminants (tobacco smoke, household and atmospheric air pollution, and occupational exposures), and improving the prevention and management of severe or untreated respiratory infections including tuberculosis, especially in early life. Policy action directed at these causes of CRDs will yield benefits in both the short-term and long-term. However, it is likely that a substantial burden of disease will remain, and evidence-based therapeutic strategies are also required to reduce ongoing morbidity and mortality in people with established CRDs.

Improved data on the epidemiology of CRDs and their risk factors in LMICs are needed. Many knowledge gaps persist, and to merely extrapolate data from HICs might mean disregarding the unique exposures, health system constraints, and social and political contexts that shape diseases in LMICs. Renewed efforts are required to understand the pathophysiology of CRDs and patient outcomes in LMICs, and to develop approaches to diagnosis and management that are feasible, acceptable, and appropriate to local contexts. These approaches should consider heterogeneity within—as well as between—countries. In a world where migration of people is increasing, the relevance of findings from LMICs to communities who have been forced or have chosen to relocate to other parts of the world should also be considered.[152] The universal health coverage agenda offers an ideal opportunity to ensure the needs of those suffering from CRDs are addressed through affordable and sustained access to appropriate and effective diagnostic evaluation, and pharmacological and non-pharmacological therapeutic interventions—goals that are relevant worldwide. CRD services would benefit from integration with broader tuberculosis and NCD care. The balance between programmatic approaches attempting to deliver simple standardised interventions, and personalised approaches seeking to target interventions more precisely, needs careful consideration and should be tailored to the local health-care setting. However, in all contexts, this will require resourcing and capacity building, with specific attention paid to the most peripheral levels of the health-care system. This goal will be a challenge for many LMICs but highlights the importance of health system strengthening, capacity building, and implementation research in realising the potential of universal health coverage to reduce the burden of CRDs worldwide.

Contributors

All authors contributed to the writing of the manuscript, approved the version to be submitted for publication, and agree to be accountable for all aspects of the work.

Declaration of interests

AA is the current Chair of the Board of Directors of GOLD. EDB is a member of the Science Committee and Board of GINA. He reports personal fees from AstraZeneca, ALK, Boehringer Ingelheim, Menarini, Novartis, Orion, Regeneron, and Sanofi Genzyme. BWA reports honoraria received from Novartis. CEB reports grants from the Global Challenges Research Fund and the University of Nottingham (Nottingham, UK). BC reports personal fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Sanofi Aventis, and Menarini. AAC reports grants and personal fees from GSK, and personal fees from Sanofi, Boehringer

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