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

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SUMMARY

Low- 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-tuberculous lung disease. CRDs are strongly associated with poverty, infectious diseases, and other non-communicable diseases, and contribute to complex multi-morbidity, with significant consequences for the lives and livelihoods of those affected.

The relevance of CRDs to health and socioeconomic wellbeing is expected to increase over time, 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 CRDs as an urgent development issue and essential to the achievement of the Sustainable Development Goals. In this review we focus on CRDs in low- and middle-income settings (LMICs). We discuss the early life origins of CRDs, challenges in 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- and middle-income countries (LMICs).[1] The United Nations' Sustainable Development Goals (SDG) aim to reduce the risk of premature mortality from NCDs by one third by 2030.[2] Chronic respiratory diseases (CRDs), such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis and post-tuberculous (TB) lung disease are common and frequently neglected NCDs that span the life course. They are frequently associated with high levels of cost, morbidity and risk of mortality due to persistent symptoms, activity limitation, and intermittent exacerbations requiring acute care. They disproportionately affect the poor in all countries, but particularly in LMICs where resources for research, prevention and management are scarce.[3]

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 toxic combination of damaging early life and environmental exposures, challenging social and political contexts, and limited 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 prevention and management, 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.

EARLY LIFE ORIGINS OF CHRONIC RESPIRATORY DISEASE

Evidence that has been acquired mainly in 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.[4,5] Although comparable data are lacking from LMICs, it is likely that the same holds true here.[6] Common to both settings are detrimental *in utero* and early childhood exposures, which may 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 may explain the lower lung volumes observed amongst asymptomatic non-smoking adults in many sub-Saharan African (sSA) settings, compared to age- and height- matched adults in HICs.[7] Reduced forced expiratory volumes in 1-second (FEV_1) and forced vital capacity (FVC) in early adulthood have been associated with cardiovascular and metabolic morbidity in both HICs and LMICs.[5,8-10] 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 may 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 immune responses in the developing foetus.[4] Data from the Drakenstein child health study in South Africa – one of the first birth cohorts in sSA – showed that infants of the one third of mothers who smoked during pregnancy had lower tidal volumes and higher lung clearance indices at age 6-weeks, compared to infants of non-smoking women, suggesting impaired lung and airway development.[11] Similar outcomes have been seen in relation to other forms of air pollution exposure, including atmospheric pollution.[12]

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 experienced on a background of structural inequality, marked gender divisions, and a lack of access to Universal Health Coverage, such that women are particularly vulnerable.[13,14] Maternal

psychological distress is negatively associated with measures of neonatal health including weight for age and head circumference,[13] and positively associated with ongoing respiratory morbidity in children.[6,15,16] Maternal alcohol exposure during pregnancy adversely impacts lung function at 6-weeks, but this effect disappears by one-year.[6,11] Better maternal nutrition may protect against childhood wheeze.[17]

HIV infection: The prevalence of HIV among women of child-bearing 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.[18] Whilst HIV-exposed but uninfected infants may have reduced early lung function, by the age of two years impairment is seen only in those children whose mothers had poorly controlled HIV disease during pregnancy.[19]

Premature birth: Premature births occur in 10% of all live births globally, but 80% of these are in LMICs.[20] Preterm birth is associated with increased respiratory symptoms, airway obstruction, abnormal lung structure, and poorer cardiovascular health in childhood and early adulthood.[21 22]

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 (RSV), rhinovirus (RV), adenovirus and Influenza A are amongst the most common viral pathogens detected in children with acute lower respiratory tract illnesses (LRTIs) in LMICs.[23,24] Wheezing illnesses associated with RV and RSV in early life are strong predictors of childhood asthma by 6-years of age,[25] whilst adenovirus related LRTIs have been associated with subsequent obliterative bronchiolitis/bronchiectasis.[26] Pneumonia is a major cause of mortality in children with an estimated incidence of 0.2-0.3 episodes/child year.[27] Contrary to previous findings in HICs, LRTIs in early childhood in sSA have been shown to be an independent risk factor for reduced lung function by 1-year.[11,28] However, pneumococcal conjugate vaccine (PCV) is still only available to approximately 50% of children globally despite having been introduced 2 decades ago.[29]

Pulmonary tuberculosis: Children <15 years account for 11% of incident TB disease globally[30] and paediatricians in LMICs routinely report a high burden of post-TB sequelae including bronchiectasis and lung destruction amongst those successfully completing treatment.[31]

Chronic HIV infection: Large numbers of children previously infected with vertically-acquired HIV are now growing into adolescence.[32] These long-term survivors experience a high burden of CRDs including bronchiectasis, bronchiolitis obliterans, and impaired lung function.[31,32] Deficits are more severe in those with delayed diagnosis and late ART initiation.[33]

Nutrition: LMICs increasingly face a dual burden of maternal and childhood malnutrition,[34] which results in foetal growth restriction, stunting, wasting, and isolated nutrient deficiencies, but also children who are overweight or obese.[35,36] The limited 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.[37]

Air pollution: Both indoor and outdoor air exposures may be relevant to child lung health. The relationship between early childhood biomass fuel exposure and lung development is unclear: delayed introduction of clean burning stoves into Guatemalan households (child age 18-57 months vs. <6months) was associated with lower, but not significantly different, rates of lung growth,[38] 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 to those who had not.[39] In HICs, reductions in outdoor air pollution over time have been associated with better lung function in children from serial birth cohorts.[40] Diesel exposure has been associated with poor asthma outcomes, and this may be particularly relevant in LMICs where trucks may be poorly maintained, use unregulated fuel, and drive in close proximity to habitations.[41-43]

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 intervention 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 ongoing uncertainty about the impact 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.[44] 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.[45] This may be particularly relevant in LMICs, given increasing marketing and interference with public health efforts

by tobacco, alcohol, food and beverage companies, and limited 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.

ASTHMA

Asthma is the most common CRD globally, affecting 272.7 million people in 2017,[46] with LMICs contributing 94.5% of global asthma-related deaths and 87.8% of global disability-adjusted life years (DALYs) (Figure 1).[47] 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 stresses the importance of measuring variability in airflow for confirmation, using peak flow monitoring or spirometry with reversibility testing.[49] Access to these tools is limited 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 disease requires the use of inhaled corticosteroid (ICS) to improve symptom control and reduce hospitalizations and mortality.[53] GINA now recommend as-required 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 demonstrate that this approach is equivalent or superior to use of regular ICS with as-needed short-acting ß$_2$ agonists (SABA) 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 young people over age 12 and adults.[55-58] Likewise, in moderate-severe asthma, joint as-required use of maintenance and reliever therapy with combination ICS-formoterol reduces severe exacerbations compared with conventional regular ICS-LABA therapy with SABA reliever.[59] For mild asthma, if combination ICS-bronchodilator preparations are not available or affordable, separate ICS may be used whenever a SABA is taken.

However, 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, with over-reliance on inhaled bronchodilators alone, or oral preparations of salbutamol, theophylline or prednisolone instead.[60-63] Health system capacity for long term follow-up with titration of medication

for symptom control is limited, and patient and clinician understanding of the need for chronic treatment may be limited, with 52-76% loss to follow-up seen within 1-year in pilot projects in China, Benin and Sudan.[60-62]

Towards solutions

There are global strategies for asthma care in LMICs that 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. There is a need for improved access to diagnostic tools (peak flow meters and spirometry) and training in their use. Similarly there is a need for access to affordable quality-assured asthma medicines listed on the WHO Essential Medicines list (Table 1). 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 LMIC, but essential for preventing over-reliance on emergency services, improving long-term symptom control, and minimising morbidity and mortality.

COPD

Data on the global burden of COPD shows widespread variability in the prevalence, causes, clinical presentation and mortality between and within LMICs.[64] This is primarily related to poor access to spirometry and limited epidemiological data, but is compounded by controversy in the definition of COPD – for example it is unclear whether fixed ratios and percent predicted cut-offs or lower limit of normal (LLN) 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.[7] Notwithstanding this, community based data indicate that the prevalence of airway obstruction is between 6–20% in Latin America,[65-67] and 5–24% in sSA.[68-71] It is thought that LMICs contribute to 76.5% of the global COPD burden, 85% of global COPD deaths and 85% 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 are seen in never smokers, and a substantial proportion of these are likely related to biomass use for cooking and heating, particularly amongst women.[72-76]

Diagnosis

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

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 (short- and long-acting ß$_2$ agonists (SABA/LABA), short- and long-acting muscarinic antagonists (SAMA/LAMA), 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 limited.[80,81] Results from the PUMA study showed that in primary care, the most widely used inhaled therapy was SABA, with long-acting bronchodilators and ICS relatively less used.[82] There are no clinical trials that have investigated the appropriate pharmacotherapy for non-smoking-related COPD, including disease related to biomass pollutant exposure in LMICs, which may differ from that recommended for smoking-related COPD.

Towards solutions

There is an urgent need for the collection of better epidemiological data, accurate diagnosis, and appropriate clinical care for COPD in LMICs.[83,84] Some of the approaches required may be similar to those outlined for asthma above, including raising awareness amongst patients and providers, use of approved standardised guidelines for diagnosis and management, better access to spirometry, availability of inhaled therapies, education for both patients and health care providers, and access to long term follow-up. However, COPD in HICs has been associated with systemic sequelae including cardiovascular disease, malignancy, osteoporosis, depression and anxiety – 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 may be required.[85] 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 globally, 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 support. Data on the risks, nature, outcomes and management of non-smoking related airway obstruction are needed in both high- and low-income settings.

BRONCHIECTASIS

The reported population prevalence of non-cystic fibrosis bronchiectasis in HICs has increased in recent years to 566/100,000,[87] with disease prevalence and severity associated with older age and female gender. Epidemiological data on bronchiectasis in LMICs is lacking,[88] but what data are available suggest that the prevalence, aetiology, and risk factors for bronchiectasis may be markedly different, with more post-infectious disease, an association with HIV infection, a higher burden of severe disease in younger adults, and differences in colonising/infecting microbiology compared to most HICs.[87,89,90]

Diagnosis

The diagnosis of bronchiectasis in LMICs is challenging. The clinical presentation is similar to that observed amongst 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 high TB incidence, low-resource settings, patients presenting with these symptoms are managed primarily as 'TB-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' tool for diagnosis, but this tool is unavailable to the majority of those living in LMICs. There is little evidence to support the use of plain chest x-ray for the diagnosis of bronchiectasis, specifically, and few guidelines which support the use of chest x-ray for the investigation of chronic respiratory symptoms, in general.

Management

Management of bronchiectasis in HICs is increasingly individualised and focused on addressing 'treatable traits' with the use of airway clearance tools, vaccination to prevent infection, appropriate treatment of infecting or colonising organisms, and early diagnosis and active management of intercurrent fungal and non-tuberculous mycobacterial (NTM) disease.[91] These individualised approaches are not widely available in LMICs and, to our knowledge, there remain no guidelines for the diagnosis and management of bronchiectasis in low-resource settings.

Towards solutions

Improved investigation and management approaches for chronic productive cough amongst 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 high TB-burden settings, these guidelines must include appropriate investigation for active TB disease, but with consideration of underlying CRD, when TB is excluded. This will require better integration between TB-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.[92] An improved understanding of the microbiology of bronchiectasis in both children and adults is needed to inform population-level antibiotic recommendations.

POST TB LUNG DISEASE (PTLD)

Pulmonary tuberculosis (PTB) survivors, estimated at 58 million in this century alone,[30] have two-to-four-fold odds of persistently abnormal spirometry after TB-treatment completion (airway obstruction and low FVC patterns) compared to TB-naïve groups, with bronchiectasis, parenchymal cavitation and destruction, and fibrotic change widely seen on imaging.[93-96] There is much heterogeneity in the prevalence, patterns and severity of residual pathology seen, but it is thought that bronchiectasis or abnormal spirometry are seen in over a third of PTB survivors.[96-98] Those with post-TB lung disease (PTLD) may be at risk of long-term chronic respiratory symptoms, recurrent respiratory exacerbations, and accelerated lung function decline.[97] TB-survivors are at increased risk of recurrent TB disease compared to TB-naïve populations, whether re-activation or re-infection,[99] but chronic respiratory symptoms amongst those with PTLD also place them at high risk of empirical and un-necessary TB retreatment,[100] with resultant treatment associated morbidity.[101] Mortality in adult survivors of TB is almost three-times greater than that in the general population, but the direct association between PTLD and mortality is unclear.[102] Of the 10 million annual cases of incident pTB, over 1 million occur in children,[30] 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 TB treatment completion and may not be available at the point of care within decentralised TB-treatment programmes. The majority of those with residual PTLD are

therefore discharged without a diagnosis and without ongoing care.[97] The diagnosis of recurrent TB amongst those with existing PTLD may be challenging: the specificity of nucleic acid amplification tests is reduced amongst TB-survivors, and the performance of screening tools including the WHO symptom screen and chest radiography in those with PTLD is unclear.[103,104]

Management

There has been little attention to long-term post-TB morbidity within International and National TB treatment guidelines to date, with no evidence-based guidelines available for the diagnosis and management of PTLD in LMICs.[105,106] 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 TB populations, airway clearance exercises, vaccinations as per national guidelines, and use of inhaled bronchodilators for reversible airway obstruction.[107] The use of ICS is not recommended given the associated increased risk of recurrent mycobacterial disease and other respiratory infections.[108-110] Pulmonary rehabilitation may improve quality of life.[111] Although sputum culture is the gold-standard tool for the diagnosis of recurrent TB disease and drug susceptibility testing in this group, culture is frequently not available in LMICs, and not feasible in young children. Further work is required to explore the performance of TB screening and diagnostic tools amongst PTB survivors and those with PTLD.

Towards solutions

TB treatment completion provides an opportunity to screen PTB 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-efficacy 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, some years later. Integration of TB and CRD services will be required to optimise PTLD diagnosis and management,[112] with improved approaches to the diagnosis of recurrent TB disease. We suggest that the broader cardiovascular, psychological and socioeconomic morbidities faced by TB-survivors should also be addressed within any packages of post-TB care.[113]

HEALTH SYSTEMS STRENGTHENING

Strong health systems which 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: (i) service delivery, (ii) health workforce, (iii) health information systems, (iv) access to essential medicines and vaccines, (v) financing, and (vi) leadership/governance (Figure 2).[114]

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 TB are few,[115] 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 lacking. National guidelines for the management of CRDs are also limited, and were identified in only 64% of countries in the seventh NCD country capacity survey 2019.[116] Access to key diagnostic tools including spirometry and imaging is limited and in 2019 peak flow or spirometry were available in 45% of primary care facilities only, compared to 88% for blood glucose measurement.[117] Access to preventative measures including vaccination, nutritional support, and smoking cessation services is limited.[118] Crucially, the health workforce is poorly equipped to deliver respiratory care, with low numbers of respiratory specialists,[119-122]and most care delivered at the primary care level by nursing staff with limited training.[123] Solutions to some of these challenges are explored below.

Integrated delivery of CRD care

Front-line primary-care staff in LMICs have a broad remit and are expected to provide preventative and curative care, for infectious and non-infectious diseases, to both children and adults. As such, it is crucial that CRD services are 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.[124,125] Early models, such as the WHO Practical Approach to Lung Disease (PAL), which was developed in part to improve case finding for TB, were focused only on respiratory diseases. These have been followed by tools with more comprehensive scope including the WHO PEN,[126] WHO IMAI,[127] and Package of Care Kit (PACK) for children, adolescents and adults.[128] 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.[129-132] It integrates local management guidelines and evidence, is regularly updated, and is supported by on-site, case-based, interactive training.[133,134] 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.[133-135]

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 high TB burden settings will usually require investigation for active TB disease. However, if TB investigations are negative it is important that alternative respiratory diagnoses are considered. Similarly, patients with PTLD at TB-treatment completion would benefit from clear and efficient integrated care pathways.

Lastly, NCD programmes in LMICs should consider including palliative care support within their services. This is particularly important for CRDs which are frequently irreversible, progressive, and may 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.[136]

Improving access to diagnostic tools

Specific challenges to accessing diagnostic tools, including spirometry and imaging, at the primary care level include the funding of these services, and training in how to perform tests, maintain quality control, and accurately interpret results.[137] Advances in the development of reliable and portable spirometry, ultrasound and chest x-ray equipment for community-based diagnosis may facilitate decentralisation, but services may prove more sustainable if accompanied by education and access to equipment maintenance services.[138] It is likely that more sophisticated diagnostics such as CT imaging, complex lung function testing, and bronchoscopy will 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 limited investment in their centralised use may be of some benefit.

Improving access to treatment

Although many key respiratory medications are included in the WHO essential medications list (Table 1),[139] access is limited: in 2019, ICS were generally available in 19% of low-income compared to 96% of high-income countries, and bronchodilators in 55% and 100% respectively.[117] Even where available, these medications were frequently unaffordable to patients. Access to non-pharmacological interventions including pulmonary rehabilitation and smoking cessation services is also limited, 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. Education programmes to improve self-management, promote health literacy, and combat stigma are lacking.

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/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 programs of care will be required. The development of a health workforce which can provide CRD services competently and compassionately is at the core of improving access.

RESEARCH PRIORITIES & RESEARCH CAPACITY STRENGTHENING

This review has highlighted several areas of uncertainty which we have formulated into research priorities for CRDs in LMICs (Table 2). However, these 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 '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 "science of doing better".[141,142] Each 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, over 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 better 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, particularly in early life. Policy action directed at these causes of CRD will yield benefits in the short- 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 amongst those with established CRDs.

Improved data on the epidemiology of CRDs and their risk factors in LMICs are needed. There are many knowledge gaps, and extrapolating data from HICs may be to ignore the unique exposures, health system constraints, and social and political contexts which shape disease 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 which are feasible, acceptable, and appropriate to local contexts. These should consider heterogeneity within, as well as between, countries. In a world where migration of peoples 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 CRD are addressed through affordable and sustained access to appropriate and effective diagnostic evaluation, and pharmacological and non-pharmacological therapeutic interventions, and is relevant worldwide. CRD services would benefit from integration with broader TB 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 healthcare system. This 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 UHC to reduce the burden of CRD.

AUTHOR CONTRIBUTIONS

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

REFERENCE SEARCH STRATEGY

Studies included in this review were identified by the authors based on their knowledge of non-communicable respiratory disease in LMICs; the studies referenced were selected by the authors, as most relevant to this field.

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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.

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GBM reports grants and other support from AstraZeneca, and grants from GSK Australia.

HKR is Chair of the GINA Science Committee and reports grants and personal fees from AstraZeneca and GlaxoSmithKline, and personal fees from Merck, Novartis, Teva, Boehringer Ingelheim, and Sanofi Genzyme.

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KM reports personal fees from AstraZeneca.

TABLES

Table 1: Medications for CRD management, from WHO Model List of Essential Medicines[134]

Category	Drug [Route of administration]
Respiratory medications – inhaled or nebulised All metered-dose inhalers to be provided with spacer device	Beclomethasone [inhaled] Budesonide [inhaled] Budesonide + Formoterol [inhaled] Ipratropium bromide [inhaled] Salbutamol [inhaled & 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 + clavulanic acid, cefalexin, cefixime*, cefotaxime*, ceftriaxone* Tetracyclines: Doxycycline Macrolides: Azithromycin*, clarithromycin* Quinolones: Ciprofloxacin* Aminoglycosides: Amikacin, gentamicin Other: Sulfamethoxazole + trimethoprim, metronidazole, chloramphenicol
Vaccines	Childhood vaccines: pertussis, measles, diptheria, and *H.influenzae* type B Influenza vaccine (seasonal) Pneumococcal vaccine (conjugate & polysaccharide)

*Antibiotics on the WHO 'Watch' list due to high resistance potential – for limited use, with guidance from local antibiotic stewardship programmes

Table 2: Suggested research and clinical care priorities, for the delivery of CRD care in LMICs

Remit	Research need
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 & early childhood exposures affect lung development
	Investigation of the long-term impact of nutrition, LRTIs and TB in children, and mechanisms for development of chronic respiratory disease
	Investigation of the origins, nature, and outcomes associated with low FVC phenomenon seen in LMICs
	New vaccine development to reduce childhood LRTI
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 ICS medications
	Investigation of the pragmatic use of GINA-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 TB
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 (E.g. using questionnaires and CXR), 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, in order to inform antibiotic guidelines
Post-TB lung disease	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 TB diagnostic tools in those with PTLD being investigated for recurrent TB disease
	Determine the pathology underlying chronic respiratory symptoms in pTB-survivors re-presenting to health services, after recurrent TB disease has been excluded
CRD diagnosis	Consensus guidelines for the use of spirometry performed 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 post-TB lung disease
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 TB disease, in high TB incidence settings
	Inclusion of epidemiological data on CRD in LMICs into international registries and consensus statements, in order 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 TB and palliative care services, and integrated with the management of other NCDs (E.g. cardiovascular disease services), with tools for the evaluation of clinical impact and health system / patient costs
	Development of key program 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

FIGURES

Figure 1: Distribution of the global burden of disease, deaths and DALYs from Chronic Respiratory Diseases (CRDs), COPD and Asthma, by World Bank defined country income strata, using Global Burden of Disease 2017 estimates[137]

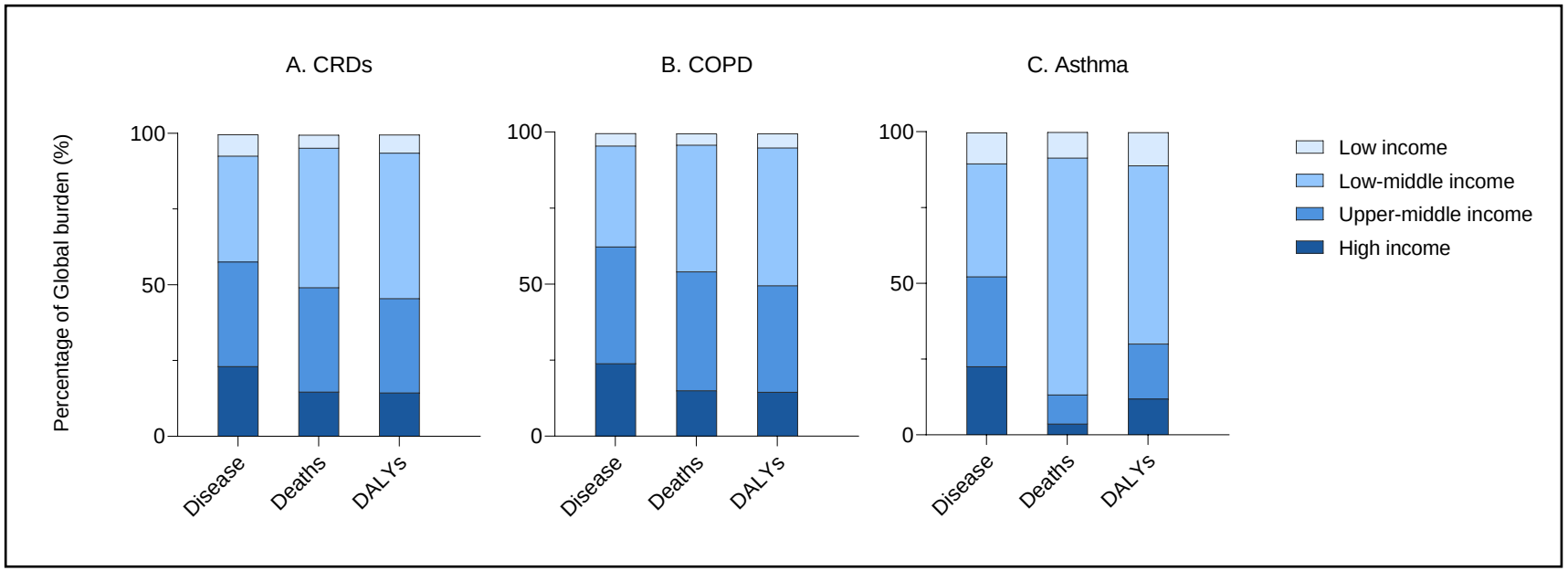
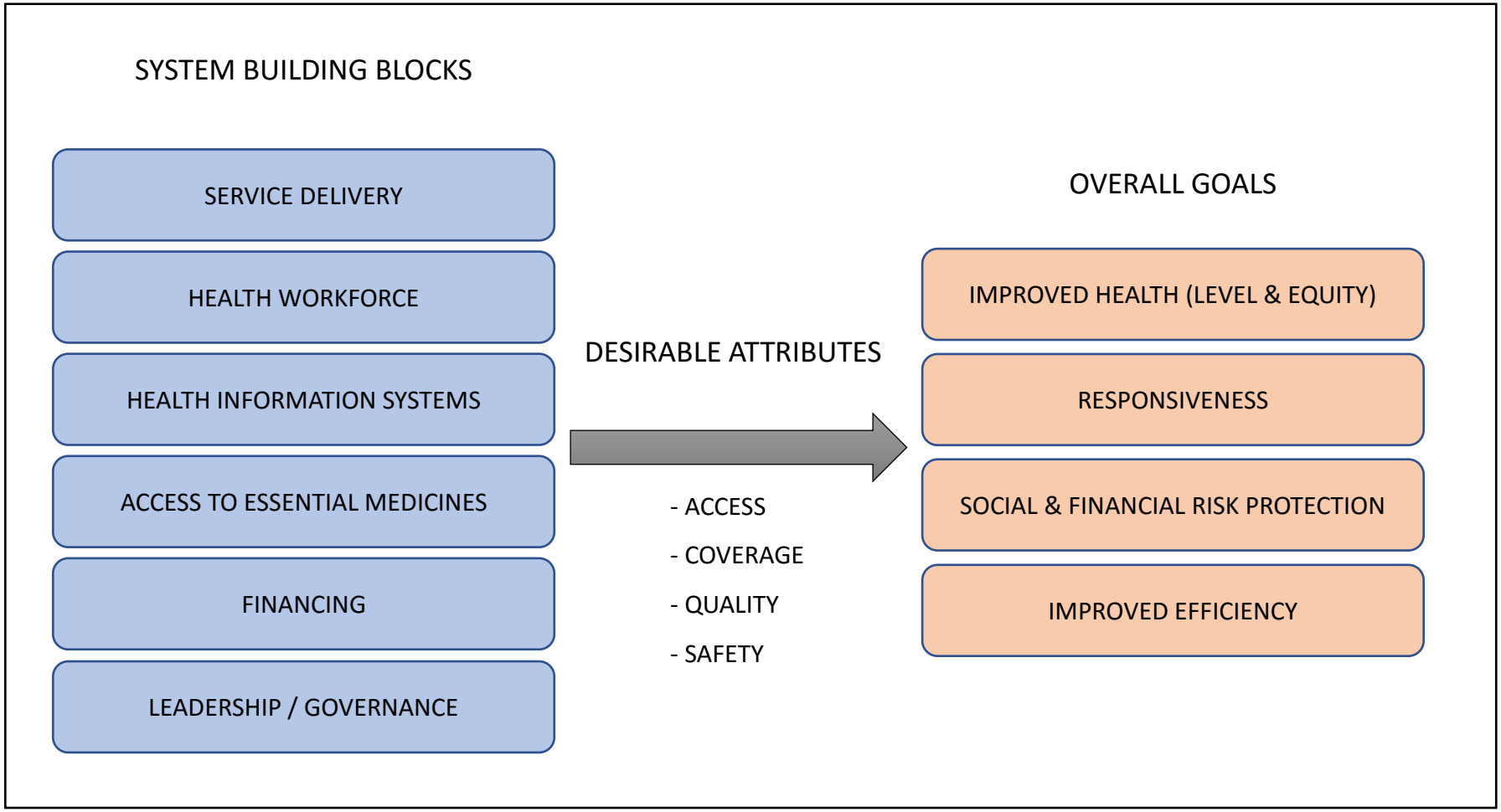


Figure 2: World Health Organisation six building blocks of Health Systems, together with aims and desirable attributes[114]



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